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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ADAMAS PHARMA, LLC, Plaintiff, v. SANDOZ INC., Defendant.	**Civil Action No. _____** **COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiff Adamas Pharma, LLC ("Adamas" or "Plaintiff"), for its Complaint against Defendant Sandoz Inc. ("Sandoz" or "Defendant"), hereby alleges as follows:

THE PARTIES

1. Plaintiff Adamas Pharma, LLC, is a limited liability company organized and existing under the laws of the State of Delaware, having a principal place of business at 1900 Powell Street, Suite 750, Emeryville, California 94608.

2. Defendant Sandoz Inc. is an entity organized and existing under the laws of the State of Colorado, having a principal place of business at 100 College Road West, Princeton, New Jersey 08540.

NATURE OF THE ACTION

3. This is a civil action for infringement of U.S. Patent Nos. 8,389,578 ("the '578 patent"), 8,796,337 ("the '337 patent"), 8,889,740 ("the '740 patent"), 8,895,614 ("the '614 patent"), 8,895,615 ("the '615 patent"), 8,895,616 ("the '616 patent"), 8,895,617 ("the '617 patent"), 8,895,618 ("the '618 patent"), 8,741,343 ("the '343 patent"), 9,867,791 ("the '791 patent"), 9,867,792 ("the '792 patent"), 9,867,793 ("the '793 patent"), and 9,877,933 ("the '933 patent") (collectively, "the patents-in-suit"). This action arises under the Patent Laws of the United States, 35 U.S.C. § 100, *et seq*., as well as the Declaratory Judgment Act, 28 U.S.C. §§ 2201–02.

JURISDICTION AND VENUE

4. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, 2202, and/or 35 U.S.C. § 271.

5. Sandoz markets, distributes, and/or sells generic pharmaceutical versions of branded products throughout the United States, including in the State of New Jersey.

6. Sandoz sent Adamas a letter dated March 29, 2018 ("Sandoz's Notice Letter"), stating that Sandoz filed Abbreviated New Drug Application ("ANDA") No. 211493 seeking approval from the United States Food and Drug Administration ("FDA") to engage in the commercial manufacture, use, offer for sale, or sale within the United States (including, upon information and belief, in the State of New Jersey) of generic amantadine hydrochloride extended-release capsules, 137 mg prior to the expiration of the patents-in-suit.

7. This Court has personal jurisdiction over Sandoz, because, *inter alia*, Sandoz: (1) has its principal place of business in the State of New Jersey; (2) has substantial, continuous, and systematic contacts with the State of New Jersey; (3) is registered with the State of New Jersey's Division of Revenue and Enterprise Service to do business in the State of New Jersey under entity ID No. 0100097265; (4) intends to market, sell, and/or distribute Sandoz's infringing ANDA Product (as defined in paragraph 26 *infra*) to residents of the State of New Jersey; (5) has secured a New Jersey wholesale drug distributor's license under Registration No. 5003732; (6) maintains a broad distributorship network within the State of New Jersey; and (7) enjoys substantial income from sales of its generic pharmaceutical products in the State of New Jersey.

8. Further, this Court has personal jurisdiction over Sandoz because, *inter alia*, Sandoz has committed, aided, abetted, contributed to, and/or participated in the commission of acts of patent infringement, including acts in the State of New Jersey, that have led to foreseeable harm and injury to Plaintiff in the State of New Jersey. Personal jurisdiction is proper for the reasons set forth above, and for other reasons that will be presented to the Court if such personal jurisdiction is challenged.

9. Venue is proper in this Court under 28 U.S.C. §§ 1391(b)–(d) and/or 1400(b) because, *inter alia*, Sandoz has its principal place of business in the State of New Jersey and has committed and will commit further acts of infringement in the State of New Jersey. Venue is proper for the reasons set forth above and for other reasons that will be presented to the Court if such venue is challenged.

THE PATENTS-IN-SUIT

10. Adamas is the holder of New Drug Application ("NDA") No. 208944, by which the FDA first granted approval for amantadine hydrochloride 68.5 mg and 137 mg extended-release capsules, marketed in the United States under the trade name Gocovri™.

11. Gocovri™ (amantadine) extended-release capsules are the first and only FDA-approved medicine for the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications.

12. Pursuant to 21 U.S.C. § 355(b)(l), the '578, '337, '740, '614, '615, '616, '617, '618, '343, '791, '792, '793, and '933 patents are listed in the FDA publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (also known as the Orange Book) as covering Adamas' Gocovri™ (amantadine) extended-release capsules.

13. Adamas Pharma, LLC owns the '578 patent, which was duly and legally issued on March 5, 2013, and is titled, "Composition and Method for Treating Neurological Disease." A copy of the '578 patent is attached as Exhibit A.

14. Adamas Pharma, LLC owns the '337 patent, which was duly and legally issued on August 5, 2014, and is titled, "Composition and Method for Treating Neurological Disease." A copy of the '337 patent is attached as Exhibit B.

15. Adamas Pharma, LLC owns the '740 patent, which was duly and legally issued on November 18, 2014, and is titled, "Composition and Method for Treating Neurological Disease." A copy of the '740 patent is attached as Exhibit C.

16. Adamas Pharma, LLC owns the '614 patent, which was duly and legally issued on November 25, 2014, and is titled, "Composition and Method for Treating Neurological Disease." A copy of the '614 patent is attached as Exhibit D.

17. Adamas Pharma, LLC owns the ’615 patent, which was duly and legally issued on November 25, 2014, and is titled, “Composition and Method for Treating Neurological Disease.” A copy of the ’615 patent is attached as Exhibit E.

18. Adamas Pharma, LLC owns the ’616 patent, which was duly and legally issued on November 25, 2014, and is titled, “Composition and Method for Treating Neurological Disease.” A copy of the ’616 patent is attached as Exhibit F.

19. Adamas Pharma, LLC owns the ’617 patent, which was duly and legally issued on November 25, 2014, and is titled, “Composition and Method for Treating Neurological Disease.” A copy of the ’617 patent is attached as Exhibit G.

20. Adamas Pharma, LLC owns the ’618 patent, which was duly and legally issued on November 25, 2014, and is titled, “Composition and Method for Treating Neurological Disease.” A copy of the ’618 patent is attached as Exhibit H.

21. Adamas Pharma, LLC owns the ’343 patent, which was duly and legally issued on June 3, 2014, and is titled, “Method of Administering Amantadine Prior to a Sleep Period.” A copy of the ’343 patent is attached as Exhibit I.

22. Adamas Pharma, LLC owns the ’791 patent, which was duly and legally issued on January 16, 2018, and is titled, “Method of Administering Amantadine Prior to a Sleep Period.” A copy of the ’791 patent is attached as Exhibit J.

23. Adamas Pharma, LLC owns the ’792 patent, which was duly and legally issued on January 16, 2018, and is titled, “Method of Administering Amantadine Prior to a Sleep Period.” A copy of the ’792 patent is attached as Exhibit K.

24. Adamas Pharma, LLC owns the ’793 patent, which was duly and legally issued on January 16, 2018, and is titled, “Method of Administering Amantadine Prior to a Sleep Period.” A copy of the ’793 patent is attached as Exhibit L.

25. Adamas Pharma, LLC owns the ’933 patent, which was duly and legally issued on January 31, 2018, and is titled, “Method of Administering Amantadine Prior to a Sleep Period.” A copy of the ’933 patent is attached as Exhibit M.

ACTS GIVING RISE TO THIS ACTION

26. Upon information and belief, Sandoz filed with the FDA ANDA No. 211493, which included a certification with respect to the patents-in-suit under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) (“Paragraph IV Certification”), seeking approval to engage in the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of generic amantadine hydrochloride extended-release capsules, 137 mg (“Sandoz’s ANDA Product”) prior to the expiration of the patents-in-suit.

27. On or about March 29, 2018, Sandoz sent Sandoz’s Notice Letter to Adamas, in which it represented that it had filed ANDA No. 211493 for Sandoz’s ANDA Product, including a Paragraph IV Certification with respect to the ’578, ’337, ’740, ’614, ’615, ’616, ’617, ’618, ’343, ’791, ’792, ’793, and ’933 patents, and that it sought approval of ANDA No. 211493 prior to the expiration of the patents-in-suit. On or about March 30, 2018, Adamas first received Sandoz’s Notice Letter.

28. Plaintiff commenced this action within 45 days of the date of receipt of Sandoz’s Notice Letter.

COUNT I – INFRINGEMENT BY SANDOZ

29. Plaintiff re-alleges paragraphs 1–28 as if fully set forth herein.

30. By seeking approval of ANDA No. 211493 to engage in the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of Sandoz's ANDA Product prior to the expiration of the patents-in-suit, Sandoz has infringed the patents-in-suit under 35 U.S.C. § 271(e)(2)(A).

31. Plaintiff is entitled to relief provided by 35 U.S.C. § 271(e)(4), including an Order of this Court that the effective date of the approval of ANDA No. 211493 be a date that is not earlier than the latest expiration date of each of the patents-in-suit, including any patent term extensions and/or patent term adjustments, and the period of any pediatric exclusivity associated with the patents-in-suit, to which Plaintiff is or may become entitled.

32. The commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of Sandoz's ANDA Product, if approved by the FDA prior to the expiration of the patents-in-suit, for use in accordance with its proposed labeling, would infringe and/or induce and/or contribute to the infringement of the patents-in-suit.

33. Plaintiff is entitled to a declaration that, if Sandoz commercially manufactures, uses, offers to sell, or sells within the United States, and/or imports into the United States, Sandoz's ANDA Product, or induces or contributes to any such conduct, it would further infringe the patents-in-suit pursuant to 35 U.S.C. §§ 271(a), (b), and/or (c).

34. Upon information and belief, Sandoz was aware of the existence of the patents-in-suit and was aware that the filing of its ANDA and Paragraph IV Certification with respect to the patents-in-suit constituted an act of infringement of those patents.

35. Sandoz's statement of the factual and legal bases for its opinion regarding the invalidity of the patents-in-suit contained in Sandoz's Notice Letter is devoid of any objective good-faith basis in either the facts or the law.

36. The sole basis in Sandoz's Notice Letter for the assertion that Sandoz's ANDA Product will not infringe the '740, '614, and '618 patents is that those patents are allegedly invalid. The bases in Sandoz's Notice Letter for the assertion that Sandoz's ANDA Product will not infringe the '578, '337, '615, '616, '617, '343, '791, '792, '793, and '933 patents is that those patents are allegedly invalid, that Sandoz will not administer Sandoz's ANDA Product to patients, or that Sandoz allegedly will not induce or contribute to the administration of Sandoz's ANDA Product pursuant to the claimed methods.

37. Plaintiff will be irreparably harmed by Sandoz's infringing activities unless those activities are enjoined by this Court. Plaintiff does not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully requests the following relief:

A. A Judgment be entered that Sandoz has infringed the '578, '337, '740, '614, '615, '616, '617, '618, '343, '791, '792, '793, and '933 patents by submitting ANDA No. 211493 to the FDA;

B. A Judgment be entered that the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of Sandoz's ANDA Product will infringe, or induce or contribute to the infringement of, the '578, '337, '740, '614, '615, '616, '617, '618, '343, '791, '792, '793, and '933 patents;

C. A Judgment be entered that this case is exceptional and that Plaintiff is entitled to its reasonable attorneys' fees pursuant to 35 U.S.C. § 285;

D. A permanent injunction be issued, pursuant to 35 U.S.C. § 271(e)(4)(B) or 35 U.S.C. § 283, restraining and enjoining Sandoz, its directors, officers, agents, attorneys, affiliates, divisions, successors, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of any drug product, or use thereof, claimed in the patents-in-suit;

E. An Order be issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of ANDA No. 211493 be a date that is not earlier than the latest expiration date of the patents-in-suit, including any patent term extensions and/or patent term adjustments, and the period of any pediatric exclusivity associated with the patents-in-suit, to which Plaintiff is or may become entitled; and

F. Such other and further relief as the Court may deem just and proper.

Dated: May 10, 2018

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that the matter in controversy is related to *Osmotica Pharmaceutical US LLC et al. v. Adamas Pharmaceuticals, Inc., et al.*, Civil Action No. 18-278-GMS (D. Del.) because the matter in controversy involves some of the same patents.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: May 10, 2018

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EXHIBIT A

US008389578B2

(12) **United States Patent**
Went et al.

(10) **Patent No.: US 8,389,578 B2**
(45) **Date of Patent: Mar. 5, 2013**

(54) **COMPOSITION AND METHOD FOR TREATING NEUROLOGICAL DISEASE**

(75) Inventors: **Gregory T. Went**, Mill Valley, CA (US); **Timothy J. Fultz**, Pleasant Hill, CA (US); **Seth Porter**, San Carlos, CA (US); **Laurence R. Meyerson**, Las Vegas, NV (US); **Timothy S. Burkoth**, San Francisco, CA (US)

(73) Assignee: **Adamas Pharmaceuticals, Inc**, Emeryville, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 594 days.

(21) Appl. No.: **11/286,448**

(22) Filed: **Nov. 23, 2005**

(65) **Prior Publication Data**

US 2006/0189694 A1 Aug. 24, 2006

Related U.S. Application Data

(60) Provisional application No. 60/631,095, filed on Nov. 24, 2004.

(51) **Int. Cl.**
A61K 31/13 (2006.01)
A61K 31/195 (2006.01)

(52) **U.S. Cl.** **514/565**; 514/656

(58) **Field of Classification Search** 514/565, 514/656

See application file for complete search history.

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(57) **ABSTRACT**

The invention provides methods and compositions for treating or preventing neurological disorders.

8 Claims, 7 Drawing Sheets

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Figure 1: Simulated Dissolution for TID Amantadine IR & SR

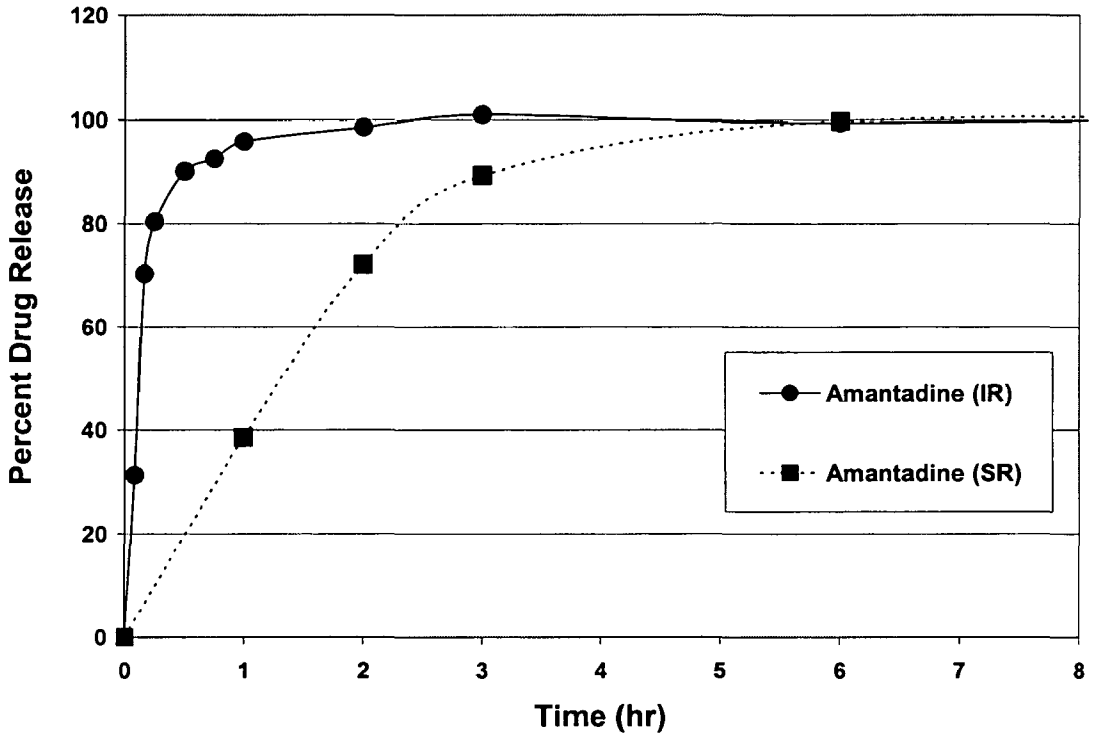


Figure 2: Simulated Plasma Concentration for TID Amantadine IR & SR over 120hrs.

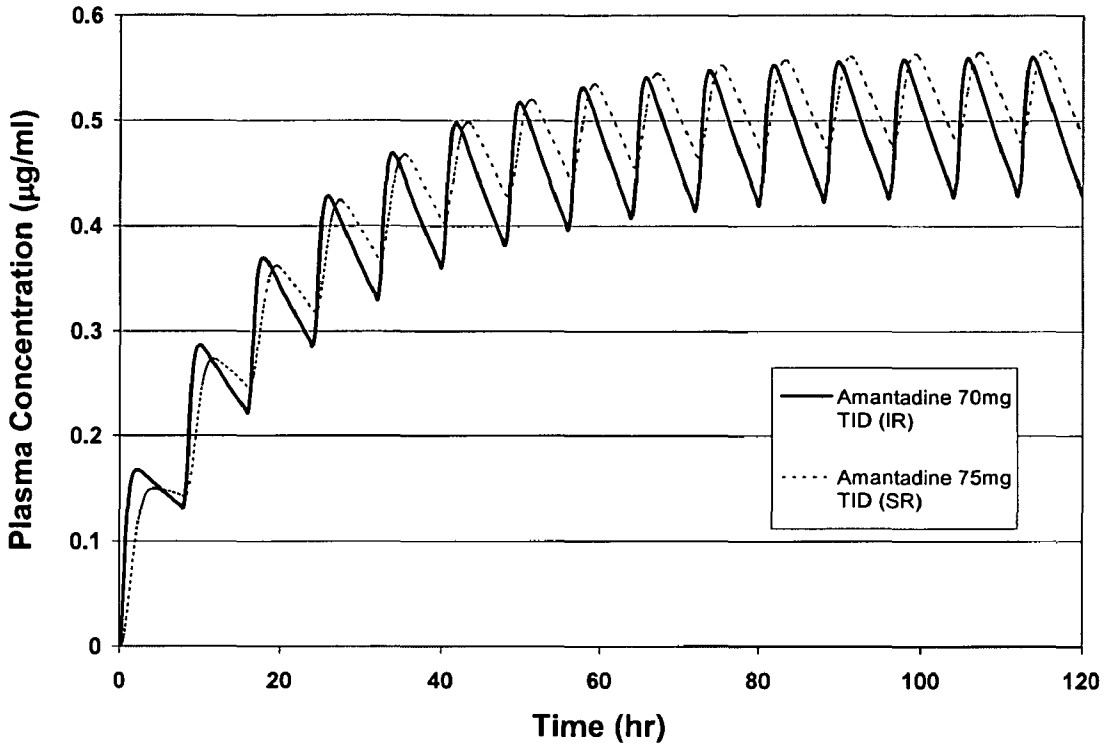


Figure 3: Simulated Plasma Concentration for TID Levodopa/Carbidopa/Amantadine (IR, IR, IR) over 24hrs

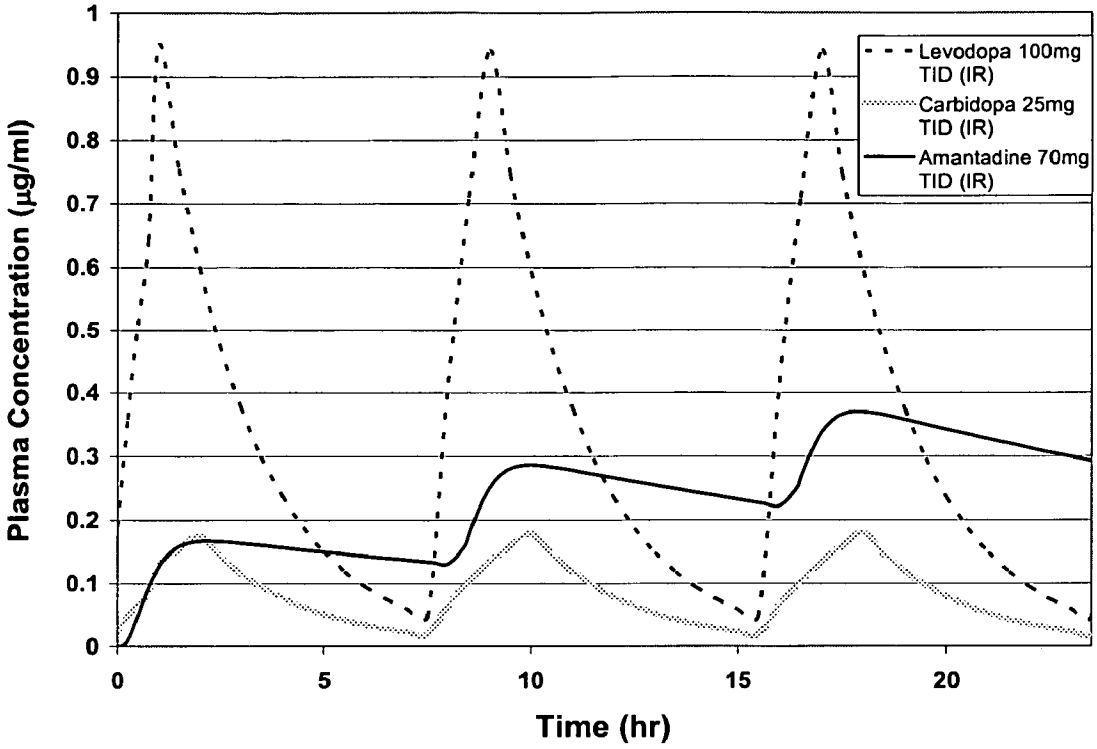


Figure 4: Simulated Plasma Concentration for TID Levodopa/Carbidopa/Amantadine (IR, IR, SR) over 24hrs

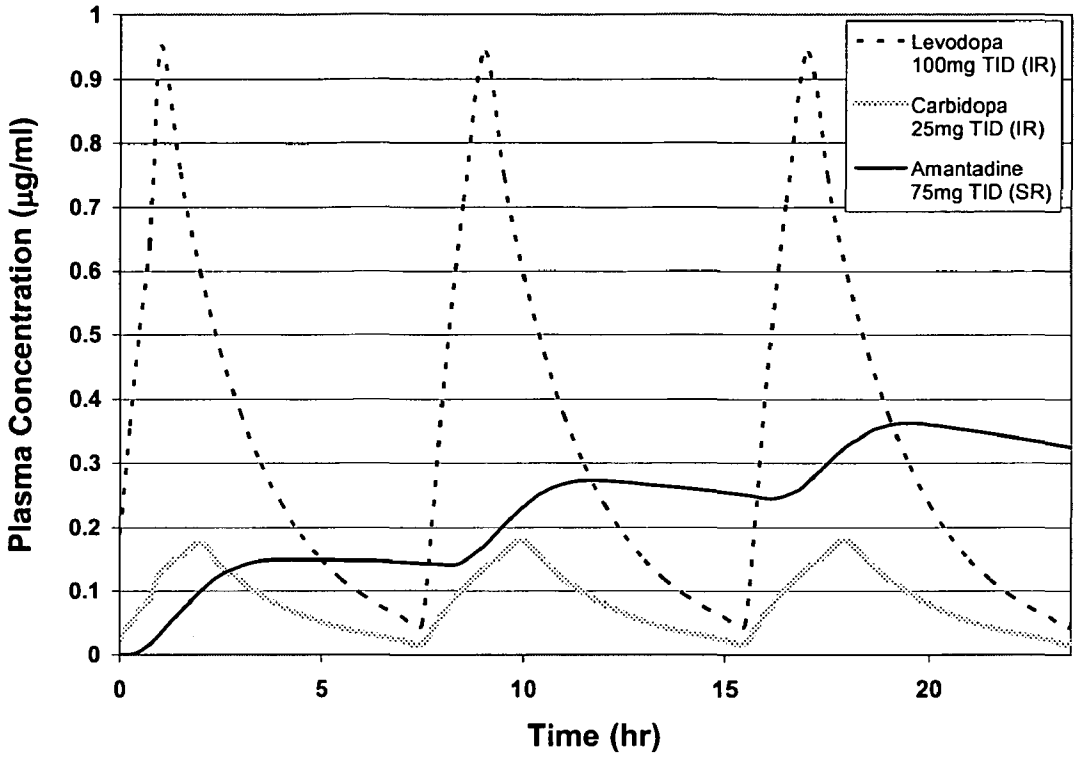


FIGURE 5

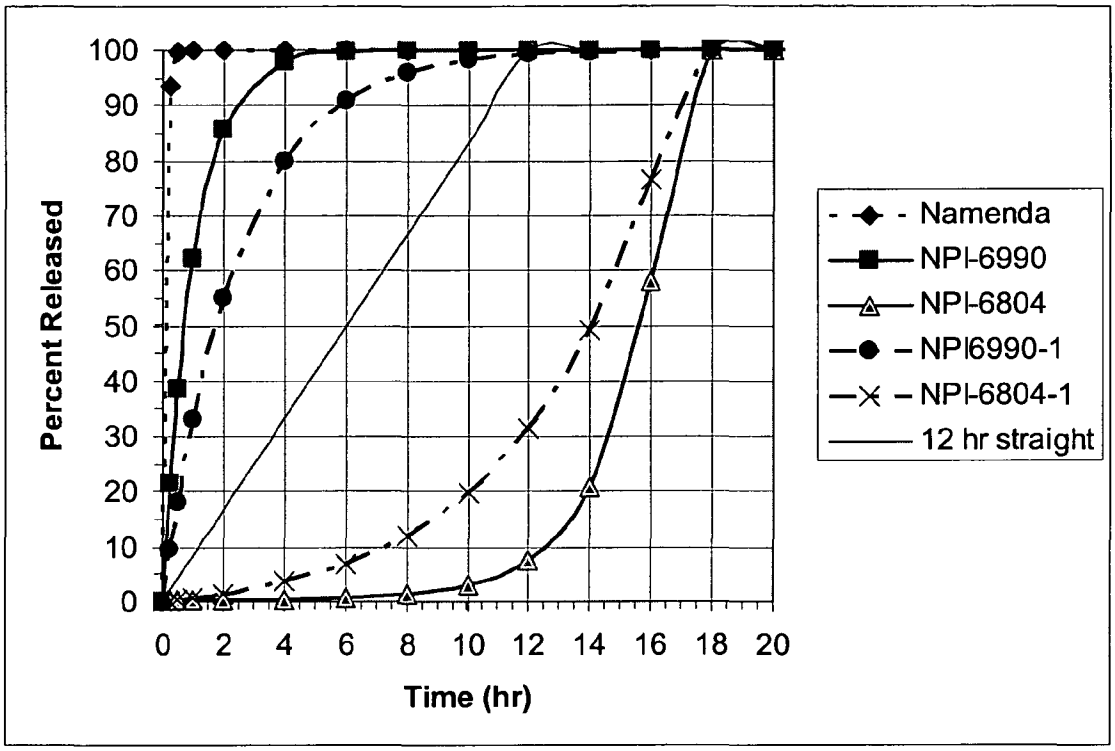

Percent Released
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20
Time (hr)
Namenda
NPI-6990
NPI-6804
NPI6990-1
NPI-6804-1
12 hr straight

Figure 6: Memantine, Levodopa and Carbidopa Human Pharmacokinetics

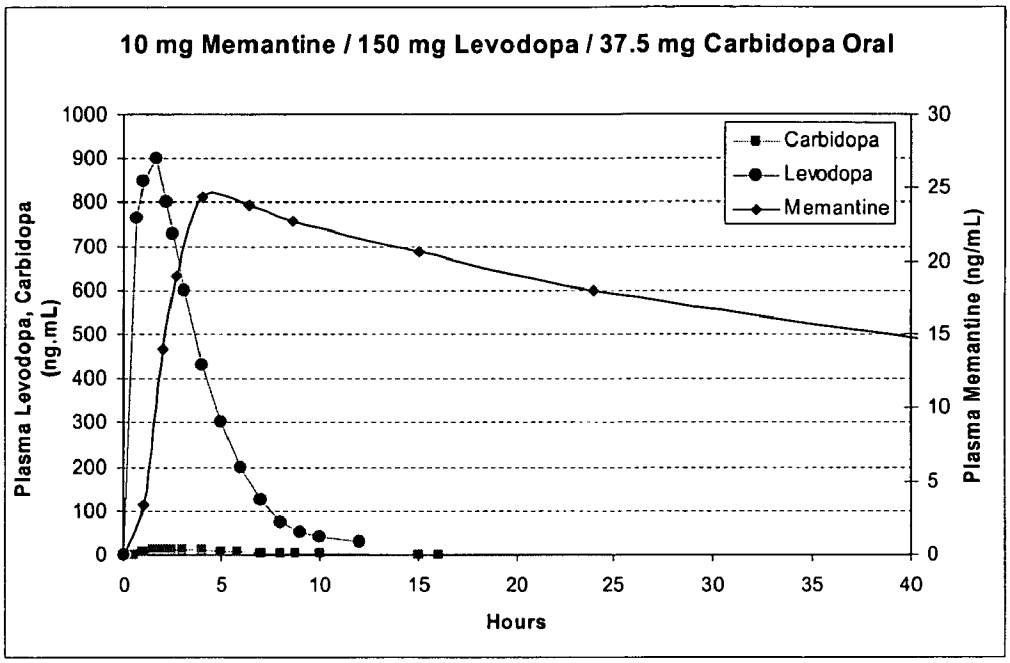


Figure 7: Target Pharmacokinetics

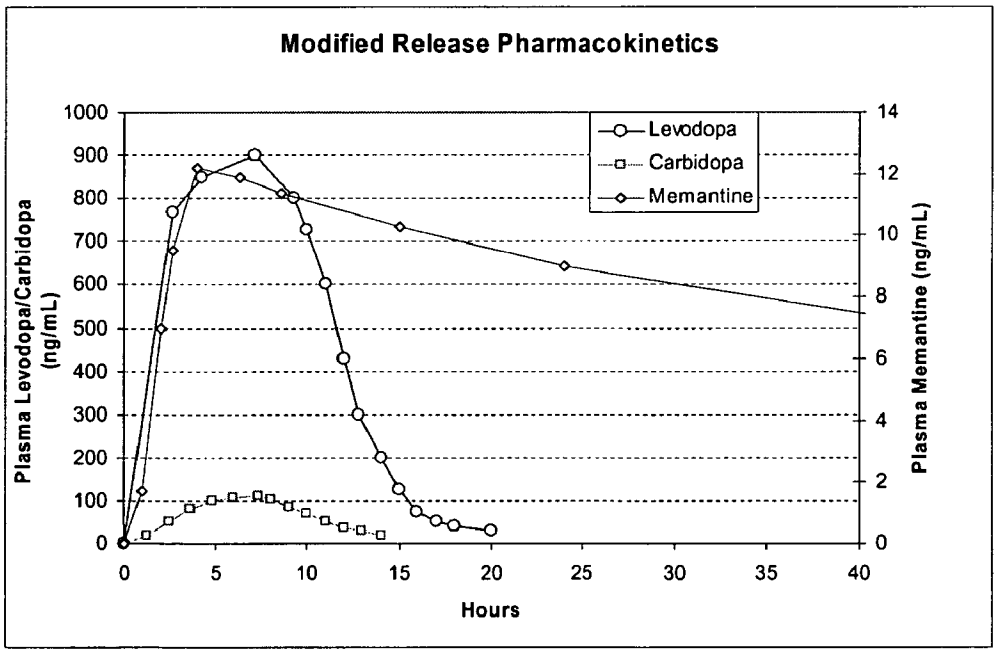
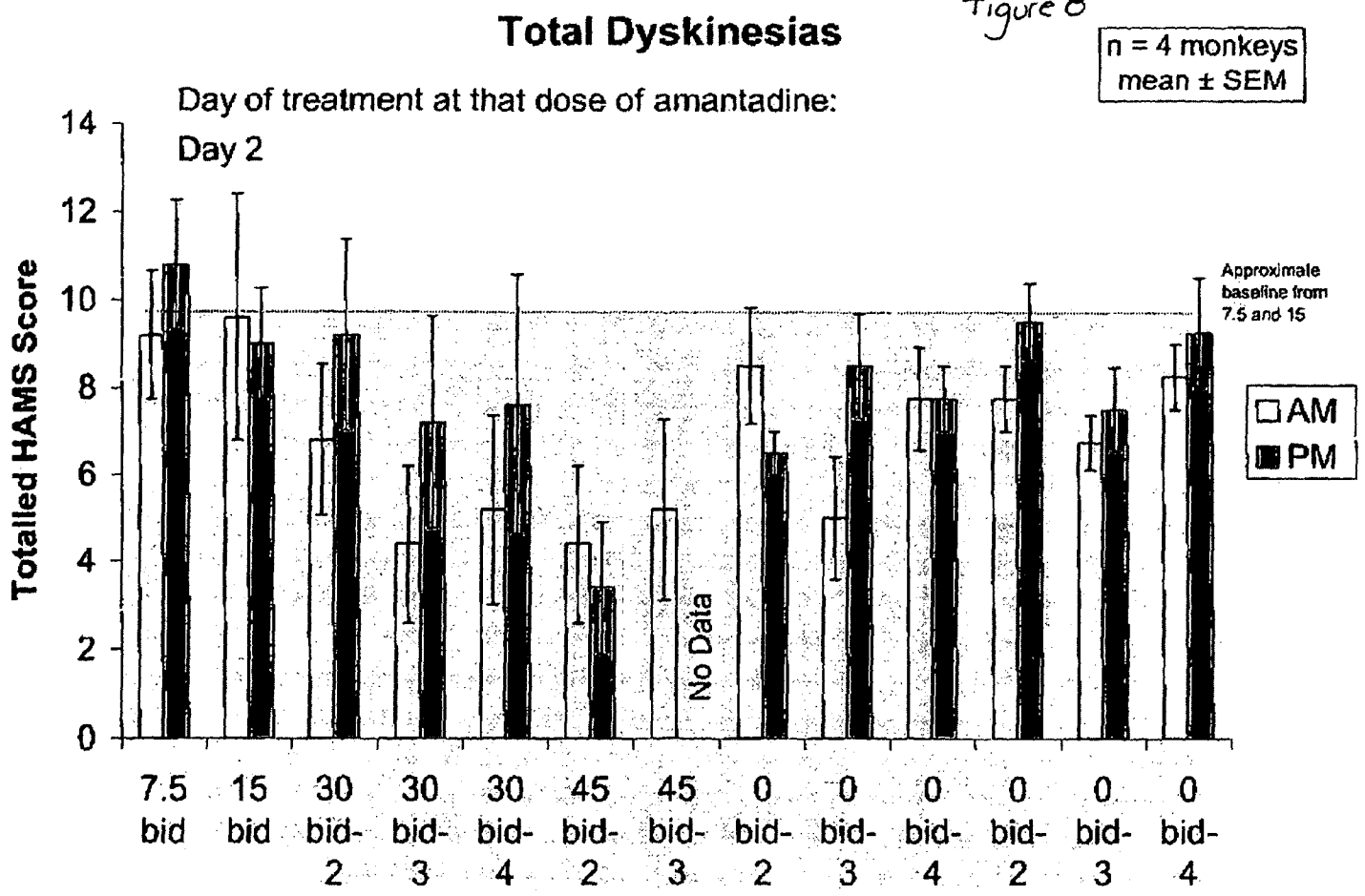


Figure 8


Total Dyskinesias
n = 4 monkeys
mean ± SEM
Day of treatment at that dose of amantadine:
Day 2
Totalled HAMS Score
14
12
10
8
6
4
2
0
Approximate baseline from 7.5 and 15
AM
PM
No Data
7.5 bid
15 bid
30 bid-2
30 bid-3
30 bid-4
45 bid-2
45 bid-3
0 bid-2
0 bid-3
0 bid-4
0 bid-2
0 bid-3
0 bid-4

COMPOSITION AND METHOD FOR TREATING NEUROLOGICAL DISEASE

RELATED APPLICATION

This application claims priority to U.S. Ser. No. 60/631,095, filed Nov. 24, 2004. The content of this application is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

This invention relates to compositions and methods for treating neurological diseases, such as Parkinson's disease.

BACKGROUND OF THE INVENTION

Parkinson's disease (PD) is a progressive, degenerative neurologic disorder which usually occurs in late mid-life. PD is clinically characterized by bradykinesia, tremor, and rigidity. Bradykinesia is characterized by a slowness in movement, slowing the pace of such routine activities as walking and eating. Tremor is a shakiness that generally affects limbs that are not otherwise in motion. For those PD patients diagnosed at a relatively young age, tremor is reported as the most disabling symptom. Older patients face their greatest challenge in walking or keeping their balance. Rigidity is caused by the inability of muscles to relax as opposing muscle groups contract, causing tension which can produce aches and pains in the back, neck, shoulders, temples, or chest.

PD predominantly affects the substantia nigra (SNc) dopamine (DA) neurons and is therefore associated with a decrease in striatal DA content. Because dopamine does not cross the blood-brain barrier, PD patients may be administered a precursor, levodopa, that does cross the blood-brain barrier where it is metabolized to dopamine. Levodopa therapy is intended to compensate for reduced dopamine levels and is a widely prescribed therapeutic agent for patients with Parkinson's disease. Chronic treatment with levodopa however, is associated with various debilitating side-effects such as dyskinesia.

Since currently available drugs containing levodopa are associated with debilitating side effects, better therapies are needed for the management of PD.

SUMMARY OF THE INVENTION

In general, the present invention provides methods and compositions for treating and preventing CNS-related conditions, such as Parkinson's disease or other Parkinson's-like diseases or conditions, by administering to a subject in need thereof a combination that includes an N-Methyl-D-Aspartate receptor (NMDAr) antagonist and levodopa. Exemplary NMDAr antagonists include the aminoadamantanes, such as memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1-aminoethyl)adamantane), or amantadine (1-amino-adamantane) as well as others described below. Because levodopa is metabolized before crossing the blood-brain barrier and has a short half-life in the circulatory system, it is typically administered in conjunction with a dopa-decarboxylase inhibitor. Examples of dopa-decarboxylase inhibitors include carbidopa, 3-hydroxy-benzylhydrazinedihydrochloride (NSD-1015), and benseraxide hydrochloride. The combination may further include a catechol-O-methyltransferase (COMT) inhibitor including, for example, talcapone and entacapone. As used herein, levodopa/carbidopa shall mean levodopa alone or in combination with a dopa-decarboxylase inhibitor such as carbidopa. Desirably, the levodopa/carbidopa is in an immediate release formulation and the NMDA receptor antagonist is in an extended release formulation. One preferred embodiment of the invention involves the combination of amantadine and levodopa/carbidopa. Desirably, amantadine is provided in an extended release formulation and levodopa/carbidopa is provided as an immediate release formulation. By combining an NMDAr antagonist (e.g., amantadine) with the second agents described herein (e.g., levodopalcarbidopa), this invention provides an effective pharmaceutical composition for treating neurological diseases such as Parkinson's disease or other Parkinson's-like diseases or conditions. The administration of this combination is postulated to maintain or enhance the efficacy of levodopa while significantly reducing its dyskinesia side effects.

The combinations described herein provide complementary benefits associated with the NMDAr antagonist or levodopa/carbidopa individually, while minimizing difficulties previously presented when each component is used separately in a patient. For example, amantadine dosing is limited by neurotoxicity that is likely associated with its short Tmax. By extending the release of amantadine, a higher effective dose can be maintained providing both dyskinesia relief and a reduction in the amount of levodopa required for treatment of the disease symptoms. Given the inherent toxicity of levodopa, such a levodopa sparing combination will result in a decline in both the dyskinesia and overall disease.

Accordingly, the pharmaceutical compositions described herein are administered so as to deliver to a subject, an amount of an NMDAr antagonist, levodopa/carbidopa or both agents that is high enough to treat symptoms or damaging effects of an underlying disease while avoiding undesirable side effects. These compositions may be employed to administer the NMDAr antagonist, the levodopa/carbidopa, or both agents at a lower frequency than presently employed, improving patient compliance, adherence, and caregiver convenience. These compositions are particularly useful as they provide the NMDAr antagonist, levodopa/carbidopa, or both agents, at a therapeutically effective amount from the onset of therapy further improving patient compliance and adherence and enable the achievement of a therapeutically effective steady-state concentration of either or both agents of the combination in a shorter period of time resulting in an earlier indication of effectiveness and increasing the utility of these therapeutic agents for diseases and conditions where time is of the essence. Also provided are methods for making and using such compositions.

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a controlled or extended release form with or without an immediate release component in order to maximize the therapeutic benefit of such agents, while reducing unwanted side effects. In preferred embodiments for oral administration, levodopa/carbidopa is provided as an immediate-release formulation.

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be administered in an amount similar to that typically administered to subjects. Preferably, the amount of the NMDAr antagonist may be administered in an amount greater than or less than the amount that is typically administered to subjects while the levodopa/carbidopa is provided at a lower dose than normally used. For example, the amount of amantadine required to positively affect the patient response (inclusive of adverse effects) may be 300, 400, 500, 600 mg per day rather than the typical 200-300 mg per day administered for presently approved indications i.e. without the improved formulation described herein, while the levodopa, and optionally the carbidopa, can be reduced inde-

pendently by 10%, 20%, 30%, 40%, 50%, 60%, 70% or up to 80% of what is currently required in the absence of the NMDAr antagonist.

Optionally, lower or reduced amounts of both the NMDAr antagonist and the levodopa/carbidopa are used in a unit dose relative to the amount of each agent when administered independently. The present invention therefore features formulations of combinations directed to dose optimization or release modification to reduce adverse effects associated with separate administration of each agent. The combination of the NMDAr antagonist and the levodopa/carbidopa may result in an additive or synergistic response, and using the unique formulations described herein, the goal of minimizing the levodopa burden is achieved. Preferably, the NMDAr antagonist and the levodopa/carbidopa are provided in a unit dosage form.

The compositions and methods of the invention are particularly useful for the treatment of Parkinson's disease or conditions associated with Parkinson's disease. These conditions include dementia, dyskinesia, dystonia, depression, fatigue and other neuropsychiatric complications of Parkinson's disease.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present Specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. All parts and percentages are by weight unless otherwise specified.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a graph showing the dissolution profiles for an immediate and sustained release formulation of amantadine. The sustained release formulation exhibits a dC/dT during the initial phase that is about 10% of that for the immediate release formulation.

FIG. **2** is a graph showing the amantadine plasma concentration over a period of 5 days, as predicted by Gastro-Plus software package v.4.0.2, following the administration of either 70 mg amantadine in an immediate release formulation t.i.d. or 75 mg amantadine in a sustained release formulation t.i.d. The sustained release formulation peaks are similar in height to the immediate release formulation even with a higher administered dose and the diurnal variation is substantially reduced.

FIG. **3** is a graph showing the plasma profiles simulated using Gastro-Plus for t.i.d. administration of amantadine (70 mg), levodopa (100 mg), and carbidopa (25 mg), all in an immediate release form.

FIG. **4** is a graph showing the plasma profiles simulated using Gastro-Plus for t.i.d. administration of amantadine (75 mg), levodopa (100 mg), and carbidopa (25 mg), where the amantadine is in a sustained release form and the levodopa and carbidopa are in an immediate release form.

FIG. **5** is a graph representing dissolution profiles for various aminoadamantane formulations including an immediate release form of the NMDAr antagonist memantine (Namenda).

FIG. **6** is a graphical representation of plasma release profiles in a human of memantine, levodopa, and carbidopa when memantine is administered separately from levodopa and carbidopa.

FIG. **7** is a graphical representation of plasma release profiles in a human of memantine, levodopa, and carbidopa when memantine, levodopa, and carbidopa are administered as part of a single controlled-release pharmaceutical composition.

FIG. **8** is a bar graph showing the effects on a primate (squirrel monkey) treated with a combination of levodopa/carbidopa and amantadine.

DETAILED DESCRIPTION OF THE INVENTION

In general, the present invention features pharmaceutical compositions that contain therapeutically effective levels of an NMDAr antagonist and levodopa/carbidopa and, optionally, a pharmaceutical carrier. Preferably the compositions are formulated for modified or extended release to provide a serum or plasma concentration of the NMDAr antagonist over a desired time period that is high enough to be therapeutically effective but at a rate low enough so as to avoid adverse events associated with the NMDAr antagonist. Control of drug release is particularly desirable for reducing and delaying the peak plasma level while maintaining the extent of drug bioavailability. Therapeutic levels are therefore achieved while minimizing debilitating side-effects that are usually associated with immediate release formulations. Furthermore, as a result of the delay in the time to obtain peak serum or plasma level and the extended period of time at the therapeutically effective serum or plasma level, the dosage frequency is reduced to, for example, once or twice daily dosage, thereby improving patient compliance and adherence. For example, side effects including psychosis and cognitive deficits associated with the administration of NMDAr antagonists may be lessened in severity and frequency through the use of controlled-release methods that shift the Tmax to longer times, thereby reducing the dC/dT of the drug. Reducing the dC/dT of the drug not only increases Tmax, but also reduces the drug concentration at Tmax and reduces the Cmax/Cmean ratio providing a more constant amount of drug to the subject being treated over a given period of time, enabling increased dosages for appropriate indications.

In addition, the present invention encompasses optimal ratios of NMDAr and levodopa/carbidopa, designed to not only treat the dyskinesia associated with levodopa, but also take advantage of the additivity and synergy between these drug classes. For example, the level of levodopa required to treat the disease symptoms can unexpectedly be reduced by up to 50% by the addition of 400 mg/day of amantadine.

Making NMDAr Antagonist Controlled Release Formulations

A pharmaceutical composition according to the invention is prepared by combining a desired NMDAr antagonist or antagonists with one or more additional ingredients that, when administered to a subject, causes the NMDAr antagonist to be released at a targeted rate for a specified period of

time. A release profile, i.e., the extent of release of the NMDAr antagonist over a desired time, can be conveniently determined for a given time by measuring the release using a USP dissolution apparatus under controlled conditions. Preferred release profiles are those which slow the rate of uptake of the NMDAr antagonist in the neural fluids while providing therapeutically effective levels of the NMDAr antagonist. One of ordinary skill in the art can prepare combinations with a desired release profile using the NMDAr antagonists and formulation methods described below.

NMDAr Antagonists

Any NMDAr antagonist can be used in the methods and compositions of the invention, particularly those that are nontoxic when used in the compositions of the invention. The term "nontoxic" is used in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to humans or, in keeping with established regulatory criteria and practice, is susceptible to approval by the FDA or similar regulatory agency for any country for administration to humans or animals.

The term "NMDAr antagonist", as used herein, includes any amino-adamantane compound including, for example, memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1-aminoethyl)adamantane), amantadine (1-aminoadamantane), as well as pharmaceutically acceptable salts thereof. Memantine is described, for example, in U.S. Pat. Nos. 3,391,142, 5,891,885, 5,919,826, and 6,187,338. Amantadine is described, for example, in U.S. Pat. Nos. 3,152,180, 5,891,885, 5,919,826, and 6,187,338. Additional aminoadamantane compounds are described, for example, in U.S. Pat. Nos. 4,346,112, 5,061,703, 5,334,618, 6,444,702, 6,620,845, and 6,662,845. All of these patents are hereby incorporated by reference.

Further NMDAr antagonists that may be employed include, for example, aminocylohexanes such as neramexane, ketamine, eliprodil, ifenprodil, dizocilpine, remacemide, iamotrigine, riluzole, aptiganel, phencyclidine, flupirtine, celfotel, felbamate, spermine, spermidine, levemopamil, dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and its metabolite, dextrorphan ((+)-3-hydroxy-N-methylmorphinan), a pharmaceutically acceptable salt, derivative, or ester thereof, or a metabolic precursor of any of the foregoing.

Optionally, the NMDAr antagonist in the instant invention is memantine and not amantadine or dextromethorphan.

Second Agents

In all foregoing aspects of the invention, the second agent is levodopa. When levodopa is in the combination, the combination preferably also includes a dopa-decarboxylase inhibitor. An example of a suitable dopa-decarboxylase inhibitor is carbidopa. Other dopa-decarboxylase inhibitors include, for example, 3-hydroxy-benzylhydrazinedihydrochloride (NSD-1015) and benseraxide hydrochloride. The combination may further include a catechol-O-methyltransferase (COMT) inhibitor including, for example, talcapone and entacapone.

Dosing, PK, & Toxicity

The NMDA receptor antagonist used in combination therapies are administered at a dosage of generally between about 1 and 5000 mg/day, between 1 and about 800 mg/day, or between 1 and 500 mg/day. For example, NMDA receptor antagonist agents may be administered at a dosage ranging between about 1 and about 500 mg/day, more preferably from about 10 to about 40, 50, 60, 70 or 80 mg/day, advantageously from about 10 to about 20 mg per day. Amantadine may be administered at a dose ranging from about 90, 100 mg/day to about 400, 500, 600, 700 or 800 mg/day, advantageously from about 100 to about 500, 600 mg per day. For example, the pharmaceutical composition may be formulated to provide memantine in an amount ranging between 1-200 mg/day, 1 and 80 mg/day, 2-80 mg/day, 10-80 mg/day, 10 and 80 mg/day, 10 and 70 mg/day, 10 and 60 mg/day, 10 and 50 mg/day, 10 and 40 mg/day, 5 and 65 mg/day, 5 and 40 mg/day, 15 and 45 mg/day, or 10 and 20 mg/day; dextromethorphan in an amount ranging between 1-5000 mg/day, 1-1000 mg/day, and 100-800 mg/day, or 200-500 mg/day. Pediatric doses will typically be lower than those determined for adults.

Table 1 shows exemplary pharmacokinetic properties (e.g., Tmax and T1/2) of memantine, amantadine, and rimantadine.

TABLE 1

Pharmacokinetics and Toxicity in humans for selected NMDAr antagonists

Compound	Human PK ($t^{1}/_{2}$) (hours)	Tmax (hours)	Normal Dose	Dose Dependent Toxicity
Memantine	60	3	10-20 mg/day, starting at 5 mg	Dose escalation required, hallucination
Amantadine	15	3	100-300 mg/day, starting at 100 mg/day	Hallucination
Rimantadine	25	6	100-200 mg/day	Insomnia

When levodopa and carbidopa are both included in the composition, the levodopa dose ranges between 100 to 3000 mg per day, 75 mg and 2500 mg/day, 100-2000 mg/day, or 250 and 1000 mg/day divided for administration t.i.d. or more frequently. Carbidopa doses may range between the amounts of 1 to 1000 mg/day, 10 to 500 mg/day, and 25 to 100 mg/day. Optionally, the carbidopa is present in the combination at about 75%, 70%, 65%, 60%, 50%, 40%, 30%, 25%, 20%, and 10% of the mass of the levodopa. Alternatively, the amount of levodopa is less than 300% than the amount of carbidopa. For example, 75 mg of carbidopa (amount that is sufficient to extend the half-life of levodopa in the circulatory system) may be used in combination with 300 to 3000 mg of levodopa per day. The combination may contain a single dosage form comprising 30 to 200 mg amantadine, 30 to 250 mg levodopa, and 10 to 100 mg of carbidopa for t.i.d. or more frequent administration, including multiple dosage forms per administration.

As a result, the preferred dosage forms for optimized use are shown in Table 2 below, with their corresponding commercial equivalent.

TABLE 2

Dosage forms with and without NMDAr antagonist (amount per unit dose)

Sinemet Compositions		Compositions of Present Invention		
Levodopa	Carbidopa	Levodopa	Carbidopa	Amantadine
100 mg IR*	25 mg IR	50-100 mg IR	25 mg IR	100-200 mg IR
100 mg IR	10 mg IR	50-100 mg IR	10 mg IR	50-100 mg IR
100 mg IR	25 mg IR	50-100 mg IR	25 mg IR	100-200 mg CR**
100 mg IR	10 mg IR	50-100 mg IR	10 mg IR	50-100 mg CR

*IR: immediate release
**CR: modified release

Excipients

"Pharmaceutically or Pharmacologically Acceptable" includes molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. "Pharmaceutically Acceptable Carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. "Pharmaceutically Acceptable Salts" include acid addition salts and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

The preparation of pharmaceutical or pharmacological compositions is known to those of skill in the art in light of the present disclosure. General techniques for formulation and administration are found in "Remington: The Science and Practice of Pharmacy, Twentieth Edition," Lippincott Williams & Wilkins, Philadelphia, Pa. Tablets, capsules, pills, powders, granules, dragées, gels, slurries, ointments, solutions suppositories, injections, inhalants and aerosols are examples of such formulations.

By way of example, modified or extended release oral formulation can be prepared using additional methods known in the art. For example, a suitable extended release form of the either active pharmaceutical ingredient or both may be a matrix tablet or capsule composition. Suitable matrix forming materials include, for example, waxes (e.g., carnauba, bees wax, paraffin wax, ceresine, shellac wax, fatty acids, and fatty alcohols), oils, hardened oils or fats (e.g., hardened rapeseed oil, castor oil, beef tallow, palm oil, and soya bean oil), and polymers (e.g., hydroxypropyl cellulose, polyvinylpyrrolidone, hydroxypropyl methyl cellulose, and polyethylene glycol). Other suitable matrix tabletting materials are microcrystalline cellulose, powdered cellulose, hydroxypropyl cellulose, ethyl cellulose, with other carriers, and fillers. Tablets may also contain granulates, coated powders, or pellets. Tablets may also be multi-layered. Multi-layered tablets are especially preferred when the active ingredients have markedly different pharmacokinetic profiles. Optionally, the finished tablet may be coated or uncoated.

The coating composition typically contains an insoluble matrix polymer (approximately 15-85% by weight of the coating composition) and a water soluble material (e.g., approximately 15-85% by weight of the coating composition). Optionally an enteric polymer (approximately 1 to 99% by weight of the coating composition) may be used or included. Suitable water soluble materials include polymers such as polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials such as sugars (e.g., lactose, sucrose, fructose, mannitol and the like), salts (e.g., sodium chloride, potassium chloride and the like), organic acids (e.g., fumaric acid, succinic acid, lactic acid, and tartaric acid), and mixtures thereof. Suitable enteric polymers include hydroxypropyl methyl cellulose, acetate succinate, hydroxypropyl methyl cellulose, phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups.

The coating composition may be plasticised according to the properties of the coating blend such as the glass transition temperature of the main component or mixture of components or the solvent used for applying the coating compositions. Suitable plasticisers may be added from 0 to 50% by weight of the coating composition and include, for example, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, acetylated citrate esters, dibutylsebacate, and castor oil. If desired, the coating composition may include a filler. The amount of the filler may be 1% to approximately 99% by weight based on the total weight of the coating composition and may be an insoluble material such as silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, MCC, or polacrilin potassium.

The coating composition may be applied as a solution or latex in organic solvents or aqueous solvents or mixtures thereof. If solutions are applied, the solvent may be present in amounts from approximate by 25-99% by weight based on the total weight of dissolved solids. Suitable solvents are water, lower alcohol, lower chlorinated hydrocarbons, ketones, or mixtures thereof. If latexes are applied, the solvent is present in amounts from approximately 25-97% by weight based on the quantity of polymeric material in the latex. The solvent may be predominantly water.

The NMDAr antagonist may be formulated using any of the following excipients or combinations thereof.

Excipient name	Chemical name	Function
Avicel PH102	Microcrystalline Cellulose	Filler, binder, wicking, disintegrant
Avicel PH101	Microcrystalline Cellulose	Filler, binder, disintegrant

-continued

Excipient name	Chemical name	Function
Eudragit RS-30D	Polymethacrylate Poly(ethyl acrylate, nethyl methacrylate, timethylammonioethyl methacrylate chloride) 1:2:0.1	Film former, tablet binder, tablet diluent; Rate controlling polymer for controlled release
Methocel K100M Premium CR	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Methocel K100M	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Magnesium Stearate	Magnesium Stearate	Lubricant
Talc	Talc	Dissolution control; anti-adherent, glidant
Triethyl Citrate	Triethyl Citrate	Plasticizer
Methocel E5	Hydroxypropyl methylcellulose	Film-former
Opadry ®	Hydroxypropyl methylcellulose	One-step customized coating system which combines polymer, plasticizer and, if desired, pigment in a dry concentrate.
Surelease ®	Aqueous Ethylcellulose Dispersion	Film-forming polymer; plasticizer and stabilizers. Rate controlling polymer coating.

The pharmaceutical composition described herein may also include a carrier such as a solvent, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents. The use of such media and agents for pharmaceutically active substances is well known in the art. Pharmaceutically acceptable salts can also be used in the composition, for example, mineral salts such as hydrochlorides, hydrobromides, phosphates, or sulfates, as well as the salts of organic acids such as acetates, proprionates, malonates, or benzoates. The composition may also contain liquids, such as water, saline, glycerol, and ethanol, as well as substances such as wetting agents, emulsifying agents, or pH buffering agents. Liposomes, such as those described in U.S. Pat. No. 5,422,120, WO 95/13796, WO 91/14445, or EP 524,968 B1, may also be used as a carrier.

Methods for Preparing Modified or Extended Release Formulations

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a controlled or extended release form with or without an immediate release component in order to maximize the therapeutic benefit of such agents, while reducing unwanted side effects. In the absence of modified release components (referred to herein as controlled, extended, or delayed release components), the NMDAr antagonist, levodopa/carbidopa, or both is released and transported into the body fluids over a period of minutes to several hours. The combination described herein however, may contain an NMDAr antagonist and a sustained release component, such as a coated sustained release matrix, a sustained release matrix, or a sustained release bead matrix. In one example, in addition to levodopa/carbidopa, amantadine (e.g., 50-400 mg) is formulated without an immediate release component using a polymer matrix (e.g., Eudragit), Hydroxypropyl methyl cellulose (HPMC) and a polymer coating (e.g., Eudragit). Such formulations are compressed into solid tablets or granules and coated with a controlled release material such as Opadry® or Surelease®. Levodopa/carbidopa may also be formulated as a sustained release formulation; in most cases, however, this will not be optimal.

Suitable methods for preparing the compositions described herein in which the NMDAr antagonist is provided in modified or extended release-formulations include those described in U.S. Pat. No. 4,606,909 (hereby incorporated by reference). This reference describes a controlled release multiple unit formulation in which a multiplicity of individually coated or microencapsulated units are made available upon disintegration of the formulation (e.g., pill or tablet) in the stomach of the subject (see, for example, column 3, line 26 through column 5, line 10 and column 6, line 29 through column 9, line 16). Each of these individually coated or microencapsulated units contains cross-sectionally substantially homogenous cores containing particles of a sparingly soluble active substance, the cores being coated with a coating that is substantially resistant to gastric conditions but which is erodable under the conditions prevailing in the gastrointestinal tract.

The composition of the invention may alternatively be formulated using the methods disclosed in U.S. Pat. No. 4,769,027, for example. Accordingly, extended release formulations involve prills of pharmaceutically acceptable material (e.g., sugar/starch, salts, and waxes) may be coated with a water permeable polymeric matrix containing an NMDAr antagonist and next overcoated with a water-permeable film containing dispersed within it a water soluble particulate pore forming material.

The NMDAr antagonist composition may additionally be prepared as described in U.S. Pat. No. 4,897,268, involving a biocompatible, biodegradable microcapsule delivery system. Thus, the NMDAr antagonist may be formulated as a composition containing a blend of free-flowing spherical particles obtained by individually microencapsulating quantities of memantine, for example, in different copolymer excipients which biodegrade at different rates, therefore releasing memantine into the circulation at a predetermined rates. A quantity of these particles may be of such a copolymer excipient that the core active ingredient is released quickly after administration, and thereby delivers the active ingredient for an initial period. A second quantity of the particles is of such type excipient that delivery of the encapsulated ingredient begins as the first quantity's delivery begins to decline. A third quantity of ingredient may be encapsulated with a still different excipient which results in delivery beginning as the delivery of the second quantity beings to decline. The rate of delivery may be altered, for example, by varying the lactide/glycolide ratio in a poly(D,L-lactide-co-glycolide) encapsulation. Other polymers that may be used include polyacetal polymers, polyorthoesters, polyesteramides, polycaprolactone and copolymers thereof, polycarbonates, polyhydroxybuterate and copolymers thereof, polymaleamides, copolyaxalates and polysaccharides.

Alternatively, the composition may be prepared as described in U.S. Pat. No. 5,395,626, which features a multilayered controlled release pharmaceutical dosage form. The dosage form contains a plurality of coated particles wherein each has multiple layers about a core containing an NMDAr antagonist whereby the drug containing core and at least one other layer of drug active is overcoated with a controlled release barrier layer therefore providing at least two controlled releasing layers of a water soluble drug from the multilayered coated particle

Release Profile

The compositions described herein are formulated such that the NMDAr antagonist, levodopa/carbidopa, or both

agents have an in vitro dissolution profile that is equal to or slower than that for an immediate release formulation. As used herein, the immediate release (IR) formulation for memantine means the present commercially available 5 mg and 10 mg tablets (i.e., Namenda from Forest Laboratories, Inc. or formulations having substantially the same release profiles as Namenda); and the immediate release (IR) formulation of amantadine means the present commercially available 100 mg tablets (i.e., Symmetrel from Endo Pharmaceuticals, Inc. or formulations having substantially the same release profiles as Symmetrel); and the immediate release (IR) formulation of levodopa/carbidopa means the present commercially available 25 mg/100 mg, 10 mg/100 mg, 25 mg/250 mg tablets of carbidopa/levodopa (i.e., Sinemet from Merck & Co. Inc. or formulations having substantially the same release profiles as Sinemet). These compositions may comprise immediate release, sustained or extended release, or delayed release components, or may include combinations of same to produce release profiles such that the fraction of NMDAr antagonist or levodopa/carbidopa released is greater or equal to $0.01(0.297+0.0153*e^{(0.515*t)})$ and less than or equal to $1-e^{(-10.9*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C., in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist or levodopa/carbidopa released is less than 93% in 15 minutes and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1N HCl) dissolution medium. Optionally, the fraction of released NMDAr antagonist or levodopa/carbidopa is greater than or equal to $0.01(0.297+0.0153*e^{(0.515*t)}$ and less than or equal to $1-e^{(-0.972*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C., in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist or levodopa/carbidopa that is released may range between 0.1%-62% in one hour, 0.2%-86% in two hours, 0.6%-100% in six hours, 2.9%-100% in 10 hours, and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1 N HCl) dissolution medium. Optionally, the NMDA receptor antagonist has a release profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 70% or greater (e.g., 70%-90%) in 10 hours, and 90% or greater (e.g., 90-95%) in 12 hours as measured in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1 N HCl) dissolution medium. For example, a formulation containing amantadine may have a release profile ranging between 0-60% or 0.1-20% in one hour, 0-86% or 5-30% at two hours, 0.6-100% or 40-80% at six hours, 3-100% or 50% or more (e.g., 50-90%) at ten hours, and 7.7-100% at twelve hours in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1 N HCl) dissolution medium. In one embodiment, the NMDAr antagonist, the levodopa/carbidopa, or both agents have an in vitro dissolution profile of less than 25%, 15%, 10%, or 5% in fifteen minutes; 50%, 30%, 25%, 20%, 15%, or 10% in 30 minutes and more than 60%, 65% 70%, 75%, 80%, 85%, 90%, 95% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water. Desirably, the NMDAr antagonist, the levodopa/carbidopa, or both agents has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% in a dissolution media having a pH of 1.2 at 10 hours. It is important to note that the dissolution profile for the NMDAr antagonist may be different than the release profile for levodopa/carbidopa. In a preferred embodiment, the levodopa/carbidopa release profile is equal to or similar to that for an immediate release formulation and the release profile for the NMDAr antagonist is controlled to provide a dissolution profile of less than 30% in one hour, less than 50% in two hours, and greater than 95% in twelve hours using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water.

Desirably, the compositions described herein have an in vitro profile that is substantially identical to the dissolution profile shown in FIG. **5** and, upon administration to a subject at a substantially constant daily dose, achieves a serum concentration profile that is substantially identical to that shown in FIGS. **2** and **4**.

As described above, the NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a modified or extended release form. Modified or extended drug release is generally controlled either by diffusion through a coating or matrix or by erosion of a coating or matrix by a process dependent on, for example, enzymes or pH. The NMDAr antagonist or the levodopa/carbidopa may be formulated for modified or extended release as described herein or using standard techniques in the art. In one example, at least 50%, 75%, 90%, 95%, 96%, 97%, 98%, 99%, or even in excess of 99% of the NMDAr antagonist or the levodopa/carbidopa is provided in an extended release dosage form. In a preferred embodiment, the levodopa/carbidopa is provided in an immediate release formulation and the NMDAr antagonist is in either an immediate or modified release form.

The composition described herein is formulated such the NMDAr antagonist or levodopa/carbidopa has an in vitro dissolution profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 50%-90% in 10 hours, and 90%-95% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. using 0.1N HCl as a dissolution medium. Alternatively, the NMDAr antagonist has an in vitro dissolution profile in a solution with a neutral pH (e.g., water) that is substantially the same as its dissolution profile in an acidic dissolution medium. Thus, the NMDAr antagonist may be released in both dissolution media at the following rate: between 0.1-20% in one hour, 5-30% in two hours, 40-80% in six hours, 70-90% in 10 hours, and 90%-95% in 12 hours as obtained using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. In one embodiment, the NMDAr antagonist has an in vitro dissolution profile of less than 15%, 10%, or 5% in fifteen minutes, 25%, 20%, 15%, or 10% in 30 minutes, and more than 60% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water. Desirably, the NMDAr antagonist has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% at 10 hours in a dissolution medium having a pH of 1.2.

Initial Rate In Vivo, Delayed Tmax

As used herein, "C" refers to the concentration of an active pharmaceutical ingredient in a biological sample, such as a patient sample (e.g. blood, serum, and cerebrospinal fluid). The time required to reach the maximal concentration ("Cmax") in a particular patient sample type is referred to as the "Tmax". The change in concentration is termed "dC" and the change over a prescribed time is "dC/dT".

The NMDAr antagonist or levodopa/carbidopa is provided as a sustained release formulation that may or may not contain an immediate release formulation. If desired, the NMDAr antagonist may be formulated so that it is released at a rate

that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In addition, the NMDAr antagonist levodopa/carbidopa may be provided such that it is released at a rate resulting in a Cmax/Cmean of approximately 2 or less for approximately 2 hours to at least 8 hours after the NMDAr antagonist is introduced into a subject. Optionally, the sustained release formulations exhibit plasma concentration curves having initial (e.g., from 0, 1, 2 hours after administration to 4, 6, 8 hours after administration) slopes less than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist. The precise slope for a given individual will vary according to the NMDAr antagonist being used or other factors, including whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose. The determination of initial slopes of plasma concentration is described, for example, by U.S. Pat. No. 6,913,768, hereby incorporated by reference.

Desirably, the NMDAr antagonist or the levodopa/carbidopa is released into a subject sample at a slower rate than observed for an immediate release (IR) formulation of the same quantity of the antagonist, such that the rate of change in the biological sample measured as the dC/dT over a defined period within the period of 0 to Tmax for the IR formulation (e.g., Namenda, a commercially available IR formulation of memantine). In some embodiments, the dC/dT rate is less than about 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. In some embodiments, the dC/dT rate is less than about 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. Similarly, the rate of release of the NMDAr antagonist or the levodopa/carbidopa from the present invention as measured in dissolution studies is less than 80%, 70%, 60% 50%, 40%, 30%, 20%, or 10% of the rate for an IR formulation of the same NMDAr antagonist or levodopa/carbidopa over the first 1, 2, 4, 6, 8, 10, or 12 hours.

In a preferred embodiment, the dosage form is provided in a non-dose escalating, three times per day (t.i.d.) form. In preferred embodiments, the concentration ramp (or Tmax effect) may be reduced so that the change in concentration as a function of time (dC/dT) is altered to reduce or eliminate the need to dose escalate the NMDAr antagonist. A reduction in dC/dT may be accomplished, for example, by increasing the Tmax in a relatively proportional manner. Accordingly, a two-fold increase in the Tmax value may reduce dC/dT by approximately a factor of 2. Thus, the NMDAr antagonist may be provided so that it is released at a rate that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In certain embodiments, this is accomplished by releasing less than 30%, 50%, 75%, 90%, or 95% of the NMDAr antagonist into the circulatory or neural system within one hour of such administration.

The concentration ramp for levodopa/carbidopa may also be reduced, however such changes will not be preferred in most oral formulations due to the marked reduction in absorption of levodopa/carbidopa after it passes the duodenal region of the gastrointestinal tract.

Optionally, the modified release formulations exhibit plasma concentration curves having initial (e.g., from 2 hours after administration to 4 hours after administration) slopes less than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist or levodopa/carbidopa. The precise slope for a given individual will vary according to the NMDAr antagonist or levodopa/carbidopa being used, the quantity delivered, or other factors, including, for some active pharmaceutical agents, whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose.

Using the sustained release formulations or administration methods described herein, the NMDAr antagonist reaches a therapeutically effective steady state plasma concentration in a subject within the course of the first two, three, five, seven, nine, ten, twelve, fifteen, or twenty days of administration. For example, the formulations described herein, when administered at a substantially constant daily dose (e.g., at a dose ranging between 200 mg and 800 mg, preferably between 200 mg and 600 mg, and more preferably between 200 mg and 400 mg per day) may reach a steady state plasma concentration in approximately 70%, 60%, 50%, 40%, 30%, or less of the time required to reach such plasma concentration when using a dose escalating regimen.

Dosing Frequency and Dose Escalation

According to the present invention, a subject (e.g., human) having or at risk of having such conditions is administered any of the compositions described herein (e.g., three times per day (t.i.d.), twice per day (b.i.d.), or once per day (q.d.)). While immediate release formulations of NMDAr antagonists are typically administered in a dose-escalating fashion, the compositions described herein may be essentially administered at a constant, therapeutically-effective dose from the onset of therapy. For example, a composition containing a sustained release formulation of amantadine may be administered three times per day, twice per day, or once per day in a unit dose comprising a total daily amantadine dose of 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, or 800 mg. In embodiments comprising a single dosage form containing an NMDAr antagonist and levodopa/carbidopa wherein the levodopa/carbidopa is in an immediate release form, the dosing frequency will be chosen according to the levodopa/carbidopa requirements, (e.g. three times per day).

Reduced Time to Therapeutic Concentration and Efficacy

Immediate release (IR) formulations of memantine (e.g., Namenda) are typically administered at low doses (e.g., 5 mg/day) and are progressively administered at increasing frequency and dose over time to reach a steady state serum concentration that is therapeutically effective. According to the manufacturer's FDA approved label, Namenda, an immediate release (IR) formulation of memantine, is first administered to subjects at a dose of 5 mg per day. After an acclimation period of typically one week, subjects are administered with this dose twice per day. Subjects are next administered with a 5 mg and 10 mg dosing per day and finally administered with 10 mg Namenda twice daily. Using this dosing regimen, a therapeutically effective steady state serum concentration may be achieved within 30 days of the onset of therapy. Using a modified release formulation comprising (22.5 mg memantine) however, a therapeutically effective steady state concentration may be achieved substantially sooner (within about 13 days), without using a dose escalating regimen. Furthermore, the slope during each absorption period for the sustained release formulation is less (i.e. not as steep) as the slope for Namenda. Accordingly, the dC/dT of the sustained release formulation is reduced relative

to the immediate release formulation even though the dose administered is larger than for the immediate release formulation. Based on this model, a sustained release formulation of an NMDAr antagonist may be administered to a subject in an amount that is approximately the full strength dose (or that effectively reaches a therapeutically effective dose) from the onset of therapy and throughout the duration of treatment. Accordingly, a dose escalation would not be required.

Treatment of a subject with the subject of the present invention may be monitored using methods known in the art. The efficacy of treatment using the composition is preferably evaluated by examining the subject's symptoms in a quantitative way, e.g., by noting a decrease in the frequency or severity of symptoms or damaging effects of the condition, or an increase in the time for sustained worsening of symptoms. In a successful treatment, the subject's status will have improved (i.e., frequency or severity of symptoms or damaging effects will have decreased, or the time to sustained progression will have increased). In the model described in the previous paragraph, the steady state (and effective) concentration of the NMDAr antagonist is reached in 25%, 40%, 50%, 60%, 70%, 75%, or 80% less time than in the dose escalated approach.

In another embodiment, a composition is prepared using the methods described herein, wherein such composition comprises memantine or amantadine and a release modifying excipient, wherein the excipient is present in an amount sufficient to ameliorate or reduce the dose-dependent toxicity associated with the memantine or amantadine relative to an immediate release (IR) formulation of memantine, such as Namenda, or amantadine, such as Symmetrel. The use of these compositions enables safer administration of these agents, and even permits the safe use of higher levels for appropriate indications, beyond the useful range for the presently available versions of memantine (5 mg and 10 mg per dose to 20 mg per day) and amantadine (100 mg to 300 mg per day with escalation).

Indications Suitable for Treatment

The compositions and methods of the present invention are particularly suitable for the treatment of Parkinson's disease or conditions associated with Parkinson's disease. These conditions include dementia, dyskinesia, dystonia, depression, fatigue and other neuropsychiatric complications of Parkinson's disease.

Formulations for Alternate Specific Routes of Administration

The pharmaceutical compositions may be optimized for particular types of delivery. For example, pharmaceutical compositions for oral delivery are formulated using pharmaceutically acceptable carriers that are well known in the art. The carriers enable the agents in the composition to be formulated, for example, as a tablet, pill, capsule, solution, suspension, sustained release formulation; powder, liquid or gel for oral ingestion by the subject.

The NMDAr antagonist may also be delivered in an aerosol spray preparation from a pressurized pack, a nebulizer or from a dry powder inhaler. Suitable propellants that can be used in a nebulizer include, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and carbon dioxide. The dosage can be determined by providing a valve to deliver a regulated amount of the compound in the case of a pressurized aerosol.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral, intranasal or respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

In some embodiments, for example, the composition may be delivered intranasally to the cribriform plate rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in U.S. Pat. No. 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Additional formulations suitable for other modes of administration include rectal capsules or suppositories. For suppositories, traditional binders and carriers may include, for example, polyalkylene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%.

The composition may optionally be formulated for delivery in a vessel that provides for continuous long-term delivery, e.g., for delivery up to 30 days, 60 days, 90 days, 180 days, or one year. For example the vessel can be provided in a biocompatible material such as titanium. Long-term delivery formulations are particularly useful in subjects with chronic conditions, for assuring improved patient compliance, and for enhancing the stability of the compositions.

Optionally, the NMDA receptor antagonist, levodopa/carbidopa, or both is prepared using the OROS® technology, described for example, in U.S. Pat. Nos. 6,919,373, 6,923,800, 6,929,803, 6,939,556, and 6,930,128, all of which are hereby incorporated by reference. This technology employs osmosis to provide precise, controlled drug delivery for up to 24 hours and can be used with a range of compounds, including poorly soluble or highly soluble drugs. OROS® technology can be used to deliver high drug doses meeting high drug loading requirements. By targeting specific areas of the gastrointestinal tract, OROS® technology may provide more efficient drug absorption and enhanced bioavailability. The osmotic driving force of OROS® and protection of the drug until the time of release eliminate the variability of drug absorption and metabolism often caused by gastric pH and motility.

Formulations for continuous long-term delivery are provided in, e.g., U.S. Pat. Nos. 6,797,283; 6,764,697; 6,635,268, and 6,648,083.

If desired, the components may be provided in a kit. The kit can additionally include instructions for using the kit.

Additional Methods for Making Modified Release Formulations

Additional methods for making modified release formulations are described in, e.g., U.S. Pat. Nos. 5,422,123, 5,601,845, 5,912,013, and 6,194,000, all of which are hereby incorporated by reference.

In some embodiments, for example, the composition may be delivered via intranasal, buccal, or sublingual routes to the brain rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in U.S. Pat. No. 6,715,485. Compositions delivered via this route may

enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Preparation of a pharmaceutical composition for delivery in a subdermally implantable device can be performed using methods known in the art, such as those described in, e.g., U.S. Pat. Nos. 3,992,518; 5,660,848; and 5,756,115.

The invention will be illustrated in the following non-limiting examples.

EXAMPLES

Example 1

Measuring Release Profiles In Vitro

Compositions containing an aminoadamantane and levodopa/carbidopa are analyzed for release of the aminoadamantane and levodopa/carbidopa, according to the USP type 2 apparatus at a speed of 50 rpm. The dissolution media used include water, 0.1N HCl, or 0.1N HCl adjusted to pH 6.8 at 2 hours with phosphate buffer. The dissolution medium is equilibrated to 37±0.5° C.

The USP reference assay method for amantadine is used to measure the fraction of memantine released from the compositions prepared herein. Briefly, 0.6 mL sample (from the dissolution apparatus at a given time point) is placed into a 15 mL culture tube. 1.6 mL 0.1% Bromocresol Purple (in acetic acid) is added and vortexed for five seconds. The mixture is allowed to stand for approximately five minutes. 3 mL Chloroform is added and vortexed for five seconds. The solution is next centrifuged (speed 50 rpm) for five minutes. The top layer is removed with a disposable pipette. A sample is drawn into 1 cm flow cell and the absorbance is measured at 408 nm at 37° C. and compared against a standard curve prepared with known quantities of the same aminoadamantane. The quantity of determined is plotted against the dissolution time for the sample.

The USP reference assay method for levodopa is used to measure the fraction of levodopa released from the compositions prepared herein. Briefly, 0.5 ml samples from the dissolution apparatus removed at various times are assayed by liquid chromatography. The chromatograph is equipped with a 280 nm detector and a 3.9 mm×30 cm column containing packing L1. The mobile phase is 0.09 N sodium phosphate, 1 mM sodium 1-decanesulfonate, pH 2.8. With the flow rate adjusted to about 2 mL per minute, the levodopa elutes in about 4 minutes and carbidopa elutes in about 11 minutes. From the saved dissolution samples, a 0.02 ml aliquot is injected into the chromatograph and the absorbance is measure and compared to standard to determine concentration & quantity. The quantity dissolved is then plotted against the dissolution time for the sample.

Example 2

Preparation of Amantadine Extended Release Capsules

Amantadine extended release capsules may be formulated as follows or as described, for example, in U.S. Pat. No. 5,395,626.

A. Composition: Unit Dose

The theoretical quantitative composition (per unit dose) for amantadine extended release capsules is provided below.

Component	% weight/weight	mg/Capsule
Amantadine	68.34	200.00
OPADRY ® Clear YS-3-7011 [1] (Colorcon, Westpoint, PA)	1.14	5.01
Purified Water, USP [2]	—	—
Sugar Spheres, NF	12.50	54.87
OPADRY ® Clear YS-1-7006 [3] (Colorcon, Westpoint, PA)	4.48	19.66
SURELEASE ® E-7-7050 [4] (Colorcon, Westpoint, PA)	13.54	59.44
Capsules [5]	—	—
TOTAL	100.00%	338.98 mg [6]

[1] A mixture of hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol.
[2] Purified Water, USP is evaporated during processing.
[3] A mixture of hydroxypropyl methylcellulose and polyethylene glycol
[4] Solid content only of a 25% aqueous dispersion of a mixture of ethyl cellulose, dibutyl sebacate, oleic acid, ammoniated water and fumed silica. The water in the dispersion is evaporated during processing.
[5] White, opaque, hard gelatin capsule, size 00.
[6] Each batch is assayed prior to filling and the capsule weight is adjusted as required to attain 200 mg amantadine per capsule.

The quantitative batch composition for amantadine extended release capsule is shown below. (Theoretical batch quantity 25,741 capsules).

Step 1: Prep of Amantadine HCl Beads (Bead Build-Up #1)

Component	Weight (kg)
Amantadine	12.000
OPADRY ® Clear YS-3-7011	0.200
Purified Water, USP	5.454
Sugar Sphere, NF	4.000
Total Weight Amantadine Beads	16.200 kg

The amantadine beads obtained from step 1 are used as follows.

Step 2: Clear & Sustained Release Bead Coating #1

Component	Weight (kg)
Amantadine Beads	8.000
OPADRY ® Clear YS-1-7006	0.360
Purified Water, USP	5.928
Surelease ® E-7-7050	0.672
Total Weight Clear Coated Sustained Release Beads	9.032 kg

The sustained release beads obtained from step 2 are used as follows.

Step 3: Amantadine HCl Beads (Build-Up #2)

Component	Weight (kg)
Sustained Release Beads	8.000
Amantadine	4.320
OPADRY ® Clear YS-3-7011	0.072
Purified Water, USP	1.964
Total Weight Amantadine Beads	12.392 kg

The amantadine beads obtained from step 3 are formulated as follows.

Step 4: Clear & Sustained Release Bead Coating #2

Component	Weight (kg)
Amantadine Beads	10.000
OPADRY ® Clear YS-1-7006	0.250
Purified Water, USP	6.450
Surelease ® E-7-7050	1.050
Total Weight Amantadine Extended Release Beads	11.300 kg

Step 5: Capsule Filling—Gelatin capsules, size 00, are filled with 339 mg of the amantadine beads prepared in step 4.

Example 3

Extended Release Amantadine Formulation with Immediate Release Carbidopa and Levodopa

Levodopa and Carbidopa are formulated into pellets suitable for filling, yet having an immediate release profile. (see, for example, U.S. Pat. No. 5,912,013).

Levodopa Plus Carbidopa Core Pellets

	Weight Percent	Kilograms
MCC	25.0	0.25
Hydroxypropylmethylcellulose Phthalate (HPMCP)	10.0	0.10
Tartaric Acid	10.0	0.10
Sodium Monoglycerate	7.5	0.075
DSS	0.5	0.005
Levodopa	35.8	0.358
Carbidopa	11.2	0.112
TOTAL	100.0%	1.00 kg
Coating		
Cellulose Acetate Phthalate (CAP)	60.0	0.60
Ethylcellulose	25.0	0.25
PEG-400	15.0	0.15
TOTAL	100.0%	1.00 kg

The pellets are assayed for levodopa and carbidopa content. It is determined that approximately 223 mg of the pellets contain 80 mg levodopa and 25 mg carbidopa. Dissolution greater than 90% in 30 minutes is also confirmed.

A total of 669 grams of the pellets are blended with 510 grams of the amantadine pellets from Example 2 in a V-blender for 30 minutes at 30 rpm. Gelatin capsules are filled with 393 mg of the mixture and the assays for content are repeated verifying a composition of 100 mg amantadine, 80 mg levodopa, and 25 mg carbidopa.

Example 4

Predicted Dissolution and Plasma Profiles of Amantadine Controlled Release

Using the formulations described above, the dissolution profiles for amantadine were simulated and used to calculate plasma profiles resulting from single or multiple administrations using the pharmacokinetic software, GastroPlus v.4.0.2, from Simulations Plus (see FIG. **2**). The initial slope of the dissolution for the sustained release formulation is less than the slope determined for the immediate release formulation (see FIG. **1**) and the corresponding serum profile also shows a slower dC/dT (see FIG. **4**).

Example 5

Release Profile of Amantadine and L-DOPA (Levodopa/Carbidopa)

Release proportions are shown in the tables below for a combination of amantadine and levodopa/carbidopa. The cumulative fraction is the amount of drug substance released from the formulation matrix to the serum or gut environment (e.g., U.S. Pat. Nos. 4,839,177 or 5,326,570) or as measured with a USP II Paddle system using 0.1N HCl as the dissolution medium.

Time	AMANTADINE T½ = 15 hrs cum. fraction A	LEVODOPA/CARBIDOPA T½ = 1.5 hrs Cum. fraction B
0	0.00	0.00
0.5	0.10	0.40
1.0	0.20	0.95
2.0	0.35	1.00
4.0	0.60	1.00
8.0	0.90	1.00
12.0	0.98	1.00

Example 6

Treating Dyskinesia in Patients with Parkinson's Disease

A Parkinson's patient experiencing dyskinesia is administered the composition of Example 3 three times each day to receive 300 mg amantadine, 240 mg levodopa, and 75 mg carbidopa daily. The Parkinsonism is reduced as measured by the UPDRS (Goetz et al., Mov. Disord. 19:1020-8, 2004, incorporated by reference) as is the dyskinesia (Vitale et al., Neurol. Sci. 22:105-6, 2001, incorporated by reference)

Example 7

Animal Models Showing Reduced Dyskinesia, Reduced Levodopa Potential

The following protocol was employed to demonstrate the beneficial effects of the compositions of this invention. Briefly, squirrel monkeys (N=4) were lesioned with MPTP according to the protocol of Di Monte et al. (Mov. Disord. 15: 459-66 (2000)). After 3 months, the monkeys showed full symptoms of Parkinson's disease as measured by a modified UPDRS (Goetz et al., Mov. Disord. 19:1020-8, 2004). Levodopa treatment at approximately 15 mg/kg (with 1.5 mg/kg carbidopa) mg/kg b.i.d. commenced a baseline UPDRS and dyskinesia measurement was established. Amantadine was added to the regimen simultaneously with the levodopa, and the amount raised from 1 mg/kg to 45 mg/kg for four of the squirrel monkeys, corresponding to an estimated 3 μm concentration. As shown in FIG. **8**, the combination led to a 60% reduction in dyskinesia. We hypothesize that this translates into a potential 40% reduction in levodopa required to maintain UPDRS.

Example 8

Levodopa Sparing Therapy

The following protocol is employed to determine the optimal reduction of levodopa achieved with the addition of Amantadine to a fixed dose combination product.

Parkinson's DISEASE PROTOCOL SUMMARY NPI Memantine CR Monotherapy

Protocol Number:	NPI-Amantadine CR
Study Phase:	2/3
Name of Drug:	NPI-Amantadine/C/L
Dosage:	25/100/100 c/l/a given t.i.d. 25/80/100 c/l/a given t.i.d. 25/60/100 c/l/a given t.i.d.
Concurrent Control:	25/100 c/l given t.i.d.
Route:	Oral
Subject Population:	Male and female patients diagnosed with Parkinson's Disease Hoehn and Yahr score of 2-4
Structure:	Parallel-group, three-arm study
Study Term	Two weeks
Study Sites:	Multi-center 10 centers
Blinding:	Double blind
Method of Subject Assignment:	Randomized to one of three treatment groups (3:1)
Total Sample Size:	320 subjects (160 men, 160 women)
Primary Efficacy Endpoints:	UPDRS Abnormal involuntary movement scale (AIMS) 0-4
Secondary Endpoints	Modified Obeso dyskinesia rating scale 0-4 Mini-mental state examination (MMSE); Neuropsychiatric Inventory Score (NPI)
Adverse Events:	Monitored and elicited by clinic personnel throughout the study, volunteered by patients

Example 9

Pharmaceutical Composition Including Memantine, Levodopa, and Carbidopa

A co-formulation of memantine, levodopa and carbidopa is prepared. This co-formulation matches the absorption properties of levodopa and carbidopa more closely than those of Memantine, thereby extending the effectiveness per dose of levodopa and carbidopa. The co-formulation provides Tmax values to about 4 hours and allows b.i.d. dosing of the combination.

FIG. **6** provides the current single oral dose pharmacokinetic (PK) profiles for levodopa, carbidopa and memantine. FIG. **7** provides idealized pharmacokinetic profiles for the target co-formulation, in which the Tmax values for levodopa and carbidopa more closely match that of Memantine.

Dosage Form:	Tablet	
Formulation Content:	Levodopa	150 mg
	Carbidopa	37.5 mg
	Memantine	10 mg

Excipients: FDA approved excipients and drug release modifiers.

Additional embodiments are within the claims.

Example 10

Pharmaceutical Composition Including Extended Release Formulations of Memantine and Levodopa

A pulsatile release dosage form for administration of memantine and levodopa may be prepared as three individual compartments. Three individual tablets are compressed, each having a different release profile, followed by encapsulation into a gelatin capsule, which are then closed and sealed. The components of the three tablets are as follows.

Component	Function	Amount per tablet
TABLET 1 (IMMEDIATE RELEASE):		
Memantine	Active agent	8 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
TABLET 2 (RELEASE DELAYED 3-5 HOURS FOLLOWING ADMINISTRATION):		
Memantine	Active agent	8 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS30D	Delayed release coating material	4.76 mg
Talc	Coating component	3.3 mg
Triethyl citrate	Coating component	0.95 mg
TABLET 3 (RELEASE DELAYED 7-9 HOURS FOLLOWING ADMINISTRATION):		
Memantine	Active agent	2.5 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS30D	Delayed release coating material	6.34 mg
Talc	Coating component	4.4 mg
Triethyl citrate	Coating component	1.27 mg

The tablets are prepared by wet granulation of the individual drug particles and other core components as may be done using a fluid-bed granulator, or are prepared by direct compression of the admixture of components. Tablet 1 is an immediate release dosage form, releasing the active agents within 1-2 hours following administration. Tablets 2 and 3 are coated with the delayed release coating material as may be carried out using conventional coating techniques such as spray-coating or the like. As will be appreciated by those skilled in the art, the specific components listed in the above tables may be replaced with other functionally equivalent components, e.g., diluents, binders, lubricants, fillers, coatings, and the like.

Oral administration of the capsule to a patient will result in a release profile having three pulses, with initial release of the

memantine and levodopa from the first tablet being substantially immediate, release of the memantine and levodopa from the second tablet occurring 3-5 hours following administration, and release of the memantine and levodopa from the third tablet occurring 7-9 hours following administration.

Example 11

Pharmaceutical Composition Including Extended Release Formulations of Memantine, Levodopa, and Carbidopa

The method of Example 9 is repeated, except that drug-containing beads are used in place of tablets. Carbidopa is also added in each of the fractions at 25% of the mass of the levodopa. A first fraction of beads is prepared by coating an inert support material such as lactose with the drug which provides the first (immediate release) pulse. A second fraction of beads is prepared by coating immediate release beads with an amount of enteric coating material sufficient to provide a drug release-free period of 3-5 hours. A third fraction of beads is prepared by coating immediate release beads having half the methylphenidate dose of the first fraction of beads with a greater amount of enteric coating material, sufficient to provide a drug release-free period of 7-9 hours. The three groups of beads may be encapsulated or compressed, in the presence of a cushioning agent, into a single pulsatile release tablet.

Alternatively, three groups of drug particles may be provided and coated as above, in lieu of the drug-coated lactose beads.

OTHER EMBODIMENTS

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

The invention claimed is:

1. A method of treating a patient with Parkinson's disease comprising orally administering to the patient a first agent and once-daily orally administering to the patient a second agent, said first agent comprising a therapeutically effective amount of levodopa/carbidopa in an immediate release form and said second agent consisting essentially of a therapeutically effective amount of amantadine or pharmaceutically acceptable salt thereof in an amount ranging from 200 mg to 500 mg in an extended release form, wherein:

the amantadine or pharmaceutically acceptable salt thereof provides change in plasma concentration as a function of time (dC/dT) over a defined period between 0 and 4 hours after administration that is less than about 40% of the dC/dT of the same quantity of an immediate release form of amantadine over said defined time period, wherein the dC/dT is measured in a single dose human pharmacokinetic study.

2. The method of claim **1** wherein the amantadine is administered at a dose of 300 to 500 mg per day.

3. A method of reducing amantadine-related neurotoxicity in a patient with Parkinson's disease comprising orally administering to the patient a first agent and once-daily orally administering to the patient a second agent, said first agent comprising a therapeutically effective amount of levodopa/carbidopa in an immediate release form and said second agent consisting essentially of a therapeutically effective amount of amantadine or pharmaceutically acceptable salt thereof in an amount ranging from 200 mg to 500 mg in an extended release form, wherein:

the extended release amantadine or pharmaceutically acceptable salt thereof provides a change in amantadine plasma concentration as a function of time (dC/dT) over a defined time period between 0 and 4 hours after administration that is less than about 40% of the dC/dT of the same quantity of an immediate release form of amantadine over said defined time period, wherein the dC/dT is measured in a single dose human pharmacokinetic study.

4. The method of claim **3**, wherein the side effect is dizziness.

5. The method of claim **3**, wherein the amantadine is administered at a dose of 300 to 500 mg per day.

6. A method of reducing levodopa/carbidopa-related CNS side effects in a patient with Parkinson's disease comprising orally administering to the patient a first agent and once-daily orally administering to the patient a second agent, said first agent comprising a therapeutically effective amount of levodopa/carbidopa in an immediate release form and said second agent consisting essentially of a therapeutically effective amount of amantadine or pharmaceutically acceptable salt thereof in an amount ranging from 200 mg to 500 mg in an extended release form, wherein:

the extended release amantadine or pharmaceutically acceptable salt thereof provides a change in amantadine plasma concentration as a function of time (dC/dT) over a defined time period between 0 and 4 hours after administration that is less than about 40% of the dC/dT of the same quantity of an immediate release form of amantadine over said defined time period, wherein the dC/dT is measured in a single dose human pharmacokinetic study.

7. The method claim **3**, wherein the levodopa/carbidopa-related side effects are dyskinesias.

8. The method of claim **3**, wherein the amantadine is administered at a dose of 300 to 500 mg per day.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,389,578 B2
APPLICATION NO. : 11/286448
DATED : March 5, 2013
INVENTOR(S) : Gregory T. Went et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 24, at Line 25:
Change: "4. The method of claim 3, wherein the side effect is dizziness." to --"4. The method of claim 3, wherein the amantadine-related neurotoxicity is dizziness."--

Column 24, at Line 48:
Change: "7. The method claim 3, wherein the levodopa/carbidopa-related side effects are dyskinesias." to --"7. The method of claim 6, wherein the levodopa/carbidopa-related CNS side effects are dyskinesias."--

Column 24, at Line 50:
Change: "8. The method of claim 3, wherein the amantadine is administered at a dose of 300 to 500 mg per day." to --"8. The method of claim 6, wherein the amantadine is administered at a dose of 300 to 500 mg per day."--

Signed and Sealed this
First Day of August, 2017

Joseph Matal
Performing the Functions and Duties of the
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

EXHIBIT B

US008796337B2

(12) **United States Patent**
Went et al.

(10) **Patent No.: US 8,796,337 B2**
(45) **Date of Patent: *Aug. 5, 2014**

(54) **COMPOSITION AND METHOD FOR TREATING NEUROLOGICAL DISEASE**

(71) Applicant: **Adamas Pharmaceuticals, Inc.**, Emeryville, CA (US)

(72) Inventors: **Gregory T. Went**, Mill Valley, CA (US); **Timothy J. Fultz**, Pleasant Hill, CA (US); **Seth Porter**, San Carlos, CA (US); **Laurence R. Meyerson**, Las Vegas, NV (US); **Timothy S. Burkoth**, Lake Bluff, IL (US)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/958,153**

(22) Filed: **Aug. 2, 2013**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 13/756,275, filed on Jan. 31, 2013, now abandoned, which is a continuation of application No. 11/286,448, filed on Nov. 23, 2005, now Pat. No. 8,389,578.

(60) Provisional application No. 60/631,095, filed on Nov. 24, 2004.

(51) **Int. Cl.**

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A61K 9/50	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/197*** (2013.01); ***A61K 31/13*** (2013.01); ***A61K 9/2054*** (2013.01); ***A61K 31/198*** (2013.01); ***A61K 9/2009*** (2013.01); ***A61K 9/1617*** (2013.01); ***A61K 9/2846*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 9/5047*** (2013.01); ***A61K 9/1652*** (2013.01); ***A61K 9/5078*** (2013.01)

USPC **514/565**; 514/656

(58) **Field of Classification Search**

USPC 514/656

See application file for complete search history.

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(57) **ABSTRACT**

A method of administering amantadine is provided. The method comprises orally administering to a subject a pharmaceutical composition comprising amantadine, or a pharmaceutically acceptable salt thereof, and one or more excipients, wherein at least one of the excipients modifies release of the amantadine. A dose of the composition provides a mean change in amantadine plasma concentration as a function of time (dC/dT) that is less than 40% of the change in amantadine plasma concentration provided by a dose of the same quantity of an immediate release form of amantadine. The change in plasma concentration over time (dC/dT) is measured in a single dose human pharmacokinetic study in a defined time period of 0 to 4 hours after administration. The amantadine, or pharmaceutically acceptable salt thereof, is administered once daily at a dose of 300 to 500 mg per day.

14 Claims, 7 Drawing Sheets

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Figure 1: Simulated Dissolution for TID Amantadine IR & SR

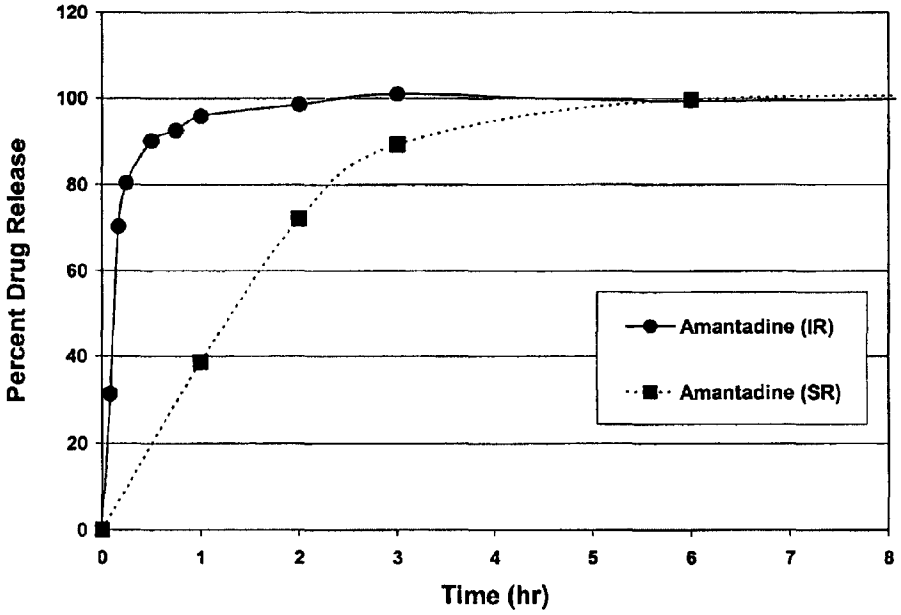


Figure 2: Simulated Plasma Concentration for TID Amantadine IR & SR over 120hrs.

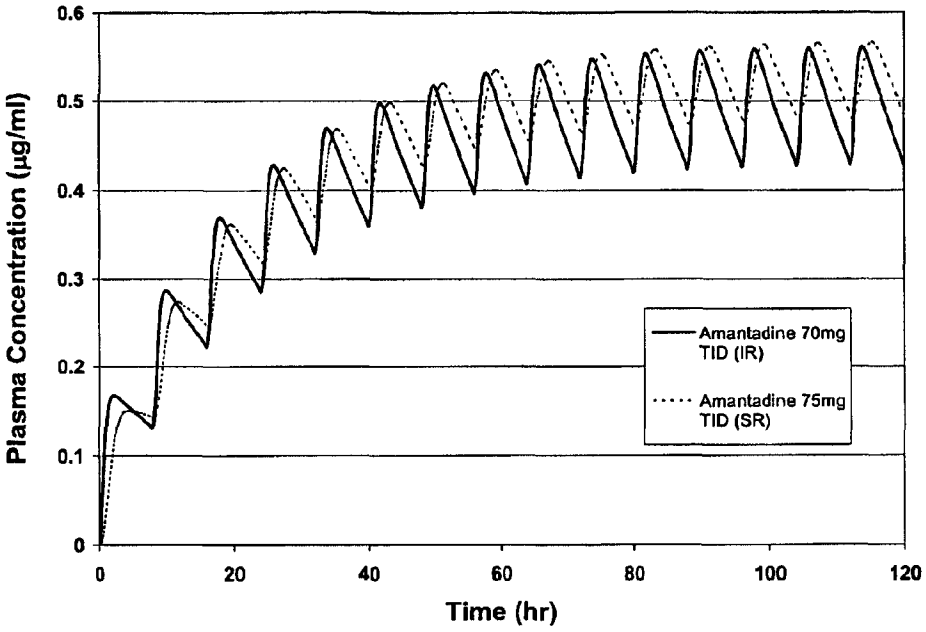


Figure 3: Simulated Plasma Concentration for TID Levodopa/Carbidopa/Amantadine (IR, IR, IR) over 24hrs

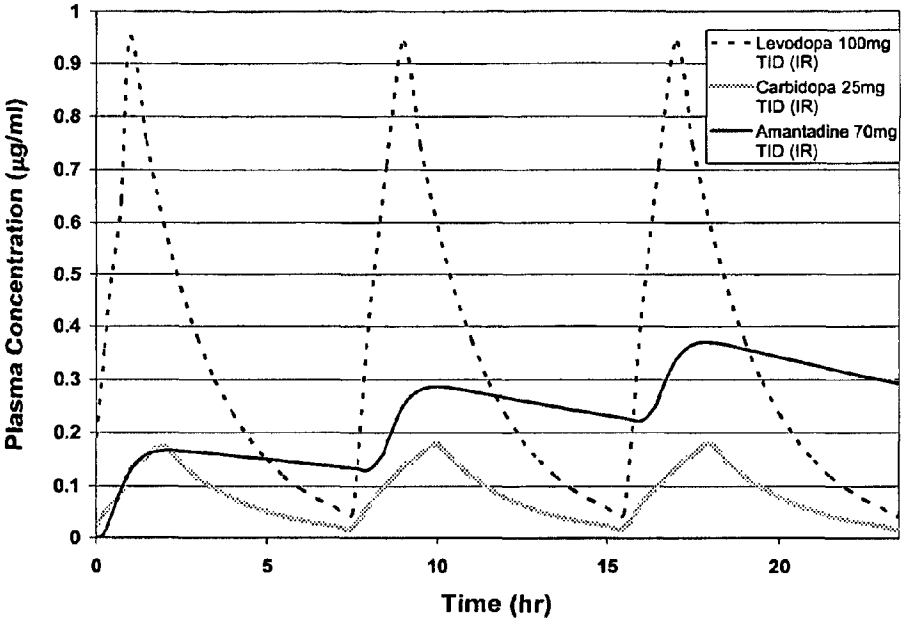


Figure 4: Simulated Plasma Concentration for TID Levodopa/Carbidopa/Amantadine (IR, IR, SR) over 24hrs

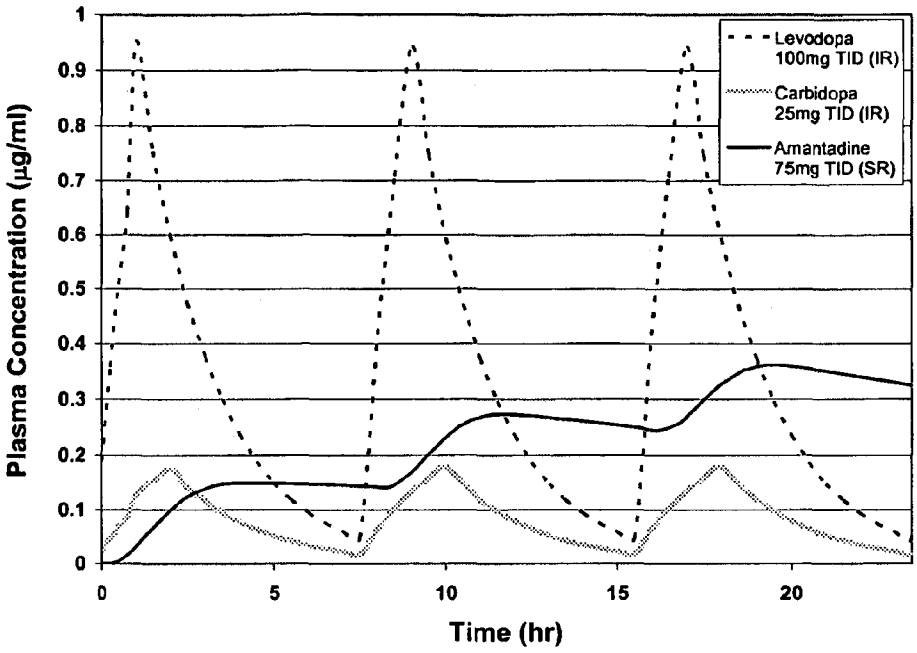


FIGURE 5

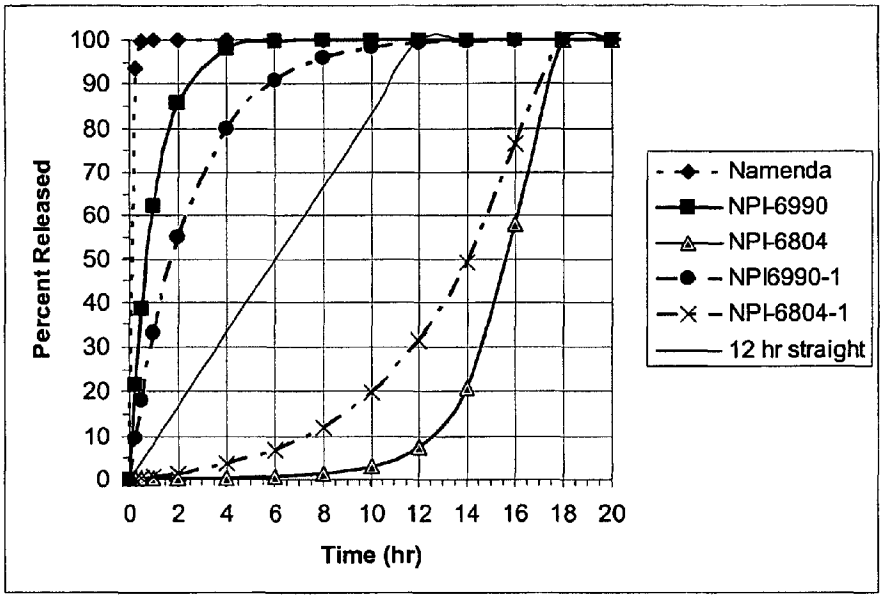

Percent Released
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20
Time (hr)
Namenda
NPI-6990
NPI-6804
NPI6990-1
NPI-6804-1
12 hr straight

Figure 6: Memantine, Levodopa and Carbidopa Human Pharmacokinetics

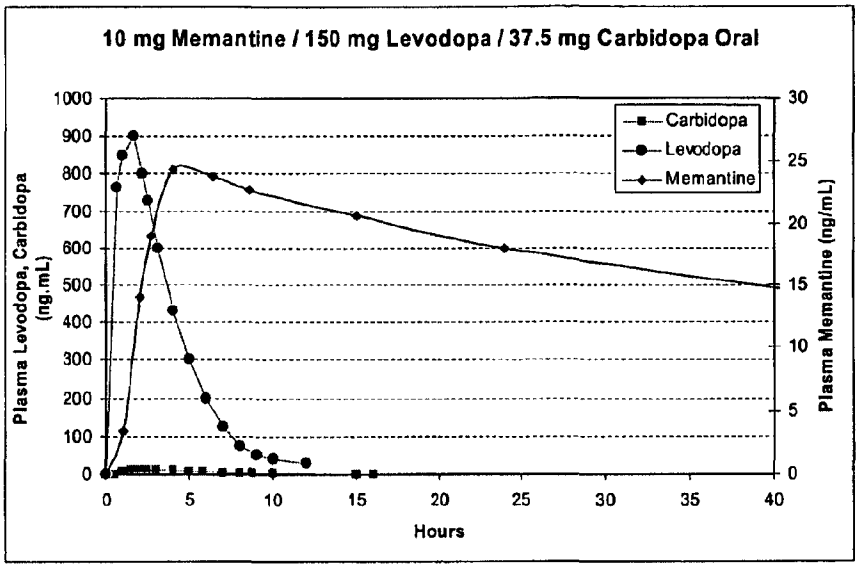
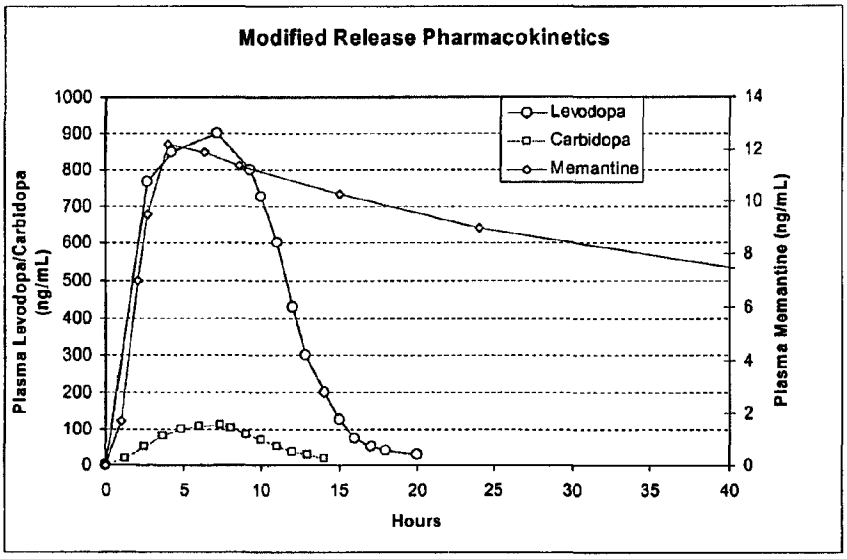


Figure 7: Target Pharmacokinetics



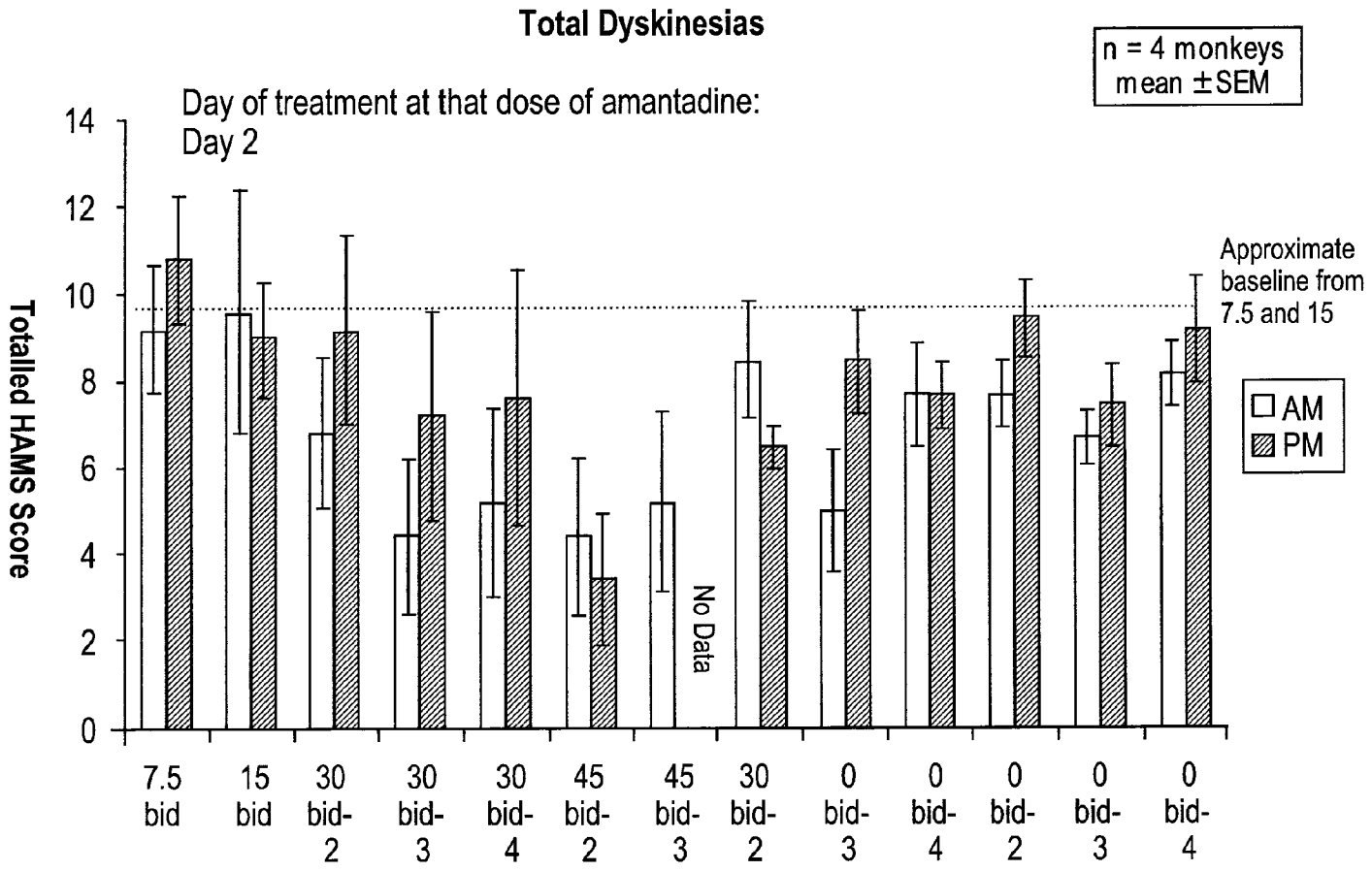

Total Dyskinesias
n = 4 monkeys
mean ±SEM
Day of treatment at that dose of amantadine:
Day 2
Totalled HAMS Score
14
12
10
8
6
4
2
0
Approximate baseline from 7.5 and 15
AM
PM
No Data
7.5 bid
15 bid
30 bid-2
30 bid-3
30 bid-4
45 bid-2
45 bid-3
30 bid-2
0 bid-3
0 bid-4
0 bid-2
0 bid-3
0 bid-4

Figure 8

COMPOSITION AND METHOD FOR TREATING NEUROLOGICAL DISEASE

RELATED APPLICATION

This application is a continuation application of U.S. patent application Ser. No. 13/756,275, filed Jan. 31, 2013, which is a continuation application of U.S. patent application Ser. No. 11/286,448 filed on Nov. 23, 2005, now U.S. Pat. No. 8,389,578, which claims priority to U.S. Provisional Application No. 60/631,095 filed on Nov. 24, 2004, which applications are all incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

This invention relates to compositions and methods for treating neurological diseases, such as Parkinson's disease.

BACKGROUND OF THE INVENTION

Parkinson's disease (PD) is a progressive, degenerative neurologic disorder which usually occurs in late mid-life. PD is clinically characterized by bradykinesia, tremor, and rigidity. Bradykinesia is characterized by a slowness in movement, slowing the pace of such routine activities as walking and eating. Tremor is a shakiness that generally affects limbs that are not otherwise in motion. For those PD-patients diagnosed at a relatively young age, tremor is reported as the most disabling symptom. Older patients face their greatest challenge in walking or keeping their balance. Rigidity is caused by the inability of muscles to relax as opposing muscle groups contract, causing tension which can produce aches and pains in the back, neck, shoulders, temples, or chest.

PD predominantly affects the substantia nigra (SNc) dopamine (DA) neurons and is therefore associated with a decrease in striatal DA content. Because dopamine does not cross the blood-brain barrier, PD patients may be administered a precursor, levodopa, that does cross the blood-brain barrier where it is metabolized to dopamine. Levodopa therapy is intended to compensate for reduced dopamine levels and is a widely prescribed therapeutic agent for patients with Parkinson's disease. Chronic treatment with levodopa however, is associated with various debilitating side-effects such as dyskinesia.

Since currently available drugs containing levodopa are associated with debilitating side effects, better therapies are needed for the management of PD.

SUMMARY OF THE INVENTION

In general, the present invention provides methods and compositions for treating and preventing CNS-related conditions, such as Parkinson's disease or other Parkinson's-like diseases or conditions, by administering to a subject in need thereof a combination that includes an N-Methyl-D-Aspartate receptor (NMDAr) antagonist and levodopa. Exemplary NMDAr antagonists include the aminoadamantanes, such as memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1-aminoethyl)adamantane), or amantadine (1-amino-adamantane) as well as others described below. Because levodopa is metabolized before crossing the blood-brain barrier and has a short half-life in the circulatory system, it is typically administered in conjunction with a dopa-decarboxylase inhibitor. Examples of dopa-decarboxylase inhibitors include carbidopa, 3-hydroxy-benzylhydrazinedihydrochloride (NSD-1015), and benseraxide hydrochloride.

The combination may further include a catechol-0-methyltransferase (COMT) inhibitor including, for example, talcapone and entacapone. As used herein, levodopa/carbidopa shall mean levodopa alone or in combination with a dopa-decarboxylase inhibitor such as carbidopa. Desirably, the levodopa/carbidopa is in an immediate release formulation and the NMDA receptor antagonist is in an extended release formulation. One preferred embodiment of the invention involves the combination of amantadine and levodopa/carbidopa. Desirably, amantadine is provided in an extended release formulation and levodopa/carbidopa is provided as an immediate release formulation. By combining an NMDAr antagonist (e.g., amantadine) with the second agents described herein (e.g., levodopa/carbidopa), this invention provides an effective pharmaceutical composition for treating neurological diseases such as Parkinson's disease or other Parkinson's-like diseases or conditions. The administration of this combination is postulated to maintain or enhance the efficacy of levodopa while significantly reducing its dyskinesia side effects.

The combinations described herein provide complementary benefits associated with the NMDAr antagonist or levodopa/carbidopa individually, while minimizing difficulties previously presented when each component is used separately in a patient. For example, amantadine dosing is limited by neurotoxicity that is likely associated with its short Tmax. By extending the release of amantadine, a higher effective dose can be maintained providing both dyskinesia relief and a reduction in the amount of levodopa required for treatment of the disease symptoms. Given the inherent toxicity of levodopa, such a levodopa sparing combination will result in a decline in both the dyskinesia and overall disease.

Accordingly, the pharmaceutical compositions described herein are administered so as to deliver to a subject, an amount of an NMDAr antagonist, levodopa/carbidopa or both agents that is high enough to treat symptoms or damaging effects of an underlying disease while avoiding undesirable side effects. These compositions may be employed to administer the NMDAr antagonist, the levodopa/carbidopa, or both agents at a lower frequency than presently employed, improving patient compliance, adherence, and caregiver convenience. These compositions are particularly useful as they provide the NMDAr antagonist, levodopa/carbidopa, or both agents, at a therapeutically effective amount from the onset of therapy further improving patient compliance and adherence and enable the achievement of a therapeutically effective steady-state concentration of either or both agents of the combination in a shorter period of time resulting in an earlier indication of effectiveness and increasing the utility of these therapeutic agents for diseases and conditions where time is of the essence. Also provided are methods for making and using such compositions.

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a controlled or extended release form with or without an immediate release component in order to maximize the therapeutic benefit of such agents, while reducing unwanted side effects. In preferred embodiments for oral administration, levodopa/carbidopa is provided as an immediate-release formulation.

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be administered in an amount similar to that typically administered to subjects. Preferably, the amount of the NMDAr antagonist may be administered in an amount greater than or less than the amount that is typically administered to subjects while the levodopa/carbidopa is provided at a lower dose than normally used. For example, the amount of amantadine required to positively affect the patient

response (inclusive of adverse effects) may be 300, 400, 500, 600 mg per day rather than the typical 200-300 mg per day administered for presently approved indications i.e. without the improved formulation described herein, while the levodopa, and optionally the carbidopa, can be reduced independently by 10%, 20%, 30%, 40%, 50%, 60%, 70% or up to 80% of what is currently required in the absence of the NMDAr antagonist.

Optionally, lower or reduced amounts of both the NMDAr antagonist and the levodopa/carbidopa are used in a unit dose relative to the amount of each agent when administered independently. The present invention therefore features formulations of combinations directed to dose optimization or release modification to reduce adverse effects associated with separate administration of each agent. The combination of the NMDAr antagonist and the levodopa/carbidopa may result in an additive or synergistic response, and using the unique formulations described herein, the goal of minimizing the levodopa burden is achieved. Preferably, the NMDAr antagonist and the levodopa/carbidopa are provided in a unit dosage form.

The compositions and methods of the invention are particularly useful for the treatment of Parkinson's disease or conditions associated with Parkinson's disease. These conditions include dementia, dyskinesia, dystonia, depression, fatigue and other neuropsychiatric complications of Parkinson's disease.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present Specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. All parts and percentages are by weight unless otherwise specified.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a graph showing the dissolution profiles for an immediate and sustained release formulation of amantadine. The sustained release formulation exhibits a dC/dT during the initial phase that is about 10% of that for the immediate release formulation.

FIG. **2** is a graph showing the amantadine plasma concentration over a period of 5 days, as predicted by Gastro-Plus software package v.4.0.2, following the administration of either 70 mg amantadine in an immediate release formulation t.i.d. or 75 mg amantadine in a sustained release formulation t.i.d. The sustained release formulation peaks are similar in height to the immediate release formulation even with a higher administered dose and the diurnal variation is substantially reduced.

FIG. **3** is a graph showing the plasma profiles simulated using Gastro-Plus for t.i.d. administration of amantadine (70 mg), levodopa (100 mg), and carbidopa (25 mg), all in an immediate release form.

FIG. **4** is a graph showing the plasma profiles simulated using Gastro-Plus for t.i.d. administration of amantadine (75 mg), levodopa (100 mg), and carbidopa (25 mg), where the amantadine is in a sustained release form and the levodopa and carbidopa are in an immediate release form.

FIG. **5** is a graph representing dissolution profiles for various aminoadamantane formulations including an immediate release form of the NMDAr antagonist memantine (Namenda).

FIG. **6** is a graphical representation of plasma release profiles in a human of memantine, levodopa, and carbidopa when memantine is administered separately from levodopa and carbidopa.

FIG. **7** is a graphical representation of plasma release profiles in a human of memantine, levodopa, and carbidopa when memantine, levodopa, and carbidopa are administered as part of a single controlled-release pharmaceutical composition.

FIG. **8** is a bar graph showing the effects on a primate (squirrel monkey) treated with a combination of levodopa/carbidopa and amantadine.

DETAILED DESCRIPTION OF THE INVENTION

In general, the present invention features pharmaceutical compositions that contain therapeutically effective levels of an NMDAr antagonist and levodopa/carbidopa and, optionally, a pharmaceutical carrier. Preferably the compositions are formulated for modified or extended release to provide a serum or plasma concentration of the NMDAr antagonist over a desired time period that is high enough to be therapeutically effective but at a rate low enough so as to avoid adverse events associated with the NMDAr antagonist. Control of drug release is particularly desirable for reducing and delaying the peak plasma level while maintaining the extent of drug bioavailability. Therapeutic levels are therefore achieved while minimizing debilitating side-effects that are usually associated with immediate release formulations. Furthermore, as a result of the delay in the time to obtain peak serum or plasma level and the extended period of time at the therapeutically effective serum or plasma level, the dosage frequency is reduced to, for example, once or twice daily dosage, thereby improving patient compliance and adherence. For example, side effects including psychosis and cognitive deficits associated with the administration of NMDAr antagonists may be lessened in severity and frequency through the use of controlled-release methods that shift the Tmax to longer times, thereby reducing the dC/dT of the drug. Reducing the dC/dT of the drug not only increases Tmax, but also reduces the drug concentration at Tmax and reduces the Cmax/cmean ratio providing a more constant amount of drug to the subject being treated over a given period of time, enabling increased dosages for appropriate indications.

In addition, the present invention encompasses optimal ratios of NMDAr and levodopa/carbidopa, designed to not only treat the dyskinesia associated with levodopa, but also take advantage of the additivity and synergy between these drug classes. For example, the level of levodopa required to treat the disease symptoms can unexpectedly be reduced by up to 50% by the addition of 400 mg/day of amantadine.

Making NMDAr Antagonist Controlled Release Formulations

A pharmaceutical composition according to the invention is prepared by combining a desired NMDAr antagonist or antagonists with one or more additional ingredients that, when administered to a subject, causes the NMDAr antagonist to be released at a targeted rate for a specified period of time. A release profile, i.e., the extent of release of the NMDAr antagonist over a desired time, can be conveniently determined for a given time by measuring the release using a USP dissolution apparatus under controlled conditions. Preferred release profiles are those which slow the rate of uptake of the NMDAr antagonist in the neural fluids while providing

therapeutically effective levels of the NMDAr antagonist. One of ordinary skill in the art can prepare combinations with a desired release profile using the NMDAr antagonists and formulation methods described below.

NMDAr Antagonists

Any NMDAr antagonist can be used in the methods and compositions of the invention, particularly those that are non-toxic when used in the compositions of the invention. The term "nontoxic" is used in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to humans or, in keeping with established regulatory criteria and practice, is susceptible to approval by the FDA or similar regulatory agency for any country for administration to humans or animals.

The term "NMDAr antagonist", as used herein, includes any amino-adamantane compound including, for example, memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1-aminoethyl)adamantane), amantadine (1-amino-adamantane), as well as pharmaceutically acceptable salts thereof. Memantine is described, for example, in U.S. Pat. Nos. 3,391,142, 5,891,885, 5,919,826, and 6,187,338 Amantadine is described, for example, in U.S. Pat. Nos. 3,152,180, 5,891,885, 5,919,826, and 6,187,338. Additional aminoadamantane compounds are described, for example, in U.S. Pat. Nos. 4,346,112, 5,061,703, 5,334,618, 6,444,702, 6,620,845, and 6,662,845. All of these patents are hereby incorporated by reference.

Further NMDAr antagonists that may be employed include, for example, aminocylohexanes such as neramexane, ketamine, eliprodil, ifenprodil, dizocilpine, remacemide, iamotrigine, riluzole, aptiganel, phencyclidine, flupirtine, celfotel, felbamate, spermine, spermidine, levemopamil, dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and its metabolite, dextrorphan ((+)-3-hydroxy-N-methylmorphinan), a pharmaceutically acceptable salt, derivative, or ester thereof, or a metabolic precursor of any of the foregoing.

Optionally, the NMDAr antagonist in the instant invention is memantine and not amantadine or dextromethorphan.

Second Agents

In all foregoing aspects of the invention, the second agent is levodopa. When levodopa is in the combination, the combination preferably also includes a dopa-decarboxylase inhibitor. An example of a suitable dopa-decarboxylase inhibitor is carbidopa. Other dopa-decarboxylase inhibitors include, for example, 3-hydroxy-benzylhydrazinedihydrochloride (NSD-1015) and benseraxide hydrochloride. The combination may further include a catechol-O-methyltransferase (COMT) inhibitor including, for example, talcapone and entacapone.

Dosing, PK, & Toxicity

The NMDA receptor antagonist used in combination therapies are administered at a dosage of generally between about 1 and 5000 mg/day, between 1 and about 800 mg/day, or between 1 and 500 mg/day. For example, NMDA receptor antagonist agents may be administered at a dosage ranging between about 1 and about 500 mg/day, more preferably from about 10 to about 40, 50, 60, 70 or 80 mg/day, advantageously from about 10 to about 20 mg per day. Amantadine may be administered at a dose ranging from about 90, 100 mg/day to about 400, 500, 600, 700 or 800 mg/day, advantageously from about 100 to about 500, 600 mg per day. For example, the pharmaceutical composition may be formulated to provide memantine in an amount ranging between 1-200 mg/day, 1 and 80 mg/day, 2-80 mg/day, 10-80 mg/day, 10 and 80 mg/day, 10 and 70 mg/day, 10 and 60 mg/day, 10 and 50 mg/day, 10 and 40 mg/day, 5 and 65 mg/day, 5 and 40 mg/day, 15 and 45 mg/day, or 10 and 20 mg/day; dextromethorphan in an amount ranging between 1-5000 mg/day, 1-1000 mg/day, and 100-800 mg/day, or 200-500 mg/day. Pediatric doses will typically be lower than those determined for adults.

Table 1 shows exemplary pharmacokinetic properties (e.g., Tmax and T1/2) of memantine, amantadine, and rimantadine.

TABLE 1

Pharmacokinetics and Toxicity in humans for selected NIVIDAr antagonists

Compound	Human PK (t½) (hours)	Tmax (hours)	Normal Dose	Dose Dependent Toxicity
Memantine	60	3	10-20 mg/day, starting at 5 mg	Dose escalation required, hallucination
Amantadine	15	3	100-300 mg/day, starting at 100 mg/day	Hallucination
Rimantadine	25	6	100-200 mg/day	Insomnia

When levodopa and carbidopa are both included in the composition, the levodopa dose ranges between 100 to 3000 mg per day, 75 mg and 2500 mg/day, 100-2000 mg/day, or 250 and 1000 mg/day divided for administration t.i.d. or more frequently. Carbidopa doses may range between the amounts of 1 to 1000 mg/day, 10 to 500 mg/day, and 25 to 100 mg/day. Optionally, the carbidopa is present in the combination at about 75%, 70%, 65%, 60%, 50%, 40%, 30%, 25%, 20%, and 10% of the mass of the levodopa. Alternatively, the amount of levodopa is less than 300% than the amount of carbidopa. For example, 75 mg of carbidopa (amount that is sufficient to extend the half-life of levodopa in the circulatory system) may be used in combination with 300 to 3000 mg of levodopa per day. The combination may contain a single dosage form comprising 30 to 200 mg amantadine, 30 to 250 mg levodopa, and 10 to 100 mg of carbidopa for t.i.d. or more frequent administration, including multiple dosage forms per administration.

As a result, the preferred dosage forms for optimized use are shown in Table 2 below, with their corresponding commercial equivalent.

TABLE 2

Dosage forms with and without NMDAr antagonist (amount per unit dose)

Sinemet Compositions		Compositions of Present Invention		
Levodopa	Carbidopa	Levodopa	Carbidopa	Amantadine
100 mg IR*	25 mg IR	50-100 mg IR	25 mg IR	100-200 mg IR
100 mg IR	10 mg IR	50-100 mg IR	10 mg IR	50-100 mg IR
100 mg IR	25 mg IR	50-100 mg IR	25 mg IR	100-200 mg CR**
100 mg IR	10 mg IR	50-100 mg IR	10 mg IR	50-100 mg CR

*IR: immediate release

**CR: modified release

Excipients

"Pharmaceutically or Pharmacologically Acceptable" includes molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. "Pharmaceutically Acceptable Carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifun-

gal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. "Pharmaceutically Acceptable Salts" include acid addition salts and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

The preparation of pharmaceutical or pharmacological compositions is known to those of skill in the art in light of the present disclosure. General techniques for formulation and administration are found in "Remington: The Science and Practice of Pharmacy, Twentieth Edition," Lippincott Williams & Wilkins, Philadelphia, Pa. Tablets, capsules, pills, powders, granules, dragees, gels, slurries, ointments, solutions suppositories, injections, inhalants and aerosols are examples of such formulations.

By way of example, modified or extended release oral formulation can be prepared using additional methods known in the art. For example, a suitable extended release form of the either active pharmaceutical ingredient or both may be a matrix tablet or capsule composition. Suitable matrix forming materials include, for example, waxes (e.g., carnauba, bees wax, paraffin wax, ceresine, shellac wax, fatty acids, and fatty alcohols), oils, hardened oils or fats (e.g., hardened rapeseed oil, castor oil, beef tallow, palm oil, and soya bean oil), and polymers (e.g., hydroxypropyl cellulose, polyvinylpyrrolidone, hydroxypropyl methyl cellulose, and polyethylene glycol). Other suitable matrix tabletting materials are microcrystalline cellulose, powdered cellulose, hydroxypropyl cellulose, ethyl cellulose, with other carriers, and fillers. Tablets may also contain granulates, coated powders, or pellets. Tablets may also be multi-layered. Multi-layered tablets are especially preferred when the active ingredients have markedly different pharmacokinetic profiles. Optionally, the finished tablet may be coated or uncoated.

The coating composition typically contains an insoluble matrix polymer (approximately 15-85% by weight of the coating composition) and a water soluble material (e.g., approximately 15-85% by weight of the coating composition). Optionally an enteric polymer (approximately 1 to 99% by weight of the coating composition) may be used or included. Suitable water soluble materials include polymers such as polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials such as sugars (e.g., lactose, sucrose, fructose, mannitol and the like), salts (e.g., sodium chloride, potassium chloride and the like), organic acids (e.g., fumaric acid, succinic acid, lactic acid, and tartaric acid), and mixtures thereof. Suitable enteric polymers include hydroxypropyl methyl cellulose, acetate succinate, hydroxypropyl methyl cellulose, phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups.

The coating composition may be plasticised according to the properties of the coating blend such as the glass transition temperature of the main component or mixture of components or the solvent used for applying the coating compositions. Suitable plasticisers may be added from 0 to 50% by weight of the coating composition and include, for example, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, acetylated citrate esters, dibutylsebacate, and castor oil. If desired, the coating composition may include a filler. The amount of the filler may be 1% to approximately 99% by weight based on the total weight of the coating composition and may be an insoluble material such as silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, MCC, or polacrilin potassium.

The coating composition may be applied as a solution or latex in organic solvents or aqueous solvents or mixtures thereof. If solutions are applied, the solvent may be present in amounts from approximate by 25-99% by weight based on the total weight of dissolved solids. Suitable solvents are water, lower alcohol, lower chlorinated hydrocarbons, ketones, or mixtures thereof. If latexes are applied, the solvent is present in amounts from approximately 25-97% by weight based on the quantity of polymeric material in the latex. The solvent may be predominantly water.

The NMDAr antagonist may be formulated using any of the following excipients or combinations thereof.

Excipient name	Chemical name	Function
Avicel PH102	Microcrystalline Cellulose	Filler, binder, wicking, disintegrant
Avicel PH101	Microcrystalline Cellulose	Filler, binder, disintegrant
Eudragit RS-30D	Polymethacrylate Poly(ethyl acrylate, nethyl methacrylate, timethylammonioethyl methacrylate chloride) 1:2:0.1	Film former, tablet binder, tablet diluent; Rate controlling polymer for controlled release
Methocel K100M Premium CR	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Methocel K100M	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Magnesium Stearate	Magnesium Stearate	Lubricant
Talc	Talc	Dissolution control; anti-adherent, glidant
Triethyl Citrate	Triethyl Citrate	Plasticizer
Methocel E5	Hydroxypropyl methylcellulose	Film-former
Opadry ®	Hydroxypropyl methylcellulose	One-step customized coating system which combines polymer, plasticizer and, if desired, pigment in a dry concentrate.
Surelease ®	Aqueous Ethylcellulose Dispersion	Film-forming polymer; plasticizer and stabilizers. Rate controlling polymer coating.

The pharmaceutical composition described herein may also include a carrier such as a solvent, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents. The use of such media and agents for pharmaceutically active substances is well known in the art. Pharmaceutically acceptable salts can also be used in the composition, for example, mineral salts such as hydrochlorides, hydrobromides, phosphates, or sulfates, as well as the salts of organic acids such as acetates, proprionates, malonates, or benzoates. The composition may also contain liquids, such as water, saline, glycerol, and ethanol, as well as substances such as wetting agents, emulsifying agents, or pH buffering agents. Liposomes, such as those described in U.S.

Pat. No. 5,422,120, WO 95/13796, WO 91/14445, or EP 524,968 B1, may also be used as a carrier.

Methods for Preparing Modified or Extended Release Formulations

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a controlled or extended release form with or without an immediate release component in order to maximize the therapeutic benefit of such agents, while reducing unwanted side effects. In the absence of modified release components (referred to herein as controlled, extended, or delayed release components), the NMDAr antagonist, levodopa/carbidopa, or both is released and transported into the body fluids over a period of minutes to several hours. The combination described herein however, may contain an NMDAr antagonist and a sustained release component, such as a coated sustained release matrix, a sustained release matrix, or a sustained release bead matrix. In one example, in addition to levodopa/carbidopa, amantadine (e.g., 50-400 mg) is formulated without an immediate release component using a polymer matrix (e.g., Eudragit), Hydroxypropyl methyl cellulose (HPMC) and a polymer coating (e.g., Eudragit). Such formulations are compressed into solid tablets or granules and coated with a controlled release material such as Opadry® or Surelease®. Levodopa/carbidopa may also be formulated as a sustained release formulation; in most cases, however, this will not be optimal.

Suitable methods for preparing the compositions described herein in which the NMDAr antagonist is provided in modified or extended release-formulations include those described in U.S. Pat. No. 4,606,909 (hereby incorporated by reference). This reference describes a controlled release multiple unit formulation in which a multiplicity of individually coated or microencapsulated units are made available upon disintegration of the formulation (e.g., pill or tablet) in the stomach of the subject (see, for example, column 3, line 26 through column 5, line 10 and column 6, line 29 through column 9, line 16). Each of these individually coated or microencapsulated units contains cross-sectionally substantially homogenous cores containing particles of a sparingly soluble active substance, the cores being coated with a coating that is substantially resistant to gastric conditions but which is erodable under the conditions prevailing in the gastrointestinal tract.

The composition of the invention may alternatively be formulated using the methods disclosed in U.S. Pat. No. 4,769,027, for example. Accordingly, extended release formulations involve prills of pharmaceutically acceptable material (e.g., sugar/starch, salts, and waxes) may be coated with a water permeable polymeric matrix containing an NMDAr antagonist and next overcoated with a water-permeable film containing dispersed within it a water soluble particulate pore forming material.

The NMDAr antagonist composition may additionally be prepared as described in U.S. Pat. No. 4,897,268, involving a biocompatible, biodegradable microcapsule delivery system. Thus, the NMDAr antagonist may be formulated as a composition containing a blend of free-flowing spherical particles obtained by individually microencapsulating quantities of memantine, for example, in different copolymer excipients which biodegrade at different rates, therefore releasing memantine into the circulation at a predetermined rates. A quantity of these particles may be of such a copolymer excipient that the core active ingredient is released quickly after administration, and thereby delivers the active ingredient for an initial period. A second quantity of the particles is of such type excipient that delivery of the encapsulated ingredient begins as the first quantity's delivery begins to decline. A third quantity of ingredient may be encapsulated with a still different excipient which results in delivery beginning as the delivery of the second quantity beings to decline. The rate of delivery may be altered, for example, by varying the lactide/glycolide ratio in a poly(D,L-lactide-co-glycolide) encapsulation. Other polymers that may be used include polyacetal polymers, polyorthoesters, polyesteramides, polycaprolactone and copolymers thereof, polycarbonates, polyhydroxybuterate and copolymers thereof, polymaleamides, copolyaxalates and polysaccharides.

Alternatively, the composition may be prepared as described in U.S. Pat. No. 5,395,626, which features a multilayered controlled release pharmaceutical dosage form. The dosage form contains a plurality of coated particles wherein each has multiple layers about a core containing an NMDAr antagonist whereby the drug containing core and at least one other layer of drug active is overcoated with a controlled release barrier layer therefore providing at least two controlled releasing layers of a water soluble drug from the multilayered coated particle

Release Profile

The compositions described herein are formulated such that the NMDAr antagonist, levodopa/carbidopa, or both agents have an in vitro dissolution profile that is equal to or slower than that for an immediate release formulation. As used herein, the immediate release (IR) formulation for memantine means the present commercially available 5 mg and 10 mg tablets (i.e., Namenda from Forest Laboratories, Inc. or formulations having substantially the same release profiles as Namenda); and the immediate release (IR) formulation of amantadine means the present commercially available 100 mg tablets (i.e., Symmetrel from Endo Pharmaceuticals, Inc. or formulations having substantially the same release profiles as Symmetrel); and the immediate release (IR) formulation of levodopa/carbidopa means the present commercially available 25 mg/100 mg, 10 mg/100 mg, 25 mg/250 mg tablets of carbidopa/levodopa (i.e., Sinemet from Merck & Co. Inc. or formulations having substantially the same release profiles as Sinemet). These compositions may comprise immediate release, sustained or extended release, or delayed release components, or may include combinations of same to produce release profiles such that the fraction of NMDAr antagonist or levodopa/carbidopa released is greater or equal to $0.01(0.297+0.0153*e^{(0.515*t)})$ and less than or equal to $1-e^{(-10.9*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C., in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist or levodopa/carbidopa released is less than 93% in 15 minutes and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1N HCl) dissolution medium. Optionally, the fraction of released NMDAr antagonist or levodopa/carbidopa is greater than or equal to $0.01(0.297+0.0153*e^{(0.515*t)})$, and less than or equal to $1-e^{(-0.972*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C., in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist or levodopa/carbidopa that is released may range between 0.1%-62% in one hour, 0.2%-86% in two hours, 0.6%-100% in six hours, 2.9%-100% in 10 hours, and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1N HCl) dissolution medium. Optionally, the NMDA receptor antagonist has a

release profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 70% or greater (e.g., 70%-90%) in 10 hours, and 90% or greater (e.g., 90-95%) in 12 hours as measured in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1N HCl) dissolution medium. For example, a formulation containing amantadine may have a release profile ranging between 0-60% or 0.1-20% in one hour, 0-86% or 5-30% at two hours, 0.6-100% or 40-80% at six hours, 3-100% or 50% or more (e.g., 50-90%) at ten hours, and 7.7-100% at twelve hours in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1N HCl) dissolution medium. In one embodiment, the NMDAr antagonist, the levodopa/carbidopa, or both agents have an in vitro dissolution profile of less than 25%, 15%, 10%, or 5% in fifteen minutes; 50%, 30%, 25%, 20%, 15%, or 10% in 30 minutes and more than 60%, 65% 70%, 75%, 80%, 85%, 90%, 95% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water. Desirably, the NMDAr antagonist, the levodopa/carbidopa, or both agents has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% in a dissolution media having a pH of 1.2 at 10 hours. It is important to note that the dissolution profile for the NMDAr antagonist may be different than the release profile for levodopa/carbidopa. In a preferred embodiment, the levodopa/carbidopa release profile is equal to or similar to that for an immediate release formulation and the release profile for the NMDAr antagonist is controlled to provide a dissolution profile of less than 30% in one hour, less than 50% in two hours, and greater than 95% in twelve hours using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water.

Desirably, the compositions described herein have an in vitro profile that is substantially identical to the dissolution profile shown in FIG. **5** and, upon administration to a subject at a substantially constant daily dose, achieves a serum concentration profile that is substantially identical to that shown in FIGS. **2** and **4**.

As described above, the NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a modified or extended release form. Modified or extended drug release is generally controlled either by diffusion through a coating or matrix or by erosion of a coating or matrix by a process dependent on, for example, enzymes or pH. The NMDAr antagonist or the levodopa/carbidopa may be formulated for modified or extended release as described herein or using standard techniques in the art. In one example, at least 50%, 75%, 90%, 95%, 96%, 97%, 98%, 99%, or even in excess of 99% of the NMDAr antagonist or the levodopa/carbidopa is provided in an extended release dosage form. In a preferred embodiment, the levodopa/carbidopa is provided in an immediate release formulation and the NMDAr antagonist is in either an immediate or modified release form.

The composition described herein is formulated such the NMDAr antagonist or levodopa/carbidopa has an in vitro dissolution profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 50%-90% in 10 hours, and 90%-95% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. using 0.1N HCl as a dissolution medium. Alternatively, the NMDAr antagonist has an in vitro dissolution profile in a solution with a neutral pH (e.g., water) that is substantially the same as its dissolution profile in an acidic dissolution medium. Thus, the NMDAr antagonist may be released in both dissolution media at the following rate: between 0.1-20% in one hour, 5-30% in two hours, 40-80% in six hours, 70-90% in 10 hours, and 90%-95% in 12 hours as obtained using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. In one embodiment, the NMDAr antagonist has an in vitro dissolution profile of less than 15%, 10%, or 5% in fifteen minutes, 25%, 20%, 15%, or 10% in 30 minutes, and more than 60% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water. Desirably, the NMDAr antagonist has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% at 10 hours in a dissolution medium having a pH of 1.2.

Initial Rate In Vivo, Delayed Tmax

As used herein, "C" refers to the concentration of an active pharmaceutical ingredient in a biological sample, such as a patient sample (e.g. blood, serum, and cerebrospinal fluid). The time required to reach the maximal concentration ("Cmax") in a particular patient sample type is referred to as the "Tmax". The change in concentration is termed "dC" and the change over a prescribed time is "dC/dT".

The NMDAr antagonist or levodopa/carbidopa is provided as a sustained release formulation that may or may not contain an immediate release formulation. If desired, the NMDAr antagonist may be formulated so that it is released at a rate that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In addition, the NMDAr antagonist levodopa/carbidopa may be provided such that it is released at a rate resulting in a Cmax/cmean of approximately 2 or less for approximately 2 hours to at least 8 hours after the NMDAr antagonist is introduced into a subject. Optionally, the sustained release formulations exhibit plasma concentration curves having initial (e.g., from 0, 1, 2 hours after administration to 4, 6, 8 hours after administration) slopes less than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist. The precise slope for a given individual will vary according to the NMDAr antagonist being used or other factors, including whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose. The determination of initial slopes of plasma concentration is described, for example, by U.S. Pat. No. 6,913,768, hereby incorporated by reference.

Desirably, the NMDAr antagonist or the levodopa/carbidopa is released into a subject sample at a slower rate than observed for an immediate release (IR) formulation of the same quantity of the antagonist, such that the rate of change in the biological sample measured as the dC/dT over a defined period within the period of 0 to Tmax for the IR formulation (e.g., Namenda, a commercially available IR formulation of memantine). In some embodiments, the dC/dT rate is less than about 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. In some embodiments, the dC/dT rate is less than about 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. Similarly, the rate of release of the NMDAr antagonist or the levodopa/carbidopa from the present invention as measured in dissolution studies is less than 80%, 70%, 60% 50%, 40%, 30%, 20%, or 10% of the rate for an IR formulation of the same NMDAr antagonist or levodopa/carbidopa over the first 1, 2, 4, 6, 8, 10, or 12 hours.

In a preferred embodiment, the dosage form is provided in a non-dose escalating, three times per day (t.i.d.) form. In preferred embodiments, the concentration ramp (or Tmax

effect) may be reduced so that the change in concentration as a function of time (dC/dT) is altered to reduce or eliminate the need to dose escalate the NMDAr antagonist. A reduction in dC/dT may be accomplished, for example, by increasing the Tmax in a relatively proportional manner. Accordingly, a two-fold increase in the Tmax value may reduce dC/dT by approximately a factor of 2. Thus, the NMDAr antagonist may be provided so that it is released at a rate that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In certain embodiments, this is accomplished by releasing less than 30%, 50%, 75%, 90%, or 95% of the NMDAr antagonist into the circulatory or neural system within one hour of such administration.

The concentration ramp for levodopa/carbidopa may also be reduced, however such changes will not be preferred in most oral formulations due to the marked reduction in absorption of levodopa/carbidopa after it passes the duodenal region of the gastrointestinal tract.

Optionally, the modified release formulations exhibit plasma concentration curves having initial (e.g., from −2 hours after administration to 4 hours after administration) slopes less-than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist or levodopa/carbidopa. The precise slope for a given individual will vary according to the NMDAr antagonist or levodopa/carbidopa being used, the quantity delivered, or other factors, including, for some active pharmaceutical agents, whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose.

Using the sustained release formulations or administration methods described herein, the NMDAr antagonist reaches a therapeutically effective steady state plasma concentration in a subject within the course of the first two, three, five, seven, nine, ten, twelve, fifteen, or twenty days of administration. For example, the formulations described herein, when administered at a substantially constant daily dose (e.g., at a dose ranging between 200 mg and 800 mg, preferably between 200 mg and 600 mg, and more preferably between 200 mg and 400 mg per day) may reach a steady state plasma concentration in approximately 70%, 60%, 50%, 40%, 30%, or less of the time required to reach such plasma concentration when using a dose escalating regimen.

Dosing Frequency and Dose Escalation

According to the present invention, a subject (e.g., human) having or at risk of having such conditions is administered any of the compositions described herein (e.g., three times per day (t.i.d.), twice per day (b.i.d.), or once per day (q.d.)). While immediate release formulations of NMDAr antagonists are typically administered in a dose-escalating fashion, the compositions described herein may be essentially administered at a constant, therapeutically-effective dose from the onset of therapy. For example, a composition containing a sustained release formulation of amantadine may be administered three times per day, twice per day, or once per day in a unit dose comprising a total daily amantadine dose of 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, or 800 mg. In embodiments comprising a single dosage form containing an NMDAr antagonist and levodopa/carbidopa wherein the levodopa/carbidopa is in an immediate release form, the dosing frequency will be chosen according to the levodopa/carbidopa requirements, (e.g. three times per day).

Reduced Time to Therapeutic Concentration and Efficacy

Immediate release (IR) formulations of memantine (e.g., Namenda) are typically administered at low doses (e.g., 5 mg/day) and are progressively administered at increasing frequency and dose over time to reach a steady state serum concentration that is therapeutically effective. According to the manufacturer's FDA approved label, Namenda, an immediate release (IR) formulation of memantine, is first administered to subjects at a dose of 5 mg per day. After an acclimation period of typically one week, subjects are administered with this dose twice per day. Subjects are next administered with a 5 mg and 10 mg dosing per day and finally administered with 10 mg Namenda twice daily. Using this dosing regimen, a therapeutically effective steady state serum concentration may be achieved within 30 days of the onset of therapy. Using a modified release formulation comprising (22.5 mg memantine,) however, a therapeutically effective steady state concentration may be achieved substantially sooner (within about 13 days), without using a dose escalating regimen. Furthermore, the slope during each absorption period for the sustained release formulation is less (i.e. not as steep) as the slope for Namenda. Accordingly, the dC/dT of the sustained release formulation is reduced relative to the immediate release formulation even though the dose administered is larger than for the immediate release formulation. Based on this model, a sustained release formulation of an NMDAr antagonist may be administered to a subject in an amount that is approximately the full strength dose (or that effectively reaches a therapeutically effective dose) from the onset of therapy and throughout the duration of treatment. Accordingly, a dose escalation would not be required.

Treatment of a subject with the subject of the present invention may be monitored using methods known in the art. The efficacy of treatment using the composition is preferably evaluated by examining the subject's symptoms in a quantitative way, e.g., by noting a decrease in the frequency or severity of symptoms or damaging effects of the condition, or an increase in the time for sustained worsening of symptoms. In a successful treatment, the subject's status will have improved (i.e., frequency or severity of symptoms or damaging effects will have decreased, or the time to sustained progression will have increased). In the model described in the previous paragraph, the steady state (and effective) concentration of the NMDAr antagonist is reached in 25%, 40%, 50%, 60%, 70%, 75%, or 80% less time than in the dose escalated approach.

In another embodiment, a composition is prepared using the methods described herein, wherein such composition comprises memantine or amantadine and a release modifying excipient, wherein the excipient is present in an amount sufficient to ameliorate or reduce the dose-dependent toxicity associated with the memantine or amantadine relative to an immediate release (IR) formulation of memantine, such as Namenda, or amantadine, such as Symmetrel. The use of these compositions enables safer administration of these agents, and even permits the safe use of higher levels for appropriate indications, beyond the useful range for the presently available versions of memantine (5 mg and 10 mg per dose to 20 mg per day) and amantadine (100 mg to 300 mg per day with escalation).

Indications Suitable for Treatment

The compositions and methods of the present invention are particularly suitable for the treatment of Parkinson's disease or conditions associated with Parkinson's disease. These conditions include dementia, dyskinesia, dystonia, depression, fatigue and other neuropsychiatric complications of Parkinson's disease.

Formulations for Alternate Specific Routes of Administration

The pharmaceutical compositions may be optimized for particular types of delivery. For example, pharmaceutical compositions for oral delivery are formulated using pharmaceutically acceptable carriers that are well known in the art. The carriers enable the agents in the composition to be formulated, for example, as a tablet, pill, capsule, solution, suspension, sustained release formulation; powder, liquid or gel for oral ingestion by the subject.

The NMDAr antagonist may also be delivered in an aerosol spray preparation from a pressurized pack, a nebulizer or from a dry powder inhaler. Suitable propellants that can be used in a nebulizer include, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and carbon dioxide. The dosage can be determined by providing a valve to deliver a regulated amount of the compound in the case of a pressurized aerosol.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral, intranasal or respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

In some embodiments, for example, the composition may be delivered intranasally to the cribriform plate rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in U.S. Pat. No. 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Additional formulations suitable for other modes of administration include rectal capsules or suppositories. For suppositories, traditional binders and carriers may include, for example, polyalkylene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%.

The composition may optionally be formulated for delivery in a vessel that provides for continuous long-term delivery, e.g., for delivery up to 30 days, 60 days, 90 days, 180 days, or one year. For example the vessel can be provided in a biocompatible material such as titanium. Long-term delivery formulations are particularly useful in subjects with chronic conditions, for assuring improved patient compliance, and for enhancing the stability of the compositions.

Optionally, the NMDA receptor antagonist, levodopa/carbidopa, or both is prepared using the OROS® technology, described for example, in U.S. Pat. Nos. 6,919,373, 6,923,800, 6,929,803, 6,939,556, and 6,930,128, all of which are hereby incorporated by reference. This technology employs osmosis to provide precise, controlled drug delivery for up to 24 hours and can be used with a range of compounds, including poorly soluble or highly soluble drugs. OROS® technology can be used to deliver high drug doses meeting high drug loading requirements. By targeting specific areas of the gastrointestinal tract, OROS® technology may provide more efficient drug absorption and enhanced bioavailability. The osmotic driving force of OROS® and protection of the drug until the time of release eliminate the variability of drug absorption and metabolism often caused by gastric pH and motility.

Formulations for continuous long-term delivery are provided in, e.g., U.S. Pat. Nos. 6,797,283; 6,764, 697; 6,635,268, and 6,648,083.

If desired, the components may be provided in a kit. The kit can additionally include instructions for using the kit.

Additional Methods for Making Modified Release Formulations

Additional methods for making modified release formulations are described in, e.g., U.S. Pat. Nos. 5,422,123, 5,601,845, 5,912,013, and 6,194,000, all of which are hereby incorporated by reference.

In some embodiments, for example, the composition may be delivered via intranasal, buccal, or sublingual routes to the brain rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in U.S. Pat. No. 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Preparation of a pharmaceutical composition for delivery in a subdermally implantable device can be performed using methods known in the art, such as those described in, e.g., U.S. Pat. Nos. 3,992,518; 5,660,848; and 5,756,115.

The invention will be illustrated in the following non-limiting examples.

EXAMPLES

Example 1

Measuring Release Profiles In Vitro

Compositions containing an aminoadamantane and levodopa/carbidopa are analyzed for release of the aminoadamantane and levodopa/carbidopa, according to the USP type 2 apparatus at a speed of 50 rpm. The dissolution media used include water, 0.1N HCl, or 0.1N HCl adjusted to pH 6.8 at 2 hours with phosphate buffer. The dissolution medium is equilibrated to 37±0.5° C.

The USP reference assay method for amantadine is used to measure the fraction of memantine released from the compositions prepared herein. Briefly, 0.6 mL sample (from the dissolution apparatus at a given time point) is placed into a 15 mL culture tube. 1.6 mL 0.1% Bromocresol Purple (in acetic acid) is added and vortexed for five seconds. The mixture is allowed to stand for approximately five minutes. 3 mL Chloroform is added and vortexed for five seconds. The solution is next centrifuged (speed 50 rpm) for five minutes. The top layer is removed with a disposable pipette. A sample is drawn into 1 cm flow cell and the absorbance is measured at 408 nm at 37° C. and compared against a standard curve prepared with known quantities of the same aminoadamantane. The quantity of determined is plotted against the dissolution time for the sample.

The USP reference assay method for levodopa is used to measure the fraction of levodopa released from the compositions prepared herein. Briefly, 0.5 ml samples from the dissolution apparatus removed at various times are assayed by liquid chromatography. The chromatograph is equipped with a 280 nm detector and a 3.9 mm×30 cm column containing packing Ll. The mobile phase is 0.09 N sodium phosphate, 1

mM sodium 1-decanesulfonate, pH 2.8. With the flow rate adjusted to about 2 mL per minute, the levodopa elutes in about 4 minutes and carbidopa elutes in about 11 minutes. From the saved dissolution samples, a 0.02 ml aliquot is injected into the chromatograph and the absorbance is measure and compared to standard to determine concentration & quantity. The quantity dissolved is then plotted against the dissolution time for the sample.

Example 2

Preparation of Amantadine Extended Release Capsules

Amantadine extended release capsules may be formulated as follows or as described, for example, in U.S. Pat. No. 5,395,626.

A. Composition: Unit Dose

The theoretical quantitative composition (per unit dose) for amantadine extended release capsules is provided below.

Component	% weight/weight	mg/Capsule
Amantadine	68.34	200.00
OPADRY ® Clear YS-3-7011[1] (Colorcon, Westpoint, PA)	1.14	5.01
Purified Water, USP[2]	—	—
Sugar Spheres, NF	12.50	54.87
OPADRY ® Clear YS-1-7006[3] (Colorcon, Westpoint, PA)	4.48	19.66
SURELEASE ® E-7-7050[4] (Colorcon, Westpoint, PA)	13.54	59.44
Capsules[5]	—	—
TOTAL.	100.00%	338.98 mg[6]

[1]A mixture of hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol.

[2]Purified Water, USP is evaporated during processing.

[3]A mixture of hydroxypropyl methylcellulose and polyethylene glycol

[4]Solid content only of a 25% aqueous dispersion of a mixture of ethyl cellulose, dibutyl sebacate, oleic acid, ammoniated water and fumed silica. The water in the dispersion is evaporated during processing.

[5]White, opaque, hard gelatin capsule, size 00.

[6]Each batch is assayed prior to filling and the capsule weight is adjusted as required to attain 200 mg amantadine per capsule.

The quantitative batch composition for amantadine extended release capsule is shown below. (Theoretical batch quantity 25,741 capsules).

Step 1: Prep of Amantadine HCl Beads (bead Build-up #1)

Component	Weight (kg)
Amantadine	12.000
OPADRY ® Clear YS-3-7011	0.200
Purified Water, USP	5.454
Sugar Sphere, NF	4.000
Total Weight Amantadine Beads	16.200 kg

The amantadine beads obtained from step 1 are used as follows.

Step 2: Clear & Sustained Release Bead Coating #1

Component	Weight (kg)
Amantadine Beads	8.000
OPADRY ® Clear YS-1-7006	0.360
Purified Water, USP	5.928
Surelease ® E-7-7050	0.672
Total Weight Clear Coated Sustained Release Beads	9.032 kg

The sustained release beads obtained from step 2 are used as follows.

Step 3: Amantadine HCl Beads (Build-up #2)

Component	Weight (kg)
Sustained Release Beads	8.000
Amantadine	4.320
OPADRY ® Clear YS-3-7011	0.072
Purified Water, USP	1.964
Total Weight Amantadine Beads	12.392 kg

The amantadine beads obtained from step 3 are formulated as follows.

Step 4: Clear & Sustained Release Bead Coating #2

Component	Weight (kg)
Amantadine Beads	10.000
OPADRY ® Clear YS-1-7006	0.250
Purified Water, USP	6.450
Surelease ® E-7-7050	1.050
Total Weight Amantadine Extended Release Beads	11.300 kg

Step 5: Capsule Filling—Gelatin capsules, size 00, are filled with 339 mg of the amantadine beads prepared in step 4.

Example 3

Extended Release Amantadine Formulation with Immediate Release Carbidopa and Levodopa

Levodopa and Carbidopa are formulated into pellets suitable for filling, yet having an immediate release profile. (see, for example, U.S. Pat. No. 5,912,013).

	Weight Percent	Kilograms
Levodopa plus Carbidopa Core Pellets		
MCC	25.0	0.25
Hydroxypropylmethylcellulose Phthalate (HPMCP)	10.0	0.10
Tartaric Acid	10.0	0.10
Sodium Monoglycerate	7.5	0.075
DSS	0.5	0.005
Levodopa	35.8	0.358
Carbidopa	11.2	0.112
TOTAL	100.0%	1.00 kg
Coating		
Cellulose Acetate Phthalate (CAP)	60.0	0.60
Ethylcellulose	25.0	0.25
PEG-400	15.0	0.15
TOTAL	100.0%	1.00 kg

The pellets are assayed for levodopa and carbidopa content. It is determined that approximately 223 mg of the pellets contain 80 mg levodopa and 25 mg carbidopa. Dissolution greater than 90% in 30 minutes is also confirmed.

A total of 669 grams of the pellets are blended with 510 grams of the amantadine pellets from Example 2 in a V-blender for 30 minutes at 30 rpm. Gelatin capsules are filled with 393 mg of the mixture and the assays for content are

repeated verifying a composition of 100 mg amantadine, 80 mg levodopa, and 25 mg carbidopa.

Example 4

Predicted Dissolution and Plasma Profiles of Amantadine Controlled Release

Using the formulations described above, the dissolution profiles for amantadine were simulated and used to calculate plasma profiles resulting from single or multiple administrations using the pharmacokinetic software, GastroPlus v.4.0.2, from Simulations Plus (see FIG. **2**). The initial slope of the dissolution for the sustained release formulation is less than the slope determined for the immediate release formulation (see FIG. **1**) and the corresponding serum profile also shows a slower dC/dT (see FIG. **4**).

Example 5

Release Profile of Amantadine and L-DOPA (Levodopa/Carbidopa)

Release proportions are shown in the tables below for a combination of amantadine and levodopa/carbidopa. The cumulative fraction is the amount of drug substance released from the formulation matrix to the serum or gut environment (e.g., U.S. Pat. Nos. 4,839,177 or 5,326,570) or as measured with a USP II Paddle system using 0.1N HCl as the dissolution medium.

Time	AMANTADINE T½ = 15 hrs cum. fraction A	LEVODOPA/CARBIDOPA T½ = 1.5 hrs Cum. fraction B
0	0.00	0.00
0.5	0.10	0.40
1.0	0.20	0.95
2.0	0.35	1.00
4.0	0.60	1.00
8.0	0.90	1.00
12.0	0.98	1.00

Example 6

Treating Dyskinesia in Patients with Parkinson's Disease

A Parkinson's patient experiencing dyskinesia is administered the composition of Example 3 three times each day to receive 300 mg amantadine, 240 mg levodopa, and 75 mg carbidopa daily. The Parkinsonism is reduced as measured by the UPDRS (Goetz et al., Mov. Disord. 19:1020-8, 2004, incorporated by reference) as is the dyskinesia (Vitale et al., Neurol. Sci. 22:105-6, 2001, incorporated by reference)

Example 7

Animal Models Showing Reduced Dyskinesia, Reduced Levodopa Potential

The following protocol was employed to demonstrate the beneficial effects of the compositions of this invention. Briefly, squirrel monkeys (N=4) were lesioned with MPTP according to the protocol of Di Monte et al. (Mov. Disord. 15: 459-66 (2000)). After 3 months, the monkeys showed full symptoms of Parkinson's disease as measured by a modified UPDRS (Goetz et al., Mov. Disord. 19:1020-8, 2004). Levodopa treatment at approximately 15 mg/kg (with 1.5 mg/kg carbidopa) mg/kg b.i.d. commenced a baseline UPDRS and dyskinesia measurement was established. Amantadine was added to the regimen simultaneously with the levodopa, and the amount raised from 1 mg/kg to 45 mg/kg for four of the squirrel monkeys, corresponding to an estimated 3 μm concentration. As shown in FIG. **8**, the combination led to a 60% reduction in dyskinesia. We hypothesize that this translates into a potential 40% reduction in levodopa required to maintain UPDRS.

Example 8

Levodopa Sparing Therapy

The following protocol is employed to determine the optimal reduction of levodopa achieved with the addition of Amantadine to a fixed dose combination product.

Parkinson's DISEASE PROTOCOL SUMMARY NPI MEMANTINE CR MONOTHERAPY

Protocol Number: NPI-Amantadine CR

Study Phase: 2/3

Name of Drug: NPI-Amantadine/C/L

Dosage: 25/100/100 c/l/a given t.i.d.

25/80/100 c/l/a given t.i.d.

25/60/100 c/l/a given t.i.d.

Concurrent Control: 25/100 c/1 given t.i.d.

Route: Oral

Subject Population: Male and female patients diagnosed with Parkinson's Disease Hoehn and Yahr score of 2-4

Structure: Parallel-group, three-arm study

Study Term Two weeks

Study Sites Multi-center 10 centers

Blinding: Double blind

Method of Subject Assignment: Randomized to one of three treatment groups (3:1)

Total Sample Size: 320 subjects (160 men, 160 women)

Primary Efficacy Endpoints: UPDRS

Abnormal involuntary movement scale (AIMS) 0-4

Secondary Endpoints: Modified Obeso dyskinesia rating scale 0-4

Mini-mental state examination (MMSE); Neuropsychiatric Inventory Score (NPI)

Adverse Events: Monitored and elicited by clinic personnel throughout the study, volunteered by patients

Example 9

Pharmaceutical Composition Including Memantine, Levodopa, and Carbidopa

A co-formulation of memantine, levodopa and carbidopa is prepared. This co-formulation matches the absorption properties of levodopa and carbidopa more closely than those of Memantine, thereby extending the effectiveness per dose of levodopa and carbidopa. The co-formulation provides Tmax values to about 4 hours and allows b.i.d. dosing of the combination.

FIG. **6** provides the current single oral dose pharmacokinetic (PK) profiles for levodopa, carbidopa and memantine. FIG. **7** provides idealized pharmacokinetic profiles for the target co-formulation, in which the Tmax values for levodopa and carbidopa more closely match that of Memantine.

Dosage Form: Tablet

Formulation Content: Levodopa 150 mg

Carbidopa 37.5 mg

Memantine 10 mg

Excipients: FDA approved excipients and drug release modifiers. Additional embodiments are within the claims.

Example 10

Pharmaceutical Composition Including Extended Release Formulations of Memantine and Levodopa

A pulsatile release dosage form for administration of memantine and levodopa may be prepared as three individual compartments. Three individual tablets are compressed, each having a different release profile, followed by encapsulation into a gelatin capsule, which are then closed and sealed. The components of the three tablets are as follows.

Component	Function	Amount per tablet
TABLET 1 (IMMEDIATE RELEASE):		
Memantine	Active agent	8 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
TABLET 2 (RELEASE DELAYED 3-5 HOURS FOLLOWING ADMINISTRATION):		
Memantine	Active agent	8 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS3OD	Delayed release coating material	4.76 mg
Talc	Coating component	3.3 mg
Triethyl citrate	Coating component	0.95 mg
TABLET 3 (RELEASE DELAYED 7-9 HOURS FOLLOWING ADMINISTRATION):		
Memantine	Active agent	2.5 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS3OD	Delayed release coating material	6.34 mg
Talc	Coating component	4.4 mg
Triethyl citrate	Coating component	1.27 mg

The tablets are prepared by wet granulation of the individual drug particles and other core components as may be done using a fluid-bed granulator, or are prepared by direct compression of the admixture of components. Tablet 1 is an immediate release dosage form, releasing the active agents within 1-2 hours following administration. Tablets 2 and 3 are coated with the delayed release coating material as may be carried out using conventional coating techniques such as spray-coating or the like. As will be appreciated by those skilled in the art, the specific components listed in the above tables may be replaced with other functionally equivalent components, e.g., diluents, binders, lubricants, fillers, coatings, and the like.

Oral administration of the capsule to a patient will result in a release profile having three pulses, with initial release of the memantine and levodopa from the first tablet being substantially immediate, release of the memantine and levodopa from the second tablet occurring 3-5 hours following administration, and release of the memantine and levodopa from the third tablet occurring 7-9 hours following administration.

Example 11

Pharmaceutical Composition Including Extended Release Formulations of Memantine, Levodopa, and Carbidopa

The method of Example 9 is repeated, except that drug-containing beads are used in place of tablets. Carbidopa is also added in each of the fractions at 25% of the mass of the levodopa. A first fraction of beads is prepared by coating an inert support material such as lactose with the drug which provides the first (immediate release) pulse. A second fraction of beads is prepared by coating immediate release beads with an amount of enteric coating material sufficient to provide a drug release-free period of 3-5 hours. A third fraction of beads is prepared by coating immediate release beads having half the methylphenidate dose of the first fraction of beads with a greater amount of enteric coating material, sufficient to provide a drug release-free period of 7-9 hours. The three groups of beads may be encapsulated or compressed, in the presence of a cushioning agent, into a single pulsatile release tablet.

Alternatively, three groups of drug particles may be provided and coated as above, in lieu of the drug-coated lactose beads.

OTHER EMBODIMENTS

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A method of treating a human subject in need of amantadine therapy, comprising orally administering to the subject a pharmaceutical composition comprising amantadine, or a pharmaceutically acceptable salt thereof, and one or more excipients,

wherein at least one of the excipients modifies release of the amantadine, or pharmaceutically acceptable salt thereof, from the pharmaceutical composition,

wherein a dose of the composition provides a mean change in amantadine plasma concentration as a function of time (dC/dT) that is less than 40% of the dC/dT provided by a dose of the same quantity of an immediate release form of amantadine, wherein dC/dT is measured in a single dose human pharmacokinetic study in a defined time period of 0 to 4 hours after administration,

and wherein the amantadine, or pharmaceutically acceptable salt thereof, is administered once daily at a dose of 300 to 500 mg per day.

2. The method of claim **1**, wherein the human subject is suffering Parkinson's disease.

3. The method of claim **1**, wherein the controlled release amantadine has an in vitro dissolution profile in water of less than 20% in one hour, less than 30% in two hours, 40-80% in six hours, and greater than or equal to 80% in 12 hours as measured using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5 C.

4. The method of claim **3**, wherein at least 95% of the amantadine, or pharmaceutically acceptable salt thereof, is in an extended release form.

5. The method of claim 1, wherein the amantadine, or pharmaceutically acceptable salt thereof, is administered at a dose of 300 to 400 mg per day.

6. The method of claim 1, wherein the amantadine, or pharmaceutically acceptable salt thereof, is administered at a dose of 400 to 500 mg per day.

7. A method of reducing the incidence of a treatment-induced debilitating side-effects in a human subject being treated for a CNS-related condition, comprising orally administering to the subject a pharmaceutical composition consisting essentially of amantadine, or a pharmaceutically acceptable salt thereof, and one or more excipients,

wherein at least one of the excipients modifies release of the amantadine, or pharmaceutically acceptable salt thereof, from the pharmaceutical composition,

wherein a dose of the composition provides a mean change in amantadine plasma concentration provided as a function of time (dC/dT) that is less than 40% of the change in amantadine plasma concentration provided by a dose of the same quantity of an immediate release form of amantadine, wherein the dC/dT is measured in a single dose human pharmacokinetic study in a defined time period of 0 to 4 hours after administration,

and wherein the amantadine, or a pharmaceutically acceptable salt thereof, is administered once daily at a dose of 300 to 500 mg per day.

8. The method of claim 7, wherein the human subject is suffering Parkinson's disease.

9. The method of claim 7, wherein the controlled release amantadine has an in vitro dissolution profile in water of less than 20% in one hour, less than 30% in two hours, 40-80% in six hours, and greater than or equal to 80% in 12 hours as measured using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5 C.

10. The method of claim 7, wherein at least 95% of the amantadine, or pharmaceutically acceptable salt thereof, is in an extended release form.

11. The method of claim 7, wherein at least 95% of the amantadine, or pharmaceutically acceptable salt thereof, is administered at a dose of 300 to 400 mg per day.

12. The method of claim 7, wherein the amantadine, or pharmaceutically acceptable salt thereof, is administered at a dose of 400 to 500 mg per day.

13. The method of claim 1, wherein the human subject has a condition associated with Parkinson's disease selected from the group consisting of dementia, dyskinesia, dystonia, depression, fatigue, and other neuropsychiatric complications of Parkinson's disease.

14. The method of claim 8, wherein the human subject has a condition associated with Parkinson's disease selected from the group consisting of dementia, dyskinesia, dystonia, depression, fatigue, and other neuropsychiatric complications of Parkinson's disease.

* * * * *

EXHIBIT C

US008889740B1

(12) **United States Patent**
Went et al.

(10) **Patent No.: US 8,889,740 B1**
(45) **Date of Patent: *Nov. 18, 2014**

(54) **COMPOSITION AND METHOD FOR TREATING NEUROLOGICAL DISEASE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

(63) Continuation of application No. 14/328,440, filed on Jul. 10, 2014, which is a continuation of application No. 13/958,153, filed on Aug. 2, 2013, now Pat. No. 8,796,337, which is a continuation of application No. 13/756,275, filed on Jan. 31, 2013, now abandoned, which is a continuation of application No. 11/286,448, filed on Nov. 23, 2005, now Pat. No. 8,389,578.

(60) Provisional application No. 60/631,095, filed on Nov. 24, 2004.

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A61K 31/195	(2006.01)
A61K 9/00	(2006.01)
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USPC **514/565**; 514/656

(58) **Field of Classification Search**
USPC 514/565, 656
See application file for complete search history.

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(57) **ABSTRACT**

Disclosed are compositions comprising amantadine, or a pharmaceutically acceptable salt thereof, and one or more excipients, wherein at least one of the excipients modifies release of amantadine. Methods of administering the same are also provided.

9 Claims, 7 Drawing Sheets

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Figure 1: Simulated Dissolution for TID Amantadine IR & SR

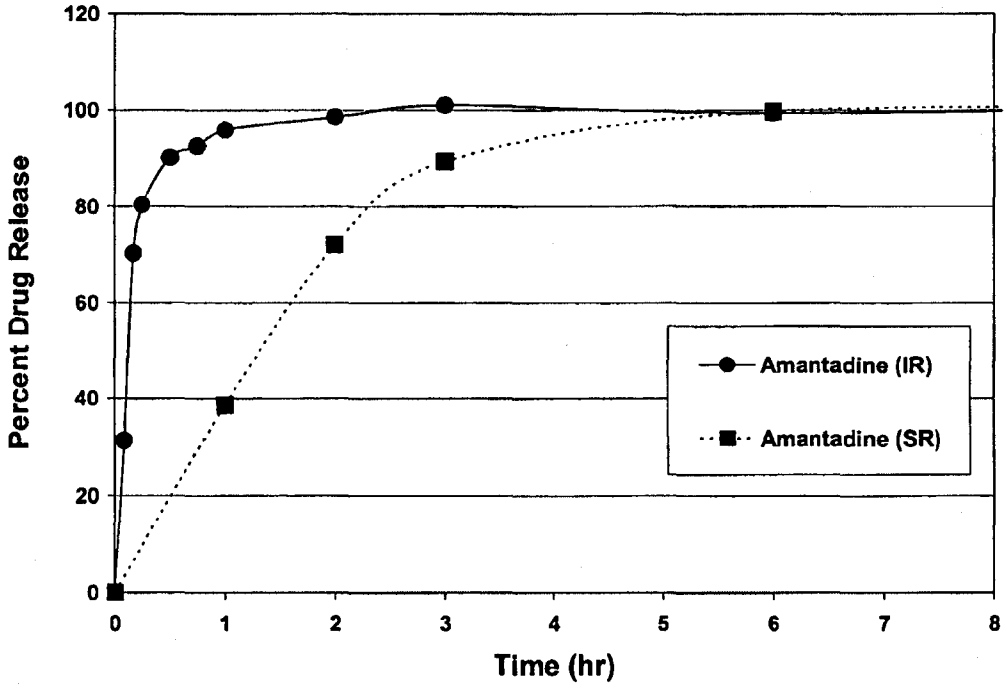


Figure 2: Simulated Plasma Concentration for TID Amantadine IR & SR over 120hrs.

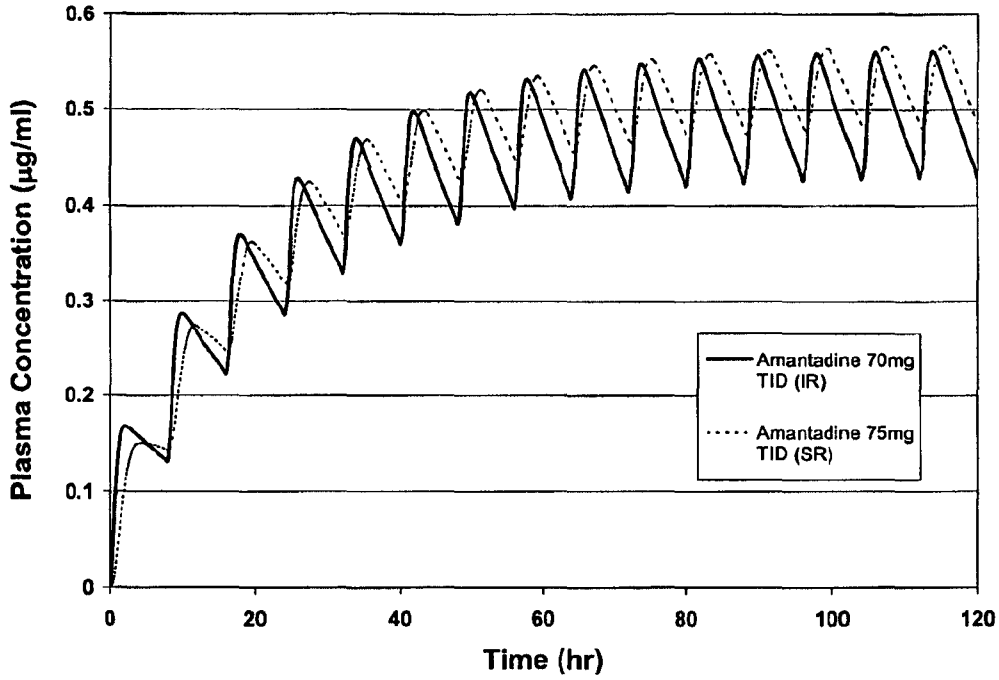


Figure 3: Simulated Plasma Concentration for TID Levodopa/Carbidopa/Amantadine (IR, IR, IR) over 24hrs

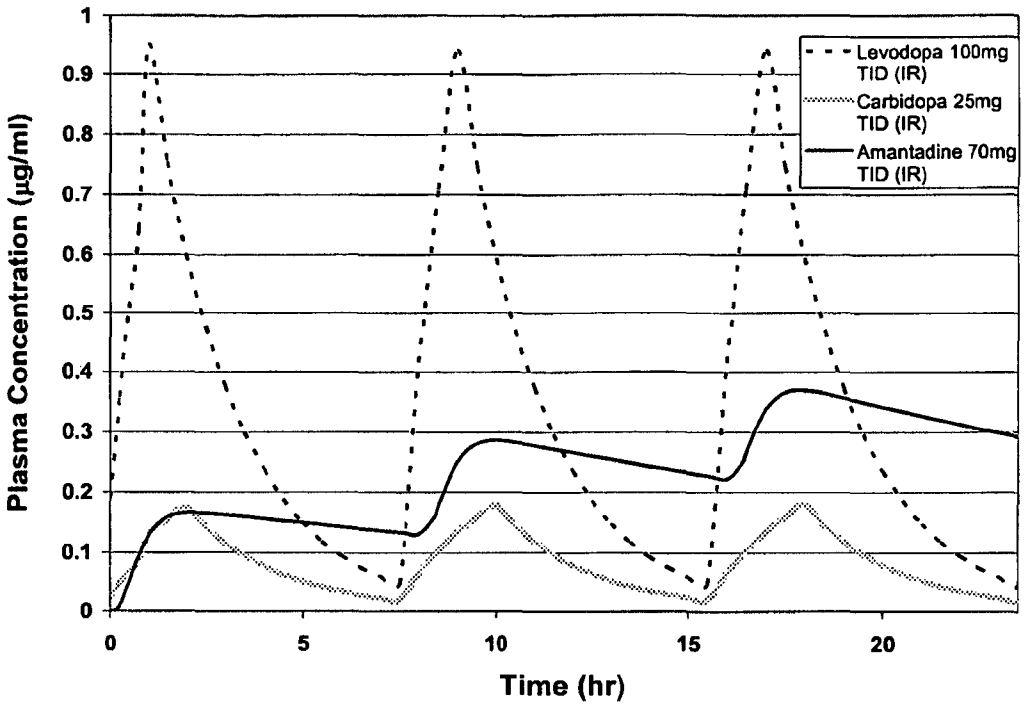


Figure 4: Simulated Plasma Concentration for TID Levodopa/Carbidopa/Amantadine (IR, IR, SR) over 24hrs

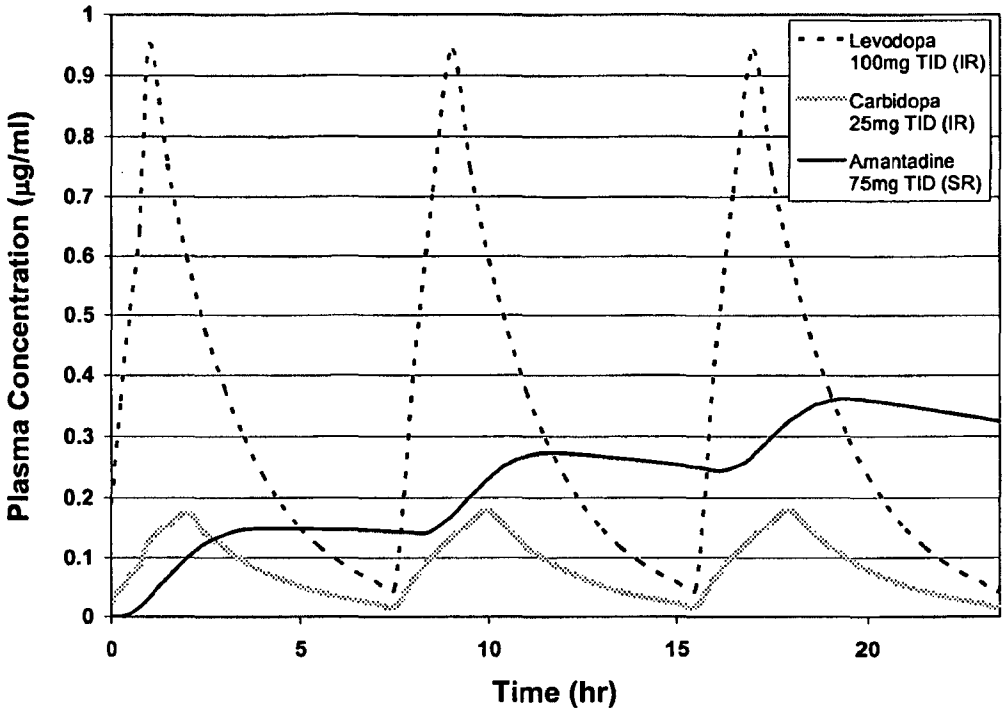


FIGURE 5

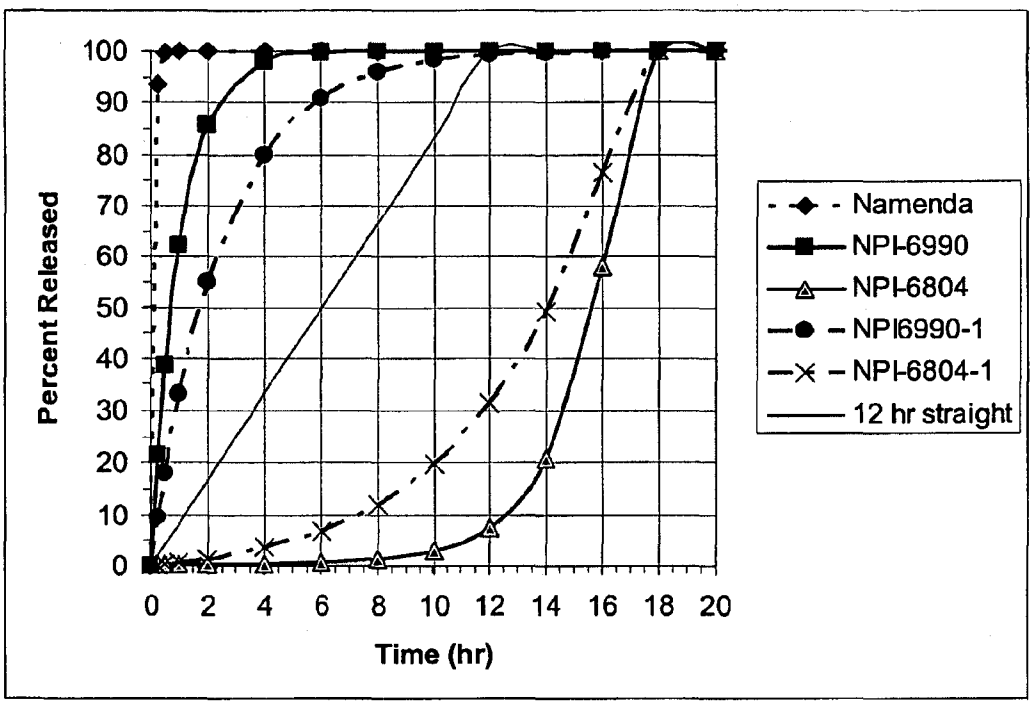

Percent Released
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20
Time (hr)
Namenda
NPI-6990
NPI-6804
NPI6990-1
NPI-6804-1
12 hr straight

Figure 6: Memantine, Levodopa and Carbidopa Human Pharmacokinetics

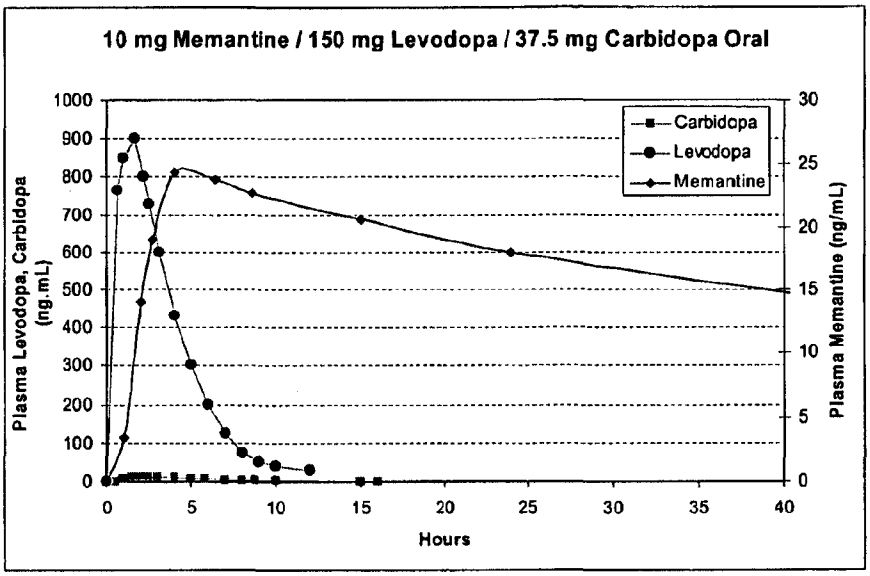
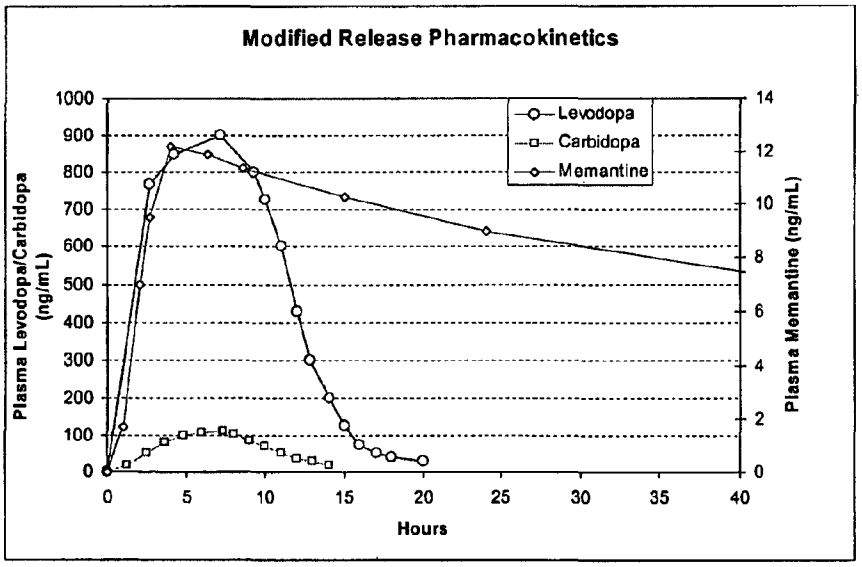


Figure 7: Target Pharmacokinetics



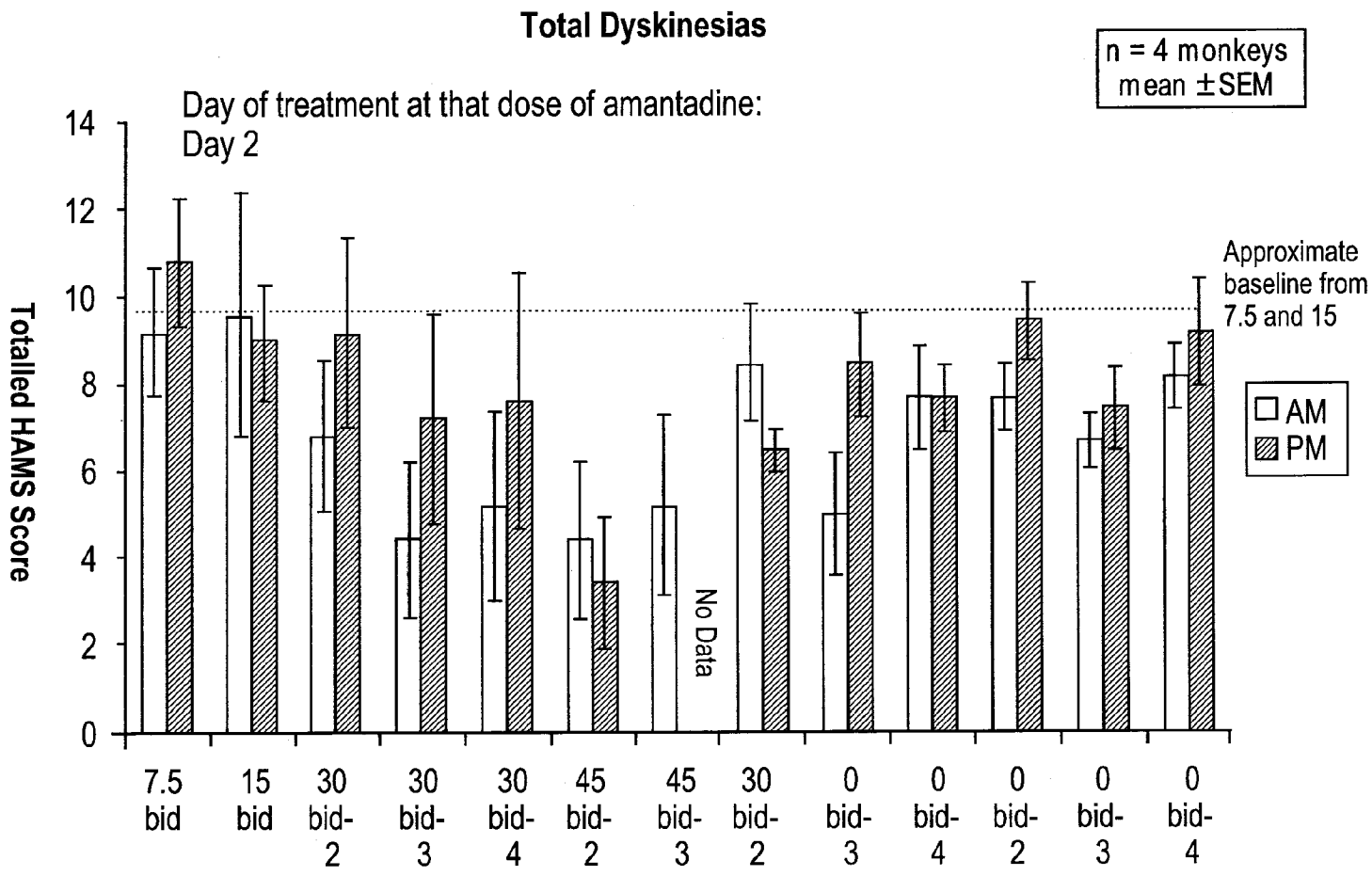

Total Dyskinesias
n = 4 monkeys
mean ±SEM
Day of treatment at that dose of amantadine:
Day 2
Totalled HAMS Score
14
12
10
8
6
4
2
0
Approximate baseline from 7.5 and 15
AM
PM
No Data
7.5 bid
15 bid
30 bid-2
30 bid-3
30 bid-4
45 bid-2
45 bid-3
30 bid-2
0 bid-3
0 bid-4
0 bid-2
0 bid-3
0 bid-4

Figure 8

COMPOSITION AND METHOD FOR TREATING NEUROLOGICAL DISEASE

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/328,440, filed Jul. 10, 2014, which is a continuation of U.S. patent application Ser. No. 13/958,153, filed Aug. 2, 2013, which is a continuation of U.S. patent application Ser. No. 13/756,275, filed Jan. 31, 2013, now abandoned, which is a continuation application of U.S. patent application Ser. No. 11/286,448, filed on Nov. 23, 2005, now U.S. Pat. No. 8,389,578, which claims priority to U.S. Provisional Application No. 60/631,095 filed on Nov. 24, 2004, all of which applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

This invention relates to compositions and methods for treating neurological diseases, such as Parkinson's disease.

BACKGROUND OF THE INVENTION

Parkinson's disease (PD) is a progressive, degenerative neurologic disorder which usually occurs in late mid-life. PD is clinically characterized by bradykinesia, tremor, and rigidity. Bradykinesia is characterized by a slowness in movement, slowing the pace of such routine activities as walking and eating. Tremor is a shakiness that generally affects limbs that are not otherwise in motion. For those PD-patients diagnosed at a relatively young age, tremor is reported as the most disabling symptom. Older patients face their greatest challenge in walking or keeping their balance. Rigidity is caused by the inability of muscles to relax as opposing muscle groups contract, causing tension which can produce aches and pains in the back, neck, shoulders, temples, or chest.

PD predominantly affects the substantia nigra (SNc) dopamine (DA) neurons and is therefore associated with a decrease in striatal DA content. Because dopamine does not cross the blood-brain barrier, PD patients may be administered a precursor, levodopa, that does cross the blood-brain barrier where it is metabolized to dopamine. Levodopa therapy is intended to compensate for reduced dopamine levels and is a widely prescribed therapeutic agent for patients with Parkinson's disease. Chronic treatment with levodopa however, is associated with various debilitating side-effects such as dyskinesia.

Since currently available drugs containing levodopa are associated with debilitating side effects, better therapies are needed for the management of PD.

SUMMARY OF THE INVENTION

In general, the present invention provides methods and compositions for treating and preventing CNS-related conditions, such as Parkinson's disease or other Parkinson's-like diseases or conditions, by administering to a subject in need thereof a combination that includes an N-Methyl-D-Aspartate receptor (NMDAr) antagonist and levodopa. Exemplary NMDAr antagonists include the aminoadamantanes, such as memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1-aminoethyl)adamantane), or amantadine (1-amino-adamantane) as well as others described below. Because levodopa is metabolized before crossing the blood-brain barrier and has a short half-life in the circulatory system, it is typically administered in conjunction with a dopa-

decarboxylase inhibitor. Examples of dopa-decarboxylase inhibitors include carbidopa, 3-hydroxy-benzylhydrazinedihydrochloride (NSD-1015), and benseraxide hydrochloride. The combination may further include a catechol-0-methyltransferase (COMT) inhibitor including, for example, talcapone and entacapone. As used herein, levodopa/carbidopa shall mean levodopa alone or in combination with a dopa-decarboxylase inhibitor such as carbidopa. Desirably, the levodopa/carbidopa is in an immediate release formulation and the NMDA receptor antagonist is in an extended release formulation. One preferred embodiment of the invention involves the combination of amantadine and levodopa/carbidopa. Desirably, amantadine is provided in an extended release formulation and levodopa/carbidopa is provided as an immediate release formulation. By combining an NMDAr antagonist (e.g., amantadine) with the second agents described herein (e.g., levodopa/carbidopa), this invention provides an effective pharmaceutical composition for treating neurological diseases such as Parkinson's disease or other Parkinson's-like diseases or conditions. The administration of this combination is postulated to maintain or enhance the efficacy of levodopa while significantly reducing its dyskinesia side effects.

The combinations described herein provide complementary benefits associated with the NMDAr antagonist or levodopa/carbidopa individually, while minimizing difficulties previously presented when each component is used separately in a patient. For example, amantadine dosing is limited by neurotoxicity that is likely associated with its short Tmax. By extending the release of amantadine, a higher effective dose can be maintained providing both dyskinesia relief and a reduction in the amount of levodopa required for treatment of the disease symptoms. Given the inherent toxicity of levodopa, such a levodopa sparing combination will result in a decline in both the dyskinesia and overall disease.

Accordingly, the pharmaceutical compositions described herein are administered so as to deliver to a subject, an amount of an NMDAr antagonist, levodopa/carbidopa or both agents that is high enough to treat symptoms or damaging effects of an underlying disease while avoiding undesirable side effects. These compositions may be employed to administer the NMDAr antagonist, the levodopa/carbidopa, or both agents at a lower frequency than presently employed, improving patient compliance, adherence, and caregiver convenience. These compositions are particularly useful as they provide the NMDAr antagonist, levodopa/carbidopa, or both agents, at a therapeutically effective amount from the onset of therapy further improving patient compliance and adherence and enable the achievement of a therapeutically effective steady-state concentration of either or both agents of the combination in a shorter period of time resulting in an earlier indication of effectiveness and increasing the utility of these therapeutic agents for diseases and conditions where time is of the essence. Also provided are methods for making and using such compositions.

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a controlled or extended release form with or without an immediate release component in order to maximize the therapeutic benefit of such agents, while reducing unwanted side effects. In preferred embodiments for oral administration, levodopa/carbidopa is provided as an immediate-release formulation.

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be administered in an amount similar to that typically administered to subjects. Preferably, the amount of the NMDAr antagonist may be administered in an amount greater than or less than the amount that is typically admin-

istered to subjects while the levodopa/carbidopa is provided at a lower dose than normally used. For example, the amount of amantadine required to positively affect the patient response (inclusive of adverse effects) may be 300, 400, 500, 600 mg per day rather than the typical 200-300 mg per day administered for presently approved indications i.e. without the improved formulation described herein, while the levodopa, and optionally the carbidopa, can be reduced independently by 10%, 20%, 30%, 40%, 50%, 60%, 70% or up to 80% of what is currently required in the absence of the NMDAr antagonist.

Optionally, lower or reduced amounts of both the NMDAr antagonist and the levodopa/carbidopa are used in a unit dose relative to the amount of each agent when administered independently. The present invention therefore features formulations of combinations directed to dose optimization or release modification to reduce adverse effects associated with separate administration of each agent. The combination of the NMDAr antagonist and the levodopa/carbidopa may result in an additive or synergistic response, and using the unique formulations described herein, the goal of minimizing the levodopa burden is achieved. Preferably, the NMDAr antagonist and the levodopa/carbidopa are provided in a unit dosage form.

The compositions and methods of the invention are particularly useful for the treatment of Parkinson's disease or conditions associated with Parkinson's disease. These conditions include dementia, dyskinesia, dystonia, depression, fatigue and other neuropsychiatric complications of Parkinson's disease.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present Specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. All parts and percentages are by weight unless otherwise specified.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a graph showing the dissolution profiles for an immediate and sustained release formulation of amantadine. The sustained release formulation exhibits a dC/dT during the initial phase that is about 10% of that for the immediate release formulation.

FIG. **2** is a graph showing the amantadine plasma concentration over a period of 5 days, as predicted by Gastro-Plus software package v.4.0.2, following the administration of either 70 mg amantadine in an immediate release formulation t.i.d. or 75 mg amantadine in a sustained release formulation t.i.d. The sustained release formulation peaks are similar in height to the immediate release formulation even with a higher administered dose and the diurnal variation is substantially reduced.

FIG. **3** is a graph showing the plasma profiles simulated using Gastro-Plus for t.i.d. administration of amantadine (70 mg), levodopa (100 mg), and carbidopa (25 mg), all in an immediate release form.

FIG. **4** is a graph showing the plasma profiles simulated using Gastro-Plus for t.i.d. administration of amantadine (75 mg), levodopa (100 mg), and carbidopa (25 mg), where the amantadine is in a sustained release form and the levodopa and carbidopa are in an immediate release form.

FIG. **5** is a graph representing dissolution profiles for various aminoadamantane formulations including an immediate release form of the NMDAr antagonist memantine (Namenda).

FIG. **6** is a graphical representation of plasma release profiles in a human of memantine, levodopa, and carbidopa when memantine is administered separately from levodopa and carbidopa.

FIG. **7** is a graphical representation of plasma release profiles in a human of memantine, levodopa, and carbidopa when memantine, levodopa, and carbidopa are administered as part of a single controlled-release pharmaceutical composition.

FIG. **8** is a bar graph showing the effects on a primate (squirrel monkey) treated with a combination of levodopa/carbidopa and amantadine.

DETAILED DESCRIPTION OF THE INVENTION

In general, the present invention features pharmaceutical compositions that contain therapeutically effective levels of an NMDAr antagonist and levodopa/carbidopa and, optionally, a pharmaceutical carrier. Preferably the compositions are formulated for modified or extended release to provide a serum or plasma concentration of the NMDAr antagonist over a desired time period that is high enough to be therapeutically effective but at a rate low enough so as to avoid adverse events associated with the NMDAr antagonist. Control of drug release is particularly desirable for reducing and delaying the peak plasma level while maintaining the extent of drug bioavailability. Therapeutic levels are therefore achieved while minimizing debilitating side-effects that are usually associated with immediate release formulations. Furthermore, as a result of the delay in the time to obtain peak serum or plasma level and the extended period of time at the therapeutically effective serum or plasma level, the dosage frequency is reduced to, for example, once or twice daily dosage, thereby improving patient compliance and adherence. For example, side effects including psychosis and cognitive deficits associated with the administration of NMDAr antagonists may be lessened in severity and frequency through the use of controlled-release methods that shift the Tmax to longer times, thereby reducing the dC/dT of the drug. Reducing the dC/dT of the drug not only increases Tmax, but also reduces the drug concentration at Tmax and reduces the Cmax/Cmean ratio providing a more constant amount of drug to the subject being treated over a given period of time, enabling increased dosages for appropriate indications.

In addition, the present invention encompasses optimal ratios of NMDAr and levodopa/carbidopa, designed to not only treat the dyskinesia associated with levodopa, but also take advantage of the additivity and synergy between these drug classes. For example, the level of levodopa required to treat the disease symptoms can unexpectedly be reduced by up to 50% by the addition of 400 mg/day of amantadine.

Making NMDAr Antagonist Controlled Release Formulations

A pharmaceutical composition according to the invention is prepared by combining a desired NMDAr antagonist or antagonists with one or more additional ingredients that, when administered to a subject, causes the NMDAr antagonist to be released at a targeted rate for a specified period of time. A release profile, i.e., the extent of release of the NMDAr antagonist over a desired time, can be conveniently determined for a given time by measuring the release using a USP dissolution apparatus under controlled conditions. Pre-

ferred release profiles are those which slow the rate of uptake of the NMDAr antagonist in the neural fluids while providing therapeutically effective levels of the NMDAr antagonist. One of ordinary skill in the art can prepare combinations with a desired release profile using the NMDAr antagonists and formulation methods described below.

NMDAr Antagonists

Any NMDAr antagonist can be used in the methods and compositions of the invention, particularly those that are non-toxic when used in the compositions of the invention. The term "nontoxic" is used in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to humans or, in keeping with established regulatory criteria and practice, is susceptible to approval by the FDA or similar regulatory agency for any country for administration to humans or animals.

The term "NMDAr antagonist", as used herein, includes any amino-adamantane compound including, for example, memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1-aminoethyl)adamantane), amantadine (1-amino-adamantane), as well as pharmaceutically acceptable salts thereof. Memantine is described, for example, in U.S. Pat. Nos. 3,391,142, 5,891,885, 5,919,826, and 6,187,338. Amantadine is described, for example, in U.S. Pat. Nos. 3,152,180, 5,891,885, 5,919,826, and 6,187,338. Additional aminoadamantane compounds are described, for example, in U.S. Pat. Nos. 4,346,112, 5,061,703, 5,334,618, 6,444,702, 6,620,845, and 6,662,845. All of these patents are hereby incorporated by reference.

Further NMDAr antagonists that may be employed include, for example, aminocylohexanes such as neramexane, ketamine, eliprodil, ifenprodil, dizocilpine, remacemide, iamotrigine, riluzole, aptiganel, phencyclidine, flupirtine, celfotel, felbamate, spermine, spermidine, levemopamil, dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and its metabolite, dextrorphan ((+)-3-hydroxy-N-methylmorphinan), a pharmaceutically acceptable salt, derivative, or ester thereof, or a metabolic precursor of any of the foregoing.

Optionally, the NMDAr antagonist in the instant invention is memantine and not amantadine or dextromethorphan.

Second Agents

In all foregoing aspects of the invention, the second agent is levodopa. When levodopa is in the combination, the combination preferably also includes a dopa-decarboxylase inhibitor. An example of a suitable dopa-decarboxylase inhibitor is carbidopa. Other dopa-decarboxylase inhibitors include, for example, 3-hydroxy-benzylhydrazinedihydrochloride (NSD-1015) and benseraxide hydrochloride. The combination may further include a catechol-O-methyltransferase (COMT) inhibitor including, for example, talcapone and entacapone.

Dosing, PK, & Toxicity

The NMDA receptor antagonist used in combination therapies are administered at a dosage of generally between about 1 and 5000 mg/day, between 1 and about 800 mg/day, or between 1 and 500 mg/day. For example, NMDA receptor antagonist agents may be administered at a dosage ranging between about 1 and about 500 mg/day, more preferably from about 10 to about 40, 50, 60, 70 or 80 mg/day, advantageously from about 10 to about 20 mg per day. Amantadine may be administered at a dose ranging from about 90, 100 mg/day to about 400, 500, 600, 700 or 800 mg/day, advantageously from about 100 to about 500, 600 mg per day. For example, the pharmaceutical composition may be formulated to provide memantine in an amount ranging between 1-200 mg/day, 1 and 80 mg/day, 2-80 mg/day, 10-80 mg/day, 10 and 80 mg/day, 10 and 70 mg/day, 10 and 60 mg/day, 10 and 50 mg/day, 10 and 40 mg/day, 5 and 65 mg/day, 5 and 40 mg/day, 15 and 45 mg/day, or 10 and 20 mg/day; dextromethorphan in an amount ranging between 1-5000 mg/day, 1-1000 mg/day, and 100-800 mg/day, or 200-500 mg/day. Pediatric doses will typically be lower than those determined for adults.

Table 1 shows exemplary pharmacokinetic properties (e.g., Tmax and T½) of memantine, amantadine, and rimantadine.

TABLE 1

Pharmacokinetics and Toxicity in humans for selected NIVIDAr antagonists

Compound	Human PK ($t_{1/2}$) (hours)	Tmax (hours)	Normal Dose	Dose Dependent Toxicity
Memantine	60	3	10-20 mg/day, starting at 5 mg	Dose escalation required, hallucination
Amantadine	15	3	100-300 mg/day, starting at 100 mg/day	Hallucination
Rimantadine	25	6	100-200 mg/day	Insomnia

When levodopa and carbidopa are both included in the composition, the levodopa dose ranges between 100 to 3000 mg per day, 75 mg and 2500 mg/day, 100-2000 mg/day, or 250 and 1000 mg/day divided for administration t.i.d. or more frequently. Carbidopa doses may range between the amounts of 1 to 1000 mg/day, 10 to 500 mg/day, and 25 to 100 mg/day. Optionally, the carbidopa is present in the combination at about 75%, 70%, 65%, 60%, 50%, 40%, 30%, 25%, 20%, and 10% of the mass of the levodopa. Alternatively, the amount of levodopa is less than 300% than the amount of carbidopa. For example, 75 mg of carbidopa (amount that is sufficient to extend the half-life of levodopa in the circulatory system) may be used in combination with 300 to 3000 mg of levodopa per day. The combination may contain a single dosage form comprising 30 to 200 mg amantadine, 30 to 250 mg levodopa, and 10 to 100 mg of carbidopa for t.i.d. or more frequent administration, including multiple dosage forms per administration.

As a result, the preferred dosage forms for optimized use are shown in Table 2 below, with their corresponding commercial equivalent.

Table 2. Dosage Forms with and without NMDAr Antagonist (Amount Per Unit Dose)

TABLE 2

Dosage forms with and without NMDAr antagonist (amount per unit dose)

Sinemet Compositions		Compositions of Present Invention		
Levodopa	Carbidopa	Levodopa	Carbidopa	Amantadine
100 mg IR*	25 mg IR	50-100 mg IR	25 mg IR	100-200 mg IR
100 mg IR	10 mg IR	50-100 mg IR	10 mg IR	50-100 mg IR
100 mg IR	25 mg IR	50-100 mg IR	25 mg IR	100-200 mg CR**
100 mg IR	10 mg IR	50-100 mg IR	10 mg IR	50-100 mg CR

*IR: immediate release

**CR: modified release

Excipients

"Pharmaceutically or Pharmacologically Acceptable" includes molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. "Pharmaceutically Acceptable Carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifun-

gal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. "Pharmaceutically Acceptable Salts" include acid addition salts and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

The preparation of pharmaceutical or pharmacological compositions is known to those of skill in the art in light of the present disclosure. General techniques for formulation and administration are found in "Remington: The Science and Practice of Pharmacy, Twentieth Edition," Lippincott Williams & Wilkins, Philadelphia, Pa. Tablets, capsules, pills, powders, granules, dragees, gels, slurries, ointments, solutions suppositories, injections, inhalants and aerosols are examples of such formulations.

By way of example, modified or extended release oral formulation can be prepared using additional methods known in the art. For example, a suitable extended release form of the either active pharmaceutical ingredient or both may be a matrix tablet or capsule composition. Suitable matrix forming materials include, for example, waxes (e.g., carnauba, bees wax, paraffin wax, ceresine, shellac wax, fatty acids, and fatty alcohols), oils, hardened oils or fats (e.g., hardened rapeseed oil, castor oil, beef tallow, palm oil, and soya bean oil), and polymers (e.g., hydroxypropyl cellulose, polyvinylpyrrolidone, hydroxypropyl methyl cellulose, and polyethylene glycol). Other suitable matrix tabletting materials are microcrystalline cellulose, powdered cellulose, hydroxypropyl cellulose, ethyl cellulose, with other carriers, and fillers. Tablets may also contain granulates, coated powders, or pellets. Tablets may also be multi-layered. Multi-layered tablets are especially preferred when the active ingredients have markedly different pharmacokinetic profiles. Optionally, the finished tablet may be coated or uncoated.

The coating composition typically contains an insoluble matrix polymer (approximately 15-85% by weight of the coating composition) and a water soluble material (e.g., approximately 15-85% by weight of the coating composition). Optionally an enteric polymer (approximately 1 to 99% by weight of the coating composition) may be used or included. Suitable water soluble materials include polymers such as polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials such as sugars (e.g., lactose, sucrose, fructose, mannitol and the like), salts (e.g., sodium chloride, potassium chloride and the like), organic acids (e.g., fumaric acid, succinic acid, lactic acid, and tartaric acid), and mixtures thereof. Suitable enteric polymers include hydroxypropyl methyl cellulose, acetate succinate, hydroxypropyl methyl cellulose, phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups.

The coating composition may be plasticised according to the properties of the coating blend such as the glass transition temperature of the main component or mixture of components or the solvent used for applying the coating compositions. Suitable plasticisers may be added from 0 to 50% by weight of the coating composition and include, for example, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, acetylated citrate esters, dibutylsebacate, and castor oil. If desired, the coating composition may include a filler. The amount of the filler may be I % to approximately 99% by weight based on the total weight of the coating composition and may be an insoluble material such as silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, MCC, or polacrilin potassium.

The coating composition may be applied as a solution or latex in organic solvents or aqueous solvents or mixtures thereof. If solutions are applied, the solvent may be present in amounts from approximate by 25-99% by weight based on the total weight of dissolved solids. Suitable solvents are water, lower alcohol, lower chlorinated hydrocarbons, ketones, or mixtures thereof. If latexes are applied, the solvent is present in amounts from approximately 25-97% by weight based on the quantity of polymeric material in the latex. The solvent may be predominantly water.

The NMDAr antagonist may be formulated using any of the following excipients or combinations thereof.

Excipient name	Chemical name	Function
Avicel PH102	Microcrystalline Cellulose	Filler, binder, wicking, disintegrant
Avicel PH101	Microcrystalline Cellulose	Filler, binder, disintegrant
Eudragit RS-30D	Polymethacrylate Poly(ethyl acrylate, nethyl methacrylate, timethylammonioethyl methacrylate chloride) 1:2:0.1	Film former, tablet binder, tablet diluent; Rate controlling polymer for controlled release
Methocel K100M Premium CR	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Methocel K100M	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Magnesium Stearate	Magnesium Stearate	Lubricant
Talc	Talc	Dissolution control; anti-adherent, glidant
Triethyl Citrate	Triethyl Citrate	Plasticizer
Methocel E5	Hydroxypropyl methylcellulose	Film-former
Opadry ®	Hydroxypropyl methylcellulose	One-step customized coating system which combines polymer, plasticizer and, if desired, pigment in a dry concentrate.
Surelease ®	Aqueous Ethylcellulose Dispersion	Film-forming polymer; plasticizer and stabilizers. Rate controlling polymer coating.

The pharmaceutical composition described herein may also include a carrier such as a solvent, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents. The use of such media and agents for pharmaceutically active substances is well known in the art. Pharmaceutically acceptable salts can also be used in the composition, for example, mineral salts such as hydrochlorides, hydrobromides, phosphates, or sulfates, as well as the salts of organic acids such as acetates, proprionates, malonates, or benzoates. The composition may also contain liquids, such as water, saline, glycerol, and ethanol, as well as substances such as wetting agents, emulsifying agents, or pH buffering agents. Liposomes, such as those described in U.S. Pat. No. 5,422,120, WO 95/13796, WO 91/14445, or EP 524,968 B1, may also be used as a carrier.

Methods for Preparing Modified or Extended Release Formulations

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a controlled or extended release form with or without an immediate release component in order to maximize the therapeutic benefit of such agents, while reducing unwanted side effects. In the absence of modified release components (referred to herein as controlled, extended, or delayed release components), the NMDAr antagonist, levodopa/carbidopa, or both is released and transported into the body fluids over a period of minutes to several hours. The combination described herein however, may contain an NMDAr antagonist and a sustained release component, such as a coated sustained release matrix, a sustained release matrix, or a sustained release bead matrix. In one example, in addition to levodopa/carbidopa, amantadine (e.g., 50-400 mg) is formulated without an immediate release component using a polymer matrix (e.g., Eudragit), Hydroxypropyl methyl cellulose (HPMC) and a polymer coating (e.g., Eudragit). Such formulations are compressed into solid tablets or granules and coated with a controlled release material such as Opadry® or Surelease®. Levodopa/carbidopa may also be formulated as a sustained release formulation; in most cases, however, this will not be optimal.

Suitable methods for preparing the compositions described herein in which the NMDAr antagonist is provided in modified or extended release-formulations include those described in U.S. Pat. No. 4,606,909 (hereby incorporated by reference). This reference describes a controlled release multiple unit formulation in which a multiplicity of individually coated or microencapsulated units are made available upon disintegration of the formulation (e.g., pill or tablet) in the stomach of the subject (see, for example, column 3, line 26 through column 5, line 10 and column 6, line 29 through column 9, line 16). Each of these individually coated or microencapsulated units contains cross-sectionally substantially homogenous cores containing particles of a sparingly soluble active substance, the cores being coated with a coating that is substantially resistant to gastric conditions but which is erodable under the conditions prevailing in the gastrointestinal tract.

The composition of the invention may alternatively be formulated using the methods disclosed in U.S. Pat. No. 4,769,027, for example. Accordingly, extended release formulations involve prills of pharmaceutically acceptable material (e.g., sugar/starch, salts, and waxes) may be coated with a water permeable polymeric matrix containing an NMDAr antagonist and next overcoated with a water-permeable film containing dispersed within it a water soluble particulate pore forming material.

The NMDAr antagonist composition may additionally be prepared as described in U.S. Pat. No. 4,897,268, involving a biocompatible, biodegradable microcapsule delivery system. Thus, the NMDAr antagonist may be formulated as a composition containing a blend of free-flowing spherical particles obtained by individually microencapsulating quantities of memantine, for example, in different copolymer excipients which biodegrade at different rates, therefore releasing memantine into the circulation at a predetermined rates. A quantity of these particles may be of such a copolymer excipient that the core active ingredient is released quickly after administration, and thereby delivers the active ingredient for an initial period. A second quantity of the particles is of such type excipient that delivery of the encapsulated ingredient begins as the first quantity's delivery begins to decline. A third quantity of ingredient may be encapsulated with a still different excipient which results in delivery beginning as the delivery of the second quantity beings to decline. The rate of delivery may be altered, for example, by varying the lactide/glycolide ratio in a poly(D,L-lactide-co-glycolide) encapsulation. Other polymers that may be used include polyacetal polymers, polyorthoesters, polyesteramides, polycaprolactone and copolymers thereof, polycarbonates, polyhydroxybuterate and copolymers thereof, polymaleamides, copolyoxalates and polysaccharides.

Alternatively, the composition may be prepared as described in U.S. Pat. No. 5,395,626, which features a multilayered controlled release pharmaceutical dosage form. The dosage form contains a plurality of coated particles wherein each has multiple layers about a core containing an NMDAr antagonist whereby the drug containing core and at least one other layer of drug active is overcoated with a controlled release barrier layer therefore providing at least two controlled releasing layers of a water soluble drug from the multilayered coated particle

Release Profile

The compositions described herein are formulated such that the NMDAr antagonist, levodopa/carbidopa, or both agents have an in vitro dissolution profile that is equal to or slower than that for an immediate release formulation. As used herein, the immediate release (IR) formulation for memantine means the present commercially available 5 mg and 10 mg tablets (i.e., Namenda from Forest Laboratories, Inc. or formulations having substantially the same release profiles as Namenda); and the immediate release (IR) formulation of amantadine means the present commercially available 100 mg tablets (i.e., Symmetrel from Endo Pharmaceuticals, Inc. or formulations having substantially the same release profiles as Symmetrel); and the immediate release (IR) formulation of levodopa/carbidopa means the present commercially available 25 mg/100 mg, 10 mg/100 mg, 25 mg/250 mg tablets of carbidopa/levodopa (i.e., Sinemet from Merck & Co. Inc. or formulations having substantially the same release profiles as Sinemet). These compositions may comprise immediate release, sustained or extended release, or delayed release components, or may include combinations of same to produce release profiles such that the fraction of NMDAr antagonist or levodopa/carbidopa released is greater or equal to $0.01(0.297+0.0153*e^{(0.515*t)})$ and less than or equal to $1-e^{(-10.9*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C., in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist or levodopa/carbidopa released is less than 93% in 15 minutes and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1N HCl) dissolution medium. Optionally, the fraction of released NMDAr antagonist or levodopa/carbidopa is greater than or equal to $0.01(0.297+0.0153*e^{(0.515*t)})$, and less than or equal to $1-e^{(-0.972*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C., in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist or levodopa/carbidopa that is released may range between 0.1%-62% in one hour, 0.2%-86% in two hours, 0.6%-100% in six hours, 2.9%-100% in 10 hours, and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1 N HCl) dissolution medium. Optionally, the NMDA receptor antagonist has a release profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 70% or greater

(e.g., 70%-90%) in 10 hours, and 90% or greater (e.g., 90-95%) in 12 hours as measured in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1 N HCl) dissolution medium. For example, a formulation containing amantadine may have a release profile ranging between 0-60% or 0.1-20% in one hour, 0-86% or 5-30% at two hours, 0.6-100% or 40-80% at six hours, 3-100% or 50% or more (e.g., 50-90%) at ten hours, and 7.7-100% at twelve hours in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1 N HCl) dissolution medium. In one embodiment, the NMDAr antagonist, the levodopa/carbidopa, or both agents have an in vitro dissolution profile of less than 25%, 15%, 10%, or 5% in fifteen minutes; 50%, 30%, 25%, 20%, 15%, or 10% in 30 minutes and more than 60%, 65% 70%, 75%, 80%, 85%, 90%, 95% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water. Desirably, the NMDAr antagonist, the levodopa/carbidopa, or both agents has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% in a dissolution media having a pH of 1.2 at 10 hours. It is important to note that the dissolution profile for the NMDAr antagonist may be different than the release profile for levodopa/carbidopa. In a preferred embodiment, the levodopa/carbidopa release profile is equal to or similar to that for an immediate release formulation and the release profile for the NMDAr antagonist is controlled to provide a dissolution profile of less than 30% in one hour, less than 50% in two hours, and greater than 95% in twelve hours using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water.

Desirably, the compositions described herein have an in vitro profile that is substantially identical to the dissolution profile shown in FIG. **5** and, upon administration to a subject at a substantially constant daily dose, achieves a serum concentration profile that is substantially identical to that shown in FIGS. **2** and **4**.

As described above, the NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a modified or extended release form. Modified or extended drug release is generally controlled either by diffusion through a coating or matrix or by erosion of a coating or matrix by a process dependent on, for example, enzymes or pH. The NMDAr antagonist or the levodopa/carbidopa may be formulated for modified or extended release as described herein or using standard techniques in the art. In one example, at least 50%, 75%, 90%, 95%, 96%, 97%, 98%, 99%, or even in excess of 99% of the NMDAr antagonist or the levodopa/carbidopa is provided in an extended release dosage form. In a preferred embodiment, the levodopa/carbidopa is provided in an immediate release formulation and the NMDAr antagonist is in either an immediate or modified release form.

The composition described herein is formulated such the NMDAr antagonist or levodopa/carbidopa has an in vitro dissolution profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 50%-90% in 10 hours, and 90%-95% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. using 0.1N HCl as a dissolution medium. Alternatively, the NMDAr antagonist has an in vitro dissolution profile in a solution with a neutral pH (e.g., water) that is substantially the same as its dissolution profile in an acidic dissolution medium. Thus, the NMDAr antagonist may be released in both dissolution media at the following rate: between 0.1-20% in one hour, 5-30% in two hours, 40-80% in six hours, 70-90% in 10 hours, and 90%-95% in 12 hours as obtained using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. In one embodiment, the NMDAr antagonist has an in vitro dissolution profile of less than 15%, 10%, or 5% in fifteen minutes, 25%, 20%, 15%, or 10% in 30 minutes, and more than 60% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water. Desirably, the NMDAr antagonist has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% at 10 hours in a dissolution medium having a pH of 1.2.

Initial Rate In Vivo, Delayed Tmax

As used herein, "C" refers to the concentration of an active pharmaceutical ingredient in a biological sample, such as a patient sample (e.g. blood, serum, and cerebrospinal fluid). The time required to reach the maximal concentration ("Cmax") in a particular patient sample type is referred to as the "Tmax". The change in concentration is termed "dC" and the change over a prescribed time is "dC/dT".

The NMDAr antagonist or levodopa/carbidopa is provided as a sustained release formulation that may or may not contain an immediate release formulation. If desired, the NMDAr antagonist may be formulated so that it is released at a rate that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In addition, the NMDAr antagonist levodopa/carbidopa may be provided such that it is released at a rate resulting in a Cmax/Cmean of approximately 2 or less for approximately 2 hours to at least 8 hours after the NMDAr antagonist is introduced into a subject. Optionally, the sustained release formulations exhibit plasma concentration curves having initial (e.g., from 0, 1, 2 hours after administration to 4, 6, 8 hours after administration) slopes less than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist. The precise slope for a given individual will vary according to the NMDAr antagonist being used or other factors, including whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose. The determination of initial slopes of plasma concentration is described, for example, by U.S. Pat. No. 6,913,768, hereby incorporated by reference.

Desirably, the NMDAr antagonist or the levodopa/carbidopa is released into a subject sample at a slower rate than observed for an immediate release (IR) formulation of the same quantity of the antagonist, such that the rate of change in the biological sample measured as the dC/dT over a defined period within the period of 0 to Tmax for the IR formulation (e.g., Namenda, a commercially available IR formulation of memantine). In some embodiments, the dC/dT rate is less than about 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. In some embodiments, the dC/dT rate is less than about 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. Similarly, the rate of release of the NMDAr antagonist or the levodopa/carbidopa from the present invention as measured in dissolution studies is less than 80%, 70%, 60% 50%, 40%, 30%, 20%, or 10% of the rate for an IR formulation of the same NMDAr antagonist or levodopa/carbidopa over the first 1, 2, 4, 6, 8, 10, or 12 hours.

In a preferred embodiment, the dosage form is provided in a non-dose escalating, three times per day (t.i.d.) form. In preferred embodiments, the concentration ramp (or Tmax effect) may be reduced so that the change in concentration as a function of time (dC/dT) is altered to reduce or eliminate the

need to dose escalate the NMDAr antagonist. A reduction in dC/dT may be accomplished, for example, by increasing the Tmax in a relatively proportional manner. Accordingly, a two-fold increase in the Tmax value may reduce dC/dT by approximately a factor of 2. Thus, the NMDAr antagonist may be provided so that it is released at a rate that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In certain embodiments, this is accomplished by releasing less than 30%, 50%, 75%, 90%, or 95% of the NMDAr antagonist into the circulatory or neural system within one hour of such administration.

The concentration ramp for levodopa/carbidopa may also be reduced, however such changes will not be preferred in most oral formulations due to the marked reduction in absorption of levodopa/carbidopa after it passes the duodenal region of the gastrointestinal tract.

Optionally, the modified release formulations exhibit plasma concentration curves having initial (e.g., from-2 hours after administration to 4 hours after administration) slopes less-than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist or levodopa/carbidopa. The precise slope for a given individual will vary according to the NMDAr antagonist or levodopa/carbidopa being used, the quantity delivered, or other factors, including, for some active pharmaceutical agents, whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose.

Using the sustained release formulations or administration methods described herein, the NMDAr antagonist reaches a therapeutically effective steady state plasma concentration in a subject within the course of the first two, three, five, seven, nine, ten, twelve, fifteen, or twenty days of administration. For example, the formulations described herein, when administered at a substantially constant daily dose (e.g., at a dose ranging between 200 mg and 800 mg, preferably between 200 mg and 600 mg, and more preferably between 200 mg and 400 mg per day) may reach a steady state plasma concentration in approximately 70%, 60%, 50%, 40%, 30%, or less of the time required to reach such plasma concentration when using a dose escalating regimen.

Dosing Frequency and Dose Escalation

According to the present invention, a subject (e.g., human) having or at risk of having such conditions is administered any of the compositions described herein (e.g., three times per day (t.i.d.), twice per day (b.i.d.), or once per day (q.d.)). While immediate release formulations of NMDAr antagonists are typically administered in a dose-escalating fashion, the compositions described herein may be essentially administered at a constant, therapeutically-effective dose from the onset of therapy. For example, a composition containing a sustained release formulation of amantadine may be administered three times per day, twice per day, or once per day in a unit dose comprising a total daily amantadine dose of 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, or 800 mg. In embodiments comprising a single dosage form containing an NMDAr antagonist and levodopa/carbidopa wherein the levodopa/carbidopa is in an immediate release form, the dosing frequency will be chosen according to the levodopa/carbidopa requirements, (e.g. three times per day).

Reduced Time to Therapeutic Concentration and Efficacy

Immediate release (IR) formulations of memantine (e.g., Namenda) are typically administered at low doses (e.g., 5 mg/day) and are progressively administered at increasing frequency and dose over time to reach a steady state serum concentration that is therapeutically effective. According to the manufacturer's FDA approved label, Namenda, an immediate release (IR) formulation of memantine, is first administered to subjects at a dose of 5 mg per day. After an acclimation period of typically one week, subjects are administered with this dose twice per day. Subjects are next administered with a 5 mg and 10 mg dosing per day and finally administered with 10 mg Namenda twice daily. Using this dosing regimen, a therapeutically effective steady state serum concentration may be achieved within 30 days of the onset of therapy. Using a modified release formulation comprising (22.5 mg memantine,) however, a therapeutically effective steady state concentration may be achieved substantially sooner (within about 13 days), without using a dose escalating regimen. Furthermore, the slope during each absorption period for the sustained release formulation is less (i.e. not as steep) as the slope for Namenda. Accordingly, the dC/dT of the sustained release formulation is reduced relative to the immediate release formulation even though the dose administered is larger than for the immediate release formulation. Based on this model, a sustained release formulation of an NMDAr antagonist may be administered to a subject in an amount that is approximately the full strength dose (or that effectively reaches a therapeutically effective dose) from the onset of therapy and throughout the duration of treatment. Accordingly, a dose escalation would not be required.

Treatment of a subject with the subject of the present invention may be monitored using methods known in the art. The efficacy of treatment using the composition is preferably evaluated by examining the subject's symptoms in a quantitative way, e.g., by noting a decrease in the frequency or severity of symptoms or damaging effects of the condition, or an increase in the time for sustained worsening of symptoms. In a successful treatment, the subject's status will have improved (i.e., frequency or severity of symptoms or damaging effects will have decreased, or the time to sustained progression will have increased). In the model described in the previous paragraph, the steady state (and effective) concentration of the NMDAr antagonist is reached in 25%, 40%, 50%, 60%, 70%, 75%, or 80% less time than in the dose escalated approach.

In another embodiment, a composition is prepared using the methods described herein, wherein such composition comprises memantine or amantadine and a release modifying excipient, wherein the excipient is present in an amount sufficient to ameliorate or reduce the dose-dependent toxicity associated with the memantine or amantadine relative to an immediate release (IR) formulation of memantine, such as Namenda, or amantadine, such as Symmetrel. The use of these compositions enables safer administration of these agents, and even permits the safe use of higher levels for appropriate indications, beyond the useful range for the presently available versions of memantine (5 mg and 10 mg per dose to 20 mg per day) and amantadine (100 mg to 300 mg per day with escalation).

Indications Suitable for Treatment

The compositions and methods of the present invention are particularly suitable for the treatment of Parkinson's disease or conditions associated with Parkinson's disease. These conditions include dementia, dyskinesia, dystonia, depression, fatigue and other neuropsychiatric complications of Parkinson's disease.

Formulations for Alternate Specific Routes of Administration

The pharmaceutical compositions may be optimized for particular types of delivery. For example, pharmaceutical compositions for oral delivery are formulated using pharmaceutically acceptable carriers that are well known in the art. The carriers enable the agents in the composition to be formulated, for example, as a tablet, pill, capsule, solution, suspension, sustained release formulation; powder, liquid or gel for oral ingestion by the subject.

The NMDAr antagonist may also be delivered in an aerosol spray preparation from a pressurized pack, a nebulizer or from a dry powder inhaler. Suitable propellants that can be used in a nebulizer include, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and carbon dioxide. The dosage can be determined by providing a valve to deliver a regulated amount of the compound in the case of a pressurized aerosol.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral, intranasal or respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

In some embodiments, for example, the composition may be delivered intranasally to the cribriform plate rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in U.S. Pat. No. 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Additional formulations suitable for other modes of administration include rectal capsules or suppositories. For suppositories, traditional binders and carriers may include, for example, polyalkylene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%.

The composition may optionally be formulated for delivery in a vessel that provides for continuous long-term delivery, e.g., for delivery up to 30 days, 60 days, 90 days, 180 days, or one year. For example the vessel can be provided in a biocompatible material such as titanium. Long-term delivery formulations are particularly useful in subjects with chronic conditions, for assuring improved patient compliance, and for enhancing the stability of the compositions.

Optionally, the NMDA receptor antagonist, levodopa/carbidopa, or both is prepared using the OROS® technology, described for example, in U.S. Pat. Nos. 6,919,373, 6,923,800, 6,929,803, 6,939,556, and 6,930,128, all of which are hereby incorporated by reference. This technology employs osmosis to provide precise, controlled drug delivery for up to 24 hours and can be used with a range of compounds, including poorly soluble or highly soluble drugs. OROS® technology can be used to deliver high drug doses meeting high drug loading requirements. By targeting specific areas of the gastrointestinal tract, OROS® technology may provide more efficient drug absorption and enhanced bioavailability. The osmotic driving force of OROS® and protection of the drug until the time of release eliminate the variability of drug absorption and metabolism often caused by gastric pH and motility.

Formulations for continuous long-term delivery are provided in, e.g., U.S. Pat. Nos. 6,797,283; 6,764, 697; 6,635,268, and 6,648,083.

If desired, the components may be provided in a kit. The kit can additionally include instructions for using the kit.

Additional Methods for Making Modified Release Formulations

Additional methods for making modified release formulations are described in, e.g., U.S. Pat. Nos. 5,422,123, 5,601,845, 5,912,013, and 6,194,000, all of which are hereby incorporated by reference.

In some embodiments, for example, the composition may be delivered via intranasal, buccal, or sublingual routes to the brain rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in U.S. Pat. No. 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Preparation of a pharmaceutical composition for delivery in a subdermally implantable device can be performed using methods known in the art, such as those described in, e.g., U.S. Pat. Nos. 3,992,518; 5,660,848; and 5,756,115.

The invention will be illustrated in the following non-limiting examples.

EXAMPLES

Example 1

Measuring Release Profiles In Vitro

Compositions containing an aminoadamantane and levodopa/carbidopa are analyzed for release of the aminoadamantane and levodopa/carbidopa, according to the USP type 2 apparatus at a speed of 50 rpm. The dissolution media used include water, 0.1N HCl, or 0.1N HCl adjusted to pH 6.8 at 2 hours with phosphate buffer. The dissolution medium is equilibrated to 37±0.5° C.

The USP reference assay method for amantadine is used to measure the fraction of memantine released from the compositions prepared herein. Briefly, 0.6 mL sample (from the dissolution apparatus at a given time point) is placed into a 15 mL culture tube. 1.6 mL 0.1% Bromocresol Purple (in acetic acid) is added and vortexed for five seconds. The mixture is allowed to stand for approximately five minutes. 3 mL Chloroform is added and vortexed for five seconds. The solution is next centrifuged (speed 50 rpm) for five minutes. The top layer is removed with a disposable pipette. A sample is drawn into 1 cm flow cell and the absorbance is measured at 408 nm at 37° C. and compared against a standard curve prepared with known quantities of the same aminoadamantane. The quantity of determined is plotted against the dissolution time for the sample.

The USP reference assay method for levodopa is used to measure the fraction of levodopa released from the compositions prepared herein. Briefly, 0.5 ml samples from the dissolution apparatus removed at various times are assayed by liquid chromatography. The chromatograph is equipped with a 280 nm detector and a 3.9 mm×30 cm column containing packing L1. The mobile phase is 0.09 N sodium phosphate, 1

mM sodium 1-decanesulfonate, pH 2.8. With the flow rate adjusted to about 2 mL per minute, the levodopa elutes in about 4 minutes and carbidopa elutes in about 11 minutes. From the saved dissolution samples, a 0.02 ml aliquot is injected into the chromatograph and the absorbance is measure and compared to standard to determine concentration & quantity. The quantity dissolved is then plotted against the dissolution time for the sample.

Example 2

Preparation of Amantadine Extended Release Capsules

Amantadine extended release capsules may be formulated as follows or as described, for example, in U.S. Pat. No. 5,395,626.

A. Composition: Unit Dose

The theoretical quantitative composition (per unit dose) for amantadine extended release capsules is provided below.

Component	% weight/weight	mg/Capsule
Amantadine	68.34	200.00
OPADRY ® Clear YS-3-7011[1] (Colorcon, Westpoint, PA)	1.14	5.01
Purified Water, USP[2]	—	—
Sugar Spheres, NF	12.50	54.87
OPADRY ® Clear YS-1-7006[3] (Colorcon, Westpoint, PA)	4.48	19.66
SURELEASE ® E-7-7050[4] (Colorcon, Westpoint, PA)	13.54	59.44
Capsules[5]	—	—
TOTAL.	100.00%	338.98 mg[6]

[1]A mixture of hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol.
[2]Purified Water, USP is evaporated during processing.
[3]A mixture of hydroxypropyl methylcellulose and polyethylene glycol
[4]Solid content only of a 25% aqueous dispersion of a mixture of ethyl cellulose, dibutyl sebacate, oleic acid, ammoniated water and fumed silica. The water in the dispersion is evaporated during processing.
[5]White, opaque, hard gelatin capsule, size 00.
[6]Each batch is assayed prior to filling and the capsule weight is adjusted as required to attain 200 mg amantadine per capsule.

The quantitative batch composition for amantadine extended release capsule is shown below. (Theoretical batch quantity 25,741 capsules).

Step 1: Prep of Amantadine HCl Beads (bead Build-up #1)

Component	Weight (kg)
Amantadine	12.000
OPADRY ® Clear YS-3-7011	0.200
Purified Water, USP	5.454
Sugar Sphere, NF	4.000
Total Weight Amantadine Beads	16.200 kg

The amantadine beads obtained from step 1 are used as follows.

Step 2: Clear & Sustained Release Bead Coating #1

Component	Weight (kg)
Amantadine Beads	8.000
OPADRY ® Clear YS-1-7006	0.360
Purified Water, USP	5.928
Surelease ® E-7-7050	0.672
Total Weight Clear Coated Sustained Release Beads	9.032 kg

The sustained release beads obtained from step 2 are used as follows.

Step 3: Amantadine HCl Beads (Build-up #2)

Component	Weight (kg)
Sustained Release Beads	8.000
Amantadine	4.320
OPADRY ® Clear YS-3-7011	0.072
Purified Water, USP	1.964
Total Weight Amantadine Beads	12.392 kg

The amantadine beads obtained from step 3 are formulated as follows.

Step 4: Clear & Sustained Release Bead Coating #2

Component	Weight (kg)
Amantadine Beads	10.000
OPADRY ® Clear YS-1-7006	0.250
Purified Water, USP	6.450
Surelease ® E-7-7050	1.050
Total Weight Amantadine Extended Release Beads	11.300 kg

Example 3

Extended Release Amantadine Formulation with Immediate Release Carbidopa and Levodopa

Levodopa and Carbidopa are formulated into pellets suitable for filling, yet having an immediate release profile. (see, for example, U.S. Pat. No. 5,912,013).

Levodopa plus Carbidopa Core Pellets

	Weight Percent	Kilograms
MCC	25.0	0.25
Hydroxypropylmethylcellulose Phthalate (HPMCP)	10.0	0.10
Tartaric Acid	10.0	0.10
Sodium Monoglycerate	7.5	0.075
DSS	0.5	0.005
Levodopa	35.8	0.358
Carbidopa	11.2	0.112
TOTAL	100.0%	1.00 kg

-continued

Levodopa plus Carbidopa Core Pellets		
	Weight Percent	Kilograms
Coating		
Cellulose Acetate Phthalate (CAP)	60.0	0.60
Ethylcellulose	25.0	0.25
PEG-400	15.0	0.15
TOTAL	100.0%	1.00 kg

The pellets are assayed for levodopa and carbidopa content. It is determined that approximately 223 mg of the pellets contain 80 mg levodopa and 25 mg carbidopa. Dissolution greater than 90% in 30 minutes is also confirmed.

A total of 669 grams of the pellets are blended with 510 grams of the amantadine pellets from Example 2 in a V-blender for 30 minutes at 30 rpm. Gelatin capsules are filled with 393 mg of the mixture and the assays for content are repeated verifying a composition of 100 mg amantadine, 80 mg levodopa, and 25 mg carbidopa.

Example 4

Predicted Dissolution and Plasma Profiles of Amantadine Controlled Release

Using the formulations described above, the dissolution profiles for amantadine were simulated and used to calculate plasma profiles resulting from single or multiple administrations using the pharmacokinetic software, GastroPlus v.4.0.2, from Simulations Plus (see FIG. **2**). The initial slope of the dissolution for the sustained release formulation is less than the slope determined for the immediate release formulation (see FIG. **1**) and the corresponding serum profile also shows a slower dC/dT (see FIG. **4**).

Example 5

Release Profile of Amantadine and L-DOPA (Levodopa/Carbidopa)

Release proportions are shown in the tables below for a combination of amantadine and levodopa/carbidopa. The cumulative fraction is the amount of drug substance released from the formulation matrix to the serum or gut environment (e.g., U.S. Pat. No. 4,839,177 or 5,326,570) or as measured with a USP II Paddle system using 0.1N HCl as the dissolution medium.

Time	AMANTADINE T½ = 15 hrs cum. fraction A	LEVODOPA/CARBIDOPA T½ = 1.5 hrs Cum. fraction B
0	0.00	0.00
0.5	0.10	0.40
1.0	0.20	0.95
2.0	0.35	1.00
4.0	0.60	1.00
8.0	0.90	1.00
12.0	0.98	1.00

Example 6

Treating Dyskinesia in Patients with Parkinson's Disease

A Parkinson's patient experiencing dyskinesia is administered the composition of Example 3 three times each day to receive 300 mg amantadine, 240 mg levodopa, and 75 mg carbidopa daily. The Parkinsonism is reduced as measured by the UPDRS (Goetz et al., Mov. Disord. 19:1020-8, 2004, incorporated by reference) as is the dyskinesia (Vitale et al., Neurol. Sci. 22:105-6, 2001, incorporated by reference)

Example 7

Animal Models Showing Reduced Dyskinesia, Reduced Levodopa Potential

The following protocol was employed to demonstrate the beneficial effects of the compositions of this invention. Briefly, squirrel monkeys (N=4) were lesioned with MPTP according to the protocol of Di Monte et al. (Mov. Disord. 15: 459-66 (2000)). After 3 months, the monkeys showed full symptoms of Parkinson's disease as measured by a modified UPDRS (Goetz et al., Mov. Disord. 19:1020-8, 2004). Levodopa treatment at approximately 15 mg/kg (with 1.5 mg/kg carbidopa) mg/kg b.i.d. commenced a baseline UPDRS and dyskinesia measurement was established. Amantadine was added to the regimen simultaneously with the levodopa, and the amount raised from 1 mg/kg to 45 mg/kg for four of the squirrel monkeys, corresponding to an estimated 3 μm concentration. As shown in FIG. **8**, the combination led to a 60% reduction in dyskinesia. We hypothesize that this translates into a potential 40% reduction in levodopa required to maintain UPDRS.

Example 8

Levodopa Sparing Therapy

The following protocol is employed to determine the optimal reduction of levodopa achieved with the addition of Amantadine to a fixed dose combination product.

Parkinson's DISEASE PROTOCOL SUMMARY NPI MEMANTINE CR MONOTHERAPY	
Protocol Number:	NPI-Amantadine CR
Study Phase:	2/3
Name of Drug:	NPI-Amantadine/C/L
Dosage:	25/100/100 c/l/a given t.i.d. 25/80/100 c/l/a given t.i.d. 25/60/100 c/l/a given t.i.d.
Concurrent Control:	25/100 c/l given t.i.d.
Route:	Oral
Subject Population:	Male and female patients diagnosed with Parkinson's Disease Hoehn and Yahr score of 2-4
Structure:	Parallel-group, three-arm study
Study Term	Two weeks
Study Sites:	Multi-center 10 centers
Blinding:	Double blind
Method of Subject Assignment:	Randomized to one of three treatment groups (3:1)
Total Sample Size:	320 subjects (160 men, 160 women)
Primary Efficacy	UPDRS

-continued

Parkinson's DISEASE PROTOCOL SUMMARY NPI MEMANTINE CR MONOTHERAPY	
Endpoints:	Abnormal involuntary movement scale (AIMS) 0-4
Secondary	Modified Obeso dyskinesia rating scale 0-4
Endpoints:	Mini-mental state examination (MMSE); Neuropsychiatric Inventory Score (NPI)
Adverse Events:	Monitored and elicited by clinic personnel throughout the study, volunteered by patients

Example 9

Pharmaceutical Composition Including Memantine, Levodopa, and Carbidopa

A co-formulation of memantine, levodopa and carbidopa is prepared. This co-formulation matches the absorption properties of levodopa and carbidopa more closely than those of Memantine, thereby extending the effectiveness per dose of levodopa and carbidopa. The co-formulation provides Tmax values to about 4 hours and allows b.i.d. dosing of the combination.

FIG. **6** provides the current single oral dose pharmacokinetic (PK) profiles for levodopa, carbidopa and memantine. FIG. **7** provides idealized pharmacokinetic profiles for the target co-formulation, in which the Tmax values for levodopa and carbidopa more closely match that of Memantine.

Dosage Form:	Tablet
Formulation Content:	Levodopa 150 mg Carbidopa 37.5 mg Memantine 10 mg

Excipients: FDA approved excipients and drug release modifiers. Additional embodiments are within the claims.

Example 10

Pharmaceutical Composition Including Extended Release Formulations of Memantine and Levodopa

A pulsatile release dosage form for administration of memantine and levodopa may be prepared as three individual compartments. Three individual tablets are compressed, each having a different release profile, followed by encapsulation into a gelatin capsule, which are then closed and sealed. The components of the three tablets are as follows.

Component	Function	Amount per tablet
TABLET 1 (IMMEDIATE RELEASE):		
Memantine	Active agent	8 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
TABLET 2 (RELEASE DELAYED 3-5 HOURS FOLLOWING ADMINISTRATION):		
Memantine	Active agent	8 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS3OD	Delayed release coating material	4.76 mg
Talc	Coating component	3.3 mg
Triethyl citrate	Coating component	0.95 mg
TABLET 3 (RELEASE DELAYED 7-9 HOURS FOLLOWING ADMINISTRATION):		
Memantine	Active agent	2.5 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS3OD	Delayed release coating material	6.34 mg
Talc	Coating component	4.4 mg
Triethyl citrate	Coating component	1.27 mg

The tablets are prepared by wet granulation of the individual drug particles and other core components as may be done using a fluid-bed granulator, or are prepared by direct compression of the admixture of components. Tablet 1 is an immediate release dosage form, releasing the active agents within 1-2 hours following administration. Tablets 2 and 3 are coated with the delayed release coating material as may be carried out using conventional coating techniques such as spray-coating or the like. As will be appreciated by those skilled in the art, the specific components listed in the above tables may be replaced with other functionally equivalent components, e.g., diluents, binders, lubricants, fillers, coatings, and the like.

Oral administration of the capsule to a patient will result in a release profile having three pulses, with initial release of the memantine and levodopa from the first tablet being substantially immediate, release of the memantine and levodopa from the second tablet occurring 3-5 hours following administration, and release of the memantine and levodopa from the third tablet occurring 7-9 hours following administration.

Example 11

Pharmaceutical Composition Including Extended Release Formulations of Memantine, Levodopa, and Carbidopa

The method of Example 9 is repeated, except that drug-containing beads are used in place of tablets. Carbidopa is also added in each of the fractions at 25% of the mass of the levodopa. A first fraction of beads is prepared by coating an inert support material such as lactose with the drug which provides the first (immediate release) pulse. A second fraction of beads is prepared by coating immediate release beads with an amount of enteric coating material sufficient to provide a drug release-free period of 3-5 hours. A third fraction of beads is prepared by coating immediate release beads having half the methylphenidate dose of the first fraction of beads with a greater amount of enteric coating material, sufficient to provide a drug release-free period of 7-19 hours. The three groups of beads may be encapsulated or compressed, in the presence of a cushioning agent, into a single pulsatile release tablet.

Alternatively, three groups of drug particles may be provided and coated as above, in lieu of the drug-coated lactose beads.

OTHER EMBODIMENTS

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A dosage form suitable for once-daily administration to a human subject consisting of (i) 50 mg to 500 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, and (ii) at least one excipient, wherein at least 50% of the drug in the dosage form is in an extended release form, and wherein the dosage form provides a mean change in amantadine plasma concentration as a function of time (dC/dT) as measured in a single dose human pharmacokinetic study over the time period between 2 hours and 4 hours after administration that is less than 30% of the dC/dT provided by the same quantity of the drug in an immediate release form as measured in a single dose human pharmacokinetic study over the time period between 0 and 2 hours after administration.

2. The dosage form of claim **1**, comprising an osmotic device, which utilizes an osmotic driving force to provide extended release of amantadine.

3. The dosage form of claim **1**, wherein the amount of drug is 100 to 500 mg.

4. The dosage form of claim **1**, wherein the amount of drug is 200 to 500 mg.

5. The dosage form of claim **1**, wherein at least 75% of the drug in the dosage form is in an extended release form.

6. The dosage form of claim **1**, wherein at least 90% of the drug in the dosage form is in an extended release form.

7. The dosage form of claim **1**, wherein the dosage form provides a shift in amantadine Tmax of 2 hours to 16 hours relative to an immediate release form of amantadine, wherein the Tmax is measured in a single dose human pharmacokinetic study.

8. The dosage form of claim **1**, wherein the extent of drug bioavailability is maintained.

9. The dosage form of claim **1**, wherein the dosage form additionally comprises the drug in an immediate release form.

* * * * *

EXHIBIT D

US008895614B2

(12) **United States Patent**
Went et al.

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(45) **Date of Patent: *Nov. 25, 2014**

(54) **COMPOSITION AND METHOD FOR TREATING NEUROLOGICAL DISEASE**

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This patent is subject to a terminal disclaimer.

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(52) **U.S. Cl.**
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USPC **514/565**; 514/656

(58) **Field of Classification Search**
USPC 514/565, 656
See application file for complete search history.

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(57) **ABSTRACT**

A method of administering amantadine is provided. The method comprises orally administering to a subject a pharmaceutical composition comprising amantadine, or a pharmaceutically acceptable salt thereof, and one or more excipients, wherein at least one of the excipients modifies release of the amantadine. A dose of the composition provides a mean change in amantadine plasma concentration as a function of time (dC/dT) that is less than 40% of the change in amantadine plasma concentration provided by a dose of the same quantity of an immediate release form of amantadine. The change in plasma concentration over time (dC/dT) is measured in a single dose human pharmacokinetic study in a defined time period of 0 to 4 hours after administration. The amantadine, or pharmaceutically acceptable salt thereof, is administered once daily at a dose of 300 to 500 mg per day.

11 Claims, 7 Drawing Sheets

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Figure 1: Simulated Dissolution for TID Amantadine IR & SR

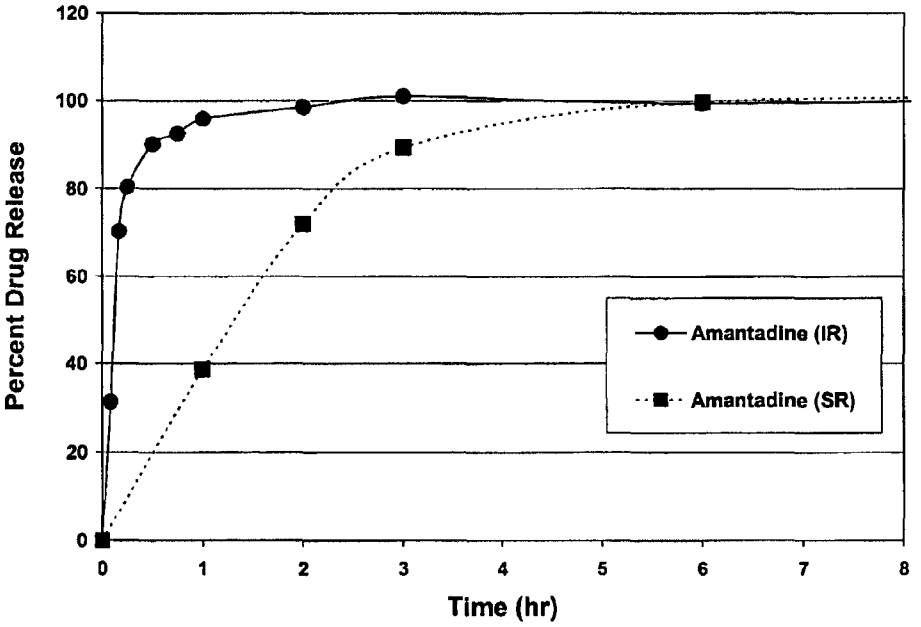


Figure 2: Simulated Plasma Concentration for TID Amantadine IR & SR over 120hrs.

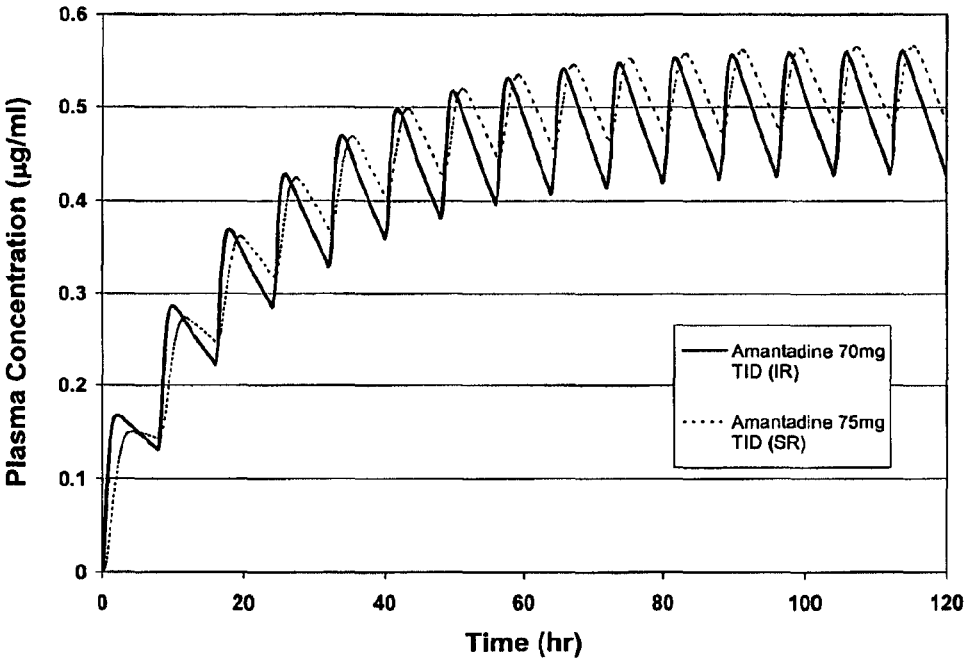


Figure 3: Simulated Plasma Concentration for TID Levodopa/Carbidopa/Amantadine (IR, IR, IR) over 24hrs

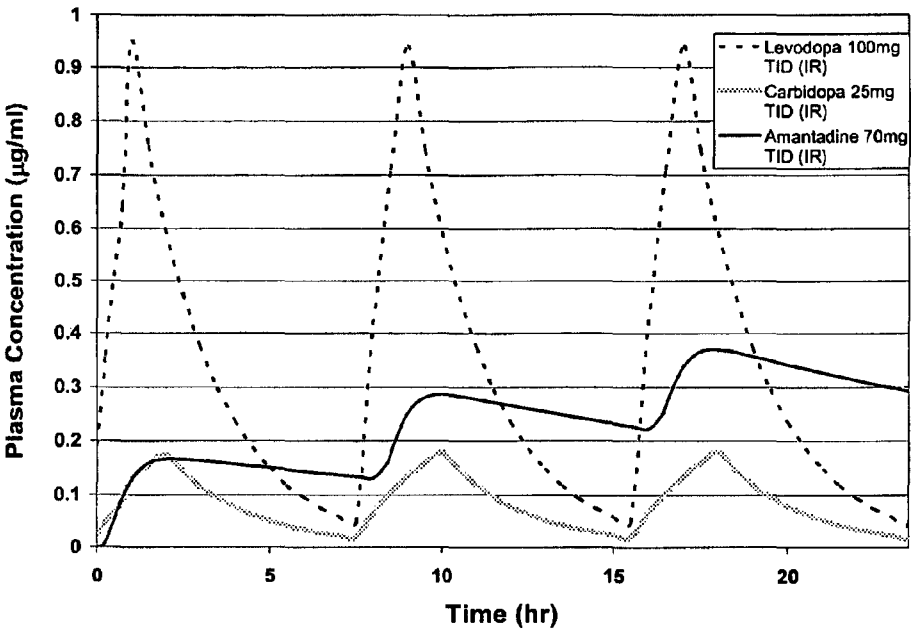


Figure 4: Simulated Plasma Concentration for TID Levodopa/Carbidopa/Amantadine (IR, IR, SR) over 24hrs

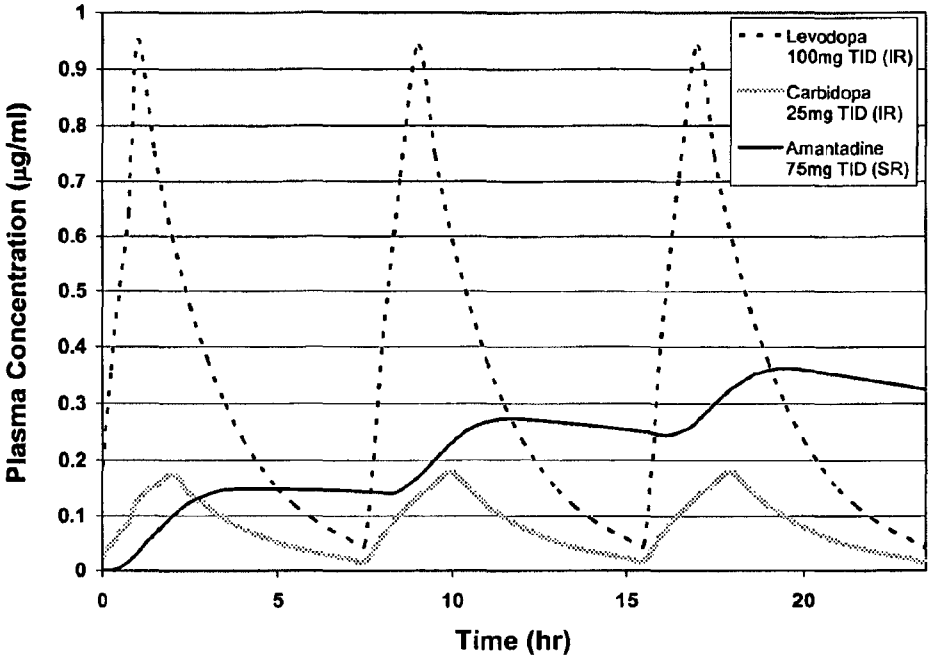


FIGURE 5

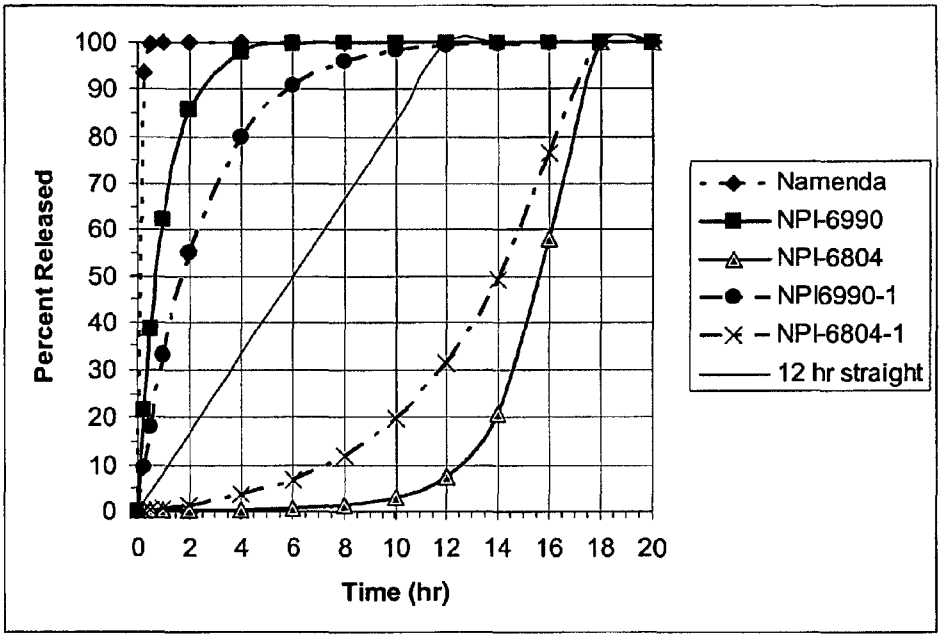

Percent Released
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20
Time (hr)
Namenda
NPI-6990
NPI-6804
NPI6990-1
NPI-6804-1
12 hr straight

Figure 6: Memantine, Levodopa and Carbidopa Human Pharmacokinetics

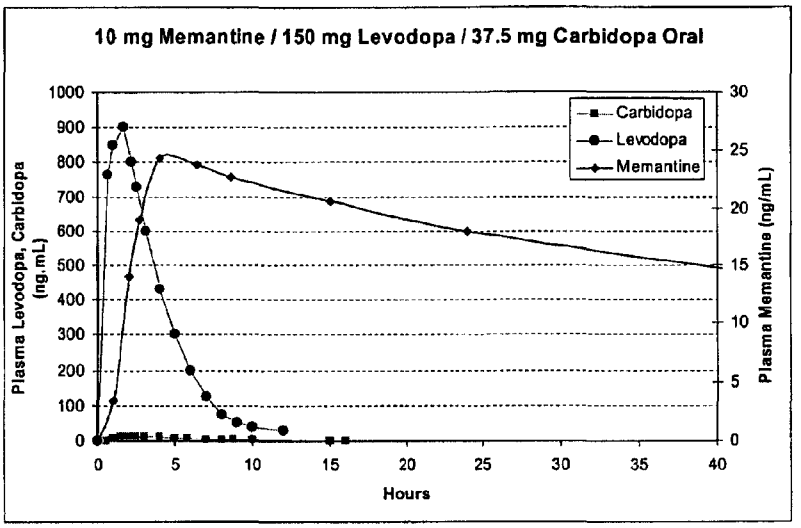
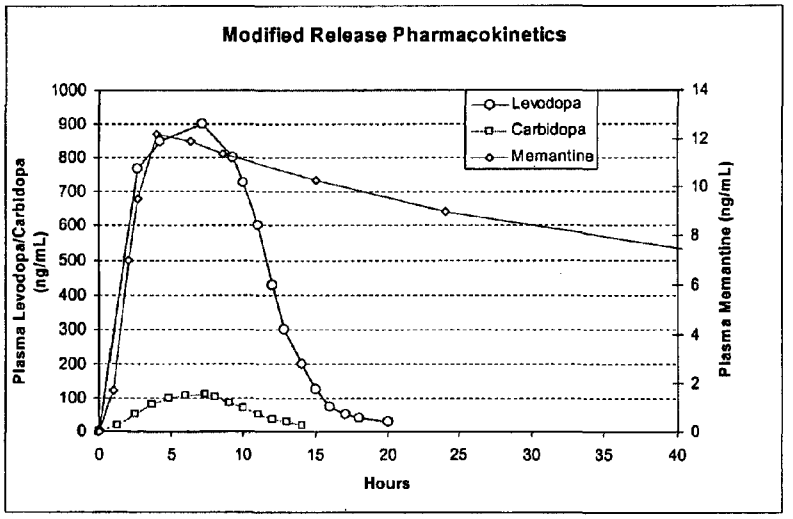


Figure 7: Target Pharmacokinetics



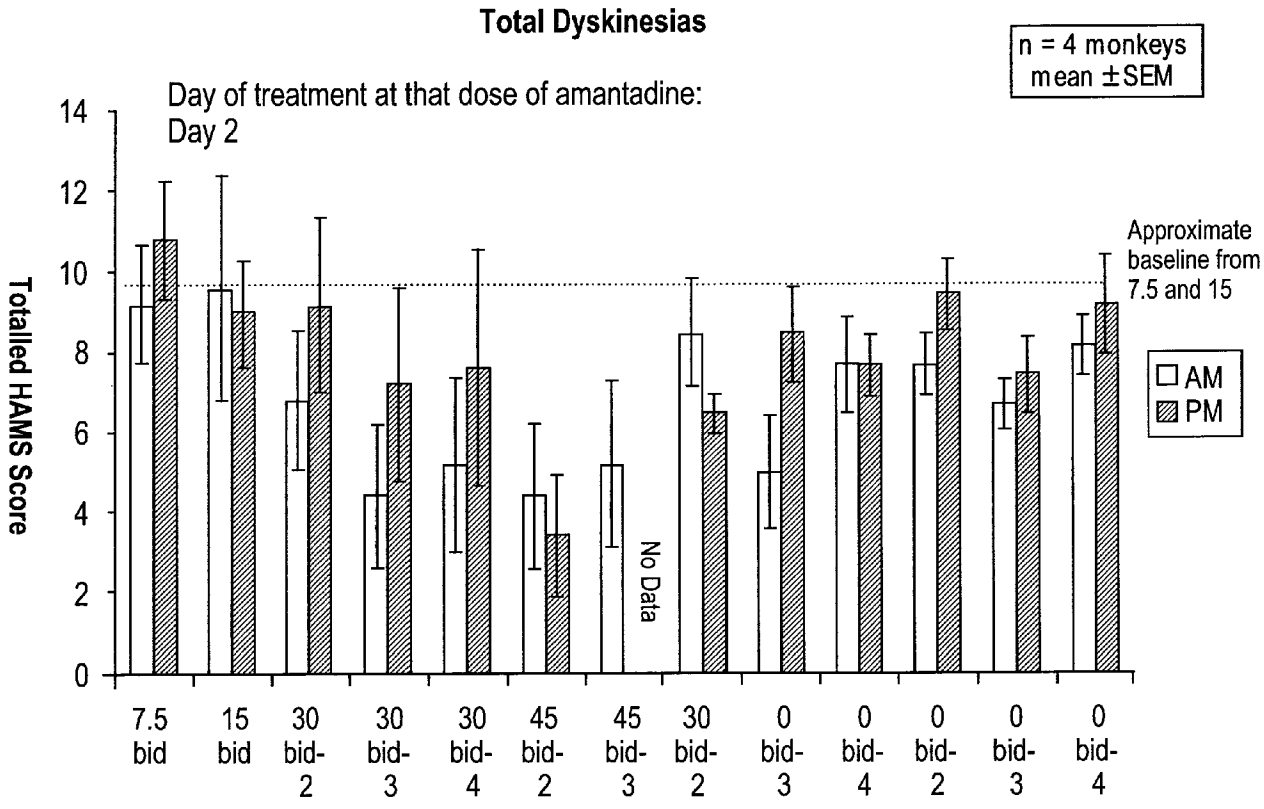

Total Dyskinesias
n = 4 monkeys
mean ±SEM
Day of treatment at that dose of amantadine:
Day 2
Totalled HAMS Score
14
12
10
8
6
4
2
0
Approximate
baseline from
7.5 and 15
AM
PM
No Data
7.5 bid
15 bid
30 bid-2
30 bid-3
30 bid-4
45 bid-2
45 bid-3
30 bid-2
0 bid-3
0 bid-4
0 bid-2
0 bid-3
0 bid-4

Figure 8

COMPOSITION AND METHOD FOR TREATING NEUROLOGICAL DISEASE

RELATED APPLICATION

This application is a continuation application of U.S. patent application Ser. No. 13/958,153, filed Aug. 2, 2013, which is a continuation application of Ser. No. 13/756,275, filed Jan. 31, 2013, which is a continuation application of U.S. patent application Ser. No. 11/286,448 filed on Nov. 23, 2005, now U.S. Pat. No. 8,389,578, which claims priority to U.S. Provisional Application No. 60/631,095 filed on Nov. 24, 2004, which applications are all incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

This invention relates to compositions and methods for treating neurological diseases, such as Parkinson's disease.

BACKGROUND OF THE INVENTION

Parkinson's disease (PD) is a progressive, degenerative neurologic disorder which usually occurs in late mid-life. PD is clinically characterized by bradykinesia, tremor, and rigidity. Bradykinesia is characterized by a slowness in movement, slowing the pace of such routine activities as walking and eating. Tremor is a shakiness that generally affects limbs that are not otherwise in motion. For those PD-patients diagnosed at a relatively young age, tremor is reported as the most disabling symptom. Older patients face their greatest challenge in walking or keeping their balance. Rigidity is caused by the inability of muscles to relax as opposing muscle groups contract, causing tension which can produce aches and pains in the back, neck, shoulders, temples, or chest.

PD predominantly affects the substantia nigra (SNc) dopamine (DA) neurons and is therefore associated with a decrease in striatal DA content. Because dopamine does not cross the blood-brain barrier, PD patients may be administered a precursor, levodopa, that does cross the blood-brain barrier where it is metabolized to dopamine. Levodopa therapy is intended to compensate for reduced dopamine levels and is a widely prescribed therapeutic agent for patients with Parkinson's disease. Chronic treatment with levodopa however, is associated with various debilitating side-effects such as dyskinesia.

Since currently available drugs containing levodopa are associated with debilitating side effects, better therapies are needed for the management of PD.

SUMMARY OF THE INVENTION

In general, the present invention provides methods and compositions for treating and preventing CNS-related conditions, such as Parkinson's disease or other Parkinson's-like diseases or conditions, by administering to a subject in need thereof a combination that includes an N-Methyl-D-Aspartate receptor (NMDAr) antagonist and levodopa. Exemplary NMDAr antagonists include the aminoadamantanes, such as memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1-aminoethyl)adamantane), or amantadine (1-amino-adamantane) as well as others described below. Because levodopa is metabolized before crossing the blood-brain barrier and has a short half-life in the circulatory system, it is typically administered in conjunction with a dopa-decarboxylase inhibitor. Examples of dopa-decarboxylase inhibitors include carbidopa, 3-hydroxy-benzylhydrazinedihydrochloride (NSD-1015), and benseraxide hydrochloride. The combination may further include a catechol-0-methyltransferase (COMT) inhibitor including, for example, talcapone and entacapone. As used herein, levodopa/carbidopa shall mean levodopa alone or in combination with a dopa-decarboxylase inhibitor such as carbidopa. Desirably, the levodopa/carbidopa is in an immediate release formulation and the NMDA receptor antagonist is in an extended release formulation. One preferred embodiment of the invention involves the combination of amantadine and levodopa/carbidopa. Desirably, amantadine is provided in an extended release formulation and levodopa/carbidopa is provided as an immediate release formulation. By combining an NMDAr antagonist (e.g., amantadine) with the second agents described herein (e.g., levodopa/carbidopa), this invention provides an effective pharmaceutical composition for treating neurological diseases such as Parkinson's disease or other Parkinson's-like diseases or conditions. The administration of this combination is postulated to maintain or enhance the efficacy of levodopa while significantly reducing its dyskinesia side effects.

The combinations described herein provide complementary benefits associated with the NMDAr antagonist or levodopa/carbidopa individually, while minimizing difficulties previously presented when each component is used separately in a patient. For example, amantadine dosing is limited by neurotoxicity that is likely associated with its short Tmax. By extending the release of amantadine, a higher effective dose can be maintained providing both dyskinesia relief and a reduction in the amount of levodopa required for treatment of the disease symptoms. Given the inherent toxicity of levodopa, such a levodopa sparing combination will result in a decline in both the dyskinesia and overall disease.

Accordingly, the pharmaceutical compositions described herein are administered so as to deliver to a subject, an amount of an NMDAr antagonist, levodopa/carbidopa or both agents that is high enough to treat symptoms or damaging effects of an underlying disease while avoiding undesirable side effects. These compositions may be employed to administer the NMDAr antagonist, the levodopa/carbidopa, or both agents at a lower frequency than presently employed, improving patient compliance, adherence, and caregiver convenience. These compositions are particularly useful as they provide the NMDAr antagonist, levodopa/carbidopa, or both agents, at a therapeutically effective amount from the onset of therapy further improving patient compliance and adherence and enable the achievement of a therapeutically effective steady-state concentration of either or both agents of the combination in a shorter period of time resulting in an earlier indication of effectiveness and increasing the utility of these therapeutic agents for diseases and conditions where time is of the essence. Also provided are methods for making and using such compositions.

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a controlled or extended release form with or without an immediate release component in order to maximize the therapeutic benefit of such agents, while reducing unwanted side effects. In preferred embodiments for oral administration, levodopa/carbidopa is provided as an immediate-release formulation.

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be administered in an amount similar to that typically administered to subjects. Preferably, the amount of the NMDAr antagonist may be administered in an amount greater than or less than the amount that is typically administered to subjects while the levodopa/carbidopa is provided at a lower dose than normally used. For example, the amount

of amantadine required to positively affect the patient response (inclusive of adverse effects) may be 300, 400, 500, 600 mg per day rather than the typical 200-300 mg per day administered for presently approved indications i.e. without the improved formulation described herein, while the levodopa, and optionally the carbidopa, can be reduced independently by 10%, 20%, 30%, 40%, 50%, 60%, 70% or up to 80% of what is currently required in the absence of the NMDAr antagonist.

Optionally, lower or reduced amounts of both the NMDAr antagonist and the levodopa/carbidopa are used in a unit dose relative to the amount of each agent when administered independently. The present invention therefore features formulations of combinations directed to dose optimization or release modification to reduce adverse effects associated with separate administration of each agent. The combination of the NMDAr antagonist and the levodopa/carbidopa may result in an additive or synergistic response, and using the unique formulations described herein, the goal of minimizing the levodopa burden is achieved. Preferably, the NMDAr antagonist and the levodopa/carbidopa are provided in a unit dosage form.

The compositions and methods of the invention are particularly useful for the treatment of Parkinson's disease or conditions associated with Parkinson's disease. These conditions include dementia, dyskinesia, dystonia, depression, fatigue and other neuropsychiatric complications of Parkinson's disease.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present Specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. All parts and percentages are by weight unless otherwise specified.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a graph showing the dissolution profiles for an immediate and sustained release formulation of amantadine. The sustained release formulation exhibits a dC/dT during the initial phase that is about 10% of that for the immediate release formulation.

FIG. **2** is a graph showing the amantadine plasma concentration over a period of 5 days, as predicted by Gastro-Plus software package v.4.0.2, following the administration of either 70 mg amantadine in an immediate release formulation t.i.d. or 75 mg amantadine in a sustained release formulation t.i.d. The sustained release formulation peaks are similar in height to the immediate release formulation even with a higher administered dose and the diurnal variation is substantially reduced.

FIG. **3** is a graph showing the plasma profiles simulated using Gastro-Plus for t.i.d. administration of amantadine (70 mg), levodopa (100 mg), and carbidopa (25 mg), all in an immediate release form.

FIG. **4** is a graph showing the plasma profiles simulated using Gastro-Plus for t.i.d. administration of amantadine (75 mg), levodopa (100 mg), and carbidopa (25 mg), where the amantadine is in a sustained release form and the levodopa and carbidopa are in an immediate release form.

FIG. **5** is a graph representing dissolution profiles for various aminoadamantane formulations including an immediate release form of the NMDAr antagonist memantine (Namenda).

FIG. **6** is a graphical representation of plasma release profiles in a human of memantine, levodopa, and carbidopa when memantine is administered separately from levodopa and carbidopa.

FIG. **7** is a graphical representation of plasma release profiles in a human of memantine, levodopa, and carbidopa when memantine, levodopa, and carbidopa are administered as part of a single controlled-release pharmaceutical composition.

FIG. **8** is a bar graph showing the effects on a primate (squirrel monkey) treated with a combination of levodopa/carbidopa and amantadine.

DETAILED DESCRIPTION OF THE INVENTION

In general, the present invention features pharmaceutical compositions that contain therapeutically effective levels of an NMDAr antagonist and levodopa/carbidopa and, optionally, a pharmaceutical carrier. Preferably the compositions are formulated for modified or extended release to provide a serum or plasma concentration of the NMDAr antagonist over a desired time period that is high enough to be therapeutically effective but at a rate low enough so as to avoid adverse events associated with the NMDAr antagonist. Control of drug release is particularly desirable for reducing and delaying the peak plasma level while maintaining the extent of drug bioavailability. Therapeutic levels are therefore achieved while minimizing debilitating side-effects that are usually associated with immediate release formulations. Furthermore, as a result of the delay in the time to obtain peak serum or plasma level and the extended period of time at the therapeutically effective serum or plasma level, the dosage frequency is reduced to, for example, once or twice daily dosage, thereby improving patient compliance and adherence. For example, side effects including psychosis and cognitive deficits associated with the administration of NMDAr antagonists may be lessened in severity and frequency through the use of controlled-release methods that shift the Tmax to longer times, thereby reducing the dC/dT of the drug. Reducing the dC/dT of the drug not only increases Tmax, but also reduces the drug concentration at Tmax and reduces the Cmax/Cmean ratio providing a more constant amount of drug to the subject being treated over a given period of time, enabling increased dosages for appropriate indications.

In addition, the present invention encompasses optimal ratios of NMDAr and levodopa/carbidopa, designed to not only treat the dyskinesia associated with levodopa, but also take advantage of the additivity and synergy between these drug classes. For example, the level of levodopa required to treat the disease symptoms can unexpectedly be reduced by up to 50% by the addition of 400 mg/day of amantadine.

Making NMDAr Antagonist Controlled Release Formulations

A pharmaceutical composition according to the invention is prepared by combining a desired NMDAr antagonist or antagonists with one or more additional ingredients that, when administered to a subject, causes the NMDAr antagonist to be released at a targeted rate for a specified period of time. A release profile, i.e., the extent of release of the NMDAr antagonist over a desired time, can be conveniently determined for a given time by measuring the release using a USP dissolution apparatus under controlled conditions. Preferred release profiles are those which slow the rate of uptake of the NMDAr antagonist in the neural fluids while providing

therapeutically effective levels of the NMDAr antagonist. One of ordinary skill in the art can prepare combinations with a desired release profile using the NMDAr antagonists and formulation methods described below.

NMDAr Antagonists

Any NMDAr antagonist can be used in the methods and compositions of the invention, particularly those that are non-toxic when used in the compositions of the invention. The term "nontoxic" is used in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to humans or, in keeping with established regulatory criteria and practice, is susceptible to approval by the FDA or similar regulatory agency for any country for administration to humans or animals.

The term "NMDAr antagonist", as used herein, includes any amino-adamantane compound including, for example, memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1-aminoethyl)adamantane), amantadine (1-amino-adamantane), as well as pharmaceutically acceptable salts thereof. Memantine is described, for example, in U.S. Pat. Nos. 3,391,142, 5,891,885, 5,919,826, and 6,187,338. Amantadine is described, for example, in U.S. Pat. Nos. 3,152,180, 5,891,885, 5,919,826, and 6,187,338. Additional aminoadamantane compounds are described, for example, in U.S. Pat. Nos. 4,346,112, 5,061,703, 5,334,618, 6,444,702, 6,620,845, and 6,662,845. All of these patents are hereby incorporated by reference.

Further NMDAr antagonists that may be employed include, for example, aminocylohexanes such as neramexane, ketamine, eliprodil, ifenprodil, dizocilpine, remacemide, iamotrigine, riluzole, aptiganel, phencyclidine, flupirtine, celfotel, felbamate, spermine, spermidine, levemopamil, dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and its metabolite, dextrorphan ((+)-3-hydroxy-N-methylmorphinan), a pharmaceutically acceptable salt, derivative, or ester thereof, or a metabolic precursor of any of the foregoing.

Optionally, the NMDAr antagonist in the instant invention is memantine and not amantadine or dextromethorphan.

Second Agents

In all foregoing aspects of the invention, the second agent is levodopa. When levodopa is in the combination, the combination preferably also includes a dopa-decarboxylase inhibitor. An example of a suitable dopa-decarboxylase inhibitor is carbidopa. Other dopa-decarboxylase inhibitors include, for example, 3-hydroxy-benzylhydrazinedihydrochloride (NSD-1015) and benseraxide hydrochloride. The combination may further include a catechol-O-methyltransferase (COMT) inhibitor including, for example, talcapone and entacapone.

Dosing, PK, & Toxicity

The NMDA receptor antagonist used in combination therapies are administered at a dosage of generally between about 1 and 5000 mg/day, between 1 and about 800 mg/day, or between 1 and 500 mg/day. For example, NMDA receptor antagonist agents may be administered at a dosage ranging between about 1 and about 500 mg/day, more preferably from about 10 to about 40, 50, 60, 70 or 80 mg/day, advantageously from about 10 to about 20 mg per day. Amantadine may be administered at a dose ranging from about 90, 100 mg/day to about 400, 500, 600, 700 or 800 mg/day, advantageously from about 100 to about 500, 600 mg per day. For example, the pharmaceutical composition may be formulated to provide memantine in an amount ranging between 1-200 mg/day, 1 and 80 mg/day, 2-80 mg/day, 10-80 mg/day, 10 and 80 mg/day, 10 and 70 mg/day, 10 and 60 mg/day, 10 and 50 mg/day, 10 and 40 mg/day, 5 and 65 mg/day, 5 and 40 mg/day, 15 and 45 mg/day, or 10 and 20 mg/day; dextromethorphan in an amount ranging between 1-5000 mg/day, 1-1000 mg/day, and 100-800 mg/day, or 200-500 mg/day. Pediatric doses will typically be lower than those determined for adults.

Table 1 shows exemplary pharmacokinetic properties (e.g., Tmax and T½) of memantine, amantadine, and rimantadine.

TABLE 1

Pharmacokinetics and Toxicity in humans for selected NIVIDAr antagonists

Compound	Human PK (t½) (hours)	Tmax (hours)	Normal Dose	Dose Dependent Toxicity
Memantine	60	3	10-20 mg/day, starting at 5 mg	Dose escalation required, hallucination
Amantadine	15	3	100-300 mg/day, starting at 100 mg/day	Hallucination
Rimantadine	25	6	100-200 mg/day	Insomnia

When levodopa and carbidopa are both included in the composition, the levodopa dose ranges between 100 to 3000 mg per day, 75 mg and 2500 mg/day, 100-2000 mg/day, or 250 and 1000 mg/day divided for administration t.i.d. or more frequently. Carbidopa doses may range between the amounts of 1 to 1000 mg/day, 10 to 500 mg/day, and 25 to 100 mg/day. Optionally, the carbidopa is present in the combination at about 75%, 70%, 65%, 60%, 50%, 40%, 30%, 25%, 20%, and 10% of the mass of the levodopa. Alternatively, the amount of levodopa is less than 300% than the amount of carbidopa. For example, 75 mg of carbidopa (amount that is sufficient to extend the half-life of levodopa in the circulatory system) may be used in combination with 300 to 3000 mg of levodopa per day. The combination may contain a single dosage form comprising 30 to 200 mg amantadine, 30 to 250 mg levodopa, and 10 to 100 mg of carbidopa for t.i.d. or more frequent administration, including multiple dosage forms per administration.

As a result, the preferred dosage forms for optimized use are shown in Table 2 below, with their corresponding commercial equivalent.

TABLE 2

Dosage forms with and without NMDAr antagonist (amount per unit dose)

Sinemet Compositions		Compositions of Present Invention		
Levodopa	Carbidopa	Levodopa	Carbidopa	Amantadine
100 mg IR*	25 mg IR	50-100 mg IR	25 mg IR	100-200 mg IR
100 mg IR	10 mg IR	50-100 mg IR	10 mg IR	50-100 mg IR
100 mg IR	25 mg IR	50-100 mg IR	25 mg IR	100-200 mg CR**
100 mg IR	10 mg IR	50-100 mg IR	10 mg IR	50-100 mg CR

*IR: immediate release
**CR: modified release

Excipients

"Pharmaceutically or Pharmacologically Acceptable" includes molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. "Pharmaceutically Acceptable Carrier" includes any and all sol-

vents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. "Pharmaceutically Acceptable Salts" include acid addition salts and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

The preparation of pharmaceutical or pharmacological compositions is known to those of skill in the art in light of the present disclosure. General techniques for formulation and administration are found in "Remington: The Science and Practice of Pharmacy, Twentieth Edition," Lippincott Williams & Wilkins, Philadelphia, Pa. Tablets, capsules, pills, powders, granules, dragees, gels, slurries, ointments, solutions suppositories, injections, inhalants and aerosols are examples of such formulations.

By way of example, modified or extended release oral formulation can be prepared using additional methods known in the art. For example, a suitable extended release form of the either active pharmaceutical ingredient or both may be a matrix tablet or capsule composition. Suitable matrix forming materials include, for example, waxes (e.g., carnauba, bees wax, paraffin wax, ceresine, shellac wax, fatty acids, and fatty alcohols), oils, hardened oils or fats (e.g., hardened rapeseed oil, castor oil, beef tallow, palm oil, and soya bean oil), and polymers (e.g., hydroxypropyl cellulose, polyvinylpyrrolidone, hydroxypropyl methyl cellulose, and polyethylene glycol). Other suitable matrix tabletting materials are microcrystalline cellulose, powdered cellulose, hydroxypropyl cellulose, ethyl cellulose, with other carriers, and fillers. Tablets may also contain granulates, coated powders, or pellets. Tablets may also be multi-layered. Multi-layered tablets are especially preferred when the active ingredients have markedly different pharmacokinetic profiles. Optionally, the finished tablet may be coated or uncoated.

The coating composition typically contains an insoluble matrix polymer (approximately 15-85% by weight of the coating composition) and a water soluble material (e.g., approximately 15-85% by weight of the coating composition). Optionally an enteric polymer (approximately 1 to 99% by weight of the coating composition) may be used or included. Suitable water soluble materials include polymers such as polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials such as sugars (e.g., lactose, sucrose, fructose, mannitol and the like), salts (e.g., sodium chloride, potassium chloride and the like), organic acids (e.g., fumaric acid, succinic acid, lactic acid, and tartaric acid), and mixtures thereof. Suitable enteric polymers include hydroxypropyl methyl cellulose, acetate succinate, hydroxypropyl methyl cellulose, phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups.

The coating composition may be plasticised according to the properties of the coating blend such as the glass transition temperature of the main component or mixture of components or the solvent used for applying the coating compositions. Suitable plasticisers may be added from 0 to 50% by weight of the coating composition and include, for example, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, acetylated citrate esters, dibutylsebacate, and castor oil. If desired, the coating composition may include a filler. The amount of the filler may be I % to approximately 99% by weight based on the total weight of the coating composition and may be an insoluble material such as silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, MCC, or polacrilin potassium.

The coating composition may be applied as a solution or latex in organic solvents or aqueous solvents or mixtures thereof. If solutions are applied, the solvent may be present in amounts from approximate by 25-99% by weight based on the total weight of dissolved solids. Suitable solvents are water, lower alcohol, lower chlorinated hydrocarbons, ketones, or mixtures thereof. If latexes are applied, the solvent is present in amounts from approximately 25-97% by weight based on the quantity of polymeric material in the latex. The solvent may be predominantly water.

The NMDAr antagonist may be formulated using any of the following excipients or combinations thereof.

Excipient name	Chemical name	Function
Avicel PH102	Microcrystalline Cellulose	Filler, binder, wicking, disintegrant
Avicel PH101	Microcrystalline Cellulose	Filler, binder, disintegrant
Eudragit RS-30D	Polymethacrylate Poly(ethyl acrylate, nethyl methacrylate, timethylammonioethyl methacrylate chloride) 1:2:0.1	Film former, tablet binder, tablet diluent; Rate controlling polymer for controlled release
Methocel K100M Premium CR	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Methocel K100M	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Magnesium Stearate	Magnesium Stearate	Lubricant
Talc	Talc	Dissolution control; anti-adherent, glidant
Triethyl Citrate	Triethyl Citrate	Plasticizer
Methocel E5	Hydroxypropyl methylcellulose	Film-former
Opadry ®	Hydroxypropyl methylcellulose	One-step customized coating system which combines polymer, plasticizer and, if desired, pigment in a dry concentrate.

-continued

Excipient name	Chemical name	Function
Surelease ®	Aqueous Ethylcellulose Dispersion	Film-forming polymer; plasticizer and stabilizers. Rate controlling polymer coating.

The pharmaceutical composition described herein may also include a carrier such as a solvent, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents. The use of such media and agents for pharmaceutically active substances is well known in the art. Pharmaceutically acceptable salts can also be used in the composition, for example, mineral salts such as hydrochlorides, hydrobromides, phosphates, or sulfates, as well as the salts of organic acids such as acetates, proprionates, malonates, or benzoates. The composition may also contain liquids, such as water, saline, glycerol, and ethanol, as well as substances such as wetting agents, emulsifying agents, or pH buffering agents. Liposomes, such as those described in U.S. Pat. No. 5,422,120, WO 95/13796, WO 91/14445, or EP 524,968 B1, may also be used as a carrier.

Methods for Preparing Modified or Extended Release Formulations

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a controlled or extended release form with or without an immediate release component in order to maximize the therapeutic benefit of such agents, while reducing unwanted side effects. In the absence of modified release components (referred to herein as controlled, extended, or delayed release components), the NMDAr antagonist, levodopa/carbidopa, or both is released and transported into the body fluids over a period of minutes to several hours. The combination described herein however, may contain an NMDAr antagonist and a sustained release component, such as a coated sustained release matrix, a sustained release matrix, or a sustained release bead matrix. In one example, in addition to levodopa/carbidopa, amantadine (e.g., 50-400 mg) is formulated without an immediate release component using a polymer matrix (e.g., Eudragit), Hydroxypropyl methyl cellulose (HPMC) and a polymer coating (e.g., Eudragit). Such formulations are compressed into solid tablets or granules and coated with a controlled release material such as Opadry® or Surelease®. Levodopa/carbidopa may also be formulated as a sustained release formulation; in most cases, however, this will not be optimal.

Suitable methods for preparing the compositions described herein in which the NMDAr antagonist is provided in modified or extended release-formulations include those described in U.S. Pat. No. 4,606,909 (hereby incorporated by reference). This reference describes a controlled release multiple unit formulation in which a multiplicity of individually coated or microencapsulated units are made available upon disintegration of the formulation (e.g., pill or tablet) in the stomach of the subject (see, for example, column 3, line 26 through column 5, line 10 and column 6, line 29 through column 9, line 16). Each of these individually coated or microencapsulated units contains cross-sectionally substantially homogenous cores containing particles of a sparingly soluble active substance, the cores being coated with a coating that is substantially resistant to gastric conditions but which is erodable under the conditions prevailing in the gastrointestinal tract.

The composition of the invention may alternatively be formulated using the methods disclosed in U.S. Pat. No. 4,769,027, for example. Accordingly, extended release formulations involve prills of pharmaceutically acceptable material (e.g., sugar/starch, salts, and waxes) may be coated with a water permeable polymeric matrix containing an NMDAr antagonist and next overcoated with a water-permeable film containing dispersed within it a water soluble particulate pore forming material.

The NMDAr antagonist composition may additionally be prepared as described in U.S. Pat. No. 4,897,268, involving a biocompatible, biodegradable microcapsule delivery system. Thus, the NMDAr antagonist may be formulated as a composition containing a blend of free-flowing spherical particles obtained by individually microencapsulating quantities of memantine, for example, in different copolymer excipients which biodegrade at different rates, therefore releasing memantine into the circulation at a predetermined rates. A quantity of these particles may be of such a copolymer excipient that the core active ingredient is released quickly after administration, and thereby delivers the active ingredient for an initial period. A second quantity of the particles is of such type excipient that delivery of the encapsulated ingredient begins as the first quantity's delivery begins to decline. A third quantity of ingredient may be encapsulated with a still different excipient which results in delivery beginning as the delivery of the second quantity beings to decline. The rate of delivery may be altered, for example, by varying the lactide/glycolide ratio in a poly(D,L-lactide-co-glycolide) encapsulation. Other polymers that may be used include polyacetal polymers, polyorthoesters, polyesteramides, polycaprolactone and copolymers thereof, polycarbonates, polyhydroxybuterate and copolymers thereof, polymaleamides, copolyaxalates and polysaccharides.

Alternatively, the composition may be prepared as described in U.S. Pat. No. 5,395,626, which features a multilayered controlled release pharmaceutical dosage form. The dosage form contains a plurality of coated particles wherein each has multiple layers about a core containing an NMDAr antagonist whereby the drug containing core and at least one other layer of drug active is overcoated with a controlled release barrier layer therefore providing at least two controlled releasing layers of a water soluble drug from the multilayered coated particle

Release Profile

The compositions described herein are formulated such that the NMDAr antagonist, levodopa/carbidopa, or both agents have an in vitro dissolution profile that is equal to or slower than that for an immediate release formulation. As used herein, the immediate release (IR) formulation for memantine means the present commercially available 5 mg and 10 mg tablets (i.e., Namenda from Forest Laboratories, Inc. or formulations having substantially the same release profiles as Namenda); and the immediate release (IR) formulation of amantadine means the present commercially available 100 mg tablets (i.e., Symmetrel from Endo Pharmaceuticals, Inc. or formulations having substantially the same release profiles as Symmetrel); and the immediate release (IR) formulation of levodopa/carbidopa means the present commercially available 25 mg/100 mg, 10 mg/100 mg, 25

mg/250 mg tablets of carbidopa/levodopa (i.e., Sinemet from Merck & Co. Inc. or formulations having substantially the same release profiles as Sinemet). These compositions may comprise immediate release, sustained or extended release, or delayed release components, or may include combinations of same to produce release profiles such that the fraction of NMDAr antagonist or levodopa/carbidopa released is greater or equal to $0.01(0.297+0.0153*e^{(0.515*t)}$ and less than or equal to $1-e^{(-10.9*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C., in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist or levodopa/carbidopa released is less than 93% in 15 minutes and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1N HCl) dissolution medium. Optionally, the fraction of released NMDAr antagonist or levodopa/carbidopa is greater than or equal to $0.01(0.297+0.0153*e^{(0.515*t)})$, and less than or equal to $1-e^{(-0.972*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C., in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist or levodopa/carbidopa that is released may range between 0.1%-62% in one hour, 0.2%-86% in two hours, 0.6%-100% in six hours, 2.9%-100% in 10 hours, and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1 N HCl) dissolution medium. Optionally, the NMDA receptor antagonist has a release profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 70% or greater (e.g., 70%-90%) in 10 hours, and 90% or greater (e.g., 90-95%) in 12 hours as measured in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1 N HCl) dissolution medium. For example, a formulation containing amantadine may have a release profile ranging between 0-60% or 0.1-20% in one hour, 0-86% or 5-30% at two hours, 0.6-100% or 40-80% at six hours, 3-100% or 50% or more (e.g., 50-90%) at ten hours, and 7.7-100% at twelve hours in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1 N HCl) dissolution medium. In one embodiment, the NMDAr antagonist, the levodopa/carbidopa, or both agents have an in vitro dissolution profile of less than 25%, 15%, 10%, or 5% in fifteen minutes; 50%, 30%, 25%, 20%, 15%, or 10% in 30 minutes and more than 60%, 65% 70%, 75%, 80%, 85%, 90%, 95% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water. Desirably, the NMDAr antagonist, the levodopa/carbidopa, or both agents has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% in a dissolution media having a pH of 1.2 at 10 hours. It is important to note that the dissolution profile for the NMDAr antagonist may be different than the release profile for levodopa/carbidopa. In a preferred embodiment, the levodopa/carbidopa release profile is equal to or similar to that for an immediate release formulation and the release profile for the NMDAr antagonist is controlled to provide a dissolution profile of less than 30% in one hour, less than 50% in two hours, and greater than 95% in twelve hours using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water.

Desirably, the compositions described herein have an in vitro profile that is substantially identical to the dissolution profile shown in FIG. **5** and, upon administration to a subject at a substantially constant daily dose, achieves a serum concentration profile that is substantially identical to that shown in FIGS. **2** and **4**.

As described above, the NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a modified or extended release form. Modified or extended drug release is generally controlled either by diffusion through a coating or matrix or by erosion of a coating or matrix by a process dependent on, for example, enzymes or pH. The NMDAr antagonist or the levodopa/carbidopa may be formulated for modified or extended release as described herein or using standard techniques in the art. In one example, at least 50%, 75%, 90%, 95%, 96%, 97%, 98%, 99%, or even in excess of 99% of the NMDAr antagonist or the levodopa/carbidopa is provided in an extended release dosage form. In a preferred embodiment, the levodopa/carbidopa is provided in an immediate release formulation and the NMDAr antagonist is in either an immediate or modified release form.

The composition described herein is formulated such the NMDAr antagonist or levodopa/carbidopa has an in vitro dissolution profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 50%-90% in 10 hours, and 90%-95% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. using 0.1N HCl as a dissolution medium. Alternatively, the NMDAr antagonist has an in vitro dissolution profile in a solution with a neutral pH (e.g., water) that is substantially the same as its dissolution profile in an acidic dissolution medium. Thus, the NMDAr antagonist may be released in both dissolution media at the following rate: between 0.1-20% in one hour, 5-30% in two hours, 40-80% in six hours, 70-90% in 10 hours, and 90%-95% in 12 hours as obtained using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. In one embodiment, the NMDAr antagonist has an in vitro dissolution profile of less than 15%, 10%, or 5% in fifteen minutes, 25%, 20%, 15%, or 10% in 30 minutes, and more than 60% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water. Desirably, the NMDAr antagonist has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% at 10 hours in a dissolution medium having a pH of 1.2.

Initial Rate In Vivo, Delayed Tmax

As used herein, "C" refers to the concentration of an active pharmaceutical ingredient in a biological sample, such as a patient sample (e.g. blood, serum, and cerebrospinal fluid). The time required to reach the maximal concentration ("Cmax") in a particular patient sample type is referred to as the "Tmax". The change in concentration is termed "dC" and the change over a prescribed time is "dC/dT".

The NMDAr antagonist or levodopa/carbidopa is provided as a sustained release formulation that may or may not contain an immediate release formulation. If desired, the NMDAr antagonist may be formulated so that it is released at a rate that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In addition, the NMDAr antagonist levodopa/carbidopa may be provided such that it is released at a rate resulting in a Cmax/Cmean of approximately 2 or less for approximately 2 hours to at least 8 hours after the NMDAr antagonist is introduced into a subject. Optionally, the sustained release formulations exhibit plasma concentration curves having initial (e.g., from 0, 1, 2 hours after administration to 4, 6, 8 hours

after administration) slopes less than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist. The precise slope for a given individual will vary according to the NMDAr antagonist being used or other factors, including whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose. The determination of initial slopes of plasma concentration is described, for example, by U.S. Pat. No. 6,913,768, hereby incorporated by reference.

Desirably, the NMDAr antagonist or the levodopa/carbidopa is released into a subject sample at a slower rate than observed for an immediate release (IR) formulation of the same quantity of the antagonist, such that the rate of change in the biological sample measured as the dC/dT over a defined period within the period of 0 to Tmax for the IR formulation (e.g., Namenda, a commercially available IR formulation of memantine). In some embodiments, the dC/dT rate is less than about 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. In some embodiments, the dC/dT rate is less than about 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. Similarly, the rate of release of the NMDAr antagonist or the levodopa/carbidopa from the present invention as measured in dissolution studies is less than 80%, 70%, 60% 50%, 40%, 30%, 20%, or 10% of the rate for an IR formulation of the same NMDAr antagonist or levodopa/carbidopa over the first 1, 2, 4, 6, 8, 10, or 12 hours.

In a preferred embodiment, the dosage form is provided in a non-dose escalating, three times per day (t.i.d.) form. In preferred embodiments, the concentration ramp (or Tmax effect) may be reduced so that the change in concentration as a function of time (dC/dT) is altered to reduce or eliminate the need to dose escalate the NMDAr antagonist. A reduction in dC/dT may be accomplished, for example, by increasing the Tmax in a relatively proportional manner. Accordingly, a two-fold increase in the Tmax value may reduce dC/dT by approximately a factor of 2. Thus, the NMDAr antagonist may be provided so that it is released at a rate that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In certain embodiments, this is accomplished by releasing less than 30%, 50%, 75%, 90%, or 95% of the NMDAr antagonist into the circulatory or neural system within one hour of such administration.

The concentration ramp for levodopa/carbidopa may also be reduced, however such changes will not be preferred in most oral formulations due to the marked reduction in absorption of levodopa/carbidopa after it passes the duodenal region of the gastrointestinal tract.

Optionally, the modified release formulations exhibit plasma concentration curves having initial (e.g., from—2 hours after administration to 4 hours after administration) slopes less-than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist or levodopa/carbidopa. The precise slope for a given individual will vary according to the NMDAr antagonist or levodopa/carbidopa being used, the quantity delivered, or other factors, including, for some active pharmaceutical agents, whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose.

Using the sustained release formulations or administration methods described herein, the NMDAr antagonist reaches a therapeutically effective steady state plasma concentration in a subject within the course of the first two, three, five, seven, nine, ten, twelve, fifteen, or twenty days of administration. For example, the formulations described herein, when administered at a substantially constant daily dose (e.g., at a dose ranging between 200 mg and 800 mg, preferably between 200 mg and 600 mg, and more preferably between 200 mg and 400 mg per day) may reach a steady state plasma concentration in approximately 70%, 60%, 50%, 40%, 30%, or less of the time required to reach such plasma concentration when using a dose escalating regimen.

Dosing Frequency and Dose Escalation

According to the present invention, a subject (e.g., human) having or at risk of having such conditions is administered any of the compositions described herein (e.g., three times per day (t.i.d.), twice per day (b.i.d.), or once per day (q.d.)). While immediate release formulations of NMDAr antagonists are typically administered in a dose-escalating fashion, the compositions described herein may be essentially administered at a constant, therapeutically-effective dose from the onset of therapy. For example, a composition containing a sustained release formulation of amantadine may be administered three times per day, twice per day, or once per day in a unit dose comprising a total daily amantadine dose of 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, or 800 mg. In embodiments comprising a single dosage form containing an NMDAr antagonist and levodopa/carbidopa wherein the levodopa/carbidopa is in an immediate release form, the dosing frequency will be chosen according to the levodopa/carbidopa requirements, (e.g. three times per day).

Reduced Time to Therapeutic Concentration and Efficacy

Immediate release (IR) formulations of memantine (e.g., Namenda) are typically administered at low doses (e.g., 5 mg/day) and are progressively administered at increasing frequency and dose over time to reach a steady state serum concentration that is therapeutically effective. According to the manufacturer's FDA approved label, Namenda, an immediate release (IR) formulation of memantine, is first administered to subjects at a dose of 5 mg per day. After an acclimation period of typically one week, subjects are administered with this dose twice per day. Subjects are next administered with a 5 mg and 10 mg dosing per day and finally administered with 10 mg Namenda twice daily. Using this dosing regimen, a therapeutically effective steady state serum concentration may be achieved within 30 days of the onset of therapy. Using a modified release formulation comprising (22.5 mg memantine,) however, a therapeutically effective steady state concentration may be achieved substantially sooner (within about 13 days), without using a dose escalating regimen. Furthermore, the slope during each absorption period for the sustained release formulation is less (i.e. not as steep) as the slope for Namenda. Accordingly, the dC/dT of the sustained release formulation is reduced relative to the immediate release formulation even though the dose administered is larger than for the immediate release formulation. Based on this model, a sustained release formulation of an NMDAr antagonist may be administered to a subject in an amount that is approximately the full strength dose (or that effectively reaches a therapeutically effective dose) from the onset of therapy and throughout the duration of treatment. Accordingly, a dose escalation would not be required.

Treatment of a subject with the subject of the present invention may be monitored using methods known in the art. The efficacy of treatment using the composition is preferably evaluated by examining the subject's symptoms in a quanti-

tative way, e.g., by noting a decrease in the frequency or severity of symptoms or damaging effects of the condition, or an increase in the time for sustained worsening of symptoms. In a successful treatment, the subject's status will have improved (i.e., frequency or severity of symptoms or damaging effects will have decreased, or the time to sustained progression will have increased). In the model described in the previous paragraph, the steady state (and effective) concentration of the NMDAr antagonist is reached in 25%, 40%, 50%, 60%, 70%, 75%, or 80% less time than in the dose escalated approach.

In another embodiment, a composition is prepared using the methods described herein, wherein such composition comprises memantine or amantadine and a release modifying excipient, wherein the excipient is present in an amount sufficient to ameliorate or reduce the dose-dependent toxicity associated with the memantine or amantadine relative to an immediate release (IR) formulation of memantine, such as Namenda, or amantadine, such as Symmetrel. The use of these compositions enables safer administration of these agents, and even permits the safe use of higher levels for appropriate indications, beyond the useful range for the presently available versions of memantine (5 mg and 10 mg per dose to 20 mg per day) and amantadine (100 mg to 300 mg per day with escalation).

Indications Suitable for Treatment

The compositions and methods of the present invention are particularly suitable for the treatment of Parkinson's disease or conditions associated with Parkinson's disease. These conditions include dementia, dyskinesia, dystonia, depression, fatigue and other neuropsychiatric complications of Parkinson's disease.

Formulations for Alternate Specific Routes of Administration

The pharmaceutical compositions may be optimized for particular types of delivery. For example, pharmaceutical compositions for oral delivery are formulated using pharmaceutically acceptable carriers that are well known in the art. The carriers enable the agents in the composition to be formulated, for example, as a tablet, pill, capsule, solution, suspension, sustained release formulation; powder, liquid or gel for oral ingestion by the subject.

The NMDAr antagonist may also be delivered in an aerosol spray preparation from a pressurized pack, a nebulizer or from a dry powder inhaler. Suitable propellants that can be used in a nebulizer include, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and carbon dioxide. The dosage can be determined by providing a valve to deliver a regulated amount of the compound in the case of a pressurized aerosol.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral, intranasal or respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

In some embodiments, for example, the composition may be delivered intranasally to the cribriform plate rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in U.S. Pat. No. 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Additional formulations suitable for other modes of administration include rectal capsules or suppositories. For suppositories, traditional binders and carriers may include, for example, polyalkylene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%.

The composition may optionally be formulated for delivery in a vessel that provides for continuous long-term delivery, e.g., for delivery up to 30 days, 60 days, 90 days, 180 days, or one year. For example the vessel can be provided in a biocompatible material such as titanium. Long-term delivery formulations are particularly useful in subjects with chronic conditions, for assuring improved patient compliance, and for enhancing the stability of the compositions.

Optionally, the NMDA receptor antagonist, levodopa/carbidopa, or both is prepared using the OROS® technology, described for example, in U.S. Pat. Nos. 6,919,373, 6,923,800, 6,929,803, 6,939,556, and 6,930,128, all of which are hereby incorporated by reference. This technology employs osmosis to provide precise, controlled drug delivery for up to 24 hours and can be used with a range of compounds, including poorly soluble or highly soluble drugs. OROS® technology can be used to deliver high drug doses meeting high drug loading requirements. By targeting specific areas of the gastrointestinal tract, OROS® technology may provide more efficient drug absorption and enhanced bioavailability. The osmotic driving force of OROS® and protection of the drug until the time of release eliminate the variability of drug absorption and metabolism often caused by gastric pH and motility.

Formulations for continuous long-term delivery are provided in, e.g., U.S. Pat. Nos. 6,797,283; 6,764,697; 6,635,268, and 6,648,083.

If desired, the components may be provided in a kit. The kit can additionally include instructions for using the kit.

Additional Methods for Making Modified Release Formulations

Additional methods for making modified release formulations are described in, e.g., U.S. Pat. Nos. 5,422,123, 5,601,845, 5,912,013, and 6,194,000, all of which are hereby incorporated by reference.

In some embodiments, for example, the composition may be delivered via intranasal, buccal, or sublingual routes to the brain rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in U.S. Pat. No. 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Preparation of a pharmaceutical composition for delivery in a subdermally implantable device can be performed using methods known in the art, such as those described in, e.g., U.S. Pat. Nos. 3,992,518; 5,660,848; and 5,756,115.

The invention will be illustrated in the following non-limiting examples.

EXAMPLES

Example 1

Measuring Release Profiles In Vitro

Compositions containing an aminoadamantane and levodopa/carbidopa are analyzed for release of the aminoadamantane and levodopa/carbidopa, according to the USP type 2 apparatus at a speed of 50 rpm. The dissolution media used include water, 0.1N HCl, or 0.1N HCl adjusted to pH 6.8 at 2 hours with phosphate buffer. The dissolution medium is equilibrated to 37±0.5° C.

The USP reference assay method for amantadine is used to measure the fraction of memantine released from the compositions prepared herein. Briefly, 0.6 mL sample (from the dissolution apparatus at a given time point) is placed into a 15 mL culture tube. 1.6 mL 0.1% Bromocresol Purple (in acetic acid) is added and vortexed for five seconds. The mixture is allowed to stand for approximately five minutes. 3 mL Chloroform is added and vortexed for five seconds. The solution is next centrifuged (speed 50 rpm) for five minutes. The top layer is removed with a disposable pipette. A sample is drawn into 1 cm flow cell and the absorbance is measured at 408 nm at 37° C. and compared against a standard curve prepared with known quantities of the same aminoadamantane. The quantity of determined is plotted against the dissolution time for the sample.

The USP reference assay method for levodopa is used to measure the fraction of levodopa released from the compositions prepared herein. Briefly, 0.5 ml samples from the dissolution apparatus removed at various times are assayed by liquid chromatography. The chromatograph is equipped with a 280 nm detector and a 3.9 mm×30 cm column containing packing Ll. The mobile phase is 0.09 N sodium phosphate, 1 mM sodium 1-decanesulfonate, pH 2.8. With the flow rate adjusted to about 2 mL per minute, the levodopa elutes in about 4 minutes and carbidopa elutes in about 11 minutes. From the saved dissolution samples, a 0.02 ml aliquot is injected into the chromatograph and the absorbance is measure and compared to standard to determine concentration & quantity. The quantity dissolved is then plotted against the dissolution time for the sample.

Example 2

Preparation of Amantadine Extended Release Capsules

Amantadine extended release capsules may be formulated as follows or as described, for example, in U.S. Pat. No. 5,395,626.

A. Composition: Unit Dose

The theoretical quantitative composition (per unit dose) for amantadine extended release capsules is provided below.

Component	% weight/weight	mg/Capsule
Amantadine	68.34	200.00
OPADRY ® Clear YS-3-7011[1] (Colorcon, Westpoint, PA)	1.14	5.01
Purified Water, USP[2]	—	—
Sugar Spheres, NF	12.50	54.87
OPADRY ® Clear YS-1-7006[3] (Colorcon, Westpoint, PA)	4.48	19.66
SURELEASE ® E-7-7050[4] (Colorcon, Westpoint, PA)	13.54	59.44
Capsules[5]	—	—
TOTAL.	100.00%	338.98 mg[6]

[1]A mixture of hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol.
[2]Purified Water, USP is evaporated during processing.
[3]A mixture of hydroxypropyl methylcellulose and polyethylene glycol
[4]Solid content only of a 25% aqueous dispersion of a mixture of ethyl cellulose, dibutyl sebacate, oleic acid, ammoniated water and fumed silica. The water in the dispersion is evaporated during processing.
[5]White, opaque, hard gelatin capsule, size 00.
[6]Each batch is assayed prior to filling and the capsule weight is adjusted as required to attain 200 mg amantadine per capsule.

The quantitative batch composition for amantadine extended release capsule is shown below. (Theoretical batch quantity 25,741 capsules).

Step 1: Prep of Amantadine HCl Beads (Bead Build-Up #1)

Component	Weight (kg)
Amantadine	12.000
OPADRY ® Clear YS-3-7011	0.200
Purified Water, USP	5.454
Sugar Sphere, NF	4.000
Total Weight Amantadine Beads	16.200 kg

The amantadine beads obtained from step 1 are used as follows.

Step 2: Clear & Sustained Release Bead Coating #1

Component	Weight (kg)
Amantadine Beads	8.000
OPADRY ® Clear YS-1-7006	0.360
Purified Water, USP	5.928
Surelease ® E-7-7050	0.672
Total Weight Clear Coated Sustained Release Beads	9.032 kg

The sustained release beads obtained from step 2 are used as follows.

Step 3: Amantadine HCl Beads (Build-Up #2)

Component	Weight (kg)
Sustained Release Beads	8.000
Amantadine	4.320
OPADRY ® Clear YS-3-7011	0.072
Purified Water, USP	1.964
Total Weight Amantadine Beads	12.392 kg

The amantadine beads obtained from step 3 are formulated as follows.

Step 4: Clear & Sustained Release Bead Coating #2

Component	Weight (kg)
Amantadine Beads	10.000
OPADRY ® Clear YS-1-7006	0.250
Purified Water, USP	6.450
Surelease ® E-7-7050	1.050
Total Weight Amantadine Extended Release Beads	11.300 kg

Step 5: Capsule Filling—Gelatin Capsules, Size 00, are Filled with 339 mg of the Amantadine Beads Prepared in Step 4.

Example 3

Extended Release Amantadine Formulation with Immediate Release Carbidopa and Levodopa

Levodopa and Carbidopa are formulated into pellets suitable for filling, yet having an immediate release profile. (see, for example, U.S. Pat. No. 5,912,013).

Levodopa Plus Carbidopa Core Pellets

	Weight Percent	Kilograms
MCC	25.0	0.25
Hydroxypropylmethylcellulose Phthalate (HPMCP)	10.0	0.10
Tartaric Acid	10.0	0.10
Sodium Monoglycerate	7.5	0.075
DSS	0.5	0.005
Levodopa	35.8	0.358
Carbidopa	11.2	0.112
TOTAL	100.0%	1.00 kg

Coating

Cellulose Acetate Phthalate (CAP)	60.0	0.60
Ethylcellulose	25.0	0.25
PEG-400	15.0	0.15
TOTAL	100.0%	1.00 kg

The pellets are assayed for levodopa and carbidopa content. It is determined that approximately 223 mg of the pellets contain 80 mg levodopa and 25 mg carbidopa. Dissolution greater than 90% in 30 minutes is also confirmed.

A total of 669 grams of the pellets are blended with 510 grams of the amantadine pellets from Example 2 in a V-blender for 30 minutes at 30 rpm. Gelatin capsules are filled with 393 mg of the mixture and the assays for content are repeated verifying a composition of 100 mg amantadine, 80 mg levodopa, and 25 mg carbidopa.

Example 4

Predicted Dissolution and Plasma Profiles of Amantadine Controlled Release

Using the formulations described above, the dissolution profiles for amantadine were simulated and used to calculate plasma profiles resulting from single or multiple administrations using the pharmacokinetic software, GastroPlus v.4.0.2, from Simulations Plus (see FIG. **2**). The initial slope of the dissolution for the sustained release formulation is less than the slope determined for the immediate release formulation (see FIG. **1**) and the corresponding serum profile also shows a slower dC/dT (see FIG. **4**).

Example 5

Release Profile of Amantadine and L-DOPA (Levodopa/Carbidopa)

Release proportions are shown in the tables below for a combination of amantadine and levodopa/carbidopa. The cumulative fraction is the amount of drug substance released from the formulation matrix to the serum or gut environment (e.g., U.S. Pat. Nos. 4,839,177 or 5,326,570) or as measured with a USP II Paddle system using 0.1N HCl as the dissolution medium.

Time	AMANTADINE T½ = 15 hrs cum. fraction A	LEVODOPA/CARBIDOPA T½ = 1.5 hrs Cum. fraction B
0	0.00	0.00
0.5	0.10	0.40
1.0	0.20	0.95
2.0	0.35	1.00
4.0	0.60	1.00
8.0	0.90	1.00
12.0	0.98	1.00

Example 6

Treating Dyskinesia in Patients with Parkinson's Disease

A Parkinson's patient experiencing dyskinesia is administered the composition of Example 3 three times each day to receive 300 mg amantadine, 240 mg levodopa, and 75 mg carbidopa daily. The Parkinsonism is reduced as measured by the UPDRS (Goetz et al., Mov. Disord. 19:1020-8, 2004, incorporated by reference) as is the dyskinesia (Vitale et al., Neurol. Sci. 22:105-6, 2001, incorporated by reference)

Example 7

Animal Models Showing Reduced Dyskinesia, Reduced Levodopa Potential

The following protocol was employed to demonstrate the beneficial effects of the compositions of this invention. Briefly, squirrel monkeys (N=4) were lesioned with MPTP according to the protocol of Di Monte et al. (Mov. Disord. 15: 459-66 (2000)). After 3 months, the monkeys showed full symptoms of Parkinson's disease as measured by a modified UPDRS (Goetz et al., Mov. Disord. 19:1020-8, 2004). Levodopa treatment at approximately 15 mg/kg (with 1.5 mg/kg carbidopa) mg/kg b.i.d. commenced a baseline UPDRS and dyskinesia measurement was established. Amantadine was added to the regimen simultaneously with the levodopa, and the amount raised from 1 mg/kg to 45 mg/kg for four of the squirrel monkeys, corresponding to an estimated 3 μm concentration. As shown in FIG. **8**, the combination led to a 60% reduction in dyskinesia. We hypothesize that this translates into a potential 40% reduction in levodopa required to maintain UPDRS.

Example 8

Levodopa Sparing Therapy

The following protocol is employed to determine the optimal reduction of levodopa achieved with the addition of Amantadine to a fixed dose combination product.

Parkinson's DISEASE PROTOCOL SUMMARY NPI MEMANTINE CR MONOTHERAPY

Protocol Number: NPI-Amantadine CR

Study Phase: 2/3

Name of Drug: NPI-Amantadine/C/L

Dosage: 25/100/100 c/l/a given t.i.d.

25/80/100 c/l/a given t.i.d.

25/60/100 c/l/a given t.i.d.

Concurrent Control: 25/100 c/l given t.i.d.
Route: Oral
Subject Population: Male and female patients diagnosed with Parkinson's Disease Hoehn and Yahr score of 2-4
Structure: Parallel-group, three-arm study
Study Term Two weeks
Study Sites: Multi-center 10 centers
Blinding: Double blind
Method of Subject Randomized to one of three treatment groups (3:1)
Assignment:
Total Sample Size: 320 subjects (160 men, 160 women)
Primary Efficacy UPDRS
Endpoints: Abnormal involuntary movement scale (AIMS) 0-4
Secondary Endpoints: Modified Obeso dyskinesia rating scale 0-4
Mini-mental state examination (MMSE); Neuropsychiatric Inventory Score (NPI)
Adverse Events: Monitored and elicited by clinic personnel throughout the study, volunteered by patients

Example 9

Pharmaceutical Composition Including Memantine, Levodopa, and Carbidopa

A co-formulation of memantine, levodopa and carbidopa is prepared. This co-formulation matches the absorption properties of levodopa and carbidopa more closely than those of Memantine, thereby extending the effectiveness per dose of levodopa and carbidopa. The co-formulation provides Tmax values to about 4 hours and allows b.i.d. dosing of the combination.

FIG. **6** provides the current single oral dose pharmacokinetic (PK) profiles for levodopa, carbidopa and memantine. FIG. **7** provides idealized pharmacokinetic profiles for the target co-formulation, in which the Tmax values for levodopa and carbidopa more closely match that of Memantine.

Dosage Form: Tablet
Formulation Content: Levodopa 150 mg
Carbidopa 37.5 mg
Memantine 10 mg
Excipients: FDA approved excipients and drug release modifiers. Additional embodiments are within the claims.

Example 10

Pharmaceutical Composition Including Extended Release Formulations of Memantine and Levodopa

A pulsatile release dosage form for administration of memantine and levodopa may be prepared as three individual compartments. Three individual tablets are compressed, each having a different release profile, followed by encapsulation into a gelatin capsule, which are then closed and sealed. The components of the three tablets are as follows.

Component	Function	Amount per tablet
TABLET 1 (IMMEDIATE RELEASE):		
Memantine	Active agent	8 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
TABLET 2 (RELEASE DELAYED 3-5 HOURS FOLLOWING ADMINISTRATION):		
Memantine	Active agent	8 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS3OD	Delayed release coating material	4.76 mg
Talc	Coating component	3.3 mg
Triethyl citrate	Coating component	0.95 mg
TABLET 3 (RELEASE DELAYED 7-9 HOURS FOLLOWING ADMINISTRATION):		
Memantine	Active agent	2.5 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS3OD	Delayed release coating material	6.34 mg
Talc	Coating component	4.4 mg
Triethyl citrate	Coating component	1.27 mg

The tablets are prepared by wet granulation of the individual drug particles and other core components as may be done using a fluid-bed granulator, or are prepared by direct compression of the admixture of components. Tablet 1 is an immediate release dosage form, releasing the active agents within 1-2 hours following administration. Tablets 2 and 3 are coated with the delayed release coating material as may be carried out using conventional coating techniques such as spray-coating or the like. As will be appreciated by those skilled in the art, the specific components listed in the above tables may be replaced with other functionally equivalent components, e.g., diluents, binders, lubricants, fillers, coatings, and the like.

Oral administration of the capsule to a patient will result in a release profile having three pulses, with initial release of the memantine and levodopa from the first tablet being substantially immediate, release of the memantine and levodopa from the second tablet occurring 3-5 hours following administration, and release of the memantine and levodopa from the third tablet occurring 7-9 hours following administration.

Example 11

Pharmaceutical Composition Including Extended Release Formulations of Memantine, Levodopa, and Carbidopa

The method of Example 9 is repeated, except that drug-containing beads are used in place of tablets. Carbidopa is also added in each of the fractions at 25% of the mass of the levodopa. A first fraction of beads is prepared by coating an inert support material such as lactose with the drug which provides the first (immediate release) pulse. A second fraction of beads is prepared by coating immediate release beads with an amount of enteric coating material sufficient to provide a drug release-free period of 3-5 hours. A third fraction of beads is prepared by coating immediate release beads having half the methylphenidate dose of the first fraction of beads with a

greater amount of enteric coating material, sufficient to provide a drug release-free period of 7-9 hours. The three groups of beads may be encapsulated or compressed, in the presence of a cushioning agent, into a single pulsatile release tablet.

Alternatively, three groups of drug particles may be provided and coated as above, in lieu of the drug-coated lactose beads.

OTHER EMBODIMENTS

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A dosage form suitable for once-daily oral administration to a human subject consisting of

(i) 50 mg to 500 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, and (ii) at least one excipient, wherein at least 50% of the drug in the dosage form is in an extended release form, and wherein the dosage form provides a mean change in amantadine plasma concentration as a function of time (dC/dT) that is less than 40% of the dC/dT provided by the same quantity of the drug in an immediate release form, wherein the dC/dT values are measured in a single dose human pharmacokinetic study over the time period between 0 and 4 hours after administration.

2. A dosage form suitable for once-daily oral administration to a human subject consisting of

(i) 50 mg to 500 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, and (ii) at least one excipient, wherein at least 50% of the drug in the dosage form is in an extended release form, and wherein the dosage form provides a mean change in amantadine plasma concentration as a function of time (dC/dT) that is less than 40% of the dC/dT provided by the same quantity of the drug in an immediate release form, wherein the dC/dT values are measured in a single dose human pharmacokinetic study over the time period between administration and Tmax of the immediate release form.

3. A dosage form suitable for once-daily oral administration to a human subject consisting of

(i) 50 mg to 500 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, and (ii) at least one excipient, wherein at least 50% of the drug in the dosage form is in an extended release form, and wherein the dosage form provides a mean change in amantadine plasma concentration as a function of time (dC/dT) that is less than 40% of the dC/dT provided by the same quantity of the drug in an immediate release form, wherein the dC/dT of the dosage form is measured in a single dose human pharmacokinetic study over the time period between 2 hours and 4 hours after administration and the dC/dT provided by the same quantity of the drug in an immediate release form is measured in a single dose human pharmacokinetic study over the time period between administration and Tmax of the immediate release form.

4. The dosage form of any of claims **1-3**, comprising an osmotic device, which utilizes an osmotic driving force to provide extended release of amantadine.

5. The dosage form of any of claims **1-3**, wherein the amount of drug is 100 to 500 mg.

6. The dosage form of any of claims **1-3**, wherein the amount of drug is 200 to 500 mg.

7. The dosage form of any of claims **1-3**, wherein at least 75% of the drug in the dosage form is in an extended release form.

8. The dosage form of any of claims **1-3**, wherein at least 90% of the drug in the dosage form is in an extended release form.

9. The dosage form of any of claims **1-3**, wherein the dosage form provides a shift in amantadine Tmax of 2 hours to 16 hours relative to an immediate release form of amantadine, wherein the Tmax is measured in a single dose human pharmacokinetic study.

10. The dosage form of any of claims **1-3**, wherein the extent of drug bioavailability is maintained.

11. The dosage form of any of claims **1-3**, any of, wherein the dosage form additionally comprises the drug in an immediate release form.

* * * * *

EXHIBIT E

US008895615B1

(12) **United States Patent**
Went et al.

(10) **Patent No.: US 8,895,615 B1**
(45) **Date of Patent: *Nov. 25, 2014**

(54) **COMPOSITION AND METHOD FOR TREATING NEUROLOGICAL DISEASE**

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This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

(63) Continuation of application No. 14/328,440, filed on Jul. 10, 2014, which is a continuation of application No. 13/958,153, filed on Aug. 2, 2013, now Pat. No. 8,796,337, which is a continuation of application No. 13/756,275, filed on Jan. 31, 2013, now abandoned, which is a continuation of application No. 11/286,448, filed on Nov. 23, 2005, now Pat. No. 8,389,578.

(60) Provisional application No. 60/631,095, filed on Nov. 24, 2004.

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USPC **514/565**; 514/656

(58) **Field of Classification Search**
USPC 514/565, 656
See application file for complete search history.

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(57) **ABSTRACT**

Disclosed are compositions comprising amantadine, or a pharmaceutically acceptable salt thereof, and one or more excipients, wherein at least one of the excipients modifies release of amantadine. Methods of administering the same are also provided.

16 Claims, 7 Drawing Sheets

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Figure 1: Simulated Dissolution for TID Amantadine IR & SR

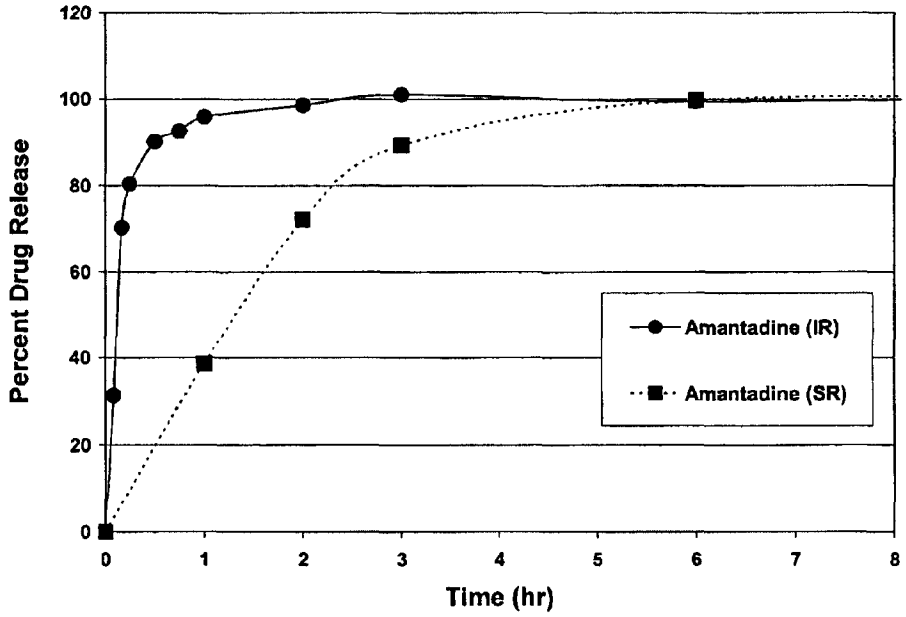


Figure 2: Simulated Plasma Concentration for TID Amantadine IR & SR over 120hrs.

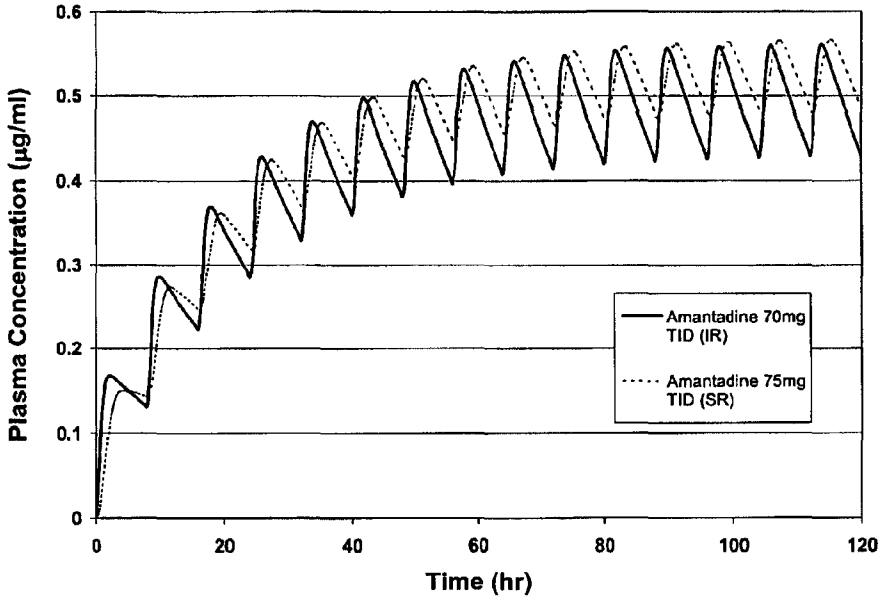


Figure 3: Simulated Plasma Concentration for TID Levodopa/Carbidopa/Amantadine (IR, IR, IR) over 24hrs

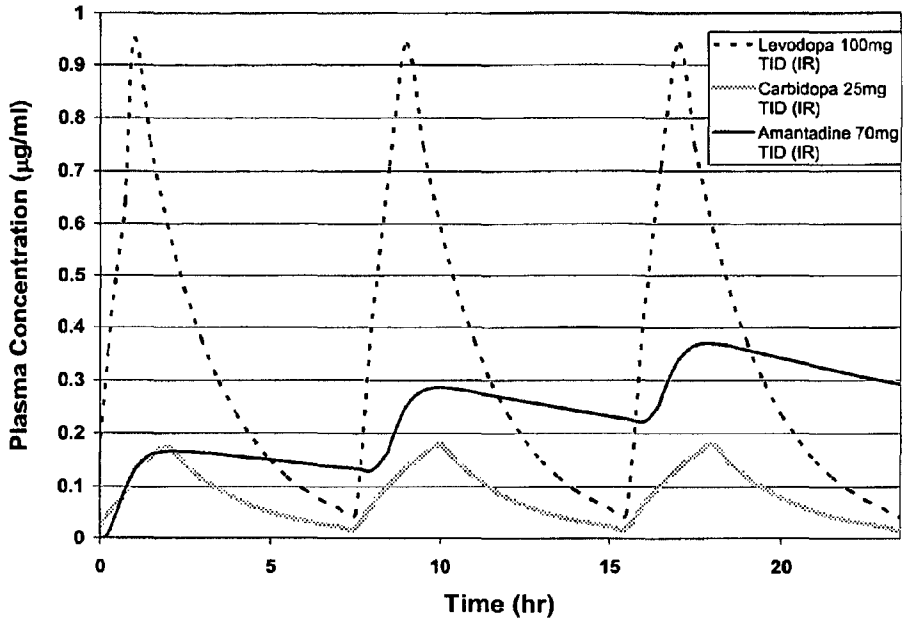


Figure 4: Simulated Plasma Concentration for TID Levodopa/Carbidopa/Amantadine (IR, IR, SR) over 24hrs

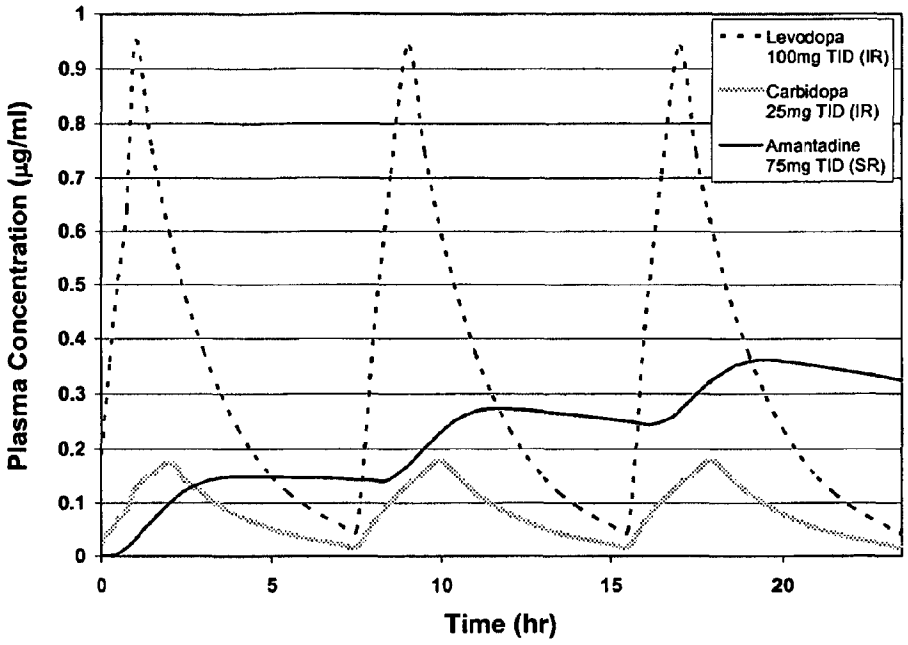


FIGURE 5

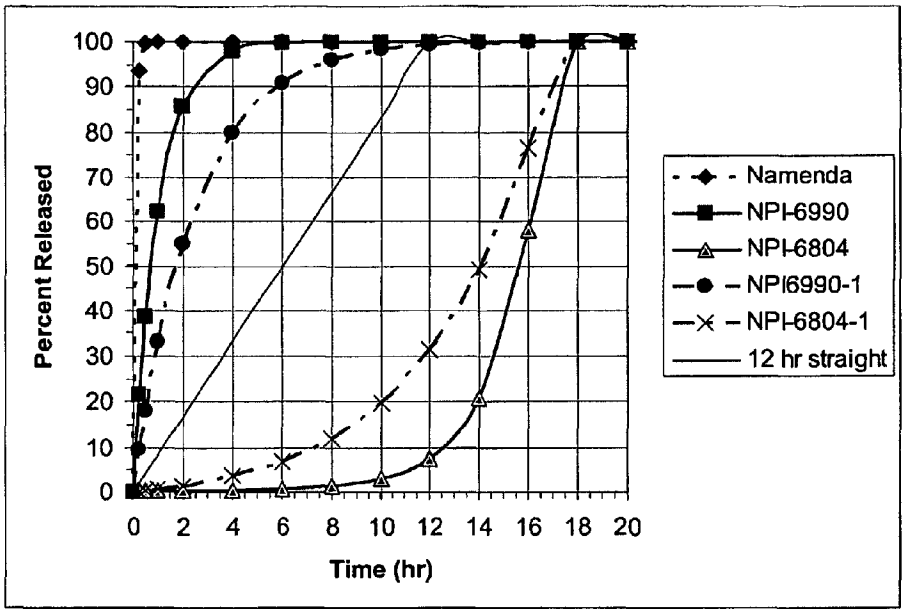

Percent Released
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20
Time (hr)
Namenda
NPI-6990
NPI-6804
NPI6990-1
NPI-6804-1
12 hr straight

Figure 6: Memantine, Levodopa and Carbidopa Human Pharmacokinetics

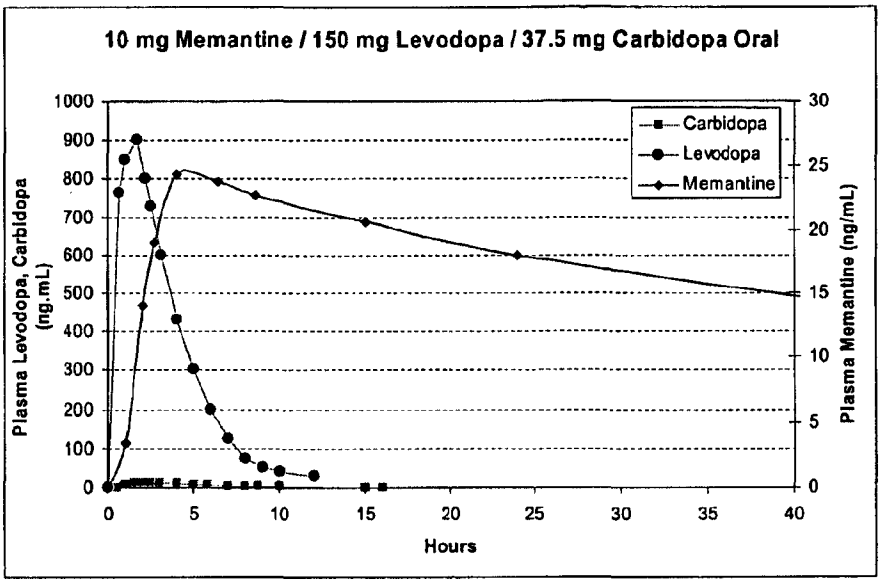
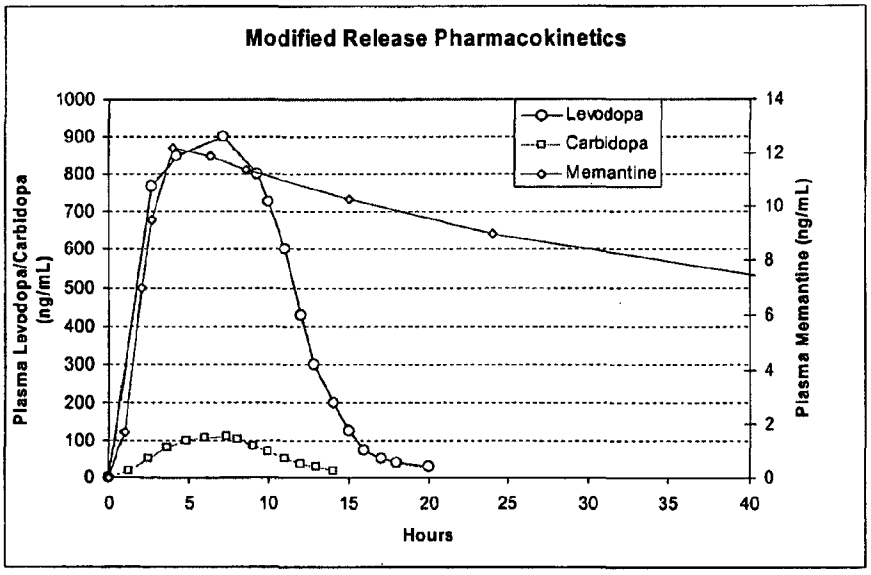


Figure 7: Target Pharmacokinetics



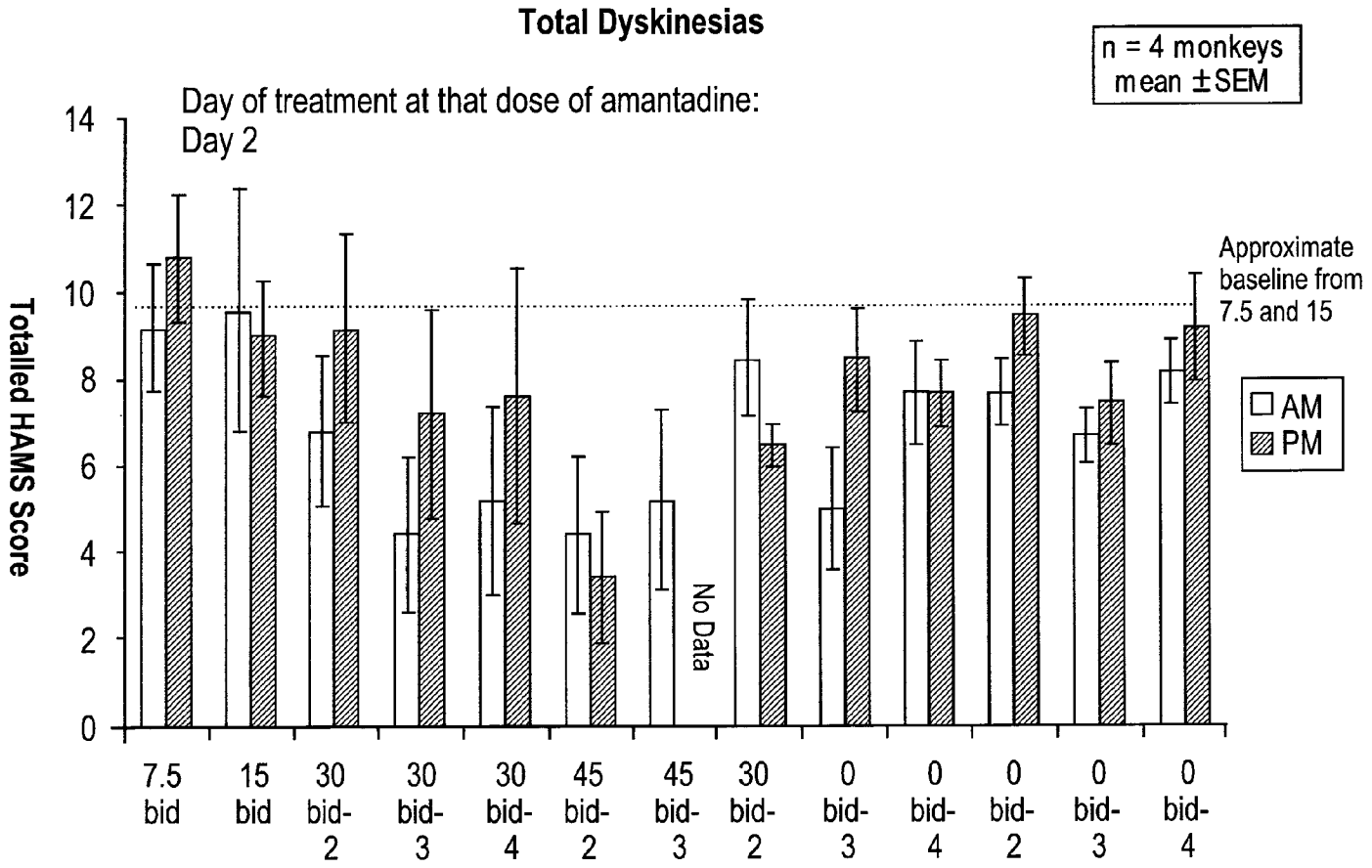

Total Dyskinesias
n = 4 monkeys
mean ±SEM
Day of treatment at that dose of amantadine:
Day 2
Totalled HAMS Score
14
12
10
8
6
4
2
0
Approximate baseline from 7.5 and 15
AM
PM
No Data
7.5 bid
15 bid
30 bid-2
30 bid-3
30 bid-4
45 bid-2
45 bid-3
30 bid-2
0 bid-3
0 bid-4
0 bid-2
0 bid-3
0 bid-4

Figure 8

COMPOSITION AND METHOD FOR TREATING NEUROLOGICAL DISEASE

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/328,440, filed Jul. 10, 2014, which is a continuation of U.S. patent application Ser. No. 13/958,153, filed Aug. 2, 2013, which is a continuation of U.S. patent application Ser. No. 13/756,275, filed Jan. 31, 2013, now abandoned, which is a continuation application of U.S. patent application Ser. No. 11/286,448, filed on Nov. 23, 2005, now U.S. Pat. No. 8,389,578, which claims priority to U.S. Provisional Application No. 60/631,095 filed on Nov. 24, 2004, all of which applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

This invention relates to compositions and methods for treating neurological diseases, such as Parkinson's disease.

BACKGROUND OF THE INVENTION

Parkinson's disease (PD) is a progressive, degenerative neurologic disorder which usually occurs in late mid-life. PD is clinically characterized by bradykinesia, tremor, and rigidity. Bradykinesia is characterized by a slowness in movement, slowing the pace of such routine activities as walking and eating. Tremor is a shakiness that generally affects limbs that are not otherwise in motion. For those PD-patients diagnosed at a relatively young age, tremor is reported as the most disabling symptom. Older patients face their greatest challenge in walking or keeping their balance. Rigidity is caused by the inability of muscles to relax as opposing muscle groups contract, causing tension which can produce aches and pains in the back, neck, shoulders, temples, or chest.

PD predominantly affects the substantia nigra (SNc) dopamine (DA) neurons and is therefore associated with a decrease in striatal DA content. Because dopamine does not cross the blood-brain barrier, PD patients may be administered a precursor, levodopa, that does cross the blood-brain barrier where it is metabolized to dopamine. Levodopa therapy is intended to compensate for reduced dopamine levels and is a widely prescribed therapeutic agent for patients with Parkinson's disease. Chronic treatment with levodopa however, is associated with various debilitating side-effects such as dyskinesia.

Since currently available drugs containing levodopa are associated with debilitating side effects, better therapies are needed for the management of PD.

SUMMARY OF THE INVENTION

In general, the present invention provides methods and compositions for treating and preventing CNS-related conditions, such as Parkinson's disease or other Parkinson's-like diseases or conditions, by administering to a subject in need thereof a combination that includes an N-Methyl-D-Aspartate receptor (NMDAr) antagonist and levodopa. Exemplary NMDAr antagonists include the aminoadamantanes, such as memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1-aminoethyl)adamantane), or amantadine (1-amino-adamantane) as well as others described below. Because levodopa is metabolized before crossing the blood-brain barrier and has a short half-life in the circulatory system, it is typically administered in conjunction with a dopa-

decarboxylase inhibitor. Examples of dopa-decarboxylase inhibitors include carbidopa, 3-hydroxy-benzylhydrazinedihydrochloride (NSD-1015), and benseraxide hydrochloride. The combination may further include a catechol-0-methyltransferase (COMT) inhibitor including, for example, talcapone and entacapone. As used herein, levodopa/carbidopa shall mean levodopa alone or in combination with a dopa-decarboxylase inhibitor such as carbidopa. Desirably, the levodopa/carbidopa is in an immediate release formulation and the NMDA receptor antagonist is in an extended release formulation. One preferred embodiment of the invention involves the combination of amantadine and levodopa/carbidopa. Desirably, amantadine is provided in an extended release formulation and levodopa/carbidopa is provided as an immediate release formulation. By combining an NMDAr antagonist (e.g., amantadine) with the second agents described herein (e.g., levodopa/carbidopa), this invention provides an effective pharmaceutical composition for treating neurological diseases such as Parkinson's disease or other Parkinson's-like diseases or conditions. The administration of this combination is postulated to maintain or enhance the efficacy of levodopa while significantly reducing its dyskinesia side effects.

The combinations described herein provide complementary benefits associated with the NMDAr antagonist or levodopa/carbidopa individually, while minimizing difficulties previously presented when each component is used separately in a patient. For example, amantadine dosing is limited by neurotoxicity that is likely associated with its short Tmax. By extending the release of amantadine, a higher effective dose can be maintained providing both dyskinesia relief and a reduction in the amount of levodopa required for treatment of the disease symptoms. Given the inherent toxicity of levodopa, such a levodopa sparing combination will result in a decline in both the dyskinesia and overall disease.

Accordingly, the pharmaceutical compositions described herein are administered so as to deliver to a subject, an amount of an NMDAr antagonist, levodopa/carbidopa or both agents that is high enough to treat symptoms or damaging effects of an underlying disease while avoiding undesirable side effects. These compositions may be employed to administer the NMDAr antagonist, the levodopa/carbidopa, or both agents at a lower frequency than presently employed, improving patient compliance, adherence, and caregiver convenience. These compositions are particularly useful as they provide the NMDAr antagonist, levodopa/carbidopa, or both agents, at a therapeutically effective amount from the onset of therapy further improving patient compliance and adherence and enable the achievement of a therapeutically effective steady-state concentration of either or both agents of the combination in a shorter period of time resulting in an earlier indication of effectiveness and increasing the utility of these therapeutic agents for diseases and conditions where time is of the essence. Also provided are methods for making and using such compositions.

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a controlled or extended release form with or without an immediate release component in order to maximize the therapeutic benefit of such agents, while reducing unwanted side effects. In preferred embodiments for oral administration, levodopa/carbidopa is provided as an immediate-release formulation.

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be administered in an amount similar to that typically administered to subjects. Preferably, the amount of the NMDAr antagonist may be administered in an amount greater than or less than the amount that is typically admin-

istered to subjects while the levodopa/carbidopa is provided at a lower dose than normally used. For example, the amount of amantadine required to positively affect the patient response (inclusive of adverse effects) may be 300, 400, 500, 600 mg per day rather than the typical 200-300 mg per day administered for presently approved indications i.e. without the improved formulation described herein, while the levodopa, and optionally the carbidopa, can be reduced independently by 10%, 20%, 30%, 40%, 50%, 60%, 70% or up to 80% of what is currently required in the absence of the NMDAr antagonist.

Optionally, lower or reduced amounts of both the NMDAr antagonist and the levodopa/carbidopa are used in a unit dose relative to the amount of each agent when administered independently. The present invention therefore features formulations of combinations directed to dose optimization or release modification to reduce adverse effects associated with separate administration of each agent. The combination of the NMDAr antagonist and the levodopa/carbidopa may result in an additive or synergistic response, and using the unique formulations described herein, the goal of minimizing the levodopa burden is achieved. Preferably, the NMDAr antagonist and the levodopa/carbidopa are provided in a unit dosage form.

The compositions and methods of the invention are particularly useful for the treatment of Parkinson's disease or conditions associated with Parkinson's disease. These conditions include dementia, dyskinesia, dystonia, depression, fatigue and other neuropsychiatric complications of Parkinson's disease.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present Specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. All parts and percentages are by weight unless otherwise specified.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a graph showing the dissolution profiles for an immediate and sustained release formulation of amantadine. The sustained release formulation exhibits a dC/dT during the initial phase that is about 10% of that for the immediate release formulation.

FIG. **2** is a graph showing the amantadine plasma concentration over a period of 5 days, as predicted by Gastro-Plus software package v.4.0.2, following the administration of either 70 mg amantadine in an immediate release formulation t.i.d. or 75 mg amantadine in a sustained release formulation t.i.d. The sustained release formulation peaks are similar in height to the immediate release formulation even with a higher administered dose and the diurnal variation is substantially reduced.

FIG. **3** is a graph showing the plasma profiles simulated using Gastro-Plus for t.i.d. administration of amantadine (70 mg), levodopa (100 mg), and carbidopa (25 mg), all in an immediate release form.

FIG. **4** is a graph showing the plasma profiles simulated using Gastro-Plus for t.i.d. administration of amantadine (75 mg), levodopa (100 mg), and carbidopa (25 mg), where the amantadine is in a sustained release form and the levodopa and carbidopa are in an immediate release form.

FIG. **5** is a graph representing dissolution profiles for various aminoadamantane formulations including an immediate release form of the NMDAr antagonist memantine (Namenda).

FIG. **6** is a graphical representation of plasma release profiles in a human of memantine, levodopa, and carbidopa when memantine is administered separately from levodopa and carbidopa.

FIG. **7** is a graphical representation of plasma release profiles in a human of memantine, levodopa, and carbidopa when memantine, levodopa, and carbidopa are administered as part of a single controlled-release pharmaceutical composition.

FIG. **8** is a bar graph showing the effects on a primate (squirrel monkey) treated with a combination of levodopa/carbidopa and amantadine.

DETAILED DESCRIPTION OF THE INVENTION

In general, the present invention features pharmaceutical compositions that contain therapeutically effective levels of an NMDAr antagonist and levodopa/carbidopa and, optionally, a pharmaceutical carrier. Preferably the compositions are formulated for modified or extended release to provide a serum or plasma concentration of the NMDAr antagonist over a desired time period that is high enough to be therapeutically effective but at a rate low enough so as to avoid adverse events associated with the NMDAr antagonist. Control of drug release is particularly desirable for reducing and delaying the peak plasma level while maintaining the extent of drug bioavailability. Therapeutic levels are therefore achieved while minimizing debilitating side-effects that are usually associated with immediate release formulations. Furthermore, as a result of the delay in the time to obtain peak serum or plasma level and the extended period of time at the therapeutically effective serum or plasma level, the dosage frequency is reduced to, for example, once or twice daily dosage, thereby improving patient compliance and adherence. For example, side effects including psychosis and cognitive deficits associated with the administration of NMDAr antagonists may be lessened in severity and frequency through the use of controlled-release methods that shift the Tmax to longer times, thereby reducing the dC/dT of the drug. Reducing the dC/dT of the drug not only increases Tmax, but also reduces the drug concentration at Tmax and reduces the Cmax/Cmean ratio providing a more constant amount of drug to the subject being treated over a given period of time, enabling increased dosages for appropriate indications.

In addition, the present invention encompasses optimal ratios of NMDAr and levodopa/carbidopa, designed to not only treat the dyskinesia associated with levodopa, but also take advantage of the additivity and synergy between these drug classes. For example, the level of levodopa required to treat the disease symptoms can unexpectedly be reduced by up to 50% by the addition of 400 mg/day of amantadine.

Making NMDAr Antagonist Controlled Release Formulations

A pharmaceutical composition according to the invention is prepared by combining a desired NMDAr antagonist or antagonists with one or more additional ingredients that, when administered to a subject, causes the NMDAr antagonist to be released at a targeted rate for a specified period of time. A release profile, i.e., the extent of release of the NMDAr antagonist over a desired time, can be conveniently determined for a given time by measuring the release using a USP dissolution apparatus under controlled conditions. Pre-

ferred release profiles are those which slow the rate of uptake of the NMDAr antagonist in the neural fluids while providing therapeutically effective levels of the NMDAr antagonist. One of ordinary skill in the art can prepare combinations with a desired release profile using the NMDAr antagonists and formulation methods described below.

NMDAr Antagonists

Any NMDAr antagonist can be used in the methods and compositions of the invention, particularly those that are non-toxic when used in the compositions of the invention. The term "nontoxic" is used in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to humans or, in keeping with established regulatory criteria and practice, is susceptible to approval by the FDA or similar regulatory agency for any country for administration to humans or animals.

The term "NMDAr antagonist", as used herein, includes any amino-adamantane compound including, for example, memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1-aminoethyl)adamantane), amantadine (1-amino-adamantane), as well as pharmaceutically acceptable salts thereof. Memantine is described, for example, in U.S. Pat. Nos. 3,391,142, 5,891,885, 5,919,826, and 6,187,338. Amantadine is described, for example, in U.S. Pat. Nos. 3,152,180, 5,891,885, 5,919,826, and 6,187,338. Additional aminoadamantane compounds are described, for example, in U.S. Pat. Nos. 4,346,112, 5,061,703, 5,334,618, 6,444,702, 6,620,845, and 6,662,845. All of these patents are hereby incorporated by reference.

Further NMDAr antagonists that may be employed include, for example, aminocylohexanes such as neramexane, ketamine, eliprodil, ifenprodil, dizocilpine, remacemide, iamotrigine, riluzole, aptiganel, phencyclidine, flupirtine, celfotel, felbamate, spermine, spermidine, levemopamil, dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and its metabolite, dextrorphan ((+)-3-hydroxy-N-methylmorphinan), a pharmaceutically acceptable salt, derivative, or ester thereof, or a metabolic precursor of any of the foregoing.

Optionally, the NMDAr antagonist in the instant invention is memantine and not amantadine or dextromethorphan.

Second Agents

In all foregoing aspects of the invention, the second agent is levodopa. When levodopa is in the combination, the combination preferably also includes a dopa-decarboxylase inhibitor. An example of a suitable dopa-decarboxylase inhibitor is carbidopa. Other dopa-decarboxylase inhibitors include, for example, 3-hydroxy-benzylhydrazinedihydrochloride (NSD-1015) and benseraxide hydrochloride. The combination may further include a catechol-O-methyltransferase (COMT) inhibitor including, for example, talcapone and entacapone.

Dosing, PK, & Toxicity

The NMDA receptor antagonist used in combination therapies are administered at a dosage of generally between about 1 and 5000 mg/day, between 1 and about 800 mg/day, or between 1 and 500 mg/day. For example, NMDA receptor antagonist agents may be administered at a dosage ranging between about 1 and about 500 mg/day, more preferably from about 10 to about 40, 50, 60, 70 or 80 mg/day, advantageously from about 10 to about 20 mg per day. Amantadine may be administered at a dose ranging from about 90, 100 mg/day to about 400, 500, 600, 700 or 800 mg/day, advantageously from about 100 to about 500, 600 mg per day. For example, the pharmaceutical composition may be formulated to provide memantine in an amount ranging between 1-200 mg/day, 1 and 80 mg/day, 2-80 mg/day, 10-80 mg/day, 10 and 80 mg/day, 10 and 70 mg/day, 10 and 60 mg/day, 10 and 50 mg/day, 10 and 40 mg/day, 5 and 65 mg/day, 5 and 40 mg/day, 15 and 45 mg/day, or 10 and 20 mg/day; dextromethorphan in an amount ranging between 1-5000 mg/day, 1-1000 mg/day, and 100-800 mg/day, or 200-500 mg/day. Pediatric doses will typically be lower than those determined for adults.

Table 1 shows exemplary pharmacokinetic properties (e.g., Tmax and T1/2) of memantine, amantadine, and rimantadine.

TABLE 1

Pharmacokinetics and Toxicity in humans for selected NIVIDAr antagonists

Compound	Human PK ($t_{1/2}$) (hours)	Tmax (hours)	Normal Dose	Dose Dependent Toxicity
Memantine	60	3	10-20 mg/day, starting at 5 mg	Dose escalation required, hallucination
Amantadine	15	3	100-300 mg/day, starting at 100 mg/day	Hallucination
Rimantadine	25	6	100-200 mg/day	Insomnia

When levodopa and carbidopa are both included in the composition, the levodopa dose ranges between 100 to 3000 mg per day, 75 mg and 2500 mg/day, 100-2000 mg/day, or 250 and 1000 mg/day divided for administration t.i.d. or more frequently. Carbidopa doses may range between the amounts of 1 to 1000 mg/day, 10 to 500 mg/day, and 25 to 100 mg/day. Optionally, the carbidopa is present in the combination at about 75%, 70%, 65%, 60%, 50%, 40%, 30%, 25%, 20%, and 10% of the mass of the levodopa. Alternatively, the amount of levodopa is less than 300% than the amount of carbidopa. For example, 75 mg of carbidopa (amount that is sufficient to extend the half-life of levodopa in the circulatory system) may be used in combination with 300 to 3000 mg of levodopa per day. The combination may contain a single dosage form comprising 30 to 200 mg amantadine, 30 to 250 mg levodopa, and 10 to 100 mg of carbidopa for t.i.d. or more frequent administration, including multiple dosage forms per administration.

As a result, the preferred dosage forms for optimized use are shown in Table 2 below, with their corresponding commercial equivalent.

TABLE 2

Dosage forms with and without NMDAr antagonist (amount per unit dose)

Sinemet Compositions		Compositions of Present Invention		
Levodopa	Carbidopa	Levodopa	Carbidopa	Amantadine
100 mg IR*	25 mg IR	50-100 mg IR	25 mg IR	100-200 mg IR
100 mg IR	10 mg IR	50-100 mg IR	10 mg IR	50-100 mg IR
100 mg IR	25 mg IR	50-100 mg IR	25 mg IR	100-200 mg CR**
100 mg IR	10 mg IR	50-100 mg IR	10 mg IR	50-100 mg CR

*IR: immediate release

**CR: modified release

Excipients

"Pharmaceutically or Pharmacologically Acceptable" includes molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. "Pharmaceutically Acceptable Carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifun-

gal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. "Pharmaceutically Acceptable Salts" include acid addition salts and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

The preparation of pharmaceutical or pharmacological compositions is known to those of skill in the art in light of the present disclosure. General techniques for formulation and administration are found in "Remington: The Science and Practice of Pharmacy, Twentieth Edition," Lippincott Williams & Wilkins, Philadelphia, Pa. Tablets, capsules, pills, powders, granules, dragees, gels, slurries, ointments, solutions suppositories, injections, inhalants and aerosols are examples of such formulations.

By way of example, modified or extended release oral formulation can be prepared using additional methods known in the art. For example, a suitable extended release form of the either active pharmaceutical ingredient or both may be a matrix tablet or capsule composition. Suitable matrix forming materials include, for example, waxes (e.g., carnauba, bees wax, paraffin wax, ceresine, shellac wax, fatty acids, and fatty alcohols), oils, hardened oils or fats (e.g., hardened rapeseed oil, castor oil, beef tallow, palm oil, and soya bean oil), and polymers (e.g., hydroxypropyl cellulose, polyvinylpyrrolidone, hydroxypropyl methyl cellulose, and polyethylene glycol). Other suitable matrix tabletting materials are microcrystalline cellulose, powdered cellulose, hydroxypropyl cellulose, ethyl cellulose, with other carriers, and fillers. Tablets may also contain granulates, coated powders, or pellets. Tablets may also be multi-layered. Multi-layered tablets are especially preferred when the active ingredients have markedly different pharmacokinetic profiles. Optionally, the finished tablet may be coated or uncoated.

The coating composition typically contains an insoluble matrix polymer (approximately 15-85% by weight of the coating composition) and a water soluble material (e.g., approximately 15-85% by weight of the coating composition). Optionally an enteric polymer (approximately 1 to 99% by weight of the coating composition) may be used or included. Suitable water soluble materials include polymers such as polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials such as sugars (e.g., lactose, sucrose, fructose, mannitol and the like), salts (e.g., sodium chloride, potassium chloride and the like), organic acids (e.g., fumaric acid, succinic acid, lactic acid, and tartaric acid), and mixtures thereof. Suitable enteric polymers include hydroxypropyl methyl cellulose, acetate succinate, hydroxypropyl methyl cellulose, phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups.

The coating composition may be plasticised according to the properties of the coating blend such as the glass transition temperature of the main component or mixture of components or the solvent used for applying the coating compositions. Suitable plasticisers may be added from 0 to 50% by weight of the coating composition and include, for example, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, acetylated citrate esters, dibutylsebacate, and castor oil. If desired, the coating composition may include a filler. The amount of the filler may be I % to approximately 99% by weight based on the total weight of the coating composition and may be an insoluble material such as silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, MCC, or polacrilin potassium.

The coating composition may be applied as a solution or latex in organic solvents or aqueous solvents or mixtures thereof. If solutions are applied, the solvent may be present in amounts from approximate by 25-99% by weight based on the total weight of dissolved solids. Suitable solvents are water, lower alcohol, lower chlorinated hydrocarbons, ketones, or mixtures thereof. If latexes are applied, the solvent is present in amounts from approximately 25-97% by weight based on the quantity of polymeric material in the latex. The solvent may be predominantly water.

The NMDAr antagonist may be formulated using any of the following excipients or combinations thereof.

Excipient name	Chemical name	Function
Avicel PH102	Microcrystalline Cellulose	Filler, binder, wicking, disintegrant
Avicel PH101	Microcrystalline Cellulose	Filler, binder, disintegrant
Eudragit RS-30D	Polymethacrylate Poly(ethyl acrylate, nethyl methacrylate, timethylammonioethyl methacrylate chloride) 1:2:0.1	Film former, tablet binder, tablet diluent; Rate controlling polymer for controlled release
Methocel K100M Premium CR	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Methocel K100M	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Magnesium Stearate	Magnesium Stearate	Lubricant
Talc	Talc	Dissolution control; anti-adherent, glidant
Triethyl Citrate	Triethyl Citrate	Plasticizer
Methocel E5	Hydroxypropyl methylcellulose	Film-former
Opadry ®	Hydroxypropyl methylcellulose	One-step customized coating system which combines polymer, plasticizer and, if desired, pigment in a dry concentrate.
Surelease ®	Aqueous Ethylcellulose Dispersion	Film-forming polymer; plasticizer and stabilizers. Rate controlling polymer coating.

The pharmaceutical composition described herein may also include a carrier such as a solvent, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents. The use of such media and agents for pharmaceutically active substances is well known in the art. Pharmaceutically acceptable salts can also be used in the composition, for example, mineral salts such as hydrochlorides, hydrobromides, phosphates, or sulfates, as well as the salts of organic acids such as acetates, proprionates, malonates, or benzoates. The composition may also contain liquids, such as water, saline, glycerol, and ethanol, as well as substances such as wetting agents, emulsifying agents, or pH buffering agents. Liposomes, such as those described in U.S.

Pat. No. 5,422,120, WO 95/13796, WO 91/14445, or EP 524,968 B1, may also be used as a carrier.

Methods for Preparing Modified or Extended Release Formulations

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a controlled or extended release form with or without an immediate release component in order to maximize the therapeutic benefit of such agents, while reducing unwanted side effects. In the absence of modified release components (referred to herein as controlled, extended, or delayed release components), the NMDAr antagonist, levodopa/carbidopa, or both is released and transported into the body fluids over a period of minutes to several hours. The combination described herein however, may contain an NMDAr antagonist and a sustained release component, such as a coated sustained release matrix, a sustained release matrix, or a sustained release bead matrix. In one example, in addition to levodopa/carbidopa, amantadine (e.g., 50¬1400 mg) is formulated without an immediate release component using a polymer matrix (e.g., Eudragit), Hydroxypropyl methyl cellulose (HPMC) and a polymer coating (e.g., Eudragit). Such formulations are compressed into solid tablets or granules and coated with a controlled release material such as Opadry® or Surelease®. Levodopa/carbidopa may also be formulated as a sustained release formulation; in most cases, however, this will not be optimal.

Suitable methods for preparing the compositions described herein in which the NMDAr antagonist is provided in modified or extended release-formulations include those described in U.S. Pat. No. 4,606,909 (hereby incorporated by reference). This reference describes a controlled release multiple unit formulation in which a multiplicity of individually coated or microencapsulated units are made available upon disintegration of the formulation (e.g., pill or tablet) in the stomach of the subject (see, for example, column 3, line 26 through column 5, line 10 and column 6, line 29 through column 9, line 16). Each of these individually coated or microencapsulated units contains cross-sectionally substantially homogenous cores containing particles of a sparingly soluble active substance, the cores being coated with a coating that is substantially resistant to gastric conditions but which is erodable under the conditions prevailing in the gastrointestinal tract.

The composition of the invention may alternatively be formulated using the methods disclosed in U.S. Pat. No. 4,769,027, for example. Accordingly, extended release formulations involve prills of pharmaceutically acceptable material (e.g., sugar/starch, salts, and waxes) may be coated with a water permeable polymeric matrix containing an NMDAr antagonist and next overcoated with a water-permeable film containing dispersed within it a water soluble particulate pore forming material.

The NMDAr antagonist composition may additionally be prepared as described in U.S. Pat. No. 4,897,268, involving a biocompatible, biodegradable microcapsule delivery system. Thus, the NMDAr antagonist may be formulated as a composition containing a blend of free-flowing spherical particles obtained by individually microencapsulating quantities of memantine, for example, in different copolymer excipients which biodegrade at different rates, therefore releasing memantine into the circulation at a predetermined rates. A quantity of these particles may be of such a copolymer excipient that the core active ingredient is released quickly after administration, and thereby delivers the active ingredient for an initial period. A second quantity of the particles is of such type excipient that delivery of the encapsulated ingredient begins as the first quantity's delivery begins to decline. A third quantity of ingredient may be encapsulated with a still different excipient which results in delivery beginning as the delivery of the second quantity beings to decline. The rate of delivery may be altered, for example, by varying the lactide/glycolide ratio in a poly(D,L-lactide-co-glycolide) encapsulation. Other polymers that may be used include polyacetal polymers, polyorthoesters, polyesteramides, polycaprolactone and copolymers thereof, polycarbonates, polyhydroxybuterate and copolymers thereof, polymaleamides, copolyaxalates and polysaccharides.

Alternatively, the composition may be prepared as described in U.S. Pat. No. 5,395,626, which features a multilayered controlled release pharmaceutical dosage form. The dosage form contains a plurality of coated particles wherein each has multiple layers about a core containing an NMDAr antagonist whereby the drug containing core and at least one other layer of drug active is overcoated with a controlled release barrier layer therefore providing at least two controlled releasing layers of a water soluble drug from the multilayered coated particle

Release Profile

The compositions described herein are formulated such that the NMDAr antagonist, levodopa/carbidopa, or both agents have an in vitro dissolution profile that is equal to or slower than that for an immediate release formulation. As used herein, the immediate release (IR) formulation for memantine means the present commercially available 5 mg and 10 mg tablets (i.e., Namenda from Forest Laboratories, Inc. or formulations having substantially the same release profiles as Namenda); and the immediate release (IR) formulation of amantadine means the present commercially available 100 mg tablets (i.e., Symmetrel from Endo Pharmaceuticals, Inc. or formulations having substantially the same release profiles as Symmetrel); and the immediate release (IR) formulation of levodopa/carbidopa means the present commercially available 25 mg/100 mg, 10 mg/100 mg, 25 mg/250 mg tablets of carbidopa/levodopa (i.e., Sinemet from Merck & Co. Inc. or formulations having substantially the same release profiles as Sinemet). These compositions may comprise immediate release, sustained or extended release, or delayed release components, or may include combinations of same to produce release profiles such that the fraction of NMDAr antagonist or levodopa/carbidopa released is greater or equal to $0.01(0.297+0.0153*e^{(0.515*t)})$ and less than or equal to $1-e^{(-10.9*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C., in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist or levodopa/carbidopa released is less than 93% in 15 minutes and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1N HCl) dissolution medium. Optionally, the fraction of released NMDAr antagonist or levodopa/carbidopa is greater than or equal to $0.01(0.297+0.0153*e^{(0.515*t)})$, and less than or equal to $1-e^{(-10.9*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C., in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist or levodopa/carbidopa that is released may range between 0.1%-62% in one hour, 0.2%-86% in two hours, 0.6%-100% in six hours, 2.9%-100% in 10 hours, and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1 N HCl) dissolution medium. Optionally, the NMDA receptor antagonist has a

release profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 70% or greater (e.g., 70%-90%) in 10 hours, and 90% or greater (e.g., 90-95%) in 12 hours as measured in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1 N HCl) dissolution medium. For example, a formulation containing amantadine may have a release profile ranging between 0-60% or 0.1-20% in one hour, 0-86% or 5-30% at two hours, 0.6-100% or 40-80% at six hours, 3-100% or 50% or more (e.g., 50-90%) at ten hours, and 7.7-100% at twelve hours in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1 N HCl) dissolution medium. In one embodiment, the NMDAr antagonist, the levodopa/carbidopa, or both agents have an in vitro dissolution profile of less than 25%, 15%, 10%, or 5% in fifteen minutes; 50%, 30%, 25%, 20%, 15%, or 10% in 30 minutes and more than 60%, 65% 70%, 75%, 80%, 85%, 90%, 95% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water. Desirably, the NMDAr antagonist, the levodopa/carbidopa, or both agents has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% in a dissolution media having a pH of 1.2 at 10 hours. It is important to note that the dissolution profile for the NMDAr antagonist may be different than the release profile for levodopa/carbidopa. In a preferred embodiment, the levodopa/carbidopa release profile is equal to or similar to that for an immediate release formulation and the release profile for the NMDAr antagonist is controlled to provide a dissolution profile of less than 30% in one hour, less than 50% in two hours, and greater than 95% in twelve hours using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water.

Desirably, the compositions described herein have an in vitro profile that is substantially identical to the dissolution profile shown in FIG. **5** and, upon administration to a subject at a substantially constant daily dose, achieves a serum concentration profile that is substantially identical to that shown in FIGS. **2** and **4**.

As described above, the NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a modified or extended release form. Modified or extended drug release is generally controlled either by diffusion through a coating or matrix or by erosion of a coating or matrix by a process dependent on, for example, enzymes or pH. The NMDAr antagonist or the levodopa/carbidopa may be formulated for modified or extended release as described herein or using standard techniques in the art. In one example, at least 50%, 75%, 90%, 95%, 96%, 97%, 98%, 99%, or even in excess of 99% of the NMDAr antagonist or the levodopa/carbidopa is provided in an extended release dosage form. In a preferred embodiment, the levodopa/carbidopa is provided in an immediate release formulation and the NMDAr antagonist is in either an immediate or modified release form.

The composition described herein is formulated such the NMDAr antagonist or levodopa/carbidopa has an in vitro dissolution profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 50%-90% in 10 hours, and 90%-95% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. using 0.1N HCl as a dissolution medium. Alternatively, the NMDAr antagonist has an in vitro dissolution profile in a solution with a neutral pH (e.g., water) that is substantially the same as its dissolution profile in an acidic dissolution medium. Thus, the NMDAr antagonist may be released in both dissolution media at the following rate: between 0.1-20% in one hour, 5-30% in two hours, 40-80% in six hours, 70-90% in 10 hours, and 90%-95% in 12 hours as obtained using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. In one embodiment, the NMDAr antagonist has an in vitro dissolution profile of less than 15%, 10%, or 5% in fifteen minutes, 25%, 20%, 15%, or 10% in 30 minutes, and more than 60% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water. Desirably, the NMDAr antagonist has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% at 10 hours in a dissolution medium having a pH of 1.2.

Initial Rate In Vivo, Delayed Tmax

As used herein, "C" refers to the concentration of an active pharmaceutical ingredient in a biological sample, such as a patient sample (e.g. blood, serum, and cerebrospinal fluid). The time required to reach the maximal concentration ("Cmax") in a particular patient sample type is referred to as the "Tmax". The change in concentration is termed "dC" and the change over a prescribed time is "dC/dT".

The NMDAr antagonist or levodopa/carbidopa is provided as a sustained release formulation that may or may not contain an immediate release formulation. If desired, the NMDAr antagonist may be formulated so that it is released at a rate that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In addition, the NMDAr antagonist levodopa/carbidopa may be provided such that it is released at a rate resulting in a Cmax/Cmean of approximately 2 or less for approximately 2 hours to at least 8 hours after the NMDAr antagonist is introduced into a subject. Optionally, the sustained release formulations exhibit plasma concentration curves having initial (e.g., from 0, 1, 2 hours after administration to 4, 6, 8 hours after administration) slopes less than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist. The precise slope for a given individual will vary according to the NMDAr antagonist being used or other factors, including whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose. The determination of initial slopes of plasma concentration is described, for example, by U.S. Pat. No. 6,913,768, hereby incorporated by reference.

Desirably, the NMDAr antagonist or the levodopa/carbidopa is released into a subject sample at a slower rate than observed for an immediate release (IR) formulation of the same quantity of the antagonist, such that the rate of change in the biological sample measured as the dC/dT over a defined period within the period of 0 to Tmax for the IR formulation (e.g., Namenda, a commercially available IR formulation of memantine). In some embodiments, the dC/dT rate is less than about 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. In some embodiments, the dC/dT rate is less than about 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. Similarly, the rate of release of the NMDAr antagonist or the levodopa/carbidopa from the present invention as measured in dissolution studies is less than 80%, 70%, 60% 50%, 40%, 30%, 20%, or 10% of the rate for an IR formulation of the same NMDAr antagonist or levodopa/carbidopa over the first 1, 2, 4, 6, 8, 10, or 12 hours.

In a preferred embodiment, the dosage form is provided in a non-dose escalating, three times per day (t.i.d.) form. In preferred embodiments, the concentration ramp (or Tmax

effect) may be reduced so that the change in concentration as a function of time (dC/dT) is altered to reduce or eliminate the need to dose escalate the NMDAr antagonist. A reduction in dC/dT may be accomplished, for example, by increasing the Tmax in a relatively proportional manner. Accordingly, a two-fold increase in the Tmax value may reduce dC/dT by approximately a factor of 2. Thus, the NMDAr antagonist may be provided so that it is released at a rate that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In certain embodiments, this is accomplished by releasing less than 30%, 50%, 75%, 90%, or 95% of the NMDAr antagonist into the circulatory or neural system within one hour of such administration.

The concentration ramp for levodopa/carbidopa may also be reduced, however such changes will not be preferred in most oral formulations due to the marked reduction in absorption of levodopa/carbidopa after it passes the duodenal region of the gastrointestinal tract.

Optionally, the modified release formulations exhibit plasma concentration curves having initial (e.g., from—2 hours after administration to 4 hours after administration) slopes less-than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist or levodopa/carbidopa. The precise slope for a given individual will vary according to the NMDAr antagonist or levodopa/carbidopa being used, the quantity delivered, or other factors, including, for some active pharmaceutical agents, whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose.

Using the sustained release formulations or administration methods described herein, the NMDAr antagonist reaches a therapeutically effective steady state plasma concentration in a subject within the course of the first two, three, five, seven, nine, ten, twelve, fifteen, or twenty days of administration. For example, the formulations described herein, when administered at a substantially constant daily dose (e.g., at a dose ranging between 200 mg and 800 mg, preferably between 200 mg and 600 mg, and more preferably between 200 mg and 400 mg per day) may reach a steady state plasma concentration in approximately 70%, 60%, 50%, 40%, 30%, or less of the time required to reach such plasma concentration when using a dose escalating regimen.

Dosing Frequency and Dose Escalation

According to the present invention, a subject (e.g., human) having or at risk of having such conditions is administered any of the compositions described herein (e.g., three times per day (t.i.d.), twice per day (b.i.d.), or once per day (q.d.)). While immediate release formulations of NMDAr antagonists are typically administered in a dose-escalating fashion, the compositions described herein may be essentially administered at a constant, therapeutically-effective dose from the onset of therapy. For example, a composition containing a sustained release formulation of amantadine may be administered three times per day, twice per day, or once per day in a unit dose comprising a total daily amantadine dose of 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, or 800 mg. In embodiments comprising a single dosage form containing an NMDAr antagonist and levodopa/carbidopa wherein the levodopa/carbidopa is in an immediate release form, the dosing frequency will be chosen according to the levodopa/carbidopa requirements, (e.g. three times per day).

Reduced Time to Therapeutic Concentration and Efficacy

Immediate release (IR) formulations of memantine (e.g., Namenda) are typically administered at low doses (e.g., 5 mg/day) and are progressively administered at increasing frequency and dose over time to reach a steady state serum concentration that is therapeutically effective. According to the manufacturer's FDA approved label, Namenda, an immediate release (IR) formulation of memantine, is first administered to subjects at a dose of 5 mg per day. After an acclimation period of typically one week, subjects are administered with this dose twice per day. Subjects are next administered with a 5 mg and 10 mg dosing per day and finally administered with 10 mg Namenda twice daily. Using this dosing regimen, a therapeutically effective steady state serum concentration may be achieved within 30 days of the onset of therapy. Using a modified release formulation comprising (22.5 mg memantine,) however, a therapeutically effective steady state concentration may be achieved substantially sooner (within about 13 days), without using a dose escalating regimen. Furthermore, the slope during each absorption period for the sustained release formulation is less (i.e. not as steep) as the slope for Namenda. Accordingly, the dC/dT of the sustained release formulation is reduced relative to the immediate release formulation even though the dose administered is larger than for the immediate release formulation. Based on this model, a sustained release formulation of an NMDAr antagonist may be administered to a subject in an amount that is approximately the full strength dose (or that effectively reaches a therapeutically effective dose) from the onset of therapy and throughout the duration of treatment. Accordingly, a dose escalation would not be required.

Treatment of a subject with the subject of the present invention may be monitored using methods known in the art. The efficacy of treatment using the composition is preferably evaluated by examining the subject's symptoms in a quantitative way, e.g., by noting a decrease in the frequency or severity of symptoms or damaging effects of the condition, or an increase in the time for sustained worsening of symptoms. In a successful treatment, the subject's status will have improved (i.e., frequency or severity of symptoms or damaging effects will have decreased, or the time to sustained progression will have increased). In the model described in the previous paragraph, the steady state (and effective) concentration of the NMDAr antagonist is reached in 25%, 40%, 50%, 60%, 70%, 75%, or 80% less time than in the dose escalated approach.

In another embodiment, a composition is prepared using the methods described herein, wherein such composition comprises memantine or amantadine and a release modifying excipient, wherein the excipient is present in an amount sufficient to ameliorate or reduce the dose-dependent toxicity associated with the memantine or amantadine relative to an immediate release (IR) formulation of memantine, such as Namenda, or amantadine, such as Symmetrel. The use of these compositions enables safer administration of these agents, and even permits the safe use of higher levels for appropriate indications, beyond the useful range for the presently available versions of memantine (5 mg and 10 mg per dose to 20 mg per day) and amantadine (100 mg to 300 mg per day with escalation).

Indications Suitable for Treatment

The compositions and methods of the present invention are particularly suitable for the treatment of Parkinson's disease or conditions associated with Parkinson's disease. These conditions include dementia, dyskinesia, dystonia, depression, fatigue and other neuropsychiatric complications of Parkinson's disease.

Formulations for Alternate Specific Routes of Administration

The pharmaceutical compositions may be optimized for particular types of delivery. For example, pharmaceutical compositions for oral delivery are formulated using pharmaceutically acceptable carriers that are well known in the art. The carriers enable the agents in the composition to be formulated, for example, as a tablet, pill, capsule, solution, suspension, sustained release formulation; powder, liquid or gel for oral ingestion by the subject.

The NMDAr antagonist may also be delivered in an aerosol spray preparation from a pressurized pack, a nebulizer or from a dry powder inhaler. Suitable propellants that can be used in a nebulizer include, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and carbon dioxide. The dosage can be determined by providing a valve to deliver a regulated amount of the compound in the case of a pressurized aerosol.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral, intranasal or respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

In some embodiments, for example, the composition may be delivered intranasally to the cribriform plate rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in U.S. Pat. No. 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Additional formulations suitable for other modes of administration include rectal capsules or suppositories. For suppositories, traditional binders and carriers may include, for example, polyalkylene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%.

The composition may optionally be formulated for delivery in a vessel that provides for continuous long-term delivery, e.g., for delivery up to 30 days, 60 days, 90 days, 180 days, or one year. For example the vessel can be provided in a biocompatible material such as titanium. Long-term delivery formulations are particularly useful in subjects with chronic conditions, for assuring improved patient compliance, and for enhancing the stability of the compositions.

Optionally, the NMDA receptor antagonist, levodopa/carbidopa, or both is prepared using the OROS® technology, described for example, in U.S. Pat. Nos. 6,919,373, 6,923,800, 6,929,803, 6,939,556, and 6,930,128, all of which are hereby incorporated by reference. This technology employs osmosis to provide precise, controlled drug delivery for up to 24 hours and can be used with a range of compounds, including poorly soluble or highly soluble drugs. OROS® technology can be used to deliver high drug doses meeting high drug loading requirements. By targeting specific areas of the gastrointestinal tract, OROS® technology may provide more efficient drug absorption and enhanced bioavailability. The osmotic driving force of OROS® and protection of the drug until the time of release eliminate the variability of drug absorption and metabolism often caused by gastric pH and motility.

Formulations for continuous long-term delivery are provided in, e.g., U.S. Pat. Nos. 6,797,283; 6,764,697; 6,635,268, and 6,648,083.

If desired, the components may be provided in a kit. The kit can additionally include instructions for using the kit.

Additional Methods for Making Modified Release Formulations

Additional methods for making modified release formulations are described in, e.g., U.S. Pat. Nos. 5,422,123, 5,601,845, 5,912,013, and 6,194,000, all of which are hereby incorporated by reference.

In some embodiments, for example, the composition may be delivered via intranasal, buccal, or sublingual routes to the brain rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in U.S. Pat. No. 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Preparation of a pharmaceutical composition for delivery in a subdermally implantable device can be performed using methods known in the art, such as those described in, e.g., U.S. Pat. Nos. 3,992,518; 5,660,848; and 5,756,115.

The invention will be illustrated in the following non-limiting examples.

EXAMPLES

Example 1

Measuring Release Profiles In Vitro

Compositions containing an aminoadamantane and levodopa/carbidopa are analyzed for release of the aminoadamantane and levodopa/carbidopa, according to the USP type 2 apparatus at a speed of 50 rpm. The dissolution media used include water, 0.1N HCl, or 0.1N HCl adjusted to pH 6.8 at 2 hours with phosphate buffer. The dissolution medium is equilibrated to 37±0.5° C.

The USP reference assay method for amantadine is used to measure the fraction of memantine released from the compositions prepared herein. Briefly, 0.6 mL sample (from the dissolution apparatus at a given time point) is placed into a 15 mL culture tube. 1.6 mL 0.1% Bromocresol Purple (in acetic acid) is added and vortexed for five seconds. The mixture is allowed to stand for approximately five minutes. 3 mL Chloroform is added and vortexed for five seconds. The solution is next centrifuged (speed 50 rpm) for five minutes. The top layer is removed with a disposable pipette. A sample is drawn into 1 cm flow cell and the absorbance is measured at 408 nm at 37° C. and compared against a standard curve prepared with known quantities of the same aminoadamantane. The quantity of determined is plotted against the dissolution time for the sample.

The USP reference assay method for levodopa is used to measure the fraction of levodopa released from the compositions prepared herein. Briefly, 0.5 ml samples from the dissolution apparatus removed at various times are assayed by liquid chromatography. The chromatograph is equipped with a 280 nm detector and a 3.9 mm×30 cm column containing packing L1. The mobile phase is 0.09 N sodium phosphate, 1

mM sodium 1-decanesulfonate, pH 2.8. With the flow rate adjusted to about 2 mL per minute, the levodopa elutes in about 4 minutes and carbidopa elutes in about 11 minutes. From the saved dissolution samples, a 0.02 ml aliquot is injected into the chromatograph and the absorbance is measure and compared to standard to determine concentration & quantity. The quantity dissolved is then plotted against the dissolution time for the sample.

Example 2

Preparation of Amantadine Extended Release Capsules

Amantadine extended release capsules may be formulated as follows or as described, for example, in U.S. Pat. No. 5,395,626.

A. Composition: Unit Dose

The theoretical quantitative composition (per unit dose) for amantadine extended release capsules is provided below.

Component	% weight/weight	mg/Capsule
Amantadine	68.34	200.00
OPADRY ® Clear YS-3-7011[1] (Colorcon, Westpoint, PA)	1.14	5.01
Purified Water, USP[2]	—	—
Sugar Spheres, NF	12.50	54.87
OPADRY ® Clear YS-1-7006[3] (Colorcon, Westpoint, PA)	4.48	19.66
SURELEASE ® E-7-7050[4] (Colorcon, Westpoint, PA)	13.54	59.44
Capsules[5]	—	—
TOTAL.	100.00%	338.98 mg[6]

[1]A mixture of hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol.

[2] Purified Water, USP is evaporated during processing.

[3]A mixture of hydroxypropyl methylcellulose and polyethylene glycol

[4]Solid content only of a 25% aqueous dispersion of a mixture of ethyl cellulose, dibutyl sebacate, oleic acid, ammoniated water and fumed silica. The water in the dispersion is evaporated during processing.

[5]White, opaque, hard gelatin capsule, size 00.

[6]Each batch is assayed prior to filling and the capsule weight is adjusted as required to attain 200 mg amantadine per capsule.

The quantitative batch composition for amantadine extended release capsule is shown below. (Theoretical batch quantity 25,741 capsules).

Step 1: Prep of Amantadine HC1 Beads (bead Build-up #1)

Component	Weight (kg)
Amantadine	12.000
OPADRY ® Clear YS-3-7011	0.200
Purified Water, USP	5.454
Sugar Sphere, NF	4.000
Total Weight Amantadine Bends	16.200 kg

The amantadine beads obtained from step 1 are used as follows.

Step 2: Clear & Sustained Release Bead Coating #1

Component	Weight (kg)
Amantadine Beads	8.000
OPADRY ® Clear YS-1-7006	0.360
Purified Water, USP	5.928

-continued

Step 2: Clear & Sustained Release Bead Coating #1

Component	Weight (kg)
Surelease ® E-7-7050	0.672
Total Weight Clear Coated Sustained Release Beads	9.032 kg

The sustained release beads obtained from step 2 are used as follows.

Step 3: Amantadine HC1 Beads (Build-up #2)

Component	Weight (kg)
Sustained Release Beads	8.000
Amantadine	4.320
OPADRY ® Clear YS-3-7011	0.072
Purified Water, USP	1.964
Total Weight Amantadine Beads	12.392 kg

The amantadine beads obtained from step 3 are formulated as follows.

Step 4: Clear & Sustained Release Bead Coating #2

Component	Weight (kg)
Amantadine Beads	10.000
OPADRY ® Clear YS-1-7006	0.250
Purified Water, USP	6.450
Surelease ® E-7-7050	1.050
Total Weight Amantadine Extended Release Beads	11.300 kg

Step 5: Capsule Filling -- Gelatin capsules, size 00, are filled with 339 mg of the amantadine beads prepared in step 4.

Example 3

Extended Release Amantadine Formulation with Immediate Release Carbidopa and Levodopa

Levodopa and Carbidopa are formulated into pellets suitable for filling, yet having an immediate release profile. (see, for example, U.S. Pat. No. 5,912,013).

	Weight Percent	Kilograms
Levodopa plus Carbidopa Core Pellets		
MCC	25.0	0.25
Hydroxypropylmethylcellulose Phthalate (HPMCP)	10.0	0.10
Tartaric Acid	10.0	0.10
Sodium Monoglycerate	7.5	0.075
DSS	0.5	0.005
Levodopa	35.8	0.358
Carbidopa	11.2	0.112
TOTAL	100.0%	1.00 kg
Coating		
Cellulose Acetate Phthalate (CAP)	60.0	0.60
Ethylcellulose	25.0	0.25
PEG-400	15.0	0.15

-continued

	Weight Percent	Kilograms
TOTAL	100.0%	1.00 kg

The pellets are assayed for levodopa and carbidopa content. It is determined that approximately 223 mg of the pellets contain 80 mg levodopa and 25 mg carbidopa. Dissolution greater than 90% in 30 minutes is also confirmed.

A total of 669 grams of the pellets are blended with 510 grams of the amantadine pellets from Example 2 in a V-blender for 30 minutes at 30 rpm. Gelatin capsules are filled with 393 mg of the mixture and the assays for content are repeated verifying a composition of 100 mg amantadine, 80 mg levodopa, and 25 mg carbidopa.

Example 4

Predicted Dissolution and Plasma Profiles of Amantadine Controlled Release

Using the formulations described above, the dissolution profiles for amantadine were simulated and used to calculate plasma profiles resulting from single or multiple administrations using the pharmacokinetic software, GastroPlus v.4.0.2, from Simulations Plus (see FIG. **2**). The initial slope of the dissolution for the sustained release formulation is less than the slope determined for the immediate release formulation (see FIG. **1**) and the corresponding serum profile also shows a slower dC/dT (see FIG. **4**).

Example 5

Release Profile of Amantadine and L-DOPA (Levodopa/Carbidopa)

Release proportions are shown in the tables below for a combination of amantadine and levodopa/carbidopa. The cumulative fraction is the amount of drug substance released from the formulation matrix to the serum or gut environment (e.g., U.S. Pat. No. 4,839,177 or 5,326,570) or as measured with a USP II Paddle system using 0.1N HCl as the dissolution medium.

Time	AMANTADINE T½ = 15 cum. fraction A	LEVODOPA/CARBIDOPA T½ = 1.5 hrs, Cum. fraction B
0	0.00	0.00
0.5	0.10	0.40
1.0	0.20	0.95
2.0	0.35	1.00
4.0	0.60	1.00
8.0	0.90	1.00
12.0	0.98	1.00

Example 6

Treating Dyskinesia in Patients with Parkinson's Disease

A Parkinson's patient experiencing dyskinesia is administered the composition of Example 3 three times each day to receive 300 mg amantadine, 240 mg levodopa, and 75 mg carbidopa daily. The Parkinsonism is reduced as measured by the UPDRS (Goetz et al., Mov. Disord. 19:1020-8, 2004, incorporated by reference) as is the dyskinesia (Vitale et al., Neurol. Sci. 22:105-6, 2001, incorporated by reference)

Example 7

Animal Models Showing Reduced Dyskinesia, Reduced Levodopa Potential

The following protocol was employed to demonstrate the beneficial effects of the compositions of this invention. Briefly, squirrel monkeys (N=4) were lesioned with MPTP according to the protocol of Di Monte et al. (Mov. Disord. 15: 459-66 (2000)). After 3 months, the monkeys showed full symptoms of Parkinson's disease as measured by a modified UPDRS (Goetz et al., Mov. Disord. 19:1020-8, 2004). Levodopa treatment at approximately 15 mg/kg (with 1.5 mg/kg carbidopa) mg/kg b.i.d. commenced a baseline UPDRS and dyskinesia measurement was established. Amantadine was added to the regimen simultaneously with the levodopa, and the amount raised from 1 mg/kg to 45 mg/kg for four of the squirrel monkeys, corresponding to an estimated 3 μm concentration. As shown in FIG. **8**, the combination led to a 60% reduction in dyskinesia. We hypothesize that this translates into a potential 40% reduction in levodopa required to maintain UPDRS.

Example 8

Levodopa Sparing Therapy

The following protocol is employed to determine the optimal reduction of levodopa achieved with the addition of Amantadine to a fixed dose combination product.

Parkinson's DISEASE PROTOCOL SUMMARY NPI MEMANTINE CR MONOTHERAPY

Protocol Number:	NPI-Amantadine CR
Study Phase:	2/3
Name of Drug:	NPI-Amantadine/C/L
Dosage:	25/100/100 c/l/a given t.i.d. 25/80/100 c/l/a given t.i.d. 25/60/100 c/l/a given t.i.d.
Concurrent Control:	25/100 c/1 given t.i.d.
Route:	Oral
Subject Population:	Male and female patients diagnosed with Parkinson's Disease Hoehn and Yahr score of 2-4
Structure:	Parallel-group, three-arm study
Study Term	Two weeks
Study Sites:	Multi-center 10 centers
Blinding:	Double blind
Method of Subject Assignment:	Randomized to one of three treatment groups (3:1)
Total Sample Size:	320 subjects (160 men, 160 women)
Primary Efficacy Endpoints:	UPDRS Abnormal involuntary movement scale (AIMS) 0-4
Secondary Endpoints:	Modified Obeso dyskinesia rating scale 0-4 Mini-mental state examination (MMSE); Neuropsychiatric InventoryScore (NPI)
Adverse Events:	Monitored and elicited by clinic personnel throughout the study, volunteered by patients

Example 9

Pharmaceutical Composition Including Memantine, Levodopa, and Carbidopa

A co-formulation of memantine, levodopa and carbidopa is prepared. This co-formulation matches the absorption prop-

erties of levodopa and carbidopa more closely than those of Memantine, thereby extending the effectiveness per dose of levodopa and carbidopa. The co-formulation provides Tmax values to about 4 hours and allows b.i.d. dosing of the combination.

FIG. **6** provides the current single oral dose pharmacokinetic (PK) profiles for levodopa, carbidopa and memantine. FIG. **7** provides idealized pharmacokinetic profiles for the target co-formulation, in which the Tmax values for levodopa and carbidopa more closely match that of Memantine.

Dosage Form:	Tablet
Formulation Content:	Levodopa 150 mg
Carbidopa	37.5 mg
Memantine	10 mg
Excipients:	FDA approved excipients and drug release modifiers. Additional embodiments are within the claims.

Example 10

Pharmaceutical Composition Including Extended Release Formulations of Memantine and Levodopa

A pulsatile release dosage form for administration of memantine and levodopa may be prepared as three individual compartments. Three individual tablets are compressed, each having a different release profile, followed by encapsulation into a gelatin capsule, which are then closed and sealed. The components of the three tablets are as follows.

Component	Function	Amount per tablet
TABLET 1 (IMMEDIATE RELEASE):		
Memantine	Active agent	8 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
TABLET 2 (RELEASE DELAYED 3-5 HOURS FOLLOWING ADMINISTRATION):		
Memantine	Active agent	8 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS3OD	Delayed release coating material	4.76 mg
Talc	Coating component	3.3 mg
Triethyl citrate	Coating component	0.95 mg
TABLET 3 (RELEASE DELAYED 7-9 HOURS FOLLOWING ADMINISTRATION):		
Memantine	Active agent	2.5 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS3OD	Delayed release coating material	6.34 mg
Talc	Coating component	4.4 mg
Triethyl citrate	Coating component	1.27 mg

The tablets are prepared by wet granulation of the individual drug particles and other core components as may be done using a fluid-bed granulator, or are prepared by direct compression of the admixture of components. Tablet 1 is an immediate release dosage form, releasing the active agents within 1-2 hours following administration. Tablets 2 and 3 are coated with the delayed release coating material as may be carried out using conventional coating techniques such as spray-coating or the like. As will be appreciated by those skilled in the art, the specific components listed in the above tables may be replaced with other functionally equivalent components, e.g., diluents, binders, lubricants, fillers, coatings, and the like.

Oral administration of the capsule to a patient will result in a release profile having three pulses, with initial release of the memantine and levodopa from the first tablet being substantially immediate, release of the memantine and levodopa from the second tablet occurring 3-5 hours following administration, and release of the memantine and levodopa from the third tablet occurring 7-9 hours following administration.

Example 11

Pharmaceutical Composition Including Extended Release Formulations of Memantine, Levodopa, and Carbidopa

The method of Example 9 is repeated, except that drug-containing beads are used in place of tablets. Carbidopa is also added in each of the fractions at 25% of the mass of the levodopa. A first fraction of beads is prepared by coating an inert support material such as lactose with the drug which provides the first (immediate release) pulse. A second fraction of beads is prepared by coating immediate release beads with an amount of enteric coating material sufficient to provide a drug release-free period of 3-5 hours. A third fraction of beads is prepared by coating immediate release beads having half the methylphenidate dose of the first fraction of beads with a greater amount of enteric coating material, sufficient to provide a drug release-free period of 7-19 hours. The three groups of beads may be encapsulated or compressed, in the presence of a cushioning agent, into a single pulsatile release tablet.

Alternatively, three groups of drug particles may be provided and coated as above, in lieu of the drug-coated lactose beads.

OTHER EMBODIMENTS

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A method comprising:

orally administering to a human subject with Parkinson's disease a once-daily dose consisting of (i) 200 mg to 500 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, and (ii) at least one excipient, wherein at least 50% of the drug in the dose is in an extended release form, and wherein the dose provides a mean change in amantadine plasma concentration as a function of time (dC/dT) that is less than 40% of the dC/dT provided by the same quantity of the drug in an immediate release form, wherein the dC/dT values are measured in a single

dose human pharmacokinetic study over the time period between 0 and 4 hours after administration.

2. A method comprising:

orally administering to a human subject with Parkinson's disease a once-daily dose consisting of (i) 200 mg to 500 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, and (ii) at least one excipient, wherein at least 50% of the drug in the dose is in an extended release form, and wherein the dose provides a mean change in amantadine plasma concentration as a function of time (dC/dT) that is less than 40% of the dC/dT provided by the same quantity of the drug in an immediate release form, wherein the dC/dT values are measured in a single dose human pharmacokinetic study over the time period between administration and Tmax of the immediate release form.

3. A method comprising:

orally administering to a human subject with Parkinson's disease a once-daily dose consisting of (i) 200 mg to 500 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, and (ii) at least one excipient, wherein at least 50% of the drug in the dose is in an extended release form, and wherein the dose provides a mean change in amantadine plasma concentration as a function of time (dC/dT) that is less than 40% of the dC/dT provided by the same quantity of the drug in an immediate release form, wherein the dC/dT of the dose is measured in a single dose human pharmacokinetic study over the time period between 2 hours and 4 hours after administration and the dC/dT provided by the same quantity of the drug in an immediate release form is measured in a single dose human pharmacokinetic study over the time period between administration and Tmax of the immediate release form.

4. The method of any of claims **1** to **3**, wherein the amount of the drug is 300 to 500 mg.

5. The method of any of claims **1** to **3**, wherein at least 75% of the drug in the dose is in an extended release form.

6. The method of any of claims **1** to **3**, wherein the dose additionally comprises the drug in an immediate release form.

7. The method of any of claims **1** to **3**, wherein at least 90% of the drug in the dose is in an extended release form.

8. The method of any of claims **1** to **3**, wherein the dose administered is therapeutically effective for the treatment of Parkinson's disease.

9. The method of any of claims **1** to **3**, wherein the human subject with Parkinson's disease suffers from dyskinesia.

10. The method of claim **9**, wherein the method reduces the frequency or severity of dyskinesia.

11. The method of claim **9**, wherein the dyskinesia is levodopa-induced dyskinesia.

12. The method of any of claims **1** to **3**, additionally comprising administering to the subject a pharmaceutically effective amount of levodopa/carbidopa.

13. The method of any of claims **1** to **3**, wherein the dose provides a shift in amantadine Tmax of 2 hours to 16 hours relative to an immediate release form of amantadine, wherein the Tmax is measured in a single dose human pharmacokinetic study.

14. The method of any of claims **1** to **3**, wherein the dose comprises an osmotic device which utilizes an osmotic driving force to provide extended release of the drug.

15. The method of any of claims **1** to **3**, wherein the extent of drug bioavailability is maintained.

16. The method of any of claims **1** to **3**, wherein the once-daily dose is administered at a therapeutically-effective dose from the onset of therapy.

* * * * *

EXHIBIT F

US008895616B1

(12) United States Patent
Went et al.

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(45) Date of Patent: *Nov. 25, 2014

(54) **COMPOSITION AND METHOD FOR TREATING NEUROLOGICAL DISEASE**

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This patent is subject to a terminal disclaimer.

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(63) Continuation of application No. 14/328,440, filed on Jul. 10, 2014, which is a continuation of application No. 13/958,153, filed on Aug. 2, 2013, now Pat. No. 8,796,337, which is a continuation of application No. 13/756,275, filed on Jan. 31, 2013, now abandoned, which is a continuation of application No. 11/286,448, filed on Nov. 23, 2005, now Pat. No. 8,389,578.

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(52) **U.S. Cl.**

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(58) **Field of Classification Search**

USPC 514/565, 656

See application file for complete search history.

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(57) **ABSTRACT**

Disclosed are compositions comprising amantadine, or a pharmaceutically acceptable salt thereof, and one or more excipients, wherein at least one of the excipients modifies release of amantadine. Methods of administering the same are also provided.

14 Claims, 7 Drawing Sheets

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Figure 1: Simulated Dissolution for TID Amantadine IR & SR

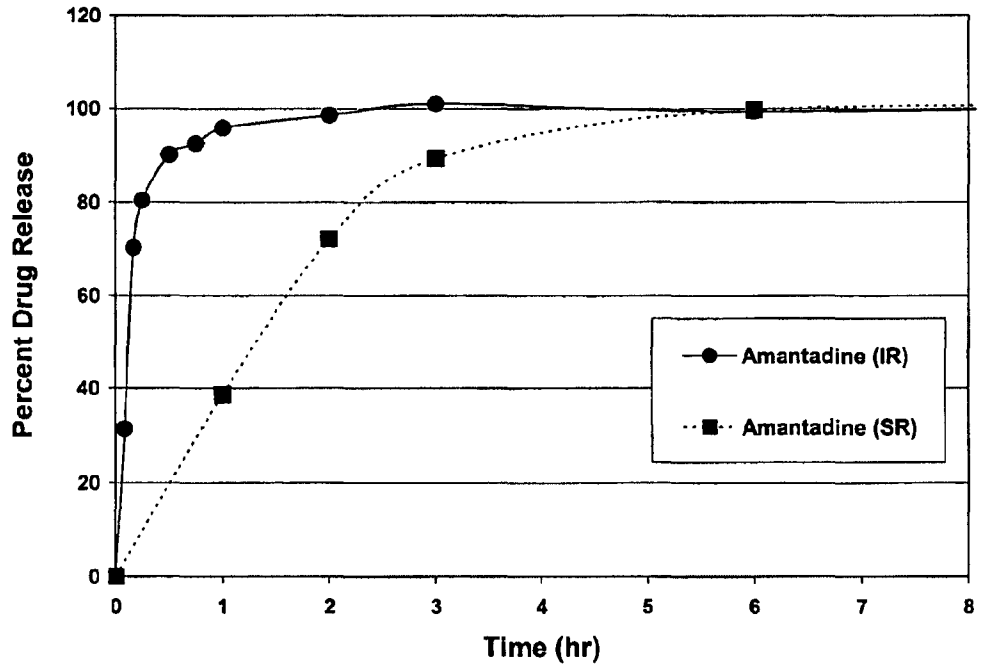


Figure 2: Simulated Plasma Concentration for TID Amantadine IR & SR over 120hrs.

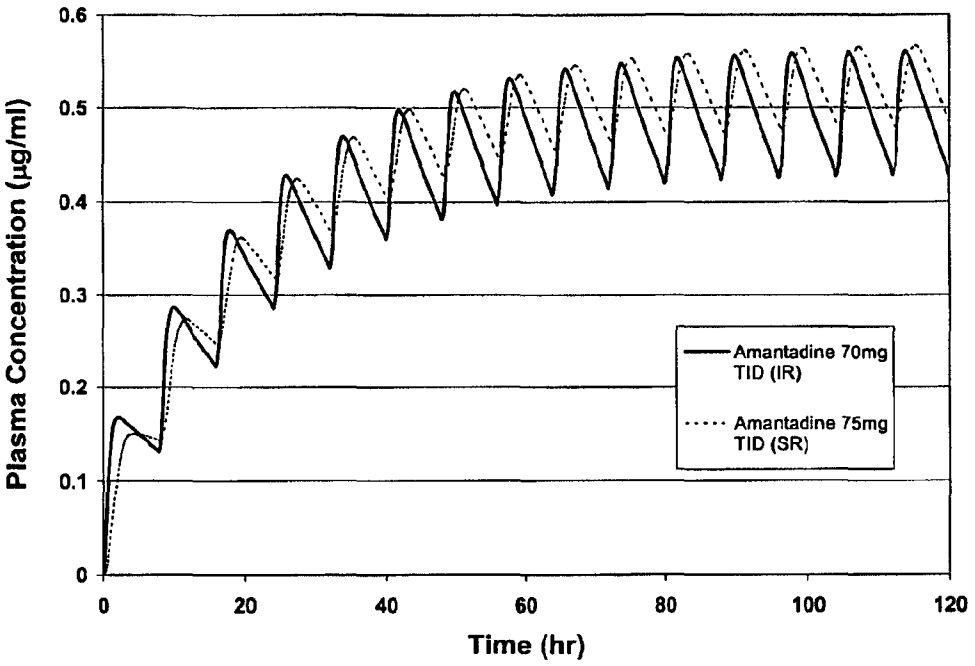


Figure 3: Simulated Plasma Concentration for TID Levodopa/Carbidopa/Amantadine (IR, IR, IR) over 24hrs

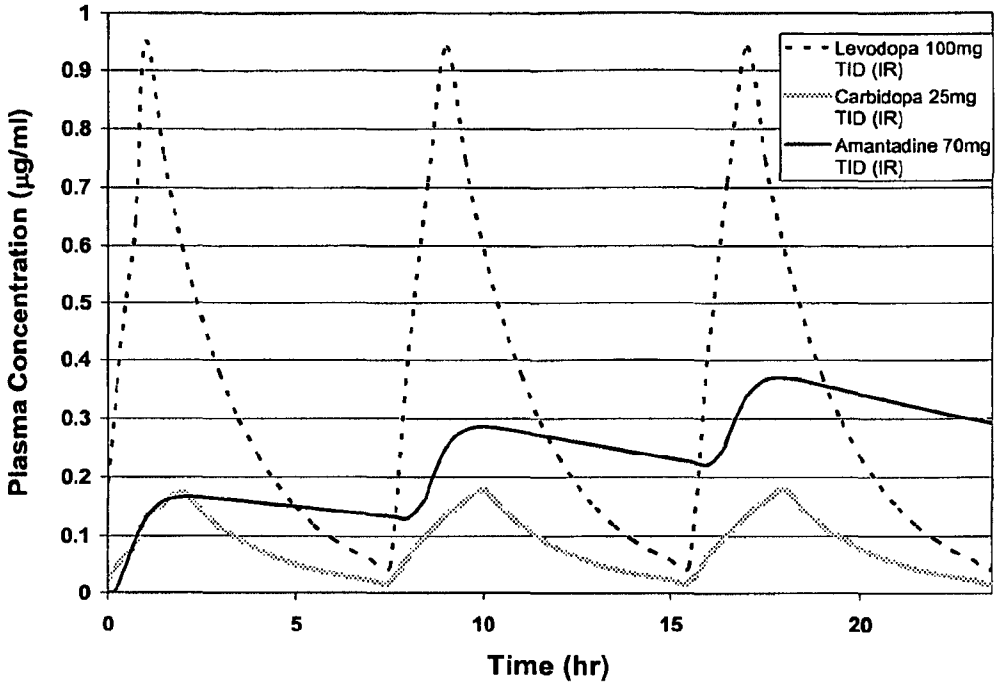


Figure 4: Simulated Plasma Concentration for TID Levodopa/Carbidopa/Amantadine (IR, IR, SR) over 24hrs

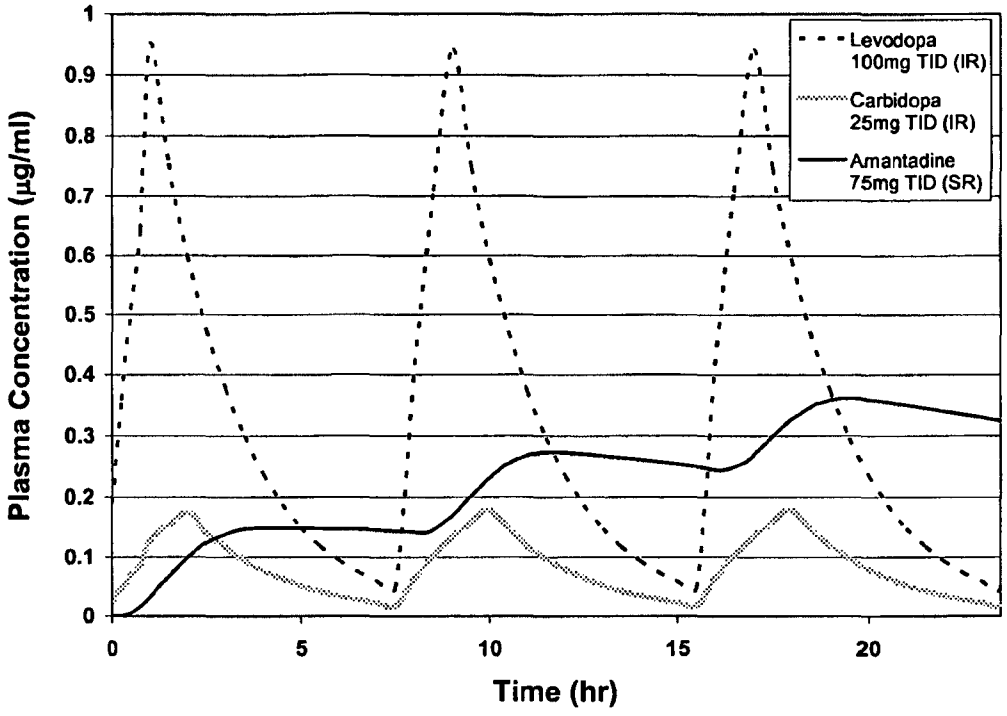


FIGURE 5

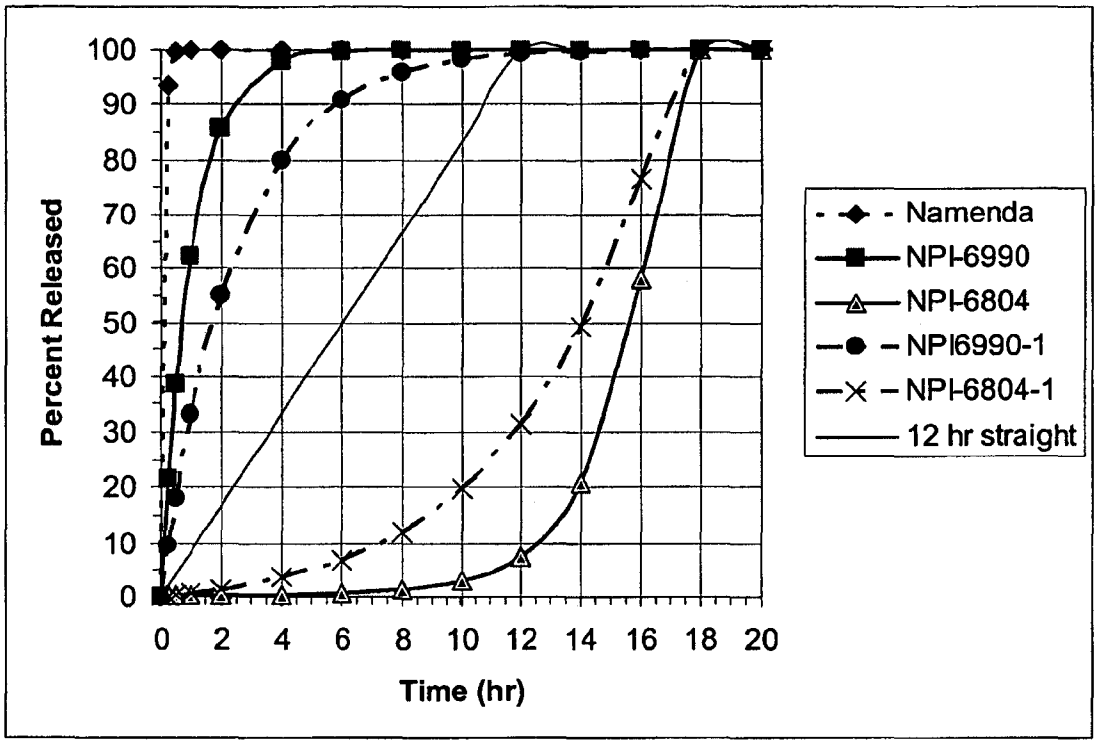

Percent Released
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20
Time (hr)
Namenda
NPI-6990
NPI-6804
NPI6990-1
NPI-6804-1
12 hr straight

Figure 6: Memantine, Levodopa and Carbidopa Human Pharmacokinetics

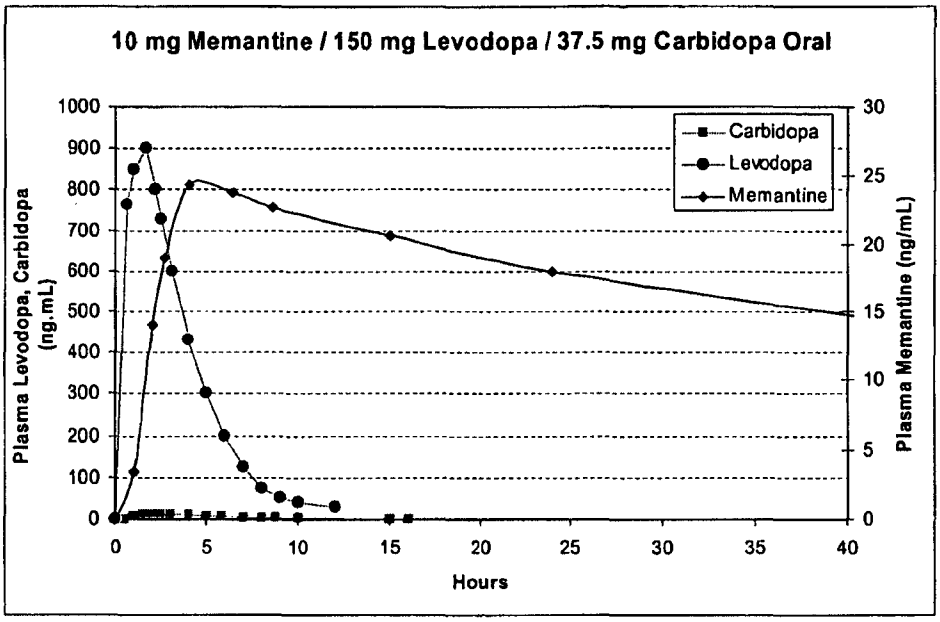
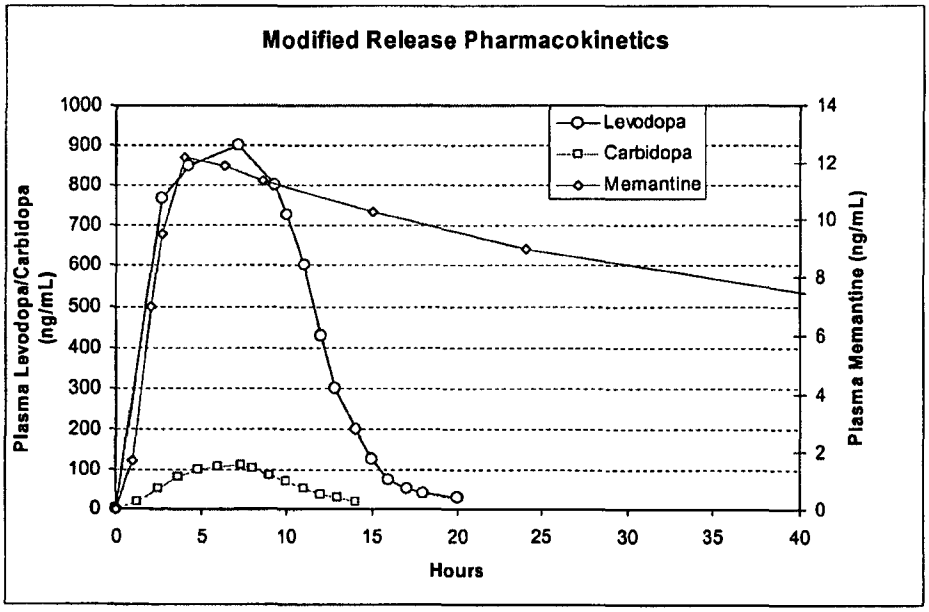


Figure 7: Target Pharmacokinetics



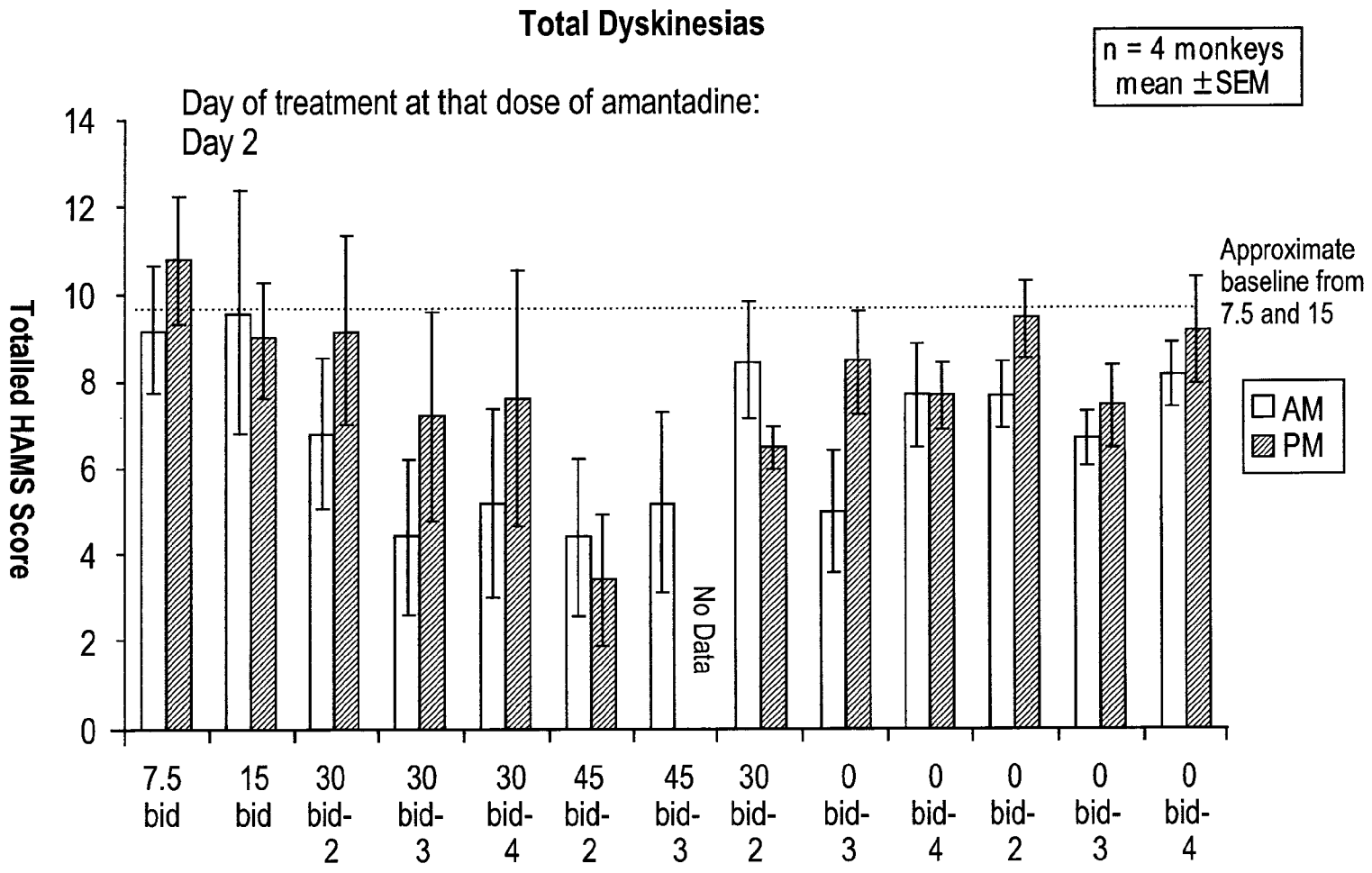

Total Dyskinesias
n = 4 monkeys
mean ±SEM
Day of treatment at that dose of amantadine:
Day 2
Totalled HAMS Score
14
12
10
8
6
4
2
0
Approximate baseline from 7.5 and 15
AM
PM
No Data
7.5 bid
15 bid
30 bid-2
30 bid-3
30 bid-4
45 bid-2
45 bid-3
30 bid-2
0 bid-3
0 bid-4
0 bid-2
0 bid-3
0 bid-4

Figure 8

COMPOSITION AND METHOD FOR TREATING NEUROLOGICAL DISEASE

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/328,440, filed Jul. 10, 2014, which is a continuation of U.S. patent application Ser. No. 13/958,153, filed Aug. 2, 2013, which is a continuation of U.S. patent application Ser. No. 13/756,275, filed Jan. 31, 2013, now abandoned, which is a continuation application of U.S. patent application Ser. No. 11/286,448, filed on Nov. 23, 2005, now U.S. Pat. No. 8,389,578, which claims priority to U.S. Provisional Application No. 60/631,095 filed on Nov. 24, 2004, all of which applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

This invention relates to compositions and methods for treating neurological diseases, such as Parkinson's disease.

BACKGROUND OF THE INVENTION

Parkinson's disease (PD) is a progressive, degenerative neurologic disorder which usually occurs in late mid-life. PD is clinically characterized by bradykinesia, tremor, and rigidity. Bradykinesia is characterized by a slowness in movement, slowing the pace of such routine activities as walking and eating. Tremor is a shakiness that generally affects limbs that are not otherwise in motion. For those PD-patients diagnosed at a relatively young age, tremor is reported as the most disabling symptom. Older patients face their greatest challenge in walking or keeping their balance. Rigidity is caused by the inability of muscles to relax as opposing muscle groups contract, causing tension which can produce aches and pains in the back, neck, shoulders, temples, or chest.

PD predominantly affects the substantia nigra (SNc) dopamine (DA) neurons and is therefore associated with a decrease in striatal DA content. Because dopamine does not cross the blood-brain barrier, PD patients may be administered a precursor, levodopa, that does cross the blood-brain barrier where it is metabolized to dopamine. Levodopa therapy is intended to compensate for reduced dopamine levels and is a widely prescribed therapeutic agent for patients with Parkinson's disease. Chronic treatment with levodopa however, is associated with various debilitating side-effects such as dyskinesia.

Since currently available drugs containing levodopa are associated with debilitating side effects, better therapies are needed for the management of PD.

SUMMARY OF THE INVENTION

In general, the present invention provides methods and compositions for treating and preventing CNS-related conditions, such as Parkinson's disease or other Parkinson's-like diseases or conditions, by administering to a subject in need thereof a combination that includes an N-Methyl-D-Aspartate receptor (NMDAr) antagonist and levodopa. Exemplary NMDAr antagonists include the aminoadamantanes, such as memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1-aminoethyl)adamantane), or amantadine (1-amino-adamantane) as well as others described below. Because levodopa is metabolized before crossing the blood-brain barrier and has a short half-life in the circulatory system, it is typically administered in conjunction with a dopa-

decarboxylase inhibitor. Examples of dopa-decarboxylase inhibitors include carbidopa, 3-hydroxy-benzylhydrazinedihydrochloride (NSD-1015), and benseraxide hydrochloride. The combination may further include a catechol-O-methyltransferase (COMT) inhibitor including, for example, talcapone and entacapone. As used herein, levodopa/carbidopa shall mean levodopa alone or in combination with a dopa-decarboxylase inhibitor such as carbidopa. Desirably, the levodopa/carbidopa is in an immediate release formulation and the NMDA receptor antagonist is in an extended release formulation. One preferred embodiment of the invention involves the combination of amantadine and levodopa/carbidopa. Desirably, amantadine is provided in an extended release formulation and levodopa/carbidopa is provided as an immediate release formulation. By combining an NMDAr antagonist (e.g., amantadine) with the second agents described herein (e.g., levodopa/carbidopa), this invention provides an effective pharmaceutical composition for treating neurological diseases such as Parkinson's disease or other Parkinson's-like diseases or conditions. The administration of this combination is postulated to maintain or enhance the efficacy of levodopa while significantly reducing its dyskinesia side effects.

The combinations described herein provide complementary benefits associated with the NMDAr antagonist or levodopa/carbidopa individually, while minimizing difficulties previously presented when each component is used separately in a patient. For example, amantadine dosing is limited by neurotoxicity that is likely associated with its short Tmax. By extending the release of amantadine, a higher effective dose can be maintained providing both dyskinesia relief and a reduction in the amount of levodopa required for treatment of the disease symptoms. Given the inherent toxicity of levodopa, such a levodopa sparing combination will result in a decline in both the dyskinesia and overall disease.

Accordingly, the pharmaceutical compositions described herein are administered so as to deliver to a subject, an amount of an NMDAr antagonist, levodopa/carbidopa or both agents that is high enough to treat symptoms or damaging effects of an underlying disease while avoiding undesirable side effects. These compositions may be employed to administer the NMDAr antagonist, the levodopa/carbidopa, or both agents at a lower frequency than presently employed, improving patient compliance, adherence, and caregiver convenience. These compositions are particularly useful as they provide the NMDAr antagonist, levodopa/carbidopa, or both agents, at a therapeutically effective amount from the onset of therapy further improving patient compliance and adherence and enable the achievement of a therapeutically effective steady-state concentration of either or both agents of the combination in a shorter period of time resulting in an earlier indication of effectiveness and increasing the utility of these therapeutic agents for diseases and conditions where time is of the essence. Also provided are methods for making and using such compositions.

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a controlled or extended release form with or without an immediate release component in order to maximize the therapeutic benefit of such agents, while reducing unwanted side effects. In preferred embodiments for oral administration, levodopa/carbidopa is provided as an immediate-release formulation.

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be administered in an amount similar to that typically administered to subjects. Preferably, the amount of the NMDAr antagonist may be administered in an amount greater than or less than the amount that is typically admin-

istered to subjects while the levodopa/carbidopa is provided at a lower dose than normally used. For example, the amount of amantadine required to positively affect the patient response (inclusive of adverse effects) may be 300, 400, 500, 600 mg per day rather than the typical 200-300 mg per day administered for presently approved indications i.e. without the improved formulation described herein, while the levodopa, and optionally the carbidopa, can be reduced independently by 10%, 20%, 30%, 40%, 50%, 60%, 70% or up to 80% of what is currently required in the absence of the NMDAr antagonist.

Optionally, lower or reduced amounts of both the NMDAr antagonist and the levodopa/carbidopa are used in a unit dose relative to the amount of each agent when administered independently. The present invention therefore features formulations of combinations directed to dose optimization or release modification to reduce adverse effects associated with separate administration of each agent. The combination of the NMDAr antagonist and the levodopa/carbidopa may result in an additive or synergistic response, and using the unique formulations described herein, the goal of minimizing the levodopa burden is achieved. Preferably, the NMDAr antagonist and the levodopa/carbidopa are provided in a unit dosage form.

The compositions and methods of the invention are particularly useful for the treatment of Parkinson's disease or conditions associated with Parkinson's disease. These conditions include dementia, dyskinesia, dystonia, depression, fatigue and other neuropsychiatric complications of Parkinson's disease.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present Specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. All parts and percentages are by weight unless otherwise specified.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a graph showing the dissolution profiles for an immediate and sustained release formulation of amantadine. The sustained release formulation exhibits a dC/dT during the initial phase that is about 10% of that for the immediate release formulation.

FIG. **2** is a graph showing the amantadine plasma concentration over a period of 5 days, as predicted by Gastro-Plus software package v.4.0.2, following the administration of either 70 mg amantadine in an immediate release formulation t.i.d. or 75 mg amantadine in a sustained release formulation t.i.d. The sustained release formulation peaks are similar in height to the immediate release formulation even with a higher administered dose and the diurnal variation is substantially reduced.

FIG. **3** is a graph showing the plasma profiles simulated using Gastro-Plus for t.i.d. administration of amantadine (70 mg), levodopa (100 mg), and carbidopa (25 mg), all in an immediate release form.

FIG. **4** is a graph showing the plasma profiles simulated using Gastro-Plus for t.i.d. administration of amantadine (75 mg), levodopa (100 mg), and carbidopa (25 mg), where the amantadine is in a sustained release form and the levodopa and carbidopa are in an immediate release form.

FIG. **5** is a graph representing dissolution profiles for various aminoadamantane formulations including an immediate release form of the NMDAr antagonist memantine (Namenda).

FIG. **6** is a graphical representation of plasma release profiles in a human of memantine, levodopa, and carbidopa when memantine is administered separately from levodopa and carbidopa.

FIG. **7** is a graphical representation of plasma release profiles in a human of memantine, levodopa, and carbidopa when memantine, levodopa, and carbidopa are administered as part of a single controlled-release pharmaceutical composition.

FIG. **8** is a bar graph showing the effects on a primate (squirrel monkey) treated with a combination of levodopa/carbidopa and amantadine.

DETAILED DESCRIPTION OF THE INVENTION

In general, the present invention features pharmaceutical compositions that contain therapeutically effective levels of an NMDAr antagonist and levodopa/carbidopa and, optionally, a pharmaceutical carrier. Preferably the compositions are formulated for modified or extended release to provide a serum or plasma concentration of the NMDAr antagonist over a desired time period that is high enough to be therapeutically effective but at a rate low enough so as to avoid adverse events associated with the NMDAr antagonist. Control of drug release is particularly desirable for reducing and delaying the peak plasma level while maintaining the extent of drug bioavailability. Therapeutic levels are therefore achieved while minimizing debilitating side-effects that are usually associated with immediate release formulations. Furthermore, as a result of the delay in the time to obtain peak serum or plasma level and the extended period of time at the therapeutically effective serum or plasma level, the dosage frequency is reduced to, for example, once or twice daily dosage, thereby improving patient compliance and adherence. For example, side effects including psychosis and cognitive deficits associated with the administration of NMDAr antagonists may be lessened in severity and frequency through the use of controlled-release methods that shift the Tmax to longer times, thereby reducing the dC/dT of the drug. Reducing the dC/dT of the drug not only increases Tmax, but also reduces the drug concentration at Tmax and reduces the Cmax/Cmean ratio providing a more constant amount of drug to the subject being treated over a given period of time, enabling increased dosages for appropriate indications.

In addition, the present invention encompasses optimal ratios of NMDAr and levodopa/carbidopa, designed to not only treat the dyskinesia associated with levodopa, but also take advantage of the additivity and synergy between these drug classes. For example, the level of levodopa required to treat the disease symptoms can unexpectedly be reduced by up to 50% by the addition of 400 mg/day of amantadine.

Making NMDAr Antagonist Controlled Release Formulations

A pharmaceutical composition according to the invention is prepared by combining a desired NMDAr antagonist or antagonists with one or more additional ingredients that, when administered to a subject, causes the NMDAr antagonist to be released at a targeted rate for a specified period of time. A release profile, i.e., the extent of release of the NMDAr antagonist over a desired time, can be conveniently determined for a given time by measuring the release using a USP dissolution apparatus under controlled conditions. Pre-

ferred release profiles are those which slow the rate of uptake of the NMDAr antagonist in the neural fluids while providing therapeutically effective levels of the NMDAr antagonist. One of ordinary skill in the art can prepare combinations with a desired release profile using the NMDAr antagonists and formulation methods described below.

NMDAr Antagonists

Any NMDAr antagonist can be used in the methods and compositions of the invention, particularly those that are non-toxic when used in the compositions of the invention. The term "nontoxic" is used in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to humans or, in keeping with established regulatory criteria and practice, is susceptible to approval by the FDA or similar regulatory agency for any country for administration to humans or animals.

The term "NMDAr antagonist", as used herein, includes any amino-adamantane compound including, for example, memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1-aminoethyl)adamantane), amantadine (1-amino-adamantane), as well as pharmaceutically acceptable salts thereof. Memantine is described, for example, in U.S. Pat. Nos. 3,391,142, 5,891,885, 5,919,826, and 6,187,338. Amantadine is described, for example, in U.S. Pat. Nos. 3,152,180, 5,891,885, 5,919,826, and 6,187,338. Additional aminoadamantane compounds are described, for example, in U.S. Pat. Nos. 4,346,112, 5,061,703, 5,334,618, 6,444,702, 6,620,845, and 6,662,845. All of these patents are hereby incorporated by reference.

Further NMDAr antagonists that may be employed include, for example, aminocylohexanes such as neramexane, ketamine, eliprodil, ifenprodil, dizocilpine, remacemide, iamotrigine, riluzole, aptiganel, phencyclidine, flupirtine, celfotel, felbamate, spermine, spermidine, levemopamil, dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and its metabolite, dextrorphan ((+)-3-hydroxy-N-methylmorphinan), a pharmaceutically acceptable salt, derivative, or ester thereof, or a metabolic precursor of any of the foregoing.

Optionally, the NMDAr antagonist in the instant invention is memantine and not amantadine or dextromethorphan.

Second Agents

In all foregoing aspects of the invention, the second agent is levodopa. When levodopa is in the combination, the combination preferably also includes a dopa-decarboxylase inhibitor. An example of a suitable dopa-decarboxylase inhibitor is carbidopa. Other dopa-decarboxylase inhibitors include, for example, 3-hydroxy-benzylhydrazinedihydrochloride (NSD-1015) and benseraxide hydrochloride. The combination may further include a catechol-O-methyltransferase (COMT) inhibitor including, for example, talcapone and entacapone.

Dosing, PK, & Toxicity

The NMDA receptor antagonist used in combination therapies are administered at a dosage of generally between about 1 and 5000 mg/day, between 1 and about 800 mg/day, or between 1 and 500 mg/day. For example, NMDA receptor antagonist agents may be administered at a dosage ranging between about 1 and about 500 mg/day, more preferably from about 10 to about 40, 50, 60, 70 or 80 mg/day, advantageously from about 10 to about 20 mg per day. Amantadine may be administered at a dose ranging from about 90, 100 mg/day to about 400, 500, 600, 700 or 800 mg/day, advantageously from about 100 to about 500, 600 mg per day. For example, the pharmaceutical composition may be formulated to provide memantine in an amount ranging between 1-200 mg/day, 1 and 80 mg/day, 2-80 mg/day, 10-80 mg/day, 10 and 80 mg/day, 10 and 70 mg/day, 10 and 60 mg/day, 10 and 50 mg/day, 10 and 40 mg/day, 5 and 65 mg/day, 5 and 40 mg/day, 15 and 45 mg/day, or 10 and 20 mg/day; dextromethorphan in an amount ranging between 1-5000 mg/day, 1-1000 mg/day, and 100-800 mg/day, or 200-500 mg/day. Pediatric doses will typically be lower than those determined for adults.

Table 1 shows exemplary pharmacokinetic properties (e.g., Tmax and T1/2) of memantine, amantadine, and rimantadine.

TABLE 1

Pharmacokinetics and Toxicity in humans for selected NIVIDAr antagonists

Compound	Human PK ($t_{1/2}$) (hours)	Tmax (hours)	Normal Dose	Dose Dependent Toxicity
Memantine	60	3	10-20 mg/day, starting at 5 mg	Dose escalation required, hallucination
Amantadine	15	3	100-300 mg/day, starting at 100 mg/day	Hallucination
Rimantadine	25	6	100-200 mg/day	Insomnia

When levodopa and carbidopa are both included in the composition, the levodopa dose ranges between 100 to 3000 mg per day, 75 mg and 2500 mg/day, 100-2000 mg/day, or 250 and 1000 mg/day divided for administration t.i.d. or more frequently. Carbidopa doses may range between the amounts of 1 to 1000 mg/day, 10 to 500 mg/day, and 25 to 100 mg/day. Optionally, the carbidopa is present in the combination at about 75%, 70%, 65%, 60%, 50%, 40%, 30%, 25%, 20%, and 10% of the mass of the levodopa. Alternatively, the amount of levodopa is less than 300% than the amount of carbidopa. For example, 75 mg of carbidopa (amount that is sufficient to extend the half-life of levodopa in the circulatory system) may be used in combination with 300 to 3000 mg of levodopa per day. The combination may contain a single dosage form comprising 30 to 200 mg amantadine, 30 to 250 mg levodopa, and 10 to 100 mg of carbidopa for t.i.d. or more frequent administration, including multiple dosage forms per administration.

As a result, the preferred dosage forms for optimized use are shown in Table 2 below, with their corresponding commercial equivalent.

TABLE 2

Dosage forms with and without NMDAr antagonist (amount per unit dose)

Sinemet Compositions		Compositions of Present Invention		
Levodopa	Carbidopa	Levodopa	Carbidopa	Amantadine
100 mg IR*	25 mg IR	50-100 mg IR	25 mg IR	100-200 mg IR
100 mg IR	10 mg IR	50-100 mg IR	10 mg IR	50-100 mg IR
100 mg IR	25 mg IR	50-100 mg IR	25 mg IR	100-200 mg CR**
100 mg IR	10 mg IR	50-100 mg IR	10 mg IR	50-100 mg CR

*IR: immediate release

**CR: modified release

Excipients

"Pharmaceutically or Pharmacologically Acceptable" includes molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. "Pharmaceutically Acceptable Carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifun-

gal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. "Pharmaceutically Acceptable Salts" include acid addition salts and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

The preparation of pharmaceutical or pharmacological compositions is known to those of skill in the art in light of the present disclosure. General techniques for formulation and administration are found in "Remington: The Science and Practice of Pharmacy, Twentieth Edition," Lippincott Williams & Wilkins, Philadelphia, Pa. Tablets, capsules, pills, powders, granules, dragees, gels, slurries, ointments, solutions suppositories, injections, inhalants and aerosols are examples of such formulations.

By way of example, modified or extended release oral formulation can be prepared using additional methods known in the art. For example, a suitable extended release form of the either active pharmaceutical ingredient or both may be a matrix tablet or capsule composition. Suitable matrix forming materials include, for example, waxes (e.g., carnauba, bees wax, paraffin wax, ceresine, shellac wax, fatty acids, and fatty alcohols), oils, hardened oils or fats (e.g., hardened rapeseed oil, castor oil, beef tallow, palm oil, and soya bean oil), and polymers (e.g., hydroxypropyl cellulose, polyvinylpyrrolidone, hydroxypropyl methyl cellulose, and polyethylene glycol). Other suitable matrix tabletting materials are microcrystalline cellulose, powdered cellulose, hydroxypropyl cellulose, ethyl cellulose, with other carriers, and fillers. Tablets may also contain granulates, coated powders, or pellets. Tablets may also be multi-layered. Multi-layered tablets are especially preferred when the active ingredients have markedly different pharmacokinetic profiles. Optionally, the finished tablet may be coated or uncoated.

The coating composition typically contains an insoluble matrix polymer (approximately 15-85% by weight of the coating composition) and a water soluble material (e.g., approximately 15-85% by weight of the coating composition). Optionally an enteric polymer (approximately 1 to 99% by weight of the coating composition) may be used or included. Suitable water soluble materials include polymers such as polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials such as sugars (e.g., lactose, sucrose, fructose, mannitol and the like), salts (e.g., sodium chloride, potassium chloride and the like), organic acids (e.g., fumaric acid, succinic acid, lactic acid, and tartaric acid), and mixtures thereof. Suitable enteric polymers include hydroxypropyl methyl cellulose, acetate succinate, hydroxypropyl methyl cellulose, phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups.

The coating composition may be plasticised according to the properties of the coating blend such as the glass transition temperature of the main component or mixture of components or the solvent used for applying the coating compositions. Suitable plasticisers may be added from 0 to 50% by weight of the coating composition and include, for example, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, acetylated citrate esters, dibutylsebacate, and castor oil. If desired, the coating composition may include a filler. The amount of the filler may be 1% to approximately 99% by weight based on the total weight of the coating composition and may be an insoluble material such as silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, MCC, or polacrilin potassium.

The coating composition may be applied as a solution or latex in organic solvents or aqueous solvents or mixtures thereof. If solutions are applied, the solvent may be present in amounts from approximate by 25-99% by weight based on the total weight of dissolved solids. Suitable solvents are water, lower alcohol, lower chlorinated hydrocarbons, ketones, or mixtures thereof. If latexes are applied, the solvent is present in amounts from approximately 25-97% by weight based on the quantity of polymeric material in the latex. The solvent may be predominantly water.

The NMDAr antagonist may be formulated using any of the following excipients or combinations thereof.

Excipient name	Chemical name	Function
Avicel PH102	Microcrystalline Cellulose	Filler, binder, wicking, disintegrant
Avicel PH101	Microcrystalline Cellulose	Filler, binder, disintegrant
Eudragit RS-30D	Polymethacrylate Poly(ethyl acrylate, nethyl methacrylate, timethylammonioethyl methacrylate chloride) 1:2:0.1	Film former, tablet binder, tablet diluent; Rate controlling polymer for controlled release
Methocel K100M Premium CR	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Methocel K100M	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Magnesium Stearate	Magnesium Stearate	Lubricant
Talc	Talc	Dissolution control; anti-adherent, glidant
Triethyl Citrate	Triethyl Citrate	Plasticizer
Methocel E5	Hydroxypropyl methylcellulose	Film-former
Opadry ®	Hydroxypropyl methylcellulose	One-step customized coating system which combines polymer, plasticizer and, if desired, pigment in a dry concentrate.
Surelease ®	Aqueous Ethylcellulose Dispersion	Film-forming polymer; plasticizer and stabilizers. Rate controlling polymer coating.

The pharmaceutical composition described herein may also include a carrier such as a solvent, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents. The use of such media and agents for pharmaceutically active substances is well known in the art. Pharmaceutically acceptable salts can also be used in the composition, for example, mineral salts such as hydrochlorides, hydrobromides, phosphates, or sulfates, as well as the salts of organic acids such as acetates, proprionates, malonates, or benzoates. The composition may also contain liquids, such as water, saline, glycerol, and ethanol, as well as substances such as wetting agents, emulsifying agents, or pH buffering agents. Liposomes, such as those described in U.S.

Pat. No. 5,422,120, WO 95/13796, WO 91/14445, or EP 524,968 B1, may also be used as a carrier.

Methods for Preparing Modified or Extended Release Formulations

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a controlled or extended release form with or without an immediate release component in order to maximize the therapeutic benefit of such agents, while reducing unwanted side effects. In the absence of modified release components (referred to herein as controlled, extended, or delayed release components), the NMDAr antagonist, levodopa/carbidopa, or both is released and transported into the body fluids over a period of minutes to several hours. The combination described herein however, may contain an NMDAr antagonist and a sustained release component, such as a coated sustained release matrix, a sustained release matrix, or a sustained release bead matrix. In one example, in addition to levodopa/carbidopa, amantadine (e.g., 50-400 mg) is formulated without an immediate release component using a polymer matrix (e.g., Eudragit), Hydroxypropyl methyl cellulose (HPMC) and a polymer coating (e.g., Eudragit). Such formulations are compressed into solid tablets or granules and coated with a controlled release material such as Opadry® or Surelease®. Levodopa/carbidopa may also be formulated as a sustained release formulation; in most cases, however, this will not be optimal.

Suitable methods for preparing the compositions described herein in which the NMDAr antagonist is provided in modified or extended release-formulations include those described in U.S. Pat. No. 4,606,909 (hereby incorporated by reference). This reference describes a controlled release multiple unit formulation in which a multiplicity of individually coated or microencapsulated units are made available upon disintegration of the formulation (e.g., pill or tablet) in the stomach of the subject (see, for example, column 3, line 26 through column 5, line 10 and column 6, line 29 through column 9, line 16). Each of these individually coated or microencapsulated units contains cross-sectionally substantially homogenous cores containing particles of a sparingly soluble active substance, the cores being coated with a coating that is substantially resistant to gastric conditions but which is erodable under the conditions prevailing in the gastrointestinal tract.

The composition of the invention may alternatively be formulated using the methods disclosed in U.S. Pat. No. 4,769,027, for example. Accordingly, extended release formulations involve prills of pharmaceutically acceptable material (e.g., sugar/starch, salts, and waxes) may be coated with a water permeable polymeric matrix containing an NMDAr antagonist and next overcoated with a water-permeable film containing dispersed within it a water soluble particulate pore forming material.

The NMDAr antagonist composition may additionally be prepared as described in U.S. Pat. No. 4,897,268, involving a biocompatible, biodegradable microcapsule delivery system. Thus, the NMDAr antagonist may be formulated as a composition containing a blend of free-flowing spherical particles obtained by individually microencapsulating quantities of memantine, for example, in different copolymer excipients which biodegrade at different rates, therefore releasing memantine into the circulation at a predetermined rates. A quantity of these particles may be of such a copolymer excipient that the core active ingredient is released quickly after administration, and thereby delivers the active ingredient for an initial period. A second quantity of the particles is of such type excipient that delivery of the encapsulated ingredient begins as the first quantity's delivery begins to decline. A third quantity of ingredient may be encapsulated with a still different excipient which results in delivery beginning as the delivery of the second quantity beings to decline. The rate of delivery may be altered, for example, by varying the lactide/glycolide ratio in a poly(D,L-lactide-co-glycolide) encapsulation. Other polymers that may be used include polyacetal polymers, polyorthoesters, polyesteramides, polycaprolactone and copolymers thereof, polycarbonates, polyhydroxybuterate and copolymers thereof, polymaleamides, copolyaxalates and polysaccharides.

Alternatively, the composition may be prepared as described in U.S. Pat. No. 5,395,626, which features a multilayered controlled release pharmaceutical dosage form. The dosage form contains a plurality of coated particles wherein each has multiple layers about a core containing an NMDAr antagonist whereby the drug containing core and at least one other layer of drug active is overcoated with a controlled release barrier layer therefore providing at least two controlled releasing layers of a water soluble drug from the multilayered coated particle

Release Profile

The compositions described herein are formulated such that the NMDAr antagonist, levodopa/carbidopa, or both agents have an in vitro dissolution profile that is equal to or slower than that for an immediate release formulation. As used herein, the immediate release (IR) formulation for memantine means the present commercially available 5 mg and 10 mg tablets (i.e., Namenda from Forest Laboratories, Inc. or formulations having substantially the same release profiles as Namenda); and the immediate release (IR) formulation of amantadine means the present commercially available 100 mg tablets (i.e., Symmetrel from Endo Pharmaceuticals, Inc. or formulations having substantially the same release profiles as Symmetrel); and the immediate release (IR) formulation of levodopa/carbidopa means the present commercially available 25 mg/100 mg, 10 mg/100 mg, 25 mg/250 mg tablets of carbidopa/levodopa (i.e., Sinemet from Merck & Co. Inc. or formulations having substantially the same release profiles as Sinemet). These compositions may comprise immediate release, sustained or extended release, or delayed release components, or may include combinations of same to produce release profiles such that the fraction of NMDAr antagonist or levodopa/carbidopa released is greater or equal to $0.01(0.297+0.0153*e^{(0.515*t)})$ and less than or equal to $1-e^{(-10.9*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C., in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist or levodopa/carbidopa released is less than 93% in 15 minutes and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1N HCl) dissolution medium. Optionally, the fraction of released NMDAr antagonist or levodopa/carbidopa is greater than or equal to $0.01(0.297+0.0153*e^{(0.515*t)})$, and less than or equal to $1-e^{(-0.972*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C., in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist or levodopa/carbidopa that is released may range between 0.1%-62% in one hour, 0.2%-86% in two hours, 0.6%-100% in six hours, 2.9%-100% in 10 hours, and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1 N HCl) dissolution medium. Optionally, the NMDA receptor antagonist has a

release profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 70% or greater (e.g., 70%-90%) in 10 hours, and 90% or greater (e.g., 90-95%) in 12 hours as measured in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1 N HCl) dissolution medium. For example, a formulation containing amantadine may have a release profile ranging between 0-60% or 0.1-20% in one hour, 0-86% or 5-30% at two hours, 0.6-100% or 40-80% at six hours, 3-100% or 50% or more (e.g., 50-90%) at ten hours, and 7.7-100% at twelve hours in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1 N HCl) dissolution medium. In one embodiment, the NMDAr antagonist, the levodopa/carbidopa, or both agents have an in vitro dissolution profile of less than 25%, 15%, 10%, or 5% in fifteen minutes; 50%, 30%, 25%, 20%, 15%, or 10% in 30 minutes and more than 60%, 65% 70%, 75%, 80%, 85%, 90%, 95% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water. Desirably, the NMDAr antagonist, the levodopa/carbidopa, or both agents has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% in a dissolution media having a pH of 1.2 at 10 hours. It is important to note that the dissolution profile for the NMDAr antagonist may be different than the release profile for levodopa/carbidopa. In a preferred embodiment, the levodopa/carbidopa release profile is equal to or similar to that for an immediate release formulation and the release profile for the NMDAr antagonist is controlled to provide a dissolution profile of less than 30% in one hour, less than 50% in two hours, and greater than 95% in twelve hours using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water.

Desirably, the compositions described herein have an in vitro profile that is substantially identical to the dissolution profile shown in FIG. **5** and, upon administration to a subject at a substantially constant daily dose, achieves a serum concentration profile that is substantially identical to that shown in FIGS. **2** and **4**.

As described above, the NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a modified or extended release form. Modified or extended drug release is generally controlled either by diffusion through a coating or matrix or by erosion of a coating or matrix by a process dependent on, for example, enzymes or pH. The NMDAr antagonist or the levodopa/carbidopa may be formulated for modified or extended release as described herein or using standard techniques in the art. In one example, at least 50%, 75%, 90%, 95%, 96%, 97%, 98%, 99%, or even in excess of 99% of the NMDAr antagonist or the levodopa/carbidopa is provided in an extended release dosage form. In a preferred embodiment, the levodopa/carbidopa is provided in an immediate release formulation and the NMDAr antagonist is in either an immediate or modified release form.

The composition described herein is formulated such the NMDAr antagonist or levodopa/carbidopa has an in vitro dissolution profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 50%-90% in 10 hours, and 90%-95% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. using 0.1N HCl as a dissolution medium. Alternatively, the NMDAr antagonist has an in vitro dissolution profile in a solution with a neutral pH (e.g., water) that is substantially the same as its dissolution profile in an acidic dissolution medium. Thus, the NMDAr antagonist may be released in both dissolution media at the following rate: between 0.1-20% in one hour, 5-30% in two hours, 40-80% in six hours, 70-90% in 10 hours, and 90%-95% in 12 hours as obtained using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. In one embodiment, the NMDAr antagonist has an in vitro dissolution profile of less than 15%, 10%, or 5% in fifteen minutes, 25%, 20%, 15%, or 10% in 30 minutes, and more than 60% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water. Desirably, the NMDAr antagonist has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% at 10 hours in a dissolution medium having a pH of 1.2.

Initial Rate In Vivo, Delayed Tmax

As used herein, "C" refers to the concentration of an active pharmaceutical ingredient in a biological sample, such as a patient sample (e.g. blood, serum, and cerebrospinal fluid). The time required to reach the maximal concentration ("Cmax") in a particular patient sample type is referred to as the "Tmax". The change in concentration is termed "dC" and the change over a prescribed time is "dC/dT".

The NMDAr antagonist or levodopa/carbidopa is provided as a sustained release formulation that may or may not contain an immediate release formulation. If desired, the NMDAr antagonist may be formulated so that it is released at a rate that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In addition, the NMDAr antagonist levodopa/carbidopa may be provided such that it is released at a rate resulting in a Cmax/Cmean of approximately 2 or less for approximately 2 hours to at least 8 hours after the NMDAr antagonist is introduced into a subject. Optionally, the sustained release formulations exhibit plasma concentration curves having initial (e.g., from 0, 1, 2 hours after administration to 4, 6, 8 hours after administration) slopes less than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist. The precise slope for a given individual will vary according to the NMDAr antagonist being used or other factors, including whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose. The determination of initial slopes of plasma concentration is described, for example, by U.S. Pat. No. 6,913,768, hereby incorporated by reference.

Desirably, the NMDAr antagonist or the levodopa/carbidopa is released into a subject sample at a slower rate than observed for an immediate release (IR) formulation of the same quantity of the antagonist, such that the rate of change in the biological sample measured as the dC/dT over a defined period within the period of 0 to Tmax for the IR formulation (e.g., Namenda, a commercially available IR formulation of memantine). In some embodiments, the dC/dT rate is less than about 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. In some embodiments, the dC/dT rate is less than about 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. Similarly, the rate of release of the NMDAr antagonist or the levodopa/carbidopa from the present invention as measured in dissolution studies is less than 80%, 70%, 60% 50%, 40%, 30%, 20%, or 10% of the rate for an IR formulation of the same NMDAr antagonist or levodopa/carbidopa over the first 1, 2, 4, 6, 8, 10, or 12 hours.

In a preferred embodiment, the dosage form is provided in a non-dose escalating, three times per day (t.i.d.) form. In preferred embodiments, the concentration ramp (or Tmax

effect) may be reduced so that the change in concentration as a function of time (dC/dT) is altered to reduce or eliminate the need to dose escalate the NMDAr antagonist. A reduction in dC/dT may be accomplished, for example, by increasing the Tmax in a relatively proportional manner. Accordingly, a two-fold increase in the Tmax value may reduce dC/dT by approximately a factor of 2. Thus, the NMDAr antagonist may be provided so that it is released at a rate that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In certain embodiments, this is accomplished by releasing less than 30%, 50%, 75%, 90%, or 95% of the NMDAr antagonist into the circulatory or neural system within one hour of such administration.

The concentration ramp for levodopa/carbidopa may also be reduced, however such changes will not be preferred in most oral formulations due to the marked reduction in absorption of levodopa/carbidopa after it passes the duodenal region of the gastrointestinal tract.

Optionally, the modified release formulations exhibit plasma concentration curves having initial (e.g., from-2 hours after administration to 4 hours after administration) slopes less-than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist or levodopa/carbidopa. The precise slope for a given individual will vary according to the NMDAr antagonist or levodopa/carbidopa being used, the quantity delivered, or other factors, including, for some active pharmaceutical agents, whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose.

Using the sustained release formulations or administration methods described herein, the NMDAr antagonist reaches a therapeutically effective steady state plasma concentration in a subject within the course of the first two, three, five, seven, nine, ten, twelve, fifteen, or twenty days of administration. For example, the formulations described herein, when administered at a substantially constant daily dose (e.g., at a dose ranging between 200 mg and 800 mg, preferably between 200 mg and 600 mg, and more preferably between 200 mg and 400 mg per day) may reach a steady state plasma concentration in approximately 70%, 60%, 50%, 40%, 30%, or less of the time required to reach such plasma concentration when using a dose escalating regimen.

Dosing Frequency and Dose Escalation

According to the present invention, a subject (e.g., human) having or at risk of having such conditions is administered any of the compositions described herein (e.g., three times per day (t.i.d.), twice per day (b.i.d.), or once per day (q.d.)). While immediate release formulations of NMDAr antagonists are typically administered in a dose-escalating fashion, the compositions described herein may be essentially administered at a constant, therapeutically-effective dose from the onset of therapy. For example, a composition containing a sustained release formulation of amantadine may be administered three times per day, twice per day, or once per day in a unit dose comprising a total daily amantadine dose of 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, or 800 mg. In embodiments comprising a single dosage form containing an NMDAr antagonist and levodopa/carbidopa wherein the levodopa/carbidopa is in an immediate release form, the dosing frequency will be chosen according to the levodopa/carbidopa requirements, (e.g. three times per day).

Reduced Time to Therapeutic Concentration and Efficacy

Immediate release (IR) formulations of memantine (e.g., Namenda) are typically administered at low doses (e.g., 5 mg/day) and are progressively administered at increasing frequency and dose over time to reach a steady state serum concentration that is therapeutically effective. According to the manufacturer's FDA approved label, Namenda, an immediate release (IR) formulation of memantine, is first administered to subjects at a dose of 5 mg per day. After an acclimation period of typically one week, subjects are administered with this dose twice per day. Subjects are next administered with a 5 mg and 10 mg dosing per day and finally administered with 10 mg Namenda twice daily. Using this dosing regimen, a therapeutically effective steady state serum concentration may be achieved within 30 days of the onset of therapy. Using a modified release formulation comprising (22.5 mg memantine,) however, a therapeutically effective steady state concentration may be achieved substantially sooner (within about 13 days), without using a dose escalating regimen. Furthermore, the slope during each absorption period for the sustained release formulation is less (i.e. not as steep) as the slope for Namenda. Accordingly, the dC/dT of the sustained release formulation is reduced relative to the immediate release formulation even though the dose administered is larger than for the immediate release formulation. Based on this model, a sustained release formulation of an NMDAr antagonist may be administered to a subject in an amount that is approximately the full strength dose (or that effectively reaches a therapeutically effective dose) from the onset of therapy and throughout the duration of treatment. Accordingly, a dose escalation would not be required.

Treatment of a subject with the subject of the present invention may be monitored using methods known in the art. The efficacy of treatment using the composition is preferably evaluated by examining the subject's symptoms in a quantitative way, e.g., by noting a decrease in the frequency or severity of symptoms or damaging effects of the condition, or an increase in the time for sustained worsening of symptoms. In a successful treatment, the subject's status will have improved (i.e., frequency or severity of symptoms or damaging effects will have decreased, or the time to sustained progression will have increased). In the model described in the previous paragraph, the steady state (and effective) concentration of the NMDAr antagonist is reached in 25%, 40%, 50%, 60%, 70%, 75%, or 80% less time than in the dose escalated approach.

In another embodiment, a composition is prepared using the methods described herein, wherein such composition comprises memantine or amantadine and a release modifying excipient, wherein the excipient is present in an amount sufficient to ameliorate or reduce the dose-dependent toxicity associated with the memantine or amantadine relative to an immediate release (IR) formulation of memantine, such as Namenda, or amantadine, such as Symmetrel. The use of these compositions enables safer administration of these agents, and even permits the safe use of higher levels for appropriate indications, beyond the useful range for the presently available versions of memantine (5 mg and 10 mg per dose to 20 mg per day) and amantadine (100 mg to 300 mg per day with escalation).

Indications Suitable for Treatment

The compositions and methods of the present invention are particularly suitable for the treatment of Parkinson's disease or conditions associated with Parkinson's disease. These conditions include dementia, dyskinesia, dystonia, depression, fatigue and other neuropsychiatric complications of Parkinson's disease.

Formulations for Alternate Specific Routes of Administration

The pharmaceutical compositions may be optimized for particular types of delivery. For example, pharmaceutical compositions for oral delivery are formulated using pharmaceutically acceptable carriers that are well known in the art. The carriers enable the agents in the composition to be formulated, for example, as a tablet, pill, capsule, solution, suspension, sustained release formulation; powder, liquid or gel for oral ingestion by the subject.

The NMDAr antagonist may also be delivered in an aerosol spray preparation from a pressurized pack, a nebulizer or from a dry powder inhaler. Suitable propellants that can be used in a nebulizer include, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and carbon dioxide. The dosage can be determined by providing a valve to deliver a regulated amount of the compound in the case of a pressurized aerosol.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral, intranasal or respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

In some embodiments, for example, the composition may be delivered intranasally to the cribriform plate rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in U.S. Pat. No. 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Additional formulations suitable for other modes of administration include rectal capsules or suppositories. For suppositories, traditional binders and carriers may include, for example, polyalkylene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%.

The composition may optionally be formulated for delivery in a vessel that provides for continuous long-term delivery, e.g., for delivery up to 30 days, 60 days, 90 days, 180 days, or one year. For example the vessel can be provided in a biocompatible material such as titanium. Long-term delivery formulations are particularly useful in subjects with chronic conditions, for assuring improved patient compliance, and for enhancing the stability of the compositions.

Optionally, the NMDA receptor antagonist, levodopa/carbidopa, or both is prepared using the OROS® technology, described for example, in U.S. Pat. Nos. 6,919,373, 6,923,800, 6,929,803, 6,939,556, and 6,930,128, all of which are hereby incorporated by reference. This technology employs osmosis to provide precise, controlled drug delivery for up to 24 hours and can be used with a range of compounds, including poorly soluble or highly soluble drugs. OROS® technology can be used to deliver high drug doses meeting high drug loading requirements. By targeting specific areas of the gastrointestinal tract, OROS® technology may provide more efficient drug absorption and enhanced bioavailability. The osmotic driving force of OROS® and protection of the drug until the time of release eliminate the variability of drug absorption and metabolism often caused by gastric pH and motility.

Formulations for continuous long-term delivery are provided in, e.g., U.S. Pat. Nos. 6,797,283; 6,764,697; 6,635,268, and 6,648,083.

If desired, the components may be provided in a kit. The kit can additionally include instructions for using the kit.

Additional Methods for Making Modified Release Formulations

Additional methods for making modified release formulations are described in, e.g., U.S. Pat. Nos. 5,422,123, 5,601,845, 5,912,013, and 6,194,000, all of which are hereby incorporated by reference.

In some embodiments, for example, the composition may be delivered via intranasal, buccal, or sublingual routes to the brain rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in U.S. Pat. No. 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Preparation of a pharmaceutical composition for delivery in a subdermally implantable device can be performed using methods known in the art, such as those described in, e.g., U.S. Pat. Nos. 3,992,518; 5,660,848; and 5,756,115.

The invention will be illustrated in the following non-limiting examples.

EXAMPLES

Example 1

Measuring Release Profiles In Vitro

Compositions containing an aminoadamantane and levodopa/carbidopa are analyzed for release of the aminoadamantane and levodopa/carbidopa, according to the USP type 2 apparatus at a speed of 50 rpm. The dissolution media used include water, 0.1N HCl, or 0.1N HCl adjusted to pH 6.8 at 2 hours with phosphate buffer. The dissolution medium is equilibrated to 37±0.5° C.

The USP reference assay method for amantadine is used to measure the fraction of memantine released from the compositions prepared herein. Briefly, 0.6 mL sample (from the dissolution apparatus at a given time point) is placed into a 15 mL culture tube. 1.6 mL 0.1% Bromocresol Purple (in acetic acid) is added and vortexed for five seconds. The mixture is allowed to stand for approximately five minutes. 3 mL Chloroform is added and vortexed for five seconds. The solution is next centrifuged (speed 50 rpm) for five minutes. The top layer is removed with a disposable pipette. A sample is drawn into 1 cm flow cell and the absorbance is measured at 408 nm at 37° C. and compared against a standard curve prepared with known quantities of the same aminoadamantane. The quantity of determined is plotted against the dissolution time for the sample.

The USP reference assay method for levodopa is used to measure the fraction of levodopa released from the compositions prepared herein. Briefly, 0.5 ml samples from the dissolution apparatus removed at various times are assayed by liquid chromatography. The chromatograph is equipped with a 280 nm detector and a 3.9 mm×30 cm column containing packing L1. The mobile phase is 0.09 N sodium phosphate, 1

mM sodium 1-decanesulfonate, pH 2.8. With the flow rate adjusted to about 2 mL per minute, the levodopa elutes in about 4 minutes and carbidopa elutes in about 11 minutes. From the saved dissolution samples, a 0.02 ml aliquot is injected into the chromatograph and the absorbance is measure and compared to standard to determine concentration & quantity. The quantity dissolved is then plotted against the dissolution time for the sample.

Example 2

Preparation of Amantadine Extended Release Capsules

Amantadine extended release capsules may be formulated as follows or as described, for example, in U.S. Pat. No. 5,395,626.

A. Composition: Unit Dose

The theoretical quantitative composition (per unit dose) for amantadine extended release capsules is provided below.

Component	% weight/weight	mg/Capsule
Amantadine	68.34	200.00
OPADRY ® Clear YS-3-7011[1] (Colorcon, Westpoint, PA)	1.14	5.01
Purified Water, USP[2]	—	—
Sugar Spheres, NF	12.50	54.87
OPADRY ® Clear YS-1-7006[3] (Colorcon, Westpoint, PA)	4.48	19.66
SURELEASE ® E-7-7050[4] (Colorcon, Westpoint, PA)	13.54	59.44
Capsules[5]	—	—
TOTAL.	100.00%	338.98 mg[6]

[1]A mixture of hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol.

[2] Purified Water, USP is evaporated during processing.

[3]A mixture of hydroxypropyl methylcellulose and polyethylene glycol

[4]Solid content only of a 25% aqueous dispersion of a mixture of ethyl cellulose, dibutyl sebacate, oleic acid, ammoniated water and fumed silica. The water in the dispersion is evaporated during processing.

[5]White, opaque, hard gelatin capsule, size 00.

[6]Each batch is assayed prior to filling and the capsule weight is adjusted as required to attain 200 mg amantadine per capsule.

The quantitative batch composition for amantadine extended release capsule is shown below. (Theoretical batch quantity 25,741 capsules).

Step 1: Prep of Amantadine HC1 Beads (bead Build-up #1)

Component	Weight (kg)
Amantadine	12.000
OPADRY ® Clear YS-3-7011	0.200
Purified Water, USP	5.454
Sugar Sphere, NF	4.000
Total Weight Amantadine Bends	16.200 kg

The amantadine beads obtained from step 1 are used as follows.

Step 2: Clear & Sustained Release Bead Coating #1

Component	Weight (kg)
Amantadine Beads	8.000
OPADRY ® Clear YS-1-7006	0.360
Purified Water, USP	5.928

-continued

Step 2: Clear & Sustained Release Bead Coating #1

Component	Weight (kg)
Surelease ® E-7-7050	0.672
Total Weight Clear Coated Sustained Release Beads	9.032 kg

The sustained release beads obtained from step 2 are used as follows.

Step 3: Amantadine HC1 Beads (Build-up #2)

Component	Weight (kg)
Sustained Release Beads	8.000
Amantadine	4.320
OPADRY ® Clear YS-3-7011	0.072
Purified Water, USP	1.964
Total Weight Amantadine Beads	12.392 kg

The amantadine beads obtained from step 3 are formulated as follows.

Step 4: Clear & Sustained Release Bead Coating #2

Component	Weight (kg)
Amantadine Beads	10.000
OPADRY ® Clear YS-1-7006	0.250
Purified Water, USP	6.450
Surelease ® E-7-7050	1.050
Total Weight Amantadine Extended Release Beads	11.300 kg

Step 5: Capsule Filling -- Gelatin capsules, size 00, are filled with 339 mg of the amantadine beads prepared in step 4.

Example 3

Extended Release Amantadine Formulation with Immediate Release Carbidopa and Levodopa

Levodopa and Carbidopa are formulated into pellets suitable for filling, yet having an immediate release profile. (see, for example, U.S. Pat. No. 5,912,013).

	Weight Percent	Kilograms
Levodopa plus Carbidopa Core Pellets		
MCC	25.0	0.25
Hydroxypropylmethylcellulose Phthalate (HPMCP)	10.0	0.10
Tartaric Acid	10.0	0.10
Sodium Monoglycerate	7.5	0.075
DSS	0.5	0.005
Levodopa	35.8	0.358
Carbidopa	11.2	0.112
TOTAL	100.0%	1.00 kg
Coating		
Cellulose Acetate Phthalate (CAP)	60.0	0.60

-continued

	Weight Percent	Kilograms
Ethylcellulose	25.0	0.25
PEG-400	15.0	0.15
TOTAL	100.0%	1.00 kg

The pellets are assayed for levodopa and carbidopa content. It is determined that approximately 223 mg of the pellets contain 80 mg levodopa and 25 mg carbidopa. Dissolution greater than 90% in 30 minutes is also confirmed.

A total of 669 grams of the pellets are blended with 510 grams of the amantadine pellets from Example 2 in a V-blender for 30 minutes at 30 rpm. Gelatin capsules are filled with 393 mg of the mixture and the assays for content are repeated verifying a composition of 100 mg amantadine, 80 mg levodopa, and 25 mg carbidopa.

Example 4

Predicted Dissolution and Plasma Profiles of Amantadine Controlled Release

Using the formulations described above, the dissolution profiles for amantadine were simulated and used to calculate plasma profiles resulting from single or multiple administrations using the pharmacokinetic software, GastroPlus v.4.0.2, from Simulations Plus (see FIG. **2**). The initial slope of the dissolution for the sustained release formulation is less than the slope determined for the immediate release formulation (see FIG. **1**) and the corresponding serum profile also shows a slower dC/dT (see FIG. **4**).

Example 5

Release Profile of Amantadine and L-DOPA (Levodopa/Carbidopa)

Release proportions are shown in the tables below for a combination of amantadine and levodopa/carbidopa. The cumulative fraction is the amount of drug substance released from the formulation matrix to the serum or gut environment (e.g., U.S. Pat. Nos. 4,839,177 or 5,326,570) or as measured with a USP II Paddle system using 0.1N HCl as the dissolution medium.

Time	AMANTADINE T½ = 15 cum. fraction A	LEVODOPA/CARBIDOPA T½ = 1.5 hrs, Cum. fraction B
0	0.00	0.00
0.5	0.10	0.40
1.0	0.20	0.95
2.0	0.35	1.00
4.0	0.60	1.00
8.0	0.90	1.00
12.0	0.98	1.00

Example 6

Treating Dyskinesia in Patients with Parkinson's Disease

A Parkinson's patient experiencing dyskinesia is administered the composition of Example 3 three times each day to receive 300 mg amantadine, 240 mg levodopa, and 75 mg carbidopa daily. The Parkinsonism is reduced as measured by the UPDRS (Goetz et al., Mov. Disord. 19:1020-8, 2004, incorporated by reference) as is the dyskinesia (Vitale et al., Neurol. Sci. 22:105-6, 2001, incorporated by reference)

Example 7

Animal Models Showing Reduced Dyskinesia, Reduced Levodopa Potential

The following protocol was employed to demonstrate the beneficial effects of the compositions of this invention. Briefly, squirrel monkeys (N=4) were lesioned with MPTP according to the protocol of Di Monte et al. (Mov. Disord. 15: 459-66 (2000)). After 3 months, the monkeys showed full symptoms of Parkinson's disease as measured by a modified UPDRS (Goetz et al., Mov. Disord. 19:1020-8, 2004). Levodopa treatment at approximately 15 mg/kg (with 1.5 mg/kg carbidopa) mg/kg b.i.d. commenced a baseline UPDRS and dyskinesia measurement was established. Amantadine was added to the regimen simultaneously with the levodopa, and the amount raised from 1 mg/kg to 45 mg/kg for four of the squirrel monkeys, corresponding to an estimated 3 μm concentration. As shown in FIG. **8**, the combination led to a 60% reduction in dyskinesia. We hypothesize that this translates into a potential 40% reduction in levodopa required to maintain UPDRS.

Example 8

Levodopa Sparing Therapy

The following protocol is employed to determine the optimal reduction of levodopa achieved with the addition of Amantadine to a fixed dose combination product.

Parkinson's DISEASE PROTOCOL SUMMARY NPI MEMANTINE CR MONOTHERAPY	
Protocol Number:	NPI-Amantadine CR
Study Phase:	2/3
Name of Drug:	NPI-Amantadine/C/L
Dosage:	25/100/100 c/l/a given t.i.d. 25/80/100 c/l/a given t.i.d. 25/60/100 c/l/a given t.i.d.
Concurrent Control:	25/100 c/1 given t.i.d.
Route:	Oral
Subject Population:	Male and female patients diagnosed with Parkinson's Disease Hoehn and Yahr score of 2-4
Structure:	Parallel-group, three-arm study
Study Term	Two weeks
Study Sites:	Multi-center 10 centers
Blinding:	Double blind
Method of Subject Assignment:	Randomized to one of three treatment groups (3:1)
Total Sample Size:	320 subjects (160 men, 160 women)
Primary Efficacy Endpoints:	UPDRS Abnormal involuntary movement scale (AIMS) 0-4
Secondary Endpoints:	Modified Obeso dyskinesia rating scale 0-4 Mini-mental state examination (MMSE); Neuropsychiatric InventoryScore (NPI)
Adverse Events:	Monitored and elicited by clinic personnel throughout the study, volunteered by patients

Example 9

Pharmaceutical Composition Including Memantine, Levodopa, and Carbidopa

A co-formulation of memantine, levodopa and carbidopa is prepared. This co-formulation matches the absorption prop-

erties of levodopa and carbidopa more closely than those of Memantine, thereby extending the effectiveness per dose of levodopa and carbidopa. The co-formulation provides Tmax values to about 4 hours and allows b.i.d. dosing of the combination.

FIG. **6** provides the current single oral dose pharmacokinetic (PK) profiles for levodopa, carbidopa and memantine. FIG. **7** provides idealized pharmacokinetic profiles for the target co-formulation, in which the Tmax values for levodopa and carbidopa more closely match that of Memantine.

Dosage Form:	Tablet
Formulation Content:	Levodopa 150 mg
Carbidopa	37.5 mg
Memantine	10 mg
Excipients:	FDA approved excipients and drug release modifiers. Additional embodiments are within the claims.

Example 10

Pharmaceutical Composition Including Extended Release Formulations of Memantine and Levodopa

A pulsatile release dosage form for administration of memantine and levodopa may be prepared as three individual compartments. Three individual tablets are compressed, each having a different release profile, followed by encapsulation into a gelatin capsule, which are then closed and sealed. The components of the three tablets are as follows.

Component	Function	Amount per tablet
TABLET 1 (IMMEDIATE RELEASE):		
Memantine	Active agent	8 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
TABLET 2 (RELEASE DELAYED 3-5 HOURS FOLLOWING ADMINISTRATION):		
Memantine	Active agent	8 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS3OD	Delayed release coating material	4.76 mg
Talc	Coating component	3.3 mg
Triethyl citrate	Coating component	0.95 mg
TABLET 3 (RELEASE DELAYED 7-9 HOURS FOLLOWING ADMINISTRATION):		
Memantine	Active agent	2.5 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS3OD	Delayed release coating material	6.34 mg
Talc	Coating component	4.4 mg
Triethyl citrate	Coating component	1.27 mg

The tablets are prepared by wet granulation of the individual drug particles and other core components as may be done using a fluid-bed granulator, or are prepared by direct compression of the admixture of components. Tablet 1 is an immediate release dosage form, releasing the active agents within 1-2 hours following administration. Tablets 2 and 3 are coated with the delayed release coating material as may be carried out using conventional coating techniques such as spray-coating or the like. As will be appreciated by those skilled in the art, the specific components listed in the above tables may be replaced with other functionally equivalent components, e.g., diluents, binders, lubricants, fillers, coatings, and the like.

Oral administration of the capsule to a patient will result in a release profile having three pulses, with initial release of the memantine and levodopa from the first tablet being substantially immediate, release of the memantine and levodopa from the second tablet occurring 3-5 hours following administration, and release of the memantine and levodopa from the third tablet occurring 7-9 hours following administration.

Example 11

Pharmaceutical Composition Including Extended Release Formulations of Memantine, Levodopa, and Carbidopa

The method of Example 9 is repeated, except that drug-containing beads are used in place of tablets. Carbidopa is also added in each of the fractions at 25% of the mass of the levodopa. A first fraction of beads is prepared by coating an inert support material such as lactose with the drug which provides the first (immediate release) pulse. A second fraction of beads is prepared by coating immediate release beads with an amount of enteric coating material sufficient to provide a drug release-free period of 3-5 hours. A third fraction of beads is prepared by coating immediate release beads having half the methylphenidate dose of the first fraction of beads with a greater amount of enteric coating material, sufficient to provide a drug release-free period of 7-19 hours. The three groups of beads may be encapsulated or compressed, in the presence of a cushioning agent, into a single pulsatile release tablet.

Alternatively, three groups of drug particles may be provided and coated as above, in lieu of the drug-coated lactose beads.

Other Embodiments

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A method comprising:

orally administering to a human subject with Parkinson's disease a once-daily dose consisting of (i) 200 mg to 500 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, and (ii) at least one excipient, wherein at least 50% of the drug in the dose is in an extended release form, and wherein the dose provides a mean change in amantadine plasma concentration as a function of time (dC/dT) as measured in a single dose human pharmacokinetic study over the time period between 2 hours and 4 hours after administration that is less than 30% of the dC/dT provided by the same quantity of the drug in an immediate release form as measured in a single dose

human pharmacokinetic study over the time period between 0 and 2 hours after administration.

2. The method of claim **1**, wherein the amount of drug is 300 to 500 mg.

3. The method of claim **1**, wherein at least 75% of the drug in the dose is in an extended release form.

4. The method of claim **1**, wherein the dose additionally comprises the drug in an immediate release form.

5. The method of claim **1**, wherein at least 90% of the drug in the dose is in an extended release form.

6. The method of claim **1**, wherein the dose administered is therapeutically effective for the treatment of Parkinson's disease.

7. The method of claim **1**, wherein the human subject with Parkinson's disease suffers from dyskinesia.

8. The method of claim **7**, wherein the method reduces the frequency or severity of dyskinesia.

9. The method of claim **7**, wherein the dyskinesia is levodopa-induced dyskinesia.

10. The method of claim **1**, additionally comprising administering to the subject a pharmaceutically effective amount of levodopa/carbidopa.

11. The method of claim **1**, wherein the dose provides a shift in amantadine Tmax of 2 hours to 16 hours relative to an immediate release form of amantadine, wherein the Tmax is measured in a single dose human pharmacokinetic study.

12. The method of claim **1**, wherein the dose comprises an osmotic device which utilizes an osmotic driving force to provide extended release of the drug.

13. The method of claim **1**, wherein the extent of drug bioavailability is maintained.

14. The method of claim **1**, wherein the once-daily dose is administered at a therapeutically-effective dose from the onset of therapy.

* * * * *

EXHIBIT G

US008895617B1

(12) **United States Patent**
Went et al.

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(45) **Date of Patent: *Nov. 25, 2014**

(54) **COMPOSITION AND METHOD FOR TREATING NEUROLOGICAL DISEASE**

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(58) **Field of Classification Search**
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See application file for complete search history.

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(57) **ABSTRACT**

Disclosed are compositions comprising amantadine, or a pharmaceutically acceptable salt thereof, and one or more excipients, wherein at least one of the excipients modifies release of amantadine. Methods of administering the same are also provided.

17 Claims, 7 Drawing Sheets

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Figure 1: Simulated Dissolution for TID Amantadine IR & SR

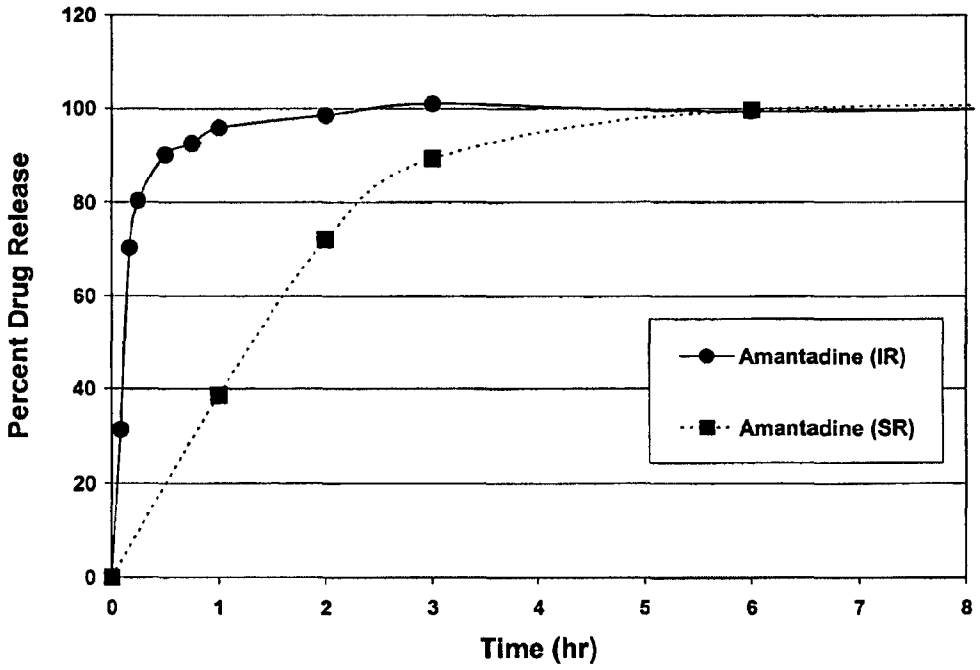


Figure 2: Simulated Plasma Concentration for TID Amantadine IR & SR over 120hrs.

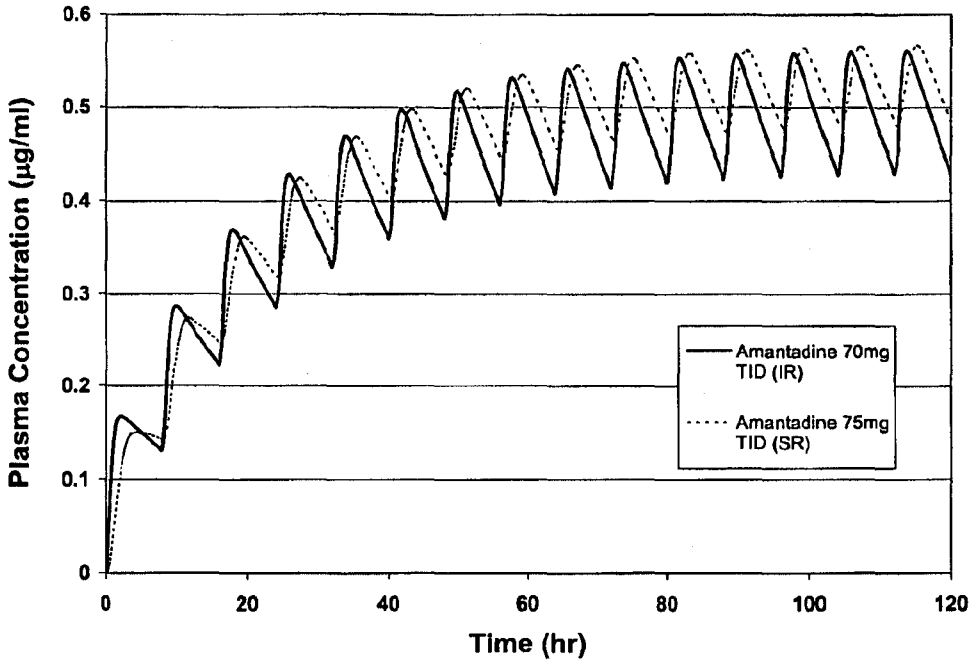


Figure 3: Simulated Plasma Concentration for TID Levodopa/Carbidopa/Amantadine (IR, IR, IR) over 24hrs

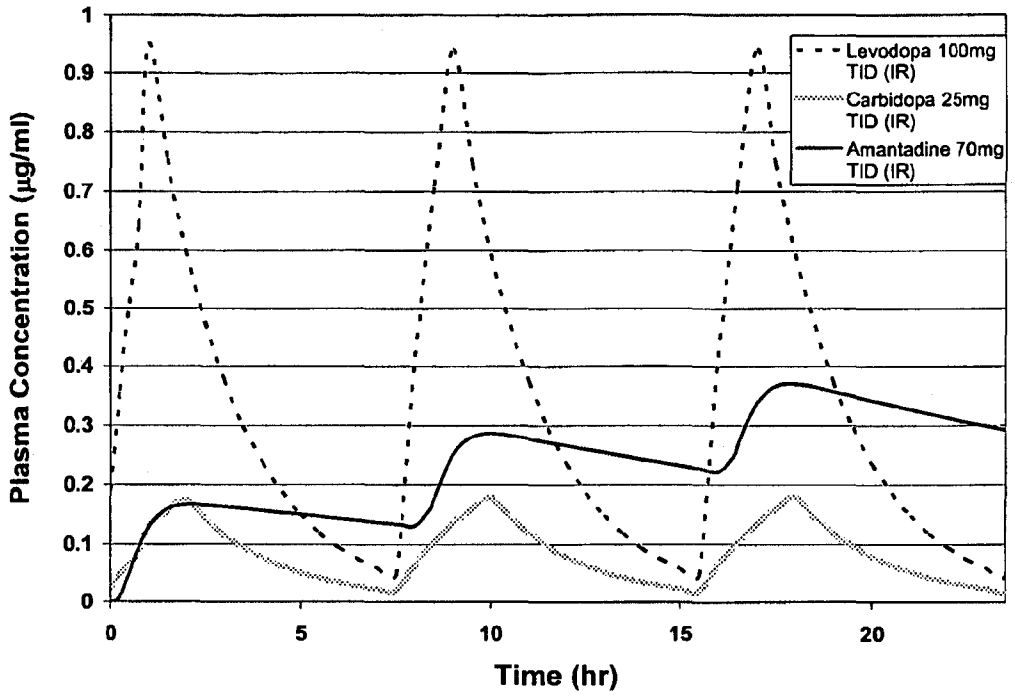


Figure 4: Simulated Plasma Concentration for TID Levodopa/Carbidopa/Amantadine (IR, IR, SR) over 24hrs

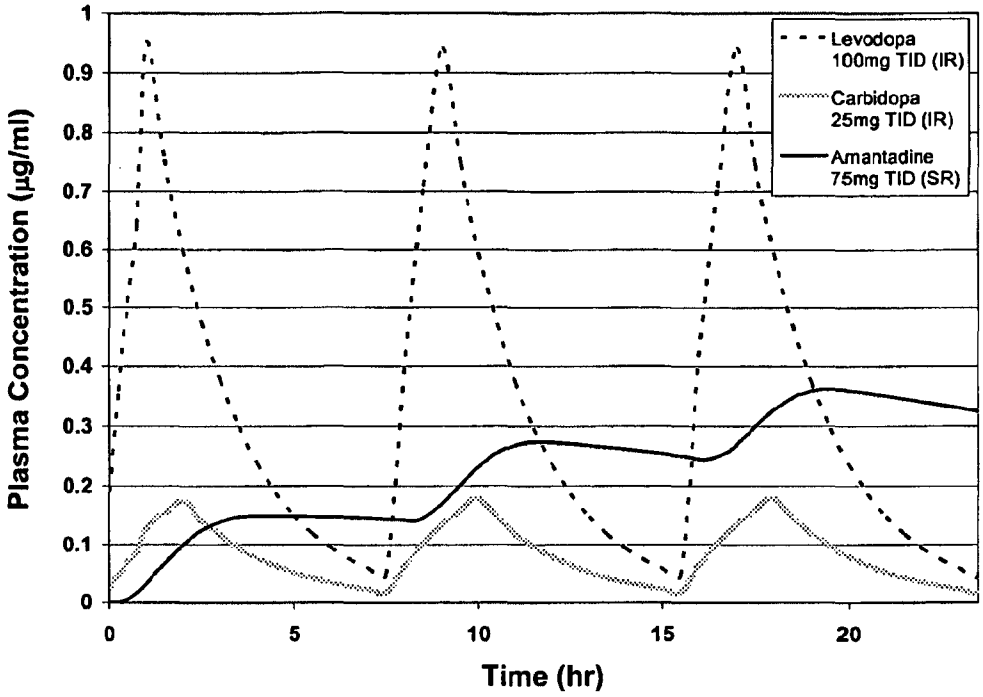


FIGURE 5

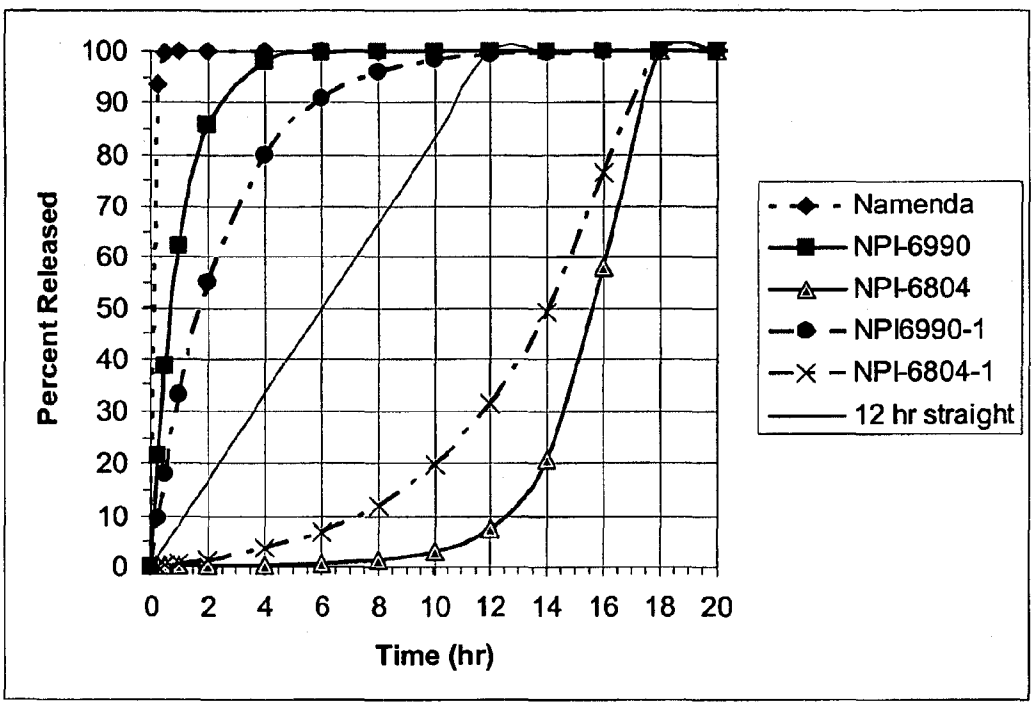

Percent Released
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20
Time (hr)
Namenda
NPI-6990
NPI-6804
NPI6990-1
NPI-6804-1
12 hr straight

Figure 6: Memantine, Levodopa and Carbidopa Human Pharmacokinetics

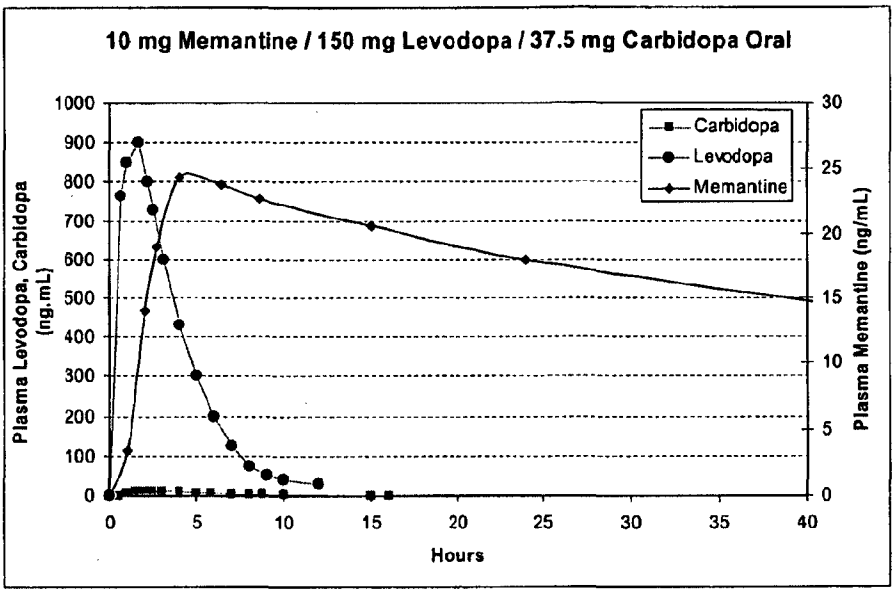
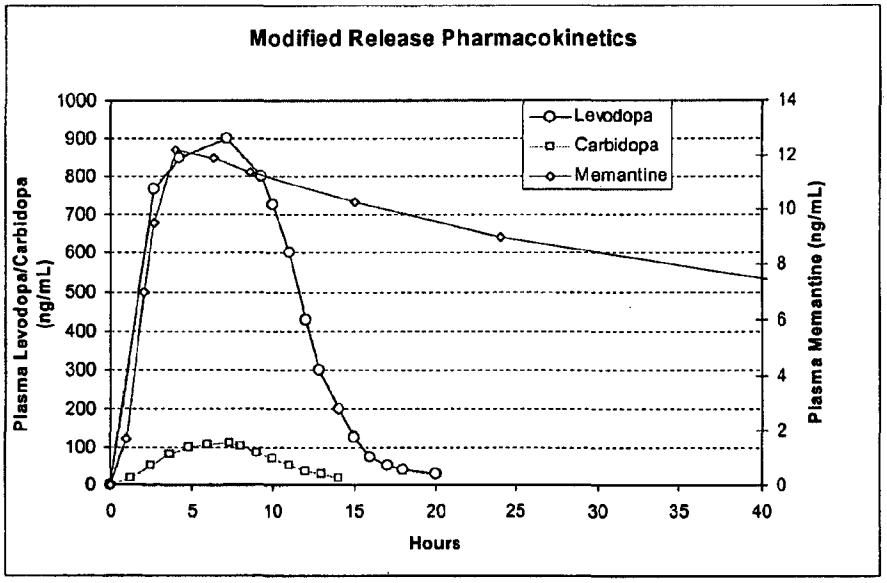


Figure 7: Target Pharmacokinetics



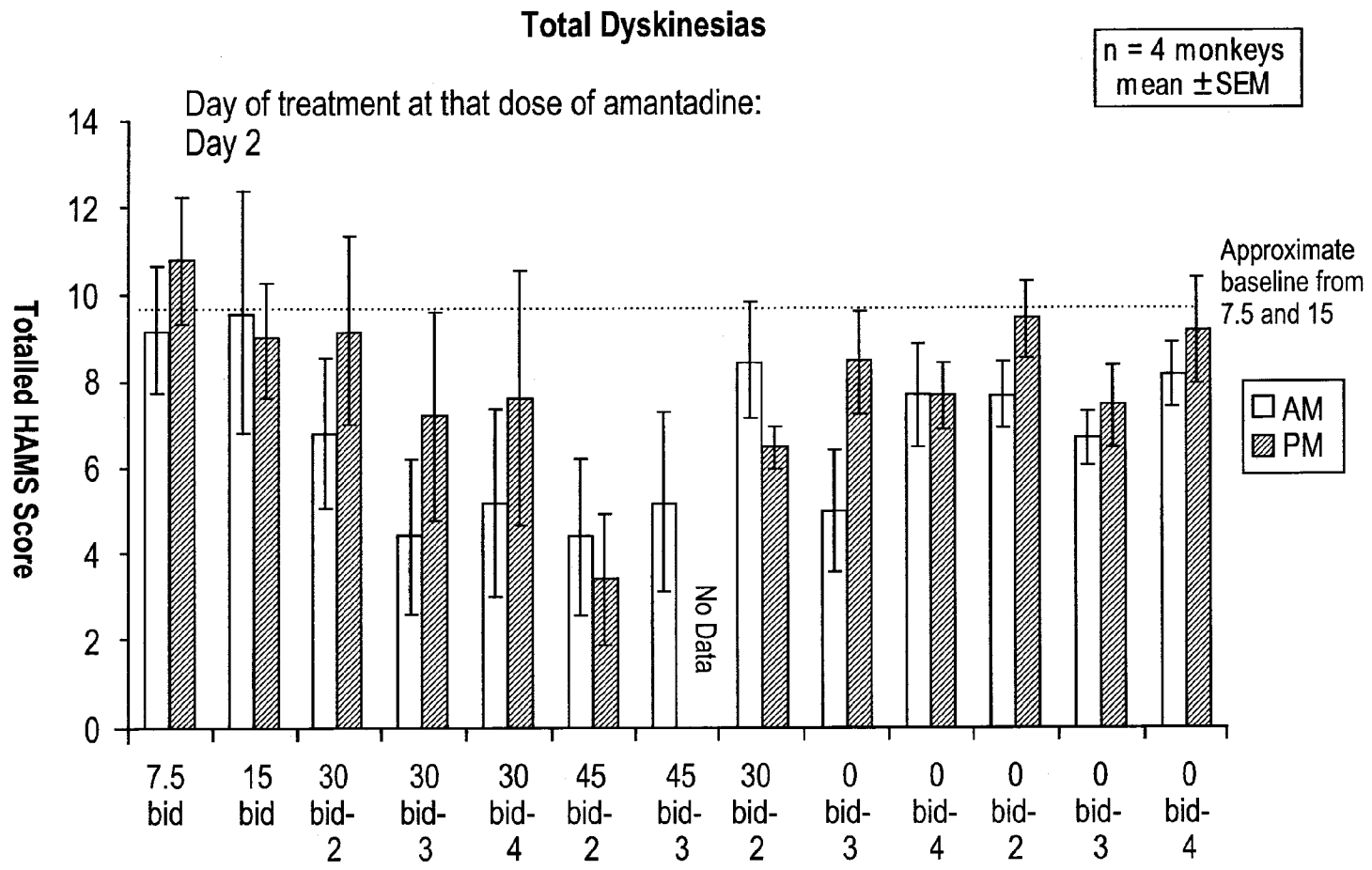

Total Dyskinesias
n = 4 monkeys
mean ±SEM
Day of treatment at that dose of amantadine:
Day 2
Totalled HAMS Score
14
12
10
8
6
4
2
0
Approximate baseline from 7.5 and 15
AM
PM
No Data
7.5 bid
15 bid
30 bid-2
30 bid-3
30 bid-4
45 bid-2
45 bid-3
30 bid-2
0 bid-3
0 bid-4
0 bid-2
0 bid-3
0 bid-4

Figure 8

COMPOSITION AND METHOD FOR TREATING NEUROLOGICAL DISEASE

RELATED APPLICATION

This application is a continuation of U.S. patent application Ser. No. 14/328,440, filed Jul. 10, 2014, which is a continuation of U.S. patent application Ser. No. 13/958,153, filed Aug. 2, 2013, which is a continuation of U.S. patent application Ser. No. 13/756,275, filed Jan. 31, 2013, now abandoned, which is a continuation application of U.S. patent application Ser. No. 11/286,448, filed on Nov. 23, 2005, now U.S. Pat. No. 8,389,578, which claims priority to U.S. Provisional Application No. 60/631,095 filed on Nov. 24, 2004, all of which applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

This invention relates to compositions and methods for treating neurological diseases, such as Parkinson's disease.

BACKGROUND OF THE INVENTION

Parkinson's disease (PD) is a progressive, degenerative neurologic disorder which usually occurs in late mid-life. PD is clinically characterized by bradykinesia, tremor, and rigidity. Bradykinesia is characterized by a slowness in movement, slowing the pace of such routine activities as walking and eating. Tremor is a shakiness that generally affects limbs that are not otherwise in motion. For those PD-patients diagnosed at a relatively young age, tremor is reported as the most disabling symptom. Older patients face their greatest challenge in walking or keeping their balance. Rigidity is caused by the inability of muscles to relax as opposing muscle groups contract, causing tension which can produce aches and pains in the back, neck, shoulders, temples, or chest.

PD predominantly affects the substantia nigra (SNc) dopamine (DA) neurons and is therefore associated with a decrease in striatal DA content. Because dopamine does not cross the blood-brain barrier, PD patients may be administered a precursor, levodopa, that does cross the blood-brain barrier where it is metabolized to dopamine. Levodopa therapy is intended to compensate for reduced dopamine levels and is a widely prescribed therapeutic agent for patients with Parkinson's disease. Chronic treatment with levodopa however, is associated with various debilitating side-effects such as dyskinesia.

Since currently available drugs containing levodopa are associated with debilitating side effects, better therapies are needed for the management of PD.

SUMMARY OF THE INVENTION

In general, the present invention provides methods and compositions for treating and preventing CNS-related conditions, such as Parkinson's disease or other Parkinson's-like diseases or conditions, by administering to a subject in need thereof a combination that includes an N-Methyl-D-Aspartate receptor (NMDAr) antagonist and levodopa. Exemplary NMDAr antagonists include the aminoadamantanes, such as memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1-aminoethyl)adamantane), or amantadine (1-amino-adamantane) as well as others described below. Because levodopa is metabolized before crossing the blood-brain barrier and has a short half-life in the circulatory system, it is typically administered in conjunction with a dopa-

decarboxylase inhibitor. Examples of dopa-decarboxylase inhibitors include carbidopa, 3-hydroxy-benzylhydrazinedihydrochloride (NSD-1015), and benseraxide hydrochloride. The combination may further include a catechol-0-methyltransferase (COMT) inhibitor including, for example, talcapone and entacapone. As used herein, levodopa/carbidopa shall mean levodopa alone or in combination with a dopa-decarboxylase inhibitor such as carbidopa. Desirably, the levodopa/carbidopa is in an immediate release formulation and the NMDA receptor antagonist is in an extended release formulation. One preferred embodiment of the invention involves the combination of amantadine and levodopa/carbidopa. Desirably, amantadine is provided in an extended release formulation and levodopa/carbidopa is provided as an immediate release formulation. By combining an NMDAr antagonist (e.g., amantadine) with the second agents described herein (e.g., levodopa/carbidopa), this invention provides an effective pharmaceutical composition for treating neurological diseases such as Parkinson's disease or other Parkinson's-like diseases or conditions. The administration of this combination is postulated to maintain or enhance the efficacy of levodopa while significantly reducing its dyskinesia side effects.

The combinations described herein provide complementary benefits associated with the NMDAr antagonist or levodopa/carbidopa individually, while minimizing difficulties previously presented when each component is used separately in a patient. For example, amantadine dosing is limited by neurotoxicity that is likely associated with its short Tmax. By extending the release of amantadine, a higher effective dose can be maintained providing both dyskinesia relief and a reduction in the amount of levodopa required for treatment of the disease symptoms. Given the inherent toxicity of levodopa, such a levodopa sparing combination will result in a decline in both the dyskinesia and overall disease.

Accordingly, the pharmaceutical compositions described herein are administered so as to deliver to a subject, an amount of an NMDAr antagonist, levodopa/carbidopa or both agents that is high enough to treat symptoms or damaging effects of an underlying disease while avoiding undesirable side effects. These compositions may be employed to administer the NMDAr antagonist, the levodopa/carbidopa, or both agents at a lower frequency than presently employed, improving patient compliance, adherence, and caregiver convenience. These compositions are particularly useful as they provide the NMDAr antagonist, levodopa/carbidopa, or both agents, at a therapeutically effective amount from the onset of therapy further improving patient compliance and adherence and enable the achievement of a therapeutically effective steady-state concentration of either or both agents of the combination in a shorter period of time resulting in an earlier indication of effectiveness and increasing the utility of these therapeutic agents for diseases and conditions where time is of the essence. Also provided are methods for making and using such compositions.

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a controlled or extended release form with or without an immediate release component in order to maximize the therapeutic benefit of such agents, while reducing unwanted side effects. In preferred embodiments for oral administration, levodopa/carbidopa is provided as an immediate-release formulation.

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be administered in an amount similar to that typically administered to subjects. Preferably, the amount of the NMDAr antagonist may be administered in an amount greater than or less than the amount that is typically admin-

istered to subjects while the levodopa/carbidopa is provided at a lower dose than normally used. For example, the amount of amantadine required to positively affect the patient response (inclusive of adverse effects) may be 300, 400, 500, 600 mg per day rather than the typical 200-300 mg per day administered for presently approved indications i.e. without the improved formulation described herein, while the levodopa, and optionally the carbidopa, can be reduced independently by 10%, 20%, 30%, 40%, 50%, 60%, 70% or up to 80% of what is currently required in the absence of the NMDAr antagonist.

Optionally, lower or reduced amounts of both the NMDAr antagonist and the levodopa/carbidopa are used in a unit dose relative to the amount of each agent when administered independently. The present invention therefore features formulations of combinations directed to dose optimization or release modification to reduce adverse effects associated with separate administration of each agent. The combination of the NMDAr antagonist and the levodopa/carbidopa may result in an additive or synergistic response, and using the unique formulations described herein, the goal of minimizing the levodopa burden is achieved. Preferably, the NMDAr antagonist and the levodopa/carbidopa are provided in a unit dosage form.

The compositions and methods of the invention are particularly useful for the treatment of Parkinson's disease or conditions associated with Parkinson's disease. These conditions include dementia, dyskinesia, dystonia, depression, fatigue and other neuropsychiatric complications of Parkinson's disease.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present Specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. All parts and percentages are by weight unless otherwise specified.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a graph showing the dissolution profiles for an immediate and sustained release formulation of amantadine. The sustained release formulation exhibits a dC/dT during the initial phase that is about 10% of that for the immediate release formulation.

FIG. **2** is a graph showing the amantadine plasma concentration over a period of 5 days, as predicted by Gastro-Plus software package v.4.0.2, following the administration of either 70 mg amantadine in an immediate release formulation t.i.d. or 75 mg amantadine in a sustained release formulation t.i.d. The sustained release formulation peaks are similar in height to the immediate release formulation even with a higher administered dose and the diurnal variation is substantially reduced.

FIG. **3** is a graph showing the plasma profiles simulated using Gastro-Plus for t.i.d. administration of amantadine (70 mg), levodopa (100 mg), and carbidopa (25 mg), all in an immediate release form.

FIG. **4** is a graph showing the plasma profiles simulated using Gastro-Plus for t.i.d. administration of amantadine (75 mg), levodopa (100 mg), and carbidopa (25 mg), where the amantadine is in a sustained release form and the levodopa and carbidopa are in an immediate release form.

FIG. **5** is a graph representing dissolution profiles for various aminoadamantane formulations including an immediate release form of the NMDAr antagonist memantine (Namenda).

FIG. **6** is a graphical representation of plasma release profiles in a human of memantine, levodopa, and carbidopa when memantine is administered separately from levodopa and carbidopa.

FIG. **7** is a graphical representation of plasma release profiles in a human of memantine, levodopa, and carbidopa when memantine, levodopa, and carbidopa are administered as part of a single controlled-release pharmaceutical composition.

FIG. **8** is a bar graph showing the effects on a primate (squirrel monkey) treated with a combination of levodopa/carbidopa and amantadine.

DETAILED DESCRIPTION OF THE INVENTION

In general, the present invention features pharmaceutical compositions that contain therapeutically effective levels of an NMDAr antagonist and levodopa/carbidopa and, optionally, a pharmaceutical carrier. Preferably the compositions are formulated for modified or extended release to provide a serum or plasma concentration of the NMDAr antagonist over a desired time period that is high enough to be therapeutically effective but at a rate low enough so as to avoid adverse events associated with the NMDAr antagonist. Control of drug release is particularly desirable for reducing and delaying the peak plasma level while maintaining the extent of drug bioavailability. Therapeutic levels are therefore achieved while minimizing debilitating side-effects that are usually associated with immediate release formulations. Furthermore, as a result of the delay in the time to obtain peak serum or plasma level and the extended period of time at the therapeutically effective serum or plasma level, the dosage frequency is reduced to, for example, once or twice daily dosage, thereby improving patient compliance and adherence. For example, side effects including psychosis and cognitive deficits associated with the administration of NMDAr antagonists may be lessened in severity and frequency through the use of controlled-release methods that shift the Tmax to longer times, thereby reducing the dC/dT of the drug. Reducing the dC/dT of the drug not only increases Tmax, but also reduces the drug concentration at Tmax and reduces the Cmax/Cmean ratio providing a more constant amount of drug to the subject being treated over a given period of time, enabling increased dosages for appropriate indications.

In addition, the present invention encompasses optimal ratios of NMDAr and levodopa/carbidopa, designed to not only treat the dyskinesia associated with levodopa, but also take advantage of the additivity and synergy between these drug classes. For example, the level of levodopa required to treat the disease symptoms can unexpectedly be reduced by up to 50% by the addition of 400 mg/day of amantadine.

Making NMDAr Antagonist Controlled Release Formulations

A pharmaceutical composition according to the invention is prepared by combining a desired NMDAr antagonist or antagonists with one or more additional ingredients that, when administered to a subject, causes the NMDAr antagonist to be released at a targeted rate for a specified period of time. A release profile, i.e., the extent of release of the NMDAr antagonist over a desired time, can be conveniently determined for a given time by measuring the release using a USP dissolution apparatus under controlled conditions. Pre-

ferred release profiles are those which slow the rate of uptake of the NMDAr antagonist in the neural fluids while providing therapeutically effective levels of the NMDAr antagonist. One of ordinary skill in the art can prepare combinations with a desired release profile using the NMDAr antagonists and formulation methods described below.

NMDAr Antagonists

Any NMDAr antagonist can be used in the methods and compositions of the invention, particularly those that are non-toxic when used in the compositions of the invention. The term "nontoxic" is used in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to humans or, in keeping with established regulatory criteria and practice, is susceptible to approval by the FDA or similar regulatory agency for any country for administration to humans or animals.

The term "NMDAr antagonist", as used herein, includes any amino-adamantane compound including, for example, memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1-aminoethyl)adamantane), amantadine (1-aminoadamantane), as well as pharmaceutically acceptable salts thereof. Memantine is described, for example, in U.S. Pat. Nos. 3,391,142, 5,891,885, 5,919,826, and 6,187,338. Amantadine is described, for example, in U.S. Pat. Nos. 3,152,180, 5,891,885, 5,919,826, and 6,187,338. Additional aminoadamantane compounds are described, for example, in U.S. Pat. Nos. 4,346,112, 5,061,703, 5,334,618, 6,444,702, 6,620,845, and 6,662,845. All of these patents are hereby incorporated by reference.

Further NMDAr antagonists that may be employed include, for example, aminocylohexanes such as neramexane, ketamine, eliprodil, ifenprodil, dizocilpine, remacemide, iamotrigine, riluzole, aptiganel, phencyclidine, flupirtine, celfotel, felbamate, spermine, spermidine, levemopamil, dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and its metabolite, dextrorphan ((+)-3-hydroxy-N-methylmorphinan), a pharmaceutically acceptable salt, derivative, or ester thereof, or a metabolic precursor of any of the foregoing.

Optionally, the NMDAr antagonist in the instant invention is memantine and not amantadine or dextromethorphan.

Second Agents

In all foregoing aspects of the invention, the second agent is levodopa. When levodopa is in the combination, the combination preferably also includes a dopa-decarboxylase inhibitor. An example of a suitable dopa-decarboxylase inhibitor is carbidopa. Other dopa-decarboxylase inhibitors include, for example, 3-hydroxy-benzylhydrazinedihydrochloride (NSD-1015) and benseraxide hydrochloride. The combination may further include a catechol-O-methyltransferase (COMT) inhibitor including, for example, talcapone and entacapone.

Dosing, PK, & Toxicity

The NMDA receptor antagonist used in combination therapies are administered at a dosage of generally between about 1 and 5000 mg/day, between 1 and about 800 mg/day, or between 1 and 500 mg/day. For example, NMDA receptor antagonist agents may be administered at a dosage ranging between about 1 and about 500 mg/day, more preferably from about 10 to about 40, 50, 60, 70 or 80 mg/day, advantageously from about 10 to about 20 mg per day. Amantadine may be administered at a dose ranging from about 90, 100 mg/day to about 400, 500, 600, 700 or 800 mg/day, advantageously from about 100 to about 500, 600 mg per day. For example, the pharmaceutical composition may be formulated to provide memantine in an amount ranging between 1-200 mg/day, 1 and 80 mg/day, 2-80 mg/day, 10-80 mg/day, 10 and 80 mg/day, 10 and 70 mg/day, 10 and 60 mg/day, 10 and 50 mg/day, 10 and 40 mg/day, 5 and 65 mg/day, 5 and 40 mg/day, 15 and 45 mg/day, or 10 and 20 mg/day; dextromethorphan in an amount ranging between 1-5000 mg/day, 1-1000 mg/day, and 100-800 mg/day, or 200-500 mg/day. Pediatric doses will typically be lower than those determined for adults.

Table 1 shows exemplary pharmacokinetic properties (e.g., Tmax and T1/2) of memantine, amantadine, and rimantadine.

TABLE 1

Pharmacokinetics and Toxicity in humans for selected NIVIDAr antagonists

Compound	Human PK ($t_{1/2}$) (hours)	Tmax (hours)	Normal Dose	Dose Dependent Toxicity
Memantine	60	3	10-20 mg/day, starting at 5 mg	Dose escalation required, hallucination
Amantadine	15	3	100-300 mg/day, starting at 100 mg/day	Hallucination
Rimantadine	25	6	100-200 mg/day	Insomnia

When levodopa and carbidopa are both included in the composition, the levodopa dose ranges between 100 to 3000 mg per day, 75 mg and 2500 mg/day, 100-2000 mg/day, or 250 and 1000 mg/day divided for administration t.i.d. or more frequently. Carbidopa doses may range between the amounts of 1 to 1000 mg/day, 10 to 500 mg/day, and 25 to 100 mg/day. Optionally, the carbidopa is present in the combination at about 75%, 70%, 65%, 60%, 50%, 40%, 30%, 25%, 20%, and 10% of the mass of the levodopa. Alternatively, the amount of levodopa is less than 300% than the amount of carbidopa. For example, 75 mg of carbidopa (amount that is sufficient to extend the half-life of levodopa in the circulatory system) may be used in combination with 300 to 3000 mg of levodopa per day. The combination may contain a single dosage form comprising 30 to 200 mg amantadine, 30 to 250 mg levodopa, and 10 to 100 mg of carbidopa for t.i.d. or more frequent administration, including multiple dosage forms per administration.

As a result, the preferred dosage forms for optimized use are shown in Table 2 below, with their corresponding commercial equivalent.

TABLE 2

Dosage forms with and without NMDAr antagonist (amount per unit dose)

Sinemet Compositions		Compositions of Present Invention		
Levodopa	Carbidopa	Levodopa	Carbidopa	Amantadine
100 mg IR*	25 mg IR	50-100 mg IR	25 mg IR	100-200 mg IR
100 mg IR	10 mg IR	50-100 mg IR	10 mg IR	50-100 mg IR
100 mg IR	25 mg IR	50-100 mg IR	25 mg IR	100-200 mg CR**
100 mg IR	10 mg IR	50-100 mg IR	10 mg IR	50-100 mg CR

* IR: immediate release
**CR: modified release

Excipients

"Pharmaceutically or Pharmacologically Acceptable" includes molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when

administered to an animal, or a human, as appropriate. "Pharmaceutically Acceptable Carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. "Pharmaceutically Acceptable Salts" include acid addition salts and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

The preparation of pharmaceutical or pharmacological compositions is known to those of skill in the art in light of the present disclosure. General techniques for formulation and administration are found in "Remington: The Science and Practice of Pharmacy, Twentieth Edition," Lippincott Williams & Wilkins, Philadelphia, Pa. Tablets, capsules, pills, powders, granules, dragees, gels, slurries, ointments, solutions suppositories, injections, inhalants and aerosols are examples of such formulations.

By way of example, modified or extended release oral formulation can be prepared using additional methods known in the art. For example, a suitable extended release form of the either active pharmaceutical ingredient or both may be a matrix tablet or capsule composition. Suitable matrix forming materials include, for example, waxes (e.g., carnauba, bees wax, paraffin wax, ceresine, shellac wax, fatty acids, and fatty alcohols), oils, hardened oils or fats (e.g., hardened rapeseed oil, castor oil, beef tallow, palm oil, and soya bean oil), and polymers (e.g., hydroxypropyl cellulose, polyvinylpyrrolidone, hydroxypropyl methyl cellulose, and polyethylene glycol). Other suitable matrix tabletting materials are microcrystalline cellulose, powdered cellulose, hydroxypropyl cellulose, ethyl cellulose, with other carriers, and fillers. Tablets may also contain granulates, coated powders, or pellets. Tablets may also be multi-layered. Multi-layered tablets are especially preferred when the active ingredients have markedly different pharmacokinetic profiles. Optionally, the finished tablet may be coated or uncoated.

The coating composition typically contains an insoluble matrix polymer (approximately 15-85% by weight of the coating composition) and a water soluble material (e.g., approximately 15-85% by weight of the coating composition). Optionally an enteric polymer (approximately 1 to 99% by weight of the coating composition) may be used or included. Suitable water soluble materials include polymers such as polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials such as sugars (e.g., lactose, sucrose, fructose, mannitol and the like), salts (e.g., sodium chloride, potassium chloride and the like), organic acids (e.g., fumaric acid, succinic acid, lactic acid, and tartaric acid), and mixtures thereof. Suitable enteric polymers include hydroxypropyl methyl cellulose, acetate succinate, hydroxypropyl methyl cellulose, phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups.

The coating composition may be plasticised according to the properties of the coating blend such as the glass transition temperature of the main component or mixture of components or the solvent used for applying the coating compositions. Suitable plasticisers may be added from 0 to 50% by weight of the coating composition and include, for example, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, acetylated citrate esters, dibutylsebacate, and castor oil. If desired, the coating composition may include a filler. The amount of the filler may be 1% to approximately 99% by weight based on the total weight of the coating composition and may be an insoluble material such as silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, MCC, or polacrilin potassium.

The coating composition may be applied as a solution or latex in organic solvents or aqueous solvents or mixtures thereof. If solutions are applied, the solvent may be present in amounts from approximate by 25-99% by weight based on the total weight of dissolved solids. Suitable solvents are water, lower alcohol, lower chlorinated hydrocarbons, ketones, or mixtures thereof. If latexes are applied, the solvent is present in amounts from approximately 25-97% by weight based on the quantity of polymeric material in the latex. The solvent may be predominantly water.

The NMDAr antagonist may be formulated using any of the following excipients or combinations thereof.

Excipient name	Chemical name	Function
Avicel PH102	Microcrystalline Cellulose	Filler, binder, wicking, disintegrant
Avicel PH101	Microcrystalline Cellulose	Filler, binder, disintegrant
Eudragit RS-30D	Polymethacrylate Poly(ethyl acrylate, nethyl methacrylate, timethylammonio-ethyl methacrylate chloride) 1:2:0.1	Film former, tablet binder, tablet diluent; Rate controlling polymer for controlled release
Methocel K100M Premium CR	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Methocel K100M agent	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing
Magnesium Stearate	Magnesium Stearate	Lubricant
Talc	Talc	Dissolution control; anti-adherent, glidant
Triethyl Citrate	Triethyl Citrate	Plasticizer
Methocel E5	Hydroxypropyl methylcellulose	Film-former
Opadry ®	Hydroxypropyl methylcellulose	One-step customized coating system which combines polymer, plasticizer and, if desired, pigment in a dry concentrate.
Surelease ®	Aqueous Ethylcellulose Dispersion	Film-forming polymer; plasticizer and stabilizers. Rate controlling polymer coating.

The pharmaceutical composition described herein may also include a carrier such as a solvent, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents. The use of such media and agents for pharmaceutically active substances is well known in the art. Pharmaceutically acceptable salts can also be used in the composition, for example, mineral salts such as hydrochlorides, hydrobromides, phosphates, or sulfates, as well as the salts of organic acids such as acetates, proprionates, malonates, or benzoates. The composition may also contain liquids, such as water, saline, glycerol, and ethanol, as well as substances such as wetting agents, emulsifying agents, or pH

buffering agents. Liposomes, such as those described in U.S. Pat. No. 5,422,120, WO 95/13796, WO 91/14445, or EP 524,968 B1, may also be used as a carrier.

Methods for Preparing Modified or Extended Release Formulations

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a controlled or extended release form with or without an immediate release component in order to maximize the therapeutic benefit of such agents, while reducing unwanted side effects. In the absence of modified release components (referred to herein as controlled, extended, or delayed release components), the NMDAr antagonist, levodopa/carbidopa, or both is released and transported into the body fluids over a period of minutes to several hours. The combination described herein however, may contain an NMDAr antagonist and a sustained release component, such as a coated sustained release matrix, a sustained release matrix, or a sustained release bead matrix. In one example, in addition to levodopa/carbidopa, amantadine (e.g., 50¬ 1400 mg) is formulated without an immediate release component using a polymer matrix (e.g., Eudragit), Hydroxypropyl methyl cellulose (HPMC) and a polymer coating (e.g., Eudragit). Such formulations are compressed into solid tablets or granules and coated with a controlled release material such as Opadry® or Surelease®. Levodopa/carbidopa may also be formulated as a sustained release formulation; in most cases, however, this will not be optimal.

Suitable methods for preparing the compositions described herein in which the NMDAr antagonist is provided in modified or extended release-formulations include those described in U.S. Pat. No. 4,606,909 (hereby incorporated by reference). This reference describes a controlled release multiple unit formulation in which a multiplicity of individually coated or microencapsulated units are made available upon disintegration of the formulation (e.g., pill or tablet) in the stomach of the subject (see, for example, column 3, line 26 through column 5, line 10 and column 6, line 29 through column 9, line 16). Each of these individually coated or microencapsulated units contains cross-sectionally substantially homogenous cores containing particles of a sparingly soluble active substance, the cores being coated with a coating that is substantially resistant to gastric conditions but which is erodable under the conditions prevailing in the gastrointestinal tract.

The composition of the invention may alternatively be formulated using the methods disclosed in U.S. Pat. No. 4,769,027, for example. Accordingly, extended release formulations involve prills of pharmaceutically acceptable material (e.g., sugar/starch, salts, and waxes) may be coated with a water permeable polymeric matrix containing an NMDAr antagonist and next overcoated with a water-permeable film containing dispersed within it a water soluble particulate pore forming material.

The NMDAr antagonist composition may additionally be prepared as described in U.S. Pat. No. 4,897,268, involving a biocompatible, biodegradable microcapsule delivery system. Thus, the NMDAr antagonist may be formulated as a composition containing a blend of free-flowing spherical particles obtained by individually microencapsulating quantities of memantine, for example, in different copolymer excipients which biodegrade at different rates, therefore releasing memantine into the circulation at a predetermined rates. A quantity of these particles may be of such a copolymer excipient that the core active ingredient is released quickly after administration, and thereby delivers the active ingredient for an initial period. A second quantity of the particles is of such type excipient that delivery of the encapsulated ingredient begins as the first quantity's delivery begins to decline. A third quantity of ingredient may be encapsulated with a still different excipient which results in delivery beginning as the delivery of the second quantity beings to decline. The rate of delivery may be altered, for example, by varying the lactide/glycolide ratio in a poly(D,L-lactide-co-glycolide) encapsulation. Other polymers that may be used include polyacetal polymers, polyorthoesters, polyesteramides, polycaprolactone and copolymers thereof, polycarbonates, polyhydroxybuterate and copolymers thereof, polymaleamides, copolyaxalates and polysaccharides.

Alternatively, the composition may be prepared as described in U.S. Pat. No. 5,395,626, which features a multilayered controlled release pharmaceutical dosage form. The dosage form contains a plurality of coated particles wherein each has multiple layers about a core containing an NMDAr antagonist whereby the drug containing core and at least one other layer of drug active is overcoated with a controlled release barrier layer therefore providing at least two controlled releasing layers of a water soluble drug from the multilayered coated particle

Release Profile

The compositions described herein are formulated such that the NMDAr antagonist, levodopa/carbidopa, or both agents have an in vitro dissolution profile that is equal to or slower than that for an immediate release formulation. As used herein, the immediate release (IR) formulation for memantine means the present commercially available 5 mg and 10 mg tablets (i.e., Namenda from Forest Laboratories, Inc. or formulations having substantially the same release profiles as Namenda); and the immediate release (IR) formulation of amantadine means the present commercially available 100 mg tablets (i.e., Symmetrel from Endo Pharmaceuticals, Inc. or formulations having substantially the same release profiles as Symmetrel); and the immediate release (IR) formulation of levodopa/carbidopa means the present commercially available 25 mg/100 mg, 10 mg/100 mg, 25 mg/250 mg tablets of carbidopa/levodopa (i.e., Sinemet from Merck & Co. Inc. or formulations having substantially the same release profiles as Sinemet). These compositions may comprise immediate release, sustained or extended release, or delayed release components, or may include combinations of same to produce release profiles such that the fraction of NMDAr antagonist or levodopa/carbidopa released is greater or equal to $0.01(0.297+0.0153*e^{(0.515*t)})$ and less than or equal to $1-e^{(-10.9*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C., in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist or levodopa/carbidopa released is less than 93% in 15 minutes and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1N HCl) dissolution medium. Optionally, the fraction of released NMDAr antagonist or levodopa/carbidopa is greater than or equal to $0.01(0.297+0.0153*e^{(0.515*t)})$, and less than or equal to $1-e^{(-0.972*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C., in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist or levodopa/carbidopa that is released may range between 0.1%-62% in one hour, 0.2%-86% in two hours, 0.6%-100% in six hours, 2.9%-100% in 10 hours, and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1 N HCl) dissolution

medium. Optionally, the NMDA receptor antagonist has a release profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 70% or greater (e.g., 70%-90%) in 10 hours, and 90% or greater (e.g., 90-95%) in 12 hours as measured in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1 N HCl) dissolution medium. For example, a formulation containing amantadine may have a release profile ranging between 0-60% or 0.1-20% in one hour, 0-86% or 5-30% at two hours, 0.6-100% or 40-80% at six hours, 3-100% or 50% or more (e.g., 50-90%) at ten hours, and 7.7-100% at twelve hours in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1 N HCl) dissolution medium. In one embodiment, the NMDAr antagonist, the levodopa/carbidopa, or both agents have an in vitro dissolution profile of less than 25%, 15%, 10%, or 5% in fifteen minutes; 50%, 30%, 25%, 20%, 15%, or 10% in 30 minutes and more than 60%, 65% 70%, 75%, 80%, 85%, 90%, 95% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water. Desirably, the NMDAr antagonist, the levodopa/carbidopa, or both agents has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% in a dissolution media having a pH of 1.2 at 10 hours. It is important to note that the dissolution profile for the NMDAr antagonist may be different than the release profile for levodopa/carbidopa. In a preferred embodiment, the levodopa/carbidopa release profile is equal to or similar to that for an immediate release formulation and the release profile for the NMDAr antagonist is controlled to provide a dissolution profile of less than 30% in one hour, less than 50% in two hours, and greater than 95% in twelve hours using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water.

Desirably, the compositions described herein have an in vitro profile that is substantially identical to the dissolution profile shown in FIG. **5** and, upon administration to a subject at a substantially constant daily dose, achieves a serum concentration profile that is substantially identical to that shown in FIGS. **2** and **4**.

As described above, the NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a modified or extended release form. Modified or extended drug release is generally controlled either by diffusion through a coating or matrix or by erosion of a coating or matrix by a process dependent on, for example, enzymes or pH. The NMDAr antagonist or the levodopa/carbidopa may be formulated for modified or extended release as described herein or using standard techniques in the art. In one example, at least 50%, 75%, 90%, 95%, 96%, 97%, 98%, 99%, or even in excess of 99% of the NMDAr antagonist or the levodopa/carbidopa is provided in an extended release dosage form. In a preferred embodiment, the levodopa/carbidopa is provided in an immediate release formulation and the NMDAr antagonist is in either an immediate or modified release form.

The composition described herein is formulated such the NMDAr antagonist or levodopa/carbidopa has an in vitro dissolution profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 50%-90% in 10 hours, and 90%-95% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. using 0.1N HCl as a dissolution medium. Alternatively, the NMDAr antagonist has an in vitro dissolution profile in a solution with a neutral pH (e.g., water) that is substantially the same as its dissolution profile in an acidic dissolution medium. Thus, the NMDAr antagonist may be released in both dissolution media at the following rate: between 0.1-20% in one hour, 5-30% in two hours, 40-80% in six hours, 70-90% in 10 hours, and 90%-95% in 12 hours as obtained using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. In one embodiment, the NMDAr antagonist has an in vitro dissolution profile of less than 15%, 10%, or 5% in fifteen minutes, 25%, 20%, 15%, or 10% in 30 minutes, and more than 60% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water. Desirably, the NMDAr antagonist has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% at 10 hours in a dissolution medium having a pH of 1.2.

Initial Rate In Vivo, Delayed Tmax

As used herein, "C" refers to the concentration of an active pharmaceutical ingredient in a biological sample, such as a patient sample (e.g. blood, serum, and cerebrospinal fluid). The time required to reach the maximal concentration ("Cmax") in a particular patient sample type is referred to as the "Tmax". The change in concentration is termed "dC" and the change over a prescribed time is "dC/dT".

The NMDAr antagonist or levodopa/carbidopa is provided as a sustained release formulation that may or may not contain an immediate release formulation. If desired, the NMDAr antagonist may be formulated so that it is released at a rate that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In addition, the NMDAr antagonist levodopa/carbidopa may be provided such that it is released at a rate resulting in a Cmax/Cmean of approximately 2 or less for approximately 2 hours to at least 8 hours after the NMDAr antagonist is introduced into a subject. Optionally, the sustained release formulations exhibit plasma concentration curves having initial (e.g., from 0, 1, 2 hours after administration to 4, 6, 8 hours after administration) slopes less than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist. The precise slope for a given individual will vary according to the NMDAr antagonist being used or other factors, including whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose. The determination of initial slopes of plasma concentration is described, for example, by U.S. Pat. No. 6,913,768, hereby incorporated by reference.

Desirably, the NMDAr antagonist or the levodopa/carbidopa is released into a subject sample at a slower rate than observed for an immediate release (IR) formulation of the same quantity of the antagonist, such that the rate of change in the biological sample measured as the dC/dT over a defined period within the period of 0 to Tmax for the IR formulation (e.g., Namenda, a commercially available IR formulation of memantine). In some embodiments, the dC/dT rate is less than about 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. In some embodiments, the dC/dT rate is less than about 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. Similarly, the rate of release of the NMDAr antagonist or the levodopa/carbidopa from the present invention as measured in dissolution studies is less than 80%, 70%, 60% 50%, 40%, 30%, 20%, or 10% of the rate for an IR formulation of the same NMDAr antagonist or levodopa/carbidopa over the first 1, 2, 4, 6, 8, 10, or 12 hours.

In a preferred embodiment, the dosage form is provided in a non-dose escalating, three times per day (t.i.d.) form. In

preferred embodiments, the concentration ramp (or Tmax effect) may be reduced so that the change in concentration as a function of time (dC/dT) is altered to reduce or eliminate the need to dose escalate the NMDAr antagonist. A reduction in dC/dT may be accomplished, for example, by increasing the Tmax in a relatively proportional manner. Accordingly, a two-fold increase in the Tmax value may reduce dC/dT by approximately a factor of 2. Thus, the NMDAr antagonist may be provided so that it is released at a rate that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In certain embodiments, this is accomplished by releasing less than 30%, 50%, 75%, 90%, or 95% of the NMDAr antagonist into the circulatory or neural system within one hour of such administration.

The concentration ramp for levodopa/carbidopa may also be reduced, however such changes will not be preferred in most oral formulations due to the marked reduction in absorption of levodopa/carbidopa after it passes the duodenal region of the gastrointestinal tract.

Optionally, the modified release formulations exhibit plasma concentration curves having initial (e.g., from-2 hours after administration to 4 hours after administration) slopes less-than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist or levodopa/carbidopa. The precise slope for a given individual will vary according to the NMDAr antagonist or levodopa/carbidopa being used, the quantity delivered, or other factors, including, for some active pharmaceutical agents, whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose.

Using the sustained release formulations or administration methods described herein, the NMDAr antagonist reaches a therapeutically effective steady state plasma concentration in a subject within the course of the first two, three, five, seven, nine, ten, twelve, fifteen, or twenty days of administration. For example, the formulations described herein, when administered at a substantially constant daily dose (e.g., at a dose ranging between 200 mg and 800 mg, preferably between 200 mg and 600 mg, and more preferably between 200 mg and 400 mg per day) may reach a steady state plasma concentration in approximately 70%, 60%, 50%, 40%, 30%, or less of the time required to reach such plasma concentration when using a dose escalating regimen.

Dosing Frequency and Dose Escalation

According to the present invention, a subject (e.g., human) having or at risk of having such conditions is administered any of the compositions described herein (e.g., three times per day (t.i.d.), twice per day (b.i.d.), or once per day (q.d.)). While immediate release formulations of NMDAr antagonists are typically administered in a dose-escalating fashion, the compositions described herein may be essentially administered at a constant, therapeutically-effective dose from the onset of therapy. For example, a composition containing a sustained release formulation of amantadine may be administered three times per day, twice per day, or once per day in a unit dose comprising a total daily amantadine dose of 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, or 800 mg. In embodiments comprising a single dosage form containing an NMDAr antagonist and levodopa/carbidopa wherein the levodopa/carbidopa is in an immediate release form, the dosing frequency will be chosen according to the levodopa/carbidopa requirements, (e.g. three times per day).

Reduced Time to Therapeutic Concentration and Efficacy

Immediate release (IR) formulations of memantine (e.g., Namenda) are typically administered at low doses (e.g., 5 mg/day) and are progressively administered at increasing frequency and dose over time to reach a steady state serum concentration that is therapeutically effective. According to the manufacturer's FDA approved label, Namenda, an immediate release (IR) formulation of memantine, is first administered to subjects at a dose of 5 mg per day. After an acclimation period of typically one week, subjects are administered with this dose twice per day. Subjects are next administered with a 5 mg and 10 mg dosing per day and finally administered with 10 mg Namenda twice daily. Using this dosing regimen, a therapeutically effective steady state serum concentration may be achieved within 30 days of the onset of therapy. Using a modified release formulation comprising (22.5 mg memantine,) however, a therapeutically effective steady state concentration may be achieved substantially sooner (within about 13 days), without using a dose escalating regimen. Furthermore, the slope during each absorption period for the sustained release formulation is less (i.e. not as steep) as the slope for Namenda. Accordingly, the dC/dT of the sustained release formulation is reduced relative to the immediate release formulation even though the dose administered is larger than for the immediate release formulation. Based on this model, a sustained release formulation of an NMDAr antagonist may be administered to a subject in an amount that is approximately the full strength dose (or that effectively reaches a therapeutically effective dose) from the onset of therapy and throughout the duration of treatment. Accordingly, a dose escalation would not be required.

Treatment of a subject with the subject of the present invention may be monitored using methods known in the art. The efficacy of treatment using the composition is preferably evaluated by examining the subject's symptoms in a quantitative way, e.g., by noting a decrease in the frequency or severity of symptoms or damaging effects of the condition, or an increase in the time for sustained worsening of symptoms. In a successful treatment, the subject's status will have improved (i.e., frequency or severity of symptoms or damaging effects will have decreased, or the time to sustained progression will have increased). In the model described in the previous paragraph, the steady state (and effective) concentration of the NMDAr antagonist is reached in 25%, 40%, 50%, 60%, 70%, 75%, or 80% less time than in the dose escalated approach.

In another embodiment, a composition is prepared using the methods described herein, wherein such composition comprises memantine or amantadine and a release modifying excipient, wherein the excipient is present in an amount sufficient to ameliorate or reduce the dose-dependent toxicity associated with the memantine or amantadine relative to an immediate release (IR) formulation of memantine, such as Namenda, or amantadine, such as Symmetrel. The use of these compositions enables safer administration of these agents, and even permits the safe use of higher levels for appropriate indications, beyond the useful range for the presently available versions of memantine (5 mg and 10 mg per dose to 20 mg per day) and amantadine (100 mg to 300 mg per day with escalation).

Indications Suitable for Treatment

The compositions and methods of the present invention are particularly suitable for the treatment of Parkinson's disease or conditions associated with Parkinson's disease. These con-

ditions include dementia, dyskinesia, dystonia, depression, fatigue and other neuropsychiatric complications of Parkinson's disease.

Formulations for Alternate Specific Routes of Administration

The pharmaceutical compositions may be optimized for particular types of delivery. For example, pharmaceutical compositions for oral delivery are formulated using pharmaceutically acceptable carriers that are well known in the art. The carriers enable the agents in the composition to be formulated, for example, as a tablet, pill, capsule, solution, suspension, sustained release formulation; powder, liquid or gel for oral ingestion by the subject.

The NMDAr antagonist may also be delivered in an aerosol spray preparation from a pressurized pack, a nebulizer or from a dry powder inhaler. Suitable propellants that can be used in a nebulizer include, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and carbon dioxide. The dosage can be determined by providing a valve to deliver a regulated amount of the compound in the case of a pressurized aerosol.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral, intranasal or respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

In some embodiments, for example, the composition may be delivered intranasally to the cribriform plate rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in U.S. Pat. No. 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Additional formulations suitable for other modes of administration include rectal capsules or suppositories. For suppositories, traditional binders and carriers may include, for example, polyalkylene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%.

The composition may optionally be formulated for delivery in a vessel that provides for continuous long-term delivery, e.g., for delivery up to 30 days, 60 days, 90 days, 180 days, or one year. For example the vessel can be provided in a biocompatible material such as titanium. Long-term delivery formulations are particularly useful in subjects with chronic conditions, for assuring improved patient compliance, and for enhancing the stability of the compositions.

Optionally, the NMDA receptor antagonist, levodopa/carbidopa, or both is prepared using the OROS® technology, described for example, in U.S. Pat. Nos. 6,919,373, 6,923,800, 6,929,803, 6,939,556, and 6,930,128, all of which are hereby incorporated by reference. This technology employs osmosis to provide precise, controlled drug delivery for up to 24 hours and can be used with a range of compounds, including poorly soluble or highly soluble drugs. OROS® technology can be used to deliver high drug doses meeting high drug loading requirements. By targeting specific areas of the gastrointestinal tract, OROS® technology may provide more efficient drug absorption and enhanced bioavailability. The osmotic driving force of OROS® and protection of the drug until the time of release eliminate the variability of drug absorption and metabolism often caused by gastric pH and motility.

Formulations for continuous long-term delivery are provided in, e.g., U.S. Pat. Nos. 6,797,283; 6,764,697; 6,635,268, and 6,648,083.

If desired, the components may be provided in a kit. The kit can additionally include instructions for using the kit.

Additional Methods for Making Modified Release Formulations

Additional methods for making modified release formulations are described in, e.g., U.S. Pat. Nos. 5,422,123, 5,601,845, 5,912,013, and 6,194,000, all of which are hereby incorporated by reference.

In some embodiments, for example, the composition may be delivered via intranasal, buccal, or sublingual routes to the brain rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in U.S. Pat. No. 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Preparation of a pharmaceutical composition for delivery in a subdermally implantable device can be performed using methods known in the art, such as those described in, e.g., U.S. Pat. Nos. 3,992,518; 5,660,848; and 5,756,115.

The invention will be illustrated in the following non-limiting examples.

EXAMPLES

Example 1

Measuring Release Profiles In Vitro

Compositions containing an aminoadamantane and levodopa/carbidopa are analyzed for release of the aminoadamantane and levodopa/carbidopa, according to the USP type 2 apparatus at a speed of 50 rpm. The dissolution media used include water, 0.1N HCl, or 0.1N HCl adjusted to pH 6.8 at 2 hours with phosphate buffer. The dissolution medium is equilibrated to 37±0.5° C.

The USP reference assay method for amantadine is used to measure the fraction of memantine released from the compositions prepared herein. Briefly, 0.6 mL sample (from the dissolution apparatus at a given time point) is placed into a 15 mL culture tube. 1.6 mL 0.1% Bromocresol Purple (in acetic acid) is added and vortexed for five seconds. The mixture is allowed to stand for approximately five minutes. 3 mL Chloroform is added and vortexed for five seconds. The solution is next centrifuged (speed 50 rpm) for five minutes. The top layer is removed with a disposable pipette. A sample is drawn into 1 cm flow cell and the absorbance is measured at 408 nm at 37° C. and compared against a standard curve prepared with known quantities of the same aminoadamantane. The quantity of determined is plotted against the dissolution time for the sample.

The USP reference assay method for levodopa is used to measure the fraction of levodopa released from the compositions prepared herein. Briefly, 0.5 ml samples from the dissolution apparatus removed at various times are assayed by

liquid chromatography. The chromatograph is equipped with a 280 nm detector and a 3.9 mm×30 cm column containing packing L1. The mobile phase is 0.09 N sodium phosphate, 1 mM sodium 1-decanesulfonate, pH 2.8. With the flow rate adjusted to about 2 mL per minute, the levodopa elutes in about 4 minutes and carbidopa elutes in about 11 minutes. From the saved dissolution samples, a 0.02 ml aliquot is injected into the chromatograph and the absorbance is measure and compared to standard to determine concentration & quantity. The quantity dissolved is then plotted against the dissolution time for the sample.

Example 2

Preparation of Amantadine Extended Release Capsules

Amantadine extended release capsules may be formulated as follows or as described, for example, in U.S. Pat. No. 5,395,626.

A. Composition: Unit Dose

The theoretical quantitative composition (per unit dose) for amantadine extended release capsules is provided below.

Component	% weight/ weight	mg/ Capsule
Amantadine	68.34	200.00
OPADRY ® Clear YS-3-7011 [1] (Colorcon, Westpoint, PA)	1.14	5.01
Purified Water, USP [2]		
Sugar Spheres, NF	12.50	54.87
OPADRY ® Clear YS-1-7006 [3] (Colorcon, Westpoint, PA)	4.48	19.66
SURELEASE ® E-7-7050 [4] (Colorcon, Westpoint, PA)	13.54	59.44
Capsules [5]		
TOTAL.	100.00%	338.98 mg [6]

[1] A mixture of hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol.

[2] Purified Water, USP is evaporated during processing.

[3] A mixture of hydroxypropyl methylcellulose and polyethylene glycol

[4] Solid content only of a 25% aqueous dispersion of a mixture of ethyl cellulose, dibutyl sebacate, oleic acid, ammoniated water and fumed silica. The water in the dispersion is evaporated during processing.

[5] White, opaque, hard gelatin capsule, size 00.

[6] Each batch is assayed prior to filling and the capsule weight is adjusted as required to attain 200 mg amantadine per capsule.

The quantitative batch composition for amantadine extended release capsule is shown below. (Theoretical batch quantity 25,741 capsules).

Step 1: Prep of Amantadine HC1 Beads (bead Build-up #1)

Component	Weight (kg)
Amantadine	12.000
OPADRY ® Clear YS-3-7011	0.200
Purified Water, USP	5.454
Sugar Sphere, NF	4.000
Total Weight Amantadine Beads	16.200 kg

The amantadine beads obtained from step 1 are used as follows.

Step 2: Clear & Sustained Release Bead Coating #1

Component	Weight (kg)
Amantadine Beads	8.000
OPADRY ® Clear YS-1-7006	0.360
Purified Water, USP	5.928
Surelease ® E-7-7050	0.672
Total Weight Clear Coated Sustained Release Beads	9.032 kg

The sustained release beads obtained from step 2 are used as follows.

Step 3: Amantadine HC1 Beads (Build-up #2)

Component	Weight (kg)
Sustained Release Beads	8.000
Amantadine	4.320
OPADRY ® Clear YS-3-7011	0.072
Purified Water, USP	1.964
Total Weight Amantadine Beads	12.392 kg

The amantadine beads obtained from step 3 are formulated as follows.

Step 4: Clear & Sustained Release Bead Coating #2

Component	Weight (kg)
Amantadine Beads	10.000
OPADRY ® Clear YS-1-7006	0.250
Purified Water, USP	6.450
Surelease ® E-7-7050	1.050
Total Weight Amantadine Extended Release Beads	11.300 kg

Step 5: Capsule Filling -- Gelatin capsules, size 00, are filled with 339 mg of the amantadine beads prepared in step 4.

Example 3

Extended Release Amantadine Formulation with Immediate Release Carbidopa and Levodopa

Levodopa and Carbidopa are formulated into pellets suitable for filling, yet having an immediate release profile. (see, for example, U.S. Pat. No. 5,912,013).

Levodopa plus Carbidopa Core Pellets

	Weight Percent	Kilograms
MCC	25.0	0.25
Hydroxypropylmethylcellulose Phthalate (HPMCP)	10.0	0.10
Tartaric Acid	10.0	0.10
Sodium Monoglycerate	7.5	0.075
DSS	0.5	0.005
Levodopa	35.8	0.358
Carbidopa	11.2	0.112
TOTAL	100.0%	1.00 kg
Coating		
Cellulose Acetate Phthalate (CAP)	60.0	0.60
Ethylcellulose	25.0	0.25
PEG-400	15.0	0.15
TOTAL	100.0%	1.00 kg

The pellets are assayed for levodopa and carbidopa content. It is determined that approximately 223 mg of the pellets contain 80 mg levodopa and 25 mg carbidopa. Dissolution greater than 90% in 30 minutes is also confirmed.

A total of 669 grams of the pellets are blended with 510 grams of the amantadine pellets from Example 2 in a V-blender for 30 minutes at 30 rpm. Gelatin capsules are filled with 393 mg of the mixture and the assays for content are repeated verifying a composition of 100 mg amantadine, 80 mg levodopa, and 25 mg carbidopa.

Example 4

Predicted Dissolution and Plasma Profiles of Amantadine Controlled Release

Using the formulations described above, the dissolution profiles for amantadine were simulated and used to calculate plasma profiles resulting from single or multiple administrations using the pharmacokinetic software, GastroPlus v.4.0.2, from Simulations Plus (see FIG. **2**). The initial slope of the dissolution for the sustained release formulation is less than the slope determined for the immediate release formulation (see FIG. **1**) and the corresponding serum profile also shows a slower dC/dT (see FIG. **4**).

Example 5

Release Profile of Amantadine and L-DOPA (Levodopa/Carbidopa)

Release proportions are shown in the tables below for a combination of amantadine and levodopa/carbidopa. The cumulative fraction is the amount of drug substance released from the formulation matrix to the serum or gut environment (e.g., U.S. Pat. No. 4,839,177 or 5,326,570) or as measured with a USP II Paddle system using 0.1N HCl as the dissolution medium.

Time	AMANTADINE T1/2 = 15 hrs cum. fraction A	LEVODOPA/ CARBIDOPA T1/2 = 1.5 hrs Cum. fraction B
0	0.00	0.00
0.5	0.10	0.40
1.0	0.20	0.95
2.0	0.35	1.00
4.0	0.60	1.00
8.0	0.90	1.00
12.0	0.98	1.00

Example 6

Treating Dyskinesia in Patients with Parkinson's Disease

A Parkinson's patient experiencing dyskinesia is administered the composition of Example 3 three times each day to receive 300 mg amantadine, 240 mg levodopa, and 75 mg carbidopa daily. The Parkinsonism is reduced as measured by the UPDRS (Goetz et al., Mov. Disord. 19:1020-8, 2004, incorporated by reference) as is the dyskinesia (Vitale et al., Neurol. Sci. 22:105-6, 2001, incorporated by reference)

Example 7

Animal Models Showing Reduced Dyskinesia, Reduced Levodopa Potential

The following protocol was employed to demonstrate the beneficial effects of the compositions of this invention. Briefly, squirrel monkeys (N=4) were lesioned with MPTP according to the protocol of Di Monte et al. (Mov. Disord. 15: 459-66 (2000)). After 3 months, the monkeys showed full symptoms of Parkinson's disease as measured by a modified UPDRS (Goetz et al., Mov. Disord. 19:1020-8, 2004). Levodopa treatment at approximately 15 mg/kg (with 1.5 mg/kg carbidopa) mg/kg b.i.d. commenced a baseline UPDRS and dyskinesia measurement was established. Amantadine was added to the regimen simultaneously with the levodopa, and the amount raised from 1 mg/kg to 45 mg/kg for four of the squirrel monkeys, corresponding to an estimated 3 μm concentration. As shown in FIG. **8**, the combination led to a 60% reduction in dyskinesia. We hypothesize that this translates into a potential 40% reduction in levodopa required to maintain UPDRS.

Example 8

Levodopa Sparing Therapy

The following protocol is employed to determine the optimal reduction of levodopa achieved with the addition of Amantadine to a fixed dose combination product.

Parkinson's DISEASE PROTOCOL SUMMARY NPI MEMANTINE CR MONOTHERAPY

Protocol Number:	NPI-Amantadine CR
Study Phase:	2/3
Name of Drug:	NPI-Amantadine/C/L
Dosage:	25/100/100 c/l/a given t.i.d. 25/80/100 c/l/a given t.i.d. 25/60/100 c/l/a given t.i.d.
Concurrent Control:	25/100 c/1 given t.i.d.
Route:	Oral
Subject Population:	Male and female patients diagnosed with Parkinson's Disease Hoehn and Yahr score of 2-4
Structure:	Parallel-group, three-arm study
Study Term	Two weeks
Study Sites:	Multi-center 10 centers
Blinding:	Double blind
Method of Subject Assignment:	Randomized to one of three treatment groups (3:1)
Total Sample Size:	320 subjects (160 men, 160 women)
Primary Efficacy Endpoints:	UPDRS Abnormal involuntary movement scale (AIMS) 0-4
Secondary Endpoints:	Modified Obeso dyskinesia rating scale 0-4 Mini-mental state examination (MMSE); Neuropsychiatric Inventory Score (NPI)
Adverse Events:	Monitored and elicited by clinic personnel throughout the study, volunteered by patients

Example 9

Pharmaceutical Composition Including Memantine, Levodopa, and Carbidopa

A co-formulation of memantine, levodopa and carbidopa is prepared. This co-formulation matches the absorption properties of levodopa and carbidopa more closely than those of

Memantine, thereby extending the effectiveness per dose of levodopa and carbidopa. The co-formulation provides Tmax values to about 4 hours and allows b.i.d. dosing of the combination.

FIG. **6** provides the current single oral dose pharmacokinetic (PK) profiles for levodopa, carbidopa and memantine. FIG. **7** provides idealized pharmacokinetic profiles for the target co-formulation, in which the Tmax values for levodopa and carbidopa more closely match that of Memantine.

Dosage Form: Tablet	
Formulation Content:	Levodopa 150 mg
	Carbidopa 37.5 mg
	Memantine 10 mg

Excipients: FDA approved excipients and drug release modifiers. Additional embodiments are within the claims.

Example 10

Pharmaceutical Composition Including Extended Release Formulations of Memantine and Levodopa

A pulsatile release dosage form for administration of memantine and levodopa may be prepared as three individual compartments. Three individual tablets are compressed, each having a different release profile, followed by encapsulation into a gelatin capsule, which are then closed and sealed. The components of the three tablets are as follows.

Component	Function	Amount per tablet
TABLET 1 (IMMEDIATE RELEASE):		
Memantine	Active agent	8 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
TABLET 2 (RELEASE DELAYED 3-5 HOURS FOLLOWING ADMINISTRATION):		
Memantine	Active agent	8 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS3OD	Delayed release coating material	4.76 mg
Talc	Coating component	3.3 mg
Triethyl citrate	Coating component	0.95 mg
TABLET 3 (RELEASE DELAYED 7-9 HOURS FOLLOWING ADMINISTRATION):		
Memantine	Active agent	2.5 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS3OD	Delayed release coating material	6.34 mg
Talc	Coating component	4.4 mg
Triethyl citrate	Coating component	1.27 mg

The tablets are prepared by wet granulation of the individual drug particles and other core components as may be done using a fluid-bed granulator, or are prepared by direct compression of the admixture of components. Tablet 1 is an immediate release dosage form, releasing the active agents within 1-2 hours following administration. Tablets 2 and 3 are coated with the delayed release coating material as may be carried out using conventional coating techniques such as spray-coating or the like. As will be appreciated by those skilled in the art, the specific components listed in the above tables may be replaced with other functionally equivalent components, e.g., diluents, binders, lubricants, fillers, coatings, and the like.

Oral administration of the capsule to a patient will result in a release profile having three pulses, with initial release of the memantine and levodopa from the first tablet being substantially immediate, release of the memantine and levodopa from the second tablet occurring 3-5 hours following administration, and release of the memantine and levodopa from the third tablet occurring 7-9 hours following administration.

Example 11

Pharmaceutical Composition Including Extended Release Formulations of Memantine, Levodopa, and Carbidopa

The method of Example 9 is repeated, except that drug-containing beads are used in place of tablets. Carbidopa is also added in each of the fractions at 25% of the mass of the levodopa. A first fraction of beads is prepared by coating an inert support material such as lactose with the drug which provides the first (immediate release) pulse. A second fraction of beads is prepared by coating immediate release beads with an amount of enteric coating material sufficient to provide a drug release-free period of 3-5 hours. A third fraction of beads is prepared by coating immediate release beads having half the methylphenidate dose of the first fraction of beads with a greater amount of enteric coating material, sufficient to provide a drug release-free period of 7¬9 hours. The three groups of beads may be encapsulated or compressed, in the presence of a cushioning agent, into a single pulsatile release tablet.

Alternatively, three groups of drug particles may be provided and coated as above, in lieu of the drug-coated lactose beads.

Other Embodiments

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A method comprising:

orally administering to a human subject with Parkinson's disease a once-daily dose consisting of (i) 200 mg to 500 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, and (ii) at least one excipient, wherein the drug in the dose comprises an extended release form, and wherein the extended release form of the drug in the dose provides a mean change in amantadine plasma concentration as a function of time (dC/dT) that is less than 40% of the dC/dT provided by the same quantity of the drug in an immediate release form, wherein the dC/dT values are measured in a single dose human pharmacokinetic study over the time period between 0 and 4 hours after administration.

2. A method comprising:

orally administering to a human subject with Parkinson's disease a once-daily dose consisting of (i) 200 mg to 500 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, and (ii) at least one excipient, wherein the drug in the dose comprises an extended release form, and wherein the extended release form of the drug in the dose provides a mean change in amantadine plasma concentration as a function of time (dC/dT) that is less than 40% of the dC/dT provided by the same quantity of the drug in an immediate release form, wherein the dC/dT values are measured in a single dose human pharmacokinetic study over the time period between administration and Tmax of the immediate release form.

3. A method comprising:

orally administering to a human subject with Parkinson's disease a once-daily dose consisting of (i) 200 mg to 500 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, and (ii) at least one excipient, wherein the drug in the dose comprises an extended release form, and wherein the extended release form of the drug in the dose provides a mean change in amantadine plasma concentration as a function of time (dC/dT) that is less than 40% of the dC/dT provided by the same quantity of the drug in an immediate release form, wherein the dC/dT of the extended release form of the drug in the dose is measured in a single dose human pharmacokinetic study over the time period between 2 hours and 4 hours after administration and the dC/dT provided by the same quantity of the drug in an immediate release form is measured in a single dose human pharmacokinetic study over the time period between administration and Tmax of the immediate release form.

4. The method of any of claims 1 to 3, wherein the amount of drug is 300 to 500 mg.

5. The method of any of claims 1 to 3, wherein at least 50% of the drug in the dose is in an extended release form.

6. The method of any of claims 1 to 3, wherein at least 75% of the drug in the dose is in an extended release form.

7. The method of any of claims 1 to 3, wherein at least 90% of the drug in the dose is in an extended release form.

8. The method of any of claims 1 to 3, wherein the dose additionally comprises the drug in an immediate release form.

9. The method of any of claims 1 to 3, the dose administered is therapeutically effective for the treatment of Parkinson's disease.

10. The method of any of claims 1 to 3, wherein the human subject with Parkinson's disease suffers from dyskinesia.

11. The method of claim 10, wherein the method reduces the frequency or severity of dyskinesia.

12. The method of claim 10, wherein the dyskinesia is levodopa-induced dyskinesia.

13. The method of any of claims 1 to 3, additionally comprising administering to the subject a pharmaceutically effective amount of levodopa/carbidopa.

14. The method of any of claims 1 to 3, wherein the dose provides a shift in amantadine Tmax of 2 hours to 16 hours relative to an immediate release form of amantadine, wherein the Tmax is measured in a single dose human pharmacokinetic study.

15. The method of any of claims 1 to 3, wherein the dose comprises an osmotic device which utilizes an osmotic driving force to provide extended release of the drug.

16. The method of any of claims 1 to 3, wherein the extent of drug bioavailability is maintained.

17. The method of any of claims 1 to 3, wherein the once-daily dose is administered at a therapeutically-effective dose from the onset of therapy.

* * * * *

EXHIBIT H

US008895618B1

(12) **United States Patent**
Went et al.

(10) **Patent No.: US 8,895,618 B1**
(45) **Date of Patent: Nov. 25, 2014**

(54) **COMPOSITION AND METHOD FOR TREATING NEUROLOGICAL DISEASE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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Related U.S. Application Data

(63) Continuation of application No. 14/328,440, filed on Jul. 10, 2014, which is a continuation of application No. 13/958,153, filed on Aug. 2, 2013, now Pat. No. 8,796,337, which is a continuation of application No. 13/756,275, filed on Jan. 31, 2013, now abandoned, which is a continuation of application No. 11/286,448, filed on Nov. 23, 2005, now Pat. No. 8,389,578.

(60) Provisional application No. 60/631,095, filed on Nov. 24, 2004.

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A61K 31/195	(2006.01)
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CPC ***A61K 31/13*** (2013.01); ***A61K 9/0004*** (2013.01); ***A61K 9/4808*** (2013.01); ***A61K 9/1652*** (2013.01)
USPC **514/565**; 514/656

(58) **Field of Classification Search**
USPC 514/565, 656
See application file for complete search history.

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(57) **ABSTRACT**

Disclosed are compositions comprising amantadine, or a pharmaceutically acceptable salt thereof, and one or more excipients, wherein at least one of the excipients modifies release of amantadine. Methods of administering the same are also provided.

12 Claims, 7 Drawing Sheets

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Figure 1: Simulated Dissolution for TID Amantadine IR & SR

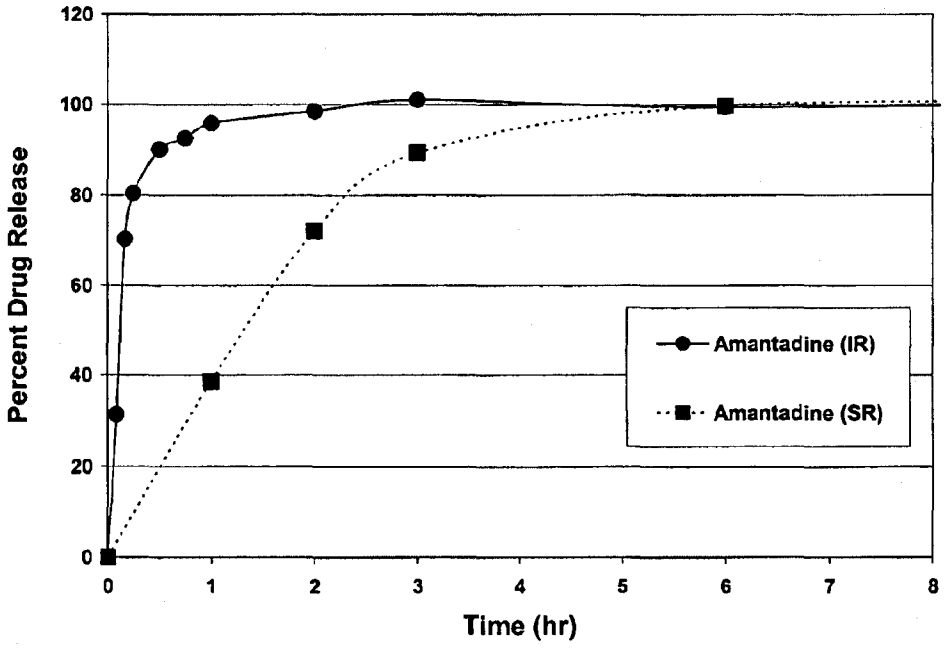


Figure 2: Simulated Plasma Concentration for TID Amantadine IR & SR over 120hrs.

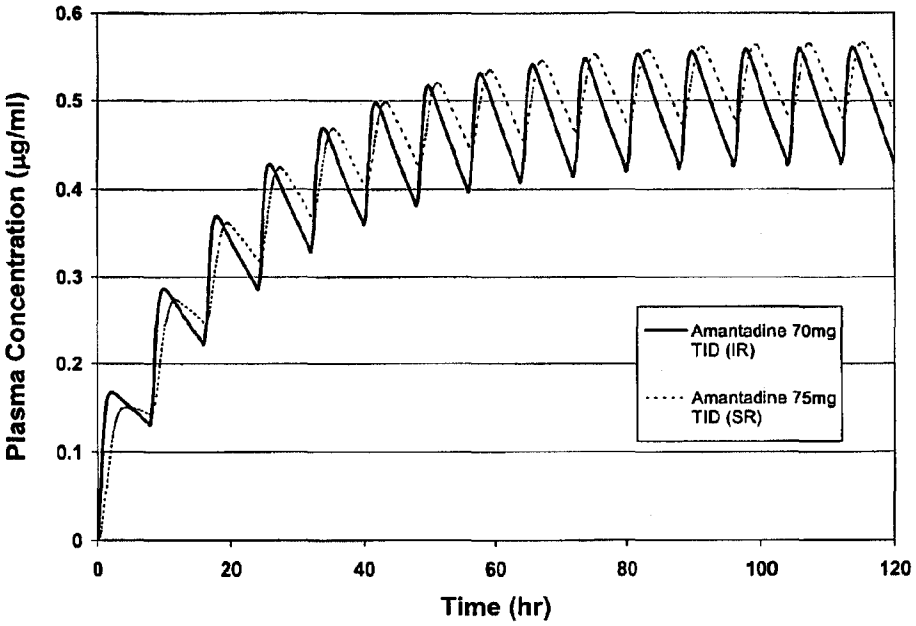


Figure 3: Simulated Plasma Concentration for TID Levodopa/Carbidopa/Amantadine (IR, IR, IR) over 24hrs

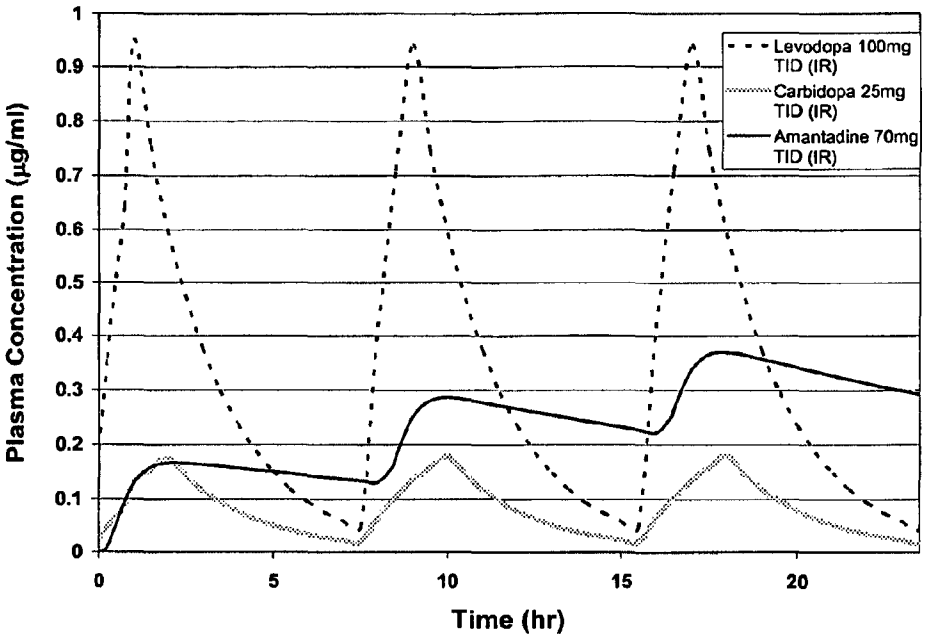


Figure 4: Simulated Plasma Concentration for TID Levodopa/Carbidopa/Amantadine (IR, IR, SR) over 24hrs

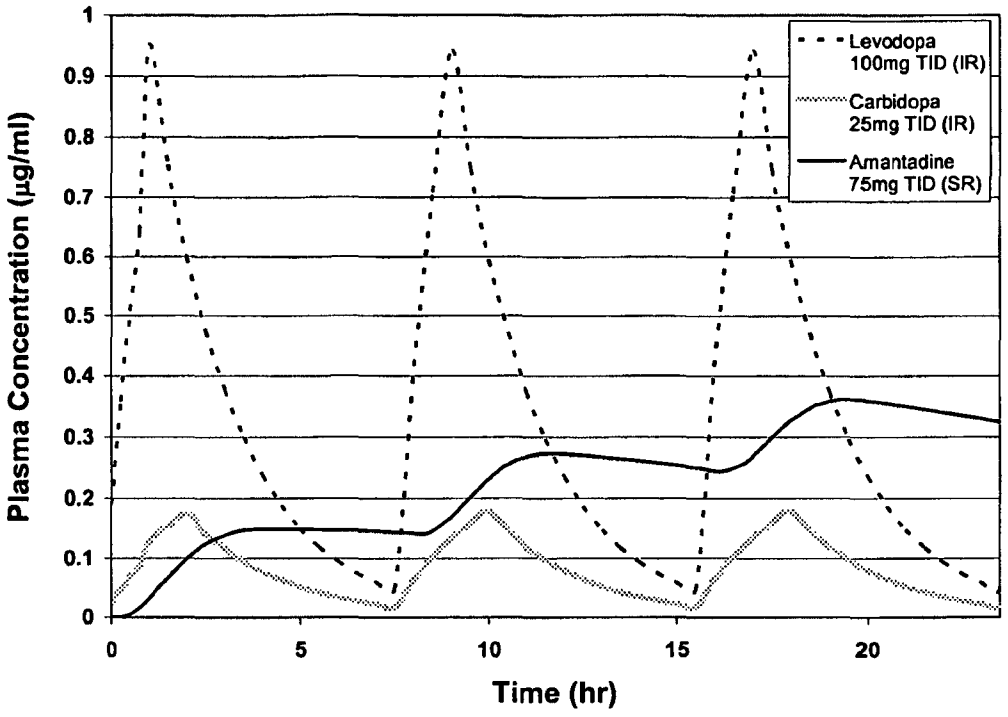


FIGURE 5

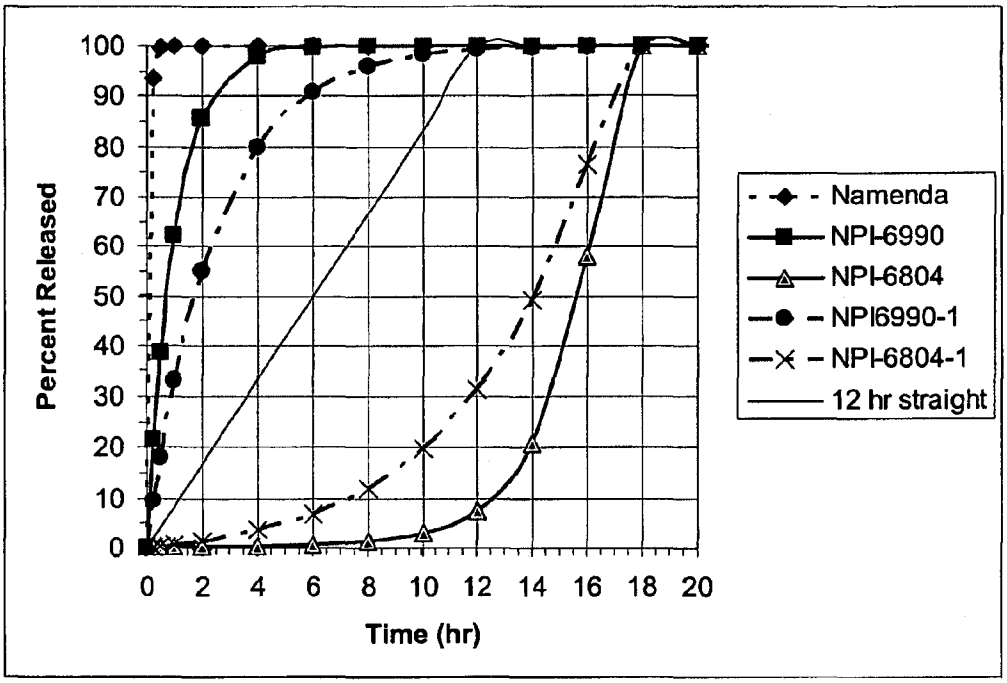

Percent Released
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20
Time (hr)
Namenda
NPI-6990
NPI-6804
NPI6990-1
NPI-6804-1
12 hr straight

Figure 6: Memantine, Levodopa and Carbidopa Human Pharmacokinetics

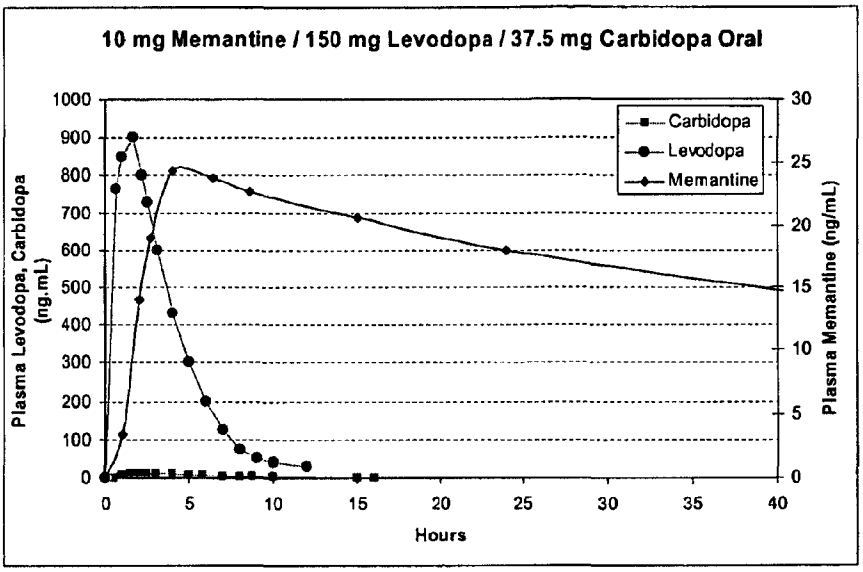
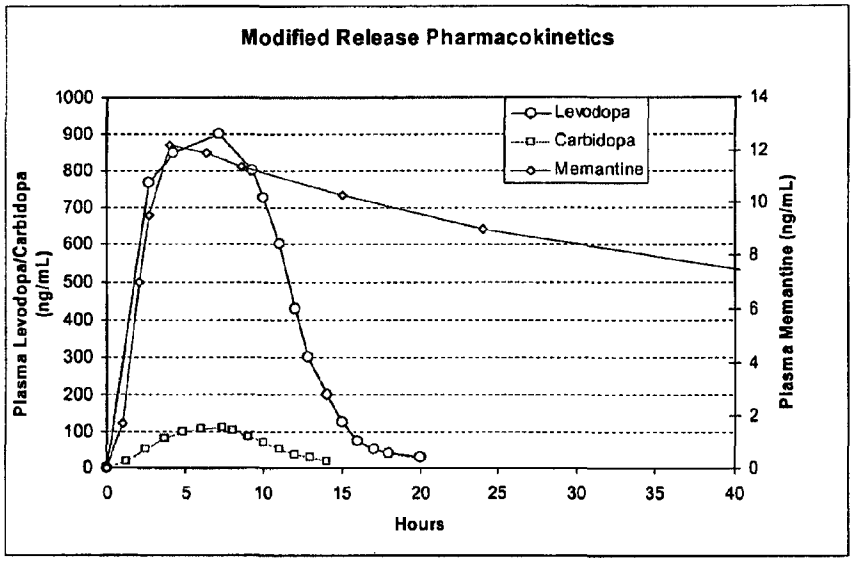


Figure 7: Target Pharmacokinetics



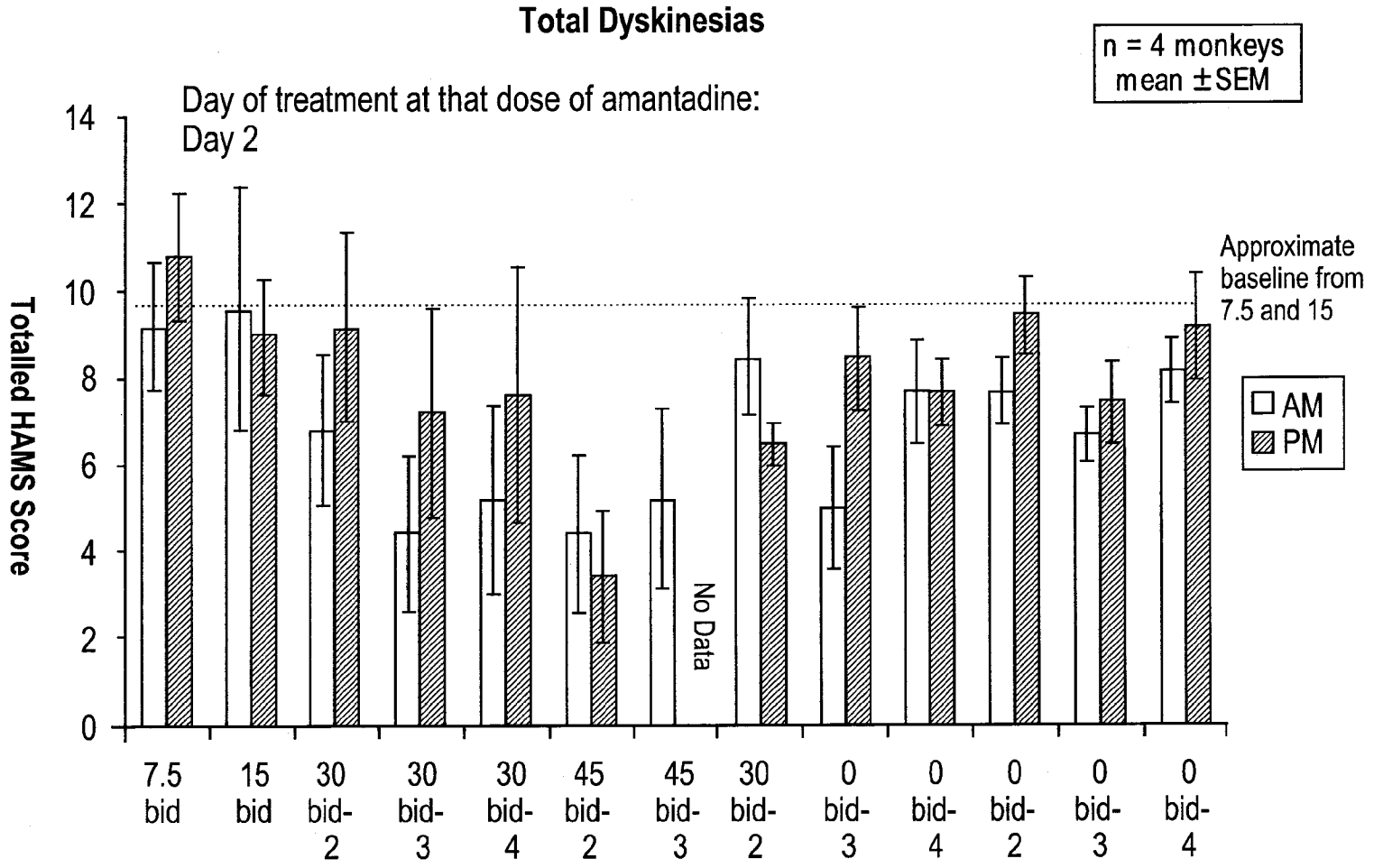

Total Dyskinesias
n = 4 monkeys
mean ±SEM
Day of treatment at that dose of amantadine:
Day 2
Totalled HAMS Score
14
12
10
8
6
4
2
0
Approximate
baseline from
7.5 and 15
AM
PM
No Data
7.5 bid
15 bid
30 bid-2
30 bid-3
30 bid-4
45 bid-2
45 bid-3
30 bid-2
0 bid-3
0 bid-4
0 bid-2
0 bid-3
0 bid-4

Figure 8

COMPOSITION AND METHOD FOR TREATING NEUROLOGICAL DISEASE

RELATED APPLICATION

This application is a continuation of U.S. patent application Ser. No. 14/328,440, filed Jul. 10, 2014, which is a continuation of U.S. patent application Ser. No. 13/958,153, filed Aug. 2, 2013, which is a continuation of U.S. patent application Ser. No. 13/756,275, filed Jan. 31, 2013, now abandoned, which is a continuation application of U.S. patent application Ser. No. 11/286,448, filed on Nov. 23, 2005, now U.S. Pat. No. 8,389,578, which claims priority to U.S. Provisional Application No. 60/631,095 filed on Nov. 24, 2004, all of which applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

This invention relates to compositions and methods for treating neurological diseases, such as Parkinson's disease.

BACKGROUND OF THE INVENTION

Parkinson's disease (PD) is a progressive, degenerative neurologic disorder which usually occurs in late mid-life. PD is clinically characterized by bradykinesia, tremor, and rigidity. Bradykinesia is characterized by a slowness in movement, slowing the pace of such routine activities as walking and eating. Tremor is a shakiness that generally affects limbs that are not otherwise in motion. For those PD-patients diagnosed at a relatively young age, tremor is reported as the most disabling symptom. Older patients face their greatest challenge in walking or keeping their balance. Rigidity is caused by the inability of muscles to relax as opposing muscle groups contract, causing tension which can produce aches and pains in the back, neck, shoulders, temples, or chest.

PD predominantly affects the substantia nigra (SNc) dopamine (DA) neurons and is therefore associated with a decrease in striatal DA content. Because dopamine does not cross the blood-brain barrier, PD patients may be administered a precursor, levodopa, that does cross the blood-brain barrier where it is metabolized to dopamine. Levodopa therapy is intended to compensate for reduced dopamine levels and is a widely prescribed therapeutic agent for patients with Parkinson's disease. Chronic treatment with levodopa however, is associated with various debilitating side-effects such as dyskinesia.

Since currently available drugs containing levodopa are associated with debilitating side effects, better therapies are needed for the management of PD.

SUMMARY OF THE INVENTION

In general, the present invention provides methods and compositions for treating and preventing CNS-related conditions, such as Parkinson's disease or other Parkinson's-like diseases or conditions, by administering to a subject in need thereof a combination that includes an N-Methyl-D-Aspartate receptor (NMDAr) antagonist and levodopa. Exemplary NMDAr antagonists include the aminoadamantanes, such as memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1-aminoethyl)adamantane), or amantadine (1-amino-adamantane) as well as others described below. Because levodopa is metabolized before crossing the blood-brain barrier and has a short half-life in the circulatory system, it is typically administered in conjunction with a dopa-

decarboxylase inhibitor. Examples of dopa-decarboxylase inhibitors include carbidopa, 3-hydroxy-benzylhydrazinedihydrochloride (NSD-1015), and benseraxide hydrochloride. The combination may further include a catechol-0-methyltransferase (COMT) inhibitor including, for example, talcapone and entacapone. As used herein, levodopa/carbidopa shall mean levodopa alone or in combination with a dopa-decarboxylase inhibitor such as carbidopa. Desirably, the levodopa/carbidopa is in an immediate release formulation and the NMDA receptor antagonist is in an extended release formulation. One preferred embodiment of the invention involves the combination of amantadine and levodopa/carbidopa. Desirably, amantadine is provided in an extended release formulation and levodopa/carbidopa is provided as an immediate release formulation. By combining an NMDAr antagonist (e.g., amantadine) with the second agents described herein (e.g., levodopa/carbidopa), this invention provides an effective pharmaceutical composition for treating neurological diseases such as Parkinson's disease or other Parkinson's-like diseases or conditions. The administration of this combination is postulated to maintain or enhance the efficacy of levodopa while significantly reducing its dyskinesia side effects.

The combinations described herein provide complementary benefits associated with the NMDAr antagonist or levodopa/carbidopa individually, while minimizing difficulties previously presented when each component is used separately in a patient. For example, amantadine dosing is limited by neurotoxicity that is likely associated with its short Tmax. By extending the release of amantadine, a higher effective dose can be maintained providing both dyskinesia relief and a reduction in the amount of levodopa required for treatment of the disease symptoms. Given the inherent toxicity of levodopa, such a levodopa sparing combination will result in a decline in both the dyskinesia and overall disease.

Accordingly, the pharmaceutical compositions described herein are administered so as to deliver to a subject, an amount of an NMDAr antagonist, levodopa/carbidopa or both agents that is high enough to treat symptoms or damaging effects of an underlying disease while avoiding undesirable side effects. These compositions may be employed to administer the NMDAr antagonist, the levodopa/carbidopa, or both agents at a lower frequency than presently employed, improving patient compliance, adherence, and caregiver convenience. These compositions are particularly useful as they provide the NMDAr antagonist, levodopa/carbidopa, or both agents, at a therapeutically effective amount from the onset of therapy further improving patient compliance and adherence and enable the achievement of a therapeutically effective steady-state concentration of either or both agents of the combination in a shorter period of time resulting in an earlier indication of effectiveness and increasing the utility of these therapeutic agents for diseases and conditions where time is of the essence. Also provided are methods for making and using such compositions.

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a controlled or extended release form with or without an immediate release component in order to maximize the therapeutic benefit of such agents, while reducing unwanted side effects. In preferred embodiments for oral administration, levodopa/carbidopa is provided as an immediate-release formulation.

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be administered in an amount similar to that typically administered to subjects. Preferably, the amount of the NMDAr antagonist may be administered in an amount greater than or less than the amount that is typically admin-

istered to subjects while the levodopa/carbidopa is provided at a lower dose than normally used. For example, the amount of amantadine required to positively affect the patient response (inclusive of adverse effects) may be 300, 400, 500, 600 mg per day rather than the typical 200-300 mg per day administered for presently approved indications i.e. without the improved formulation described herein, while the levodopa, and optionally the carbidopa, can be reduced independently by 10%, 20%, 30%, 40%, 50%, 60%, 70% or up to 80% of what is currently required in the absence of the NMDAr antagonist.

Optionally, lower or reduced amounts of both the NMDAr antagonist and the levodopa/carbidopa are used in a unit dose relative to the amount of each agent when administered independently. The present invention therefore features formulations of combinations directed to dose optimization or release modification to reduce adverse effects associated with separate administration of each agent. The combination of the NMDAr antagonist and the levodopa/carbidopa may result in an additive or synergistic response, and using the unique formulations described herein, the goal of minimizing the levodopa burden is achieved. Preferably, the NMDAr antagonist and the levodopa/carbidopa are provided in a unit dosage form.

The compositions and methods of the invention are particularly useful for the treatment of Parkinson's disease or conditions associated with Parkinson's disease. These conditions include dementia, dyskinesia, dystonia, depression, fatigue and other neuropsychiatric complications of Parkinson's disease.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present Specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. All parts and percentages are by weight unless otherwise specified.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a graph showing the dissolution profiles for an immediate and sustained release formulation of amantadine. The sustained release formulation exhibits a dC/dT during the initial phase that is about 10% of that for the immediate release formulation.

FIG. **2** is a graph showing the amantadine plasma concentration over a period of 5 days, as predicted by Gastro-Plus software package v.4.0.2, following the administration of either 70 mg amantadine in an immediate release formulation t.i.d. or 75 mg amantadine in a sustained release formulation t.i.d. The sustained release formulation peaks are similar in height to the immediate release formulation even with a higher administered dose and the diurnal variation is substantially reduced.

FIG. **3** is a graph showing the plasma profiles simulated using Gastro-Plus for t.i.d. administration of amantadine (70 mg), levodopa (100 mg), and carbidopa (25 mg), all in an immediate release form.

FIG. **4** is a graph showing the plasma profiles simulated using Gastro-Plus for t.i.d. administration of amantadine (75 mg), levodopa (100 mg), and carbidopa (25 mg), where the amantadine is in a sustained release form and the levodopa and carbidopa are in an immediate release form.

FIG. **5** is a graph representing dissolution profiles for various aminoadamantane formulations including an immediate release form of the NMDAr antagonist memantine (Namenda).

FIG. **6** is a graphical representation of plasma release profiles in a human of memantine, levodopa, and carbidopa when memantine is administered separately from levodopa and carbidopa.

FIG. **7** is a graphical representation of plasma release profiles in a human of memantine, levodopa, and carbidopa when memantine, levodopa, and carbidopa are administered as part of a single controlled-release pharmaceutical composition.

FIG. **8** is a bar graph showing the effects on a primate (squirrel monkey) treated with a combination of levodopa/carbidopa and amantadine.

DETAILED DESCRIPTION OF THE INVENTION

In general, the present invention features pharmaceutical compositions that contain therapeutically effective levels of an NMDAr antagonist and levodopa/carbidopa and, optionally, a pharmaceutical carrier. Preferably the compositions are formulated for modified or extended release to provide a serum or plasma concentration of the NMDAr antagonist over a desired time period that is high enough to be therapeutically effective but at a rate low enough so as to avoid adverse events associated with the NMDAr antagonist. Control of drug release is particularly desirable for reducing and delaying the peak plasma level while maintaining the extent of drug bioavailability. Therapeutic levels are therefore achieved while minimizing debilitating side-effects that are usually associated with immediate release formulations. Furthermore, as a result of the delay in the time to obtain peak serum or plasma level and the extended period of time at the therapeutically effective serum or plasma level, the dosage frequency is reduced to, for example, once or twice daily dosage, thereby improving patient compliance and adherence. For example, side effects including psychosis and cognitive deficits associated with the administration of NMDAr antagonists may be lessened in severity and frequency through the use of controlled-release methods that shift the Tmax to longer times, thereby reducing the dC/dT of the drug. Reducing the dC/dT of the drug not only increases Tmax, but also reduces the drug concentration at Tmax and reduces the Cmax/cmean ratio providing a more constant amount of drug to the subject being treated over a given period of time, enabling increased dosages for appropriate indications.

In addition, the present invention encompasses optimal ratios of NMDAr and levodopa/carbidopa, designed to not only treat the dyskinesia associated with levodopa, but also take advantage of the additivity and synergy between these drug classes. For example, the level of levodopa required to treat the disease symptoms can unexpectedly be reduced by up to 50% by the addition of 400 mg/day of amantadine.

Making NMDAr Antagonist Controlled Release Formulations

A pharmaceutical composition according to the invention is prepared by combining a desired NMDAr antagonist or antagonists with one or more additional ingredients that, when administered to a subject, causes the NMDAr antagonist to be released at a targeted rate for a specified period of time. A release profile, i.e., the extent of release of the NMDAr antagonist over a desired time, can be conveniently determined for a given time by measuring the release using a USP dissolution apparatus under controlled conditions. Pre-

ferred release profiles are those which slow the rate of uptake of the NMDAr antagonist in the neural fluids while providing therapeutically effective levels of the NMDAr antagonist. One of ordinary skill in the art can prepare combinations with a desired release profile using the NMDAr antagonists and formulation methods described below.

NMDAr Antagonists

Any NMDAr antagonist can be used in the methods and compositions of the invention, particularly those that are non-toxic when used in the compositions of the invention. The term "nontoxic" is used in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to humans or, in keeping with established regulatory criteria and practice, is susceptible to approval by the FDA or similar regulatory agency for any country for administration to humans or animals.

The term "NMDAr antagonist", as used herein, includes any amino-adamantane compound including, for example, memantine (1-amino-3,5-dimethyladamantane), rimantadine (1-(1-aminoethyl)adamantane), amantadine (1-aminoadamantane), as well as pharmaceutically acceptable salts thereof. Memantine is described, for example, in U.S. Pat. Nos. 3,391,142, 5,891,885, 5,919,826, and 6,187,338. Amantadine is described, for example, in U.S. Pat. Nos. 3,152,180, 5,891,885, 5,919,826, and 6,187,338. Additional aminoadamantane compounds are described, for example, in U.S. Pat. Nos. 4,346,112, 5,061,703, 5,334,618, 6,444,702, 6,620,845, and 6,662,845. All of these patents are hereby incorporated by reference.

Further NMDAr antagonists that may be employed include, for example, aminocylohexanes such as neramexane, ketamine, eliprodil, ifenprodil, dizocilpine, remacemide, iamotrigine, riluzole, aptiganel, phencyclidine, flupirtine, celfotel, felbamate, spermine, spermidine, levemopamil, dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and its metabolite, dextrorphan ((+)-3-hydroxy-N-methylmorphinan), a pharmaceutically acceptable salt, derivative, or ester thereof, or a metabolic precursor of any of the foregoing.

Optionally, the NMDAr antagonist in the instant invention is memantine and not amantadine or dextromethorphan.

Second Agents

In all foregoing aspects of the invention, the second agent is levodopa. When levodopa is in the combination, the combination preferably also includes a dopa-decarboxylase inhibitor. An example of a suitable dopa-decarboxylase inhibitor is carbidopa. Other dopa-decarboxylase inhibitors include, for example, 3-hydroxy-benzylhydrazinedihydrochloride (NSD-1015) and benseraxide hydrochloride. The combination may further include a catechol-O-methyltransferase (COMT) inhibitor including, for example, talcapone and entacapone.

Dosing, PK, & Toxicity

The NMDA receptor antagonist used in combination therapies are administered at a dosage of generally between about 1 and 5000 mg/day, between 1 and about 800 mg/day, or between 1 and 500 mg/day. For example, NMDA receptor antagonist agents may be administered at a dosage ranging between about 1 and about 500 mg/day, more preferably from about 10 to about 40, 50, 60, 70 or 80 mg/day, advantageously from about 10 to about 20 mg per day. Amantadine may be administered at a dose ranging from about 90, 100 mg/day to about 400, 500, 600, 700 or 800 mg/day, advantageously from about 100 to about 500, 600 mg per day. For example, the pharmaceutical composition may be formulated to provide memantine in an amount ranging between 1-200 mg/day, 1 and 80 mg/day, 2-80 mg/day, 10-80 mg/day, 10 and 80 mg/day, 10 and 70 mg/day, 10 and 60 mg/day, 10 and 50 mg/day, 10 and 40 mg/day, 5 and 65 mg/day, 5 and 40 mg/day, 15 and 45 mg/day, or 10 and 20 mg/day; dextromethorphan in an amount ranging between 1-5000 mg/day, 1-1000 mg/day, and 100-800 mg/day, or 200-500 mg/day. Pediatric doses will typically be lower than those determined for adults.

Table 1 shows exemplary pharmacokinetic properties (e.g., Tmax and T½) of memantine, amantadine, and rimantadine.

TABLE 1

Pharmacokinetics and Toxicity in humans for selected NIVIDAr antagonists

Compound	Human PK (t½) (hours)	Tmax (hours)	Normal Dose	Dose Dependent Toxicity
Memantine	60	3	10-20 mg/day, starting at 5 mg	Dose escalation required, hallucination
Amantadine	15	3	100-300 mg/day, starting at 100 mg/day	Hallucination
Rimantadine	25	6	100-200 mg/day	Insomnia

When levodopa and carbidopa are both included in the composition, the levodopa dose ranges between 100 to 3000 mg per day, 75 mg and 2500 mg/day, 100-2000 mg/day, or 250 and 1000 mg/day divided for administration t.i.d. or more frequently. Carbidopa doses may range between the amounts of 1 to 1000 mg/day, 10 to 500 mg/day, and 25 to 100 mg/day. Optionally, the carbidopa is present in the combination at about 75%, 70%, 65%, 60%, 50%, 40%, 30%, 25%, 20%, and 10% of the mass of the levodopa. Alternatively, the amount of levodopa is less than 300% than the amount of carbidopa. For example, 75 mg of carbidopa (amount that is sufficient to extend the half-life of levodopa in the circulatory system) may be used in combination with 300 to 3000 mg of levodopa per day. The combination may contain a single dosage form comprising 30 to 200 mg amantadine, 30 to 250 mg levodopa, and 10 to 100 mg of carbidopa for t.i.d. or more frequent administration, including multiple dosage forms per administration.

As a result, the preferred dosage forms for optimized use are shown in Table 2 below, with their corresponding commercial equivalent.

TABLE 2

Dosage forms with and without NMDAr antagonist (amount per unit dose)

Sinemet Compositions		Compositions of Present Invention		
Levodopa	Carbidopa	Levodopa	Carbidopa	Amantadine
100 mg IR*	25 mg IR	50-100 mg IR	25 mg IR	100-200 mg IR
100 mg IR	10 mg IR	50-100 mg IR	10 mg IR	50-100 mg IR
100 mg IR	25 mg IR	50-100 mg IR	25 mg IR	100-200 mg CR**
100 mg IR	10 mg IR	50-100 mg IR	10 mg IR	50-100 mg CR

*IR: immediate release
**CR: modified release

Excipients

"Pharmaceutically or Pharmacologically Acceptable" includes molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. "Pharmaceutically Acceptable Carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the

like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. "Pharmaceutically Acceptable Salts" include acid addition salts and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

The preparation of pharmaceutical or pharmacological compositions is known to those of skill in the art in light of the present disclosure. General techniques for formulation and administration are found in "Remington: The Science and Practice of Pharmacy, Twentieth Edition," Lippincott Williams & Wilkins, Philadelphia, Pa. Tablets, capsules, pills, powders, granules, dragees, gels, slurries, ointments, solutions suppositories, injections, inhalants and aerosols are examples of such formulations.

By way of example, modified or extended release oral formulation can be prepared using additional methods known in the art. For example, a suitable extended release form of the either active pharmaceutical ingredient or both may be a matrix tablet or capsule composition. Suitable matrix forming materials include, for example, waxes (e.g., carnauba, bees wax, paraffin wax, ceresine, shellac wax, fatty acids, and fatty alcohols), oils, hardened oils or fats (e.g., hardened rapeseed oil, castor oil, beef tallow, palm oil, and soya bean oil), and polymers (e.g., hydroxypropyl cellulose, polyvinylpyrrolidone, hydroxypropyl methyl cellulose, and polyethylene glycol). Other suitable matrix tabletting materials are microcrystalline cellulose, powdered cellulose, hydroxypropyl cellulose, ethyl cellulose, with other carriers, and fillers. Tablets may also contain granulates, coated powders, or pellets. Tablets may also be multi-layered. Multi-layered tablets are especially preferred when the active ingredients have markedly different pharmacokinetic profiles. Optionally, the finished tablet may be coated or uncoated.

The coating composition typically contains an insoluble matrix polymer (approximately 15-85% by weight of the coating composition) and a water soluble material (e.g., approximately 15-85% by weight of the coating composition). Optionally an enteric polymer (approximately 1 to 99% by weight of the coating composition) may be used or included. Suitable water soluble materials include polymers such as polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials such as sugars (e.g., lactose, sucrose, fructose, mannitol and the like), salts (e.g., sodium chloride, potassium chloride and the like), organic acids (e.g., fumaric acid, succinic acid, lactic acid, and tartaric acid), and mixtures thereof. Suitable enteric polymers include hydroxypropyl methyl cellulose, acetate succinate, hydroxypropyl methyl cellulose, phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups.

The coating composition may be plasticised according to the properties of the coating blend such as the glass transition temperature of the main component or mixture of components or the solvent used for applying the coating compositions. Suitable plasticisers may be added from 0 to 50% by weight of the coating composition and include, for example, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, acetylated citrate esters, dibutylsebacate, and castor oil. If desired, the coating composition may include a filler. The amount of the filler may be 1% to approximately 99% by weight based on the total weight of the coating composition and may be an insoluble material such as silicon dioxide, titanium dioxide, talc, kaolin, alumina, starch, powdered cellulose, MCC, or polacrilin potassium.

The coating composition may be applied as a solution or latex in organic solvents or aqueous solvents or mixtures thereof. If solutions are applied, the solvent may be present in amounts from approximate by 25-99% by weight based on the total weight of dissolved solids. Suitable solvents are water, lower alcohol, lower chlorinated hydrocarbons, ketones, or mixtures thereof. If latexes are applied, the solvent is present in amounts from approximately 25-97% by weight based on the quantity of polymeric material in the latex. The solvent may be predominantly water.

The NMDAr antagonist may be formulated using any of the following excipients or combinations thereof.

Excipient name	Chemical name	Function
Avicel PH102	Microcrystalline Cellulose	Filler, binder, wicking, disintegrant
Avicel PH101	Microcrystalline Cellulose	Filler, binder, disintegrant
Eudragit RS-30D	Polymethacrylate Poly(ethyl acrylate, nethyl methacrylate, timethylammonioethyl methacrylate chloride) 1:2:0.1	Film former, tablet binder, tablet diluent; Rate controlling polymer for controlled release
Methocel K100M Premium CR	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Methocel K100M	Hydroxypropyl methylcellulose	Rate controlling polymer for controlled release; binder; viscosity-increasing agent
Magnesium Stearate	Magnesium Stearate	Lubricant
Talc	Talc	Dissolution control; anti-adherent, glidant
Triethyl Citrate	Triethyl Citrate	Plasticizer
Methocel E5	Hydroxypropyl methylcellulose	Film-former
Opadry ®	Hydroxypropyl methylcellulose	One-step customized coating system which combines polymer, plasticizer and, if desired, pigment in a dry concentrate.
Surelease ®	Aqueous Ethylcellulose Dispersion	Film-forming polymer; plasticizer and

-continued

Excipient name	Chemical name	Function
		stabilizers. Rate controlling polymer coating.

The pharmaceutical composition described herein may also include a carrier such as a solvent, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents. The use of such media and agents for pharmaceutically active substances is well known in the art. Pharmaceutically acceptable salts can also be used in the composition, for example, mineral salts such as hydrochlorides, hydrobromides, phosphates, or sulfates, as well as the salts of organic acids such as acetates, proprionates, malonates, or benzoates. The composition may also contain liquids, such as water, saline, glycerol, and ethanol, as well as substances such as wetting agents, emulsifying agents, or pH buffering agents. Liposomes, such as those described in U.S. Pat. No. 5,422,120, WO 95/13796, WO 91/14445, or EP 524,968 B1, may also be used as a carrier.

Methods for Preparing Modified or Extended Release Formulations

The NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a controlled or extended release form with or without an immediate release component in order to maximize the therapeutic benefit of such agents, while reducing unwanted side effects. In the absence of modified release components (referred to herein as controlled, extended, or delayed release components), the NMDAr antagonist, levodopa/carbidopa, or both is released and transported into the body fluids over a period of minutes to several hours. The combination described herein however, may contain an NMDAr antagonist and a sustained release component, such as a coated sustained release matrix, a sustained release matrix, or a sustained release bead matrix. In one example, in addition to levodopa/carbidopa, amantadine (e.g., 50-400 mg) is formulated without an immediate release component using a polymer matrix (e.g., Eudragit), Hydroxypropyl methyl cellulose (HPMC) and a polymer coating (e.g., Eudragit). Such formulations are compressed into solid tablets or granules and coated with a controlled release material such as Opadry® or Surelease®. Levodopa/carbidopa may also be formulated as a sustained release formulation; in most cases, however, this will not be optimal.

Suitable methods for preparing the compositions described herein in which the NMDAr antagonist is provided in modified or extended release-formulations include those described in U.S. Pat. No. 4,606,909 (hereby incorporated by reference). This reference describes a controlled release multiple unit formulation in which a multiplicity of individually coated or microencapsulated units are made available upon disintegration of the formulation (e.g., pill or tablet) in the stomach of the subject (see, for example, column 3, line 26 through column 5, line 10 and column 6, line 29 through column 9, line 16). Each of these individually coated or microencapsulated units contains cross-sectionally substantially homogenous cores containing particles of a sparingly soluble active substance, the cores being coated with a coating that is substantially resistant to gastric conditions but which is erodable under the conditions prevailing in the gastrointestinal tract.

The composition of the invention may alternatively be formulated using the methods disclosed in U.S. Pat. No. 4,769,027, for example. Accordingly, extended release formulations involve prills of pharmaceutically acceptable material (e.g., sugar/starch, salts, and waxes) may be coated with a water permeable polymeric matrix containing an NMDAr antagonist and next overcoated with a water-permeable film containing dispersed within it a water soluble particulate pore forming material.

The NMDAr antagonist composition may additionally be prepared as described in U.S. Pat. No. 4,897,268, involving a biocompatible, biodegradable microcapsule delivery system. Thus, the NMDAr antagonist may be formulated as a composition containing a blend of free-flowing spherical particles obtained by individually microencapsulating quantities of memantine, for example, in different copolymer excipients which biodegrade at different rates, therefore releasing memantine into the circulation at a predetermined rates. A quantity of these particles may be of such a copolymer excipient that the core active ingredient is released quickly after administration, and thereby delivers the active ingredient for an initial period. A second quantity of the particles is of such type excipient that delivery of the encapsulated ingredient begins as the first quantity's delivery begins to decline. A third quantity of ingredient may be encapsulated with a still different excipient which results in delivery beginning as the delivery of the second quantity beings to decline. The rate of delivery may be altered, for example, by varying the lactide/glycolide ratio in a poly(D,L-lactide-co-glycolide) encapsulation. Other polymers that may be used include polyacetal polymers, polyorthoesters, polyesteramides, polycaprolactone and copolymers thereof, polycarbonates, polyhydroxybuterate and copolymers thereof, polymaleamides, copolyoxalates and polysaccharides.

Alternatively, the composition may be prepared as described in U.S. Pat. No. 5,395,626, which features a multilayered controlled release pharmaceutical dosage form. The dosage form contains a plurality of coated particles wherein each has multiple layers about a core containing an NMDAr antagonist whereby the drug containing core and at least one other layer of drug active is overcoated with a controlled release barrier layer therefore providing at least two controlled releasing layers of a water soluble drug from the multilayered coated particle

Release Profile

The compositions described herein are formulated such that the NMDAr antagonist, levodopa/carbidopa, or both agents have an in vitro dissolution profile that is equal to or slower than that for an immediate release formulation. As used herein, the immediate release (IR) formulation for memantine means the present commercially available 5 mg and 10 mg tablets (i.e., Namenda from Forest Laboratories, Inc. or formulations having substantially the same release profiles as Namenda); and the immediate release (IR) formulation of amantadine means the present commercially available 100 mg tablets (i.e., Symmetrel from Endo Pharmaceuticals, Inc. or formulations having substantially the same release profiles as Symmetrel); and the immediate release (IR) formulation of levodopa/carbidopa means the present commercially available 25 mg/100 mg, 10 mg/100 mg, 25 mg/250 mg tablets of carbidopa/levodopa (i.e., Sinemet from Merck & Co. Inc. or formulations having substantially the

same release profiles as Sinemet). These compositions may comprise immediate release, sustained or extended release, or delayed release components, or may include combinations of same to produce release profiles such that the fraction of NMDAr antagonist or levodopa/carbidopa released is greater or equal to $0.01(0.297+0.0153*e^{(0.515*t)})$ and less than or equal to $1-e^{(-10.9*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C., in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist or levodopa/carbidopa released is less than 93% in 15 minutes and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1N HCl) dissolution medium. Optionally, the fraction of released NMDAr antagonist or levodopa/carbidopa is greater than or equal to $0.01(0.297+0.0153*e^{(0.515*t)})$, and less than or equal to $1-e^{(-0.972*t)}$ as measured using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C., in water, where t is the time in hours and t is greater than zero and equal or less than 17. Thus, the fraction of NMDAr antagonist or levodopa/carbidopa that is released may range between 0.1%-62% in one hour, 0.2%-86% in two hours, 0.6%-100% in six hours, 2.9%-100% in 10 hours, and 7.7%-100% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in a neutral pH (e.g. water or buffered aqueous solution) or acidic (e.g. 0.1 N HCl) dissolution medium. Optionally, the NMDA receptor antagonist has a release profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 70% or greater (e.g., 70%-90%) in 10 hours, and 90% or greater (e.g., 90-95%) in 12 hours as measured in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1 N HCl) dissolution medium. For example, a formulation containing amantadine may have a release profile ranging between 0-60% or 0.1-20% in one hour, 0-86% or 5-30% at two hours, 0.6-100% or 40-80% at six hours, 3-100% or 50% or more (e.g., 50-90%) at ten hours, and 7.7-100% at twelve hours in a dissolution media having a neutral pH (e.g. water or buffered aqueous solution) or in an acidic (e.g. 0.1 N HCl) dissolution medium. In one embodiment, the NMDAr antagonist, the levodopa/carbidopa, or both agents have an in vitro dissolution profile of less than 25%, 15%, 10%, or 5% in fifteen minutes; 50%, 30%, 25%, 20%, 15%, or 10% in 30 minutes and more than 60%, 65% 70%, 75%, 80%, 85%, 90%, 95% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water. Desirably, the NMDAr antagonist, the levodopa/carbidopa, or both agents has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% in a dissolution media having a pH of 1.2 at 10 hours. It is important to note that the dissolution profile for the NMDAr antagonist may be different than the release profile for levodopa/carbidopa. In a preferred embodiment, the levodopa/carbidopa release profile is equal to or similar to that for an immediate release formulation and the release profile for the NMDAr antagonist is controlled to provide a dissolution profile of less than 30% in one hour, less than 50% in two hours, and greater than 95% in twelve hours using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water.

Desirably, the compositions described herein have an in vitro profile that is substantially identical to the dissolution profile shown in FIG. **5** and, upon administration to a subject at a substantially constant daily dose, achieves a serum concentration profile that is substantially identical to that shown in FIGS. **2** and **4**.

As described above, the NMDAr antagonist, the levodopa/carbidopa, or both agents may be provided in a modified or extended release form. Modified or extended drug release is generally controlled either by diffusion through a coating or matrix or by erosion of a coating or matrix by a process dependent on, for example, enzymes or pH. The NMDAr antagonist or the levodopa/carbidopa may be formulated for modified or extended release as described herein or using standard techniques in the art. In one example, at least 50%, 75%, 90%, 95%, 96%, 97%, 98%, 99%, or even in excess of 99% of the NMDAr antagonist or the levodopa/carbidopa is provided in an extended release dosage form. In a preferred embodiment, the levodopa/carbidopa is provided in an immediate release formulation and the NMDAr antagonist is in either an immediate or modified release form.

The composition described herein is formulated such the NMDAr antagonist or levodopa/carbidopa has an in vitro dissolution profile ranging between 0.1%-20% in one hour, 5%-30% in two hours, 40%-80% in six hours, 50%-90% in 10 hours, and 90%-95% in 12 hours using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. using 0.1N HCl as a dissolution medium. Alternatively, the NMDAr antagonist has an in vitro dissolution profile in a solution with a neutral pH (e.g., water) that is substantially the same as its dissolution profile in an acidic dissolution medium. Thus, the NMDAr antagonist may be released in both dissolution media at the following rate: between 0.1-20% in one hour, 5-30% in two hours, 40-80% in six hours, 70-90% in 10 hours, and 90%-95% in 12 hours as obtained using a USP type 2 (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. In one embodiment, the NMDAr antagonist has an in vitro dissolution profile of less than 15%, 10%, or 5% in fifteen minutes, 25%, 20%, 15%, or 10% in 30 minutes, and more than 60% at 16 hours as obtained using a USP type II (paddle) dissolution system at 50 rpm, at a temperature of 37±0.5° C. in water. Desirably, the NMDAr antagonist has a dissolution of at least 65%, 70%, 75%, 80%, 85%, 90%, or 95% at 10 hours in a dissolution medium having a pH of 1.2.

Initial Rate in Vivo, Delayed Tmax

As used herein, "C" refers to the concentration of an active pharmaceutical ingredient in a biological sample, such as a patient sample (e.g. blood, serum, and cerebrospinal fluid). The time required to reach the maximal concentration ("Cmax") in a particular patient sample type is referred to as the "Tmax". The change in concentration is termed "dC" and the change over a prescribed time is "dC/dT".

The NMDAr antagonist or levodopa/carbidopa is provided as a sustained release formulation that may or may not contain an immediate release formulation. If desired, the NMDAr antagonist may be formulated so that it is released at a rate that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In addition, the NMDAr antagonist levodopa/carbidopa may be provided such that it is released at a rate resulting in a Cmax/cmean of approximately 2 or less for approximately 2 hours to at least 8 hours after the NMDAr antagonist is introduced into a subject. Optionally, the sustained release formulations exhibit plasma concentration curves having initial (e.g., from 0, 1, 2 hours after administration to 4, 6, 8 hours

after administration) slopes less than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist. The precise slope for a given individual will vary according to the NMDAr antagonist being used or other factors, including whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose. The determination of initial slopes of plasma concentration is described, for example, by U.S. Pat. No. 6,913,768, hereby incorporated by reference.

Desirably, the NMDAr antagonist or the levodopa/carbidopa is released into a subject sample at a slower rate than observed for an immediate release (IR) formulation of the same quantity of the antagonist, such that the rate of change in the biological sample measured as the dC/dT over a defined period within the period of 0 to Tmax for the IR formulation (e.g., Namenda, a commercially available IR formulation of memantine). In some embodiments, the dC/dT rate is less than about 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. In some embodiments, the dC/dT rate is less than about 60%, 50%, 40%, 30%, 20%, or 10% of the rate for the IR formulation. Similarly, the rate of release of the NMDAr antagonist or the levodopa/carbidopa from the present invention as measured in dissolution studies is less than 80%, 70%, 60% 50%, 40%, 30%, 20%, or 10% of the rate for an IR formulation of the same NMDAr antagonist or levodopa/carbidopa over the first 1, 2, 4, 6, 8, 10, or 12 hours.

In a preferred embodiment, the dosage form is provided in a non-dose escalating, three times per day (t.i.d.) form. In preferred embodiments, the concentration ramp (or Tmax effect) may be reduced so that the change in concentration as a function of time (dC/dT) is altered to reduce or eliminate the need to dose escalate the NMDAr antagonist. A reduction in dC/dT may be accomplished, for example, by increasing the Tmax in a relatively proportional manner. Accordingly, a two-fold increase in the Tmax value may reduce dC/dT by approximately a factor of 2. Thus, the NMDAr antagonist may be provided so that it is released at a rate that is significantly reduced over an immediate release (IR) dosage form, with an associated delay in the Tmax. The pharmaceutical composition may be formulated to provide a shift in Tmax by 24 hours, 16 hours, 8 hours, 4 hours, 2 hours, or at least 1 hour. The associated reduction in dC/dT may be by a factor of approximately 0.05, 0.10, 0.25, 0.5 or at least 0.8. In certain embodiments, this is accomplished by releasing less than 30%, 50%, 75%, 90%, or 95% of the NMDAr antagonist into the circulatory or neural system within one hour of such administration.

The concentration ramp for levodopa/carbidopa may also be reduced, however such changes will not be preferred in most oral formulations due to the marked reduction in absorption of levodopa/carbidopa after it passes the duodenal region of the gastrointestinal tract.

Optionally, the modified release formulations exhibit plasma concentration curves having initial (e.g., from—2 hours after administration to 4 hours after administration) slopes less-than 75%, 50%, 40%, 30%, 20% or 10% of those for an IR formulation of the same dosage of the same NMDAr antagonist or levodopa/carbidopa. The precise slope for a given individual will vary according to the NMDAr antagonist or levodopa/carbidopa being used, the quantity delivered, or other factors, including, for some active pharmaceutical agents, whether the patient has eaten or not. For other doses, e.g., those mentioned above, the slopes vary directly in relationship to dose.

Using the sustained release formulations or administration methods described herein, the NMDAr antagonist reaches a therapeutically effective steady state plasma concentration in a subject within the course of the first two, three, five, seven, nine, ten, twelve, fifteen, or twenty days of administration. For example, the formulations described herein, when administered at a substantially constant daily dose (e.g., at a dose ranging between 200 mg and 800 mg, preferably between 200 mg and 600 mg, and more preferably between 200 mg and 400 mg per day) may reach a steady state plasma concentration in approximately 70%, 60%, 50%, 40%, 30%, or less of the time required to reach such plasma concentration when using a dose escalating regimen.

Dosing Frequency and Dose Escalation

According to the present invention, a subject (e.g., human) having or at risk of having such conditions is administered any of the compositions described herein (e.g., three times per day (t.i.d.), twice per day (b.i.d.), or once per day (q.d.)). While immediate release formulations of NMDAr antagonists are typically administered in a dose-escalating fashion, the compositions described herein may be essentially administered at a constant, therapeutically-effective dose from the onset of therapy. For example, a composition containing a sustained release formulation of amantadine may be administered three times per day, twice per day, or once per day in a unit dose comprising a total daily amantadine dose of 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, or 800 mg. In embodiments comprising a single dosage form containing an NMDAr antagonist and levodopa/carbidopa wherein the levodopa/carbidopa is in an immediate release form, the dosing frequency will be chosen according to the levodopa/carbidopa requirements, (e.g. three times per day).

Reduced Time to Therapeutic Concentration and Efficacy

Immediate release (IR) formulations of memantine (e.g., Namenda) are typically administered at low doses (e.g., 5 mg/day) and are progressively administered at increasing frequency and dose over time to reach a steady state serum concentration that is therapeutically effective. According to the manufacturer's FDA approved label, Namenda, an immediate release (IR) formulation of memantine, is first administered to subjects at a dose of 5 mg per day. After an acclimation period of typically one week, subjects are administered with this dose twice per day. Subjects are next administered with a 5 mg and 10 mg dosing per day and finally administered with 10 mg Namenda twice daily. Using this dosing regimen, a therapeutically effective steady state serum concentration may be achieved within 30 days of the onset of therapy. Using a modified release formulation comprising (22.5 mg memantine,) however, a therapeutically effective steady state concentration may be achieved substantially sooner (within about 13 days), without using a dose escalating regimen. Furthermore, the slope during each absorption period for the sustained release formulation is less (i.e. not as steep) as the slope for Namenda. Accordingly, the dC/dT of the sustained release formulation is reduced relative to the immediate release formulation even though the dose administered is larger than for the immediate release formulation. Based on this model, a sustained release formulation of an NMDAr antagonist may be administered to a subject in an amount that is approximately the full strength dose (or that effectively reaches a therapeutically effective dose) from the onset of therapy and throughout the duration of treatment. Accordingly, a dose escalation would not be required.

Treatment of a subject with the subject of the present invention may be monitored using methods known in the art. The efficacy of treatment using the composition is preferably evaluated by examining the subject's symptoms in a quanti-

tative way, e.g., by noting a decrease in the frequency or severity of symptoms or damaging effects of the condition, or an increase in the time for sustained worsening of symptoms. In a successful treatment, the subject's status will have improved (i.e., frequency or severity of symptoms or damaging effects will have decreased, or the time to sustained progression will have increased). In the model described in the previous paragraph, the steady state (and effective) concentration of the NMDAr antagonist is reached in 25%, 40%, 50%, 60%, 70%, 75%, or 80% less time than in the dose escalated approach.

In another embodiment, a composition is prepared using the methods described herein, wherein such composition comprises memantine or amantadine and a release modifying excipient, wherein the excipient is present in an amount sufficient to ameliorate or reduce the dose-dependent toxicity associated with the memantine or amantadine relative to an immediate release (IR) formulation of memantine, such as Namenda, or amantadine, such as Symmetrel. The use of these compositions enables safer administration of these agents, and even permits the safe use of higher levels for appropriate indications, beyond the useful range for the presently available versions of memantine (5 mg and 10 mg per dose to 20 mg per day) and amantadine (100 mg to 300 mg per day with escalation).

Indications Suitable for Treatment

The compositions and methods of the present invention are particularly suitable for the treatment of Parkinson's disease or conditions associated with Parkinson's disease. These conditions include dementia, dyskinesia, dystonia, depression, fatigue and other neuropsychiatric complications of Parkinson's disease.

Formulations for Alternate Specific Routes of Administration

The pharmaceutical compositions may be optimized for particular types of delivery. For example, pharmaceutical compositions for oral delivery are formulated using pharmaceutically acceptable carriers that are well known in the art. The carriers enable the agents in the composition to be formulated, for example, as a tablet, pill, capsule, solution, suspension, sustained release formulation; powder, liquid or gel for oral ingestion by the subject.

The NMDAr antagonist may also be delivered in an aerosol spray preparation from a pressurized pack, a nebulizer or from a dry powder inhaler. Suitable propellants that can be used in a nebulizer include, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and carbon dioxide. The dosage can be determined by providing a valve to deliver a regulated amount of the compound in the case of a pressurized aerosol.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral, intranasal or respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

In some embodiments, for example, the composition may be delivered intranasally to the cribriform plate rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in U.S. Pat. No. 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Additional formulations suitable for other modes of administration include rectal capsules or suppositories. For suppositories, traditional binders and carriers may include, for example, polyalkylene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%.

The composition may optionally be formulated for delivery in a vessel that provides for continuous long-term delivery, e.g., for delivery up to 30 days, 60 days, 90 days, 180 days, or one year. For example the vessel can be provided in a biocompatible material such as titanium. Long-term delivery formulations are particularly useful in subjects with chronic conditions, for assuring improved patient compliance, and for enhancing the stability of the compositions.

Optionally, the NMDA receptor antagonist, levodopa/carbidopa, or both is prepared using the OROS® technology, described for example, in U.S. Pat. Nos. 6,919,373, 6,923,800, 6,929,803, 6,939,556, and 6,930,128, all of which are hereby incorporated by reference. This technology employs osmosis to provide precise, controlled drug delivery for up to 24 hours and can be used with a range of compounds, including poorly soluble or highly soluble drugs. OROS® technology can be used to deliver high drug doses meeting high drug loading requirements. By targeting specific areas of the gastrointestinal tract, OROS® technology may provide more efficient drug absorption and enhanced bioavailability. The osmotic driving force of OROS® and protection of the drug until the time of release eliminate the variability of drug absorption and metabolism often caused by gastric pH and motility.

Formulations for continuous long-term delivery are provided in, e.g., U.S. Pat. Nos. 6,797,283; 6,764,697; 6,635,268, and 6,648,083.

If desired, the components may be provided in a kit. The kit can additionally include instructions for using the kit.

Additional Methods for Making Modified Release Formulations

Additional methods for making modified release formulations are described in, e.g., U.S. Pat. Nos. 5,422,123, 5,601,845, 5,912,013, and 6,194,000, all of which are hereby incorporated by reference.

In some embodiments, for example, the composition may be delivered via intranasal, buccal, or sublingual routes to the brain rather than by inhalation to enable transfer of the active agents through the olfactory passages into the CNS and reducing the systemic administration. Devices commonly used for this route of administration are included in U.S. Pat. No. 6,715,485. Compositions delivered via this route may enable increased CNS dosing or reduced total body burden reducing systemic toxicity risks associated with certain drugs.

Preparation of a pharmaceutical composition for delivery in a subdermally implantable device can be performed using methods known in the art, such as those described in, e.g., U.S. Pat. Nos. 3,992,518; 5,660,848; and 5,756,115.

The invention will be illustrated in the following non-limiting examples.

EXAMPLES

Example 1

Measuring Release Profiles in Vitro

Compositions containing an aminoadamantane and levodopa/carbidopa are analyzed for release of the aminoadamantane and levodopa/carbidopa, according to the USP type 2 apparatus at a speed of 50 rpm. The dissolution media used include water, 0.1N HCl, or 0.1N HCl adjusted to pH 6.8 at 2 hours with phosphate buffer. The dissolution medium is equilibrated to 37±0.5° C.

The USP reference assay method for amantadine is used to measure the fraction of memantine released from the compositions prepared herein. Briefly, 0.6 mL sample (from the dissolution apparatus at a given time point) is placed into a 15 mL culture tube. 1.6 mL 0.1% Bromocresol Purple (in acetic acid) is added and vortexed for five seconds. The mixture is allowed to stand for approximately five minutes. 3 mL Chloroform is added and vortexed for five seconds. The solution is next centrifuged (speed 50 rpm) for five minutes. The top layer is removed with a disposable pipette. A sample is drawn into 1 cm flow cell and the absorbance is measured at 408 nm at 37° C. and compared against a standard curve prepared with known quantities of the same aminoadamantane. The quantity of determined is plotted against the dissolution time for the sample.

The USP reference assay method for levodopa is used to measure the fraction of levodopa released from the compositions prepared herein. Briefly, 0.5 ml samples from the dissolution apparatus removed at various times are assayed by liquid chromatography. The chromatograph is equipped with a 280 nm detector and a 3.9 mm×30 cm column containing packing Ll. The mobile phase is 0.09 N sodium phosphate, 1 mM sodium 1-decanesulfonate, pH 2.8. With the flow rate adjusted to about 2 mL per minute, the levodopa elutes in about 4 minutes and carbidopa elutes in about 11 minutes. From the saved dissolution samples, a 0.02 ml aliquot is injected into the chromatograph and the absorbance is measure and compared to standard to determine concentration & quantity. The quantity dissolved is then plotted against the dissolution time for the sample.

Example 2

Preparation of Amantadine Extended Release Capsules

Amantadine extended release capsules may be formulated as follows or as described, for example, in U.S. Pat. No. 5,395,626.

A. Composition: Unit Dose

The theoretical quantitative composition (per unit dose) for amantadine extended release capsules is provided below.

Component	% weight/ weight	mg/Capsule
Amantadine	68.34	200.00
OPADRY ® Clear YS-3-7011 [1] (Colorcon, Westpoint, PA)	1.14	5.01
Purified Water, USP [2]	—	—
Sugar Spheres, NF	12.50	54.87
OPADRY ® Clear YS-1-7006 [3] (Colorcon, Westpoint, PA)	4.48	19.66
SURELEASE ® E-7-7050 [4]	13.54	59.44
Capsules [5]	—	—
TOTAL.	100.00%	338.98 mg [6]

[1] A mixture of hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol.

[2] Purified Water, USP is evaporated during processing.

[3] A mixture of hydroxypropyl methylcellulose and polyethylene glycol

[4] Solid content only of a 25% aqueous dispersion of a mixture of ethyl cellulose, dibutyl sebacate, oleic acid, ammoniated water and fumed silica. The water in the dispersion is evaporated during processing.

[5] White, opaque, hard gelatin capsule, size 00.

[6] Each batch is assayed prior to filling and the capsule weight is adjusted as required to attain 200 mg amantadine per capsule.

The quantitative batch composition for amantadine extended release capsule is shown below. (Theoretical batch quantity 25,741 capsules).

Step 1: Prep of Amantadine HC1 Beads (bead Build-up #1)

Component	Weight (kg)
Amantadine	12.000
OPADRY ® Clear YS-3-7011	0.200
Purified Water, USP	5.454
Sugar Sphere, NF	4.000
Total Weight Amantadine Beads	16.200 kg

The amantadine beads obtained from step 1 are used as follows.

Step 2: Clear & Sustained Release Bead Coating #1

Component	Weight (kg)
Amantadine Beads	8.000
OPADRY ® Clear YS-1-7006	0.360
Purified Water, USP	5.928
Surelease ® E-7-7050	0.672
Total Weight Clear Coated Sustained Release Beads	9.032 kg

The sustained release beads obtained from step 2 are used as follows.

Step 3: Amantadine HC1 Beads (Build-up #2)

Component	Weight (kg)
Sustained Release Beads	8.000
Amantadine	4.320
OPADRY ® Clear YS-3-7011	0.072
Purified Water, USP	1.964
Total Weight Amantadine Beads	12.392 kg

The amantadine beads obtained from step 3 are formulated as follows.

Step 4: Clear & Sustained Release Bead Coating #2	
Component	Weight (kg)
Amantadine Beads	10.000
OPADRY ® Clear YS-1-7006	0.250
Purified Water, USP	6.450
Surelease ® E-7-7050	1.050
Total Weight Amantadine Extended Release Beads	11.300 kg

Step 5: Capsule Filling—Gelatin capsules, size 00, are filled with 339 mg of the amantadine beads prepared in step 4.

Example 3

Extended Release Amantadine Formulation with Immediate Release Carbidopa and Levodopa

Levodopa and Carbidopa are formulated into pellets suitable for filling, yet having an immediate release profile. (see, for example, U.S. Pat. No. 5,912,013).

Levodopa plus Carbidopa Core Pellets		
	Weight Percent	Kilograms
MCC	25.0	0.25
Hydroxypropylmethylcellulose Phthalate (HPMCP)	10.0	0.10
Tartaric Acid	10.0	0.10
Sodium Monoglycerate	7.5	0.075
DSS	0.5	0.005
Levodopa	35.8	0.358
Carbidopa	11.2	0.112
TOTAL	100.0%	1.00 kg
Coating		
Cellulose Acetate Phthalate (CAP)	60.0	0.60
Ethylcellulose	25.0	0.25
PEG-400	15.0	0.15
TOTAL	100.0%	1.00 kg

The pellets are assayed for levodopa and carbidopa content. It is determined that approximately 223 mg of the pellets contain 80 mg levodopa and 25 mg carbidopa. Dissolution greater than 90% in 30 minutes is also confirmed.

A total of 669 grams of the pellets are blended with 510 grams of the amantadine pellets from Example 2 in a V-blender for 30 minutes at 30 rpm. Gelatin capsules are filled with 393 mg of the mixture and the assays for content are repeated verifying a composition of 100 mg amantadine, 80 mg levodopa, and 25 mg carbidopa.

Example 4

Predicted Dissolution and Plasma Profiles of Amantadine Controlled Release

Using the formulations described above, the dissolution profiles for amantadine were simulated and used to calculate plasma profiles resulting from single or multiple administrations using the pharmacokinetic software, GastroPlus v.4.0.2, from Simulations Plus (see FIG. **2**). The initial slope of the dissolution for the sustained release formulation is less than the slope determined for the immediate release formulation (see FIG. **1**) and the corresponding serum profile also shows a slower dC/dT (see FIG. **4**).

Example 5

Release Profile of Amantadine and L-DOPA (Levodopa/Carbidopa)

Release proportions are shown in the tables below for a combination of amantadine and levodopa/carbidopa. The cumulative fraction is the amount of drug substance released from the formulation matrix to the serum or gut environment (e.g., U.S. Pat. No. 4,839,177 or U.S. Pat. No. 5,326,570) or as measured with a USP II Paddle system using 0.1N HCl as the dissolution medium.

Time	AMANTADINE T1/2 = 15 hrs cum. fraction A	LEVODOPA/CARBIDOPA T1/2 = 1.5 hrs Cum. fraction B
0	0.00	0.00
0.5	0.10	0.40
1.0	0.20	0.95
2.0	0.35	1.00
4.0	0.60	1.00
8.0	0.90	1.00
12.0	0.98	1.00

Example 6

Treating Dyskinesia in Patients with Parkinson's Disease

A Parkinson's patient experiencing dyskinesia is administered the composition of Example 3 three times each day to receive 300 mg amantadine, 240 mg levodopa, and 75 mg carbidopa daily. The Parkinsonism is reduced as measured by the UPDRS (Goetz et al., Mov. Disord. 19:1020-8, 2004, incorporated by reference) as is the dyskinesia (Vitale et al., Neurol. Sci. 22:105-6, 2001, incorporated by reference)

Example 7

Animal Models Showing Reduced Dyskinesia, Reduced Levodopa Potential

The following protocol was employed to demonstrate the beneficial effects of the compositions of this invention. Briefly, squirrel monkeys (N=4) were lesioned with MPTP according to the protocol of Di Monte et al. (Mov. Disord. 15: 459-66 (2000)). After 3 months, the monkeys showed full symptoms of Parkinson's disease as measured by a modified UPDRS (Goetz et al., Mov. Disord. 19:1020-8, 2004). Levodopa treatment at approximately 15 mg/kg (with 1.5 mg/kg carbidopa) mg/kg b.i.d. commenced a baseline UPDRS and dyskinesia measurement was established. Amantadine was added to the regimen simultaneously with the levodopa, and the amount raised from 1 mg/kg to 45 mg/kg for four of the squirrel monkeys, corresponding to an estimated 3 μm concentration. As shown in FIG. **8**, the combination led to a 60% reduction in dyskinesia. We hypothesize that this translates into a potential 40% reduction in levodopa required to maintain UPDRS.

Example 8

Levodopa Sparing Therapy

The following protocol is employed to determine the optimal reduction of levodopa achieved with the addition of Amantadine to a fixed dose combination product.
Parkinson's DISEASE PROTOCOL SUMMARY NPI

MEMANTINE CR MONOTHERAPY

Protocol Number: NPI-Amantadine CR
Study Phase: 2/3
Name of Drug: NPI-Amantadine/C/L
Dosage: 25/100/100 c/l/a given t.i.d. 25/80/100 c/l/a given t.i.d. 25/60/100 c/l/a given t.i.d.
Concurrent Control: Route: 25/100 c/1 given t.i.d.
Route: Oral
Subject Population: Male and female patients diagnosed with Parkinson's Disease Hoehn and Yahr score of 2-4
Structure: Parallel-group, three-arm study
Study Term Two weeks
Study Sites: Multi-center 10 centers
Blinding: Double blind
Method of Subject Randomized to one of three treatment groups (3:1)
Assignment:
Total Sample Size: 320 subjects (160 men, 160 women)
Primary Efficacy UPDRS
End points: Abnormal involuntary movement scale (AIMS) 0-4
Secondary Endpoints: Modified Obeso dyskinesia rating scale 0-4 Mini-mental state examination (MMSE); Neuropsychiatry Inventory Score (NPI)
Adverse Events: Monitored and elicited by clinic personnel throughout the study, volunteered by patients

Example 9

Pharmaceutical Composition Including Memantine, Levodopa, and Carbidopa

A co-formulation of memantine, levodopa and carbidopa is prepared. This co-formulation matches the absorption properties of levodopa and carbidopa more closely than those of Memantine, thereby extending the effectiveness per dose of levodopa and carbidopa. The co-formulation provides Tmax values to about 4 hours and allows b.i.d. dosing of the combination.

FIG. **6** provides the current single oral dose pharmacokinetic (PK) profiles for levodopa, carbidopa and memantine. FIG. **7** provides idealized pharmacokinetic profiles for the target co-formulation, in which the Tmax values for levodopa and carbidopa more closely match that of Memantine.
Dosage Form: Tablet
Formulation Content Levodopa 150 mg
Carbidopa 37.5 mg
Memantine 10 mg
Excipients: FDA approved excipients and drug release modifiers. Additional embodiments are within the claims.

Example 10

Pharmaceutical Composition Including Extended Release Formulations of Memantine and Levodopa

A pulsatile release dosage form for administration of memantine and levodopa may be prepared as three individual compartments. Three individual tablets are compressed, each having a different release profile, followed by encapsulation into a gelatin capsule, which are then closed and sealed. The components of the three tablets are as follows.

Component TABLET 1 (IMMEDIATE RELEASE):	Function	Amount per tablet
Memantine	Active agent	8 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg

TABLET 2 (RELEASE DELAYED 3-5 HOURS FOLLOWING ADMINISTRATION):		
Memantine	Active agent	8 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS3OD	Delayed release coating material	4.76 mg
Talc	Coating component	3.3 mg
Triethyl citrate	Coating component	0.95 mg

TABLET 3 (RELEASE DELAYED 7-9 HOURS FOLLOWING ADMINISTRATION):		
Memantine	Active agent	2.5 mg
Levodopa	Active agent	70 mg
Dicalcium phosphate dihydrate	Diluent	26.6 mg
Microcrystalline cellulose	Diluent	26.6 mg
Sodium starch glycolate	Disintegrant	1.2 mg
Magnesium Stearate	Lubricant	0.6 mg
Eudragit RS3OD	Delayed release coating material	6.34 mg
Talc	Coating component	4.4 mg
Triethyl citrate	Coating component	1.27 mg

The tablets are prepared by wet granulation of the individual drug particles and other core components as may be done using a fluid-bed granulator, or are prepared by direct compression of the admixture of components. Tablet 1 is an immediate release dosage form, releasing the active agents within 1-2 hours following administration. Tablets 2 and 3 are coated with the delayed release coating material as may be carried out using conventional coating techniques such as spray-coating or the like. As will be appreciated by those skilled in the art, the specific components listed in the above tables may be replaced with other functionally equivalent components, e.g., diluents, binders, lubricants, fillers, coatings, and the like.

Oral administration of the capsule to a patient will result in a release profile having three pulses, with initial release of the memantine and levodopa from the first tablet being substantially immediate, release of the memantine and levodopa from the second tablet occurring 3-5 hours following administration, and release of the memantine and levodopa from the third tablet occurring 7-9 hours following administration.

Example 11

Pharmaceutical Composition Including Extended Release Formulations of Memantine, Levodopa, and Carbidopa

The method of Example 9 is repeated, except that drug-containing beads are used in place of tablets. Carbidopa is also added in each of the fractions at 25% of the mass of the levodopa. A first fraction of beads is prepared by coating an inert support material such as lactose with the drug which provides the first (immediate release) pulse. A second fraction of beads is prepared by coating immediate release beads with an amount of enteric coating material sufficient to provide a drug release-free period of 3-5 hours. A third fraction of beads is prepared by coating immediate release beads having half the methylphenidate dose of the first fraction of beads with a greater amount of enteric coating material, sufficient to provide a drug release-free period of 7-9 hours. The three groups of beads may be encapsulated or compressed, in the presence of a cushioning agent, into a single pulsatile release tablet.

Alternatively, three groups of drug particles may be provided and coated as above, in lieu of the drug-coated lactose beads.

Other Embodiments

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A dosage form suitable for once-daily administration to a human subject consisting of (i) 50 mg to 500 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, and (ii) at least one excipient, wherein the drug in the dosage form comprises an extended release form, and wherein the extended release form of the drug in the dosage form provides a mean change in amantadine plasma concentration as a function of time (dC/dT) that is less than 40% of the dC/dT provided by the same quantity of the drug in an immediate release form, wherein the dC/dT values are measured in a single dose human pharmacokinetic study over the time period between 0 and 4 hours after administration.

2. A dosage form suitable for once-daily administration to a human subject consisting of (i) 50 mg to 500 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, and (ii) at least one excipient, wherein the drug in the dosage form comprises an extended release form, and wherein the extended release form of the drug in the dosage form provides a mean change in amantadine plasma concentration as a function of time (dC/dT) that is less than 40% of the dC/dT provided by the same quantity of the drug in an immediate release form, wherein the dC/dT values are measured in a single dose human pharmacokinetic study over the time period between administration and Tmax of the immediate release form.

3. A dosage form suitable for once-daily administration to a human subject consisting of (i) 50 mg to 500 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, and (ii) at least one excipient, wherein the drug in the dosage form comprises an extended release form, and wherein the extended release form of the drug in the dosage form provides a mean change in amantadine plasma concentration as a function of time (dC/dT) that is less than 40% of the dC/dT provided by the same quantity of the drug in an immediate release form, wherein the dC/dT of the extended release form of the drug in the dosage form is measured in a single dose human pharmacokinetic study over the time period between 2 hours and 4 hours after administration and the dC/dT provided by the same quantity of the drug in an immediate release form is measured in a single dose human pharmacokinetic study over the time period between administration and Tmax of the immediate release form.

4. The dosage form of any of claims **1** to **3**, comprising an osmotic device, which utilizes an osmotic driving force to provide extended release of amantadine.

5. The dosage form of any of claims **1** to **3**, wherein the amount of drug is 100 to 500 mg.

6. The dosage form of any of claims **1** to **3**, wherein the amount of drug is 200 to 500 mg.

7. The dosage form of any of claims **1** to **3**, wherein at least 50% of the drug in the dosage form is in an extended release form.

8. The dosage form of any of claims **1** to **3**, wherein at least 75% of the drug in the dosage form is in an extended release form.

9. The dosage form of any of claims **1** to **3**, wherein at least 90% of the drug in the dosage form is in an extended release form.

10. The dosage form of any of claims **1** to **3**, wherein the dosage form additionally comprises the drug in an immediate release form.

11. The dosage form of any of claims **1** to **3**, wherein the extent of drug bioavailability is maintained.

12. The dosage form of any of claims **1** to **3**, wherein the dosage form provides a shift in amantadine Tmax of 2 hours to 16 hours relative to an immediate release form of amantadine, wherein the Tmax is measured in a single dose human pharmacokinetic study.

* * * * *

EXHIBIT I

US008741343B2

(12) **United States Patent**
Went et al.

(10) **Patent No.: US 8,741,343 B2**
(45) **Date of Patent: Jun. 3, 2014**

(54) **METHOD OF ADMINISTERING AMANTADINE PRIOR TO A SLEEP PERIOD**

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USPC **424/457**; 424/458; 424/461; 514/662

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Methods of nighttime administration of amantadine to reduce sleep disturbances in patient undergoing treatment with amantadine are described, as well as compositions of extended release amantadine that are suitable for nighttime administration.

29 Claims, 7 Drawing Sheets

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FIG. 1

Dissolution Profiles of Amantadine ER Formulations

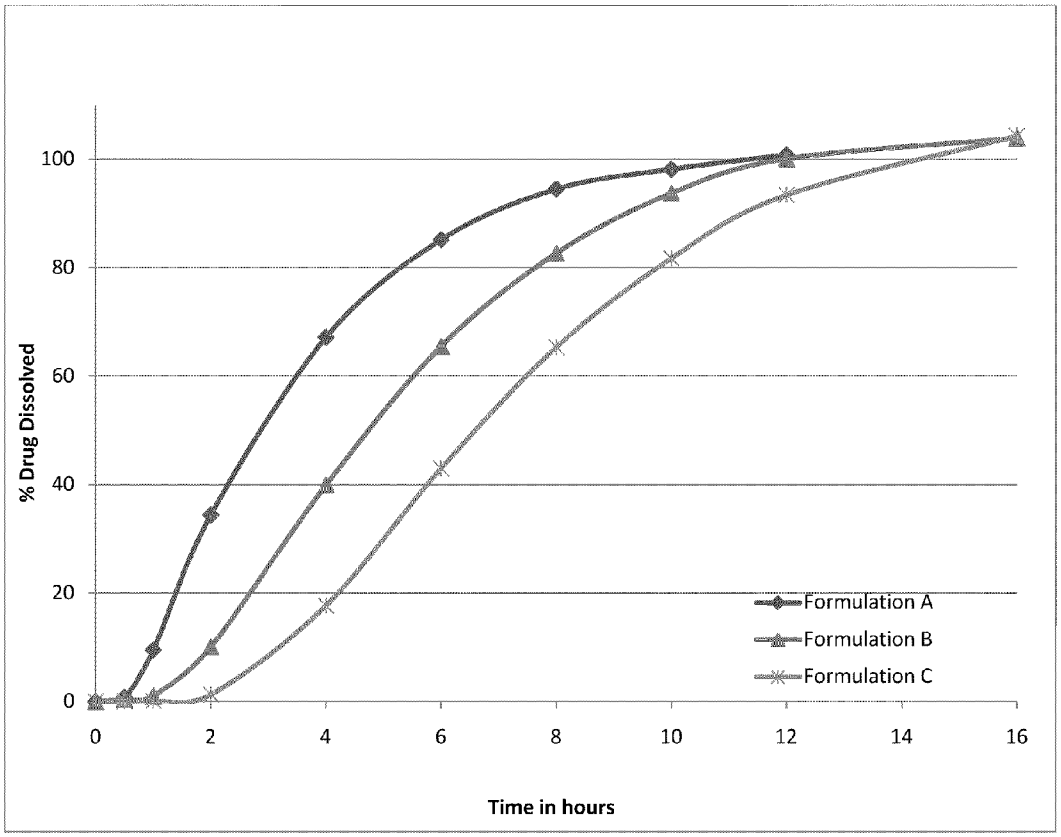


FIG. 2A

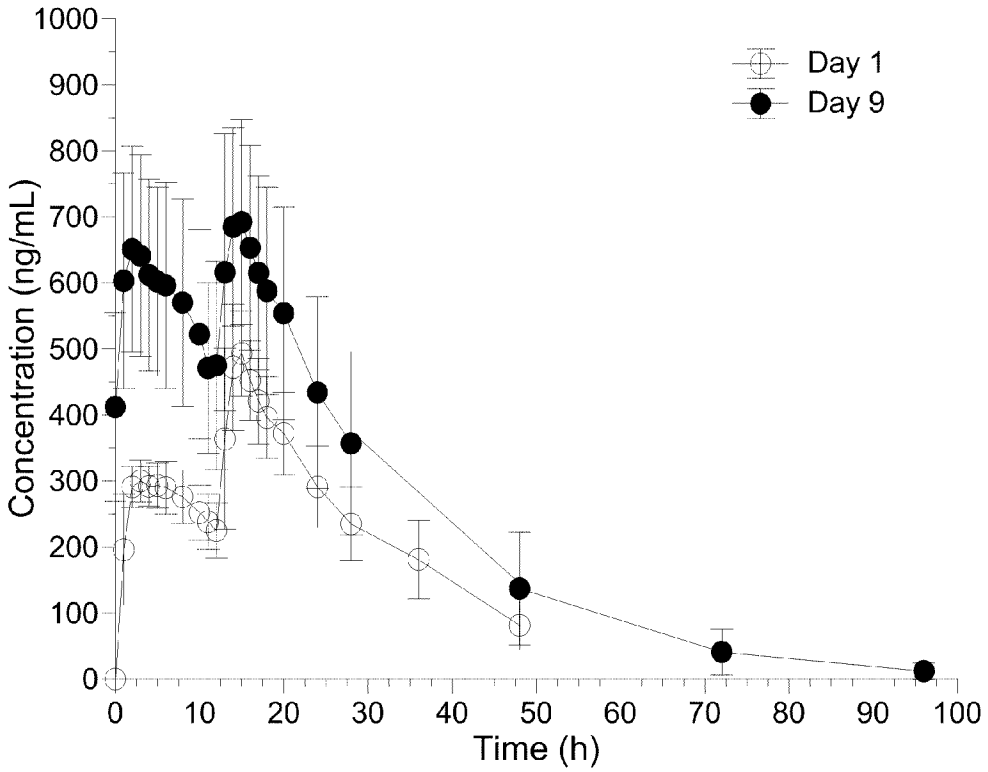

Day 1
Day 9
Concentration (ng/mL)
Time (h)
0
100
200
300
400
500
600
700
800
900
1000
0
10
20
30
40
50
60
70
80
90
100

FIG. 2B

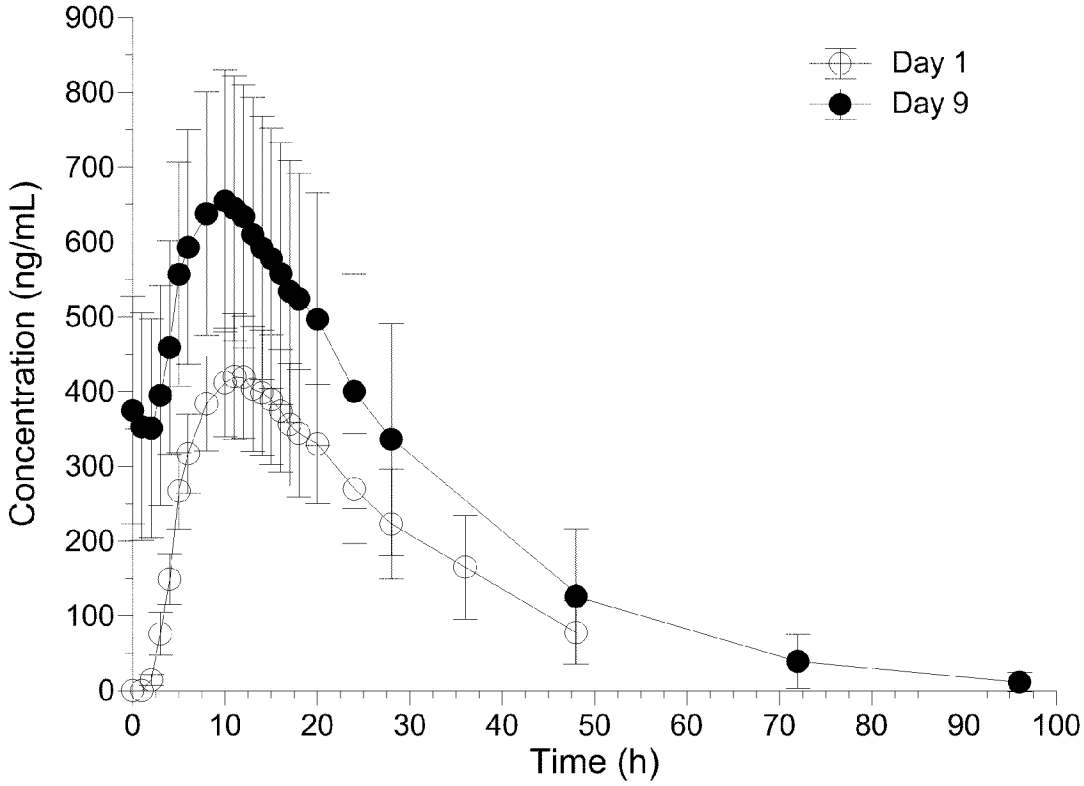

Day 1
Day 9
Concentration (ng/mL)
Time (h)
0
100
200
300
400
500
600
700
800
900
0
10
20
30
40
50
60
70
80
90
100

FIG. 3

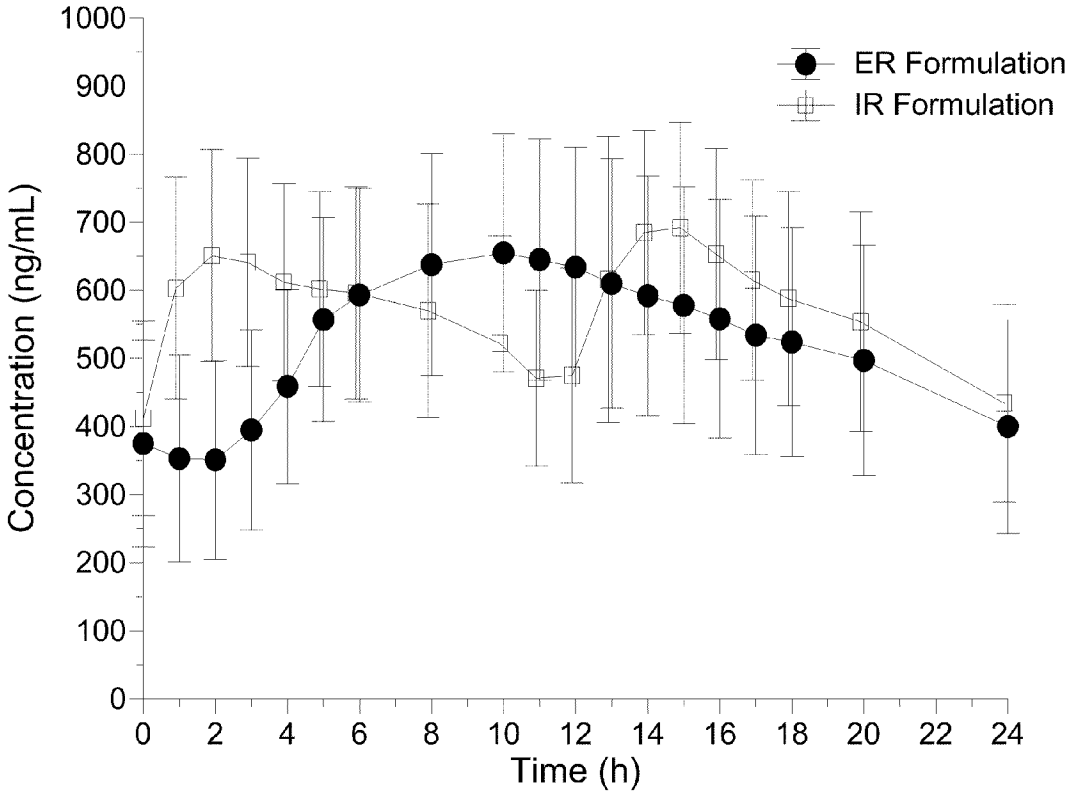
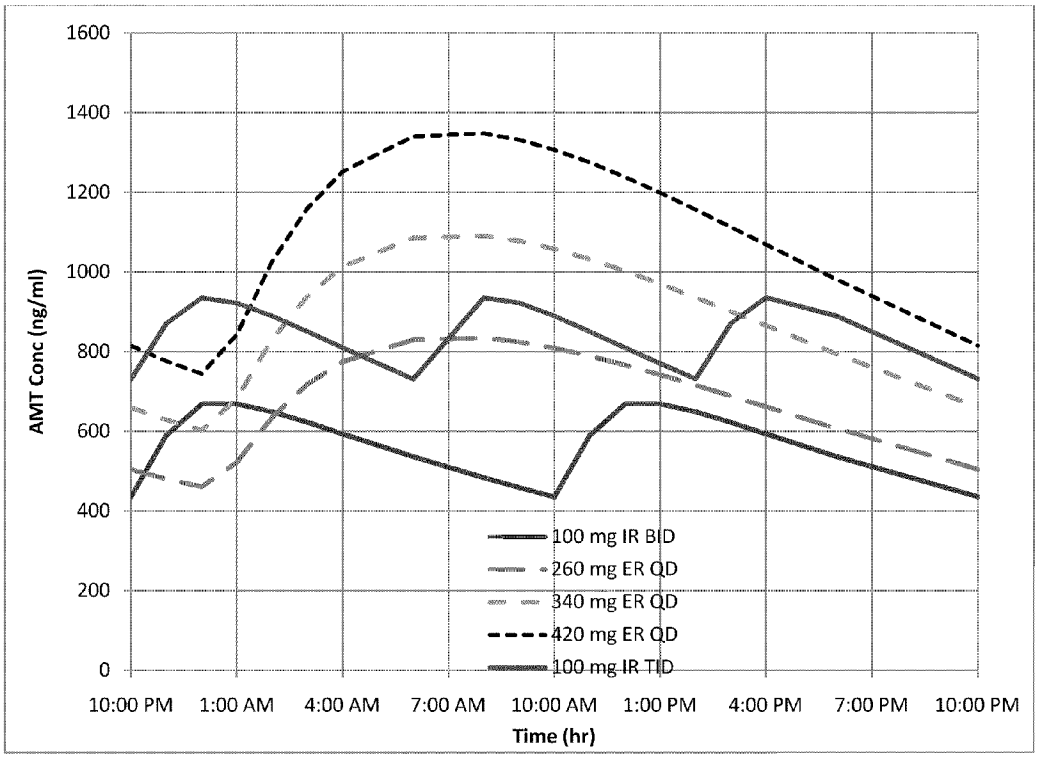

ER Formulation
IR Formulation
Concentration (ng/mL)
Time (h)
0
100
200
300
400
500
600
700
800
900
1000
0
2
4
6
8
10
12
14
16
18
20
22
24

Fig 4.



Simulation based on results of Adamas steady state PK study ADS-PD-104.

FIG. 5

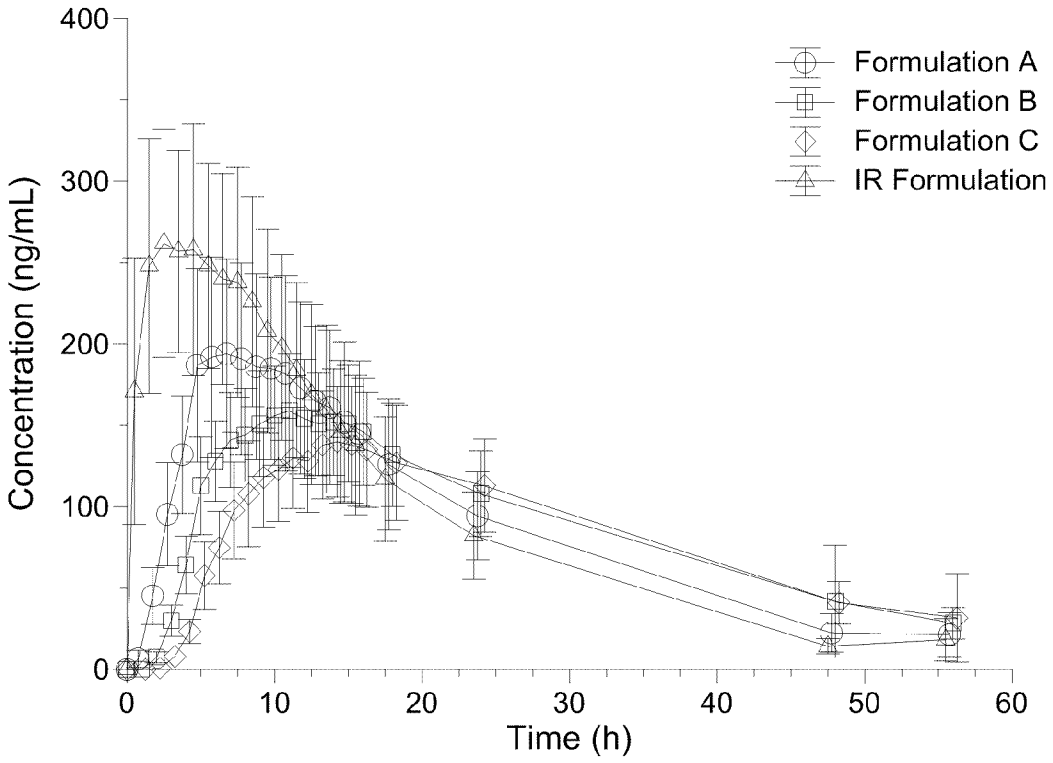

Formulation A
Formulation B
Formulation C
IR Formulation
Concentration (ng/mL)
Time (h)
0
100
200
300
400
0
10
20
30
40
50
60

FIG. 6

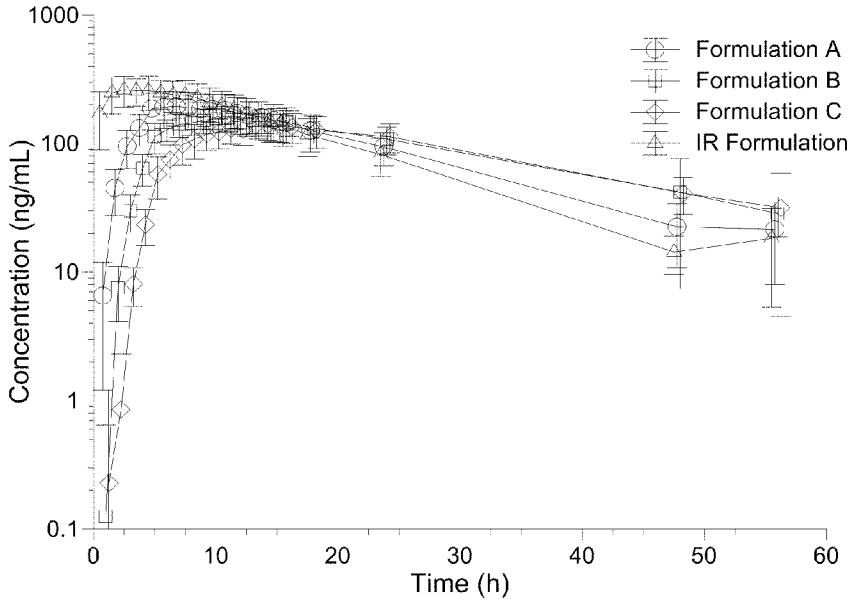
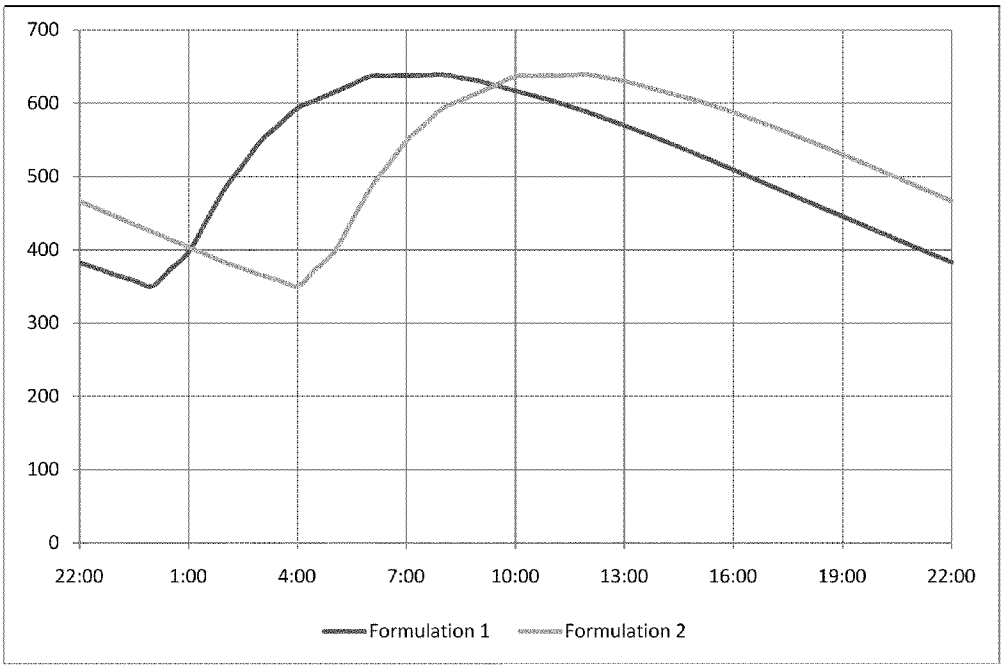

1000
100
10
1
0.1
Concentration (ng/mL)
0
10
20
30
40
50
60
Time (h)
Formulation A
Formulation B
Formulation C
IR Formulation

FIG 7.


700
600
500
400
300
200
100
0
22:00
1:00
4:00
7:00
10:00
13:00
16:00
19:00
22:00
Formulation 1
Formulation 2

METHOD OF ADMINISTERING AMANTADINE PRIOR TO A SLEEP PERIOD

CROSS-REFERENCE

This application claims the benefit of U.S. Provisional Application No. 61/266,053, filed Dec. 2, 2009, which application is incorporated herein by reference.

BACKGROUND OF THE INVENTION

The field of the invention is extended release compositions of amantadine and uses thereof.

Amantadine is indicated for various conditions that can be treated by NMDA receptor antagonists including the treatment of idiopathic Parkinson's disease (Parlysis Agitans), postencephalitic Parkinsonism, and symptomatic Parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication. Amantadine also has activity as a viral M2 channel inhibitor and is used for the prophylaxis and treatment of infection of viral diseases, especially influenza A virus.

Currently marketed forms of amantadine are immediate release formulations that are typically administered two or more times a day. Amantadine's use is limited by dose related CNS side effects including dizziness, confusion, hallucinations, insomnia and nightmares (Gracies J M, Olanow C W; Current and Experimental Therapeutics of Parkinson's Disease; *Neuropsychopharmacology: the Fifth Generation of Progress pp* 1802; American College of Neuropsychopharmacology 2002), which can be particularly exacerbated when amantadine is administered at night.

It is known that immediate release amantadine can act as a stimulant, causing insomnia and sleep disturbance. Therefore, the last dose is typically administered no later than 4 pm in order to minimize these side effects. Such dosing of amantadine results in peak plasma amantadine concentrations occurring in the evening or night, and very low plasma concentrations in the morning.

Extended release forms of amantadine have been described in the art. U.S. Pat. No. 5,358,721, to Guittard et al., and U.S. Pat. No. 6,217,905, to Edgren et al., each disclose an oral osmotic dosage form comprising an antiviral or anti-Parkinson's drug, respectively, where in each case amantadine is listed as a possible drug to be utilized in the dosage form. U.S. Pat. No. 6,194,000, to Smith et al., discloses analgesic immediate and controlled release pharmaceutical compositions utilizing NMDA receptor antagonists, such as amantadine, as the active agent. U.S. Patent Appl. Publication Nos. US 2006/0252788, US 2006/0189694, US 2006/0142398, and US 2008/0227743, all to Went et al., each disclose the administration of an NMDA receptor antagonist, such as amantadine, optionally in controlled release form.

SUMMARY OF THE INVENTION

The inventors have identified a need in the art for improved formulations of amantadine that result in a patient having higher plasma concentrations of amantadine upon waking in the morning without adversely affecting sleep. Further, the inventors have identified a need in the art for a method of administering amantadine in the late afternoon or evening, e.g. after 4 pm, which reduces side effects of insomnia and sleep disturbance and provides effective plasma concentrations of amantadine upon waking.

Therefore, there exists a need in the art for improved methods of amantadine therapy which can be administered to a patient shortly before they wish to sleep (e.g., at bedtime) without causing insomnia or sleep disturbance. In addition, there is a need for an amantadine therapy which can be taken by the patient before they go to sleep and then provides a suitable plasma concentration of amantadine when they wake up, e.g. in the morning, after a full night's sleep.

In addition, many Parkinson's disease patients have difficulty swallowing and are on multiple medications. Hence there is a need for amantadine therapy that delivers a therapeutically effective dose of the drug, can be administered once daily and is in an oral dosage form that is small in size and does not unduly increase the pill burden

One aspect of the invention is a method of administering amantadine to a patient in need thereof, said method comprising orally administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below. Alternatively, the composition is administered less than about 4 hours before bedtime.

In a second aspect, the invention provides a method of reducing sleep disturbance in a human subject undergoing treatment with amantadine, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below. Alternatively, the composition is administered less than about 4 hours before bedtime.

In a third aspect, the invention provides a method of treating levodopa induced dyskinesia, or fatigue, or dementia, or any other symptom of Parkinson's disease, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below.

In a fourth aspect, the invention provides a method of treating brain injury, brain trauma, dementia, Alzheimer's disease, stroke, Huntington's disease, ALS, Multiple Sclerosis, neurodegenerative diseases, dementias, cerebrovascular conditions, movement disorders, cranial nerve disorders, neuropsychiatric disorders, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below.

In one embodiment of any of the above aspects, administration occurs less than two and a half, less than two, less than one and a half, less than one or less than half hour before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).

In one embodiment of any of the above aspects the patient has been diagnosed with Parkinson's disease.

In one embodiment of any of the above aspects, the composition is administered once daily. In another aspect, the daily dose exceeds 200 mg, and is given in 1, 2 or 3 capsules of size 0, 1 or 2.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in levodopa induced dyskinesia (LID). In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% reduction in levodopa induced dyskinesia. In further embodiments, the reduction in levodopa induced dyskinesia is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce LID. In further specific embodiments, the scale used in measuring the reduction in LID could be UDysRS, UPDRS Part IV (subscores 32, 33), Dyskinesia Rating Scale (DRS), Abnormal Involuntary Movement Scale (AIMS), or other scales developed for this purpose.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease fatigue. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60% reduction in Parkinson's disease fatigue. In further specific embodiments, the reduction in fatigue is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce fatigue. In further specific embodiments, the scale used in measuring the reduction in fatigue could be the Fatigue Severity Scale (FSS).

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease symptoms. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's symptoms. In further specific embodiments, the reduction in Parkinson's symptoms is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce Parkinson's symptoms. In further specific embodiments, the scale used in measuring the reduction in Parkinson's symptoms could be the Unified Parkinson's Disease Rating Scale (UPDRS).

In one embodiment of any of the above aspects, the composition is added to food, and in a more specific embodiment to a small amount of soft food (e.g. applesauce or chocolate pudding), prior to administration. Addition to food may involve a capsule being opened and the contents sprinkled over the patient's food. This is advantageous if the patient is unable or unwilling to swallow the composition.

In one embodiment of any of the above aspects, there is no increase in plasma concentration of amantadine for at least one hour after the administration at steady state plasma concentrations.

In one embodiment of any of the above aspects, there is no increase in the plasma concentration of amantadine for at least two hours after the administration at steady state plasma concentrations.

In one embodiment of any of the above aspects, the administration of the composition to a human subject at steady state amantadine plasma concentrations increases the amantadine plasma concentration by less than 5%, 10%, 15%, 20% or 25% at 1, 2, 2.5 or 3 hours following such administration. For example, administration of the composition to a human subject at steady state amantadine plasma concentrations increases the amantadine plasma concentration by less than 5% at 1, 2, 2.5 or 3 hours following such administration; or by less than 10% at 1, 2, 2.5 or 3 hours following such administration; or by less than 15% at 1, 2, 2.5 or 3 hours following such administration; or by less than 20% at 1, 2, 2.5 or 3 hours following such administration; or by less than 25% at 1, 2, 2.5 or 3 hours following such administration.

In one embodiment of any of the above aspects the amantadine has a single dose Tmax of 9 to 15 hours. In a more specific embodiment, the amantadine has a single dose Tmax of 10 to 14 hours after administration. In another more specific embodiment, the amantadine has a single dose Tmax of 11 to 13 hours after administration.

In one embodiment of any of the above aspects the amantadine has a steady state Tmax of 7 to 13 hours. In a more specific embodiment, the amantadine has a steady state Tmax of 8 to 12 hours after administration. In another more specific embodiment, the amantadine has a steady state Tmax of 9 to 11 hours after administration.

In one embodiment of any of the above aspects peak plasma concentration of amantadine is achieved between 6 and 16 hours after administration of a single dose of the composition. In a more specific embodiment, peak amantadine plasma concentration is achieved 8 to 14 hours after administration of a single dose of the composition. In another more specific embodiment, peak amantadine plasma concentration is achieved 10 to 12 hours after administration of a single dose of the composition. In additional specific embodiments, peak amantadine plasma concentration is achieved between 6, 7, 8, 9, 10, 11 or 12 hours to about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 hours after administration of a single dose of the composition.

In one embodiment of any of the above aspects, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In a more specific embodiment, the steady state plasma concentration profile is characterized by a concentration increase of amantadine of less than 25% at four hours after the administration.

In one embodiment of any of the above aspects, the composition is administered once a day and the ratio of Cmax to Cmin at steady state is 1.5 to 2.0, or, more specifically, 1.7 to 1.9, or, more specifically, about 1.8.

In one embodiment of any of the above aspects, the steady state plasma concentration profile following multiple administrations to a human subject of the composition at bedtime is characterized by an average plasma concentration during the day ("C-ave-day", defined as the average day time amantadine plasma concentration as measured in a human PK study) that is 1.1 to 2.0 times the average plasma concentration during the night ("C-ave-night", defined as the average night time amantadine plasma concentration as measured in a human PK study). In more specific embodiments the C-ave-day is the average amantadine plasma concentration as measured between the hours of 5 am, 6 am, 7 am, 8 am or 9 am to the hours of 4 pm, 5 pm, 6 pm, 7 pm or 8 pm; for example, between the hours of 6 am and 4 pm, between the hours of 7 am and 6 pm, or between the hours of 7 am and 5 pm. The C-ave-night is the average amantadine plasma concentration as measured between the hours of 4 pm, 5 pm, 6pm, 7 pm, 8 pm, 9 pm, 10 pm or 11 pm to the hours of 5 am, 6 am, 7 am, 8 am or 9 am; for example, between the hours of 10 pm and 6 am, between the hours of 7 pm and 6 am, or between the hours of 8 pm and 6 am.

In one embodiment of any of the above aspects, the steady state plasma concentration profile following multiple administrations to a human subject of the composition at bedtime is characterized by an average plasma concentration during the morning ("C-ave-morning", defined as the average amantadine plasma concentration as measured in a human PK study during the morning hours) that is 1.1 to 2.0 times the average

plasma concentration during the night. In one embodiment the C-ave-morning is the average amantadine plasma concentration as measured between the hours of 5 am, 6 am, 7 am, 8 am or 9 am to the hours of 11 am, 11:30 am, 12 pm, 12:30 pm or 1:00 pm; for example, between the hours of 5 am and 11 am, or between the hours of 7 am and 12 pm. More preferably, the ratio of C-ave-morning/C-ave-night at steady state is 1.2 to 1.6.

In one embodiment of any of the above aspects, the steady state plasma concentration profile following daily administration of the composition is characterized by an average plasma concentration during the period 8 hours to 12 hours after administration ("C-ave-8-12 hrs") that is 1.1 to 2.0 times the average plasma concentration during the first 8 hours after administration ("C-ave-0-8 hrs"). More preferably, the ratio of C-ave-8-12 hrs/C-ave-0-8 hrs at steady state is 1.2 to 1.6.

In one embodiment of any of the above aspects, administration of a single dose of the composition to a human subject provides a plasma concentration profile characterized by: a fractional AUC from 0 to 4 hours that is less than 5%, and preferably less than 3% of AUC_{0-inf}; a fractional AUC from 0 to 8 hours that is about 5 to 15%, and preferably about 8 to 12% of AUC_{0-inf}; a fractional AUC from 0 to 12 hours that is about 10 to 40%, and preferably about 15 to 30% of AUC_{0-inf}; a fractional AUC from 0 to 18 hours that is about 25 to 60%, and preferably about 30 to 50% of AUC_{0-inf}; and a fractional AUC from 0 to 24 hours that is about 40 to 75%, and preferably about 50 to 70% of AUC_{0-inf}.

In one embodiment of any of the above aspects, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25%, and preferably about 5 to 20% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50%, and preferably about 20 to 40% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70%, and preferably about 40 to 60% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95%, and preferably about 75 to 90% of AUC_{24}.

In one embodiment of any of the above aspects, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by: a fractional AUC from 0 to 8 hours that is about 15 to 40%, and preferably about 20 to 32% of AUC_{24}; a fractional AUC from 8 to 16 hours that is about 30 to 50%, and preferably about 35 to 45% of AUC_{24}; and a fractional AUC from 16 to 24 hours that is about 20 to 35%, and preferably about 25 to 33% of AUC_{24}.

In one embodiment of any of the above aspects the amantadine is administered as a pharmaceutically acceptable salt. In a more specific embodiment, the amantadine is administered as hydrochloride or amantadine sulfate.

In one embodiment of any of the above aspects, a total daily dose of 50 mg to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof is administered to a patient. More specifically the daily dose of amantadine or pharmaceutically acceptable salt thereof administered may be in the range of 100 to 440 mg. In another specific embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof maybe in the range of 260 to 420 mg. In another embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof administered exceeds 300 mg per day. In various specific embodiments, the daily dose of amantadine or pharmaceutically acceptable salt thereof may be 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg.

In one embodiment of any of the above aspects, the composition comprises 50 mg to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. More specifically, the composition may comprise 100 mg to 450 mg of amantadine, or a pharmaceutically acceptable salt thereof. Still more specifically, the composition may comprise 130-210 mg of amantadine, or a pharmaceutically acceptable salt thereof. In various specific embodiments, a dosage form containing the composition comprises 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg of amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition comprises about 110, 120, 130, 140, 150, 160 170, 180, 190, 210, or 220 mg amantadine, or a pharmaceutically acceptable salt thereof. In another more specific embodiment, the composition comprises 110 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 130 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 170 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 210 mg amantadine hydrochloride.

In one embodiment of any of the above aspects, the composition is administered as one, two, three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof.

In one embodiment of any of the above aspects, the composition is administered as one, two, or three unit dosage forms each comprising 50 to 250 mg amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition is administered as one or two unit dosage forms each comprising 65 to 220 mg amantadine, or a pharmaceutically acceptable salt thereof.

In one embodiment of any of the above aspects, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.0 to 2.8 ng/ml per mg of amantadine. In a more specific embodiment, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine and an AUC_{0-inf} (Area under the concentration-curve curve from t=0 to t=infinity) of 40 to 75 ng*h/mL per mg of amantadine.

In one embodiment of any of the above aspects, the daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by at least one of: (i) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine, (ii) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (iii) an AUC_{0-24} of 44 to 83 ng*h/mL per mg of amantadine. In a more specific example, all three criteria of (i), (ii) and (iii) are met.

In a more specific embodiment, the steady state plasma concentration profile is further characterized by: (iv) no increase in concentration of amantadine for at least one hour

after the administration; and (v) Cmax/Cmin ratio of 1.5 to 2.0. In a more specific embodiment, both criteria of (iv) and (v) are met.

In another more specific embodiment, the steady state plasma concentration profile is further characterized by at least one of: (iv) no increase in plasma concentration of amantadine for at least two hours after the administration; and (v) a Cmax/Cmin ratio of 1.7 to 1.9. In a more specific embodiment, both criteria of (iv) and (v) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more 55-85% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more than 25-55% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 20% dissolution at 1 hour, (ii) about 25-45% dissolution at 2 hours, (iii) not more than 50-80% dissolution at 4 hours, and (iv) at least 80% dissolution at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii), (iii) and (iv) are met. In a more specific embodiment, all four of criteria (i), (ii), (iii) and (iv) are met.

In one embodiment of any of the above aspects the in vitro dissolution profile of amantadine is further characterized by release of amantadine of: (i) not more than 10% at 1 hour, or (ii) 30-50% at 4 hours, or (iii) at least 90% at 12 hours using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three criteria of (i), (ii) and (iii) are met.

In another aspect, the present invention provides a pharmaceutical composition comprising or consisting of a pellet-in-capsule, wherein a pellet comprises a core that comprises a core seed with a mixture of amantadine and a binder coated onto the core seed, and an extended release coating surrounding the core comprising ethyl cellulose, a pore forming agent such as hydroxypropyl methyl cellulose or povidone, and a plasticizer.

In another aspect, the present invention provides a pharmaceutical composition for use in the methods of the aspects described above, wherein said composition is for oral administration and comprises a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core.

In one embodiment, the extended release coating comprises ethyl cellulose and at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In a more specific embodiment, the extended release coating comprises ethyl cellulose, povidone, and a plasticizer.

In one embodiment, the pellet core comprises amantadine and a binder coated onto a core seed. In one embodiment, the core seed is a sugar sphere (nonpareil) or microcrystalline cellulose seed (e.g. Celphere®). In a more specific embodiment, the core seed is a microcrystalline cellulose core. In another specific embodiment, the core seed has a diameter in the range of 100 microns to 1,000 microns. In additional specific embodiments, the core seed has a diameter of 100, 200, 300, 400, 500, 600 or 700 microns. In preferred specific embodiments, the core seed has a diameter of less than 500 microns.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 20 to 80 wt %, with a bulk density of 0.3 to 1.2 g/cm^3.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 40 to 60 wt %, with a bulk density of 0.5 to 1.2 g/cm^3.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 60 to 80 wt %, with a bulk density of 0.5 to 1.2 g/cm^3.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the binder is present in amounts from 8 to 25 wt %,

In one embodiment, based on the combined weight of the pellet core and extended release coating, the core seed is present in amounts from 8 to 25 wt %,

In one embodiment, based on the combined weight of the pellet core and extended release coating, the ethyl cellulose is present in amounts from 10 to 20 wt %,

In one embodiment, based on the combined weight of the pellet core and extended release coating, the povidone is present in amounts from 1 to 4 wt %,

In one embodiment, based on the combined weight of the pellet core and extended release coating, and the plasticizer is present in amounts from 1 to 4 wt %.

In one embodiment, the coated pellet has a diameter in the range of 200 microns to 1700 micros. In additional specific embodiments, the coated pellet has a diameter of 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300 or 1500 microns. In certain specific embodiments, the coated pellet has a diameter of less than 1000 microns, e.g., from 500 to 1000 microns.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the binder is present in amounts from 5 to 25 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the core seed is present in amounts from 1 to 15 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the ethyl cellulose is present in amounts from 5 to 20 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the povidone is present in amounts from 0.25 to 4 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, and the plasticizer is present in amounts from 0.25 to 4 wt %.

In one embodiment, the pellet further comprises a seal coating between the pellet core and the extended release coating. In some embodiments, an inert coating can be applied to the inert core prior to drug coating or on drug-

coated pellets or on controlled release coated pellets. In another embodiment, an enteric coating can be applied to the drug coated pellets or controlled release pellets.

In one embodiment, the pellet core comprises a binder, selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof.

In one embodiment, the above composition is provided in a size 3, size 2, size 1, size 0 or size 00 capsule.

In one embodiment, the therapeutically effective daily dose of the above composition is administered in no more than two capsules. In another embodiment, the therapeutically effective daily dose of the composition is administered in no more than three size 1 capsules. In another embodiment, the therapeutically effective daily dose of the composition is administered in no more than two size 0 capsules. In a still more preferred embodiment, the therapeutically effective daily dose of the composition is administered in no more than two size 1 capsules. In another embodiment, the therapeutically effective daily dose of the composition is administered in no more than three size 2 capsules.

In a preferred embodiment, the above composition is provided in an amount of 50 to 110 mg of amantadine or a pharmaceutically acceptable salt thereof in a size 2 capsule, and in the amount of 110 mg to 210 mg of amantadine or a pharmaceutically acceptable salt thereof in a size 1 capsule. In additional embodiments, the above composition comprises coated pellets of diameter 300 to 1000 microns, with amantadine or pharmaceutically acceptable salt thereof content of 40-80% wt % and at a bulk density of 0.5-1.2 g/cm^3. In a further preferred embodiment, the above composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more than 55-85% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, and castor oil. In a more specific embodiment, the plasticizer is medium chain triglycerides, e.g. Miglyol 812 N.

In another aspect, the present invention provides method of administering amantadine, or a pharmaceutically acceptable salt thereof, to a human subject in need thereof, said method comprising orally administering a composition of any of the above aspects.

In another aspect, the present invention provides a method of treating Parkinson's disease in a human subject in need thereof, said method comprising orally administering a composition of any of the above aspects. In a preferred aspect, the present invention provides a method of treating disease in a human subject in need thereof, said method comprising orally administering a composition of any of the above aspects once daily at nighttime, administering 1, 2 or 3 capsules.

References to administering amantadine to a subject in need thereof include treating a patient with a disease or condition which may be treated, prevented or cured by a NMDA antagonist. More specifically, administering amantadine to a subject in need thereof includes treating a patient with Parkinson's Disease, brain injury, brain trauma, dementia, Alzheimer's disease, stroke, Huntington's disease, ALS, Multiple Sclerosis, neurodegenerative diseases, dementias, cerebrovascular conditions, movement disorders, cranial nerve disorders, neuropsychiatric disorders.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the dissolution profiles for three amantadine ER formulations, A, B, C referred to in Example 3.

FIGS. **2**A and **2**B show the mean plasma concentration-time curves after administration of amantadine IR twice daily (A) and amantadine ER once daily (B) to healthy, adult, male and female subjects under fasting conditions on days 1 and 9.

FIG. **3** shows a plot of mean plasma concentration of amantadine versus time curves after administration of amantadine IR twice daily and amantadine ER once daily to healthy, adult, male and female subjects under fasting conditions on day 9.

FIG. **4** shows the simulated mean plasma concentration of amantadine versus time curves following multiple dose administration of various strengths of immediate release amantadine dosed twice or thrice daily and various strengths of amantadine ER administered once daily.

FIG. **5** shows a plot of mean (SD) plasma amantadine concentrations versus scheduled time for four (4) amantadine treatments.

FIG. **6** shows a semi-logarithmic mean (SD) plasma amantadine concentrations versus scheduled time for four (4) amantadine treatments.

FIG. **7** shows simulated steady state plasma concentration time profiles for the ER amantadine formulations as described in Example 12. The ER amantadine formulation 2, administered once daily at night, results at steady state in about 4 hour delay in achieving peak plasma concentration relative to formulation 1.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a method of reducing sleep disturbances in a patient undergoing treatment with amantadine. The method comprises administering amantadine to a patient in need thereof, such that the amantadine does not interfere with sleep, yet provides maximum benefit in morning hours when often needed most by many patients who take amantadine and further, provides nighttime coverage of symptoms of Parkinson's disease if needed. Nighttime coverage includes providing benefit if the patient wakes up and wishes to return to sleep.

The method of the invention comprises orally administering to the patient an extended release (ER) amantadine composition designed for nighttime administration. The composition is taken less than three hours before bedtime, and preferably less than two and a half, less than two, less than one and a half, or less than one hour before bedtime. Most preferably the ER amantadine composition is taken less than half hour before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). As used herein, a reference to amantadine is intended to encompass pharmaceutically acceptable salts thereof (e.g. amantadine hydrochloride, amantadine sulfate, etc.). Alternatively, the composition is administered less than about 4 hours before bedtime.

As used herein, "extended release" includes "controlled release", "modified release", "sustained release", "timed release", "delayed release", and also mixtures of delayed release, immediate release, enteric coated, etc. with each of the above.

The patient may be diagnosed with any disease or disorder for which amantadine is prescribed, such as Parkinson's disease, multiple sclerosis, drug-induced extrapyramidal reactions, levodopa-induced dyskinesia, and viral diseases (e.g. influenza, HBV, and HCV). In a specific embodiment, the patient has Parkinson's disease, which, as used herein, also

encompasses a diagnosis of parkinsonism. In one embodiment, the patient has early stage Parkinson's disease, and the amantadine is used as a monotherapy or in combination with a monoamine oxidase type B (MAO-B) inhibitor without concomitant use of levodopa. In another embodiment, the patient has late stage Parkinson's disease and the patient takes levodopa in addition to the amantadine. In another embodiment, the patient has multiple sclerosis and the amantadine is used for the treatment of fatigue. In other embodiments, the patient has a brain injury, brain injury, brain trauma, dementia, Alzheimer's disease, stroke, Huntington's disease, ALS, Multiple Sclerosis, neurodegenerative diseases, dementias, cerebrovascular conditions, movement disorders, cranial nerve disorders, neuropsychiatric disorders

An ER amantadine composition for use in the invention is adapted for nighttime administration by providing a plasma concentration profile that does not interfere with the subject's sleep. The composition of the invention will, upon administration to a human subject, result in a gradual initial increase in plasma concentration of amantadine such that, at steady state conditions, administration of a dose of the composition results in an increase in plasma concentration of amantadine of less than 25% at three hours after the dose is administered. For example, if a subject's steady state plasma concentration of amantadine is 500 ng/ml at the time a dose of the composition is administered, three hours later the subject's plasma concentration of amantadine will be less than 625 ng/ml. Preferably, the increase in plasma concentration of amantadine is less than 15%, and most preferably, less than 10%. Particularly preferred compositions have a plasma concentration profile further characterized by no increase in amantadine plasma concentration, or even a decrease (at steady state conditions), for at least one or, in a preferred embodiment, two hours after the administration. The composition for use in the invention is further adapted for bedtime (i.e. the time at which the subject wishes to go to sleep for the night) administration by providing a maximum concentration of amantadine (Cmax) in the morning hours. The time to reach Cmax (Tmax), as measured after single dose administration in the fasted state, is at least, 8 hours and up to 13, 14, 15, or 16 hours, or at least 9 hours and up to 13, 14, 15, or 16 hours, or at least 10 hours, and up to 13, 14, 15, or 16 hours. In specific embodiments, the Tmax is 9 to 15 hours, preferably 10 to 14 hours, and most preferably 11 to 13 hours. At steady state, with once daily administration of the composition, the Tmax is 7 to 13 hours, preferably 8 to 12 hours, and most preferably 9 to 11 hours. A suitable ER amantadine composition may be further characterized by having a steady-state Cmax/Cmin ratio of 1.5 to 2.0, and preferably 1.7 to 1.9, resulting in a composition with optimal fluctuation.

In more specific, preferred embodiments, the plasma concentration profile is further characterized by having an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5%, and preferably less than 3% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 8 hours that is about 5 to 15%, and preferably about 8 to 12% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 12 hours that is about 10 to 40%, and preferably about 15 to 30% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 18 hours that is about 25 to 60%, and preferably about 30 to 50% of $AUC_{0\text{-}inf}$; and a fractional AUC from 0 to 24 hours that is about 40 to 75%, and preferably about 50 to 70% of $AUC_{0\text{-}inf}$.

In a further preferred embodiment, the plasma concentration profile is further characterized by having an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25%, and preferably about 5 to 20% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50%, and preferably about 20 to 40% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70%, and preferably about 40 to 60% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95%, and preferably about 75 to 90% of AUC_{24}.

In some embodiments of any of the above aspects, the steady state plasma concentration profile following multiple administrations to a human subject of the composition at bedtime is characterized by an average plasma concentration during the day ("C-ave-day", defined as the average day time amantadine plasma concentration as measured in a human PK study) that is 1.1 to 2.0 times the average plasma concentration during the night ("C-ave-night", defined as the average night time amantadine plasma concentration as measured in a human PK study). In some embodiments, the ratio of C-ave-day/C-ave-night at steady state is within one of the ranges 1.1 to 1.9, 1.1 to 1.8, 1.1 to 1.7, 1.1 to 1.6, 1.1 to 1.5, 1.1 to 1.4, 1.2 to 1.9, 1.2 to 1.7, 1.2 to 1.6, 1.2 to 1.5, 1.3 to 1.9, 1.3 to 1.8, 1.3 to 1.7, 1.3 to 1.6, 1.4 to 1.9, 1.4 to 1.7, 1.5 to 1.9, 1.5 to 1.8, 1.5 to 1.7, 1.6 to 1.9, 1.6 to 1.8 or 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave-night at steady state is 1.1, 1.15, 1.2, 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, or 2.0. In some embodiments, the C-ave-day is the average amantadine plasma concentration as measured between the hours of 5 am, 6 am, 7 am, 8 am or 9 am to the hours of 4 pm, 5 pm, 6 pm, 7 pm or 8 pm and the C-ave-night is the average amantadine plasma concentration as measured between the hours of 4 pm, 5 pm, 6pm, 7 pm, 8 pm, 9 pm, 10 pm or 11 pm to the hours of 5 am, 6 am, 7 am, 8 am or 9 am. In some embodiments, the C-ave-day is the average amantadine plasma concentration as measured within any four to twelve hour period between the hours of 5 am and 8 pm; and the C-ave-night is the average amantadine plasma concentration as measured within any four to twelve hour period between the hours of 8 pm and 5 am. In some embodiments, the C-ave-day is the average amantadine plasma concentration as measured within any four, five, six, seven, eight, nine, ten, eleven or twelve hour period between the hours of 5 am and 8 pm; and the C-ave-night is the average amantadine plasma concentration as measured within any four, five, six, seven, eight, nine, ten, eleven or twelve hour period between the hours of 8 pm and 5 am.

In some embodiments described herein an amantadine composition is administered to a patient from 0 to 4 hours prior to bedtime. In some embodiments, the amantadine composition is administered to a patient from 0 to 3, 0 to 2 or 0 to 1 hours prior to bedtime. In some embodiments, the amantadine composition is administered to a patient from 0 to 240 minutes, from 0 to 180 minutes, e.g. from 0 to 120 minutes, from 0 to 60 minutes, from 0 to 45 minutes, from 0 to 30 minutes, from 0 to 15 minutes or from 0 to 10 minutes prior to bedtime. In some embodiments, the amantadine composition is administered to a patient from 60 to 240 minutes, from 60 to 180 minutes, from 60 to 120 minutes or from 60 to 90 minutes prior to bedtime.

It is to be understood that administration to a patient includes administration by a healthcare professional and self administration by the patient.

Unless otherwise specified herein, the term "bedtime" has the normal meaning of a time when a person retires for the primary sleep period during a twenty-four hour period of time. While for the general populace, bedtime occurs at night, there are patients, such as those who work nights, for whom bedtime occurs during the day. Thus, in some embodiments, bedtime may be anytime during the day or night.

As used herein, unless otherwise indicated, reference to a plasma concentration profile or a specific pharmacokinetic property (e.g. Cmax, Cmin, AUC, Tmax, etc.) in a human subject refers to a mean value obtained from healthy adults s determined in a typical phase I clinical trial designed to measure pharmacokinetic properties of a drug (see e.g. Examples 5, 6 and 7, below). References herein to Tmax refer to values obtained after administration of a single dose at fasted states, unless otherwise indicated.

In some embodiments of the invention, the dose of the amantadine administered in accordance with the present invention is within or above the ranges normally prescribed for immediate release compositions of amantadine. In other embodiments, the doses of the amantadine administered with the present invention are higher than the ranges normally prescribed for immediate release compositions of amantadine. For example, the recommended dose of amantadine for the treatment of Parkinson's disease is 100 mg administered twice daily. In limited cases of the patient not deriving sufficient benefit at that dose and subject to the patient being able to tolerate such higher dose, the dose may be increased to 300 mg or 400 mg in divided doses. The most commonly prescribed doses of amantadine are 100 mg to 200 mg per day, with the latter administered in divided doses. More than 200 mg (for example 300 mg) is always given in divided doses. For the present invention, doses of 50 to 600 mg, or more preferably, 200 to 450 mg are administered for treatment of Parkinson's disease, and the methods and compositions of the invention may comprise administration of a dose as defined by any of these ranges. In specific embodiments the administration of such higher doses may be once daily. In additional embodiments the administration of such higher doses may be at night. In additional embodiments the administration of such higher doses may be in the form of 1, 2 or 3 capsules of size 0, 1 or 2 administered once daily.

In one embodiment of any of the above aspects the amantadine is administered as a pharmaceutically acceptable salt. In a more specific embodiment, the amantadine is administered as hydrochloride or amantadine sulfate.

In one embodiment of any of the above aspects, a total daily dose of 50 mg to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof is administered to a patient. More specifically the daily dose of amantadine or pharmaceutically acceptable salt thereof administered may be in the range of 100 mg to 440 mg. In another specific embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof maybe in the range of 260 mg to 420 mg. In another embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof administered exceeds 300 mg per day. In various specific embodiments, the daily dose of amantadine or pharmaceutically acceptable salt thereof may be 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg.

In one embodiment of any of the above aspects, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. More specifically, the composition may comprise 100 to 450 mg of amantadine, or a pharmaceutically acceptable salt thereof. Still more specifically, the composition may comprise 130-210 mg of amantadine, or a pharmaceutically acceptable salt thereof In various specific embodiments, the dosage form comprises 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg of amantadine, or a pharmaceutically acceptable salt thereof In a more specific embodiment, the composition comprises about 110, 120, 130, 140, 150, 160 170, 180, 190, 210, or 220 mg amantadine, or a pharmaceutically acceptable salt thereof In another more specific embodiment, the composition comprises 110 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 130 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 170 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 210 mg amantadine hydrochloride.

In one embodiment of any of the above aspects, the composition comprises from about 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg of amantadine, or a pharmaceutically acceptable salt thereof to about 75 mg, 85 mg, 95 mg, 105 mg, 115 mg, 125 mg, 135 mg, 145 mg, 155 mg, 165 mg, 175 mg, 185 mg, 195 mg, 205 mg, 215 mg, 225 mg, 235 mg, 245 mg, 255 mg, 265 mg, 275 mg, 285 mg, 295 mg, 305 mg, 315 mg, 325 mg, 335 mg, 345 mg, 355 mg, 365 mg, 375 mg, 385 mg, 395 mg, 405 mg, 415 mg, 425 mg, 435 mg, 445 mg of amantadine, or a pharmaceutically acceptable salt thereof.

In a specific embodiment of the invention, a subject's entire daily dose of amantadine is administered once, during a period of less than about three, two or one hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). In other embodiments, at least one half of the daily dose of amantadine is taken during said period before bedtime. Preferably at least ⅔ of the dose of amantadine is taken in said period before bedtime, with the remainder taken in morning or afternoon. The morning or afternoon dose of the amantadine may be provided in a conventional, immediate release dosage form, or in an extended release form.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in levodopa induced dyskinesia. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% reduction in levodopa induced dyskinesia. In further embodiments, the reduction in levodopa induced dyskinesia is measured on a numeric scale that is used by or accepted by the FDA or other regulatory agencies to evaluate the effectiveness of and to approve for licensure drugs for the treatment of LID. In further specific embodiments, the scale used in measuring the reduction in LID could be UDysRS, UPDRS Part IV (subscores 32, 33), Dyskinesia Rating Scale (DRS), Abnormal Involuntary Movement Scale (AIMS), Rush Dyskinesia Rating Scale, Parkinson Disease Dyskinesia Scale (PDYS-26), Obeso Dyskinesia Rating Scale (CAPIT), Clinical Dyskinesia Rating Scale (CDRS), Lang-Fahn Activities of Daily Living Dyskinesia or other scales developed for this purpose.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease fatigue. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%,

35%, 40%, 45%, 50%, 55%, or 60% reduction in Parkinson's disease fatigue. In further specific embodiments, the reduction in fatigue is measured on a numerical scale used by or accepted by the FDA or other regulatory agencies to evaluate the effectiveness of and to approve for licensure drugs for the treatment of fatigue. In further specific embodiments, the scale used in measuring the reduction in fatigue could be the Fatigue Severity Scale (FSS), Fatigue Assessment Inventory, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue), Multidimensional Fatigue Inventory (MFI-20), Parkinson Fatigue Scale (PFS-16) and the Fatigue Severity Inventory. In other specific embodiments, the reduction in fatigue is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in fatigue is measured relative to baseline in a controlled clinical trial.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease symptoms. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's symptoms. In further specific embodiments, the reduction in Parkinson's symptoms is measured on a numerical scale used by or accepted by the FDA or other regulatory agencies to evaluate the effectiveness of and to approve for licensure drugs for the treatment of Parkinson's symptoms. In further specific embodiments, the scale used in measuring the reduction in Parkinson's symptoms could be the Unified Parkinson's Disease Rating Scale (UPDRS). Unified Parkinson's Disease Rating Scale (UPDRS, MDS revision)—Part I: non-motor aspects of experiences of daily living (13 items), Part II: motor aspects of experiences of daily living (13 items)—Part III: motor examination (33 scored items)—Part I: mental status, behavior and mood—Part II: activities of daily living—Part III: motor examination (27 scored items) Hoehn and Yahr Staging Scale (Original or Modified).

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in levodopa induced dyskinesia. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% reduction in levodopa induced dyskinesia. In further embodiments, the reduction in levodopa induced dyskinesia is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce LID. In further specific embodiments, the scale used in measuring the reduction in LID could be UDysRS, UPDRS Part IV (subscores 32, 33), Dyskinesia Rating Scale (DRS), Abnormal Involuntary Movement Scale (AIMS), or other scales developed for this purpose. In other specific embodiments, the reduction in LID is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in LID is measured relative to baseline in a controlled clinical trial.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease fatigue. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's disease fatigue. In further specific embodiments, the reduction fatigue is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce fatigue. In further specific embodiments, the scale used in measuring the reduction in fatigue could be the Fatigue Severity Scale (FSS). In other specific embodiments, the reduction in fatigue is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in fatigue is measured relative to baseline in a controlled clinical trial.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease symptoms. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's symptoms. In further specific embodiments, the reduction in Parkinson's symptoms is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce Parkinson's symptoms. In further specific embodiments, the scale used in measuring the reduction in Parkinson's symptoms could be the Unified Parkinson's Disease Rating Scale (UPDRS). In other specific embodiments, the reduction in Parkinson's disease symptoms is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in Parkinson's disease symptoms is measured relative to baseline in a controlled clinical trial.

Extended Release Formulations

Extended release amantadine compositions suitable for use in the method of the invention can be made using a variety of extended release technologies, such as those described in the patent publications referenced in the above background section, which publications are incorporated herein by reference in their entireties. In some embodiments, the invention is a pellet in capsule dosage form. In some embodiments, the pellets comprise a pellet core, which is coated with at least one drug layer and at least one extended release coating layer. In some embodiments, the pellets are coated with at least one drug layer, an intermediate layer such as a seal coat and an extended release coating layer. In some embodiments, the pellet, the drug layer or both comprise one or more binders

In some embodiments, the dosage unit comprises a plurality of coated pellets. In some embodiments, the pellets have a diameter of for example 300 to 1700 microns, in some cases 500 to 1200 microns. The pellets will comprise, for example, inert substrates, such as sugar spheres, microcrystalline cellulose (MCC) spheres, starch pellets. In some embodiments, pellets can be prepared by other processes such as pelletization, extrusion, spheronization, etc. or combinations thereof. The core pellets will comprise of amantadine hydrochloride and pharmaceutically acceptable excipients.

Coated Pellets

The pellet cores are coated with the active ingredient, e.g., amantadine or a pharmaceutically acceptable salt and/or polymorph thereof. In some embodiments, in addition to the active ingredient, the pellets also comprise one or more binders, such as for example hydroxypropyl methyl cellulose, copovidone, povidone, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose etc. In some embodiments, the pellets also contain one or more additional excipients, such as anti-tack agents (e.g. talc, magnesium stearate etc.)

In some embodiments, the pellets cores are coated with a drug layer comprising active ingredient, and optionally one or more binders, anti-tack agents and/or solvents by conventional coating techniques such as fluidized bed coating, pan coating.

Intermediate Layer Coating

In some embodiments, the pellets are coated with an intermediate layer, such as a seal coat. In some embodiments, the seal coat is adapted to prevent ingredients in the extended release coating from interacting with ingredients in the pellet core, to prevent migration of the ingredients in the pellet core from diffusing out of the pellet core into the extended release layer, etc. As described herein, the seal coat of the present

invention can comprise one or more film forming polymers including but not limited to hydroxypropylmethyl cellulose (HPMC), copovidone, povidone, polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose or any combination thereof and the like.

The seal coat can further comprise other additives like plasticizers, such as, propylene glycol, triacetin, polyethylene glycol, tributyl citrate and optionally anti-tacking agents, such as, magnesium stearate, calcium silicate, magnesium silicate, and colloidal silicon dioxide or talc.

Apart from plasticizers and anti-tacking agents as mentioned above, the seal coat can optionally contain buffers, colorants, opacifiers, surfactants or bases, which are known to those skilled in the art.

Seal coating can be applied to the core using conventional coating techniques such as fluidized bed coating, pan coating etc. In some embodiments, the drug coated pellets cores are coated with a seal coat layer that optionally comprises one or more binders, anti-tack agents and/or solvents by fluidized bed coating or pan coating.

Binders

In some embodiments, either the pellet cores, the intermediate coating layer, or both may comprise one or more binders (e.g., film forming polymers). Suitable binders for use herein include, e.g.: alginic acid and salts thereof; cellulose derivatives such as carboxymethylcellulose, methylcellulose (e.g., Methocel®), hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose (e.g., Klucel®), ethylcellulose (e.g., Ethocel®), and microcrystalline cellulose (e.g., Avicel®); microcrystalline dextrose; amylose; magnesium aluminum silicate; polysaccharide acids; bentonites; gelatin; polyvinylpyrrolidone/vinyl acetate copolymer; crospovidone; povidone; starch; pregelatinized starch; tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitab®), and lactose; a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, polyvinylpyrrolidone (e.g., Polyvidone® CL, Kollidon® CL, Polyplasdone® XL-10), larch arabogalactan, Veegum®, polyethylene glycol, waxes, sodium alginate, and the like.

Extended Release Coating

The pellets are coated with an extended release coating. The extended release coating is adapted to delay release of the drug from the coated drug cores for a period of time after introduction of the dosage form into the use environment. In some embodiments, the extended release coating includes one or more pH-dependent or non-pH-dependent extended release excipients. Examples of non-pH dependent extended release polymers include ethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, copolymer of ethyl acrylate, methyl methacrylate (e.g. Eudgrait RS) etc. Examples of pH dependent extended release excipients include methacrylic acic copolymers, hydroxypropylmethyl cellulose acetate succinate, hydroxypropylmethyl cellulose phthalate, and cellulose acetate phthalate etc. The extended release coating may also include a pore former, such as povidone, polyethylene glycol, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, etc., sugars such as sucrose, mannitol, lactose, and salts, such as sodium chloride, sodium citrate, etc., a plasticizer, such as acetylated citrated esters, acetylated glycerides, castor oil, citrate esters, dibutylsebacate, glyceryl monostearate, diethyl phthalate, glycerol, medium chain triglycerides, propylene glycol, polyethylene glycol. The extended release coating may also include one or more additional excipients, such as lubricants (e.g., magnesium stearate, talc etc.).

Extended release coating can be applied using conventional coating techniques such as fluidized bed coating, pan coating etc. The drug coated pellets cores, which optionally comprise a seal coat, are coated with the extended release coating by fluidized bed coating.

Extended Release Excipients (Coating Polymers)

As described herein, exemplary extended release excipients include, but are not limited to, insoluble plastics, hydrophilic polymers, and fatty compounds. Plastic matrices include, but are not limited to, methyl acrylate-methyl methacrylate, polyvinyl chloride, and polyethylene. Hydrophilic polymers include, but are not limited to, cellulosic polymers such as methyl and ethyl cellulose, hydroxyalkyl celluloses such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, and cross-linked acrylic acid polymers like Carbopol® 934, polyethylene oxides and mixtures thereof. Fatty compounds include, but are not limited to, various waxes such as carnauba wax and glyceryl tristearate and wax-type substances including hydrogenated castor oil or hydrogenated vegetable oil, or mixtures thereof.

In certain embodiments, the plastic material can be a pharmaceutically acceptable acrylic polymer, including but not limited to, acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain other embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In still other embodiments, the acrylic polymer is an acrylic resin lacquer such as that which is commercially available from Rohm Pharma under the trade name Eudragit®. In further embodiments, the acrylic polymer comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the trade names Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. Edragit® S-100 and Eudragit® L-100 are also suitable for use herein. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, multiparticulate systems formed to include the same are swellable and permeable in aqueous solutions and digestive fluids.

The polymers described above such as Eudragit® RL/RS may be mixed together in any desired ratio in order to ultimately obtain an extended release formulation having a desirable dissolution profile. One skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L.

Pore Formers

In some embodiments, the extended release coating includes a pore former. Pore formers suitable for use in the extended release coating can be organic or inorganic agents, and include materials that can be dissolved, extracted or

leached from the coating in the environment of use. Examples of pore formers include but are not limited to organic compounds such as mono-, oligo-, and polysaccharides including sucrose, glucose, fructose, mannitol, mannose, galactose, lactose, sorbitol, pullulan, dextran; polymers soluble in the environment of use such as water-soluble hydrophilic polymers, such as povidone, crospovidone, polyethylene glycol, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyalkyl celluloses, carboxyalkyl celluloses, cellulose ethers, acrylic resins, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, polyethylene oxide, carbowaxes, Carbopol®, and the like, diols, polyols, polyhydric alcohols, polyalkylene glycols, polyethylene glycols, polypropylene glycols, or block polymers thereof, polyglycols, poly(α-Ω) alkylenediols; inorganic compounds such as alkali metal salts, lithium carbonate, sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium acetate, sodium citrate, suitable calcium salts, and the like. In certain embodiments, plasticizers can also be used as a pore former.

Capsules

The extended release pellets are introduced into a suitable capsule by using an encapsulator equipped with pellet dosing chamber. The capsule sizes may be 00, 0, 0EL, 1, 1EL, 2, 2EL, 3, 4 or 5. A particularly preferred composition that provides ideal pharmacokinetic properties and plasma concentration profiles is a pellet-in-capsule composition that comprises a plurality of pellets, typically having a diameter of about 500 μm to 1.2 mm, and preferably about 700 μm to 1000 μm, where each pellet comprises a core comprising amantadine and a binder, and an extended release coating surrounding the core that extends release of the amantadine so as to provide the desired pharmacokinetic properties and amantadine plasma concentration profiles described above.

In some embodiments, the pellets in the pellet-in-capsule are in a size 0 or smaller, preferably a size 1 or smaller capsule. Mean pellet diameters in some embodiments may be in a range of 500 μm to 1200 μm, e.g. from 500 μm to 1100 μm, from 500 μm to 1000 μm, from 500 μm to 900 μm, from 500 μm to 800 μm, from 500 μm to 700 μm, from 600 μm to 1100 μm, from 600 μm to 1000 μm, from 600 μm to 900 μm, from 600 μm to 800 μm, from 600 μm to 700 μm, from 700 μm to 1100 μm, from 700 μm to 1000 μm, from 700 μm to 900 μm, or from 700 μm to 800 μm. In some embodiments the mean particle diameters are, ±10%, e.g.: 500 μm, 550 μm, 600 μm, 650 μm, 700 μm, 750 μm, 800 μm, 850 μm, 900 μm, 950 μm, 1000 μm, 1050 μm, 1100 μm, 1150 μm or 1200 μm.

One preferred composition of the invention is a pellet-in-capsule composition wherein each pellet comprises a core that comprises a core seed with a mixture of amantadine and a binder coated onto the core seed, and an extended release coating surrounding the core comprising ethyl cellulose, a pore forming agent such as hydroxypropyl methyl cellulose or povidone, and a plasticizer. In some embodiments, the pellets may further comprise a seal coating between the pellet core and the extended release coating. The pellets are formulated using methods known in the art, such as those described in Example 1 below. In a specific embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 20-80 wt %, 45-70 wt %, 40-50 wt %, 45-55 wt %, 50-60 wt %, 55-65 wt %, 60-70 wt %, 65-75 wt %, 70-80 wt %, or 40 to 60 wt %, the binder, which is preferably hydroxypropyl methyl cellulose, copovidone, or mixtures thereof, is present in amounts from 1 to 25 wt %, the core seed, preferably a sugar sphere (nonpareil) or microcrystalline cellulose seed (e.g. Celphere®), is present in amounts from 8 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the pore forming agent, preferably povidone, is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %. In another specific embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 50 to 70 wt %, the binder, which is preferably hydroxypropyl methyl cellulose, copovidone, or mixtures thereof, is present in amounts from 1 to 25 wt %, the core seed, preferably a sugar sphere (nonpareil) or microcrystalline cellulose seed (e.g. Celphere®), is present in amounts from 5 to 15 wt %, the ethyl cellulose is present in amounts from 1 to 15 wt %, the pore forming agent, preferably povidone, is present in amounts from 0.25 to 4 wt %, and the plasticizer is present in amounts from 0.25 to 4 wt %.

Additional embodiments of the invention are illustrated in the Table, below, entitled "Various Amantadine ER Capsule Size 1 Formulations". By means of methods and compositions described herein, formulations can be made that achieve the desired dissolution characteristics and target pharmacokinetic profiles described herein. More specifically, therapeutically effective doses of amantadine can be administered once daily in no more than two size 1 (or smaller, e.g. size 2 or 3) capsules using the manufacturing methods and compositions that have been described herein to achieve these results. In particular, higher drug loading can be achieved using compositions and manufacturing methods described herein. In some embodiments, higher drug loading may be achieved, with the required dissolution profile, using smaller core pellet sizes and concomitantly increased drug layering on smaller cores, but with no change in the extended release coat. In some embodiments, using alternative manufacturing approaches described herein, e.g. extrusion and spheronization, even higher drug loads can be achieved to realize the desired dissolution profile, enabling high amantadine drug loads with suitable pharmacokinetic profiles, resulting in compositions that are therapeutically more effective, and at least as well tolerated, and can be filled in relatively small sized capsules (e.g., size 1, 2 or 3), enabling ease of administration to patients.

TABLE

Various Amantadine ER Capsule Size 1 Formulations

AMT Strength (mg)	Manufacture Method	Inert Core Pellet Size (mm)	Active Drug % w/w	Extended Release Coating % w/w	Bulk Density (g/cm^3)	% Fill in Size 1 Capsule	AMT Dissolution (%) (at T (hrs)): 2 hrs	6 hrs	12 hrs
110 mg	Fluid bed coating	0.3-0.5	40-50%	10-30%	0.6-1.0	60-70%	<25%	40-80%	>80%

TABLE-continued

Various Amantadine ER Capsule Size 1 Formulations

AMT Strength (mg)	Manufacture Method	Inert Core Pellet Size (mm)	Active Drug % w/w	Extended Release Coating % w/w	Bulk Density (g/cm^3)	% Fill in Size 1 Capsule	AMT Dissolution (%) (at T (hrs)): 2 hrs	6 hrs	12 hrs
140 mg	Fluid bed coating	0.3-0.5	45-50%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
150 mg	Fluid bed coating	0.3-0.5	50-55%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
170 mg	Fluid bed coating	0.2-0.3	50-55%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
170 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	65-75%	<25%		>80%
190 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	75-85%	<25%	40-80%	>80%
210 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
230 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	85-95%	<25%	40-80%	>80%

In some embodiment, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 20 to 80 wt % (based on the combined weight of the pellet core and extended release coating), with a bulk density of 0.3 to 1.2 g/cm^3. In some embodiments, the amantadine or pharmaceutically acceptable salt thereof is present in amounts from 20 to 77.5 wt %, from 20 to 75 wt %, from 20 to 72.5 wt %, from 20 to 70 wt %, from 20 to 67.5 wt %, from 20 to 65 wt %, from 20 to 62.5 wt %, from 20 to 60 wt %, from 20 to 57.5 wt %, from 20 to 55 wt %, from 20 to 52.5 wt %, from 20 to 50 wt %, from 20 to 47.5 wt %, from 20 to 45 wt %, from 20 to 42.5 wt %, from 20 to 40 wt %, from 20 to 37.5 wt %, from 20 to 35 wt %, from 20 to 32.5 wt %, from 20 to 30 wt %, from 30 to 80 wt %, from 30 to 77.5 wt %, from 30 to 75 wt %, from 30 to 72.5 wt %, from 30 to 70 wt %, from 30 to 67.5 wt %, from 30 to 65 wt %, from 30 to 62.5 wt %, from 30 to 60 wt %, from 30 to 57.5 wt %, from 30 to 55 wt %, from 30 to 52.5 wt %, from 30 to 50 wt %, from 30 to 47.5 wt %, from 30 to 45 wt %, from 30 to 42.5 wt %, from 30 to 40 wt %, from 40 to 80 wt %, from 40 to 77.5 wt %, from 40 to 75 wt %, from 40 to 72.5 wt %, from 40 to 70 wt %, from 40 to 67.5 wt %, from 40 to 65 wt %, from 40 to 62.5 wt %, from 40 to 60 wt %, from 40 to 57.5 wt %, from 40 to 55 wt %, from 40 to 52.5 wt %, from 40 to 50 wt %, from 40 to 47.5 wt %, from 40 to 45 wt %, from 50 to 80 wt %, from 50 to 77.5 wt %, from 50 to 75 wt %, from 50 to 72.5 wt %, from 50 to 70 wt %, from 50 to 67.5 wt %, from 50 to 65 wt %, from 50 to 62.5 wt %, from 50 to 60 wt %, from 50 to 57.5 wt %, from 50 to 55 wt %, from 60 to 80 wt %, from 60 to 77.5 wt %, from 60 to 75 wt %, from 60 to 72.5 wt %, from 60 to 70 wt %, from 60 to 67.5 wt %, from 60 to 65 wt %. In some embodiments, the bulk density is 0.3 to 1.2 g/cm^3, 0.3 to 1.15 g/cm^3, 0.3 to 1.1 g/cm^3, 0.3 to 1.05 g/cm^3, 0.3 to 1.0 g/cm^3, 0.3 to 0.9 g/cm^3, 0.3 to 0.8 g/cm^3, 0.3 to 0.7 g/cm^3, 0.3 to 0.6 g/cm^3, 0.3 to 0.5 g/cm^3, 0.3 to 0.4 g/cm^3, 0.4 to 1.2 g/cm^3, 0.4 to 1.15 g/cm^3, 0.4 to 1.1 g/cm^3, 0.4 to 1.05 g/cm^3, 0.4 to 1.0 g/cm^3, 0.4 to 0.9 g/cm^3, 0.4 to 0.8 g/cm^3, 0.4 to 0.7 g/cm^3, 0.4 to 0.6 g/cm^3, 0.4 to 0.5 g/cm^3, 0.5 to 1.2 g/cm^3, 0.5 to 1.15 g/cm^3, 0.5 to 1.1 g/cm^3, 0.5 to 1.05 g/cm^3, 0.5 to 1.0 g/cm^3, 0.5 to 0.9 g/cm^3, 0.5 to 0.8 g/cm^3, 0.5 to 0.7 g/cm^3, 0.5 to 0.6 g/cm^3, 0.6 to 1.2 g/cm^3, 0.6 to 1.15 g/cm^3, 0.6 to 1.1 g/cm^3, 0.6 to 1.05 g/cm^3, 0.6 to 1.0 g/cm^3, 0.6 to 0.9 g/cm^3, 0.6 to 0.8 g/cm^3, 0.6 to 0.7 g/cm^3, 0.7 to 1.2 g/cm^3, 0.7 to 1.15 g/cm^3, 0.7 to 1.1 g/cm^3, 0.7 to 1.05 g/cm^3, 0.7 to 1.0 g/cm^3, 0.7 to 0.9 g/cm^3, 0.7 to 0.8 g/cm^3, 0.5 to 1.2 g/cm^3, 0.8 to 1.15 g/cm^3, 0.8 to 1.1 g/cm^3, 0.8 to 1.05 g/cm^3, 0.8 to 1.0 g/cm^3, 0.8 to 0.9 g/cm^3, 0.9 to 1.2 g/cm^3, 0.9 to 1.15 g/cm^3, 0.9 to 1.1 g/cm^3, 0.9 to 1.05 g/cm^3, or 0.9 to 1.0 g/cm^3. In some embodiments, the composition is in a dosage unit comprising a pellet in capsule formulation, wherein the capsule size is size 00, size 0, size 1, size 2 or size 3. In some preferred embodiments, the dosage unit includes pellets containing from 50 to 250 mg of amantadine in a size 0, 1, 2 or 3 capsule. In some embodiments, the dosage unit includes pellets containing from 100 to 250 mg, e.g. 100 to 200 mg of amantadine in a size 0, 1, 2 or 3 capsule, preferably a size 1, 2 or 3 capsule. In a more specific embodiment, the dosage unit comprises about 110, 120, 130, 140, 150, 160 170, 180, 190, 210, or 220 mg amantadine, or a pharmaceutically acceptable salt thereof. In another more specific embodiment, the dosage unit comprises 110 mg amantadine hydrochloride. In another more specific embodiment, the dosage unit comprises 130 mg amantadine hydrochloride. In another more specific embodiment, the dosage unit comprises 170 mg amantadine hydrochloride. In another more specific embodiment, the dosage unit comprises 210 mg amantadine hydrochloride.

Suitable plasticizers include medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, castor oil, and the like. The pellets are filled into capsules to provide the desired strength of amantadine. An advantage of this composition is it provides the desired release properties that make the composition suitable for administration during said period before bedtime. A further advantage is that the extended release coating is sufficiently durable so that the capsule can be opened and the pellets sprinkled onto food for administration to patients who

have difficulty swallowing pills, without adversely affecting the release properties of the composition. When the composition is administered by sprinkling onto food, it is preferred to use a soft food such as applesauce or chocolate pudding, which is consumed within 30 minutes, and preferably within 15 minutes. A yet further advantage of the above-described composition is that it has very good batch-to-batch reproducibility and shelf-life stability.

In some embodiments, the composition of the invention has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, as measured using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. More preferably, the in vitro dissolution is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours.

In additional embodiments, 110 mg to 210 mg of ER amantadine in a size 1 capsule of the composition of the invention has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, as measured using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. More preferably, the in vitro dissolution is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more than 25-55% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 20% dissolution at 1 hour, (ii) about 25-45% dissolution at 2 hours, (iii) not more than 50-80% dissolution at 4 hours, and (iii) at least 80% dissolution at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

A preferred pellet-in-capsule composition of the invention, in addition to having the above in vitro dissolution properties and any of the above-described pharmacokinetic properties (e.g. in vivo release profile, Tmax, Cmax/Cmin ratio, etc) that make the composition suitable for administration in said period before bedtime. The composition is further characterized by providing a Cmax of 1.6-2.4 ng/ml per mg of amantadine and an $AUC_{0\text{-}inf}$ of 40-75 ng*h/mL per mg of amantadine after oral administration of a single dose of the capsule to a human subject in a fasted state. A preferred pellet-in-capsule composition is further characterized by a steady state plasma concentration in which once daily oral administration of the capsule to a human subject provides a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine, a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and an $AUC_{0\text{-}24}$ of 48-73 ng*h/mL per mg of amantadine.

The above-described pellet-in-capsule compositions may be provided at a strength suitable for amantadine therapy. Typical strengths range from at least about 50 mg to about 250 mg. In a specific embodiment, the capsule strength is 70 mg, 80 mg, 90 mg, 110 mg, 120 mg, 125 mg, 130 mg, 140 mg, 150 mg, 160 mg, 160mg, 170 mg, 180 mg, 190 mg, 210 mg, and 220 mg, that provides a single dose $AUC_{0\text{-}inf}$ per mg that is equivalent to a 100 mg tablet of an immediate release formulation of amantadine HCl (e.g. Symmetrel®, or other FDA Orange Book reference listed drug). One, two, or three, of such capsules can be administered to a subject in the period before bedtime. In a preferred embodiment, between 220 mg and 650 mg of amantadine is adminstered using 2 capsules of a suitable ER formulations once daily.

The invention may also be described in terms of the following numbered embodiments:

1. An extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, for use in a method of administering amantadine to a subject in need thereof, said method comprising orally administering said composition less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).
2. Use of amantadine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by the NMDA receptor to a subject in need thereof, said medicament being an extended release (ER) composition, and said treatment comprising orally administering said composition less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).
3. An extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing sleep disturbance in a human subject undergoing treatment with amantadine, said method comprising administering said composition less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).
4. Use of amantadine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing sleep disturbance in a human subject undergoing treatment with amantadine, said medicament being an extended release (ER) composition and being adapted for administration less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).
5. The use or composition of any one of embodiments 1-4 wherein administration occurs less than 1 hour before bedtime.
6. The use or composition of any one of embodiments 1-5, wherein the patient has been diagnosed with Parkinson's disease.
7. The use or composition of any one of embodiments 1-6, wherein the composition is administered once daily.
8. The use or composition of any one of embodiments 1-7, wherein the composition is added to food prior to administration.
9. The use or composition of any one of embodiments 1-8, wherein there is no increase in plasma concentration of amantadine for at least one hour after the administration at steady state.
10. The use or composition of any one of embodiments 1-9, wherein there is no increase in plasma concentration of amantadine for at least two hours after the administration at steady state.
11. The use of composition of any one of embodiments 1-10, wherein, the amantadine has a single dose Tmax of 9 to 15 hours and/or a steady state Tmax of 7 to 13 hours after administration.
12. The use or composition of any one of embodiments 1-11, wherein the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours after administration.

13. The use of composition of any one of embodiments 1-10, wherein, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours after administration.
14. The use or composition of any one of embodiments 1-11, wherein the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours after administration.
15. The use of composition of any one of embodiments 1-10, wherein, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours after administration.
16. The use or composition of any one of embodiments 1-11, wherein the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours after administration.
17. The use or composition of any one of embodiments 1-12, wherein the amantadine has a single dose Tmax of 11 to 13 hours after administration, and or a steady state Tmax of 9 to 11 hours after administration.
18. The use or composition of any one of embodiments 1-13, wherein a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration.
19. The use or composition of any one of embodiments 1-14 having a Cmax/Cmin ratio of 1.5 to 2.0.
20. The use or composition of any one of embodiments 1-15 having a Cmax/Cmin ratio of 1.7 to 1.9.
21. The use or composition of any one of embodiments 1-16, wherein the amantadine is amantadine hydrochloride or amantadine sulfate.
22. The use or composition of any one of embodiments 1-17 wherein the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof
23. The use or composition of embodiment 18, wherein the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof.
24. The use or composition of any one of embodiments 1-19 wherein the composition comprises 200 to 420 mg of amantadine, or a pharmaceutically acceptable salt thereof.
25. The use or composition of embodiment 20, wherein the composition is administered as two unit dosage forms each comprising 110 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof.
26. The use or composition of any one of embodiments 1 to 17, wherein the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof.
27. The use or composition of embodiment 22, wherein the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof.
28. The use or composition of embodiment 23, wherein the composition comprises 110 mg amantadine hydrochloride.
29. The use or composition of any one of embodiments 1-24, wherein oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of amantadine of 1.6 to 2.4 ng/ml per mg of amantadine and an AUC_{0-inf} of 40 to 75 ng*h/mL per mg of amantadine.
30. The use or composition of any one of embodiments 1-25, wherein once daily oral administration of a dose of the composition to a human subject provides a steady state plasma amantadine concentration profile characterized by:
(i) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine,
(ii) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and
(iii) an AUC_{0-24} of 44 to 83 ng*h/mL per mg of amantadine.
31. The use or composition of embodiment 26, wherein the steady state plasma concentration profile is further characterized by:
(iv) no increase in plasma concentration of amantadine for at least one hour after the administration; and
(v) a Cmax/Cmin ratio of 1.5 to 2.0.
32. The use or composition of embodiment 27, wherein the steady state plasma concentration profile is further characterized by:
(iv) no increase in concentration of amantadine for at least two hours after the administration; and
(v) a Cmax/Cmin ratio of 1.7 to 1.9.
33. The use or composition of any one of embodiments 1-28, wherein the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium.
34. The use or composition of embodiment 29, wherein the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours
35. The use or composition of any one of embodiments 1-30, wherein the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of AUC_{0-inf}; a fractional AUC from 0 to 8 hours that is about 5 to 15% of AUC_{0-inf}; a fractional AUC from 0 to 12 hours that is about 10 to 40% of AUC_{0-inf}; a fractional AUC from 0 to 18 hours that is about 25 to 60% of AUC_{0-inf}; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of AUC_{0-inf}
36. The use or composition of any one of embodiments 1-31, wherein the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.
37. A pharmaceutical composition as embodied in any one of embodiments 1, 3, or 5 to 32, or the use of any one of embodiments 2, 4 or 5 to 32, wherein said composition is for oral administration and comprises a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising:
(a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and
(b) an extended release coating surrounding the pellet core.
38. The use or composition of embodiment 32, wherein the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer.
39. The use or composition of any one of embodiments 33 or 34, wherein the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed.
40. The use or composition of embodiment 35, wherein, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 60 wt %, the binder is present in amounts from 8 to 25 wt %, the core seed is present in amounts from 8 to 25 wt %, the ethyl cellulose is present in

amounts from 10 to 20 wt %, the povidone is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %.

41. The use or composition of any one of embodiments 33 to 36, further comprising a seal coating between the pellet core and the extended release coating.

42. The use or composition of any one of embodiments 35 to 37, wherein the wherein the pellet core comprises a binder, selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof.

43. The use or composition of any one of embodiments 18 to 38, wherein the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.

44. A composition of any one of embodiments 33 to 39, for use in a method of treating Parkinson's disease in a human subject in need thereof, said method comprising orally administering said composition.

Some embodiments herein provide a method of administering amantadine to a subject in need thereof, said method comprising orally administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than three hours before bedtime. In some embodiments, administration occurs less than 1 hour before bedtime. In some embodiments, the patient has been diagnosed with Parkinson's disease. In some embodiments, the composition is administered once daily. In some embodiments, the composition is added to food prior to administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least one hour after the administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least two hours after the administration. In some embodiments, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours. In some embodiments, the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours. In some embodiments, the amantadine has a single dose Tmax of 11 to 13 hours after administration, and/or a steady state Tmax of 9 to 11 hours. In some embodiments, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave night at steady state is 1.2 to 1.6. In some embodiments, the ratio of C-ave-morning/C-ave night at steady state is 1.3 to 1.5. In some embodiments, the average amantadine plasma concentration during the day (C-ave-day) at steady state is 500-2000 ng/ml. In some embodiments, the average amantadine plasma concentration in the morning (C-ave-morning) at steady state is 500-2000 ng/ml. In some embodiments, the amantadine is amantadine hydrochloride or amantadine sulfate. In some embodiments, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one or two unit dosage forms each comprising 130 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is within a capsule of capsule size #1. In some embodiments, the composition comprises 200 to 350 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 110 mg amantadine hydrochloride. In some embodiments, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine, and an AUC_{0-inf} of 40 to 75 ng*h/mL per mg of amantadine. In some embodiments, once daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by: (a) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine; (b) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (c) an AUC_{0-24} of 44 to 83 ng*h/mL per mg of amantadine. In some embodiments, the steady state plasma concentration profile is further characterized by: (d) no increase in plasma concentration of amantadine for at least one hour after the administration; and (e) a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the steady state plasma concentration profile is further characterized by: (f) no increase in concentration of amantadine for at least two hours after the administration; and (g) a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 25-55% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 20% at 1 hour, 25-45% at 2 hours, 50-80% at 4 hours, and at least 80% at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours. In some embodiments, the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of AUC_{0-inf}; a fractional AUC from 0 to 8 hours that is about 5 to 15% of AUC_{0-inf}; a fractional AUC from 0 to 12 hours that is about 10 to 40% of AUC_{0-inf}; a fractional AUC from 0 to 18 hours that is about 25 to 60% of AUC_{0-inf}; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of AUC_{0-inf}. In some embodiments, the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

Some embodiments herein provide a method of reducing sleep disturbance in a human subject undergoing treatment with amantadine, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than three hours before bedtime. In some embodiments, administration

occurs less than 1 hour before bedtime. In some embodiments, the patient has been diagnosed with Parkinson's disease. In some embodiments, the composition is administered once daily. In some embodiments, the composition is added to food prior to administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least one hour after the administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least two hours after the administration. In some embodiments, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours. In some embodiments, the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours. In some embodiments, the amantadine has a single dose Tmax of 11 to 13 hours after administration, and/or a steady state Tmax of 9 to 11 hours. In some embodiments, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave night at steady state is 1.2 to 1.6. In some embodiments, the ratio of C-ave-morning/C-ave night at steady state is 1.3 to 1.5. In some embodiments, the average amantadine plasma concentration during the day (C-ave-day) at steady state is 500-2000 ng/ml. In some embodiments, the average amantadine plasma concentration in the morning (C-ave-morning) at steady state is 500-2000 ng/ml. In some embodiments, the amantadine is amantadine hydrochloride or amantadine sulfate. In some embodiments, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one or two unit dosage forms each comprising 130 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is within a capsule of capsule size #1. In some embodiments, the composition comprises 200 to 350 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 110 mg amantadine hydrochloride. In some embodiments, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine, and an AUC_{0-inf} of 40 to 75 ng*h/mL per mg of amantadine. In some embodiments, once daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by: (a) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine; (b) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (c) an AUC_{0-24} of 44 to 83 ng*h/mL per mg of amantadine. In some embodiments, the steady state plasma concentration profile is further characterized by: (d) no increase in plasma concentration of amantadine for at least one hour after the administration; and (e) a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the steady state plasma concentration profile is further characterized by: (f) no increase in concentration of amantadine for at least two hours after the administration; and (g) a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 25-55% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 20% at 1 hour, 25-45% at 2 hours, 50-80% at 4 hours, and at least 80% at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours. In some embodiments, the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of AUC_{0-inf}; a fractional AUC from 0 to 8 hours that is about 5 to 15% of AUC_{0-inf}; a fractional AUC from 0 to 12 hours that is about 10 to 40% of AUC_{0-inf}; a fractional AUC from 0 to 18 hours that is about 25 to 60% of AUC_{0-inf}; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of AUC_{0-inf}. In some embodiments, the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

Some embodiments herein provide a method of treating levodopa induced dyskinesia in a patient with Parkinson's disease, said method comprising orally administering once daily an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime. In some embodiments, administration occurs less than 1 hour before bedtime. In some embodiments, the patient has been diagnosed with Parkinson's disease. In some embodiments, the composition is administered once daily. In some embodiments, the composition is added to food prior to administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least one hour after the administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least two hours after the administration. In some embodiments, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours. In some embodiments, the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours. In some embodiments, the amantadine has a single dose Tmax of 11 to 13 hours after administration, and/or a steady state Tmax of 9 to 11 hours. In some embodiments, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave night at steady state is 1.2 to 1.6. In some embodiments, the ratio of

C-ave-morning/C-ave night at steady state is 1.3 to 1.5. In some embodiments, the average amantadine plasma concentration during the day (C-ave-day) at steady state is 500-2000 ng/ml. In some embodiments, the average amantadine plasma concentration in the morning (C-ave-morning) at steady state is 500-2000 ng/ml. In some embodiments, the amantadine is amantadine hydrochloride or amantadine sulfate. In some embodiments, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one or two unit dosage forms each comprising 130 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is within a capsule of capsule size #1. In some embodiments, the composition comprises 200 to 350 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 110 mg amantadine hydrochloride. In some embodiments, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine, and an AUC_{0-inf} of 40 to 75 ng*h/mL per mg of amantadine. In some embodiments, once daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by: (a) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine; (b) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (c) an AUC_{0-24} of 44 to 83 ng*h/mL per mg of amantadine. In some embodiments, the steady state plasma concentration profile is further characterized by: (d) no increase in plasma concentration of amantadine for at least one hour after the administration; and (e) a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the steady state plasma concentration profile is further characterized by: (f) no increase in concentration of amantadine for at least two hours after the administration; and (g) a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 25-55% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 20% at 1 hour, 25-45% at 2 hours, 50-80% at 4 hours, and at least 80% at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours. In some embodiments, the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of AUC_{0-inf}; a fractional AUC from 0 to 8 hours that is about 5 to 15% of AUC_{0-inf}; a fractional AUC from 0 to 12 hours that is about 10 to 40% of AUC_{0-inf}; a fractional AUC from 0 to 18 hours that is about 25 to 60% of AUC_{0-inf}; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of AUC_{0-inf}. In some embodiments, the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

Some embodiments herein provide a pharmaceutical composition for any of the methods described herein, wherein said composition is for oral administration and comprises a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 60 wt %, the binder is present in amounts from 8 to 25 wt %, the core seed is present in amounts from 1 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the povidone is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %. In some embodiments, the composition further comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.

Some embodiments herein provide a method of administering amantadine, or a pharmaceutically acceptable salt thereof, to a human subject in need thereof, said method comprising orally administering a pharmaceutical composition comprising amantadine in a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 60 wt %, the binder is present in amounts from 8 to 25 wt %, the core seed is present in amounts from 1 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the povidone is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %. In some embodiments, the composition further comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone,

and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil. Some embodiments comprise treating Parkinson's disease in a human subject in need thereof.

Some embodiments herein provide a pharmaceutical composition suitable for once daily oral administration to a patient in need thereof said composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. In some embodiments, the composition comprises 110-220 mg of amantadine or pharmaceutically acceptable salt thereof. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 40-80% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition comprises a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, the composition comprises amantadine and, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 70 wt %. In some embodiments, the pellet core comprises a core seed comprising sugar or microcrystalline cellulose that is between 100 and 500 microns in diameter. In some embodiments, the bulk density is between 0.5 and 1 gm/cm^3. In some embodiments, the composition comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.

Some embodiments herein provide a method of treating Parkinson's disease in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. In some embodiments, the composition comprises 110-220 mg of amantadine or pharmaceutically acceptable salt thereof. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 40-80% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition comprises a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, the composition comprises amantadine and, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 70 wt %. In some embodiments, the pellet core comprises a core seed comprising sugar or microcrystalline cellulose that is between 100 and 500 microns in diameter. In some embodiments, the bulk density is between 0.5 and 1 gm/cm^3. In some embodiments, the composition comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.

Some embodiments herein provide a method of treating levodopa induced dyskinesia in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. Some embodiments herein provide a method of treating traumatic brain injury in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. Some embodiments provide a method of treating traumatic brain injury in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. Some embodiments provide a method of treating fatigue in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. In some embodiments, the composition comprises 110-220 mg of amantadine or pharmaceutically acceptable salt thereof. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 40-80% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition comprises a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, the composition comprises amantadine and, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 70 wt %. In some embodiments, the pellet core comprises a core seed comprising sugar or microcrystalline cellulose that is between 100 and 500 microns in diameter. In some embodiments, the bulk density is between 0.5 and 1 gm/cm^3. In some

embodiments, the composition comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil. In some embodiments, the method comprises administering the composition to a patient less than three hours before bed time.

The present invention may be better understood by reference to the following examples, which are not intended to limit the scope of the claims.

EXAMPLE 1

Amantadine Extended Release Coated Pellet Formulations

Amantadine HCl extended release coated pellet compositions designed for nighttime administration were prepared using the components and relative amounts shown in Table 1 below. For each composition, the drug coating solution was prepared by adding HPMC 5 cps and Copovidone to isopropyl alcohol with continuous stirring. Purified water was added to this dispersion and stirring continued until a clear solution is formed. Drug (Amantadine HCl) was then added to this binder solution and stirring continued until the drug was completely dissolved. Finally, talc was added and dispersed uniformly by stirring.

Celphere beads (screen sizes #35 to #50 i.e. 300 to 500 micron) were loaded in a Wurster coating unit. The drug coating dispersion was sprayed onto the beads followed by a period of drying. The resulting drug coated pellets were sieved to retain the fraction between screens #18 and #24 (approximately 700 μm to 1 mm diameter).

The seal coating solution was prepared by adding HPMC 5 cps to isopropyl alcohol with continuous stirring. Purified water was added to this dispersion and stirring continued until a clear solution was formed. Talc was added and dispersed uniformly by stirring. The sieved drug coated pellets were loaded in a Wurster coating unit. The seal coating dispersion was sprayed over the drug coated pellets followed by a period of drying to remove the residual solvent and water in the pellets. The resulting seal coated pellets were sieved to retain the fraction between screens #18 and #24.

The ER coating solution was prepared by dissolving ethyl cellulose (viscosity 7 cps) in isopropyl alcohol and purified water and stirring until a clear solution was formed. Povidone K-90 was then dissolved in this clear solution followed by addition of plasticizer Miglyol 812N with continuous stirring to form a clear solution. The sieved seal coated pellets were loaded in a Wurster coating unit. The ER coating solution was sprayed over the seal coated pellets followed by a period of drying to affect the ER coat and remove the residual solvent and water in the pellets. After drying, magnesium stearate was spread on the top bed of the coated pellets in the annulus region followed by recirculation of the pellets in the Wurster unit to blend the magnesium stearate with the coated pellets. The resulting ER coated pellets were sieved to retain the fraction between screens #18 and #24.

The desired weight of the ER coated pellets containing the unit dose were filled into empty 1 hard gelatin capsule shell (size 1 for 100-140 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 1

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Pellet Core		
Amantadine Hydrochloride USP	Active	40-50%
Microcrystalline cellulose spheres (Celphere ®)	Core seeds	10-15%
Hydroxypropyl methyl cellulose 5 cps USP	Binder	10-15%
Copovidone	Binder	1-5%
Talc USP	Anti-tack	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Seal Coating (optional)		
Hydroxypropyl methyl cellulose 3 cps USP	Coating polymer	5-10%
Talc USP	Anti-tack	0-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Extended Release Coating		
Ethyl cellulose	Coating polymer	10-20%
Povidone	Pore former	1-5%
Medium chain triglycerides	Plasticizer	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Magnesium Stearate NF	Lubricant	0-1%
Density of pellets		0.6-0.9 gm/cm^3

NF = National Formulary

[1]Purified water and isopropyl alcohol are removed during processing.

The in vitro dissolution of capsules prepared above was tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. Capsules meeting desired dissolution specifications released not more than 25% of the drug in 2 hours, 40-80% in 6 hours, and at least 80% at 12 hours. In an exemplary dissolution profile, there was 0% drug release at 1 hour, 12% release at 2 hours, 43% release at 4 hours, 68% release at 6 hours, 83% release at 8 hours, 92% release at 10 hours, and 97% release at 12 hours. Capsules prepared in accordance with the above method exhibited good shelf-stability, and batch-to-batch reproducibility upon scale-up.

EXAMPLE 2

Amantadine Extended Release Coated Pellet Formulation with Higher Drug Loading

Amantadine HCl extended release coated pellet compositions designed for nighttime administration are prepared using the components and relative amounts shown in Table 2 below and the manufacturing process described in example 1.

The diameter of the inert cores is 200-300 microns. The diameter of the coated pellets is 600-1200 microns. The bulk density of the coated pellets is 0.7-1.2 g/cm^3.

The desired weight of the ER coated pellets containing the unit dose are filled into an empty hard gelatin capsule shell (size 1 for 170 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 2

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Pellet Core		
Amantadine Hydrochloride USP	Active	50-65%
Microcrystalline cellulose spheres (Celphere ®)	Core seeds	1-15%
Hydroxypropyl methyl cellulose USP	Binder	5-25%
Copovidone	Binder	1-5%
Talc USP	Anti-tack	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Seal Coating (optional)		
Hydroxypropyl methyl cellulose USP	Coating polymer	0-10%
Talc USP	Anti-tack	0-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Extended Release Coating		
Ethyl cellulose	Coating polymer	10-20%
Povidone	Pore former	1-5%
Medium chain triglycerides	Plasticizer	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Magnesium Stearate NF	Lubricant	0-1%

NF = National Formulary

[1]Purified water and isopropyl alcohol are removed during processing.

The in vitro dissolution of capsules prepared above are tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium and release not more than 25% of the drug in 2 hours, 40-80% in 6 hours, and at least 80% at 12 hours.

EXAMPLE 3

Amantadine Extended Release Coated Pellet Formulations

Amantadine HCl extended release coated pellet compositions suitable for nighttime administration were prepared using the components and relative amounts shown in Table 3 below and the manufacturing process described in Example 1.

The desired weight of the ER coated pellets containing the unit dose was filled into empty #1 hard gelatin capsule shell (100 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 3

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule A	B	C
Pellet Core				
Amantadine Hydrochloride USP	Active	50.15%	47.94%	45.15%
Microcrystalline cellulose spheres (Celphere ®)	Core seeds	14.33%	13.70%	12.90%
Hydroxypropyl methyl cellulose USP	Binder	13.37%	12.79%	12.04%
Copovidone	Binder	3.34%	3.2%	3.01%
Talc USP	Anti-tack	2.51%	2.4%	2.26%
Isopropyl alcohol	Solvent	—[1]	—[1]	—[1]
Water	Solvent	—[1]	—[1]	—[1]

TABLE 3-continued

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule A	B	C
Seal Coating (optional)				
Hydroxypropyl methyl cellulose USP	Coating polymer	7.61%	7.27%	6.85%
Talc USP	Anti-tack	0.76%	0.73%	0.69%
Isopropyl alcohol	Solvent	—[1]	—[1]	—[1]
Water	Solvent	—[1]	—[1]	—[1]
Extended Release Coating				
Ethyl cellulose	Coating polymer	6.23%	9.46%	13.53%
Povidone	Pore former	0.85%	1.29%	1.84%
Medium chain triglycerides	Plasticizer	0.75%	1.13%	1.62%
Isopropyl alcohol	Solvent	—[1]	—[1]	—[1]
Water	Solvent	—[1]	—[1]	—[1]
Magnesium Stearate NF	Lubricant	0.1%	0.1%	0.1%

NF = National Formulary

[1]Purified water and isopropyl alcohol are removed during processing.

The in vitro dissolution of capsules prepared above were tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. The results are shown in FIG. **1**.

EXAMPLE 4

Amantadine Extended Release Formulation made by Extrusion Spheronization

Amantadine HCl extended release compositions designed for nighttime administration are prepared using the components and relative amounts shown in Table 4 below and the manufacturing process described below.

A blend of amantadine HCl, microcrystalline cellulose and lactose monohydrate was prepared and a wet mass is prepared in a high shear granulator using an aqueous solution of povidone. The wet mass is extruded using 1 mm sieve and extruded mass is spheronized using a spheronizer. The pellets are dried in a tray drier to yield core pellets. The core pellets are coated with extended release coating solution in a pan coater. The desired weight of the ER coated pellets containing the unit dose is filled into empty 1 hard gelatin capsule shell (170 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 4

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Pellet Core		
Amantadine Hydrochloride USP	Active	59.40%
Microcrystalline cellulose	Diluent	18.67%
Lactose monohydrate	Diluent	6.15%
Povidone	Binder	0.64%
Water	Solvent	—[1]
Extended Release Coating		
Ethyl cellulose	Coating polymer	12.41%
Polyethylene glycol	Pore former	1.24%

TABLE 4-continued

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Dibutyl sebacate	Plasticizer	1.49%
Ethanol	Solvent	—[1]

The in vitro dissolution of capsules prepared above are tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium and release not more than 25% of the drug in 2 hours, 40-80% in 6 hours, and at least 80% at 12 hours.

EXAMPLE 5

Pharmacokinetic Measurement of Formulations of Amantadine ER Compared to IR Amantadine

Objective: The primary objective of the study was to confirm the PK properties of extended release formulations in example 3, to determine the pharmacokinetic profiles, safety and tolerability of three prototype formulations of ER capsules of amantadine HCl described with different release properties in Example 3 relative to a 100 mg film-coated IR amantadine HCl tablet (SYMMETREL®) given as single doses to healthy adult subjects under fasting conditions.

Study design: This was a Phase 1, randomized, single dose, open-label, four-period, crossover, fasting pharmacokinetic study in which single 100 mg doses of three formulations of Amantadine ER capsules with different release properties were compared to single 100 mg doses of marketed amantadine IR tablets (SYMMETREL®). The three ER formulations differed in the amantadine release rates in vitro, as shown in FIG. **1**.

Methods: Subjects were admitted to the unit for the first period of dosing within 21 days of study screening. Subjects were dosed on the day after checking into the unit and discharged at 24 hours post dose. Subjects were asked to return after discharge for follow-up visits at 56 hours and 152 hours after dosing. Each dosing period was separated by at least 7 day washout.

After an overnight fast, the formulation was administered to the subjects while in a sitting position with 240 mL of water. Blood samples were collected at 0 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 24 (discharge), and 56 hours following each dose. Plasma samples were assayed for amantadine by a validated liquid chromatography/tandem mass spectroscopy (LC/MS/MS) method. Pharmacokinetic parameters were calculated using a non-compartmental analysis with WinNonlin software (version 4.1 or higher; Pharsight Corporation).

An analysis of variance (ANOVA) was performed on the natural logarithms of Cmax and AUCO-∞ determined from the data following a single dose of study drug using linear mixed effects model. The model included effects for subject, sequence, period, and regimen. The effects of sequence, period, and regimen were fixed, while the effect of subject was random. Ratio of ER to IR for both AUC (relative bioavailability for ER formualtions) and Cmax was calculated. (Adverse events were monitored throughout the study. Vital signs (pulse rate, blood pressure and body temperature), clinical laboratory measures (biochemistry, hematology, and urinalysis) and ECGs were collected at various times during the study.

Results: A total of 20 subjects participated in the study. The mean age was 25.5 years old (range 20-38 years). The study consisted of 8 male (40%) and 12 female (60%) subjects with a mean body mass index (BMI) of 23.6 kg/m2±2.85. The racial makeup was 100% Caucasian. Fifteen subjects received all 4 treatments.

The PK results from this study showed that all three of the Amantadine ER formulations reduced the rate of absorption, based on the reduced values of Cmax and increased Tmax, compared to SYMMETREL® (Table 5, FIGS. **5**, **6**). The IR formulation had the highest mean Cmax (277±73.9 ng/mL) and shortest median Tmax (4 h) values. Formulations A, B, and C produced progressively lower Cmax and longer Tmax values. Cmax decreased from 204±61.4 to 166±34.8 to 149±34.4 ng/mL, and median Tmax increased from 7.0, to 11.0, to 14.0 h for formulations A, B, and C, respectively. Total amantadine exposure, as measured by AUCO-∞, was slightly lower in all three Amantadine ER formulations than SYMMETREL® but all three formulations had acceptable bioavailability (85-95%).

TABLE 5

Single Dose Pharmacokinetic Parameters of Three Formulations of Amantadine ER (Formulation A, B, and C), as Compared to SYMMETREL ® (Formulation IR)

Parameter[a]	100 mg Formulation A (n = 19)	100 mg Formulation B (n = 17)	100 mg Formulation C (n = 18)	100 mg Formulation IR (n = 18)
C_{max} (ng/mL)	204 ± 61	166 ± 35	149 ± 34	277 ± 74
T_{max} (h) [range]	7 [5-11]	11 [5-15]	14 [9-18]	4 [2-6]
$A_{UC0\text{-}last}$ (ng*h/mL)	5064 ± 1573	5028 ± 2328	4525 ± 1268	5488 ± 1730
$AUC_{0\text{-}\infty}$ (ng*h/mL)	5545 ± 1904	5724 ± 2369	5652 ± 2581	5907 ± 1907
$t_{1/2}$ (h)	13.9 ± 3.0	16.3 ± 5.2	18.3 ± 7.5	12.3 ± 3.5

[a]All parameters are reported as the mean ± standard deviation (SD), except t_{max} which is reported as a median value (min to max range)

TABLE 6

Ratio ER/IR for C_{max} and $AUC_{0\text{-}\infty}$

Comparison	Variable	ER/IR[a]
A vs. IR	C_{max} (ng/mL)	66.0%
	$AUC_{0\text{-}\infty}$ (ng*h/mL)	85.3%
B vs. IR	C_{max} (ng/mL)	60.9%
	$AUC_{0\text{-}\infty}$ (ng*h/mL)	94.6%
C vs. IR	C_{max} (ng/mL)	51.2%
	$AUC_{0\text{-}\infty}$ (ng*h/mL)	88.5%

[a]Point estimate of the geometric mean ratio (ER/IR).

EXAMPLE 6

Food-Effect Evaluation of Amantadine ER

Objective:

The primary objective was to demonstrate that the amantadine ER formulations suitable for nighttime administration exhibit excellent bioavailability when administered with food. We determined the pharmacokinetics of a 100 mg capsule of an amantadine ER formulation (Example 3, Formulation B), when administered both with a high fat meal and in a fasted state.

Study Design:

This was a Phase 1, randomized, single dose, open-label, two-period, crossover, food-effect study to compare single 100 mg doses of Formulation I in healthy adult (18 to 45 years of age) male and female subjects in fed and fasted states. The study consisted of a 21-day to −2 day screening phase (prior to the scheduled dosing day) and two treatment periods, Period 1 and Period 2, with an 8-day wash-out period between treatment periods.

Methods:

After an overnight fast, the formulation was administered to the subjects while in a sitting position with 240 mL of water at ambient temperature for the fasted condition. For the fed condition, after the overnight fast, subjects were served a high fat and high calorie test meal (Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies, December 2002) as breakfast, which they were required to consume completely within 30 minutes before taking the study medication. Subjects were randomized to one of two sequences, each composed of treatment administration under fed and fasted conditions separated by an eight day wash out period.

For each period, pharmacokinetic blood samples were collected at pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 24, 28, 48, 72, 96 and 144 hours after dosing in each period. Subjects were housed in the clinical facility at least 15 hours before investigational product administration and remained in the clinical facility for at least 28 hours after administration of the investigational product in each period. Samples after 28 hours in each period were collected on an ambulatory basis. Amantadine in plasma was quantified by a validated LC/MS/MS method. The pharmacokinetic parameters were calculated from the drug concentration-time profile by non-compartmental model using WinNonlin Professional Software-Version 5.0.1 (Pharsight Corporation, USA) for amantadine. Absence of food effect was defined as met if the point estimates and 90% confidence intervals (CI) for the ln-transformed C_{max}, AUC_{last} and AUG_{∞} fed/fasting ratios of the population means were entirely within the standard accepted range of 80% to 125%. All statistical analyses for amantadine were performed using PROC MIXED of SAS® Release 9.1.3 (SAS Institute Inc., USA).

Routine safety monitoring was conducted during and after dosing in all subjects.

Results:

A total of 26 subjects participated in the study, 19 (73%) male and 7 (27%) female. The mean age was 26 years (range 19-44) and the mean BMI was 22.4 kg/m^2 (range 18.1-29.8). The racial makeup was 100% Asian. All subjects received at least one dose of study drug and were included in the safety analysis. Twenty-four (92.3%) subjects completed the study and were included in the pharmacokinetic analysis. Two subjects (7.7%) were withdrawn prior to completion of the study due protocol deviations.

The results of this study (Table 7) indicate that the single dose pharmacokinetics of Formulation B are not affected by food. The rate, as measured by C_{max}, and the extent, as measured by $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$, of absorption of amantadine, administered with and without food, were equivalent (Table 8).

TABLE 7

Mean ± SD Pharmacokinetic Parameters after Single Dose Administration of 100 mg of Formulation B in Fed and Fasted States

	Mean ± SD (Un-transformed data) n = 24	
Parameters (Units)[a]	Fasted State	Fed State
T_{max} (h)	11.9 ± 2.1 (8-15)	9.5 ± 2.4 (5-16)
C_{max} (ng/mL)	198.8 ± 34.7	219.4 ± 41.5
$AUC_{0\text{-}last}$ (ng*h/mL)	5571.2 ± 1654.2	5394.4 ± 1581.5
$AUC_{0\text{-}\infty}$ (ng*h/mL)	5663.1 ± 1677.4	5476.6 ± 1590.7
$t_{1/2}$ (h)	11.9 ± 2.8	11.5 ± 2.0
t_{lag} (h)	1.0	2.0

[a]All parameters are reported as the mean ± standard deviation (SD). t_{max} is reported as the mean ± SD (min to max range).

TABLE 8

Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Formulation B (n = 24) in Fed and Fasted States

	ln-transformed data Geometric Least Squares Mean			90% Confidence
Parameters (Units)	Fed State	Fasted State	Ratio (Fed/Fasted)%	Interval (Parametric)
C_{max} (ng/mL)	215.6	195.8	110.1	104.4-116.2%
$AUC_{0\text{-}last}$ (ng*h/mL)	5195.9	5344.2	97.2	91.0-103.8%
$AUC_{0\text{-}\infty}$ (ng*h/mL)	5280.3	5434.7	97.2	90.9-103.8%

Conclusion:

The results of this study indicate that the single dose pharmacokinetics of amantadine ER are not affected by food. The rate, as measured by C_{max}, and the extent, as measured by $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$, of absorption of amantadine, administered with and without food, were equivalent.

EXAMPLE 7

Pharmacokinetic Study Comparing Once-Daily Administration of Amantadine HCl ER Capsules with Twice-Daily Administration of Amantadine HCl IR Tablets in Healthy Adults Under Fasting Conditions

Objective:

The primary objective of this study was to measure at steady state under repeat or chronic dosing the pharmacokinetics of an ER amantadine formulation suitable for nighttime administration, and enable the calculation of critical PK parameters for future safety and efficacy studies (i.e., Cave-morning, Cave-day, Cave-night) of ER amantadine formulations administered at night. We compared the single dose and repeat dose pharmacokinetics of amantadine HCl administered twice daily as a commercially available immediate release (IR) formulation to a once daily amantadine extended release (ER) formulation (Example 3, Formulation B).

Study Design:

This was a two period, multiple dose, crossover study. After a 21 day screening period, 26 healthy male and female subjects were randomized to receive one of two treatments (amantadine ER 200 mg once daily or amantadine IR 100 mg twice daily) in Period-I, then crossed over to receive the other treatment in Period-II.

Methods:

Study drug administration started on day 1. Study drug was not administered on Day 2. Multiple dosing commenced on day 3 and continued for 7 days (through day 9). A washout period of 8 days separated the dose administrations. The study drug was administered with 240 mL of drinking water. No other fluids were allowed within 1 hour of dosing. For each period, pharmacokinetic blood samples were collected at pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 24, 28, 36, and 48 hours after the first dose. The morning trough (pre-dose) blood samples were collected on Days 7 and 8. Blood samples were again collected immediately before the morning dose on Day 9 and at 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 24, 28, 48, 72, and 96 hours thereafter. Samples after 28 hours following the morning dose on day 9 were collected on an ambulatory basis in each period. Amantadine in plasma was quantified by a validated LC/MS/MS method. The pharmacokinetic parameters were calculated from the drug concentration-time profile by non-compartmental model using WinNonlin Professional Software-Version 5.0.1 (Pharsight Corporation, USA) for amantadine.

Statistical analyses were conducted to assess the pharmacokinetic profile of single dose and repeat dose amantadine HCl administered twice daily as a commercially available immediate release (IR) formulation compared to a once daily extended release (ER) formulation (Formulation B). An analysis of variance (ANOVA) was performed on the natural logarithms of C_{max}, C_{min}, and AUC_{24} determined from the data following the dose of study drug on study day 9 using linear mixed effects model. The model included the fixed effects for sequence, period, regimen and a random subject effect. The confidence intervals were used to perform the 2 one-sided tests procedure for equivalence assessment. The confidence intervals were obtained by exponentiating the endpoints of the confidence intervals for the difference of mean logarithms obtained within the framework of the ANOVA model. The upper and lower limits of confidence intervals from the natural-log transformed data were back-exponentiated to obtain the 90% confidence interval for the ratio of geometric means. Equivalence was established if the exponentiated 90% confidence interval fell entirely within the interval (80.00%, 125.00%).

Repeated measures ANOVA was carried out for comparison of C_{min} for day 7, 8 and 9 at 5% level of significance on both untransformed and ln-transformed data. Steady state was demonstrated if the repeated measures ANOVA test was found to be non-significant. The statistical analysis for amantadine was performed using PROC MIXED of SAS® Release 9.1.3 (SAS Institute Inc., USA).

Routine safety monitoring was conducted during and after dosing in all subjects, and at the end of the study.

Results:

A total of 26 subjects participated in the study, 22 (84.6%) male and 4 (15.4%) female. The mean age was 26 years (range 19-42) and the mean BMI was 22.9 kg/m^2 (range 18.1-28.8). The racial makeup was 100% Asian. All subjects received at least one dose of study drug and were included in the safety analysis. Twenty-four (92.3%) subjects completed the study and were included in the pharmacokinetic analysis. Two subjects (7.7%) were withdrawn from the PK analysis prior to completion of the study due to vomiting within 12 hours of dosing, which was a pharmacokinetic exclusion criterion.

As expected from its half-life, once daily administration of amantadine ER and twice daily dosing of amantadine IR resulted in accumulation as measured by higher C_{max} and AUC on Day 9 compared to Day 1 (Table 9 and FIG. **2**). Steady state was achieved by Day 9 for both formulations as demonstrated by similar trough levels on Days 7, 8 and 9 (data not shown). At steady state (Day 9) plasma concentrations (FIG. **2**, Table 9) and pharmacokinetic parameters (Table 9) were comparable for both formulations. Furthermore, the formulations are equivalent in terms of the extent and the rate of absorption of amantadine as measured by steady state C_{max}, C_{min} and AUC_{0-24} (Table 9), where equivalency is defined by the 90% CIs of the ratio of the least square means of the test versus reference for steady state C_{max}, C_{min} and AUC_{0-24} of Amantadine ER to Amantadine IR falling within 80%-125%.

TABLE 9

Mean (±SD) Pharmacokinetic Parameters of Amantadine after Single and Multiple Dose Administration of IR (100 mg BID) and ER (200 mg QD) Formulations

	Formulation			
	IR (n = 24)		ER (n = 24)	
Parameter (Units)[a]	Day 1	Day 9	Day 1	Day 9
$t_{1/2}$ (h)	13.2 ± 2.8 [9.1-18.8]	12.6 ± 2.4 [9.4-18.1]	13.7 ± 3.6 [9.1-22.7]	12.8 ± 2.2 [9.2-17.4]
t_{max} (h)	14.42 ± 0.88 [13-16]	12.6 ± 4.5 [1-15]	11.4 ± 1.9 [8-18]	10.3 ± 2.0 [8-18]
C_{max} (ng/mL)	530 ± 80 [407.5-752.7]	728 ± 153 [538.4-1101.8]	431 ± 84 [313.5-559.9]	665 ± 179 [444.4-1140.0]
AUC_{0-last} (ng h/mL)	11989 ± 2224 [9243-17106]	23040 ± 8273 [13133-46446]	11171 ± 2773 [7326-16970]	21362 ± 8946 [10821-47134]
$AUC_{0-\infty}$ (ng h/mL)	13685 ± 3324 [10167-20989]	NA	12900 ± 4087 [7817-22153]	NA
AUC_{0-24} (ng h/mL)	7695 ± 1026 [5967-10171]	13752 ± 3586 [9085-22519]	7173 ± 1367 [5021-9552]	12680 ± 3879 [7896-23058]

TABLE 9-continued

Mean (±SD) Pharmacokinetic Parameters of Amantadine after Single and Multiple Dose Administration of IR (100 mg BID) and ER (200 mg QD) Formulations

	Formulation			
	IR (n = 24)		ER (n = 24)	
Parameter (Units)[a]	Day 1	Day 9	Day 1	Day 9
C_{min} (ng/mL)	—	412.4 ± 142.6 [218.5-795.2]	—	374.9 ± 151.7 [172.2-767.1]

[a]All parameters are reported as the mean ± SD, [min to max range]
NA = not applicable

Certain additional PK parameters that are important in determining the suitability of the ER amantadine formulation for once daily, night time administration are also reported in Table 10.

TABLE 10

Additional Steady State PK parameters of Amantadine ER

	ER 200 mg QD	IR 100 mg BID
Cmax/Cmin	1.86	1.68
C-ave-8-16 hrs(ng/ml)	614	586
C-ave-8-12 hrs (ng/ml)	643	510
C-ave-16-24 hrs (ng/ml)	502	569
C-ave-0-8 hrs (ng/ml)	465	586
C-ave-8-16 hrs/C-ave-0-8 hrs	1.32	1.00
C-ave-8-12 hrs/C-ave-0-8 hrs	1.38	0.87
% Change in Plasma Concentration 0-3 hrs	5%	55%
% Change in Plasma Concentration 0-4 hrs	23%	48%
AUC 0-4 as % of AUC 24	12%	N/A
AUC 0-8 as % of AUC 24	30%	N/A
AUC 0-12 as % of AUC 24	51%	N/A

Conclusion:

The ER amantadine formulation exhibits the desired steady state PK properties that would make the same suitable for administration at night and for achieving desired efficacy and tolerability benefits. Specifically, the ER amantadine formulation administered once daily at night results in relatively slow initial rise in amantadine plasma concentration, higher average amantadine plasma concentrations 8 to 12 hours after administration relative to 0-8 hours after administration and thus if administered at night higher ratios of average day time to night time amantadine plasma concentrations relative to IR amantadine. Thus this formulation is well suited for administration at higher doses than current practice that are expected to be relatively well tolerated and potentially provide superior efficacy in the treatment of LID, fatigue and Parkinson's disease.

EXAMPLE 8

Study Comparing Administration of Amantadine HCl ER Capsules Once Nightly with Twice-Daily Administration of Amantadine HCl IR Tablets in Normal Healthy Volunteers

Objective: The primary objective is to compare the effects on sleep of amantadine extended release (ER) capsules (Formulation B) administered once daily at bedtime with amantadine immediate release (IR) tablets administered twice daily in normal healthy volunteers. This ER formulation exhibits a Cave,day/Cave, night=1.30.

Study Design:

This is a single-center, double-blind, triple-dummy, randomized, crossover study to compare the effects on sleep of amantadine ER capsules, QHS, amantadine IR tablets BID, and caffeine caplets (active comparator) in 30 normal healthy volunteers as assessed by overnight polysomnography (PSG) and standardized questionnaires (Stanford Sleepiness Scale (SSS); Modified Epworth Sleepiness Scale (m-ESS)/Karolinska Sleepiness Scale (KSS); Toronto Hospital Alertness Test (THAT)/ZOGIM Alertness Scale (ZOGIM-A); Visual analog scale of sleepiness/alertness (VAS)).

Study drugs are administered in 3 dosing periods. A single day's dosage of one drug is administered per dosing period. Each day of dosing is separated by a washout period of 1 week. A single day's dosage of amantadine ER (Formulation B) consists of one 220 mg capsule (or 2×110 mg capsule) administered at bed time (QHS; defined as 23:00 h for the purposes of this study). A single day's dosage of amantadine IR consists of one 100 mg capsule administered twice a day (BID; defined as 8:00 h and 16:00 h for the purposes of this study). A single day's dosage of caffeine consists of one 100 mg capsule administered three times a day (TID; defined as 8:00 h, 16:00 h, & 23:00 h for the purposes of this study).

All subjects are dosed three times a day, at 8:00 h, 16:00 h, & 23:00 h. At each hour of dosing, every subject receives either the active drug or the matching placebo for each of the 3 treatments. Whether the capsule, tablet, or caplet administered at a specific hour of dosing contains active study drug or is a placebo dummy is determined according to the dosing sequence and period to which the subject is assigned.

Consented subjects who meet eligibility criteria are randomized equally to one of 3 treatment sequences (groups), each comprising 3 single-day treatment periods separated by 1 week washout periods as described above. Additionally, there is a one-day, single-blind, placebo run-in prior to each double-blind dosing day. This is to allow subjects to acclimate to sleeping in the Clinical Research Unit (CRU) under conditions of PSG recording and to establish individual baseline (BL) PSG characteristics.

For each dosing period, subjects are admitted to a CRU equipped with a sleep laboratory the day before the first day of dosing with active study drug. They stay in the CRU overnight and through the entirety of the active drug-dosing day. They again stay overnight and then are discharged from the CRU the morning of the following day. For the first dosing period, the day of admission to the CRU (Day −1) constitutes the last day of the screening phase, and the day of discharge from the CRU constitutes the first day of the first washout period (Day 2). For the second dosing period, the day of re-admission to the CRU (Day 7) constitutes the last day of the first washout period, and the day of discharge (Day 9) will constitute the first day of the second washout period. For the third dosing

period, the day of re-admission to the CRU (Day 14) constitutes the last day of the second washout period, and the day of discharge (Day 16) constitutes the first day of the follow-up phase.

On the day of admission (or re-admission) to the CRU, subjects undergo routine laboratory and vital sign testing. They are administered one each of the placebo dummies (for amantadine ER, amantadine IR, & caffeine) at 16:00 h and at 23:00 h in single-blind fashion. They are questioned for adverse events (AEs) and have vital signs checked immediately prior to each dosing. Blood is drawn for routine laboratory testing and toxicology screen prior to the 16:00 h dosing. Subjects spend the night in the sleep lab under conditions of PSG recording.

On the day of dosing with active study drug, subjects are awakened at 7:00 h and fill out a battery of sleep and alertness questionnaires. They receive study drug (active or placebo) at 8:00 h, 16:00, and 23:00 h. They are questioned for AEs and have vital signs checked immediately prior to each dosing. Blood is drawn to measure plasma amantadine concentrations prior to the 23:00 h dosing.

On the day after dosing with active study drug, subjects are awakened at 7:00 h and fill out a battery of sleep and alertness questionnaires. Shortly before 8:00 h, i.e., 9 hours after the last dosing time, they are questioned for AEs and have vital signs checked. Also, blood is drawn to measure plasma amantadine concentrations. Instructions for contacting the site to report any AEs are reviewed with the subjects prior to their discharge from the CRU. The schedule for returning to the PSU for the next dosing period (this applies to returning for Periods 2 & 3) or for telephone contact (this applies to the follow-up after the third dosing period) is be reviewed.

All subjects receive a follow-up telephone call 3 days following discharge from the CRU (Day 19).

AEs and concomitant medications are monitored throughout the study. Blood samples for measurement of blood plasma concentrations are drawn immediately prior to the 23:00 h dosing time on Days 1, 8, and 15, and at approximately 8:00 h on Days 2, 9, and 16.

Sleep parameters and measurements of sleepiness and alertness at each time point are listed by subject. Both composite scores and scores from the individual components of the PSG and questionnaires are tabulated and analyzed. For each parameter measured, descriptive summary statistics are calculated by sequence and treatment, including means (or medians, as appropriate), ranges, and standard deviations (SDs).

Inferential statistics are performed on selected results wherein the magnitude of the differences between the means across treatment groups relative to the variance suggests a possible differential treatment effect. Continuous variable data is analyzed by parametric statistics (repeated measures analysis of variance with appropriate supplemental post-hoc analyses and/or paired t-test). Categorical data and data not conforming to a normal distribution is analyzed by non-parametric statistics (Wilcoxon signed rank test). PSG data may also be assessed by multivariate analyses and/or spectral analyses.

Results:

A lack of increase in, or reduction of, sleep disturbances with QD administration of 220 mg of amantadine ER compared to BID administration of amantadine IR, as measured by PSG and a standardized sleep questionnaire (e.g. SSS, m-ESS, KSS, THAT, ZOGIM-A, or VAS), demonstrates the suitability of amantadine ER for once daily administration at bedtime

EXAMPLE 9

Study Comparing the Effects on Sleep and Efficacy of Amantadine HCl ER Capsules Administered Once Daily at Night Relative to Amantadine HCl IR Capsules Administered Twice Daily in Parkinson's Patients

Objective:

To compare the effects on sleep and efficacy of amantadine extended release (ER) capsules.

Study Design:

This is a Multi-Center, Double-Blind, Randomized Study to Compare the Effects on Sleep and Efficacy of Amantadine Extended Release (ER) Capsules in 120 Parkinsons Patients as assessed by UPDRS (Unified Parkinson's Disease Rating Scale), UPDRS-IV (Unified Parkinson's Disease Rating Scale Part IV), AIMS (Abnormal Involuntary Movement Scale), overnight polysomnography (PSG) and standardized questionnaires (Stanford Sleepiness Scale (SSS); Modified Epworth Sleepiness Scale (m-ESS)/Karolinska Sleepiness Scale (KSS); Toronto Hospital Alertness Test (THAT)/ ZOGIM Alertness Scale (ZOGIM-A); Visual analog scale of sleepiness/alertness (VAS)).

All study drugs are administered orally. Treatment A consists of a placebo capsule administered in the morning and two 110 mg capsules of Amantadine (ER) and a placebo capsule administered at bed time. Treatment B consists of a placebo capsule administered in the morning and three 110 mg capsules of Amantadine (ER) administered at bed time. Treatment C consists of a 100 mg capsule of Amantadine IR administered in the morning and a 100 mg capsule of Amantadine IR and two placebo capsules administered at bed time. Treatment D consists of a placebo capsule administered in the morning and 3 placebo capsules administered at bed time.

Consented subjects who meet eligibility criteria are randomized equally to one of 3 treatment groups, each comprising 14-day treatment periods. Additionally, there is a one-day, single-blind, placebo run-in prior to each double-blind dosing day. This is to allow subjects to acclimate to sleeping in the Clinical Research Unit (CRU) under conditions of PSG recording and to establish individual baseline (BL) PSG characteristics.

For each dosing period, subjects are admitted to a CRU equipped with a sleep laboratory the day before the first day of dosing with active study drug. They stay in the CRU overnight and through the entirety of the active drug-dosing day. They again stay overnight and then are discharged from the CRU the morning of the following day.

Parkinson's scores are recorded in the mornings on days 1, 7 and 14 using standard scoring methods, including the UPDRS and AIM.

AEs and concomitant medications are monitored throughout the study.

Sleep parameters and measurements of sleepiness and alertness at each time point are listed by subject. Both composite scores and scores from the individual components of the PSG and questionnaires are tabulated and analyzed. For each parameter measured, descriptive summary statistics are calculated by sequence and treatment, including means (or medians, as appropriate), ranges, and standard deviations (SDs).

Inferential statistics are performed on selected results wherein the magnitude of the differences between the means across treatment groups relative to the variance suggests a possible differential treatment effect. Continuous variable data is analyzed by parametric statistics (repeated measures

analysis of variance with appropriate supplemental post-hoc analyses and/or paired t-test). Categorical data and data not conforming to a normal distribution is analyzed by non-parametric statistics (Wilcoxon signed rank test). PSG data may also be assessed by multivariate analyses and/or spectral analyses.

Results:

An improvement in UPDRS, UPDRS-IV, AIM, lack of increase in, or reduction of, sleep disturbances, as measured by PSG and a standardized sleep questionnaire (e.g. SSS, m-ESS, KSS, THAT, ZOGIM-A, or VAS), demonstrates the suitability of amantadine ER for once daily administration at bedtime.

EXAMPLE 10

Simulated Pharmacokinetic Characteristics of Higher Strength, Amantadine ER Formulations Administered at Nighttime

Objective:

The objective is to use the data generated in the clinical study described in Example 7 to predict steady state plasma concentration-time profiles of various IR and ER amantadine regimens at different dose levels to show the benefits of higher strength amantadine ER formulations administered at nighttime.

Methodology:

Plasma concentration-time profiles from healthy volunteers that received multiple doses of the ER and IR formulations of amantadine per study procedures described in Example 7 (ADS-5101-MD-104) were used to develop a pharmacokinetic model describing each of the two formulations. This study was an open-label, randomized, two-treatment, two-period, two-way crossover study comparing once-daily amantadine ER capsules and twice-daily amantadine IR tablets in 26 healthy, adult male and female volunteers. Complete data from 24 individuals were used in this exercise. Blood samples for pharmacokinetic evaluation were collected after single dosing on Day 1 and at steady state on Day 9. In the first step of the analysis, WinNonlin 5.2.1 (Pharsight Corp., Mountain View, Calif.) was used to fit a one-compartment model with first-order input and first-order output, weighted 1/y (where y is the amantadine plasma concentration), to each individual's plasma concentration-time data obtained after single (Day 1) and repeated (Day 9) dose administration of amantadine IR and ER; the fitting was done separately for both formulations, but simultaneously for both days. Modeling assumptions employed include dose proportionality and constant clearance as a function of time.

The model is described by the following equation:

$$C = \frac{FD}{V(k_a - k)}[\exp(-k(t - t_{lag})) - \exp(-k_a(t - t_{lag}))] \quad \text{Equation 1}$$

where C is the plasma concentration, F is the absolute bioavailability, D is dose, V is the volume of distribution, k_a is the absorption rate constant, k is the elimination rate constant, t is time, and t_{lag} is the lag time of absorption. The goodness of fit was verified by comparing the individual model predicted and observed concentration-time data from Study ADS-5101-MD-104. After Equation 1 was fitted to each individual's plasma concentration-time data, model parameter estimates of V/F, k_a, k, and t_{lag} were obtained for each of the 24 subjects. The goodness of the prediction at steady state was confirmed by comparing the observed data and predicted steady-state concentrations of amantadine obtained after daily dosing of 200 mg as the ER and IR formulations (Day 9).

In the second step of the analysis, individual model parameter estimates were used to simulate steady-state concentration-time profiles for each individual for both formulations by reinserting the individual parameter estimates into Equation 1, and summing the contribution of 7 sequential days of dosing, according to the following dosing regimens:

1. Once Daily (QD) dosing of 260, 340, and 420 mg of the ER formulation to steady state
2. Three times daily (TID) dosing of 100 mg of the IR formulation to steady state
3. Twice daily (BID) dosing of 100 mg of the IR formulation to steady state

Results:

FIG. **4** shows the simulated steady state plasma concentration time profiles for various ER amantadine doses along with various regimes of IR amantadine. Table 11 summarizes values of the pharmacokinetic parameters that affect the efficacy and tolerability of ER amantadine when administered at night.

TABLE 11

PK parameters associated with nighttime administration - morning peak benefit measured for ER Amantadine formulation

	IR 100 mg BID	IR 100 mg TID	ER 260 mg QD	ER 340 mg QD	ER 420 mg QD
Cmax (ng/ml)	669	936	834	1091	1348
Cmin (ng/ml)	435	731	461	603	745
Cmax/Cmin	1.54	1.28	1.81	1.81	1.81
C-ave-day (6 am-4 pm) (ng/ml)	571	845	766	1002	1238
C-ave-morn (6 am-10 am) (ng/ml)	479	870	824	1078	1332
C-ave-even (4 pm-10 pm) (ng/ml)	522	852	591	773	955
C-ave-night (10 pm-6 am) (ng/ml)	596	843	616	805	995
C-ave-day/C-ave-night	0.96	1.00	1.24	1.24	1.24
C-ave-morn/C-ave-night	0.80	1.03	1.34	1.34	1.34
C-ave-day relative to 100 mg BID IR	1.00	1.48	1.34	1.76	2.17

As shown in Table 11 and in the figures, the ER amantadine formulations administered once daily at night result in higher ratios of average day time to night time amantadine plasma concentrations relative to IR amantadine and are predicted to be relatively well tolerated. The ER formulations also result in average day time amantadine plasma concentrations that are 1.3 to 2.2 fold that of IR amantadine administered at 100mg twice daily and is predicted to result in significantly enhanced efficacy when administered to patients in the clinical study described in Example 11 below.

EXAMPLE 11

A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Amantadine Extended Release Oral Capsules for the Treatment of Levodopa-Induced Dyskinesia in Parkinson's Disease

Study Objectives:

This study is designed to confirm dose range of Amantadine Extended Release (ER) oral capsules dosed once daily at nighttime for the treatment of levodopa-induced dyskinesia

(LID) in subjects with Parkinson's Disease (PD). In addition, the study is designed to demonstrate the safety and tolerability of Amantadine ER oral capsules dosed once daily for the treatment of LID in subjects with PD. Finally, to confirm the steady-state pharmacokinetics of the Amantadine ER dosing regimens in Parkinsons patients and to correlate C-ave-day, Cave-morning, C-ave-morning/C-ave-night and C-ave-day/C-ave-night with the efficacy and tolerability of amantadine.

Study Design:

This will be a multi-center, randomized, double-blind, placebo-controlled, 4-arm parallel group study of Amantadine ER in subjects with PD and LID/Consenting subjects who meet eligibility criteria will be randomized 1:1:1:1 to receive one of the following 4 treatments, each administered as once daily, dosed at night, for 8 weeks:

Treatment A: Placebo,

Treatment B: 260 mg Amantadine ER (ADS-5102),

Treatment C: 340 mg Amantadine ER (ADS-5102)

Treatment D: 420 mg Amantadine ER (ADS-5102)

Subjects who are randomized to Treatment C or D (higher dose amantadine groups) will receive, in double-blind fashion, 260 mg Amantadine ER once daily during week 1, with an increase to either 340 mg or 420 mg once daily at the beginning of week 2. Dosing will continue through week 8.

Following completion of the baseline visit and randomization, subjects will return to the clinic after 1, 2, 4, 6, and 8 weeks of dosing, with a follow-up visit 14 days following the last dose of study drug. Study visits and assessments will be scheduled during morning hours when possible (9 am through 1 pm). A set of two 24-hour diaries will be completed during 48 hours prior to randomization and 48 hours prior to selected study visits. The diary will be used to score five different conditions in 30-minute intervals: Sleep, OFF, ON without dyskinesias, ON with nontroublesome dyskinesias, ON with troublesome dyskinesias.

Blood samples will be collected at selected study visits for determination of amantadine plasma concentrations, and evaluation of steady-state population pharmacokinetics. Subject participation during the study will be up to 12 weeks and will include a 2-week (maximum) screening period, 8-week (maximum) treatment period, and a 2-week follow-up period. Subjects who are unable to tolerate their assigned study drug assignment will permanently discontinue study drug and continue to be followed for safety through 2 weeks following the last dose of study drug.

Patient Eligibility Criteria:

Subjects are eligible to take part in the study if they meet the inclusion and do not meet the exclusion criteria. Selected key criteria are as follows:

Inclusion Criteria:

- Male or female adults, residing in the community (i.e. not residing in an institution)
- Between 30 and 75 years of age, inclusive
- Ambulatory or ambulatory-aided (e.g. walker or cane) ability, such that the subject can come to required study visits
- Knowledgeable and reliable caregiver/study partner, if appropriate, to accompany the subject to study visits
- Signed a current IRB/IEC-approved informed consent form
- Following training, the subject is willing and able to understand and complete the 24-hour home diary (caregiver assistance allowed)
- Idiopathic Parkinson's Disease, complicated by dyskinesia (a MDS-UPDRS score will be determined during screening, but a minimum score is not required)
- On a stable regimen of antiparkinson's medications, including levodopa, for at least 30 days prior to screening, and willing to continue that regimen during study participation
- Presence of dyskinesia, defined as a minimum UDysRS score

Exclusion Criteria:

- Presence of other neurological disease that may affect cognition, including, but not limited to Alzheimer's dementia, Huntington's disease, Lewy body dementia, frontotemporal dementia, corticobasal degeneration, or motor or sensory dysfunction secondary to stroke or brain trauma.
- Presence of cognitive impairment, as evidenced by a Mini-mental State Examination (MMSE) score of less than 24 during screening.
- Presence of an acute major psychiatric disorder (e.g., Major Depressive Disorder) according to DSM-IV-TR or symptom (e.g., hallucinations, agitation, paranoia) that could affect the subject's ability to complete study assessments
- Presence of sensory impairments (e.g., hearing, vision) that would impair the subject's ability to complete study assessments
- History of alcohol or drug dependence or abuse, according to DSM-IV criteria, within 2 years prior to screening
- History of seizures (excluding febrile seizures of childhood)
- History of stroke or TIA within 2 years prior to screening
- History of myocardial infarction, NYHA Congestive Heart Failure Class 3 or 4, or atrial fibrillation within 2 years prior to screening
- History of cancer within 5 years prior to screening, with the following exceptions: adequately treated non-melanomatous skin cancers, localized bladder cancer, non-metastatic prostate cancer or in situ cervical cancer (these exceptions must be discussed with and approved by the Medical Monitor before study entry)
- Any of the following lab abnormalities; Hemoglobin<10 g/dL, WBC<3.0×10^9/L, Neutrophils<1.5×10^9/L, Lymphocytes<0.5×10^9/L, Platelets<100×10^9/L, Hemoglobin A1C>9%, or Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT)>2 times the upper limit of normal
- Estimated GFR<50 mL/min/1.73 m^2 by Modification of Diet in Renal Disease (MDRD) or Cockcroft-Gault equation
- Any clinically significant ECG abnormalities
- Inability to swallow oral capsules, or a history of gastrointestinal malabsorption that would preclude the use of oral medication

Study Endpoints:

The primary efficacy endpoint will be the change from baseline to week 8 in the Unified Dyskinesia Rating Scale (UDysRS) score. Key secondary endpoints will include:

- ON time without troublesome dyskinesia (ON without dyskinesia plus ON with non-troublesome dyskinesia), based on a standardized PD home diary
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), overall score
- Fatigue as measured by the Fatigue Severity Scale (FSS). This scale includes 9 questions that are completed by the patient using a rating scale from 1 (strongly disagree) to 7 (strongly agree). This fatigue scale is recommended by MDS for both screening and severity rating (2010)
- Safety, including adverse events, safety-related study drug discontinuations, vital signs, and laboratory tests.

The following mixture of traditional and new scales have been selected for this phase 2 study:

- Unified Dyskinesia Rating Scale (UDysRS) will be used for primary outcome measure. This scale has four parts, and a total possible score of 104:
  - I: Historical Disability (patient perceptions) of On-Dyskinesia impact
  - II: Historical Disability (patient perceptions) of Off-Dystonia impact
  - III: Objective Impairment (dyskinesia severity, anatomic distribution, and type, based on 4 observed activities)
  - IV: Objective Disability based on Part III activities
- ON time without troublesome dyskinesia, based on a standardized Parkinson's Disease home diary (suggest *Test Diary II,* [33] will be a secondary outcome measure. This scale has been used in number of studies with mixed success [34]. However, most KOLs feel that subject-reported dairy data must be collected, and needs to support the primary outcome measure.
- Unified Parkinson's Disease Rating Scale (UPDRS), part IV, items 32 (duration of dyskinesias: 0=none, 4=76-100% of the waking day) and 33 (disability of dyskinesias: 0=not disabling, 4=completely disabling) will be a secondary outcome measure. This scale is a traditional scale used in PD for many years and these items have been utilized in most LID studies.
- Cognitive Scales: Global caregiver impression, depression and other scales will be employed to measure the mental status benefits of ER amantadine.

Statistical Methods

Efficacy Analyses:

The efficacy analysis population will include all randomized and dosed subjects who provide at least one post-baseline efficacy assessment. For the efficacy endpoint of UDysRS score, the change from baseline to week 8 will be analyzed using an analysis of covariance (ANCOVA) model with treatment group as a factor and the UDysRS baseline value as a covariate. The primary analysis will compare the 260 mg ADS-5102 group to the placebo group using a two-sided test at the 5% level of significance. If the primary comparison is statistically significant ($p<0.05$), then the 340 mg and 420 mg ADS-5102 groups will be compared to placebo, also using a two-sided test at the 5% level of significance.

The secondary endpoints will be analyzed using the same types of ANCOVA models as described for the primary endpoint. All secondary comparisons between treatment groups will be performed using two-sided tests at the 5% level of significance. A last observation carried forward (LOCF) approach will be utilized for missing data. The primary efficacy analysis will be repeated for the per-protocol population, a subset of the efficacy analysis population who provide week 8 efficacy assessments.

Safety Analyses:

The safety analysis population will include all randomized subjects who receive at least one dose of study drug. All safety endpoints will be analyzed from the time of first dose through the completion of follow-up (or 2 weeks following the last dose of study drug). A safety analysis will also be done on the safety reported during the first 2 weeks of study drug treatment, in order to assess tolerability of initial dosing with ADS-5102 amantadine ER.

Results:

following improvements are expected from this study are shown in the table below. Additional endpoints are described that

- Significant (20-60%) reduction in dyskinesia score measured by acceptable primary endpoint (e.g., UDysRS)
- Increase in ON time without troubling dyskinesia by 20-60%
- Improvement in UPDRS from 5% to 20%.
- Improvement in Parkinson's fatigue (FSS) from 5% to 60%.
- Improvement in mood by PGI from 5% to 20%.

Instruments for Dyskinesia	% Clinical Effect (Placebo - Active/Placebo)	Range of Scores
Unified Dyskinesia Rating Scale (UDysRS)	5-60%	0-104 (4 parts, 26 items total, each 0, normal-4, severe)
Unified Parkinson's Disease Rating Scale (UPDRS, MDS revision)	5-20%	
Part IV	5-60%	0-24 (6 items, each 0, normal-4, severe)
Part IV, dyskinesia items only	5-60%	0-8 (2 dyskinesia items, 4.1 and 4.2, each 0, normal-4, severe)
Parkinson's Disease Home Diary (Hauser et al)	5-40%	0-100% (on time without dyskinesia or with nontroublesome dyskinesia)

EXAMPLE 12

Simulated Pharmacokinetic Characteristics of Amantadine ER Formulations with a Delayed Release Coat Suitable for Night Time Administration

Objective:

The objective is to evaluate the pharmacokinetic profile of two alternative ER formulations of amantadine suitable for nighttime administration—Formulation 1, which is the formulation tested in Example 7, and Formulation 2, which is the formulation tested in Example 7, but with a delayed release over coat on top of the extended release coat.

Plasma concentration-time profiles from healthy volunteers, who received multiple doses of the ER and IR formulations of amantadine per study procedures described in Example 7 (ADS-5101-MD-104), were used to develop a pharmacokinetic model describing each of the two formulations. This study was an open-label, randomized, two-treatment, two-period, two-way crossover study comparing once-daily amantadine ER capsules and twice-daily amantadine IR tablets in 26 healthy, adult male and female volunteers. Complete data from 24 individuals were used in this exercise. Blood samples for pharmacokinetic evaluation were collected after single dosing on Day 1 and at steady state on Day 9. In the first step of the analysis, WinNonlin 5.2.1 (Pharsight Corp., Mountain View, Calif.) was used to fit a one-compartment model with first-order input and first-order output, weighted 1/y (where y is the amantadine plasma concentration), to each individual's plasma concentration-time data obtained after single (Day 1) and repeated (Day 9) dose administration of amantadine IR and ER; the fitting was done separately for both formulations, but simultaneously for both days. Modeling assumptions employed include dose proportionality and constant clearance as a function of time.

The model is described by the following equation

$$C = \frac{FD}{V(k_a - k)}[\exp(-k(t - t_{lag})) - \exp(-k_a(t - t_{lag}))] \quad \text{Equation 1}$$

where C is the plasma concentration, F is the absolute bioavailability, D is dose, V is the volume of distribution, k_a is the absorption rate constant, k is the elimination rate constant, t is time, and t_{lag} is the lag time of absorption. The goodness of fit was verified by comparing the individual model predicted and observed concentration-time data from Study ADS-5101-MD-104. After Equation 1 was fitted to each individual's plasma concentration-time data, model parameter estimates of V/F, k_a, k, and t_{lag} were obtained for each of the 24 subjects. The goodness of the prediction at steady state was confirmed by comparing the observed data and predicted steady-state concentrations of amantadine obtained after daily dosing of 200 mg as the ER and IR formulations (Day 9).

In the second step of the analysis, individual model parameter estimates were used to simulate steady-state concentration-time profiles for each individual for both formulations by reinserting the individual parameter estimates into Equation 1, and summing the contribution of 7 sequential days of dosing, according to the following dosing regimens:

1. Once Daily (QD) dosing of 200 mg of the ER Formulation 1 to steady state
2. Once Daily (QD) dosing of 200 mg of the ER Formulation 2 to steady state

Results:

FIG. **7** shows the simulated steady state plasma concentration time profiles for the two ER amantadine formulations. (Amantadine blood plasma concentrations are shown on the y, time of day on the x-axis.) As shown in FIG. **7**, the ER amantadine formulation 2 administered once daily at night results in about a 4 hour delay in achieving peak plasma concentration at steady state relative to formulation 1. Thus, a formulation comprising a delayed release coat on top of the extended release coat has a very favorable pharmacokinetic profile in that it maximizes the daytime plasma exposure to amantadine whilst minimizing night plasma exposure at steady state.

While preferred embodiments of the present invention have been shown and described herein, such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. All references cited herein are incorporated herein by reference in their entirety.

We claim:

1. A method of administering amantadine, or a pharmaceutically acceptable salt thereof, to a human subject in need thereof, said method comprising the steps of:

providing an extended release (ER) composition comprising 220 mg to 445 mg of amantadine, or a pharmaceutically acceptable salt thereof, and at least one release modifying excipient, said composition having a median amantadine Tmax between 8 and 18 hours, as determined by a single dose, fasting human pharmacokinetic study, and

orally administering said composition once daily 0 to 4 hours before bedtime to a human subject.

2. The method of claim **1**, wherein the method comprises reducing sleep disturbance in a human subject undergoing treatment with amantadine.

3. The method of claim **1**, wherein the method comprises treating levodopa-induced dyskinesia in a patient with Parkinson's disease.

4. The method of claim **1**, wherein the composition is administered 0 to 3 hours before bedtime.

5. The method of claim **1**, wherein the composition is administered 0 to 2 hours before bedtime.

6. The method of claim **1**, wherein the composition is administered as two or three unit dosage forms each comprising 110 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof, and the amantadine, or pharmaceutically acceptable salt thereof in the unit dosage forms together totals 220 mg to 445 mg.

7. The method of claim **1**, wherein the composition is administered as two or three unit dosage forms each comprising 130 mg of amantadine, or a pharmaceutically acceptable salt thereof.

8. The method of claim **1**, wherein the composition is administered as two or three unit dosage forms each comprising 140 mg of amantadine, or a pharmaceutically acceptable salt thereof.

9. The method of claim **1**, wherein the composition is administered as two unit dosage forms each comprising 170 mg of amantadine, or a pharmaceutically acceptable salt thereof.

10. A method of administering amantadine, or a pharmaceutically acceptable salt thereof, to a human subject in need thereof, said method comprising the steps of:

providing an extended release (ER) composition comprising 220 mg to 445 mg of amantadine, or a pharmaceutically acceptable salt thereof and at least one release modifying excipient, said composition having a mean Cmax for amantadine of 1.0 to 2.8 ng/mL/mg amantadine and a mean amantadine $AUC_{0\text{-}inf}$ of 40 to 75 ng·hr/mL/mg, as determined by a single dose, fasting human pharmacokinetic study, and

orally administering said composition once daily, 0 to 4 hours before bedtime to a human subject.

11. The method of claim **10**, wherein said composition has a mean AUC per mg of amantadine equivalent to a mean AUC per mg of amantadine for a 100 mg tablet of an immediate release formulation of amantadine HCl.

12. The method of claim **10**, wherein the method comprises reducing sleep disturbance in a human subject undergoing treatment with amantadine.

13. The method of claim **10**, wherein the method comprises treating levodopa-induced dyskinesia in a patient with Parkinson's disease.

14. The method of claim **10**, wherein the composition is administered 0 to 3 hours before bedtime.

15. The method of claim **10**, wherein the composition is administered 0 to 2 hours before bedtime.

16. The method of claim **10**, wherein the composition is administered as one or two or three unit dosage forms each comprising 110 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof, and the amantadine, or pharmaceutically acceptable salt thereof in the unit dosage forms together totals 220 mg to 445 mg.

17. The method of claim **10**, wherein the composition is administered as two or three unit dosage forms each comprising 130 mg of amantadine, or a pharmaceutically acceptable salt thereof.

18. The method of claim **10**, wherein the composition is administered as two or three unit dosage forms each comprising 140 mg of amantadine, or a pharmaceutically acceptable salt thereof.

19. The method of claim **10**, wherein the composition is administered as two unit dosage forms each comprising 170 mg of amantadine, or a pharmaceutically acceptable salt thereof.

20. The method of claim **10**, wherein administration of a dose of the composition to a human subject in a single-dose human pharmacokinetic study provides a mean amantadine Cmax of 1.0 to 2.4 ng/mL/mg.

21. The method of claim **20**, wherein said composition has a mean AUC per mg of amantadine equivalent to a mean AUC per mg of amantadine for a 100 mg tablet of an immediate release formulation of amantadine HCl.

22. The method of claim **20**, wherein the method comprises reducing sleep disturbance in a human subject undergoing treatment with amantadine.

23. The method of claim **20**, wherein the method comprises treating levodopa-induced dyskinesia in a patient with Parkinson's disease.

24. The method of claim **20**, wherein the composition is administered 0 to 3 hours before bedtime.

25. The method of claim **20**, wherein the composition is administered 0 to 2 hours before bedtime.

26. The method of claim **20**, wherein the composition is administered as one or two or three unit dosage forms each comprising 110 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof, and the amantadine, or pharmaceutically acceptable salt thereof in the unit dosage forms together totals 220 mg to 445 mg.

27. The method of claim **20**, wherein the composition is administered as two or three unit dosage forms each comprising 130 mg of amantadine, or a pharmaceutically acceptable salt thereof.

28. The method of claim **20**, wherein the composition is administered as two or three unit dosage forms each comprising 140 mg of amantadine, or a pharmaceutically acceptable salt thereof.

29. The method of claim **20**, wherein the composition is administered as two unit dosage forms each comprising 170 mg of amantadine, or a pharmaceutically acceptable salt thereof.

* * * * *

EXHIBIT J

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(12) **United States Patent**
Went et al.

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(54) **METHOD OF ADMINISTERING AMANTADINE PRIOR TO A SLEEP PERIOD**

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Methods of nighttime administration of amantadine to reduce sleep disturbances in patient undergoing treatment with amantadine are described, as well as compositions of extended release amantadine that are suitable for nighttime administration.

56 Claims, 7 Drawing Sheets

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FIG. 1

Dissolution Profiles of Amantadine ER Formulations

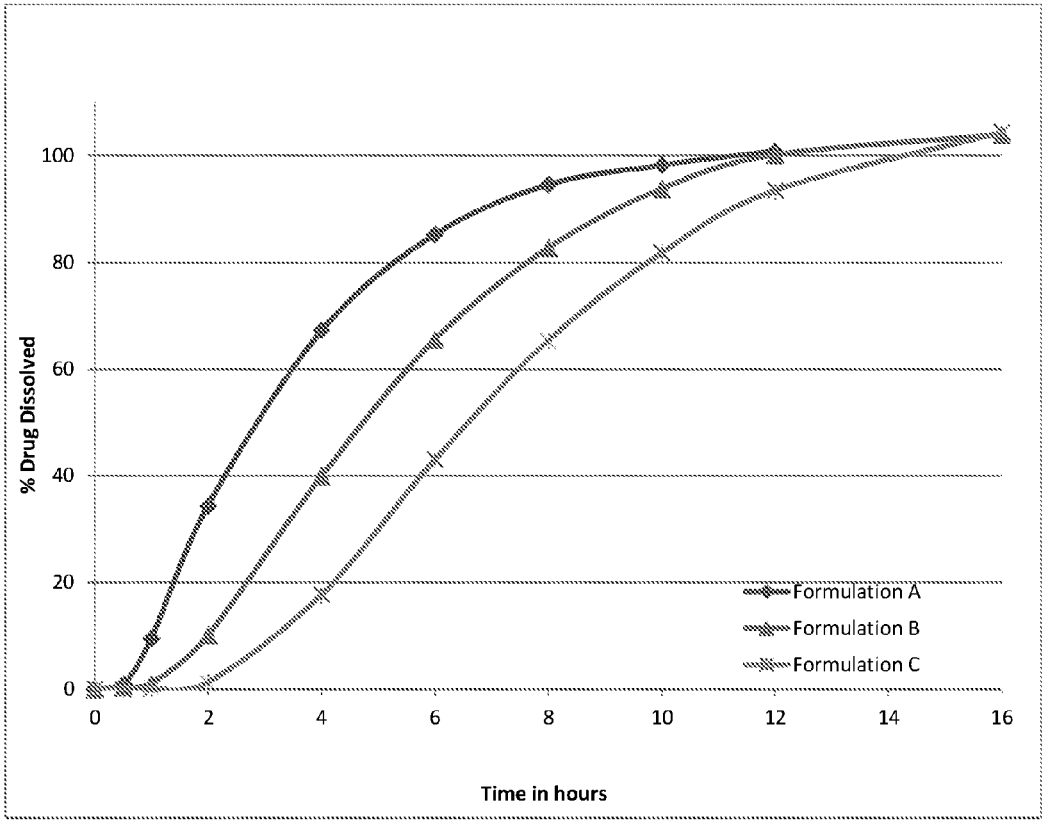


FIG. 2A

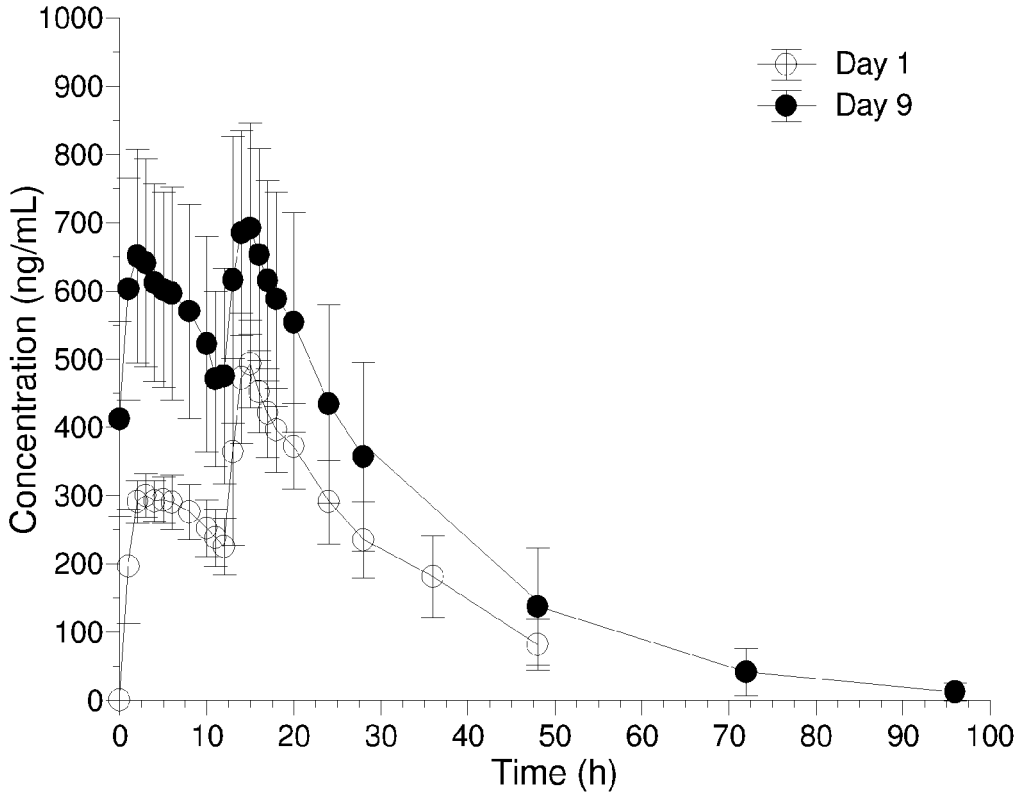

Day 1
Day 9
Concentration (ng/mL)
Time (h)
0
100
200
300
400
500
600
700
800
900
1000
0
10
20
30
40
50
60
70
80
90
100

FIG. 2B

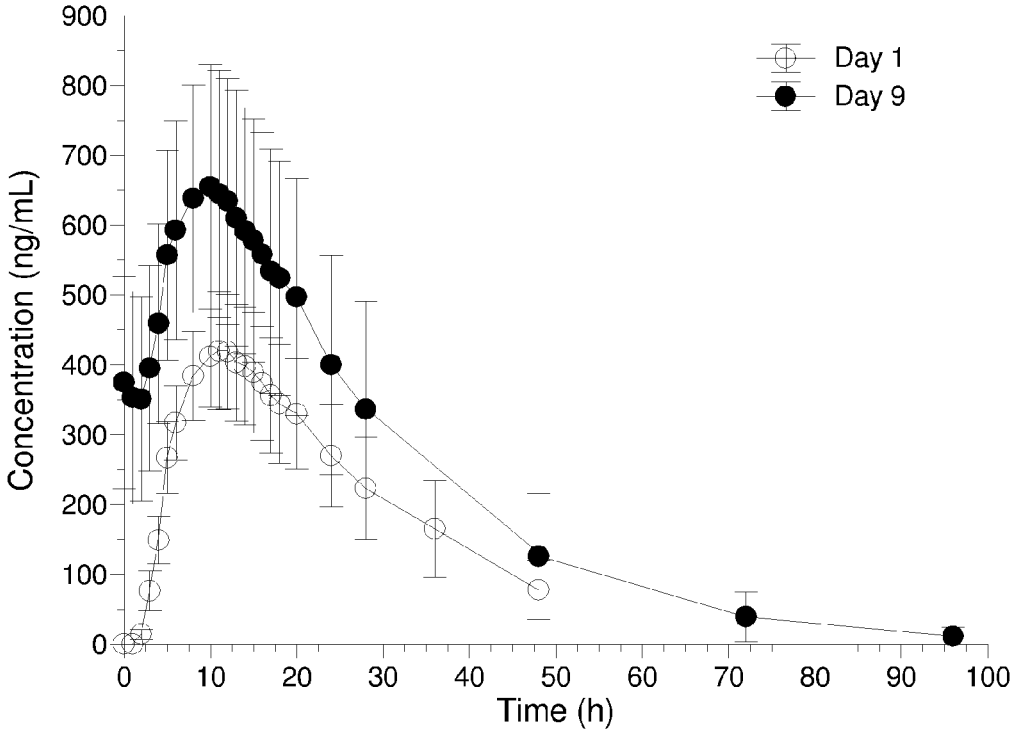

Day 1
Day 9
Concentration (ng/mL)
Time (h)
0
100
200
300
400
500
600
700
800
900
0
10
20
30
40
50
60
70
80
90
100

FIG. 3

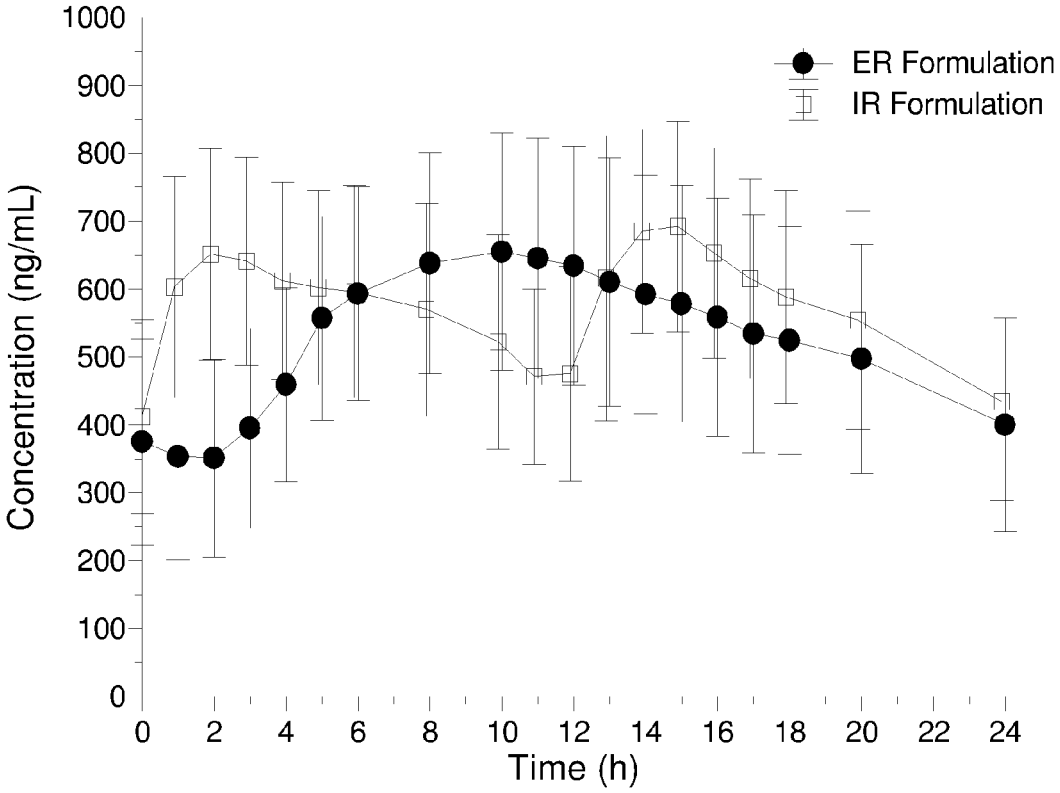
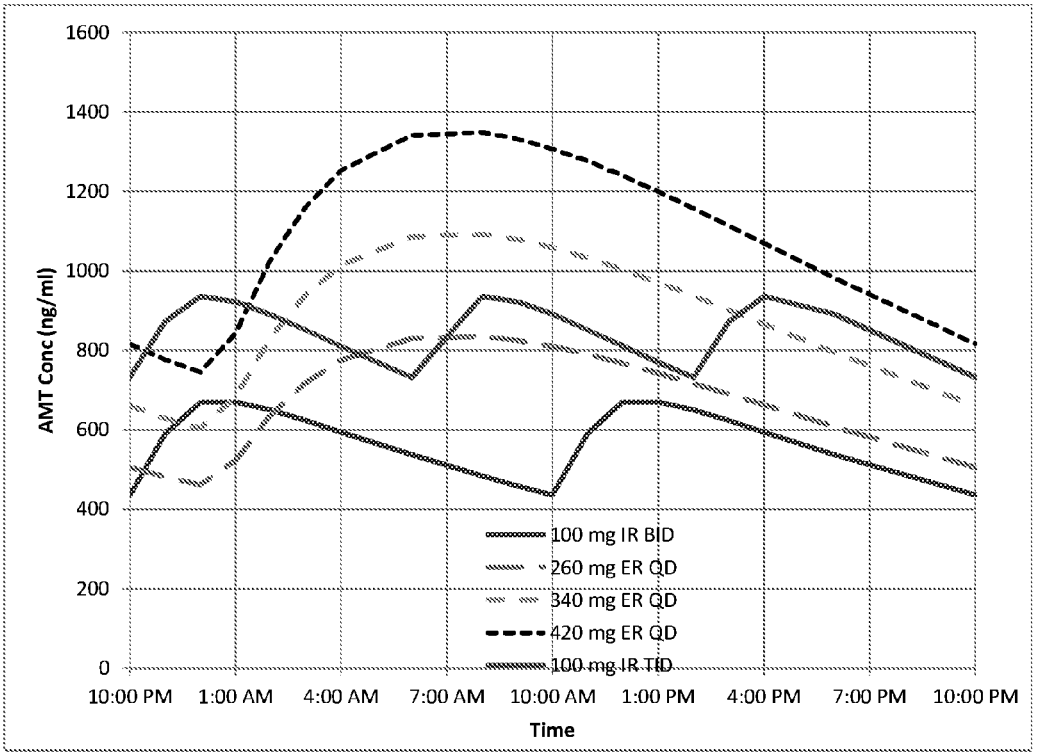

ER Formulation
IR Formulation
Concentration (ng/mL)
Time (h)
0
100
200
300
400
500
600
700
800
900
1000
0
2
4
6
8
10
12
14
16
18
20
22
24

Fig 4.



Simulation based on results of Adamas steady state PK study ADS-PD-104.

FIG. 5

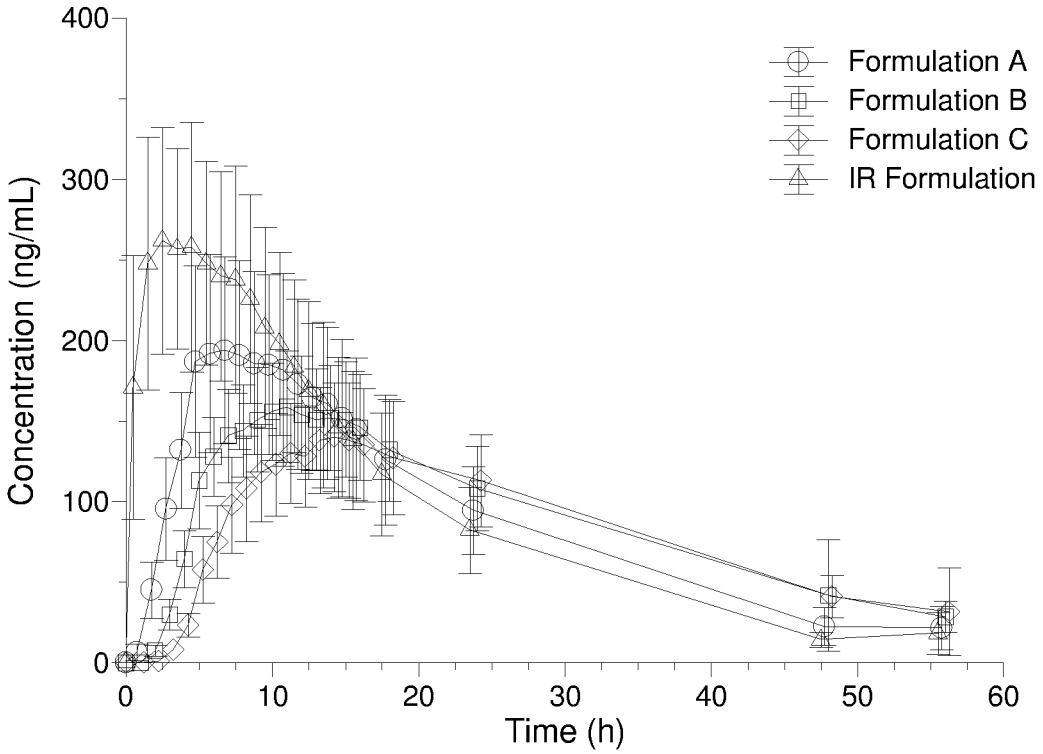

Formulation A
Formulation B
Formulation C
IR Formulation
Concentration (ng/mL)
Time (h)
0
100
200
300
400
0
10
20
30
40
50
60

FIG. 6

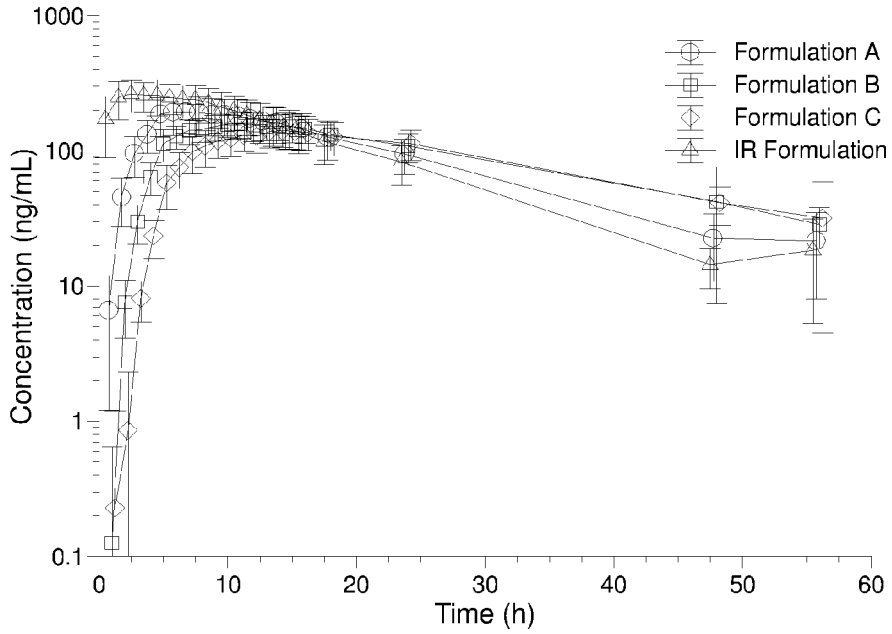
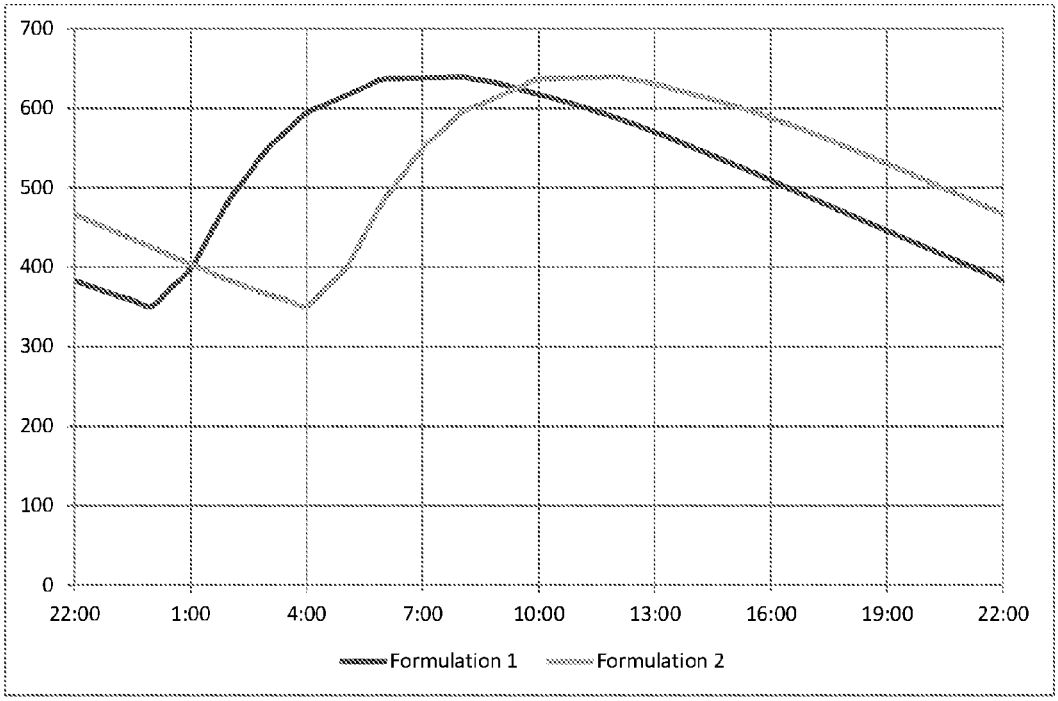

1000
100
10
1
0.1
Concentration (ng/mL)
0
10
20
30
40
50
60
Time (h)
Formulation A
Formulation B
Formulation C
IR Formulation

FIG 7.


700
600
500
400
300
200
100
0
22:00
1:00
4:00
7:00
10:00
13:00
16:00
19:00
22:00
Formulation 1
Formulation 2

METHOD OF ADMINISTERING AMANTADINE PRIOR TO A SLEEP PERIOD

CROSS-REFERENCE

This application is a continuation of U.S. patent application Ser. No. 14/863,035, filed Sep. 23, 2015, which is a continuation of U.S. patent application Ser. No. 14/523,535, filed Oct. 24, 2014, now abandoned, which is a continuation of U.S. patent application Ser. No. 14/267,597, filed May 1, 2014, now abandoned, which is a continuation of U.S. patent application Ser. No. 12/959,321, filed Dec. 2, 2010, now U.S. Pat. No. 8,741,343, which claims benefit of U.S. Provisional Application No. 61/266,053, filed Dec. 2, 2009, all of which applications are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

The field of the invention is extended release compositions of amantadine and uses thereof.

Amantadine is indicated for various conditions that can be treated by NMDA receptor antagonists including the treatment of idiopathic Parkinson's disease (Parlysis Agitans), postencephalitic Parkinsonism, and symptomatic Parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication. Amantadine also has activity as a viral M2 channel inhibitor and is used for the prophylaxis and treatment of infection of viral diseases, especially influenza A virus.

Currently marketed forms of amantadine are immediate release formulations that are typically administered two or more times a day. Amantadine's use is limited by dose related CNS side effects including dizziness, confusion, hallucinations, insomnia and nightmares (Gracies J M, Olanow C W; Current and Experimental Therapeutics of Parkinson's Disease; *Neuropsychopharmacology: the Fifth Generation of Progress*, p. 1802; American College of Neuropsychopharmacology 2002), which can be particularly exacerbated when amantadine is administered at night.

It is known that immediate release amantadine can act as a stimulant, causing insomnia and sleep disturbance. Therefore, the last dose is typically administered no later than 4 pm in order to minimize these side effects. Such dosing of amantadine results in peak plasma amantadine concentrations occurring in the evening or night, and very low plasma concentrations in the morning.

Extended release forms of amantadine have been described in the art. U.S. Pat. No. 5,358,721, to Guittard et al., and U.S. Pat. No. 6,217,905, to Edgren et al., each disclose an oral osmotic dosage form comprising an antiviral or anti-Parkinson's drug, respectively, where in each case amantadine is listed as a possible drug to be utilized in the dosage form. U.S. Pat. No. 6,194,000, to Smith et al., discloses analgesic immediate and controlled release pharmaceutical compositions utilizing NMDA receptor antagonists, such as amantadine, as the active agent. U.S. Patent Appl. Publication Nos. US 2006/0252788, US 2006/0189694, US 2006/0142398, and US 2008/0227743, all to Went et al., each disclose the administration of an NMDA receptor antagonist, such as amantadine, optionally in controlled release form.

SUMMARY OF THE INVENTION

The inventors have identified a need in the art for improved formulations of amantadine that result in a patient having higher plasma concentrations of amantadine upon waking in the morning without adversely affecting sleep. Further, the inventors have identified a need in the art for a method of administering amantadine in the late afternoon or evening, e.g. after 4 pm, which reduces side effects of insomnia and sleep disturbance and provides effective plasma concentrations of amantadine upon waking.

Therefore, there exists a need in the art for improved methods of amantadine therapy which can be administered to a patient shortly before they wish to sleep (e.g., at bedtime) without causing insomnia or sleep disturbance. In addition, there is a need for an amantadine therapy which can be taken by the patient before they go to sleep and then provides a suitable plasma concentration of amantadine when they wake up, e.g. in the morning, after a full night's sleep.

In addition, many Parkinson's disease patients have difficulty swallowing and are on multiple medications. Hence there is a need for amantadine therapy that delivers a therapeutically effective dose of the drug, can be administered once daily and is in an oral dosage form that is small in size and does not unduly increase the pill burden.

One aspect of the invention is a method of administering amantadine to a patient in need thereof, said method comprising orally administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below. Alternatively, the composition is administered less than about 4 hours before bedtime.

In a second aspect, the invention provides a method of reducing sleep disturbance in a human subject undergoing treatment with amantadine, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below. Alternatively, the composition is administered less than about 4 hours before bedtime.

In a third aspect, the invention provides a method of treating levodopa induced dyskinesia, or fatigue, or dementia, or any other symptom of Parkinson's disease, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below.

In a fourth aspect, the invention provides a method of treating brain injury, brain trauma, dementia, Alzheimer's disease, stroke, Huntington's disease, ALS, Multiple Sclerosis, neurodegenerative diseases, dementias, cerebrovascular conditions, movement disorders, cranial nerve disorders, neuropsychiatric disorders, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below.

In one embodiment of any of the above aspects, administration occurs less than two and a half, less than two, less than one and a half, less than one or less than half hour before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).

In one embodiment of any of the above aspects the patient has been diagnosed with Parkinson's disease.

In one embodiment of any of the above aspects, the composition is administered once daily. In another aspect, the daily dose exceeds 200 mg, and is given in 1, 2 or 3 capsules of size 0, 1 or 2.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in levodopa induced dyskinesia (LID). In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% reduction in levodopa induced dyskinesia. In further embodiments, the reduction in levodopa induced dyskinesia is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce LID. In further specific embodiments, the scale used in measuring the reduction in LID could be UDysRS, UPDRS Part IV (subscores 32, 33), Dyskinesia Rating Scale (DRS), Abnormal Involuntary Movement Scale (AIMS), or other scales developed for this purpose.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease fatigue. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60% reduction in Parkinson's disease fatigue. In further specific embodiments, the reduction in fatigue is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce fatigue. In further specific embodiments, the scale used in measuring the reduction in fatigue could be the Fatigue Severity Scale (FSS).

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease symptoms. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's symptoms. In further specific embodiments, the reduction in Parkinson's symptoms is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce Parkinson's symptoms. In further specific embodiments, the scale used in measuring the reduction in Parkinson's symptoms could be the Unified Parkinson's Disease Rating Scale (UPDRS).

In one embodiment of any of the above aspects, the composition is added to food, and in a more specific embodiment to a small amount of soft food (e.g. applesauce or chocolate pudding), prior to administration. Addition to food may involve a capsule being opened and the contents sprinkled over the patient's food. This is advantageous if the patient is unable or unwilling to swallow the composition.

In one embodiment of any of the above aspects, there is no increase in plasma concentration of amantadine for at least one hour after the administration at steady state plasma concentrations.

In one embodiment of any of the above aspects, there is no increase in the plasma concentration of amantadine for at least two hours after the administration at steady state plasma concentrations.

In one embodiment of any of the above aspects, the administration of the composition to a human subject at steady state amantadine plasma concentrations increases the amantadine plasma concentration by less than 5%, 10%, 15%, 20% or 25% at 1, 2, 2.5 or 3 hours following such administration. For example, administration of the composition to a human subject at steady state amantadine plasma concentrations increases the amantadine plasma concentration by less than 5% at 1, 2, 2.5 or 3 hours following such administration; or by less than 10% at 1, 2, 2.5 or 3 hours following such administration; or by less than 15% at 1, 2, 2.5 or 3 hours following such administration; or by less than 20% at 1, 2, 2.5 or 3 hours following such administration; or by less than 25% at 1, 2, 2.5 or 3 hours following such administration.

In one embodiment of any of the above aspects the amantadine has a single dose Tmax of 9 to 15 hours. In a more specific embodiment, the amantadine has a single dose Tmax of 10 to 14 hours after administration. In another more specific embodiment, the amantadine has a single dose Tmax of 11 to 13 hours after administration.

In one embodiment of any of the above aspects the amantadine has a steady state Tmax of 7 to 13 hours. In a more specific embodiment, the amantadine has a steady state Tmax of 8 to 12 hours after administration. In another more specific embodiment, the amantadine has a steady state Tmax of 9 to 11 hours after administration.

In one embodiment of any of the above aspects peak plasma concentration of amantadine is achieved between 6 and 16 hours after administration of a single dose of the composition. In a more specific embodiment, peak amantadine plasma concentration is achieved 8 to 14 hours after administration of a single dose of the composition. In another more specific embodiment, peak amantadine plasma concentration is achieved 10 to 12 hours after administration of a single dose of the composition. In additional specific embodiments, peak amantadine plasma concentration is achieved between 6, 7, 8, 9, 10, 11 or 12 hours to about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 hours after administration of a single dose of the composition.

In one embodiment of any of the above aspects, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In a more specific embodiment, the steady state plasma concentration profile is characterized by a concentration increase of amantadine of less than 25% at four hours after the administration.

In one embodiment of any of the above aspects, the composition is administered once a day and the ratio of Cmax to Cmin at steady state is 1.5 to 2.0, or, more specifically, 1.7 to 1.9, or, more specifically, about 1.8.

In one embodiment of any of the above aspects, the steady state plasma concentration profile following multiple administrations to a human subject of the composition at bedtime is characterized by an average plasma concentration during the day ("C-ave-day", defined as the average day time amantadine plasma concentration as measured in a human PK study) that is 1.1 to 2.0 times the average plasma concentration during the night ("C-ave-night", defined as the average night time amantadine plasma concentration as measured in a human PK study). In more specific embodiments the C-ave-day is the average amantadine plasma concentration as measured between the hours of 5 am, 6 am, 7 am, 8 am or 9 am to the hours of 4 pm, 5 pm, 6 pm, 7 pm

or 8 pm; for example, between the hours of 6 am and 4 pm, between the hours of 7 am and 6 pm, or between the hours of 7 am and 5 pm. The C-ave-night is the average amantadine plasma concentration as measured between the hours of 4 pm, 5 pm, 6 pm, 7 pm, 8 pm, 9 pm, 10 pm or 11 pm to the hours of 5 am, 6 am, 7 am, 8 am or 9 am; for example, between the hours of 10 pm and 6 am, between the hours of 7 pm and 6 am, or between the hours of 8 pm and 6 am.

In one embodiment of any of the above aspects, the steady state plasma concentration profile following multiple administrations to a human subject of the composition at bedtime is characterized by an average plasma concentration during the morning ("C-ave-morning", defined as the average amantadine plasma concentration as measured in a human PK study during the morning hours) that is 1.1 to 2.0 times the average plasma concentration during the night. In one embodiment the C-ave-morning is the average amantadine plasma concentration as measured between the hours of 5 am, 6 am, 7 am, 8 am or 9 am to the hours of 11 am, 11:30 am, 12 pm, 12:30 pm or 1:00 pm; for example, between the hours of 5 am and 11 am, or between the hours of 7 am and 12 pm. More preferably, the ratio of C-ave-morning/C-ave-night at steady state is 1.2 to 1.6.

In one embodiment of any of the above aspects, the steady state plasma concentration profile following daily administration of the composition is characterized by an average plasma concentration during the period 8 hours to 12 hours after administration ("C-ave-8-12 hrs") that is 1.1 to 2.0 times the average plasma concentration during the first 8 hours after administration ("C-ave-0-8 hrs"). More preferably, the ratio of C-ave-8-12 hrs/C-ave-0-8 hrs at steady state is 1.2 to 1.6.

In one embodiment of any of the above aspects, administration of a single dose of the composition to a human subject provides a plasma concentration profile characterized by: a fractional AUC from 0 to 4 hours that is less than 5%, and preferably less than 3% of AUC_{0-inf}; a fractional AUC from 0 to 8 hours that is about 5 to 15%, and preferably about 8 to 12% of AUC_{0-inf}; a fractional AUC from 0 to 12 hours that is about 10 to 40%, and preferably about 15 to 30% of AUC_{0-inf}; a fractional AUC from 0 to 18 hours that is about 25 to 60%, and preferably about 30 to 50% of AUC_{0-inf}; and a fractional AUC from 0 to 24 hours that is about 40 to 75%, and preferably about 50 to 70% of AUC_{0-inf}.

In one embodiment of any of the above aspects, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25%, and preferably about 5 to 20% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50%, and preferably about 20 to 40% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70%, and preferably about 40 to 60% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95%, and preferably about 75 to 90% of AUC_{24}.

In one embodiment of any of the above aspects, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by: a fractional AUC from 0 to 8 hours that is about 15 to 40%, and preferably about 20 to 32% of AUC_{24}; a fractional AUC from 8 to 16 hours that is about 30 to 50%, and preferably about 35 to 45% of AUC_{24}; and a fractional AUC from 16 to 24 hours that is about 20 to 35%, and preferably about 25 to 33% of AUC_{24}.

In one embodiment of any of the above aspects the amantadine is administered as a pharmaceutically acceptable salt. In a more specific embodiment, the amantadine is administered as hydrochloride or amantadine sulfate.

In one embodiment of any of the above aspects, a total daily dose of 50 mg to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof is administered to a patient. More specifically the daily dose of amantadine or pharmaceutically acceptable salt thereof administered may be in the range of 100 to 440 mg. In another specific embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof maybe in the range of 260 to 420 mg. In another embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof administered exceeds 300 mg per day. In various specific embodiments, the daily dose of amantadine or pharmaceutically acceptable salt thereof may be 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg.

In one embodiment of any of the above aspects, the composition comprises 50 mg to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. More specifically, the composition may comprise 100 mg to 450 mg of amantadine, or a pharmaceutically acceptable salt thereof. Still more specifically, the composition may comprise 130-210 mg of amantadine, or a pharmaceutically acceptable salt thereof. In various specific embodiments, a dosage form containing the composition comprises 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg of amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition comprises about 110, 120, 130, 140, 150, 160 170, 180, 190, 210, or 220 mg amantadine, or a pharmaceutically acceptable salt thereof. In another more specific embodiment, the composition comprises 110 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 130 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 170 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 210 mg amantadine hydrochloride.

In one embodiment of any of the above aspects, the composition is administered as one, two, three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof.

In one embodiment of any of the above aspects, the composition is administered as one, two, or three unit dosage forms each comprising 50 to 250 mg amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition is administered as one or two unit dosage forms each comprising 65 to 220 mg amantadine, or a pharmaceutically acceptable salt thereof.

In one embodiment of any of the above aspects, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma

concentration (Cmax) of 1.0 to 2.8 ng/ml per mg of amantadine. In a more specific embodiment, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine and an AUC_{0-inf}(Area under the concentration-curve curve from t=0 to t=infinity) of 40 to 75 ng*h/mL per mg of amantadine.

In one embodiment of any of the above aspects, the daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by at least one of: (i) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine, (ii) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (iii) an AUC_{0-24} of 44 to 83 ng*h/mL per mg of amantadine. In a more specific example, all three criteria of (i), (ii) and (iii) are met.

In a more specific embodiment, the steady state plasma concentration profile is further characterized by: (iv) no increase in concentration of amantadine for at least one hour after the administration; and (v) Cmax/Cmin ratio of 1.5 to 2.0. In a more specific embodiment, both criteria of (iv) and (v) are met.

In another more specific embodiment, the steady state plasma concentration profile is further characterized by at least one of: (iv) no increase in plasma concentration of amantadine for at least two hours after the administration; and (v) a Cmax/Cmin ratio of 1.7 to 1.9. In a more specific embodiment, both criteria of (iv) and (v) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more 55-85% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more than 25-55% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 20% dissolution at 1 hour, (ii) about 25-45% dissolution at 2 hours, (iii) not more than 50-80% dissolution at 4 hours, and (iv) at least 80% dissolution at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii), (iii) and (iv) are met. In a more specific embodiment, all four of criteria (i), (ii), (iii) and (iv) are met.

In one embodiment of any of the above aspects the in vitro dissolution profile of amantadine is further characterized by release of amantadine of: (i) not more than 10% at 1 hour, or (ii) 30-50% at 4 hours, or (iii) at least 90% at 12 hours using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three criteria of (i), (ii) and (iii) are met.

In another aspect, the present invention provides a pharmaceutical composition comprising or consisting of a pellet-in-capsule, wherein a pellet comprises a core that comprises a core seed with a mixture of amantadine and a binder coated onto the core seed, and an extended release coating surrounding the core comprising ethyl cellulose, a pore forming agent such as hydroxypropyl methyl cellulose or povidone, and a plasticizer.

In another aspect, the present invention provides a pharmaceutical composition for use in the methods of the aspects described above, wherein said composition is for oral administration and comprises a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core.

In one embodiment, the extended release coating comprises ethyl cellulose and at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In a more specific embodiment, the extended release coating comprises ethyl cellulose, povidone, and a plasticizer.

In one embodiment, the pellet core comprises amantadine and a binder coated onto a core seed. In one embodiment, the core seed is a sugar sphere (nonpareil) or microcrystalline cellulose seed (e.g. Celphere®). In a more specific embodiment, the core seed is a microcrystalline cellulose core. In another specific embodiment, the core seed has a diameter in the range of 100 microns to 1,000 microns. In additional specific embodiments, the core seed has a diameter of 100, 200, 300, 400, 500, 600 or 700 microns. In preferred specific embodiments, the core seed has a diameter of less than 500 microns.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 20 to 80 wt %, with a bulk density of 0.3 to 1.2 g/cm^3.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 40 to 60 wt %, with a bulk density of 0.5 to 1.2 g/cm^3.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 60 to 80 wt %, with a bulk density of 0.5 to 1.2 g/cm^3.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the binder is present in amounts from 8 to 25 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the core seed is present in amounts from 8 to 25 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the ethyl cellulose is present in amounts from 10 to 20 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the povidone is present in amounts from 1 to 4 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, and the plasticizer is present in amounts from 1 to 4 wt %.

In one embodiment, the coated pellet has a diameter in the range of 200 microns to 1700 micros. In additional specific embodiments, the coated pellet has a diameter of 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300 or

1500 microns. In certain specific embodiments, the coated pellet has a diameter of less than 1000 microns, e.g., from 500 to 1000 microns.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the binder is present in amounts from 5 to 25 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the core seed is present in amounts from 1 to 15 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the ethyl cellulose is present in amounts from 5 to 20 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the povidone is present in amounts from 0.25 to 4 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, and the plasticizer is present in amounts from 0.25 to 4 wt %.

In one embodiment, the pellet further comprises a seal coating between the pellet core and the extended release coating. In some embodiments, an inert coating can be applied to the inert core prior to drug coating or on drug-coated pellets or on controlled release coated pellets. In another embodiment, an enteric coating can be applied to the drug coated pellets or controlled release pellets.

In one embodiment, the pellet core comprises a binder, selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof.

In one embodiment, the above composition is provided in a size 3, size 2, size 1, size 0 or size 00 capsule.

In one embodiment, the therapeutically effective daily dose of the above composition is administered in no more than two capsules. In another embodiment, the therapeutically effective daily dose of the composition is administered in no more than three size 1 capsules. In another embodiment, the therapeutically effective daily dose of the composition is administered in no more than two size 0 capsules. In a still more preferred embodiment, the therapeutically effective daily dose of the composition is administered in no more than two size 1 capsules. In another embodiment, the therapeutically effective daily dose of the composition is administered in no more than three size 2 capsules.

In a preferred embodiment, the above composition is provided in an amount of 50 to 110 mg of amantadine or a pharmaceutically acceptable salt thereof in a size 2 capsule, and in the amount of 110 mg to 210 mg of amantadine or a pharmaceutically acceptable salt thereof in a size 1 capsule. In additional embodiments, the above composition comprises coated pellets of diameter 300 to 1000 microns, with amantadine or pharmaceutically acceptable salt thereof content of 40-80% wt % and at a bulk density of 0.5-1.2 g/cm^3. In a further preferred embodiment, the above composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more than 55-85% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, and castor oil. In a more specific embodiment, the plasticizer is medium chain triglycerides, e.g. Miglyol 812 N.

In another aspect, the present invention provides method of administering amantadine, or a pharmaceutically acceptable salt thereof, to a human subject in need thereof, said method comprising orally administering a composition of any of the above aspects.

In another aspect, the present invention provides a method of treating Parkinson's disease in a human subject in need thereof, said method comprising orally administering a composition of any of the above aspects. In a preferred aspect, the present invention provides a method of treating disease in a human subject in need thereof, said method comprising orally administering a composition of any of the above aspects once daily at nighttime, administering 1, 2 or 3 capsules.

References to administering amantadine to a subject in need thereof include treating a patient with a disease or condition which may be treated, prevented or cured by a NMDA antagonist. More specifically, administering amantadine to a subject in need thereof includes treating a patient with Parkinson's Disease, brain injury, brain trauma, dementia, Alzheimer's disease, stroke, Huntington's disease, ALS, Multiple Sclerosis, neurodegenerative diseases, dementias, cerebrovascular conditions, movement disorders, cranial nerve disorders, neuropsychiatric disorders.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the dissolution profiles for three amantadine ER formulations, A, B, C referred to in Example 3.

FIGS. **2**A and **2**B show the mean plasma concentration-time curves after administration of amantadine IR twice daily (A) and amantadine ER once daily (B) to healthy, adult, male and female subjects under fasting conditions on days 1 and 9.

FIG. **3** shows a plot of mean plasma concentration of amantadine versus time curves after administration of amantadine IR twice daily and amantadine ER once daily to healthy, adult, male and female subjects under fasting conditions on day 9.

FIG. **4** shows the simulated mean plasma concentration of amantadine versus time curves following multiple dose administration of various strengths of immediate release amantadine dosed twice or thrice daily and various strengths of amantadine ER administered once daily.

FIG. **5** shows a plot of mean (SD) plasma amantadine concentrations versus scheduled time for four (4) amantadine treatments.

FIG. **6** shows a semi-logarithmic mean (SD) plasma amantadine concentrations versus scheduled time for four (4) amantadine treatments.

FIG. **7** shows simulated steady state plasma concentration time profiles for the ER amantadine formulations as described in Example 12. The ER amantadine formulation 2, administered once daily at night, results at steady state in about 4 hour delay in achieving peak plasma concentration relative to formulation 1.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a method of reducing sleep disturbances in a patient undergoing treatment with amantadine. The method comprises administering amantadine to a patient in need thereof, such that the amantadine does not interfere with sleep, yet provides maximum benefit in morning hours when often needed most by many patients who take amantadine and further, provides nighttime coverage of

symptoms of Parkinson's disease if needed. Nighttime coverage includes providing benefit if the patient wakes up and wishes to return to sleep.

The method of the invention comprises orally administering to the patient an extended release (ER) amantadine composition designed for nighttime administration. The composition is taken less than three hours before bedtime, and preferably less than two and a half, less than two, less than one and a half, or less than one hour before bedtime. Most preferably the ER amantadine composition is taken less than half hour before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). As used herein, a reference to amantadine is intended to encompass pharmaceutically acceptable salts thereof (e.g. amantadine hydrochloride, amantadine sulfate, etc.). Alternatively, the composition is administered less than about 4 hours before bedtime.

As used herein, "extended release" includes "controlled release", "modified release", "sustained release", "timed release", "delayed release", and also mixtures of delayed release, immediate release, enteric coated, etc. with each of the above.

The patient may be diagnosed with any disease or disorder for which amantadine is prescribed, such as Parkinson's disease, multiple sclerosis, drug-induced extrapyramidal reactions, levodopa-induced dyskinesia, and viral diseases (e.g. influenza, HBV, and HCV). In a specific embodiment, the patient has Parkinson's disease, which, as used herein, also encompasses a diagnosis of parkinsonism. In one embodiment, the patient has early stage Parkinson's disease, and the amantadine is used as a monotherapy or in combination with a monoamine oxidase type B (MAO-B) inhibitor without concomitant use of levodopa. In another embodiment, the patient has late stage Parkinson's disease and the patient takes levodopa in addition to the amantadine. In another embodiment, the patient has multiple sclerosis and the amantadine is used for the treatment of fatigue. In other embodiments, the patient has a brain injury, brain injury, brain trauma, dementia, Alzheimer's disease, stroke, Huntington's disease, ALS, Multiple Sclerosis, neurodegenerative diseases, dementias, cerebrovascular conditions, movement disorders, cranial nerve disorders, neuropsychiatric disorders.

An ER amantadine composition for use in the invention is adapted for nighttime administration by providing a plasma concentration profile that does not interfere with the subject's sleep. The composition of the invention will, upon administration to a human subject, result in a gradual initial increase in plasma concentration of amantadine such that, at steady state conditions, administration of a dose of the composition results in an increase in plasma concentration of amantadine of less than 25% at three hours after the dose is administered. For example, if a subject's steady state plasma concentration of amantadine is 500 ng/ml at the time a dose of the composition is administered, three hours later the subject's plasma concentration of amantadine will be less than 625 ng/ml. Preferably, the increase in plasma concentration of amantadine is less than 15%, and most preferably, less than 10%. Particularly preferred compositions have a plasma concentration profile further characterized by no increase in amantadine plasma concentration, or even a decrease (at steady state conditions), for at least one or, in a preferred embodiment, two hours after the administration. The composition for use in the invention is further adapted for bedtime (i.e. the time at which the subject wishes to go to sleep for the night) administration by providing a maximum concentration of amantadine (Cmax) in the morning hours. The time to reach Cmax (Tmax), as measured after single dose administration in the fasted state, is at least, 8 hours and up to 13, 14, 15, or 16 hours, or at least 9 hours and up to 13, 14, 15, or 16 hours, or at least 10 hours, and up to 13, 14, 15, or 16 hours. In specific embodiments, the Tmax is 9 to 15 hours, preferably 10 to 14 hours, and most preferably 11 to 13 hours. At steady state, with once daily administration of the composition, the Tmax is 7 to 13 hours, preferably 8 to 12 hours, and most preferably 9 to 11 hours. A suitable ER amantadine composition may be further characterized by having a steady-state Cmax/Cmin ratio of 1.5 to 2.0, and preferably 1.7 to 1.9, resulting in a composition with optimal fluctuation.

In more specific, preferred embodiments, the plasma concentration profile is further characterized by having an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5%, and preferably less than 3% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 8 hours that is about 5 to 15%, and preferably about 8 to 12% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 12 hours that is about 10 to 40%, and preferably about 15 to 30% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 18 hours that is about 25 to 60%, and preferably about 30 to 50% of $AUC_{0\text{-}inf}$; and a fractional AUC from 0 to 24 hours that is about 40 to 75%, and preferably about 50 to 70% of $AUC_{0\text{-}inf}$.

In a further preferred embodiment, the plasma concentration profile is further characterized by having an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25%, and preferably about 5 to 20% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50%, and preferably about 20 to 40% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70%, and preferably about 40 to 60% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95%, and preferably about 75 to 90% of AUC_{24}.

In some embodiments of any of the above aspects, the steady state plasma concentration profile following multiple administrations to a human subject of the composition at bedtime is characterized by an average plasma concentration during the day ("C-ave-day", defined as the average day time amantadine plasma concentration as measured in a human PK study) that is 1.1 to 2.0 times the average plasma concentration during the night ("C-ave-night", defined as the average night time amantadine plasma concentration as measured in a human PK study). In some embodiments, the ratio of C-ave-day/C-ave-night at steady state is within one of the ranges 1.1 to 1.9, 1.1 to 1.8, 1.1 to 1.7, 1.1 to 1.6, 1.1 to 1.5, 1.1 to 1.4, 1.2 to 1.9, 1.2 to 1.7, 1.2 to 1.6, 1.2 to 1.5, 1.3 to 1.9, 1.3 to 1.8, 1.3 to 1.7, 1.3 to 1.6, 1.4 to 1.9, 1.4 to 1.8, 1.4 to 1.7, 1.5 to 1.9, 1.5 to 1.8, 1.5 to 1.7, 1.6 to 1.9, 1.6 to 1.8 or 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave-night at steady state is 1.1, 1.15, 1.2, 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, or 2.0. In some embodiments, the C-ave-day is the average amantadine plasma concentration as measured between the hours of 5 am, 6 am, 7 am, 8 am or 9 am to the hours of 4 pm, 5 pm, 6 pm, 7 pm or 8 pm and the C-ave-night is the average amantadine plasma concentration as measured between the hours of 4 pm, 5 pm, 6 pm, 7 pm, 8 pm, 9 pm, 10 pm or 11 pm to the hours of 5 am, 6 am, 7 am, 8 am or 9 am. In some embodiments, the C-ave-day is the average amantadine plasma concentration as measured within any four to twelve hour period between the hours of 5 am and 8 pm; and the C-ave-night is the average amantadine plasma concentration as measured within any four to twelve hour

period between the hours of 8 pm and 5 am. In some embodiments, the C-ave-day is the average amantadine plasma concentration as measured within any four, five, six, seven, eight, nine, ten, eleven or twelve hour period between the hours of 5 am and 8 pm; and the C-ave-night is the average amantadine plasma concentration as measured within any four, five, six, seven, eight, nine, ten, eleven or twelve hour period between the hours of 8 pm and 5 am.

In some embodiments described herein an amantadine composition is administered to a patient from 0 to 4 hours prior to bedtime. In some embodiments, the amantadine composition is administered to a patient from 0 to 3, 0 to 2 or 0 to 1 hours prior to bedtime. In some embodiments, the amantadine composition is administered to a patient from 0 to 240 minutes, from 0 to 180 minutes, e.g. from 0 to 120 minutes, from 0 to 60 minutes, from 0 to 45 minutes, from 0 to 30 minutes, from 0 to 15 minutes or from 0 to 10 minutes prior to bedtime. In some embodiments, the amantadine composition is administered to a patient from 60 to 240 minutes, from 60 to 180 minutes, from 60 to 120 minutes or from 60 to 90 minutes prior to bedtime.

It is to be understood that administration to a patient includes administration by a healthcare professional and self administration by the patient.

Unless otherwise specified herein, the term "bedtime" has the normal meaning of a time when a person retires for the primary sleep period during a twenty-four hour period of time. While for the general populace, bedtime occurs at night, there are patients, such as those who work nights, for whom bedtime occurs during the day. Thus, in some embodiments, bedtime may be anytime during the day or night.

As used herein, unless otherwise indicated, reference to a plasma concentration profile or a specific pharmacokinetic property (e.g. Cmax, Cmin, AUC, Tmax, etc.) in a human subject refers to a mean value obtained from healthy adults s determined in a typical phase I clinical trial designed to measure pharmacokinetic properties of a drug (see e.g. Examples 5, 6 and 7, below). References herein to Tmax refer to values obtained after administration of a single dose at fasted states, unless otherwise indicated.

In some embodiments of the invention, the dose of the amantadine administered in accordance with the present invention is within or above the ranges normally prescribed for immediate release compositions of amantadine. In other embodiments, the doses of the amantadine administered with the present invention are higher than the ranges normally prescribed for immediate release compositions of amantadine. For example, the recommended dose of amantadine for the treatment of Parkinson's disease is 100 mg administered twice daily. In limited cases of the patient not deriving sufficient benefit at that dose and subject to the patient being able to tolerate such higher dose, the dose may be increased to 300 mg or 400 mg in divided doses. The most commonly prescribed doses of amantadine are 100 mg to 200 mg per day, with the latter administered in divided doses. More than 200 mg (for example 300 mg) is always given in divided doses. For the present invention, doses of 50 to 600 mg, or more preferably, 200 to 450 mg are administered for treatment of Parkinson's disease, and the methods and compositions of the invention may comprise administration of a dose as defined by any of these ranges. In specific embodiments the administration of such higher doses may be once daily. In additional embodiments the administration of such higher doses may be at night. In additional embodiments the administration of such higher doses may be in the form of 1, 2 or 3 capsules of size 0, 1 or 2 administered once daily.

In one embodiment of any of the above aspects the amantadine is administered as a pharmaceutically acceptable salt. In a more specific embodiment, the amantadine is administered as hydrochloride or amantadine sulfate.

In one embodiment of any of the above aspects, a total daily dose of 50 mg to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof is administered to a patient. More specifically the daily dose of amantadine or pharmaceutically acceptable salt thereof administered may be in the range of 100 mg to 440 mg. In another specific embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof maybe in the range of 260 mg to 420 mg. In another embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof administered exceeds 300 mg per day. In various specific embodiments, the daily dose of amantadine or pharmaceutically acceptable salt thereof may be 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg.

In one embodiment of any of the above aspects, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. More specifically, the composition may comprise 100 to 450 mg of amantadine, or a pharmaceutically acceptable salt thereof. Still more specifically, the composition may comprise 130-210 mg of amantadine, or a pharmaceutically acceptable salt thereof. In various specific embodiments, the dosage form comprises 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg of amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition comprises about 110, 120, 130, 140, 150, 160 170, 180, 190, 210, or 220 mg amantadine, or a pharmaceutically acceptable salt thereof. In another more specific embodiment, the composition comprises 110 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 130 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 170 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 210 mg amantadine hydrochloride.

In one embodiment of any of the above aspects, the composition comprises from about 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg of amantadine, or a pharmaceutically acceptable salt thereof to about 75 mg, 85 mg, 95 mg, 105 mg, 115 mg, 125 mg, 135 mg, 145 mg, 155 mg, 165 mg, 175 mg, 185 mg, 195 mg, 205 mg, 215 mg, 225 mg, 235 mg, 245 mg, 255 mg, 265 mg, 275 mg, 285 mg, 295 mg, 305 mg, 315 mg, 325 mg, 335 mg, 345 mg, 355 mg, 365 mg, 375 mg, 385 mg, 395 mg, 405 mg, 415 mg, 425 mg, 435 mg, 445 mg of amantadine, or a pharmaceutically acceptable salt thereof.

In a specific embodiment of the invention, a subject's entire daily dose of amantadine is administered once, during a period of less than about three, two or one hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). In other embodiments, at least one half of the daily dose of amantadine is taken during said period before bedtime. Preferably at least ⅔ of the dose of amantadine is taken in said period before bedtime, with the remainder taken in morning or afternoon. The morning or afternoon dose of the amantadine may be provided in a conventional, immediate release dosage form, or in an extended release form.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in levodopa induced dyskinesia. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% reduction in levodopa induced dyskinesia. In further embodiments, the reduction in levodopa induced dyskinesia is measured on a numeric scale that is used by or accepted by the FDA or other regulatory agencies to evaluate the effectiveness of and to approve for licensure drugs for the treatment of LID. In further specific embodiments, the scale used in measuring the reduction in LID could be UDysRS, UPDRS Part IV (subscores 32, 33), Dyskinesia Rating Scale (DRS), Abnormal Involuntary Movement Scale (AIMS), Rush Dyskinesia Rating Scale, Parkinson Disease Dyskinesia Scale (PDYS-26), Obeso Dyskinesia Rating Scale (CAPIT), Clinical Dyskinesia Rating Scale (CDRS), Lang-Fahn Activities of Daily Living Dyskinesia or other scales developed for this purpose.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease fatigue. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, or 60% reduction in Parkinson's disease fatigue. In further specific embodiments, the reduction in fatigue is measured on a numerical scale used by or accepted by the FDA or other regulatory agencies to evaluate the effectiveness of and to approve for licensure drugs for the treatment of fatigue. In further specific embodiments, the scale used in measuring the reduction in fatigue could be the Fatigue Severity Scale (FSS), Fatigue Assessment Inventory, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue), Multidimensional Fatigue Inventory (MFI-20), Parkinson Fatigue Scale (PFS-16) and the Fatigue Severity Inventory. In other specific embodiments, the reduction in fatigue is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in fatigue is measured relative to baseline in a controlled clinical trial.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease symptoms. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's symptoms. In further specific embodiments, the reduction in Parkinson's symptoms is measured on a numerical scale used by or accepted by the FDA or other regulatory agencies to evaluate the effectiveness of and to approve for licensure drugs for the treatment of Parkinson's symptoms. In further specific embodiments, the scale used in measuring the reduction in Parkinson's symptoms could be the Unified Parkinson's Disease Rating Scale (UPDRS). Unified Parkinson's Disease Rating Scale (UPDRS, MDS revision)—Part I: non-motor aspects of experiences of daily living (13 items), Part II: motor aspects of experiences of daily living (13 items)—Part III: motor examination (33 scored items)—Part I: mental status, behavior and mood—Part II: activities of daily living—Part III: motor examination (27 scored items) Hoehn and Yahr Staging Scale (Original or Modified).

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in levodopa induced dyskinesia. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% reduction in levodopa induced dyskinesia. In further embodiments, the reduction in levodopa induced dyskinesia is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce LID. In further specific embodiments, the scale used in measuring the reduction in LID could be UDysRS, UPDRS Part IV (subscores 32, 33), Dyskinesia Rating Scale (DRS), Abnormal Involuntary Movement Scale (AIMS), or other scales developed for this purpose. In other specific embodiments, the reduction in LID is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in LID is measured relative to baseline in a controlled clinical trial.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease fatigue. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's disease fatigue. In further specific embodiments, the reduction fatigue is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce fatigue. In further specific embodiments, the scale used in measuring the reduction in fatigue could be the Fatigue Severity Scale (FSS). In other specific embodiments, the reduction in fatigue is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in fatigue is measured relative to baseline in a controlled clinical trial.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease symptoms. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's symptoms. In further specific embodiments, the reduction in Parkinson's symptoms is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce Parkinson's symptoms. In further specific embodiments, the scale used in measuring the reduction in Parkinson's symptoms could be the Unified Parkinson's Disease Rating Scale (UPDRS). In other specific embodiments, the reduction in Parkinson's disease symptoms is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in Parkinson's disease symptoms is measured relative to baseline in a controlled clinical trial.

Extended Release Formulations

Extended release amantadine compositions suitable for use in the method of the invention can be made using a variety of extended release technologies, such as those described in the patent publications referenced in the above background section, which publications are incorporated herein by reference in their entireties. In some embodiments, the invention is a pellet in capsule dosage form. In some embodiments, the pellets comprise a pellet core, which is

coated with at least one drug layer and at least one extended release coating layer. In some embodiments, the pellets are coated with at least one drug layer, an intermediate layer such as a seal coat and an extended release coating layer. In some embodiments, the pellet, the drug layer or both comprise one or more binders.

In some embodiments, the dosage unit comprises a plurality of coated pellets. In some embodiments, the pellets have a diameter of for example 300 to 1700 microns, in some cases 500 to 1200 microns. The pellets will comprise, for example, inert substrates, such as sugar spheres, microcrystalline cellulose (MCC) spheres, starch pellets. In some embodiments, pellets can be prepared by other processes such as pelletization, extrusion, spheronization, etc. or combinations thereof. The core pellets will comprise of amantadine hydrochloride and pharmaceutically acceptable excipients.

Coated Pellets

The pellet cores are coated with the active ingredient, e.g., amantadine or a pharmaceutically acceptable salt and/or polymorph thereof. In some embodiments, in addition to the active ingredient, the pellets also comprise one or more binders, such as for example hydroxypropyl methyl cellulose, copovidone, povidone, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose etc. In some embodiments, the pellets also contain one or more additional excipients, such as anti-tack agents (e.g. talc, magnesium stearate etc.)

In some embodiments, the pellets cores are coated with a drug layer comprising active ingredient, and optionally one or more binders, anti-tack agents and/or solvents by conventional coating techniques such as fluidized bed coating, pan coating.

Intermediate Layer Coating

In some embodiments, the pellets are coated with an intermediate layer, such as a seal coat. In some embodiments, the seal coat is adapted to prevent ingredients in the extended release coating from interacting with ingredients in the pellet core, to prevent migration of the ingredients in the pellet core from diffusing out of the pellet core into the extended release layer, etc. As described herein, the seal coat of the present invention can comprise one or more film forming polymers including but not limited to hydroxypropylmethyl cellulose (HPMC), copovidone, povidone, polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose or any combination thereof and the like.

The seal coat can further comprise other additives like plasticizers, such as, propylene glycol, triacetin, polyethylene glycol, tributyl citrate and optionally anti-tacking agents, such as, magnesium stearate, calcium silicate, magnesium silicate, and colloidal silicon dioxide or talc.

Apart from plasticizers and anti-tacking agents as mentioned above, the seal coat can optionally contain buffers, colorants, opacifiers, surfactants or bases, which are known to those skilled in the art.

Seal coating can be applied to the core using conventional coating techniques such as fluidized bed coating, pan coating etc. In some embodiments, the drug coated pellets cores are coated with a seal coat layer that optionally comprises one or more binders, anti-tack agents and/or solvents by fluidized bed coating or pan coating.

Binders

In some embodiments, either the pellet cores, the intermediate coating layer, or both may comprise one or more binders (e.g., film forming polymers). Suitable binders for use herein include, e.g.: alginic acid and salts thereof; cellulose derivatives such as carboxymethylcellulose, methylcellulose (e.g., Methocel®), hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose (e.g., Klucel®), ethylcellulose (e.g., Ethocel®), and microcrystalline cellulose (e.g., Avicel®); microcrystalline dextrose; amylose; magnesium aluminum silicate; polysaccharide acids; bentonites; gelatin; polyvinylpyrrolidone/vinyl acetate copolymer; crospovidone; povidone; starch; pregelatinized starch; tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitab®), and lactose; a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, polyvinylpyrrolidone (e.g., Polyvidone® CL, Kollidon® CL, Polyplasdone® XL-10), larch arabogalactan, Veegum®, polyethylene glycol, waxes, sodium alginate, and the like.

Extended Release Coating

The pellets are coated with an extended release coating. The extended release coating is adapted to delay release of the drug from the coated drug cores for a period of time after introduction of the dosage form into the use environment. In some embodiments, the extended release coating includes one or more pH-dependent or non-pH-dependent extended release excipients. Examples of non-pH dependent extended release polymers include ethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, copolymer of ethyl acrylate, methyl methacrylate (e.g. Eudgrait RS) etc. Examples of pH dependent extended release excipients include methacrylic acic copolymers, hydroxypropylmethyl cellulose acetate succinate, hydroxypropylmethyl cellulose phthalate, and cellulose acetate phthalate etc. The extended release coating may also include a pore former, such as povidone, polyethylene glycol, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, etc., sugars such as sucrose, mannitol, lactose, and salts, such as sodium chloride, sodium citrate, etc., a plasticizer, such as acetylated citrated esters, acetylated glycerides, castor oil, citrate esters, dibutylsebacate, glyceryl monostearate, diethyl phthalate, glycerol, medium chain triglycerides, propylene glycol, polyethylene glycol. The extended release coating may also include one or more additional excipients, such as lubricants (e.g., magnesium stearate, talc etc.).

Extended release coating can be applied using conventional coating techniques such as fluidized bed coating, pan coating etc. The drug coated pellets cores, which optionally comprise a seal coat, are coated with the extended release coating by fluidized bed coating.

Extended Release Excipients (Coating Polymers)

As described herein, exemplary extended release excipients include, but are not limited to, insoluble plastics, hydrophilic polymers, and fatty compounds. Plastic matrices include, but are not limited to, methyl acrylate-methyl methacrylate, polyvinyl chloride, and polyethylene. Hydrophilic polymers include, but are not limited to, cellulosic polymers such as methyl and ethyl cellulose, hydroxyalkyl celluloses such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, and cross-linked acrylic acid polymers like Carbopol® 934, polyethylene oxides and mixtures thereof. Fatty compounds include, but are not limited to, various waxes such as carnauba wax and glyceryl tristearate and wax-type substances including hydrogenated castor oil or hydrogenated vegetable oil, or mixtures thereof.

In certain embodiments, the plastic material can be a pharmaceutically acceptable acrylic polymer, including but not limited to, acrylic acid and methacrylic acid copolymers,

methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain other embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In still other embodiments, the acrylic polymer is an acrylic resin lacquer such as that which is commercially available from Rohm Pharma under the trade name Eudragit®. In further embodiments, the acrylic polymer comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the trade names Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. Edragit® S-100 and Eudragit® L-100 are also suitable for use herein. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, multiparticulate systems formed to include the same are swellable and permeable in aqueous solutions and digestive fluids.

The polymers described above such as Eudragit® RL/RS may be mixed together in any desired ratio in order to ultimately obtain an extended release formulation having a desirable dissolution profile. One skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L.

Pore Formers

In some embodiments, the extended release coating includes a pore former. Pore formers suitable for use in the extended release coating can be organic or inorganic agents, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. Examples of pore formers include but are not limited to organic compounds such as mono-, oligo-, and polysaccharides including sucrose, glucose, fructose, mannitol, mannose, galactose, lactose, sorbitol, pullulan, dextran; polymers soluble in the environment of use such as water-soluble hydrophilic polymers, such as povidone, crospovidone, polyethylene glycol, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyalkyl celluloses, carboxyalkyl celluloses, cellulose ethers, acrylic resins, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, polyethylene oxide, carbowaxes, Carbopol®, and the like, diols, polyols, polyhydric alcohols, polyalkylene glycols, polyethylene glycols, polypropylene glycols, or block polymers thereof, polyglycols, poly(α-Ω) alkylenediols; inorganic compounds such as alkali metal salts, lithium carbonate, sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium acetate, sodium citrate, suitable calcium salts, and the like. In certain embodiments, plasticizers can also be used as a pore former.

Capsules

The extended release pellets are introduced into a suitable capsule by using an encapsulator equipped with pellet dosing chamber. The capsule sizes may be 00, 0, 0EL, 1, 1EL, 2, 2EL, 3, 4 or 5. A particularly preferred composition that provides ideal pharmacokinetic properties and plasma concentration profiles is a pellet-in-capsule composition that comprises a plurality of pellets, typically having a diameter of about 500 μm to 1.2 mm, and preferably about 700 μm to 1000 μm, where each pellet comprises a core comprising amantadine and a binder, and an extended release coating surrounding the core that extends release of the amantadine so as to provide the desired pharmacokinetic properties and amantadine plasma concentration profiles described above.

In some embodiments, the pellets in the pellet-in-capsule are in a size 0 or smaller, preferably a size 1 or smaller capsule. Mean pellet diameters in some embodiments may be in a range of 500 μm to 1200 μm, e.g. from 500 μm to 1100 μm, from 500 μm to 1000 μm, from 500 μm to 900 μm, from 500 μm to 800 μm, from 500 μm to 700 μm, from 600 μm to 1100 μm, from 600 μm to 1000 μm, from 600 μm to 900 μm, from 600 μm to 800 μm, from 600 μm to 700 μm, from 700 μm to 1100 μm, from 700 μm to 1000 μm, from 700 μm to 900 μm, or from 700 μm to 800 μm. In some embodiments the mean particle diameters are, ±10%, e.g.: 500 μm, 550 μm, 600 μm, 650 μm, 700 μm, 750 μm, 800 μm, 850 μm, 900 μm, 950 μm, 1000 μm, 1050 μm, 1100 μm, 1150 μm or 1200 μm.

One preferred composition of the invention is a pellet-in-capsule composition wherein each pellet comprises a core that comprises a core seed with a mixture of amantadine and a binder coated onto the core seed, and an extended release coating surrounding the core comprising ethyl cellulose, a pore forming agent such as hydroxypropyl methyl cellulose or povidone, and a plasticizer. In some embodiments, the pellets may further comprise a seal coating between the pellet core and the extended release coating. The pellets are formulated using methods known in the art, such as those described in Example 1 below. In a specific embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 20-80 wt %, 45-70 wt %, 40-50 wt %, 45-55 wt %, 50-60 wt %, 55-65 wt %, 60-70 wt %, 65-75 wt %, 70-80 wt %, or 40 to 60 wt %, the binder, which is preferably hydroxypropyl methyl cellulose, copovidone, or mixtures thereof, is present in amounts from 1 to 25 wt %, the core seed, preferably a sugar sphere (nonpareil) or microcrystalline cellulose seed (e.g. Celphere®), is present in amounts from 8 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the pore forming agent, preferably povidone, is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %. In another specific embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 50 to 70 wt %, the binder, which is preferably hydroxypropyl methyl cellulose, copovidone, or mixtures thereof, is present in amounts from 1 to 25 wt %, the core seed, preferably a sugar sphere (nonpareil) or microcrystalline cellulose seed (e.g. Celphere®), is present in amounts from 5 to 15 wt %, the ethyl cellulose is present in amounts from 1 to 15 wt %, the pore forming agent, preferably povidone, is present in amounts from 0.25 to 4 wt %, and the plasticizer is present in amounts from 0.25 to 4 wt %.

Additional embodiments of the invention are illustrated in the Table, below, entitled "Various Amantadine ER Capsule Size 1 Formulations". By means of methods and compositions described herein, formulations can be made that achieve the desired dissolution characteristics and target pharmacokinetic profiles described herein. More specifi-

cally, therapeutically effective doses of amantadine can be administered once daily in no more than two size 1 (or smaller, e.g. size 2 or 3) capsules using the manufacturing methods and compositions that have been described herein to achieve these results. In particular, higher drug loading can be achieved using compositions and manufacturing methods described herein. In some embodiments, higher drug loading may be achieved, with the required dissolution profile, using smaller core pellet sizes and concomitantly increased drug layering on smaller cores, but with no change in the extended release coat. In some embodiments, using alternative manufacturing approaches described herein, e.g. extrusion and spheronization, even higher drug loads can be achieved to realize the desired dissolution profile, enabling high amantadine drug loads with suitable pharmacokinetic profiles, resulting in compositions that are therapeutically more effective, and at least as well tolerated, and can be filled in relatively small sized capsules (e.g., size 1, 2 or 3), enabling ease of administration to patients.

TABLE

Various Amantadine ER Capsule Size 1 Formulations

AMT Strength (mg)	Manufacture Method	Inert Core Pellet Size (mm)	Active Drug % w/w	Extended Release Coating % w/w	Bulk Density (g/cm^3)	% Fill in Size 1 Capsule	AMT Dissolution (%) (at T (hrs)): 2 hrs	6 hrs	12 hrs
110 mg	Fluid bed coating	0.3-0.5	40-50%	10-30%	0.6-1.0	60-70%	<25%	40-80%	>80%
140 mg	Fluid bed coating	0.3-0.5	45-50%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
150 mg	Fluid bed coating	0.3-0.5	50-55%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
170 mg	Fluid bed coating	0.2-0.3	50-55%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
170 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	65-75%	<25%		>80%
190 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	75-85%	<25%	40-80%	>80%
210 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
230 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	85-95%	<25%	40-80%	>80%

In some embodiment, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 20 to 80 wt (based on the combined weight of the pellet core and extended release coating), with a bulk density of 0.3 to 1.2 g/cm^3. In some embodiments, the amantadine or pharmaceutically acceptable salt thereof is present in amounts from 20 to 77.5 wt %, from 20 to 75 wt %, from 20 to 72.5 wt %, from 20 to 70 wt %, from 20 to 67.5 wt %, from 20 to 65 wt %, from 20 to 62.5 wt %, from 20 to 60 wt %, from 20 to 57.5 wt %, from 20 to 55 wt %, from 20 to 52.5 wt %, from 20 to 50 wt %, from 20 to 47.5 wt %, from 20 to 45 wt %, from 20 to 42.5 wt %, from 20 to 40 wt %, from 20 to 37.5 wt %, from 20 to 35 wt %, from 20 to 32.5 wt %, from 20 to 30 wt %, from 30 to 80 wt %, from 30 to 77.5 wt %, from 30 to 75 wt %, from 30 to 72.5 wt %, from 30 to 70 wt %, from 30 to 67.5 wt %, from 30 to 65 wt %, from 30 to 62.5 wt %, from 30 to 60 wt %, from 30 to 57.5 wt %, from 30 to 55 wt %, from 30 to 52.5 wt %, from 30 to 50 wt %, from 30 to 47.5 wt %, from 30 to 45 wt %, from 30 to 42.5 wt %, from 30 to 40 wt %, from 40 to 80 wt %, from 40 to 77.5 wt %, from 40 to 75 wt %, from 40 to 72.5 wt %, from 40 to 70 wt %, from 40 to 67.5 wt %, from 40 to 65 wt %, from 40 to 62.5 wt %, from 40 to 60 wt %, from 40 to 57.5 wt %, from 40 to 55 wt %, from 40 to 52.5 wt %, from 40 to 50 wt %, from 40 to 47.5 wt %, from 40 to 45 wt %, from 50 to 80 wt %, from 50 to 77.5 wt %, from 50 to 75 wt %, from 50 to 72.5 wt %, from 50 to 70 wt %, from 50 to 67.5 wt %, from 50 to 65 wt %, from 50 to 62.5 wt %, from 50 to 60 wt %, from 50 to 57.5 wt %, from 50 to 55 wt %, from 60 to 80 wt %, from 60 to 77.5 wt %, from 60 to 75 wt %, from 60 to 72.5 wt %, from 60 to 70 wt %, from 60 to 67.5 wt %, from 60 to 65 wt %. In some embodiments, the bulk density is 0.3 to 1.2 g/cm^3, 0.3 to 1.15 g/cm^3, 0.3 to 1.1 g/cm^3, 0.3 to 1.05 g/cm^3, 0.3 to 1.0 g/cm^3, 0.3 to 0.9 g/cm^3, 0.3 to 0.8 g/cm^3, 0.3 to 0.7 g/cm^3, 0.3 to 0.6 g/cm^3, 0.3 to 0.5 g/cm^3, 0.3 to 0.4 g/cm^3, 0.4 to 1.2 g/cm^3, 0.4 to 1.15 g/cm^3, 0.4 to 1.1 g/cm^3, 0.4 to 1.05 g/cm^3, 0.4 to 1.0 g/cm^3, 0.4 to 0.9 g/cm^3, 0.4 to 0.8 g/cm^3, 0.4 to 0.7 g/cm^3, 0.4 to 0.6 g/cm^3, 0.4 to 0.5 g/cm^3, 0.5 to 1.2 g/cm^3, 0.5 to 1.15 g/cm^3, 0.5 to 1.1 g/cm^3, 0.5 to 1.05 g/cm^3, 0.5 to 1.0 g/cm^3, 0.5 to 0.9 g/cm^3, 0.5 to 0.8 g/cm^3, 0.5 to 0.7 g/cm^3, 0.5 to 0.6 g/cm^3, 0.6 to 1.2 g/cm^3, 0.6 to 1.15 g/cm^3, 0.6 to 1.1 g/cm^3, 0.6 to 1.05 g/cm^3, 0.6 to 1.0 g/cm^3, 0.6 to 0.9 g/cm^3, 0.6 to 0.8 g/cm^3, 0.6 to 0.7 g/cm^3, 0.7 to 1.2 g/cm^3, 0.7 to 1.15 g/cm^3, 0.7 to 1.1 g/cm^3, 0.7 to 1.05 g/cm^3, 0.7 to 1.0 g/cm^3, 0.7 to 0.9 g/cm^3, 0.7 to 0.8 g/cm^3, 0.5 to 1.2 g/cm^3, 0.8 to 1.15 g/cm^3, 0.8 to 1.1 g/cm^3, 0.8 to 1.05 g/cm^3, 0.8 to 1.0 g/cm^3, 0.8 to 0.9 g/cm^3, 0.9 to 1.2 g/cm^3, 0.9 to 1.15 g/cm^3, 0.9 to 1.1 g/cm^3, 0.9 to 1.05 g/cm^3, or 0.9 to 1.0 g/cm^3. In some embodiments, the composition is in a dosage unit comprising a pellet in capsule formulation, wherein the capsule size is size 00, size 0, size 1, size 2 or size 3. In some preferred embodiments, the dosage unit includes pellets containing from 50 to 250 mg of amantadine in a size 0, 1, 2 or 3 capsule. In some embodiments, the dosage unit includes pellets containing from 100 to 250 mg, e.g. 100 to 200 mg of amantadine in a size 0, 1, 2 or 3 capsule, preferably a size 1, 2 or 3 capsule. In a more specific embodiment, the dosage unit comprises about 110, 120, 130,

140, 150, 160 170, 180, 190, 210, or 220 mg amantadine, or a pharmaceutically acceptable salt thereof. In another more specific embodiment, the dosage unit comprises 110 mg amantadine hydrochloride. In another more specific embodiment, the dosage unit comprises 130 mg amantadine hydrochloride. In another more specific embodiment, the dosage unit comprises 170 mg amantadine hydrochloride. In another more specific embodiment, the dosage unit comprises 210 mg amantadine hydrochloride.

Suitable plasticizers include medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, castor oil, and the like. The pellets are filled into capsules to provide the desired strength of amantadine. An advantage of this composition is it provides the desired release properties that make the composition suitable for administration during said period before bedtime. A further advantage is that the extended release coating is sufficiently durable so that the capsule can be opened and the pellets sprinkled onto food for administration to patients who have difficulty swallowing pills, without adversely affecting the release properties of the composition. When the composition is administered by sprinkling onto food, it is preferred to use a soft food such as applesauce or chocolate pudding, which is consumed within 30 minutes, and preferably within 15 minutes. A yet further advantage of the above-described composition is that it has very good batch-to-batch reproducibility and shelf-life stability.

In some embodiments, the composition of the invention has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, as measured using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. More preferably, the in vitro dissolution is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours.

In additional embodiments, 110 mg to 210 mg of ER amantadine in a size 1 capsule of the composition of the invention has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, as measured using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. More preferably, the in vitro dissolution is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more than 25-55% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 20% dissolution at 1 hour, (ii) about 25-45% dissolution at 2 hours, (iii) not more than 50-80% dissolution at 4 hours, and (iii) at least 80% dissolution at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

A preferred pellet-in-capsule compostion of the invention, in addition to having the above in vitro dissolution properties and any of the above-described pharmacokinetic properties (e.g. in vivo release profile, Tmax, Cmax/Cmin ratio, etc) that make the composition suitable for administration in said period before bedtime. The composition is further characterized by providing a Cmax of 1.6-2.4 ng/ml per mg of amantadine and an $AUC_{0\text{-}inf}$ of 40-75 ng*h/mL per mg of amantadine after oral administration of a single dose of the capsule to a human subject in a fasted state. A preferred pellet-in-capsule composition is further characterized by a steady state plasma concentration in which once daily oral administration of the capsule to a human subject provides a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine, a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and an $AUC_{0\text{-}24}$ of 48-73 ng*h/mL per mg of amantadine.

The above-described pellet-in-capsule compositions may be provided at a strength suitable for amantadine therapy. Typical strengths range from at least about 50 mg to about 250 mg. In a specific embodiment, the capsule strength is 70 mg, 80 mg, 90 mg, 110 mg, 120 mg, 125 mg, 130 mg, 140 mg, 150 mg, 160 mg, 160 mg, 170 mg, 180 mg, 190 mg, 210 mg, and 220 mg, that provides a single dose $AUC_{0\text{-}inf}$ per mg that is equivalent to a 100 mg tablet of an immediate release formulation of amantadine HCl (e.g. Symmetrel®, or other FDA Orange Book reference listed drug). One, two, or three, of such capsules can be administered to a subject in the period before bedtime. In a preferred embodiment, between 220 mg and 650 mg of amantadine is adminstered using 2 capsules of a suitable ER formulations once daily.

The invention may also be described in terms of the following numbered embodiments:

1. An extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, for use in a method of administering amantadine to a subject in need thereof, said method comprising orally administering said composition less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).
2. Use of amantadine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by the NMDA receptor to a subject in need thereof, said medicament being an extended release (ER) composition, and said treatment comprising orally administering said composition less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).
3. An extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing sleep disturbance in a human subject undergoing treatment with amantadine, said method comprising administering said composition less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).
4. Use of amantadine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing sleep disturbance in a human subject undergoing treatment with amantadine, said medicament being an extended release (ER) composition and being adapted for administration less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).
5. The use or composition of any one of embodiments 1-4 wherein administration occurs less than 1 hour before bedtime.

6. The use or composition of any one of embodiments 1-5, wherein the patient has been diagnosed with Parkinson's disease.
7. The use or composition of any one of embodiments 1-6, wherein the composition is administered once daily.
8. The use or composition of any one of embodiments 1-7, wherein the composition is added to food prior to administration.
9. The use or composition of any one of embodiments 1-8, wherein there is no increase in plasma concentration of amantadine for at least one hour after the administration at steady state.
10. The use or composition of any one of embodiments 1-9, wherein there is no increase in plasma concentration of amantadine for at least two hours after the administration at steady state.
11. The use of composition of any one of embodiments 1-10, wherein, the amantadine has a single dose Tmax of 9 to 15 hours and/or a steady state Tmax of 7 to 13 hours after administration.
12. The use or composition of any one of embodiments 1-11, wherein the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours after administration.
13. The use of composition of any one of embodiments 1-10, wherein, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours after administration.
14. The use or composition of any one of embodiments 1-11, wherein the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours after administration.
15. The use of composition of any one of embodiments 1-10, wherein, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours after administration.
16. The use or composition of any one of embodiments 1-11, wherein the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours after administration.
17. The use or composition of any one of embodiments 1-12, wherein the amantadine has a single dose Tmax of 11 to 13 hours after administration, and or a steady state Tmax of 9 to 11 hours after administration.
18. The use or composition of any one of embodiments 1-13, wherein a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration.
19. The use or composition of any one of embodiments 1-14 having a Cmax/Cmin ratio of 1.5 to 2.0.
20. The use or composition of any one of embodiments 1-15 having a Cmax/Cmin ratio of 1.7 to 1.9.
21. The use or composition of any one of embodiments 1-16, wherein the amantadine is amantadine hydrochloride or amantadine sulfate.
22. The use or composition of any one of embodiments 1-17 wherein the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof.
23. The use or composition of embodiment 18, wherein the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof.
24. The use or composition of any one of embodiments 1-19 wherein the composition comprises 200 to 420 mg of amantadine, or a pharmaceutically acceptable salt thereof.
25. The use or composition of embodiment 20, wherein the composition is administered as two unit dosage forms each comprising 110 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof.
26. The use or composition of any one of embodiments 1 to 17, wherein the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof.
27. The use or composition of embodiment 22, wherein the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof.
28. The use or composition of embodiment 23, wherein the composition comprises 110 mg amantadine hydrochloride.
29. The use or composition of any one of embodiments 1-24, wherein oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of amantadine of 1.6 to 2.4 ng/ml per mg of amantadine and an $AUC_{0\text{-}inf}$ of 40 to 75 ng*h/mL per mg of amantadine.
30. The use or composition of any one of embodiments 1-25, wherein once daily oral administration of a dose of the composition to a human subject provides a steady state plasma amantadine concentration profile characterized by:
    (i) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine,
    (ii) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and
    (iii) an $AUC_{0\text{-}24}$ of 44 to 83 ng*h/mL per mg of amantadine.
31. The use or composition of embodiment 26, wherein the steady state plasma concentration profile is further characterized by:
    (iv) no increase in plasma concentration of amantadine for at least one hour after the administration; and
    (v) a Cmax/Cmin ratio of 1.5 to 2.0.
32. The use or composition of embodiment 27, wherein the steady state plasma concentration profile is further characterized by:
    (iv) no increase in concentration of amantadine for at least two hours after the administration; and
    (v) a Cmax/Cmin ratio of 1.7 to 1.9.
33. The use or composition of any one of embodiments 1-28, wherein the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium.
34. The use or composition of embodiment 29, wherein the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours
35. The use or composition of any one of embodiments 1-30, wherein the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 8 hours that is about 5 to 15% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 12 hours that is about 10 to 40% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 18 hours that is about 25 to 60% of $AUC_{0\text{-}inf}$; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of $AUC_{0\text{-}inf}$
36. The use or composition of any one of embodiments 1-31, wherein the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional

AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

37. A pharmaceutical composition as embodied in any one of embodiments 1, 3, or 5 to 32, or the use of any one of embodiments 2, 4 or 5 to 32, wherein said composition is for oral administration and comprises a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising:
    (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and
    (b) an extended release coating surrounding the pellet core.
38. The use or composition of embodiment 32, wherein the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer.
39. The use or composition of any one of embodiments 33 or 34, wherein the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed.
40. The use or composition of embodiment 35, wherein, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 60 wt %, the binder is present in amounts from 8 to 25 wt %, the core seed is present in amounts from 8 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the povidone is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %.
41. The use or composition of any one of embodiments 33 to 36, further comprising a seal coating between the pellet core and the extended release coating.
42. The use or composition of any one of embodiments 35 to 37, wherein the wherein the pellet core comprises a binder, selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof.
43. The use or composition of any one of embodiments 18 to 38, wherein the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.
44. A composition of any one of embodiments 33 to 39, for use in a method of treating Parkinson's disease in a human subject in need thereof, said method comprising orally administering said composition.

Some embodiments herein provide a method of administering amantadine to a subject in need thereof, said method comprising orally administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than three hours before bedtime. In some embodiments, administration occurs less than 1 hour before bedtime. In some embodiments, the patient has been diagnosed with Parkinson's disease. In some embodiments, the composition is administered once daily. In some embodiments, the composition is added to food prior to administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least one hour after the administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least two hours after the administration. In some embodiments, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours. In some embodiments, the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours. In some embodiments, the amantadine has a single dose Tmax of 11 to 13 hours after administration, and/or a steady state Tmax of 9 to 11 hours. In some embodiments, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave night at steady state is 1.2 to 1.6. In some embodiments, the ratio of C-ave-morning/C-ave night at steady state is 1.3 to 1.5. In some embodiments, the average amantadine plasma concentration during the day (C-ave-day) at steady state is 500-2000 ng/ml. In some embodiments, the average amantadine plasma concentration in the morning (C-ave-morning) at steady state is 500-2000 ng/ml. In some embodiments, the amantadine is amantadine hydrochloride or amantadine sulfate. In some embodiments, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one or two unit dosage forms each comprising 130 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is within a capsule of capsule size #1. In some embodiments, the composition comprises 200 to 350 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 110 mg amantadine hydrochloride. In some embodiments, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine, and an $AUC_{0\text{-}inf}$ of 40 to 75 ng*h/mL per mg of amantadine. In some embodiments, once daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by: (a) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine; (b) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (c) an $AUC_{0\text{-}24}$ of 44 to 83 ng*h/mL per mg of amantadine. In some embodiments, the steady state plasma concentration profile is further characterized by: (d) no increase in plasma concentration of amantadine for at least one hour after the administration; and (e) a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the steady state plasma concentration profile is further characterized by: (f) no increase in concentration of amantadine for at least two hours after the administration; and (g) a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 25-55% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution

medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 20% at 1 hour, 25-45% at 2 hours, 50-80% at 4 hours, and at least 80% at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours. In some embodiments, the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of AUC_{0-inf}; a fractional AUC from 0 to 8 hours that is about 5 to 15% of AUC_{0-inf}; a fractional AUC from 0 to 12 hours that is about 10 to 40% of AUC_{0-inf}; a fractional AUC from 0 to 18 hours that is about 25 to 60% of AUC_{0-inf}; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of AUC_{0-inf}. In some embodiments, the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

Some embodiments herein provide a method of reducing sleep disturbance in a human subject undergoing treatment with amantadine, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than three hours before bedtime. In some embodiments, administration occurs less than 1 hour before bedtime. In some embodiments, the patient has been diagnosed with Parkinson's disease. In some embodiments, the composition is administered once daily. In some embodiments, the composition is added to food prior to administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least one hour after the administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least two hours after the administration. In some embodiments, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours. In some embodiments, the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours. In some embodiments, the amantadine has a single dose Tmax of 11 to 13 hours after administration, and/or a steady state Tmax of 9 to 11 hours. In some embodiments, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave night at steady state is 1.2 to 1.6. In some embodiments, the ratio of C-ave-morning/C-ave night at steady state is 1.3 to 1.5. In some embodiments, the average amantadine plasma concentration during the day (C-ave-day) at steady state is 500-2000 ng/ml. In some embodiments, the average amantadine plasma concentration in the morning (C-ave-morning) at steady state is 500-2000 ng/ml. In some embodiments, the amantadine is amantadine hydrochloride or amantadine sulfate. In some embodiments, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one or two unit dosage forms each comprising 130 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is within a capsule of capsule size #1. In some embodiments, the composition comprises 200 to 350 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 110 mg amantadine hydrochloride. In some embodiments, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine, and an AUC_{0-inf} of 40 to 75 ng*h/mL per mg of amantadine. In some embodiments, once daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by: (a) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine; (b) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (c) an AUC_{0-24} of 44 to 83 ng*h/mL per mg of amantadine. In some embodiments, the steady state plasma concentration profile is further characterized by: (d) no increase in plasma concentration of amantadine for at least one hour after the administration; and (e) a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the steady state plasma concentration profile is further characterized by: (f) no increase in concentration of amantadine for at least two hours after the administration; and (g) a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 25-55% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 20% at 1 hour, 25-45% at 2 hours, 50-80% at 4 hours, and at least 80% at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours. In some embodiments, the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of AUC_{0-inf}; a fractional AUC from 0 to 8 hours that is about 5 to 15% of AUC_{0-inf}; a fractional AUC from 0 to 12 hours that is about 10 to 40% of AUC_{0-inf}; a fractional AUC from 0 to 18 hours that is about 25 to 60% of AUC_{0-inf}; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of AUC_{0-inf}. In some embodiments, the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of

AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

Some embodiments herein provide a method of treating levodopa induced dyskinesia in a patient with Parkinson's disease, said method comprising orally administering once daily an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime. In some embodiments, administration occurs less than 1 hour before bedtime. In some embodiments, the patient has been diagnosed with Parkinson's disease. In some embodiments, the composition is administered once daily. In some embodiments, the composition is added to food prior to administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least one hour after the administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least two hours after the administration. In some embodiments, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours. In some embodiments, the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours. In some embodiments, the amantadine has a single dose Tmax of 11 to 13 hours after administration, and/or a steady state Tmax of 9 to 11 hours. In some embodiments, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave night at steady state is 1.2 to 1.6. In some embodiments, the ratio of C-ave-morning/C-ave night at steady state is 1.3 to 1.5. In some embodiments, the average amantadine plasma concentration during the day (C-ave-day) at steady state is 500-2000 ng/ml. In some embodiments, the average amantadine plasma concentration in the morning (C-ave-morning) at steady state is 500-2000 ng/ml. In some embodiments, the amantadine is amantadine hydrochloride or amantadine sulfate. In some embodiments, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one or two unit dosage forms each comprising 130 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is within a capsule of capsule size #1. In some embodiments, the composition comprises 200 to 350 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 110 mg amantadine hydrochloride. In some embodiments, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine, and an $AUC_{0\text{-}inf}$ of 40 to 75 ng*h/mL per mg of amantadine. In some embodiments, once daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by: (a) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine; (b) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (c) an $AUC_{0\text{-}24}$ of 44 to 83 ng*h/mL per mg of amantadine. In some embodiments, the steady state plasma concentration profile is further characterized by: (d) no increase in plasma concentration of amantadine for at least one hour after the administration; and (e) a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the steady state plasma concentration profile is further characterized by: (f) no increase in concentration of amantadine for at least two hours after the administration; and (g) a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 25-55% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 20% at 1 hour, 25-45% at 2 hours, 50-80% at 4 hours, and at least 80% at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours. In some embodiments, the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 8 hours that is about 5 to 15% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 12 hours that is about 10 to 40% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 18 hours that is about 25 to 60% of $AUC_{0\text{-}inf}$; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of $AUC_{0\text{-}inf}$. In some embodiments, the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

Some embodiments herein provide a pharmaceutical composition for any of the methods described herein, wherein said composition is for oral administration and comprises a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 60 wt %, the binder is present in amounts from 8 to 25 wt %, the core seed is present in amounts from 1 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the povidone is present in

amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %. In some embodiments, the composition further comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.

Some embodiments herein provide a method of administering amantadine, or a pharmaceutically acceptable salt thereof, to a human subject in need thereof, said method comprising orally administering a pharmaceutical composition comprising amantadine in a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 60 wt %, the binder is present in amounts from 8 to 25 wt %, the core seed is present in amounts from 1 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the povidone is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %. In some embodiments, the composition further comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil. Some embodiments comprise treating Parkinson's disease in a human subject in need thereof.

Some embodiments herein provide a pharmaceutical composition suitable for once daily oral administration to a patient in need thereof said composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. In some embodiments, the composition comprises 110-220 mg of amantadine or pharmaceutically acceptable salt thereof. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 40-80% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition comprises a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, the composition comprises amantadine and, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 70 wt %. In some embodiments, the pellet core comprises a core seed comprising sugar or microcrystalline cellulose that is between 100 and 500 microns in diameter. In some embodiments, the bulk density is between 0.5 and 1 gm/cm^3. In some embodiments, the composition comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.

Some embodiments herein provide a method of treating Parkinson's disease in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. In some embodiments, the composition comprises 110-220 mg of amantadine or pharmaceutically acceptable salt thereof. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 40-80% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition comprises a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, the composition comprises amantadine and, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 70 wt %. In some embodiments, the pellet core comprises a core seed comprising sugar or microcrystalline cellulose that is between 100 and 500 microns in diameter. In some embodiments, the bulk density is between 0.5 and 1 gm/cm^3. In some embodiments, the composition comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.

Some embodiments herein provide a method of treating levodopa induced dyskinesia in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. Some embodiments herein provide a method of treating traumatic brain injury in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size

0 or smaller capsules in a single daily administration. Some embodiments provide a method of treating traumatic brain injury in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. Some embodiments provide a method of treating fatigue in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. In some embodiments, the composition comprises 110-220 mg of amantadine or pharmaceutically acceptable salt thereof. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 40-80% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition comprises a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, the composition comprises amantadine and, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 70 wt %. In some embodiments, the pellet core comprises a core seed comprising sugar or microcrystalline cellulose that is between 100 and 500 microns in diameter. In some embodiments, the bulk density is between 0.5 and 1 gm/cm^3. In some embodiments, the composition comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil. In some embodiments, the method comprises administering the composition to a patient less than three hours before bed time.

The present invention may be better understood by reference to the following examples, which are not intended to limit the scope of the claims.

EXAMPLE 1

Amantadine Extended Release Coated Pellet Formulations

Amantadine HCl extended release coated pellet compositions designed for nighttime administration were prepared using the components and relative amounts shown in Table 1 below. For each composition, the drug coating solution was prepared by adding HPMC 5 cps and Copovidone to isopropyl alcohol with continuous stirring. Purified water was added to this dispersion and stirring continued until a clear solution is formed. Drug (Amantadine HCl) was then added to this binder solution and stirring continued until the drug was completely dissolved. Finally, talc was added and dispersed uniformly by stirring.

Celphere beads (screen sizes #35 to #50 i.e. 300 to 500 micron) were loaded in a Wurster coating unit. The drug coating dispersion was sprayed onto the beads followed by a period of drying. The resulting drug coated pellets were sieved to retain the fraction between screens #18 and #24 (approximately 700 μm to 1 mm diameter).

The seal coating solution was prepared by adding HPMC 5 cps to isopropyl alcohol with continuous stirring. Purified water was added to this dispersion and stirring continued until a clear solution was formed. Talc was added and dispersed uniformly by stirring. The sieved drug coated pellets were loaded in a Wurster coating unit. The seal coating dispersion was sprayed over the drug coated pellets followed by a period of drying to remove the residual solvent and water in the pellets. The resulting seal coated pellets were sieved to retain the fraction between screens #18 and #24.

The ER coating solution was prepared by dissolving ethyl cellulose (viscosity 7 cps) in isopropyl alcohol and purified water and stirring until a clear solution was formed. Povidone K-90 was then dissolved in this clear solution followed by addition of plasticizer Miglyol 812N with continuous stirring to form a clear solution. The sieved seal coated pellets were loaded in a Wurster coating unit. The ER coating solution was sprayed over the seal coated pellets followed by a period of drying to affect the ER coat and remove the residual solvent and water in the pellets. After drying, magnesium stearate was spread on the top bed of the coated pellets in the annulus region followed by recirculation of the pellets in the Wurster unit to blend the magnesium stearate with the coated pellets. The resulting ER coated pellets were sieved to retain the fraction between screens #18 and #24.

The desired weight of the ER coated pellets containing the unit dose were filled into empty 1 hard gelatin capsule shell (size 1 for 100-140 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 1

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Pellet Core		
Amantadine Hydrochloride USP	Active	40-50%
Microcrystalline cellulose spheres (Celphere ®)	Core seeds	10-15%
Hydroxypropyl methyl cellulose 5 cps USP	Binder	10-15%
Copovidone	Binder	1-5%
Talc USP	Anti-tack	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Seal Coating (optional)		
Hydroxypropyl methyl cellulose 3 cps USP	Coating polymer	5-10%
Talc USP	Anti-tack	0-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Extended Release Coating		
Ethyl cellulose	Coating polymer	10-20%
Povidone	Pore former	1-5%
Medium chain triglycerides	Plasticizer	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]

TABLE 1-continued

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Magnesium Stearate NF	Lubricant	0-1%
Density of pellets		0.6-0.9 gm/cm^3

NF = National Formulary
[1]Purified water and isopropyl alcohol are removed during processing.

The in vitro dissolution of capsules prepared above was tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. Capsules meeting desired dissolution specifications released not more than 25% of the drug in 2 hours, 40-80% in 6 hours, and at least 80% at 12 hours. In an exemplary dissolution profile, there was 0% drug release at 1 hour, 12% release at 2 hours, 43% release at 4 hours, 68% release at 6 hours, 83% release at 8 hours, 92% release at 10 hours, and 97% release at 12 hours. Capsules prepared in accordance with the above method exhibited good shelf-stability, and batch-to-batch reproducibility upon scale-up.

EXAMPLE 2

Amantadine Extended Release Coated Pellet Formulation with Higher Drug Loading

Amantadine HCl extended release coated pellet compositions designed for nighttime administration are prepared using the components and relative amounts shown in Table 2 below and the manufacturing process described in example 1.

The diameter of the inert cores is 200-300 microns. The diameter of the coated pellets is 600-1200 microns. The bulk density of the coated pellets is 0.7-1.2 g/cm^3.

The desired weight of the ER coated pellets containing the unit dose are filled into an empty hard gelatin capsule shell (size 1 for 170 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 2

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Pellet Core		
Amantadine Hydrochloride USP	Active	50-65%
Microcrystalline cellulose spheres (Celphere ®)	Core seeds	1-15%
Hydroxypropyl methyl cellulose USP	Binder	5-25%
Copovidone	Binder	1-5%
Talc USP	Anti-tack	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Seal Coating (optional)		
Hydroxypropyl methyl cellulose USP	Coating polymer	0-10%
Talc USP	Anti-tack	0-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Extended Release Coating		
Ethyl cellulose	Coating polymer	10-20%
Povidone	Pore former	1-5%
Medium chain triglycerides	Plasticizer	1-5%
Isopropyl alcohol	Solvent	—[1]

TABLE 2-continued

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Water	Solvent	—[1]
Magnesium Stearate NF	Lubricant	0-1%

NF = National Formulary
[1]Purified water and isopropyl alcohol are removed during processing.

The in vitro dissolution of capsules prepared above are tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium and release not more than 25% of the drug in 2 hours, 40-80% in 6 hours, and at least 80% at 12 hours.

EXAMPLE 3

Amantadine Extended Release Coated Pellet Formulations

Amantadine HCl extended release coated pellet compositions suitable for nighttime administration were prepared using the components and relative amounts shown in Table 3 below and the manufacturing process described in Example 1.

The desired weight of the ER coated pellets containing the unit dose was filled into empty #1 hard gelatin capsule shell (100 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 3

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule A	B	C
Pellet Core				
Amantadine Hydrochloride USP	Active	50.15%	47.94%	45.15%
Microcrystalline cellulose spheres (Celphere ®)	Core seeds	14.33%	13.70%	12.90%
Hydroxypropyl methyl cellulose USP	Binder	13.37%	12.79%	12.04%
Copovidone	Binder	3.34%	3.2%	3.01%
Talc USP	Anti-tack	2.51%	2.4%	2.26%
Isopropyl alcohol	Solvent	—[1]	—[1]	—[1]
Water	Solvent	—[1]	—[1]	—[1]
Seal Coating (optional)				
Hydroxypropyl methyl cellulose USP	Coating polymer	7.61%	7.27%	6.85%
Talc USP	Anti-tack	0.76%	0.73%	0.69%
Isopropyl alcohol	Solvent	—[1]	—[1]	—[1]
Water	Solvent	—[1]	—[1]	—[1]
Extended Release Coating				
Ethyl cellulose	Coating polymer	6.23%	9.46%	13.53%
Povidone	Pore former	0.85%	1.29%	1.84%
Medium chain triglycerides	Plasticizer	0.75%	1.13%	1.62%
Isopropyl alcohol	Solvent	—[1]	—[1]	—[1]
Water	Solvent	—[1]	—[1]	—[1]
Magnesium Stearate NF	Lubricant	0.1%	0.1%	0.1%

NF = National Formulary
[1]Purified water and isopropyl alcohol are removed during processing.

The in vitro dissolution of capsules prepared above were tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. The results are shown in FIG. **1**.

EXAMPLE 4

Amantadine Extended Release Formulation Made by Extrusion Spheronization

Amantadine HCl extended release compositions designed for nighttime administration are prepared using the components and relative amounts shown in Table 4 below and the manufacturing process described below.

A blend of amantadine HCl, microcrystalline cellulose and lactose monohydrate was prepared and a wet mass is prepared in a high shear granulator using an aqueous solution of povidone. The wet mass is extruded using 1 mm sieve and extruded mass is spheronized using a spheronizer. The pellets are dried in a tray drier to yield core pellets. The core pellets are coated with extended release coating solution in a pan coater. The desired weight of the ER coated pellets containing the unit dose is filled into empty 1 hard gelatin capsule shell (170 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 4

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Pellet Core		
Amantadine Hydrochloride USP	Active	59.40%
Microcrystalline cellulose	Diluent	18.67%
Lactose monohydrate	Diluent	6.15%
Povidone	Binder	0.64%
Water	Solvent	—[1]
Extended Release Coating		
Ethyl cellulose	Coating polymer	12.41%
Polyethylene glycol	Pore former	1.24%
Dibutyl sebacate	Plasticizer	1.49%
Ethanol	Solvent	—[1]

The in vitro dissolution of capsules prepared above are tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium and release not more than 25% of the drug in 2 hours, 40-80% in 6 hours, and at least 80% at 12 hours.

EXAMPLE 5

Pharmacokinetic Measurement of Formulations of Amantadine ER Compared to IR Amantadine

Objective: The primary objective of the study was to confirm the PK properties of extended release formulations in example 3, to determine the pharmacokinetic profiles, safety and tolerability of three prototype formulations of ER capsules of amantadine HCl described with different release properties in Example 3 relative to a 100 mg film-coated IR amantadine HCl tablet (SYMMETREL®) given as single doses to healthy adult subjects under fasting conditions.

Study design: This was a Phase 1, randomized, single dose, open-label, four-period, crossover, fasting pharmacokinetic study in which single 100 mg doses of three formulations of Amantadine ER capsules with different release properties were compared to single 100 mg doses of marketed amantadine IR tablets (SYMMETREL®). The three ER formulations differed in the amantadine release rates in vitro, as shown in FIG. **1**.

Methods: Subjects were admitted to the unit for the first period of dosing within 21 days of study screening. Subjects were dosed on the day after checking into the unit and discharged at 24 hours post dose. Subjects were asked to return after discharge for follow-up visits at 56 hours and 152 hours after dosing. Each dosing period was separated by at least 7 day washout.

After an overnight fast, the formulation was administered to the subjects while in a sitting position with 240 mL of water. Blood samples were collected at 0 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 24 (discharge), and 56 hours following each dose. Plasma samples were assayed for amantadine by a validated liquid chromatography/tandem mass spectroscopy (LC/MS/MS) method. Pharmacokinetic parameters were calculated using a non-compartmental analysis with WinNonlin software (version 4.1 or higher; Pharsight Corporation).

An analysis of variance (ANOVA) was performed on the natural logarithms of Cmax and AUC0-∞ determined from the data following a single dose of study drug using linear mixed effects model. The model included effects for subject, sequence, period, and regimen. The effects of sequence, period, and regimen were fixed, while the effect of subject was random. Ratio of ER to IR for both AUC (relative bioavailability for ER formualtions) and Cmax was calculated. (Adverse events were monitored throughout the study. Vital signs (pulse rate, blood pressure and body temperature), clinical laboratory measures (biochemistry, hematology, and urinalysis) and ECGs were collected at various times during the study.

Results: A total of 20 subjects participated in the study. The mean age was 25.5 years old (range 20-38 years). The study consisted of 8 male (40%) and 12 female (60%) subjects with a mean body mass index (BMI) of 23.6 kg/m2±2.85. The racial makeup was 100% Caucasian. Fifteen subjects received all 4 treatments.

The PK results from this study showed that all three of the Amantadine ER formulations reduced the rate of absorption, based on the reduced values of Cmax and increased Tmax, compared to SYMMETREL® (Table 5, FIGS. **5**, **6**). The IR formulation had the highest mean Cmax (277±73.9 ng/mL) and shortest median Tmax (4 h) values. Formulations A, B, and C produced progressively lower Cmax and longer Tmax values. Cmax decreased from 204±61.4 to 166±34.8 to 149±34.4 ng/mL, and median Tmax increased from 7.0, to 11.0, to 14.0 h for formulations A, B, and C, respectively. Total amantadine exposure, as measured by AUC0-∞, was slightly lower in all three Amantadine ER formulations than SYMMETREL® but all three formulations had acceptable bioavailability (85-95%).

TABLE 5

Single Dose Pharmacokinetic Parameters of Three Formulations of Amantadine ER (Formulation A, B, and C), as Compared to SYMMETREL ® (Formulation IR)

Parameter[a]	100 mg Formulation A (n = 19)	100 mg Formulation B (n = 17)	100 mg Formulation C (n = 18)	100 mg Formulation IR (n = 18)
C_{max} (ng/mL)	204 ± 61	166 ± 35	149 ± 34	277 ± 74
T_{max} (h) [range]	7 [5-11]	11 [5-15]	14 [9-18]	4 [2-6]
$A_{UC0\text{-}last}$ (ng * h/mL)	5064 ± 1573	5028 ± 2328	4525 ± 1268	5488 ± 1730
$AUC_{0\text{-}\infty}$ (ng * h/mL)	5545 ± 1904	5724 ± 2369	5652 ± 2581	5907 ± 1907
$t_{1/2}$ (h)	13.9 ± 3.0	16.3 ± 5.2	18.3 ± 7.5	12.3 ± 3.5

[a]All parameters are reported as the mean ± standard deviation (SD), except t_{max} which is reported as a median value (min to max range)

TABLE 6

Ratio ER/IR for C_{max} and $AUC_{0\text{-}\infty}$

Comparison	Variable	ER/IR[a]
A vs. IR	C_{max} (ng/mL)	66.0%
	$AUC_{0\text{-}\infty}$ (ng * h/mL)	85.3%
B vs. IR	C_{max} (ng/mL)	60.9%
	$AUC_{0\text{-}\infty}$ (ng * h/mL)	94.6%
C vs. IR	C_{max} (ng/mL)	51.2%
	$AUC_{0\text{-}\infty}$ (ng * h/mL)	88.5%

[a]Point estimate of the geometric mean ratio (ER/IR).

EXAMPLE 6

Food-Effect Evaluation of Amantadine ER

Objective: The primary objective was to demonstrate that the amantadine ER formulations suitable for nighttime administration exhibit excellent bioavailability when administered with food. We determined the pharmacokinetics of a 100 mg capsule of an amantadine ER formulation (Example 3, Formulation B), when administered both with a high fat meal and in a fasted state.

Study Design: This was a Phase 1, randomized, single dose, open-label, two-period, crossover, food-effect study to compare single 100 mg doses of Formulation I in healthy adult (18 to 45 years of age) male and female subjects in fed and fasted states. The study consisted of a 21-day to −2 day screening phase (prior to the scheduled dosing day) and two treatment periods, Period 1 and Period 2, with an 8-day wash-out period between treatment periods.

Methods: After an overnight fast, the formulation was administered to the subjects while in a sitting position with 240 mL of water at ambient temperature for the fasted condition. For the fed condition, after the overnight fast, subjects were served a high fat and high calorie test meal (Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies, December 2002) as breakfast, which they were required to consume completely within 30 minutes before taking the study medication. Subjects were randomized to one of two sequences, each composed of treatment administration under fed and fasted conditions separated by an eight day wash out period.

For each period, pharmacokinetic blood samples were collected at pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 24, 28, 48, 72, 96 and 144 hours after dosing in each period. Subjects were housed in the clinical facility at least 15 hours before investigational product administration and remained in the clinical facility for at least 28 hours after administration of the investigational product in each period. Samples after 28 hours in each period were collected on an ambulatory basis. Amantadine in plasma was quantified by a validated LC/MS/MS method. The pharmacokinetic parameters were calculated from the drug concentration-time profile by non-compartmental model using WinNonlin Professional Software-Version 5.0.1 (Pharsight Corporation, USA) for amantadine. Absence of food effect was defined as met if the point estimates and 90% confidence intervals (CI) for the ln-transformed C_{max}, AUC_{last} and AUC_{∞} fed/fasting ratios of the population means were entirely within the standard accepted range of 80% to 125%. All statistical analyses for amantadine were performed using PROC MIXED of SAS® Release 9.1.3 (SAS Institute Inc., USA).

Routine safety monitoring was conducted during and after dosing in all subjects.

Results: A total of 26 subjects participated in the study, 19 (73%) male and 7 (27%) female. The mean age was 26 years (range 19-44) and the mean BMI was 22.4 kg/m^2 (range 18.1-29.8). The racial makeup was 100% Asian. All subjects received at least one dose of study drug and were included in the safety analysis. Twenty-four (92.3%) subjects completed the study and were included in the pharmacokinetic analysis. Two subjects (7.7%) were withdrawn prior to completion of the study due protocol deviations.

The results of this study (Table 7) indicate that the single dose pharmacokinetics of Formulation B are not affected by food. The rate, as measured by C_{max}, and the extent, as measured by $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$, of absorption of amantadine, administered with and without food, were equivalent (Table 8).

TABLE 7

Mean ± SD Pharmacokinetic Parameters after Single Dose Administration of 100 mg of Formulation B in Fed and Fasted States

	Mean ± SD (Un-transformed data) n = 24	
Parameters (Units)[a]	Fasted State	Fed State
T_{max} (h)	11.9 ± 2.1 (8-15)	9.5 ± 2.4 (5-16)
C_{max} (ng/mL)	198.8 ± 34.7	219.4 ± 41.5
$AUC_{0\text{-}last}$ (ng * h/mL)	5571.2 ± 1654.2	5394.4 ± 1581.5
$AUC_{0\text{-}\infty}$ (ng * h/mL)	5663.1 ± 1677.4	5476.6 ± 1590.7
$t_{1/2}$ (h)	11.9 ± 2.8	11.5 ± 2.0
t_{lag} (h)	1.0	2.0

[a]All parameters are reported as the mean ± standard deviation (SD). t_{max} is reported as the mean ± SD (min to max range).

TABLE 8

Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Formulation B (n = 24) in Fed and Fasted States

Parameters (Units)	ln-transformed data Geometric Least Squares Mean Fed State	Fasted State	Ratio (Fed/Fasted)%	90% Confidence Interval (Parametric)
C_{max} (ng/mL)	215.6	195.8	110.1	104.4-116.2%
$AUC_{0\text{-}last}$ (ng * h/mL)	5195.9	5344.2	97.2	91.0-103.8%
$AUC_{0\text{-}\infty}$ (ng * h/mL)	5280.3	5434.7	97.2	90.9-103.8%

Conclusion: The results of this study indicate that the single dose pharmacokinetics of amantadine ER are not affected by food. The rate, as measured by C_{max}, and the extent, as measured by $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$, of absorption of amantadine, administered with and without food, were equivalent.

EXAMPLE 7

Pharmacokinetic Study Comparing Once-daily Administration of Amantadine HCl ER Capsules with Twice-daily Administration of Amantadine HCl IR Tablets in Healthy Adults Under Fasting Conditions

Objective: The primary objective of this study was to measure at steady state under repeat or chronic dosing the pharmacokinetics of an ER amantadine formulation suitable for nighttime administration, and enable the calculation of critical PK parameters for future safety and efficacy studies (i.e., Cave-morning, Cave-day, Cave-night) of ER amantadine formulations administered at night. We compared the single dose and repeat dose pharmacokinetics of amantadine HCl administered twice daily as a commercially available immediate release (IR) formulation to a once daily amantadine extended release (ER) formulation (Example 3, Formulation B).

Study Design: This was a two period, multiple dose, crossover study. After a 21 day screening period, 26 healthy male and female subjects were randomized to receive one of two treatments (amantadine ER 200 mg once daily or amantadine IR 100 mg twice daily) in Period-I, then crossed over to receive the other treatment in Period-II.

Methods: Study drug administration started on day 1. Study drug was not administered on Day 2. Multiple dosing commenced on day 3 and continued for 7 days (through day 9). A washout period of 8 days separated the dose administrations. The study drug was administered with 240 mL of drinking water. No other fluids were allowed within 1 hour of dosing. For each period, pharmacokinetic blood samples were collected at pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 24, 28, 36, and 48 hours after the first dose. The morning trough (pre-dose) blood samples were collected on Days 7 and 8. Blood samples were again collected immediately before the morning dose on Day 9 and at 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 24, 28, 48, 72, and 96 hours thereafter. Samples after 28 hours following the morning dose on day 9 were collected on an ambulatory basis in each period. Amantadine in plasma was quantified by a validated LC/MS/MS method. The pharmacokinetic parameters were calculated from the drug concentration-time profile by non-compartmental model using WinNonlin Professional Software-Version 5.0.1 (Pharsight Corporation, USA) for amantadine.

Statistical analyses were conducted to assess the pharmacokinetic profile of single dose and repeat dose amantadine HCl administered twice daily as a commercially available immediate release (IR) formulation compared to a once daily extended release (ER) formulation (Formulation B). An analysis of variance (ANOVA) was performed on the natural logarithms of C_{max}, C_{min}, and AUC_{24} determined from the data following the dose of study drug on study day 9 using linear mixed effects model. The model included the fixed effects for sequence, period, regimen and a random subject effect. The confidence intervals were used to perform the 2 one-sided tests procedure for equivalence assessment. The confidence intervals were obtained by exponentiating the endpoints of the confidence intervals for the difference of mean logarithms obtained within the framework of the ANOVA model. The upper and lower limits of confidence intervals from the natural-log transformed data were back-exponentiated to obtain the 90% confidence interval for the ratio of geometric means. Equivalence was established if the exponentiated 90% confidence interval fell entirely within the interval (80.00%, 125.00%).

Repeated measures ANOVA was carried out for comparison of C_{min} for day 7, 8 and 9 at 5% level of significance on both untransformed and ln-transformed data. Steady state was demonstrated if the repeated measures ANOVA test was found to be non-significant. The statistical analysis for amantadine was performed using PROC MIXED of SAS® Release 9.1.3 (SAS Institute Inc., USA).

Routine safety monitoring was conducted during and after dosing in all subjects, and at the end of the study.

Results: A total of 26 subjects participated in the study, 22 (84.6%) male and 4 (15.4%) female. The mean age was 26 years (range 19-42) and the mean BMI was 22.9 kg/m^2 (range 18.1-28.8). The racial makeup was 100% Asian. All subjects received at least one dose of study drug and were included in the safety analysis. Twenty-four (92.3%) subjects completed the study and were included in the pharmacokinetic analysis. Two subjects (7.7%) were withdrawn from the PK analysis prior to completion of the study due to vomiting within 12 hours of dosing, which was a pharmacokinetic exclusion criterion.

As expected from its half-life, once daily administration of amantadine ER and twice daily dosing of amantadine IR resulted in accumulation as measured by higher C_{max} and AUC on Day 9 compared to Day 1 (Table 9 and FIG. **2**). Steady state was achieved by Day 9 for both formulations as demonstrated by similar trough levels on Days 7, 8 and 9 (data not shown). At steady state (Day 9) plasma concentrations (FIG. **2**, Table 9) and pharmacokinetic parameters (Table 9) were comparable for both formulations. Furthermore, the formulations are equivalent in terms of the extent and the rate of absorption of amantadine as measured by steady state C_{max}, C_{min} and $AUC_{0\text{-}24}$ (Table 9), where equivalency is defined by the 90% CIs of the ratio of the least square means of the test versus reference for steady state C_{max}, C_{min} and $AUC_{0\text{-}24}$ of Amantadine ER to Amantadine IR falling within 80%-125%.

TABLE 9

Mean (±SD) Pharmacokinetic Parameters of Amantadine after Single and Multiple Dose Administration of IR (100 mg BID) and ER (200 mg QD) Formulations

	Formulation			
	IR (n = 24)		ER (n = 24)	
Parameter (Units)[a]	Day 1	Day 9	Day 1	Day 9
$t_{1/2}$ (h)	13.2 ± 2.8 [9.1-18.8]	12.6 ± 2.4 [9.4-18.1]	13.7 ± 3.6 [9.1-22.7]	12.8 ± 2.2 [9.2-17.4]
t_{max} (h)	14.42 ± 0.88 [13-16]	12.6 ± 4.5 [1-15]	11.4 ± 1.9 [8-18]	10.3 ± 2.0 [8-18]
C_{max} (ng/mL)	530 ± 80 [407.5-752.7]	728 ± 153 [538.4-1101.8]	431 ± 84 [313.5-559.9]	665 ± 179 [444.4-1140.0]
$AUC_{0\text{-}last}$ (ng h/mL)	11989 ± 2224 [9243-17106]	23040 ± 8273 [13133-46446]	11171 ± 2773 [7326-16970]	21362 ± 8946 [10821-47134]
$AUC_{0\text{-}\infty}$ (ng h/mL)	13685 ± 3324 [10167-20989]	NA	12900 ± 4087 [7817-22153]	NA
$AUC_{0\text{-}24}$ (ng h/mL)	7695 ± 1026 [5967-10171]	13752 ± 3586 [9085-22519]	7173 ± 1367 [5021-9552]	12680 ± 3879 [7896-23058]
C_{min} (ng/mL)	—	412.4 ± 142.6 [218.5-795.2]	—	374.9 ± 151.7 [172.2-767.1]

[a]All parameters are reported as the mean ± SD, [min to max range]
NA = not applicable

Certain additional PK parameters that are important in determining the suitability of the ER amantadine formulation for once daily, night time administration are also reported in Table 10.

TABLE 10

Additional Steady State PK parameters of Amantadine ER

	ER 200 mg QD	IR 100 mg BID
Cmax/Cmin	1.86	1.68
C-ave-8-16 hrs (ng/ml)	614	586
C-ave-8-12 hrs (ng/ml)	643	510
C-ave-16-24 hrs (ng/ml)	502	569
C-ave-0-8 hrs (ng/ml)	465	586
C-ave-8-16 hrs/C-ave-0-8 hrs	1.32	1.00
C-ave-8-12 hrs/C-ave-0-8 hrs	1.38	0.87
% Change in Plasma Concentration 0-3 hrs	5%	55%
% Change in Plasma Concentration 0-4 hrs	23%	48%
AUC 0-4 as % of AUC 24	12%	N/A
AUC 0-8 as % of AUC 24	30%	N/A
AUC 0-12 as % of AUC 24	51%	N/A

Conclusion: the ER amantadine formulation exhibits the desired steady state PK properties that would make the same suitable for administration at night and for achieving desired efficacy and tolerability benefits. Specifically, the ER amantadine formulation administered once daily at night results in relatively slow initial rise in amantadine plasma concentration, higher average amantadine plasma concentrations 8 to 12 hours after administration relative to 0-8 hours after administration and thus if administered at night higher ratios of average day time to night time amantadine plasma concentrations relative to IR amantadine. Thus this formulation is well suited for administration at higher doses than current practice that are expected to be relatively well tolerated and potentially provide superior efficacy in the treatment of LID, fatigue and Parkinson's disease.

EXAMPLE 8

Study Comparing Administration of Amantadine HCl ER Capsules Once Nightly with Twice-daily Administration of Amantadine HCl IR Tablets in Normal Healthy Volunteers

Objective: The primary objective is to compare the effects on sleep of amantadine extended release (ER) capsules (Formulation B) administered once daily at bedtime with amantadine immediate release (IR) tablets administered twice daily in normal healthy volunteers. This ER formulation exhibits a Cave,day/Cave, night=1.30.

Study Design: This is a single-center, double-blind, triple-dummy, randomized, crossover study to compare the effects on sleep of amantadine ER capsules, QHS, amantadine IR tablets BID, and caffeine caplets (active comparator) in 30 normal healthy volunteers as assessed by overnight polysomnography (PSG) and standardized questionnaires (Stanford Sleepiness Scale (SSS); Modified Epworth Sleepiness Scale (m-ESS)/Karolinska Sleepiness Scale (KSS); Toronto Hospital Alertness Test (THAT)/ZOGIM Alertness Scale (ZOGIM-A); Visual analog scale of sleepiness/alertness (VAS)).

Study drugs are administered in 3 dosing periods. A single day's dosage of one drug is administered per dosing period. Each day of dosing is separated by a washout period of 1 week. A single day's dosage of amantadine ER (Formulation B) consists of one 220 mg capsule (or 2×110 mg capsule) administered at bed time (QHS; defined as 23:00 h for the purposes of this study). A single day's dosage of amantadine IR consists of one 100 mg capsule administered twice a day (BID; defined as 8:00 h and 16:00 h for the purposes of this study). A single day's dosage of caffeine consists of one 100 mg capsule administered three times a day (TID; defined as 8:00 h, 16:00 h, & 23:00 h for the purposes of this study).

All subjects are dosed three times a day, at 8:00 h, 16:00 h, & 23:00 h. At each hour of dosing, every subject receives either the active drug or the matching placebo for each of the 3 treatments. Whether the capsule, tablet, or caplet administered at a specific hour of dosing contains active study drug

or is a placebo dummy is determined according to the dosing sequence and period to which the subject is assigned.

Consented subjects who meet eligibility criteria are randomized equally to one of 3 treatment sequences (groups), each comprising 3 single-day treatment periods separated by 1 week washout periods as described above. Additionally, there is a one-day, single-blind, placebo run-in prior to each double-blind dosing day. This is to allow subjects to acclimate to sleeping in the Clinical Research Unit (CRU) under conditions of PSG recording and to establish individual baseline (BL) PSG characteristics.

For each dosing period, subjects are admitted to a CRU equipped with a sleep laboratory the day before the first day of dosing with active study drug. They stay in the CRU overnight and through the entirety of the active drug-dosing day. They again stay overnight and then are discharged from the CRU the morning of the following day. For the first dosing period, the day of admission to the CRU (Day-1) constitutes the last day of the screening phase, and the day of discharge from the CRU constitutes the first day of the first washout period (Day 2). For the second dosing period, the day of re-admission to the CRU (Day 7) constitutes the last day of the first washout period, and the day of discharge (Day 9) will constitute the first day of the second washout period. For the third dosing period, the day of re-admission to the CRU (Day 14) constitutes the last day of the second washout period, and the day of discharge (Day 16) constitutes the first day of the follow-up phase.

On the day of admission (or re-admission) to the CRU, subjects undergo routine laboratory and vital sign testing. They are administered one each of the placebo dummies (for amantadine ER, amantadine IR, & caffeine) at 16:00 h and at 23:00 h in single-blind fashion. They are questioned for adverse events (AEs) and have vital signs checked immediately prior to each dosing. Blood is drawn for routine laboratory testing and toxicology screen prior to the 16:00 h dosing. Subjects spend the night in the sleep lab under conditions of PSG recording.

On the day of dosing with active study drug, subjects are awakened at 7:00 h and fill out a battery of sleep and alertness questionnaires They receive study drug (active or placebo) at 8:00 h, 16:00, and 23:00 h. They are questioned for AEs and have vital signs checked immediately prior to each dosing. Blood is drawn to measure plasma amantadine concentrations prior to the 23:00 h dosing.

On the day after dosing with active study drug, subjects are awakened at 7:00 h and fill out a battery of sleep and alertness questionnaires Shortly before 8:00 h, i.e., 9 hours after the last dosing time, they are questioned for AEs and have vital signs checked. Also, blood is drawn to measure plasma amantadine concentrations. Instructions for contacting the site to report any AEs are reviewed with the subjects prior to their discharge from the CRU. The schedule for returning to the PSU for the next dosing period (this applies to returning for Periods 2 & 3) or for telephone contact (this applies to the follow-up after the third dosing period) is be reviewed.

All subjects receive a follow-up telephone call 3 days following discharge from the CRU (Day 19).

AEs and concomitant medications are monitored throughout the study. Blood samples for measurement of blood plasma concentrations are drawn immediately prior to the 23:00 h dosing time on Days 1, 8, and 15, and at approximately 8:00 h on Days 2, 9, and 16.

Sleep parameters and measurements of sleepiness and alertness at each time point are listed by subject. Both composite scores and scores from the individual components of the PSG and questionnaires are tabulated and analyzed. For each parameter measured, descriptive summary statistics are calculated by sequence and treatment, including means (or medians, as appropriate), ranges, and standard deviations (SDs).

Inferential statistics are performed on selected results wherein the magnitude of the differences between the means across treatment groups relative to the variance suggests a possible differential treatment effect. Continuous variable data is analyzed by parametric statistics (repeated measures analysis of variance with appropriate supplemental post-hoc analyses and/or paired t-test). Categorical data and data not conforming to a normal distribution is analyzed by non-parametric statistics (Wilcoxon signed rank test). PSG data may also be assessed by multivariate analyses and/or spectral analyses.

Results: A lack of increase in, or reduction of, sleep disturbances with QD administration of 220 mg of amantadine ER compared to BID administration of amantadine IR, as measured by PSG and a standardized sleep questionnaire (e.g. SSS, m-ESS, KSS, THAT, ZOGIM-A, or VAS), demonstrates the suitability of amantadine ER for once daily administration at bedtime.

EXAMPLE 9

Study Comparing the Effects on Sleep and Efficacy of Amantadine HCl ER Capsules Administered once Daily at Night Relative to Amantadine HCl IR Capsules Administered Twice Daily in Parkinson's Patients

Objective: To compare the effects on sleep and efficacy of amantadine extended release (ER) capsules.

Study Design: This is a Multi-Center, Double-Blind, Randomized Study to Compare the Effects on Sleep and Efficacy of Amantadine Extended Release (ER) Capsules in 120 Parkinsons Patients as assessed by UPDRS (Unified Parkinson's Disease Rating Scale), UPDRS-IV (Unified Parkinson's Disease Rating Scale Part IV), AIMS (Abnormal Involuntary Movement Scale), overnight polysomnography (PSG) and standardized questionnaires (Stanford Sleepiness Scale (SSS); Modified Epworth Sleepiness Scale (m-ESS)/Karolinska Sleepiness Scale (KSS); Toronto Hospital Alertness Test (THAT)/ZOGIM Alertness Scale (ZOGIM-A); Visual analog scale of sleepiness/alertness (VAS)).

All study drugs are administered orally. Treatment A consists of a placebo capsule administered in the morning and two 110 mg capsules of Amantadine (ER) and a placebo capsule administered at bed time. Treatment B consists of a placebo capsule administered in the morning and three 110 mg capsules of Amantadine (ER) administered at bed time. Treatment C consists of a 100 mg capsule of Amantadine IR administered in the morning and a 100 mg capsule of Amantadine IR and two placebo capsules administered at bed time. Treatment D consists of a placebo capsule administered in the morning and 3 placebo capsules administered at bed time.

Consented subjects who meet eligibility criteria are randomized equally to one of 3 treatment groups, each comprising 14-day treatment periods. Additionally, there is a one-day, single-blind, placebo run-in prior to each double-blind dosing day. This is to allow subjects to acclimate to sleeping in the Clinical Research Unit (CRU) under conditions of PSG recording and to establish individual baseline (BL) PSG characteristics.

For each dosing period, subjects are admitted to a CRU equipped with a sleep laboratory the day before the first day of dosing with active study drug. They stay in the CRU overnight and through the entirety of the active drug-dosing day. They again stay overnight and then are discharged from the CRU the morning of the following day.

Parkinson's scores are recorded in the mornings on days 1, 7 and 14 using standard scoring methods, including the UPDRS and AIM.

AEs and concomitant medications are monitored throughout the study.

Sleep parameters and measurements of sleepiness and alertness at each time point are listed by subject. Both composite scores and scores from the individual components of the PSG and questionnaires are tabulated and analyzed. For each parameter measured, descriptive summary statistics are calculated by sequence and treatment, including means (or medians, as appropriate), ranges, and standard deviations (SDs).

Inferential statistics are performed on selected results wherein the magnitude of the differences between the means across treatment groups relative to the variance suggests a possible differential treatment effect. Continuous variable data is analyzed by parametric statistics (repeated measures analysis of variance with appropriate supplemental post-hoc analyses and/or paired t-test). Categorical data and data not conforming to a normal distribution is analyzed by non-parametric statistics (Wilcoxon signed rank test). PSG data may also be assessed by multivariate analyses and/or spectral analyses.

Results: An improvement in UPDRS, UPDRS-IV, AIM, lack of increase in, or reduction of, sleep disturbances, as measured by PSG and a standardized sleep questionnaire (e.g. SSS, m-ESS, KSS, THAT, ZOGIM-A, or VAS), demonstrates the suitability of amantadine ER for once daily administration at bedtime.

EXAMPLE 10

Simulated Pharmacokinetic Characteristics of Higher Strength, Amantadine ER Formulations Administered at Nighttime

Objective: The objective is to use the data generated in the clinical study described in Example 7 to predict steady state plasma concentration-time profiles of various IR and ER amantadine regimens at different dose levels to show the benefits of higher strength amantadine ER formulations administered at nighttime.

Methodology: Plasma concentration-time profiles from healthy volunteers that received multiple doses of the ER and IR formulations of amantadine per study procedures described in Example 7 (ADS-5101-MD-104) were used to develop a pharmacokinetic model describing each of the two formulations. This study was an open-label, randomized, two-treatment, two-period, two-way crossover study comparing once-daily amantadine ER capsules and twice-daily amantadine IR tablets in 26 healthy, adult male and female volunteers. Complete data from 24 individuals were used in this exercise. Blood samples for pharmacokinetic evaluation were collected after single dosing on Day 1 and at steady state on Day 9. In the first step of the analysis, WinNonlin 5.2.1 (Pharsight Corp., Mountain View, Calif.) was used to fit a one-compartment model with first-order input and first-order output, weighted 1/y (where y is the amantadine plasma concentration), to each individual's plasma concentration-time data obtained after single (Day 1) and repeated (Day 9) dose administration of amantadine IR and ER; the fitting was done separately for both formulations, but simultaneously for both days. Modeling assumptions employed include dose proportionality and constant clearance as a function of time.

The model is described by the following equation:

$$C = \frac{FD}{V(k_a - k)}[\exp(-k(t - t_{lag})) - \exp(-k_a(t - t_{lag}))] \quad \text{Equation 1}$$

where C is the plasma concentration, F is the absolute bioavailability, D is dose, V is the volume of distribution, k_a is the absorption rate constant, k is the elimination rate constant, t is time, and t_{lag} is the lag time of absorption. The goodness of fit was verified by comparing the individual model predicted and observed concentration-time data from Study ADS-5101-MD-104. After Equation 1 was fitted to each individual's plasma concentration-time data, model parameter estimates of V/F, k_a, k, and t_{lag} were obtained for each of the 24 subjects. The goodness of the prediction at steady state was confirmed by comparing the observed data and predicted steady-state concentrations of amantadine obtained after daily dosing of 200 mg as the ER and IR formulations (Day 9).

In the second step of the analysis, individual model parameter estimates were used to simulate steady-state concentration-time profiles for each individual for both formulations by reinserting the individual parameter estimates into Equation 1, and summing the contribution of 7 sequential days of dosing, according to the following dosing regimens:

1. Once Daily (QD) dosing of 260, 340, and 420 mg of the ER formulation to steady state
2. Three times daily (TID) dosing of 100 mg of the IR formulation to steady state
3. Twice daily (BID) dosing of 100 mg of the IR formulation to steady state

Results: FIG. **4** shows the simulated steady state plasma concentration time profiles for various ER amantadine doses along with various regimes of IR amantadine. Table 11 summarizes values of the pharmacokinetic parameters that affect the efficacy and tolerability of ER amantadine when administered at night.

TABLE 11

PK parameters associated with nighttime administration - morning peak benefit measured for ER Amantadine formulation

	IR 100 mg BID	IR 100 mg TID	ER 260 mg QD	ER 340 mg QD	ER 420 mg QD
Cmax (ng/ml)	669	936	834	1091	1348
Cmin (ng/ml)	435	731	461	603	745
Cmax/Cmin	1.54	1.28	1.81	1.81	1.81

TABLE 11-continued

PK parameters associated with nighttime administration - morning peak benefit measured for ER Amantadine formulation

	IR 100 mg BID	IR 100 mg TID	ER 260 mg QD	ER 340 mg QD	ER 420 mg QD
C-ave-day (6 am-4 pm) (ng/ml)	571	845	766	1002	1238
C-ave-morn (6 am-10 am) (ng/ml)	479	870	824	1078	1332
C-ave-even (4 pm-10 pm) (ng/ml)	522	852	591	773	955
C-ave-night (10 pm-6 am) (ng/ml)	596	843	616	805	995
C-ave-day/C-ave-night	0.96	1.00	1.24	1.24	1.24
C-ave-morn/C-ave-night	0.80	1.03	1.34	1.34	1.34
C-ave-day relative to 100 mg BID IR	1.00	1.48	1.34	1.76	2.17

As shown in Table 11 and in the figures, the ER amantadine formulations administered once daily at night result in higher ratios of average day time to night time amantadine plasma concentrations relative to IR amantadine and are predicted to be relatively well tolerated. The ER formulations also result in average day time amantadine plasma concentrations that are 1.3 to 2.2 fold that of IR amantadine administered at 100 mg twice daily and is predicted to result in significantly enhanced efficacy when administered to patients in the clinical study described in Example 11 below.

EXAMPLE 11

A Randomized, Double-blind, Placebo-controlled Study of the Efficacy and Safety of Amantadine Extended Release Oral Capsules for the Treatment of Levodopa-induced Dyskinesia in Parkinson's Disease

Study Objectives: This study is designed to confirm dose range of Amantadine Extended Release (ER) oral capsules dosed once daily at nighttime for the treatment of levodopa-induced dyskinesia (LID) in subjects with Parkinson's Disease (PD). In addition, the study is designed to demonstrate the safety and tolerability of Amantadine ER oral capsules dosed once daily for the treatment of LID in subjects with PD. Finally, to confirm the steady-state pharmacokinetics of the Amantadine ER dosing regimens in Parkinsons patients and to correlate C-ave-day,Cave-morning, C-ave-morning/C-ave-night and C-ave-day/C-ave-night with the efficacy and tolerability of amantadine.

Study Design: This will be a multi-center, randomized, double-blind, placebo-controlled, 4-arm parallel group study of Amantadine ER in subjects with PD and LID/Consenting subjects who meet eligibility criteria will be randomized 1:1:1:1 to receive one of the following 4 treatments, each administered as once daily, dosed at night, for 8 weeks:

Treatment A: Placebo,

Treatment B: 260 mg Amantadine ER (ADS-5102),

Treatment C: 340 mg Amantadine ER (ADS-5102)

Treatment D: 420 mg Amantadine ER (ADS-5102)

Subjects who are randomized to Treatment C or D (higher dose amantadine groups) will receive, in double-blind fashion, 260 mg Amantadine ER once daily during week 1, with an increase to either 340 mg or 420 mg once daily at the beginning of week 2. Dosing will continue through week 8.

Following completion of the baseline visit and randomization, subjects will return to the clinic after 1, 2, 4, 6, and 8 weeks of dosing, with a follow-up visit 14 days following the last dose of study drug. Study visits and assessments will be scheduled during morning hours when possible (9 am through 1 pm). A set of two 24-hour diaries will be completed during 48 hours prior to randomization and 48 hours prior to selected study visits. The diary will be used to score five different conditions in 30-minute intervals: Sleep, OFF, ON without dyskinesias, ON with nontroublesome dyskinesias, ON with troublesome dyskinesias.

Blood samples will be collected at selected study visits for determination of amantadine plasma concentrations, and evaluation of steady-state population pharmacokinetics. Subject participation during the study will be up to 12 weeks and will include a 2-week (maximum) screening period, 8-week (maximum) treatment period, and a 2-week follow-up period. Subjects who are unable to tolerate their assigned study drug assignment will permanently discontinue study drug and continue to be followed for safety through 2 weeks following the last dose of study drug.

Patient Eligibility Criteria: Subjects are eligible to take part in the study if they meet the inclusion and do not meet the exclusion criteria. Selected key criteria are as follows:

Inclusion Criteria:

- Male or female adults, residing in the community (i.e. not residing in an institution)
- Between 30 and 75 years of age, inclusive
- Ambulatory or ambulatory-aided (e.g. walker or cane) ability, such that the subject can come to required study visits
- Knowledgeable and reliable caregiver/study partner, if appropriate, to accompany the subject to study visits
- Signed a current IRB/IEC-approved informed consent form
- Following training, the subject is willing and able to understand and complete the 24-hour home diary (caregiver assistance allowed)
- Idiopathic Parkinson's Disease, complicated by dyskinesia (a MDS-UPDRS score will be determined during screening, but a minimum score is not required)
- On a stable regimen of antiparkinson's medications, including levodopa, for at least 30 days prior to screening, and willing to continue that regimen during study participation
- Presence of dyskinesia, defined as a minimum UDysRS score

Exclusion Criteria:

- Presence of other neurological disease that may affect cognition, including, but not limited to Alzheimer's dementia, Huntington's disease, Lewy body dementia, frontotemporal dementia, corticobasal degeneration, or motor or sensory dysfunction secondary to stroke or brain trauma.
- Presence of cognitive impairment, as evidenced by a Mini-mental State Examination (MMSE) score of less than 24 during screening.

Presence of an acute major psychiatric disorder (e.g., Major Depressive Disorder) according to DSM-IV-TR or symptom (e.g., hallucinations, agitation, paranoia) that could affect the subject's ability to complete study assessments

Presence of sensory impairments (e.g., hearing, vision) that would impair the subject's ability to complete study assessments

History of alcohol or drug dependence or abuse, according to DSM-IV criteria, within 2 years prior to screening

History of seizures (excluding febrile seizures of childhood)

History of stroke or TIA within 2 years prior to screening

History of myocardial infarction, NYHA Congestive Heart Failure Class 3 or 4, or atrial fibrillation within 2 years prior to screening

History of cancer within 5 years prior to screening, with the following exceptions: adequately treated non-melanomatous skin cancers, localized bladder cancer, non-metastatic prostate cancer or in situ cervical cancer (these exceptions must be discussed with and approved by the Medical Monitor before study entry)

Any of the following lab abnormalities; Hemoglobin <10 g/dL, WBC $<3.0\times10^9$/L, Neutrophils $<1.5\times10^9$/L, Lymphocytes $<0.5\times10^9$/L, Platelets $<100\times10^9$/L, Hemoglobin AlC >9%, or Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >2 times the upper limit of normal

Estimated GFR <50 mL/min/1.73 m^2 by Modification of Diet in Renal Disease (MDRD) or Cockcroft-Gault equation

Any clinically significant ECG abnormalities

Inability to swallow oral capsules, or a history of gastrointestinal malabsorption that would preclude the use of oral medication

Study Endpoints: The primary efficacy endpoint will be the change from baseline to week 8 in the Unified Dyskinesia Rating Scale (UDysRS) score. Key secondary endpoints will include:

ON time without troublesome dyskinesia (ON without dyskinesia plus ON with nontroublesome dyskinesia), based on a standardized PD home diary

Unified Parkinson's Disease Rating Scale (MDS-UPDRS), overall score

Fatigue as measured by the Fatigue Severity Scale (FSS). This scale includes 9 questions that are completed by the patient using a rating scale from 1 (strongly disagree) to 7 (strongly agree). This fatigue scale is recommended by MDS for both screening and severity rating (2010)

Safety, including adverse events, safety-related study drug discontinuations, vital signs, and laboratory tests.

The following mixture of traditional and new scales have been selected for this phase 2 study:

Unified Dyskinesia Rating Scale (UDysRS) will be used for primary outcome measure. This scale has four parts, and a total possible score of 104:

I: Historical Disability (patient perceptions) of On-Dyskinesia impact

II: Historical Disability (patient perceptions) of Off-Dystonia impact

III: Objective Impairment (dyskinesia severity, anatomic distribution, and type, based on 4 observed activities)

IV: Objective Disability based on Part III activities

ON time without troublesome dyskinesia, based on a standardized Parkinson's Disease home diary (suggest Test Diary II), [33] will be a secondary outcome measure. This scale has been used in number of studies with mixed success [34]. However, most KOLs feel that subject-reported dairy data must be collected, and needs to support the primary outcome measure.

Unified Parkinson's Disease Rating Scale (UPDRS), part IV, items 32 (duration of dyskinesias: 0=none, 4=76-100% of the waking day) and 33 (disability of dyskinesias: 0=not disabling, 4=completely disabling) will be a secondary outcome measure. This scale is a traditional scale used in PD for many years and these items have been utilized in most LID studies.

Cognitive Scales: Global caregiver impression, depression and other scales will be employed to measure the mental status benefits of ER amantadine.

Statistical Methods

Efficacy Analyses: The efficacy analysis population will include all randomized and dosed subjects who provide at least one post-baseline efficacy assessment. For the efficacy endpoint of UDysRS score, the change from baseline to week 8 will be analyzed using an analysis of covariance (ANCOVA) model with treatment group as a factor and the UDysRS baseline value as a covariate. The primary analysis will compare the 260 mg ADS-5102 group to the placebo group using a two-sided test at the 5% level of significance. If the primary comparison is statistically significant ($p<0.05$), then the 340 mg and 420 mg ADS-5102 groups will be compared to placebo, also using a two-sided test at the 5% level of significance.

The secondary endpoints will be analyzed using the same types of ANCOVA models as described for the primary endpoint. All secondary comparisons between treatment groups will be performed using two-sided tests at the 5% level of significance. A last observation carried forward (LOCF) approach will be utilized for missing data. The primary efficacy analysis will be repeated for the per-protocol population, a subset of the efficacy analysis population who provide week 8 efficacy assessments.

Safety Analyses: The safety analysis population will include all randomized subjects who receive at least one dose of study drug. All safety endpoints will be analyzed from the time of first dose through the completion of follow-up (or 2 weeks following the last dose of study drug). A safety analysis will also be done on the safety reported during the first 2 weeks of study drug treatment, in order to assess tolerability of initial dosing with ADS-5102 amantadine ER.

Results: following improvements are expected from this study are shown in the table below. Additional endpoints are described that

Significant (20-60%) reduction in dyskinesia score measured by acceptable primary endpoint (e.g., UDysRS)

Increase in ON time without troubling dyskinesia by 20-60%

Improvement in UPDRS from 5% to 20%.

Improvement in Parkinson's fatigue (FSS) from 5% to 60%.

Improvement in mood by PGI from 5% to 20%.

Instruments for Dyskinesia	% Clinical Effect (Placebo-Active/Placebo)	Range of Scores
Unified Dyskinesia Rating Scale (UDysRS)	5-60%	0-104 (4 parts, 26 items total, each 0, normal-4, severe)
Unified Parkinson's Disease Rating Scale (UPDRS, MDS revision)	5-20%	
Part IV	5-60%	0-24 (6 items, each 0, normal-4, severe)
Part IV, dyskinesia items only	5-60%	0-8 (2 dyskinesia items, 4.1 and 4.2, each 0, normal-4, severe)
Parkinson's Disease Home Diary (Hauser et al)	5-40%	0-100% (on time without dyskinesia or with nontroublesome dyskinesia)

EXAMPLE 12

Simulated Pharmacokinetic Characteristics of Amantadine ER Formulations with a Delayed Release Coat Suitable for Night Time Administration

Objective: The objective is to evaluate the pharmacokinetic profile of two alternative ER formulations of amantadine suitable for nighttime administration—Formulation 1, which is the formulation tested in Example 7, and Formulation 2, which is the formulation tested in Example 7, but with a delayed release over coat on top of the extended release coat.

Plasma concentration-time profiles from healthy volunteers, who received multiple doses of the ER and IR formulations of amantadine per study procedures described in Example 7 (ADS-5101-MD-104), were used to develop a pharmacokinetic model describing each of the two formulations. This study was an open-label, randomized, two-treatment, two-period, two-way crossover study comparing once-daily amantadine ER capsules and twice-daily amantadine IR tablets in 26 healthy, adult male and female volunteers. Complete data from 24 individuals were used in this exercise. Blood samples for pharmacokinetic evaluation were collected after single dosing on Day 1 and at steady state on Day 9. In the first step of the analysis, WinNonlin 5.2.1 (Pharsight Corp., Mountain View, Calif.) was used to fit a one-compartment model with first-order input and first-order output, weighted 1/y (where y is the amantadine plasma concentration), to each individual's plasma concentration-time data obtained after single (Day 1) and repeated (Day 9) dose administration of amantadine IR and ER; the fitting was done separately for both formulations, but simultaneously for both days. Modeling assumptions employed include dose proportionality and constant clearance as a function of time.

The model is described by the following equation

$$C = \frac{FD}{V(k_a - k)}[\exp(-k(t - t_{lag})) - \exp(-k_a(t - t_{lag}))] \quad \text{Equation 1}$$

where C is the plasma concentration, F is the absolute bioavailability, D is dose, V is the volume of distribution, k_a is the absorption rate constant, k is the elimination rate constant, t is time, and t_{lag} is the lag time of absorption. The goodness of fit was verified by comparing the individual model predicted and observed concentration-time data from Study ADS-5101-MD-104. After Equation 1 was fitted to each individual's plasma concentration-time data, model parameter estimates of V/F, k_a, k, and t_{lag} were obtained for each of the 24 subjects. The goodness of the prediction at steady state was confirmed by comparing the observed data and predicted steady-state concentrations of amantadine obtained after daily dosing of 200 mg as the ER and IR formulations (Day 9).

In the second step of the analysis, individual model parameter estimates were used to simulate steady-state concentration-time profiles for each individual for both formulations by reinserting the individual parameter estimates into Equation 1, and summing the contribution of 7 sequential days of dosing, according to the following dosing regimens:

1. Once Daily (QD) dosing of 200 mg of the ER Formulation 1 to steady state
2. Once Daily (QD) dosing of 200 mg of the ER Formulation 2 to steady state

Results: FIG. **7** shows the simulated steady state plasma concentration time profiles for the two ER amantadine formulations. (Amantadine blood plasma concentrations are shown on the y, time of day on the x-axis.) As shown in FIG. **7**, the ER amantadine formulation 2 administered once daily at night results in about a 4 hour delay in achieving peak plasma concentration at steady state relative to formulation 1. Thus, a formulation comprising a delayed release coat on top of the extended release coat has a very favorable pharmacokinetic profile in that it maximizes the daytime plasma exposure to amantadine whilst minimizing night plasma exposure at steady state.

While preferred embodiments of the present invention have been shown and described herein, such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. All references cited herein are incorporated herein by reference in their entirety.

We claim:

1. A method of administering a dose of a pharmaceutical composition of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof to a human patient in need thereof, comprising administering said dose of said pharmaceutical composition to said human patient orally, once daily 0 to 4 hours before bedtime, wherein said dose of said pharmaceutical composition comprises: (i) 250 mg to 600 mg of the drug; and (ii) one or more excipients, wherein at least one of said one or more excipients modifies the release of said drug to provide an extended release dosage form, and

wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the fractional AUC_{0-4} for amantadine is less than 5% of AUC_{0-inf} and the Tmax of amantadine is 8 to 20 hours.

2. A method of administering a dose of a pharmaceutical composition of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof to a human patient in need thereof, comprising administering said dose of said pharmaceutical composition to said human patient orally, once daily 0 to 4 hours before bedtime, wherein said dose of said pharmaceutical composition comprises: (i) 250 mg to 600 mg of the drug; and (ii) one or more

excipients, wherein at least one of said one or more excipients modifies the release of said drug to provide an extended release dosage form, and

wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the fractional AUC_{0-8} for amantadine is 5% to 15% of AUC_{0-inf} and the Tmax for amantadine is 8 to 20 hours.

3. A method of administering a dose of a pharmaceutical composition of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof to a human patient in need thereof, comprising administering said dose of said pharmaceutical composition to said human patient orally, once daily 0 to 4 hours before bedtime, wherein said dose of said pharmaceutical composition comprises: (i) 250 mg to 600 mg of the drug; and (ii) one or more excipients, wherein at least one of said one or more excipients modifies the release of said drug to provide an extended release dosage form, and

wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the fractional AUC_{0-4} for amantadine is less than 5% of AUC_{0-inf} and the Cmax for amantadine is 1.0 to 2.4 ng/ml per mg of amantadine.

4. A method of administering a dose of a pharmaceutical composition of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof to a human patient in need thereof, comprising administering said dose of said pharmaceutical composition to said human patient orally, once daily 0 to 4 hours before bedtime, wherein said dose of said pharmaceutical composition comprises: (i) 250 mg to 600 mg of the drug; and (ii) one or more excipients, wherein at least one of said one or more excipients modifies the release of said drug to provide an extended release dosage form, and

wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the fractional AUC_{0-8} for amantadine is 5% to 15% of AUC_{0-inf} and the Cmax for amantadine is 1.0 to 2.4 ng/ml per mg of amantadine.

5. The method of claim **1**, wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the Cmax for amantadine is 1.0 to 2.4 ng/ml per mg of amantadine.

6. The method of claim **1**, wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the AUC_{0-inf} for amantadine is 40 to 75 ng*h/ml per mg of amantadine.

7. The method of claim **5**, wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the AUC_{0-inf} for amantadine is 40 to 75 ng*h/ml per mg of amantadine.

8. The method of claim **1**, wherein when said pharmaceutical composition is dosed in a multiple dose, fasted, human pharmacokinetic study in healthy subjects, the steady state AUC_{0-24} for amantadine is 44 to 83 ng*h/ml per mg of amantadine.

9. The method of claim **5**, wherein when said pharmaceutical composition is dosed in a multiple dose, fasted, human pharmacokinetic study in healthy subjects, the steady state AUC_{0-24} for amantadine is 44 to 83 ng*h/ml per mg of amantadine.

10. The method of claim **1**, wherein said patient is being treated for Parkinson's disease.

11. The method of claim **5**, wherein said patient is being treated for Parkinson's disease.

12. The method of claim **8**, wherein said patient is being treated for Parkinson's disease.

13. The method of claim **10**, wherein said patient suffers from levodopa-induced dyskinesia.

14. The method of claim **13**, wherein the method reduces the frequency or severity of levodopa-induced dyskinesia in said patient.

15. The method of claim **1**, wherein said dose of said pharmaceutical composition comprises 1 or 2 unit dosage forms.

16. The method of claim **15**, wherein said unit dosage form comprises a capsule.

17. The method of claim **2**, wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the Cmax for amantadine is 1.0 to 2.4 ng/ml per mg of amantadine.

18. The method of claim **2**, wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the AUC_{0-inf} for amantadine is 40 to 75 ng*h/ml per mg of amantadine.

19. The method of claim **17**, wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the AUC_{0-inf} for amantadine is 40 to 75 ng*h/ml per mg of amantadine.

20. The method of claim **2**, wherein when said pharmaceutical composition is dosed in a multiple dose, fasted, human pharmacokinetic study in healthy subjects, the steady state AUC_{0-24} for amantadine is 44 to 83 ng*h/ml per mg of amantadine.

21. The method of claim **17**, wherein when said pharmaceutical composition is dosed in a multiple dose, fasted, human pharmacokinetic study in healthy subjects, the steady state AUC_{0-24} for amantadine is 44 to 83 ng*h/ml per mg of amantadine.

22. The method of claim **2**, wherein said patient is being treated for Parkinson's disease.

23. The method of claim **17**, wherein said patient is being treated for Parkinson's disease.

24. The method of claim **20**, wherein said patient is being treated for Parkinson's disease.

25. The method of claim **22**, wherein said patient suffers from levodopa-induced dyskinesia.

26. The method of claim **25**, wherein the method reduces the frequency or severity of levodopa-induced dyskinesia in said patient.

27. The method of claim **2**, wherein said dose of said pharmaceutical composition comprises 1 or 2 unit dosage forms.

28. The method of claim **27**, wherein said unit dosage form comprises a capsule.

29. The method of claim **3**, wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the AUC_{0-inf} for amantadine is 40 to 75 ng*h/ml per mg of amantadine.

30. The method of claim **3**, wherein when said pharmaceutical composition is dosed in a multiple dose, fasted, human pharmacokinetic study in healthy subjects, the steady state AUC_{0-24} for amantadine is 44 to 83 ng*h/ml per mg of amantadine.

31. The method of claim **3**, wherein said patient is being treated for Parkinson's disease.

32. The method of claim **29**, wherein said patient is being treated for Parkinson's disease.

33. The method of claim **31**, wherein said patient suffers from levodopa-induced dyskinesia.

34. The method of claim **33**, wherein the method reduces the frequency or severity of levodopa-induced dyskinesia in said patient.

35. The method of claim **3**, wherein said dose of said pharmaceutical composition comprises 1 or 2 unit dosage forms.

36. The method of claim **35**, wherein said unit dosage form comprises a capsule.

37. The method of claim **4**, wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the $AUC_{0\text{-}inf}$ for amantadine is 40 to 75 ng*h/ml per mg of amantadine.

38. The method of claim **4**, wherein when said pharmaceutical composition is dosed in a multiple dose, fasted, human pharmacokinetic study in healthy subjects, the steady state $AUC_{0\text{-}24}$ for amantadine is 44 to 83 ng*h/ml per mg of amantadine.

39. The method of claim **4**, wherein said patient is being treated for Parkinson's disease.

40. The method of claim **37**, wherein said patient is being treated for Parkinson's disease.

41. The method of claim **39**, wherein said patient suffers from levodopa-induced dyskinesia.

42. The method of claim **41**, wherein the method reduces the frequency or severity of levodopa-induced dyskinesia in said patient.

43. The method of claim **4**, wherein said dose of said pharmaceutical composition comprises 1 or 2 unit dosage forms.

44. The method of claim **43**, wherein said unit dosage form comprises a capsule.

45. The method of claim **1**, wherein said fractional $AUC_{0\text{-}4}$ for amantadine, said $AUC_{0\text{-}inf}$ for amantadine and said Tmax for amantadine are determined from one subject of said human pharmacokinetic study.

46. The method of claim **1**, wherein said fractional $AUC_{0\text{-}4}$ for amantadine and said $AUC_{0\text{-}inf}$ for amantadine are mean values determined from said human pharmacokinetic study, and said Tmax for amantadine is the median value determined from said human pharmacokinetic study.

47. The method of claim **2**, wherein said fractional $AUC_{0\text{-}8}$ for amantadine, said $AUC_{0\text{-}inf}$ for amantadine, and said Tmax for amantadine are determined from one subject of said human pharmacokinetic study.

48. The method of claim **2**, wherein said fractional $AUC_{0\text{-}8}$ for amantadine and said $AUC_{0\text{-}inf}$ for amantadine are mean values determined from said human pharmacokinetic study, and said Tmax for amantadine is the median value determined from said human pharmacokinetic study.

49. The method of claim **3**, wherein said fractional $AUC_{0\text{-}4}$ for amantadine, said $AUC_{0\text{-}inf}$ for amantadine, and said Cmax for amantadine are determined from one subject of said human pharmacokinetic study.

50. The method of claim **3**, wherein said fractional $AUC_{0\text{-}4}$ for amantadine, said $AUC_{0\text{-}inf}$ for amantadine, and said Cmax for amantadine are mean values determined from said human pharmacokinetic study.

51. The method of claim **4**, wherein said fractional $AUC_{0\text{-}8}$ for amantadine, said $AUC_{0\text{-}inf}$ for amantadine, and said Cmax for amantadine are determined from one subject of said human pharmacokinetic study.

52. The method of claim **4**, wherein said fractional $AUC_{0\text{-}8}$ for amantadine, said $AUC_{0\text{-}inf}$ for amantadine, and said Cmax for amantadine are mean values determined from said human pharmacokinetic study.

53. The method of claim **1**, wherein said pharmaceutical composition is selected from the group consisting of one unit dosage form comprising 340 mg of said drug and two unit dosage forms each comprising 170 mg of said drug.

54. The method of claim **2**, wherein said pharmaceutical composition is selected from the group consisting of one unit dosage form comprising 340 mg of said drug and two unit dosage forms each comprising 170 mg of said drug.

55. The method of claim **3**, wherein said pharmaceutical composition is selected from the group consisting of one unit dosage form comprising 340 mg of said drug and two unit dosage forms each comprising 170 mg of said drug.

56. The method of claim **4**, wherein said pharmaceutical composition is selected from the group consisting of one unit dosage form comprising 340 mg of said drug and two unit dosage forms each comprising 170 mg of said drug.

* * * * *

EXHIBIT K

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(12) **United States Patent**
Went et al.

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(54) **METHOD OF ADMINISTERING AMANTADINE PRIOR TO A SLEEP PERIOD**

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(51) **Int. Cl.**

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Methods of nighttime administration of amantadine to reduce sleep disturbances in patient undergoing treatment with amantadine are described, as well as compositions of extended release amantadine that are suitable for nighttime administration.

19 Claims, 7 Drawing Sheets

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FIG. 1

Dissolution Profiles of Amantadine ER Formulations

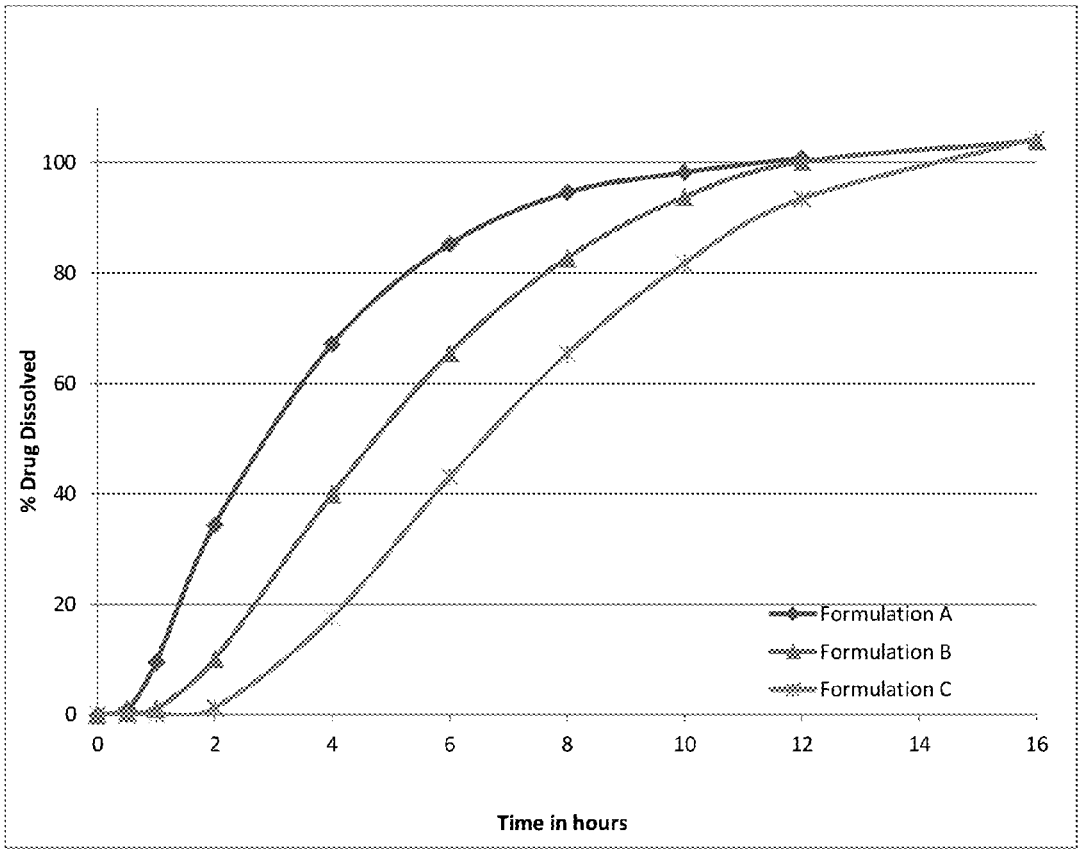


FIG. 2A

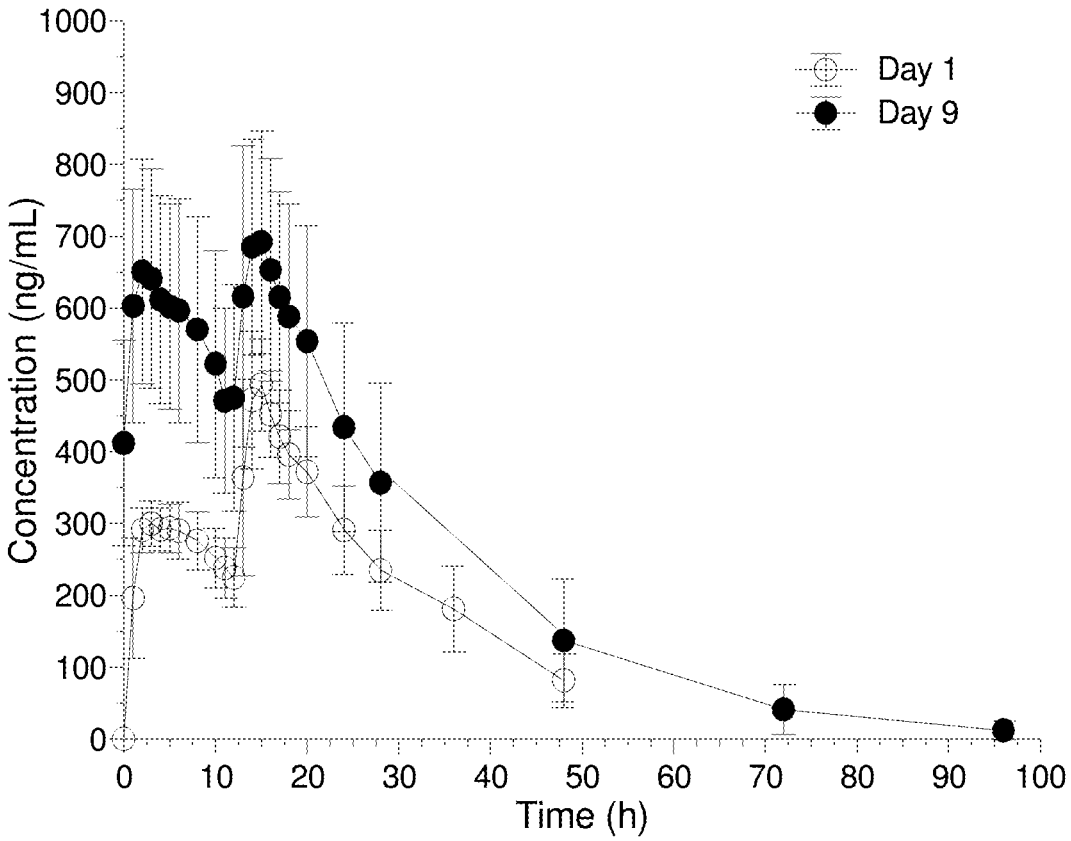

Day 1
Day 9
Concentration (ng/mL)
Time (h)
0
100
200
300
400
500
600
700
800
900
1000
0
10
20
30
40
50
60
70
80
90
100

FIG. 2B

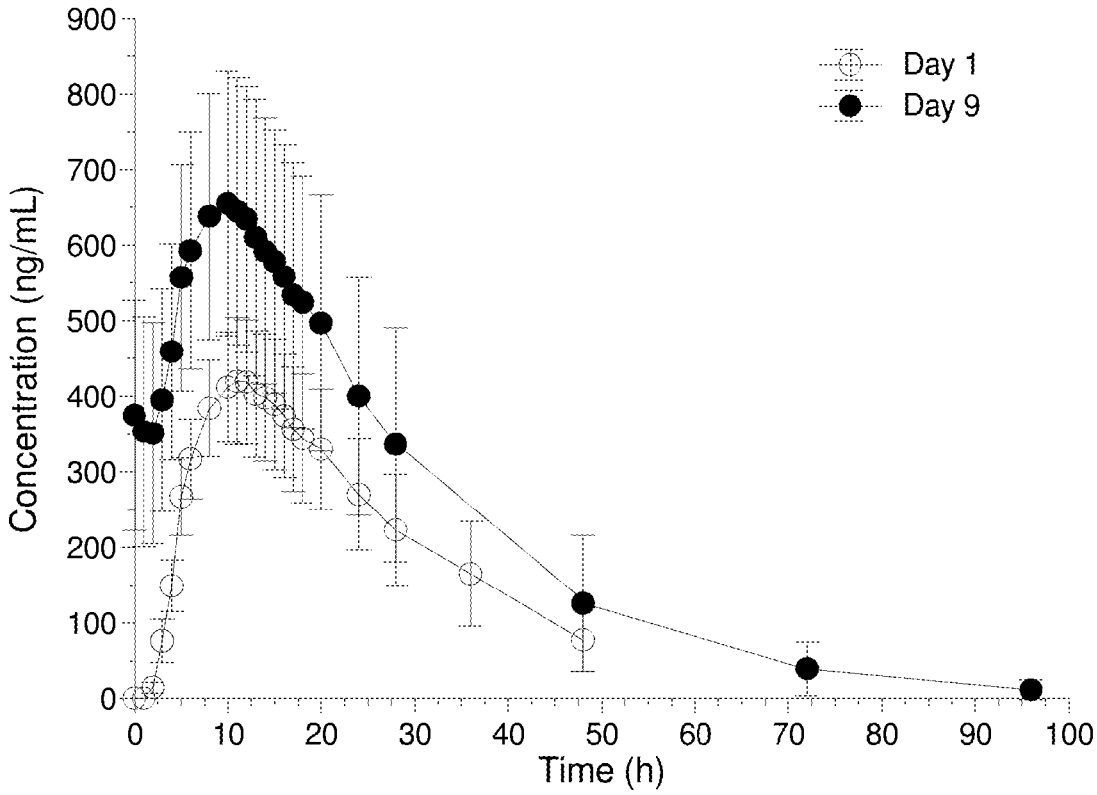

Day 1
Day 9
Concentration (ng/mL)
Time (h)
0
100
200
300
400
500
600
700
800
900
0
10
20
30
40
50
60
70
80
90
100

FIG. 3

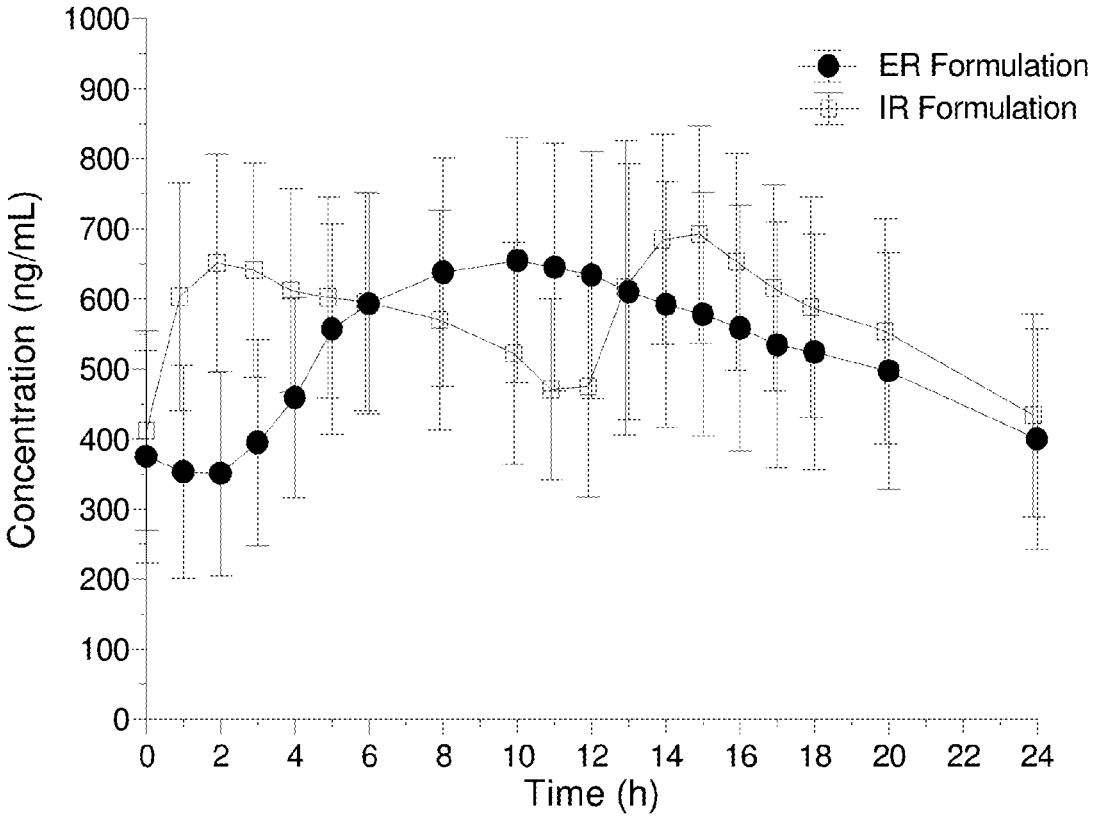
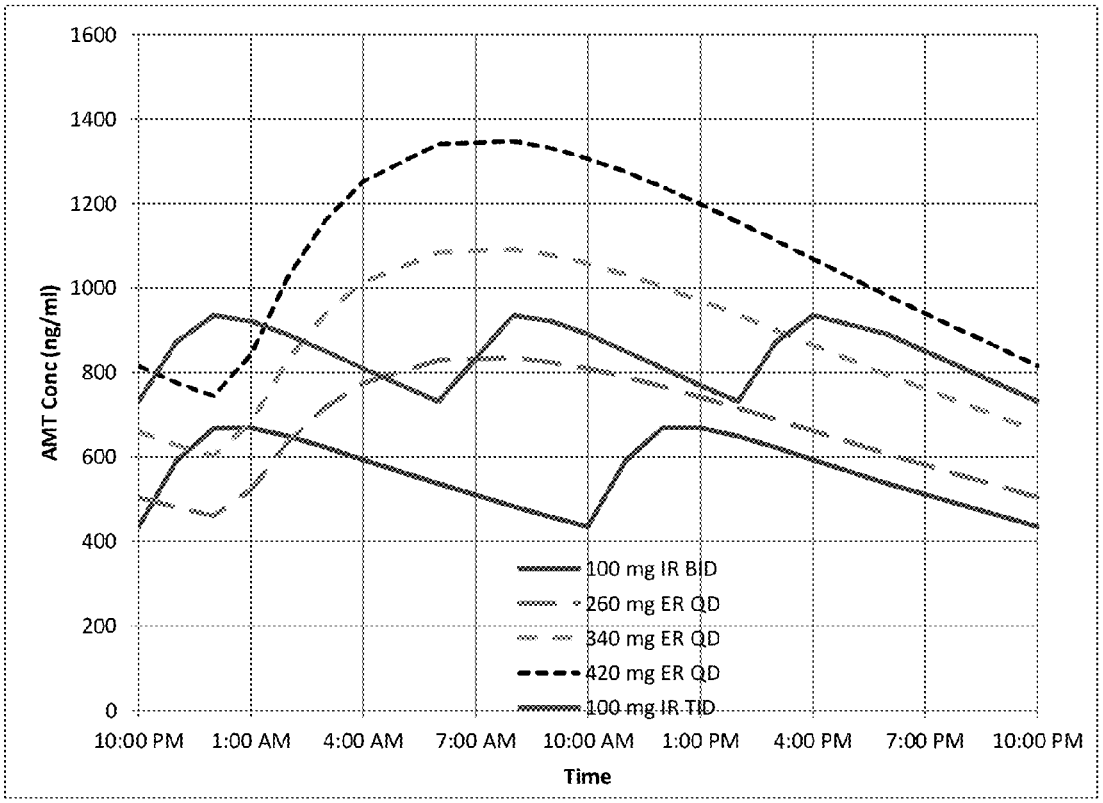

ER Formulation
IR Formulation
Concentration (ng/mL)
Time (h)
0
100
200
300
400
500
600
700
800
900
1000
0
2
4
6
8
10
12
14
16
18
20
22
24

Fig 4.



Simulation based on results of Adamas steady state PK study ADS-PD-104.

FIG. 5

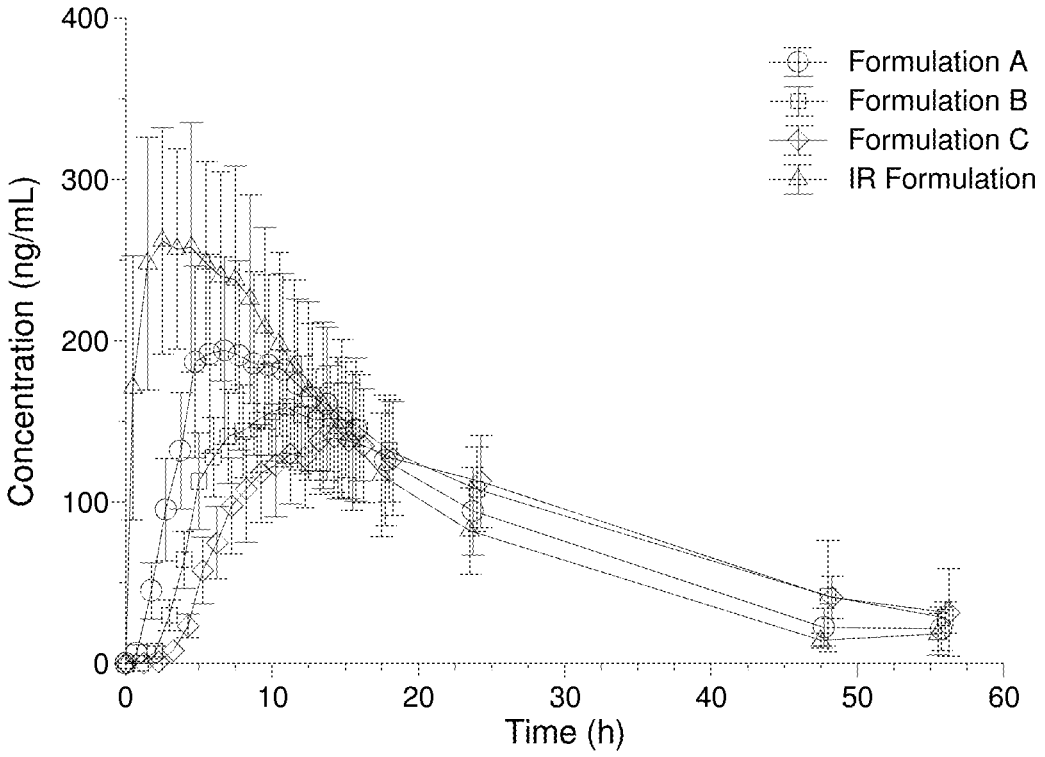

400
300
200
100
0
Concentration (ng/mL)
0
10
20
30
40
50
60
Time (h)
Formulation A
Formulation B
Formulation C
IR Formulation

FIG. 6

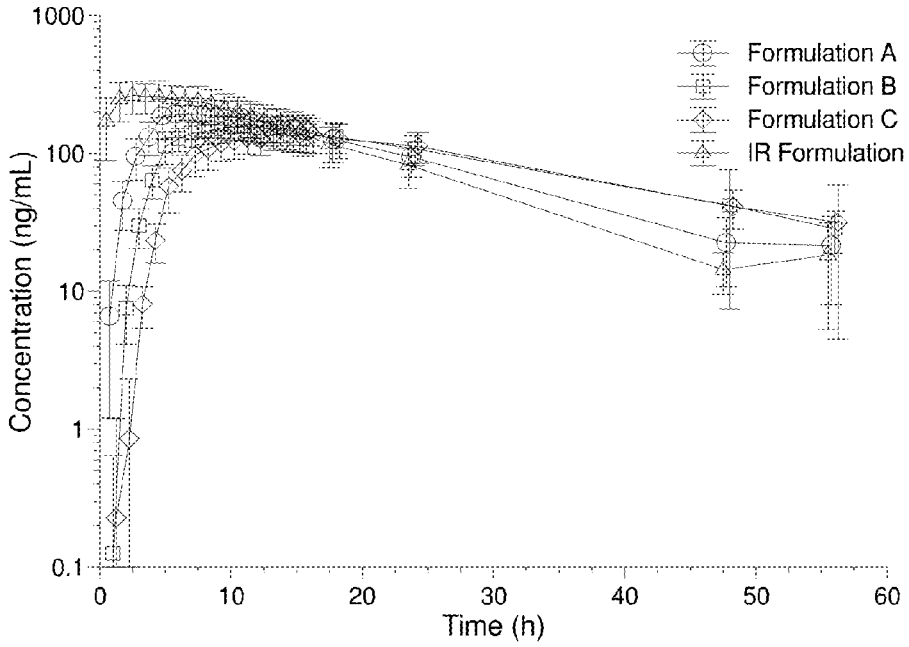
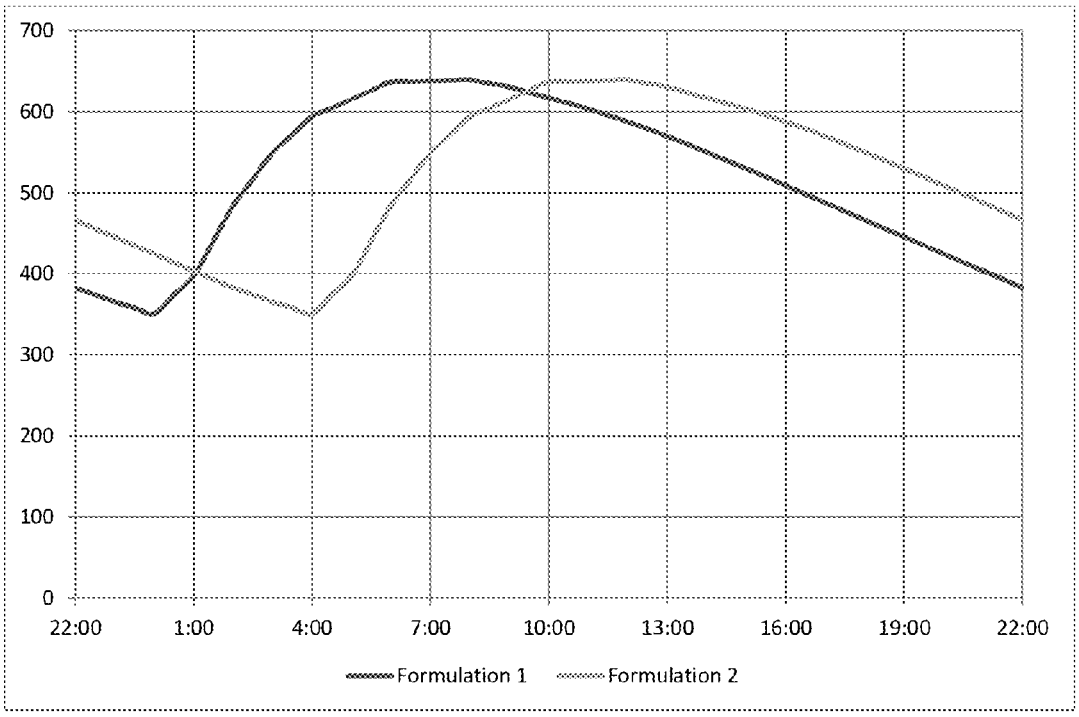

1000
100
10
1
0.1
Concentration (ng/mL)
0
10
20
30
40
50
60
Time (h)
Formulation A
Formulation B
Formulation C
IR Formulation

FIG 7.


700
600
500
400
300
200
100
0
22:00
1:00
4:00
7:00
10:00
13:00
16:00
19:00
22:00
Formulation 1
Formulation 2

METHOD OF ADMINISTERING AMANTADINE PRIOR TO A SLEEP PERIOD

CROSS-REFERENCE

This application is a continuation of U.S. patent application Ser. No. 14/863,035, filed Sep. 23, 2015, which is a continuation of U.S. patent application Ser. No. 14/523,535, filed Oct. 24, 2014, now abandoned, which is a continuation of U.S. patent application Ser. No. 14/267,597, filed May 1, 2014, now abandoned, which is a continuation of U.S. patent application Ser. No. 12/959,321, filed Dec. 2, 2010, now U.S. Pat. No. 8,741,343, which claims benefit of U.S. Provisional Application No. 61/266,053, filed Dec. 2, 2009, all of which applications are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

The field of the invention is extended release compositions of amantadine and uses thereof.

Amantadine is indicated for various conditions that can be treated by NMDA receptor antagonists including the treatment of idiopathic Parkinson's disease (Parlysis Agitans), postencephalitic Parkinsonism, and symptomatic Parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication. Amantadine also has activity as a viral M2 channel inhibitor and is used for the prophylaxis and treatment of infection of viral diseases, especially influenza A virus.

Currently marketed forms of amantadine are immediate release formulations that are typically administered two or more times a day. Amantadine's use is limited by dose related CNS side effects including dizziness, confusion, hallucinations, insomnia and nightmares (Gracies J M, Olanow C W; Current and Experimental Therapeutics of Parkinson's Disease; *Neuropsychopharmacology: the Fifth Generation of Progress*, p. 1802; American College of Neuropsychopharmacology 2002), which can be particularly exacerbated when amantadine is administered at night.

It is known that immediate release amantadine can act as a stimulant, causing insomnia and sleep disturbance. Therefore, the last dose is typically administered no later than 4 pm in order to minimize these side effects. Such dosing of amantadine results in peak plasma amantadine concentrations occurring in the evening or night, and very low plasma concentrations in the morning.

Extended release forms of amantadine have been described in the art. U.S. Pat. No. 5,358,721, to Guittard et al., and U.S. Pat. No. 6,217,905, to Edgren et al., each disclose an oral osmotic dosage form comprising an antiviral or anti-Parkinson's drug, respectively, where in each case amantadine is listed as a possible drug to be utilized in the dosage form. U.S. Pat. No. 6,194,000, to Smith et al., discloses analgesic immediate and controlled release pharmaceutical compositions utilizing NMDA receptor antagonists, such as amantadine, as the active agent. U.S. Patent Appl. Publication Nos. US 2006/0252788, US 2006/0189694, US 2006/0142398, and US 2008/0227743, all to Went et al., each disclose the administration of an NMDA receptor antagonist, such as amantadine, optionally in controlled release form.

SUMMARY OF THE INVENTION

The inventors have identified a need in the art for improved formulations of amantadine that result in a patient having higher plasma concentrations of amantadine upon waking in the morning without adversely affecting sleep. Further, the inventors have identified a need in the art for a method of administering amantadine in the late afternoon or evening, e.g. after 4 pm, which reduces side effects of insomnia and sleep disturbance and provides effective plasma concentrations of amantadine upon waking.

Therefore, there exists a need in the art for improved methods of amantadine therapy which can be administered to a patient shortly before they wish to sleep (e.g., at bedtime) without causing insomnia or sleep disturbance. In addition, there is a need for an amantadine therapy which can be taken by the patient before they go to sleep and then provides a suitable plasma concentration of amantadine when they wake up, e.g. in the morning, after a full night's sleep.

In addition, many Parkinson's disease patients have difficulty swallowing and are on multiple medications. Hence there is a need for amantadine therapy that delivers a therapeutically effective dose of the drug, can be administered once daily and is in an oral dosage form that is small in size and does not unduly increase the pill burden.

One aspect of the invention is a method of administering amantadine to a patient in need thereof, said method comprising orally administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below. Alternatively, the composition is administered less than about 4 hours before bedtime.

In a second aspect, the invention provides a method of reducing sleep disturbance in a human subject undergoing treatment with amantadine, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below. Alternatively, the composition is administered less than about 4 hours before bedtime.

In a third aspect, the invention provides a method of treating levodopa induced dyskinesia, or fatigue, or dementia, or any other symptom of Parkinson's disease, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below.

In a fourth aspect, the invention provides a method of treating brain injury, brain trauma, dementia, Alzheimer's disease, stroke, Huntington's disease, ALS, Multiple Sclerosis, neurodegenerative diseases, dementias, cerebrovascular conditions, movement disorders, cranial nerve disorders, neuropsychiatric disorders, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below.

In one embodiment of any of the above aspects, administration occurs less than two and a half, less than two, less than one and a half, less than one or less than half hour before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).

In one embodiment of any of the above aspects the patient has been diagnosed with Parkinson's disease.

In one embodiment of any of the above aspects, the composition is administered once daily. In another aspect, the daily dose exceeds 200 mg, and is given in 1, 2 or 3 capsules of size 0, 1 or 2.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in levodopa induced dyskinesia (LID). In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% reduction in levodopa induced dyskinesia. In further embodiments, the reduction in levodopa induced dyskinesia is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce LID. In further specific embodiments, the scale used in measuring the reduction in LID could be UDysRS, UPDRS Part IV (subscores 32, 33), Dyskinesia Rating Scale (DRS), Abnormal Involuntary Movement Scale (AIMS), or other scales developed for this purpose.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease fatigue. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60% reduction in Parkinson's disease fatigue. In further specific embodiments, the reduction in fatigue is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce fatigue. In further specific embodiments, the scale used in measuring the reduction in fatigue could be the Fatigue Severity Scale (FSS).

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease symptoms. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's symptoms. In further specific embodiments, the reduction in Parkinson's symptoms is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce Parkinson's symptoms. In further specific embodiments, the scale used in measuring the reduction in Parkinson's symptoms could be the Unified Parkinson's Disease Rating Scale (UPDRS).

In one embodiment of any of the above aspects, the composition is added to food, and in a more specific embodiment to a small amount of soft food (e.g. applesauce or chocolate pudding), prior to administration. Addition to food may involve a capsule being opened and the contents sprinkled over the patient's food. This is advantageous if the patient is unable or unwilling to swallow the composition.

In one embodiment of any of the above aspects, there is no increase in plasma concentration of amantadine for at least one hour after the administration at steady state plasma concentrations.

In one embodiment of any of the above aspects, there is no increase in the plasma concentration of amantadine for at least two hours after the administration at steady state plasma concentrations.

In one embodiment of any of the above aspects, the administration of the composition to a human subject at steady state amantadine plasma concentrations increases the amantadine plasma concentration by less than 5%, 10%, 15%, 20% or 25% at 1, 2, 2.5 or 3 hours following such administration. For example, administration of the composition to a human subject at steady state amantadine plasma concentrations increases the amantadine plasma concentration by less than 5% at 1, 2, 2.5 or 3 hours following such administration; or by less than 10% at 1, 2, 2.5 or 3 hours following such administration; or by less than 15% at 1, 2, 2.5 or 3 hours following such administration; or by less than 20% at 1, 2, 2.5 or 3 hours following such administration; or by less than 25% at 1, 2, 2.5 or 3 hours following such administration.

In one embodiment of any of the above aspects the amantadine has a single dose Tmax of 9 to 15 hours. In a more specific embodiment, the amantadine has a single dose Tmax of 10 to 14 hours after administration. In another more specific embodiment, the amantadine has a single dose Tmax of 11 to 13 hours after administration.

In one embodiment of any of the above aspects the amantadine has a steady state Tmax of 7 to 13 hours. In a more specific embodiment, the amantadine has a steady state Tmax of 8 to 12 hours after administration. In another more specific embodiment, the amantadine has a steady state Tmax of 9 to 11 hours after administration.

In one embodiment of any of the above aspects peak plasma concentration of amantadine is achieved between 6 and 16 hours after administration of a single dose of the composition. In a more specific embodiment, peak amantadine plasma concentration is achieved 8 to 14 hours after administration of a single dose of the composition. In another more specific embodiment, peak amantadine plasma concentration is achieved 10 to 12 hours after administration of a single dose of the composition. In additional specific embodiments, peak amantadine plasma concentration is achieved between 6, 7, 8, 9, 10, 11 or 12 hours to about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 hours after administration of a single dose of the composition.

In one embodiment of any of the above aspects, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In a more specific embodiment, the steady state plasma concentration profile is characterized by a concentration increase of amantadine of less than 25% at four hours after the administration.

In one embodiment of any of the above aspects, the composition is administered once a day and the ratio of Cmax to Cmin at steady state is 1.5 to 2.0, or, more specifically, 1.7 to 1.9, or, more specifically, about 1.8.

In one embodiment of any of the above aspects, the steady state plasma concentration profile following multiple administrations to a human subject of the composition at bedtime is characterized by an average plasma concentration during the day ("C-ave-day", defined as the average day time amantadine plasma concentration as measured in a human PK study) that is 1.1 to 2.0 times the average plasma concentration during the night ("C-ave-night", defined as the average night time amantadine plasma concentration as measured in a human PK study). In more specific embodiments the C-ave-day is the average amantadine plasma concentration as measured between the hours of 5 am, 6 am, 7 am, 8 am or 9 am to the hours of 4 pm, 5 pm, 6 pm, 7 pm

or 8 pm; for example, between the hours of 6 am and 4 pm, between the hours of 7 am and 6 pm, or between the hours of 7 am and 5 pm. The C-ave-night is the average amantadine plasma concentration as measured between the hours of 4 pm, 5 pm, 6 pm, 7 pm, 8 pm, 9 pm, 10 pm or 11 pm to the hours of 5 am, 6 am, 7 am, 8 am or 9 am; for example, between the hours of 10 pm and 6 am, between the hours of 7 pm and 6 am, or between the hours of 8 pm and 6 am.

In one embodiment of any of the above aspects, the steady state plasma concentration profile following multiple administrations to a human subject of the composition at bedtime is characterized by an average plasma concentration during the morning ("C-ave-morning", defined as the average amantadine plasma concentration as measured in a human PK study during the morning hours) that is 1.1 to 2.0 times the average plasma concentration during the night. In one embodiment the C-ave-morning is the average amantadine plasma concentration as measured between the hours of 5 am, 6 am, 7 am, 8 am or 9 am to the hours of 11 am, 11:30 am, 12 pm, 12:30 pm or 1:00 pm; for example, between the hours of 5 am and 11 am, or between the hours of 7 am and 12 pm. More preferably, the ratio of C-ave-morning/C-ave-night at steady state is 1.2 to 1.6.

In one embodiment of any of the above aspects, the steady state plasma concentration profile following daily administration of the composition is characterized by an average plasma concentration during the period 8 hours to 12 hours after administration ("C-ave-8-12 hrs") that is 1.1 to 2.0 times the average plasma concentration during the first 8 hours after administration ("C-ave-0-8 hrs"). More preferably, the ratio of C-ave-8-12 hrs/C-ave-0-8 hrs at steady state is 1.2 to 1.6.

In one embodiment of any of the above aspects, administration of a single dose of the composition to a human subject provides a plasma concentration profile characterized by: a fractional AUC from 0 to 4 hours that is less than 5%, and preferably less than 3% of AUC_{0-inf}; a fractional AUC from 0 to 8 hours that is about 5 to 15%, and preferably about 8 to 12% of AUC_{0-inf}; a fractional AUC from 0 to 12 hours that is about 10 to 40%, and preferably about 15 to 30% of AUC_{0-inf}; a fractional AUC from 0 to 18 hours that is about 25 to 60%, and preferably about 30 to 50% of AUC_{0-inf}; and a fractional AUC from 0 to 24 hours that is about 40 to 75%, and preferably about 50 to 70% of AUC_{0-inf}.

In one embodiment of any of the above aspects, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25%, and preferably about 5 to 20% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50%, and preferably about 20 to 40% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70%, and preferably about 40 to 60% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95%, and preferably about 75 to 90% of AUC_{24}.

In one embodiment of any of the above aspects, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by: a fractional AUC from 0 to 8 hours that is about 15 to 40%, and preferably about 20 to 32% of AUC_{24}; a fractional AUC from 8 to 16 hours that is about 30 to 50%, and preferably about 35 to 45% of AUC_{24}; and a fractional AUC from 16 to 24 hours that is about 20 to 35%, and preferably about 25 to 33% of AUC_{24}.

In one embodiment of any of the above aspects the amantadine is administered as a pharmaceutically acceptable salt. In a more specific embodiment, the amantadine is administered as hydrochloride or amantadine sulfate.

In one embodiment of any of the above aspects, a total daily dose of 50 mg to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof is administered to a patient. More specifically the daily dose of amantadine or pharmaceutically acceptable salt thereof administered may be in the range of 100 to 440 mg. In another specific embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof maybe in the range of 260 to 420 mg. In another embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof administered exceeds 300 mg per day. In various specific embodiments, the daily dose of amantadine or pharmaceutically acceptable salt thereof may be 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg.

In one embodiment of any of the above aspects, the composition comprises 50 mg to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. More specifically, the composition may comprise 100 mg to 450 mg of amantadine, or a pharmaceutically acceptable salt thereof. Still more specifically, the composition may comprise 130-210 mg of amantadine, or a pharmaceutically acceptable salt thereof. In various specific embodiments, a dosage form containing the composition comprises 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg of amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition comprises about 110, 120, 130, 140, 150, 160 170, 180, 190, 210, or 220 mg amantadine, or a pharmaceutically acceptable salt thereof. In another more specific embodiment, the composition comprises 110 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 130 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 170 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 210 mg amantadine hydrochloride.

In one embodiment of any of the above aspects, the composition is administered as one, two, three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof.

In one embodiment of any of the above aspects, the composition is administered as one, two, or three unit dosage forms each comprising 50 to 250 mg amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition is administered as one or two unit dosage forms each comprising 65 to 220 mg amantadine, or a pharmaceutically acceptable salt thereof.

In one embodiment of any of the above aspects, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma

concentration (Cmax) of 1.0 to 2.8 ng/ml per mg of amantadine. In a more specific embodiment, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine and an $AUC_{0\text{-}inf}$ (Area under the concentration-curve curve from t=0 to t=infinity) of 40 to 75 ng*h/mL per mg of amantadine.

In one embodiment of any of the above aspects, the daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by at least one of: (i) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine, (ii) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (iii) an $AUC_{0\text{-}24}$ of 44 to 83 ng*h/mL per mg of amantadine. In a more specific example, all three criteria of (i), (ii) and (iii) are met.

In a more specific embodiment, the steady state plasma concentration profile is further characterized by: (iv) no increase in concentration of amantadine for at least one hour after the administration; and (v) Cmax/Cmin ratio of 1.5 to 2.0. In a more specific embodiment, both criteria of (iv) and (v) are met.

In another more specific embodiment, the steady state plasma concentration profile is further characterized by at least one of: (iv) no increase in plasma concentration of amantadine for at least two hours after the administration; and (v) a Cmax/Cmin ratio of 1.7 to 1.9. In a more specific embodiment, both criteria of (iv) and (v) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more 55-85% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more than 25-55% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 20% dissolution at 1 hour, (ii) about 25-45% dissolution at 2 hours, (iii) not more than 50-80% dissolution at 4 hours, and (iv) at least 80% dissolution at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii), (iii) and (iv) are met. In a more specific embodiment, all four of criteria (i), (ii), (iii) and (iv) are met.

In one embodiment of any of the above aspects the in vitro dissolution profile of amantadine is further characterized by release of amantadine of: (i) not more than 10% at 1 hour, or (ii) 30-50% at 4 hours, or (iii) at least 90% at 12 hours using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three criteria of (i), (ii) and (iii) are met.

In another aspect, the present invention provides a pharmaceutical composition comprising or consisting of a pellet-in-capsule, wherein a pellet comprises a core that comprises a core seed with a mixture of amantadine and a binder coated onto the core seed, and an extended release coating surrounding the core comprising ethyl cellulose, a pore forming agent such as hydroxypropyl methyl cellulose or povidone, and a plasticizer.

In another aspect, the present invention provides a pharmaceutical composition for use in the methods of the aspects described above, wherein said composition is for oral administration and comprises a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core.

In one embodiment, the extended release coating comprises ethyl cellulose and at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In a more specific embodiment, the extended release coating comprises ethyl cellulose, povidone, and a plasticizer.

In one embodiment, the pellet core comprises amantadine and a binder coated onto a core seed. In one embodiment, the core seed is a sugar sphere (nonpareil) or microcrystalline cellulose seed (e.g. Celphere®). In a more specific embodiment, the core seed is a microcrystalline cellulose core. In another specific embodiment, the core seed has a diameter in the range of 100 microns to 1,000 microns. In additional specific embodiments, the core seed has a diameter of 100, 200, 300, 400, 500, 600 or 700 microns. In preferred specific embodiments, the core seed has a diameter of less than 500 microns.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 20 to 80 wt %, with a bulk density of 0.3 to 1.2 g/cm^3.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 40 to 60 wt %, with a bulk density of 0.5 to 1.2 g/cm^3.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 60 to 80 wt %, with a bulk density of 0.5 to 1.2 g/cm^3.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the binder is present in amounts from 8 to 25 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the core seed is present in amounts from 8 to 25 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the ethyl cellulose is present in amounts from 10 to 20 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the povidone is present in amounts from 1 to 4 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, and the plasticizer is present in amounts from 1 to 4 wt %.

In one embodiment, the coated pellet has a diameter in the range of 200 microns to 1700 micros. In additional specific embodiments, the coated pellet has a diameter of 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300 or

1500 microns. In certain specific embodiments, the coated pellet has a diameter of less than 1000 microns, e.g., from 500 to 1000 microns.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the binder is present in amounts from 5 to 25 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the core seed is present in amounts from 1 to 15 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the ethyl cellulose is present in amounts from 5 to 20 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the povidone is present in amounts from 0.25 to 4 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, and the plasticizer is present in amounts from 0.25 to 4 wt %.

In one embodiment, the pellet further comprises a seal coating between the pellet core and the extended release coating. In some embodiments, an inert coating can be applied to the inert core prior to drug coating or on drug-coated pellets or on controlled release coated pellets. In another embodiment, an enteric coating can be applied to the drug coated pellets or controlled release pellets.

In one embodiment, the pellet core comprises a binder, selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof.

In one embodiment, the above composition is provided in a size 3, size 2, size 1, size 0 or size 00 capsule.

In one embodiment, the therapeutically effective daily dose of the above composition is administered in no more than two capsules. In another embodiment, the therapeutically effective daily dose of the composition is administered in no more than three size 1 capsules. In another embodiment, the therapeutically effective daily dose of the composition is administered in no more than two size 0 capsules. In a still more preferred embodiment, the therapeutically effective daily dose of the composition is administered in no more than two size 1 capsules. In another embodiment, the therapeutically effective daily dose of the composition is administered in no more than three size 2 capsules.

In a preferred embodiment, the above composition is provided in an amount of 50 to 110 mg of amantadine or a pharmaceutically acceptable salt thereof in a size 2 capsule, and in the amount of 110 mg to 210 mg of amantadine or a pharmaceutically acceptable salt thereof in a size 1 capsule. In additional embodiments, the above composition comprises coated pellets of diameter 300 to 1000 microns, with amantadine or pharmaceutically acceptable salt thereof content of 40-80% wt % and at a bulk density of 0.5-1.2 g/cm^3. In a further preferred embodiment, the above composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more than 55-85% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, and castor oil. In a more specific embodiment, the plasticizer is medium chain triglycerides, e.g. Miglyol 812 N.

In another aspect, the present invention provides method of administering amantadine, or a pharmaceutically acceptable salt thereof, to a human subject in need thereof, said method comprising orally administering a composition of any of the above aspects.

In another aspect, the present invention provides a method of treating Parkinson's disease in a human subject in need thereof, said method comprising orally administering a composition of any of the above aspects. In a preferred aspect, the present invention provides a method of treating disease in a human subject in need thereof, said method comprising orally administering a composition of any of the above aspects once daily at nighttime, administering 1, 2 or 3 capsules.

References to administering amantadine to a subject in need thereof include treating a patient with a disease or condition which may be treated, prevented or cured by a NMDA antagonist. More specifically, administering amantadine to a subject in need thereof includes treating a patient with Parkinson's Disease, brain injury, brain trauma, dementia, Alzheimer's disease, stroke, Huntington's disease, ALS, Multiple Sclerosis, neurodegenerative diseases, dementias, cerebrovascular conditions, movement disorders, cranial nerve disorders, neuropsychiatric disorders.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the dissolution profiles for three amantadine ER formulations, A, B, C referred to in Example 3.

FIGS. **2**A and **2**B show the mean plasma concentration-time curves after administration of amantadine IR twice daily (A) and amantadine ER once daily (B) to healthy, adult, male and female subjects under fasting conditions on days 1 and 9.

FIG. **3** shows a plot of mean plasma concentration of amantadine versus time curves after administration of amantadine IR twice daily and amantadine ER once daily to healthy, adult, male and female subjects under fasting conditions on day 9.

FIG. **4** shows the simulated mean plasma concentration of amantadine versus time curves following multiple dose administration of various strengths of immediate release amantadine dosed twice or thrice daily and various strengths of amantadine ER administered once daily.

FIG. **5** shows a plot of mean (SD) plasma amantadine concentrations versus scheduled time for four (4) amantadine treatments.

FIG. **6** shows a semi-logarithmic mean (SD) plasma amantadine concentrations versus scheduled time for four (4) amantadine treatments.

FIG. **7** shows simulated steady state plasma concentration time profiles for the ER amantadine formulations as described in Example 12. The ER amantadine formulation 2, administered once daily at night, results at steady state in about 4 hour delay in achieving peak plasma concentration relative to formulation 1.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a method of reducing sleep disturbances in a patient undergoing treatment with amantadine. The method comprises administering amantadine to a patient in need thereof, such that the amantadine does not interfere with sleep, yet provides maximum benefit in morning hours when often needed most by many patients who take amantadine and further, provides nighttime coverage of

symptoms of Parkinson's disease if needed. Nighttime coverage includes providing benefit if the patient wakes up and wishes to return to sleep.

The method of the invention comprises orally administering to the patient an extended release (ER) amantadine composition designed for nighttime administration. The composition is taken less than three hours before bedtime, and preferably less than two and a half, less than two, less than one and a half, or less than one hour before bedtime. Most preferably the ER amantadine composition is taken less than half hour before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). As used herein, a reference to amantadine is intended to encompass pharmaceutically acceptable salts thereof (e.g. amantadine hydrochloride, amantadine sulfate, etc.). Alternatively, the composition is administered less than about 4 hours before bedtime.

As used herein, "extended release" includes "controlled release", "modified release", "sustained release", "timed release", "delayed release", and also mixtures of delayed release, immediate release, enteric coated, etc. with each of the above.

The patient may be diagnosed with any disease or disorder for which amantadine is prescribed, such as Parkinson's disease, multiple sclerosis, drug-induced extrapyramidal reactions, levodopa-induced dyskinesia, and viral diseases (e.g. influenza, HBV, and HCV). In a specific embodiment, the patient has Parkinson's disease, which, as used herein, also encompasses a diagnosis of parkinsonism. In one embodiment, the patient has early stage Parkinson's disease, and the amantadine is used as a monotherapy or in combination with a monoamine oxidase type B (MAO-B) inhibitor without concomitant use of levodopa. In another embodiment, the patient has late stage Parkinson's disease and the patient takes levodopa in addition to the amantadine. In another embodiment, the patient has multiple sclerosis and the amantadine is used for the treatment of fatigue. In other embodiments, the patient has a brain injury, brain injury, brain trauma, dementia, Alzheimer's disease, stroke, Huntington's disease, ALS, Multiple Sclerosis, neurodegenerative diseases, dementias, cerebrovascular conditions, movement disorders, cranial nerve disorders, neuropsychiatric disorders.

An ER amantadine composition for use in the invention is adapted for nighttime administration by providing a plasma concentration profile that does not interfere with the subject's sleep. The composition of the invention will, upon administration to a human subject, result in a gradual initial increase in plasma concentration of amantadine such that, at steady state conditions, administration of a dose of the composition results in an increase in plasma concentration of amantadine of less than 25% at three hours after the dose is administered. For example, if a subject's steady state plasma concentration of amantadine is 500 ng/ml at the time a dose of the composition is administered, three hours later the subject's plasma concentration of amantadine will be less than 625 ng/ml. Preferably, the increase in plasma concentration of amantadine is less than 15%, and most preferably, less than 10%. Particularly preferred compositions have a plasma concentration profile further characterized by no increase in amantadine plasma concentration, or even a decrease (at steady state conditions), for at least one or, in a preferred embodiment, two hours after the administration. The composition for use in the invention is further adapted for bedtime (i.e. the time at which the subject wishes to go to sleep for the night) administration by providing a maximum concentration of amantadine (Cmax) in the morning hours. The time to reach Cmax (Tmax), as measured after single dose administration in the fasted state, is at least, 8 hours and up to 13, 14, 15, or 16 hours, or at least 9 hours and up to 13, 14, 15, or 16 hours, or at least 10 hours, and up to 13, 14, 15, or 16 hours. In specific embodiments, the Tmax is 9 to 15 hours, preferably 10 to 14 hours, and most preferably 11 to 13 hours. At steady state, with once daily administration of the composition, the Tmax is 7 to 13 hours, preferably 8 to 12 hours, and most preferably 9 to 11 hours. A suitable ER amantadine composition may be further characterized by having a steady-state Cmax/Cmin ratio of 1.5 to 2.0, and preferably 1.7 to 1.9, resulting in a composition with optimal fluctuation.

In more specific, preferred embodiments, the plasma concentration profile is further characterized by having an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5%, and preferably less than 3% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 8 hours that is about 5 to 15%, and preferably about 8 to 12% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 12 hours that is about 10 to 40%, and preferably about 15 to 30% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 18 hours that is about 25 to 60%, and preferably about 30 to 50% of $AUC_{0\text{-}inf}$; and a fractional AUC from 0 to 24 hours that is about 40 to 75%, and preferably about 50 to 70% of $AUC_{0\text{-}inf}$.

In a further preferred embodiment, the plasma concentration profile is further characterized by having an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25%, and preferably about 5 to 20% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50%, and preferably about 20 to 40% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70%, and preferably about 40 to 60% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95%, and preferably about 75 to 90% of AUC_{24}.

In some embodiments of any of the above aspects, the steady state plasma concentration profile following multiple administrations to a human subject of the composition at bedtime is characterized by an average plasma concentration during the day ("C-ave-day", defined as the average day time amantadine plasma concentration as measured in a human PK study) that is 1.1 to 2.0 times the average plasma concentration during the night ("C-ave-night", defined as the average night time amantadine plasma concentration as measured in a human PK study). In some embodiments, the ratio of C-ave-day/C-ave-night at steady state is within one of the ranges 1.1 to 1.9, 1.1 to 1.8, 1.1 to 1.7, 1.1 to 1.6, 1.1 to 1.5, 1.1 to 1.4, 1.2 to 1.9, 1.2 to 1.7, 1.2 to 1.6, 1.2 to 1.5, 1.3 to 1.9, 1.3 to 1.8, 1.3 to 1.7, 1.3 to 1.6, 1.4 to 1.9, 1.4 to 1.8, 1.4 to 1.7, 1.5 to 1.9, 1.5 to 1.8, 1.5 to 1.7, 1.6 to 1.9, 1.6 to 1.8 or 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave-night at steady state is 1.1, 1.15, 1.2, 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, or 2.0. In some embodiments, the C-ave-day is the average amantadine plasma concentration as measured between the hours of 5 am, 6 am, 7 am, 8 am or 9 am to the hours of 4 pm, 5 pm, 6 pm, 7 pm or 8 pm and the C-ave-night is the average amantadine plasma concentration as measured between the hours of 4 pm, 5 pm, 6 pm, 7 pm, 8 pm, 9 pm, 10 pm or 11 pm to the hours of 5 am, 6 am, 7 am, 8 am or 9 am. In some embodiments, the C-ave-day is the average amantadine plasma concentration as measured within any four to twelve hour period between the hours of 5 am and 8 pm; and the C-ave-night is the average amantadine plasma concentration as measured within any four to twelve hour

period between the hours of 8 pm and 5 am. In some embodiments, the C-ave-day is the average amantadine plasma concentration as measured within any four, five, six, seven, eight, nine, ten, eleven or twelve hour period between the hours of 5 am and 8 pm; and the C-ave-night is the average amantadine plasma concentration as measured within any four, five, six, seven, eight, nine, ten, eleven or twelve hour period between the hours of 8 pm and 5 am.

In some embodiments described herein an amantadine composition is administered to a patient from 0 to 4 hours prior to bedtime. In some embodiments, the amantadine composition is administered to a patient from 0 to 3, 0 to 2 or 0 to 1 hours prior to bedtime. In some embodiments, the amantadine composition is administered to a patient from 0 to 240 minutes, from 0 to 180 minutes, e.g. from 0 to 120 minutes, from 0 to 60 minutes, from 0 to 45 minutes, from 0 to 30 minutes, from 0 to 15 minutes or from 0 to 10 minutes prior to bedtime. In some embodiments, the amantadine composition is administered to a patient from 60 to 240 minutes, from 60 to 180 minutes, from 60 to 120 minutes or from 60 to 90 minutes prior to bedtime.

It is to be understood that administration to a patient includes administration by a healthcare professional and self administration by the patient.

Unless otherwise specified herein, the term "bedtime" has the normal meaning of a time when a person retires for the primary sleep period during a twenty-four hour period of time. While for the general populace, bedtime occurs at night, there are patients, such as those who work nights, for whom bedtime occurs during the day. Thus, in some embodiments, bedtime may be anytime during the day or night.

As used herein, unless otherwise indicated, reference to a plasma concentration profile or a specific pharmacokinetic property (e.g. Cmax, Cmin, AUC, Tmax, etc.) in a human subject refers to a mean value obtained from healthy adults s determined in a typical phase I clinical trial designed to measure pharmacokinetic properties of a drug (see e.g. Examples 5, 6 and 7, below). References herein to Tmax refer to values obtained after administration of a single dose at fasted states, unless otherwise indicated.

In some embodiments of the invention, the dose of the amantadine administered in accordance with the present invention is within or above the ranges normally prescribed for immediate release compositions of amantadine. In other embodiments, the doses of the amantadine administered with the present invention are higher than the ranges normally prescribed for immediate release compositions of amantadine. For example, the recommended dose of amantadine for the treatment of Parkinson's disease is 100 mg administered twice daily. In limited cases of the patient not deriving sufficient benefit at that dose and subject to the patient being able to tolerate such higher dose, the dose may be increased to 300 mg or 400 mg in divided doses. The most commonly prescribed doses of amantadine are 100 mg to 200 mg per day, with the latter administered in divided doses. More than 200 mg (for example 300 mg) is always given in divided doses. For the present invention, doses of 50 to 600 mg, or more preferably, 200 to 450 mg are administered for treatment of Parkinson's disease, and the methods and compositions of the invention may comprise administration of a dose as defined by any of these ranges. In specific embodiments the administration of such higher doses may be once daily. In additional embodiments the administration of such higher doses may be at night. In additional embodiments the administration of such higher doses may be in the form of 1, 2 or 3 capsules of size 0, 1 or 2 administered once daily.

In one embodiment of any of the above aspects the amantadine is administered as a pharmaceutically acceptable salt. In a more specific embodiment, the amantadine is administered as hydrochloride or amantadine sulfate.

In one embodiment of any of the above aspects, a total daily dose of 50 mg to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof is administered to a patient. More specifically the daily dose of amantadine or pharmaceutically acceptable salt thereof administered may be in the range of 100 mg to 440 mg. In another specific embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof maybe in the range of 260 mg to 420 mg. In another embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof administered exceeds 300 mg per day. In various specific embodiments, the daily dose of amantadine or pharmaceutically acceptable salt thereof may be 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg.

In one embodiment of any of the above aspects, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. More specifically, the composition may comprise 100 to 450 mg of amantadine, or a pharmaceutically acceptable salt thereof. Still more specifically, the composition may comprise 130-210 mg of amantadine, or a pharmaceutically acceptable salt thereof. In various specific embodiments, the dosage form comprises 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg of amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition comprises about 110, 120, 130, 140, 150, 160 170, 180, 190, 210, or 220 mg amantadine, or a pharmaceutically acceptable salt thereof. In another more specific embodiment, the composition comprises 110 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 130 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 170 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 210 mg amantadine hydrochloride.

In one embodiment of any of the above aspects, the composition comprises from about 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg of amantadine, or a pharmaceutically acceptable salt thereof to about 75 mg, 85 mg, 95 mg, 105 mg, 115 mg, 125 mg, 135 mg, 145 mg, 155 mg, 165 mg, 175 mg, 185 mg, 195 mg, 205 mg, 215 mg, 225 mg, 235 mg, 245 mg, 255 mg, 265 mg, 275 mg, 285 mg, 295 mg, 305 mg, 315 mg, 325 mg, 335 mg, 345 mg, 355 mg, 365 mg, 375 mg, 385 mg, 395 mg, 405 mg, 415 mg, 425 mg, 435 mg, 445 mg of amantadine, or a pharmaceutically acceptable salt thereof.

In a specific embodiment of the invention, a subject's entire daily dose of amantadine is administered once, during a period of less than about three, two or one hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). In other embodiments, at least one half of the daily dose of amantadine is taken during said period before bedtime. Preferably at least ⅔ of the dose of amantadine is taken in said period before bedtime, with the remainder taken in morning or afternoon. The morning or afternoon dose of the amantadine may be provided in a conventional, immediate release dosage form, or in an extended release form.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in levodopa induced dyskinesia. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% reduction in levodopa induced dyskinesia. In further embodiments, the reduction in levodopa induced dyskinesia is measured on a numeric scale that is used by or accepted by the FDA or other regulatory agencies to evaluate the effectiveness of and to approve for licensure drugs for the treatment of LID. In further specific embodiments, the scale used in measuring the reduction in LID could be UDysRS, UPDRS Part IV (subscores 32, 33), Dyskinesia Rating Scale (DRS), Abnormal Involuntary Movement Scale (AIMS), Rush Dyskinesia Rating Scale, Parkinson Disease Dyskinesia Scale (PDYS-26), Obeso Dyskinesia Rating Scale (CAPIT), Clinical Dyskinesia Rating Scale (CDRS), Lang-Fahn Activities of Daily Living Dyskinesia or other scales developed for this purpose.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease fatigue. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, or 60% reduction in Parkinson's disease fatigue. In further specific embodiments, the reduction in fatigue is measured on a numerical scale used by or accepted by the FDA or other regulatory agencies to evaluate the effectiveness of and to approve for licensure drugs for the treatment of fatigue. In further specific embodiments, the scale used in measuring the reduction in fatigue could be the Fatigue Severity Scale (FSS), Fatigue Assessment Inventory, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue), Multidimensional Fatigue Inventory (MFI-20), Parkinson Fatigue Scale (PFS-16) and the Fatigue Severity Inventory. In other specific embodiments, the reduction in fatigue is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in fatigue is measured relative to baseline in a controlled clinical trial.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease symptoms. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's symptoms. In further specific embodiments, the reduction in Parkinson's symptoms is measured on a numerical scale used by or accepted by the FDA or other regulatory agencies to evaluate the effectiveness of and to approve for licensure drugs for the treatment of Parkinson's symptoms. In further specific embodiments, the scale used in measuring the reduction in Parkinson's symptoms could be the Unified Parkinson's Disease Rating Scale (UPDRS). Unified Parkinson's Disease Rating Scale (UPDRS, MDS revision)—Part I: non-motor aspects of experiences of daily living (13 items), Part II: motor aspects of experiences of daily living (13 items)—Part III: motor examination (33 scored items)—Part I: mental status, behavior and mood—Part II: activities of daily living—Part III: motor examination (27 scored items) Hoehn and Yahr Staging Scale (Original or Modified).

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in levodopa induced dyskinesia. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% reduction in levodopa induced dyskinesia. In further embodiments, the reduction in levodopa induced dyskinesia is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce LID. In further specific embodiments, the scale used in measuring the reduction in LID could be UDysRS, UPDRS Part IV (subscores 32, 33), Dyskinesia Rating Scale (DRS), Abnormal Involuntary Movement Scale (AIMS), or other scales developed for this purpose. In other specific embodiments, the reduction in LID is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in LID is measured relative to baseline in a controlled clinical trial.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease fatigue. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's disease fatigue. In further specific embodiments, the reduction fatigue is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce fatigue. In further specific embodiments, the scale used in measuring the reduction in fatigue could be the Fatigue Severity Scale (FSS). In other specific embodiments, the reduction in fatigue is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in fatigue is measured relative to baseline in a controlled clinical trial.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease symptoms. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's symptoms. In further specific embodiments, the reduction in Parkinson's symptoms is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce Parkinson's symptoms. In further specific embodiments, the scale used in measuring the reduction in Parkinson's symptoms could be the Unified Parkinson's Disease Rating Scale (UPDRS). In other specific embodiments, the reduction in Parkinson's disease symptoms is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in Parkinson's disease symptoms is measured relative to baseline in a controlled clinical trial.

Extended Release Formulations

Extended release amantadine compositions suitable for use in the method of the invention can be made using a variety of extended release technologies, such as those described in the patent publications referenced in the above background section, which publications are incorporated herein by reference in their entireties. In some embodiments, the invention is a pellet in capsule dosage form. In some embodiments, the pellets comprise a pellet core, which is

coated with at least one drug layer and at least one extended release coating layer. In some embodiments, the pellets are coated with at least one drug layer, an intermediate layer such as a seal coat and an extended release coating layer. In some embodiments, the pellet, the drug layer or both comprise one or more binders.

In some embodiments, the dosage unit comprises a plurality of coated pellets. In some embodiments, the pellets have a diameter of for example 300 to 1700 microns, in some cases 500 to 1200 microns. The pellets will comprise, for example, inert substrates, such as sugar spheres, microcrystalline cellulose (MCC) spheres, starch pellets. In some embodiments, pellets can be prepared by other processes such as pelletization, extrusion, spheronization, etc. or combinations thereof. The core pellets will comprise of amantadine hydrochloride and pharmaceutically acceptable excipients.

Coated Pellets

The pellet cores are coated with the active ingredient, e.g., amantadine or a pharmaceutically acceptable salt and/or polymorph thereof. In some embodiments, in addition to the active ingredient, the pellets also comprise one or more binders, such as for example hydroxypropyl methyl cellulose, copovidone, povidone, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose etc. In some embodiments, the pellets also contain one or more additional excipients, such as anti-tack agents (e.g. talc, magnesium stearate etc.)

In some embodiments, the pellets cores are coated with a drug layer comprising active ingredient, and optionally one or more binders, anti-tack agents and/or solvents by conventional coating techniques such as fluidized bed coating, pan coating.

Intermediate Layer Coating

In some embodiments, the pellets are coated with an intermediate layer, such as a seal coat. In some embodiments, the seal coat is adapted to prevent ingredients in the extended release coating from interacting with ingredients in the pellet core, to prevent migration of the ingredients in the pellet core from diffusing out of the pellet core into the extended release layer, etc. As described herein, the seal coat of the present invention can comprise one or more film forming polymers including but not limited to hydroxypropylmethyl cellulose (HPMC), copovidone, povidone, polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose or any combination thereof and the like.

The seal coat can further comprise other additives like plasticizers, such as, propylene glycol, triacetin, polyethylene glycol, tributyl citrate and optionally anti-tacking agents, such as, magnesium stearate, calcium silicate, magnesium silicate, and colloidal silicon dioxide or talc.

Apart from plasticizers and anti-tacking agents as mentioned above, the seal coat can optionally contain buffers, colorants, opacifiers, surfactants or bases, which are known to those skilled in the art.

Seal coating can be applied to the core using conventional coating techniques such as fluidized bed coating, pan coating etc. In some embodiments, the drug coated pellets cores are coated with a seal coat layer that optionally comprises one or more binders, anti-tack agents and/or solvents by fluidized bed coating or pan coating.

Binders

In some embodiments, either the pellet cores, the intermediate coating layer, or both may comprise one or more binders (e.g., film forming polymers). Suitable binders for use herein include, e.g.: alginic acid and salts thereof; cellulose derivatives such as carboxymethylcellulose, methylcellulose (e.g., Methocel®), hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose (e.g., Klucel®), ethylcellulose (e.g., Ethocel®), and microcrystalline cellulose (e.g., Avicel®); microcrystalline dextrose; amylose; magnesium aluminum silicate; polysaccharide acids; bentonites; gelatin; polyvinylpyrrolidone/vinyl acetate copolymer; crospovidone; povidone; starch; pregelatinized starch; tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitab®), and lactose; a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, polyvinylpyrrolidone (e.g., Polyvidone® CL, Kollidon® CL, Polyplasdone® XL-10), larch arabogalactan, Veegum®, polyethylene glycol, waxes, sodium alginate, and the like.

Extended Release Coating

The pellets are coated with an extended release coating. The extended release coating is adapted to delay release of the drug from the coated drug cores for a period of time after introduction of the dosage form into the use environment. In some embodiments, the extended release coating includes one or more pH-dependent or non-pH-dependent extended release excipients. Examples of non-pH dependent extended release polymers include ethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, copolymer of ethyl acrylate, methyl methacrylate (e.g. Eudgrait RS) etc. Examples of pH dependent extended release excipients include methacrylic acic copolymers, hydroxypropylmethyl cellulose acetate succinate, hydroxypropylmethyl cellulose phthalate, and cellulose acetate phthalate etc. The extended release coating may also include a pore former, such as povidone, polyethylene glycol, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, etc., sugars such as sucrose, mannitol, lactose, and salts, such as sodium chloride, sodium citrate, etc., a plasticizer, such as acetylated citrated esters, acetylated glycerides, castor oil, citrate esters, dibutylsebacate, glyceryl monostearate, diethyl phthalate, glycerol, medium chain triglycerides, propylene glycol, polyethylene glycol. The extended release coating may also include one or more additional excipients, such as lubricants (e.g., magnesium stearate, talc etc.).

Extended release coating can be applied using conventional coating techniques such as fluidized bed coating, pan coating etc. The drug coated pellets cores, which optionally comprise a seal coat, are coated with the extended release coating by fluidized bed coating.

Extended Release Excipients (Coating Polymers)

As described herein, exemplary extended release excipients include, but are not limited to, insoluble plastics, hydrophilic polymers, and fatty compounds. Plastic matrices include, but are not limited to, methyl acrylate-methyl methacrylate, polyvinyl chloride, and polyethylene. Hydrophilic polymers include, but are not limited to, cellulosic polymers such as methyl and ethyl cellulose, hydroxyalkyl celluloses such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, and cross-linked acrylic acid polymers like Carbopol® 934, polyethylene oxides and mixtures thereof. Fatty compounds include, but are not limited to, various waxes such as carnauba wax and glyceryl tristearate and wax-type substances including hydrogenated castor oil or hydrogenated vegetable oil, or mixtures thereof.

In certain embodiments, the plastic material can be a pharmaceutically acceptable acrylic polymer, including but not limited to, acrylic acid and methacrylic acid copolymers,

methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain other embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In still other embodiments, the acrylic polymer is an acrylic resin lacquer such as that which is commercially available from Rohm Pharma under the trade name Eudragit®. In further embodiments, the acrylic polymer comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the trade names Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. Edragit® S-100 and Eudragit® L-100 are also suitable for use herein. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, multiparticulate systems formed to include the same are swellable and permeable in aqueous solutions and digestive fluids.

The polymers described above such as Eudragit® RL/RS may be mixed together in any desired ratio in order to ultimately obtain an extended release formulation having a desirable dissolution profile. One skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L.

Pore Formers

In some embodiments, the extended release coating includes a pore former. Pore formers suitable for use in the extended release coating can be organic or inorganic agents, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. Examples of pore formers include but are not limited to organic compounds such as mono-, oligo-, and polysaccharides including sucrose, glucose, fructose, mannitol, mannose, galactose, lactose, sorbitol, pullulan, dextran; polymers soluble in the environment of use such as water-soluble hydrophilic polymers, such as povidone, crospovidone, polyethylene glycol, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyalkyl celluloses, carboxyalkyl celluloses, cellulose ethers, acrylic resins, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, polyethylene oxide, carbowaxes, Carbopol®, and the like, diols, polyols, polyhydric alcohols, polyalkylene glycols, polyethylene glycols, polypropylene glycols, or block polymers thereof, polyglycols, poly(α-Ω) alkylenediols; inorganic compounds such as alkali metal salts, lithium carbonate, sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium acetate, sodium citrate, suitable calcium salts, and the like. In certain embodiments, plasticizers can also be used as a pore former.

Capsules

The extended release pellets are introduced into a suitable capsule by using an encapsulator equipped with pellet dosing chamber. The capsule sizes may be 00, 0, 0EL, 1, 1EL, 2, 2EL, 3, 4 or 5. A particularly preferred composition that provides ideal pharmacokinetic properties and plasma concentration profiles is a pellet-in-capsule composition that comprises a plurality of pellets, typically having a diameter of about 500 μm to 1.2 mm, and preferably about 700 μm to 1000 μm, where each pellet comprises a core comprising amantadine and a binder, and an extended release coating surrounding the core that extends release of the amantadine so as to provide the desired pharmacokinetic properties and amantadine plasma concentration profiles described above.

In some embodiments, the pellets in the pellet-in-capsule are in a size 0 or smaller, preferably a size 1 or smaller capsule. Mean pellet diameters in some embodiments may be in a range of 500 μm to 1200 μm, e.g. from 500 μm to 1100 μm, from 500 μm to 1000 μm, from 500 μm to 900 μm, from 500 μm to 800 μm, from 500 μm to 700 μm, from 600 μm to 1100 μm, from 600 μm to 1000 μm, from 600 μm to 900 μm, from 600 μm to 800 μm, from 600 μm to 700 μm, from 700 μm to 1100 μm, from 700 μm to 1000 μm, from 700 μm to 900 μm, or from 700 μm to 800 μm. In some embodiments the mean particle diameters are, ±10%, e.g.: 500 μm, 550 μm, 600 μm, 650 μm, 700 μm, 750 μm, 800 μm, 850 μm, 900 μm, 950 μm, 1000 μm, 1050 μm, 1100 μm, 1150 μm or 1200 μm.

One preferred composition of the invention is a pellet-in-capsule composition wherein each pellet comprises a core that comprises a core seed with a mixture of amantadine and a binder coated onto the core seed, and an extended release coating surrounding the core comprising ethyl cellulose, a pore forming agent such as hydroxypropyl methyl cellulose or povidone, and a plasticizer. In some embodiments, the pellets may further comprise a seal coating between the pellet core and the extended release coating. The pellets are formulated using methods known in the art, such as those described in Example 1 below. In a specific embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 20-80 wt %, 45-70 wt %, 40-50 wt %, 45-55 wt %, 50-60 wt %, 55-65 wt %, 60-70 wt %, 65-75 wt %, 70-80 wt %, or 40 to 60 wt %, the binder, which is preferably hydroxypropyl methyl cellulose, copovidone, or mixtures thereof, is present in amounts from 1 to 25 wt %, the core seed, preferably a sugar sphere (nonpareil) or microcrystalline cellulose seed (e.g. Celphere®), is present in amounts from 8 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the pore forming agent, preferably povidone, is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %. In another specific embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 50 to 70 wt %, the binder, which is preferably hydroxypropyl methyl cellulose, copovidone, or mixtures thereof, is present in amounts from 1 to 25 wt %, the core seed, preferably a sugar sphere (nonpareil) or microcrystalline cellulose seed (e.g. Celphere®), is present in amounts from 5 to 15 wt %, the ethyl cellulose is present in amounts from 1 to 15 wt %, the pore forming agent, preferably povidone, is present in amounts from 0.25 to 4 wt %, and the plasticizer is present in amounts from 0.25 to 4 wt %.

Additional embodiments of the invention are illustrated in the Table, below, entitled "Various Amantadine ER Capsule Size 1 Formulations". By means of methods and compositions described herein, formulations can be made that achieve the desired dissolution characteristics and target pharmacokinetic profiles described herein. More specifi-

cally, therapeutically effective doses of amantadine can be administered once daily in no more than two size 1 (or smaller, e.g. size 2 or 3) capsules using the manufacturing methods and compositions that have been described herein to achieve these results. In particular, higher drug loading can be achieved using compositions and manufacturing methods described herein. In some embodiments, higher drug loading may be achieved, with the required dissolution profile, using smaller core pellet sizes and concomitantly increased drug layering on smaller cores, but with no change in the extended release coat. In some embodiments, using alternative manufacturing approaches described herein, e.g. extrusion and spheronization, even higher drug loads can be achieved to realize the desired dissolution profile, enabling high amantadine drug loads with suitable pharmacokinetic profiles, resulting in compositions that are therapeutically more effective, and at least as well tolerated, and can be filled in relatively small sized capsules (e.g., size 1, 2 or 3), enabling ease of administration to patients.

TABLE

Various Amantadine ER Capsule Size 1 Formulations

AMT Strength (mg)	Manufacture Method	Inert Core Pellet Size (mm)	Active Drug % w/w	Extended Release Coating % w/w	Bulk Density (g/cm^3)	% Fill in Size 1 Capsule	AMT Dissolution (%) (at T (hrs)): 2 hrs	6 hrs	12 hrs
110 mg	Fluid bed coating	0.3-0.5	40-50%	10-30%	0.6-1.0	60-70%	<25%	40-80%	>80%
140 mg	Fluid bed coating	0.3-0.5	45-50%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
150 mg	Fluid bed coating	0.3-0.5	50-55%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
170 mg	Fluid bed coating	0.2-0.3	50-55%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
170 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	65-75%	<25%		>80%
190 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	75-85%	<25%	40-80%	>80%
210 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
230 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	85-95%	<25%	40-80%	>80%

In some embodiment, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 20 to 80 wt % (based on the combined weight of the pellet core and extended release coating), with a bulk density of 0.3 to 1.2 g/cm^3. In some embodiments, the amantadine or pharmaceutically acceptable salt thereof is present in amounts from 20 to 77.5 wt %, from 20 to 75 wt %, from 20 to 72.5 wt %, from 20 to 70 wt %, from 20 to 67.5 wt %, from 20 to 65 wt %, from 20 to 62.5 wt %, from 20 to 60 wt %, from 20 to 57.5 wt %, from 20 to 55 wt %, from 20 to 52.5 wt %, from 20 to 50 wt %, from 20 to 47.5 wt %, from 20 to 45 wt %, from 20 to 42.5 wt %, from 20 to 40 wt %, from 20 to 37.5 wt %, from 20 to 35 wt %, from 20 to 32.5 wt %, from 20 to 30 wt %, from 30 to 80 wt %, from 30 to 77.5 wt %, from 30 to 75 wt %, from 30 to 72.5 wt %, from 30 to 70 wt %, from 30 to 67.5 wt %, from 30 to 65 wt %, from 30 to 62.5 wt %, from 30 to 60 wt %, from 30 to 57.5 wt %, from 30 to 55 wt %, from 30 to 52.5 wt %, from 30 to 50 wt %, from 30 to 47.5 wt %, from 30 to 45 wt %, from 30 to 42.5 wt %, from 30 to 40 wt %, from 40 to 80 wt %, from 40 to 77.5 wt %, from 40 to 75 wt %, from 40 to 72.5 wt %, from 40 to 70 wt %, from 40 to 67.5 wt %, from 40 to 65 wt %, from 40 to 62.5 wt %, from 40 to 60 wt %, from 40 to 57.5 wt %, from 40 to 55 wt %, from 40 to 52.5 wt %, from 40 to 50 wt %, from 40 to 47.5 wt %, from 40 to 45 wt %, from 50 to 80 wt %, from 50 to 77.5 wt %, from 50 to 75 wt %, from 50 to 72.5 wt %, from 50 to 70 wt %, from 50 to 67.5 wt %, from 50 to 65 wt %, from 50 to 62.5 wt %, from 50 to 60 wt %, from 50 to 57.5 wt %, from 50 to 55 wt %, from 60 to 80 wt %, from 60 to 77.5 wt %, from 60 to 75 wt %, from 60 to 72.5 wt %, from 60 to 70 wt %, from 60 to 67.5 wt %, from 60 to 65 wt %. In some embodiments, the bulk density is 0.3 to 1.2 g/cm^3, 0.3 to 1.15 g/cm^3, 0.3 to 1.1 g/cm^3, 0.3 to 1.05 g/cm^3, 0.3 to 1.0 g/cm^3, 0.3 to 0.9 g/cm^3, 0.3 to 0.8 g/cm^3, 0.3 to 0.7 g/cm^3, 0.3 to 0.6 g/cm^3, 0.3 to 0.5 g/cm^3, 0.3 to 0.4 g/cm^3, 0.4 to 1.2 g/cm^3, 0.4 to 1.15 g/cm^3, 0.4 to 1.1 g/cm^3, 0.4 to 1.05 g/cm^3, 0.4 to 1.0 g/cm^3, 0.4 to 0.9 g/cm^3, 0.4 to 0.8 g/cm^3, 0.4 to 0.7 g/cm^3, 0.4 to 0.6 g/cm^3, 0.4 to 0.5 g/cm^3, 0.5 to 1.2 g/cm^3, 0.5 to 1.15 g/cm^3, 0.5 to 1.1 g/cm^3, 0.5 to 1.05 g/cm^3, 0.5 to 1.0 g/cm^3, 0.5 to 0.9 g/cm^3, 0.5 to 0.8 g/cm^3, 0.5 to 0.7 g/cm^3, 0.5 to 0.6 g/cm^3, 0.6 to 1.2 g/cm^3, 0.6 to 1.15 g/cm^3, 0.6 to 1.1 g/cm^3, 0.6 to 1.05 g/cm^3, 0.6 to 1.0 g/cm^3, 0.6 to 0.9 g/cm^3, 0.6 to 0.8 g/cm^3, 0.6 to 0.7 g/cm^3, 0.7 to 1.2 g/cm^3, 0.7 to 1.15 g/cm^3, 0.7 to 1.1 g/cm^3, 0.7 to 1.05 g/cm^3, 0.7 to 1.0 g/cm^3, 0.7 to 0.9 g/cm^3, 0.7 to 0.8 g/cm^3, 0.5 to 1.2 g/cm^3, 0.8 to 1.15 g/cm^3, 0.8 to 1.1 g/cm^3, 0.8 to 1.05 g/cm^3, 0.8 to 1.0 g/cm^3, 0.8 to 0.9 g/cm^3, 0.9 to 1.2 g/cm^3, 0.9 to 1.15 g/cm^3, 0.9 to 1.1 g/cm^3, 0.9 to 1.05 g/cm^3, or 0.9 to 1.0 g/cm^3. In some embodiments, the composition is in a dosage unit comprising a pellet in capsule formulation, wherein the capsule size is size 00, size 0, size 1, size 2 or size 3. In some preferred embodiments, the dosage unit includes pellets

containing from 50 to 250 mg of amantadine in a size 0, 1, 2 or 3 capsule. In some embodiments, the dosage unit includes pellets containing from 100 to 250 mg, e.g. 100 to 200 mg of amantadine in a size 0, 1, 2 or 3 capsule, preferably a size 1, 2 or 3 capsule. In a more specific embodiment, the dosage unit comprises about 110, 120, 130, 140, 150, 160 170, 180, 190, 210, or 220 mg amantadine, or a pharmaceutically acceptable salt thereof. In another more specific embodiment, the dosage unit comprises 110 mg amantadine hydrochloride. In another more specific embodiment, the dosage unit comprises 130 mg amantadine hydrochloride. In another more specific embodiment, the dosage unit comprises 170 mg amantadine hydrochloride. In another more specific embodiment, the dosage unit comprises 210 mg amantadine hydrochloride.

Suitable plasticizers include medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, castor oil, and the like. The pellets are filled into capsules to provide the desired strength of amantadine. An advantage of this composition is it provides the desired release properties that make the composition suitable for administration during said period before bedtime. A further advantage is that the extended release coating is sufficiently durable so that the capsule can be opened and the pellets sprinkled onto food for administration to patients who have difficulty swallowing pills, without adversely affecting the release properties of the composition. When the composition is administered by sprinkling onto food, it is preferred to use a soft food such as applesauce or chocolate pudding, which is consumed within 30 minutes, and preferably within 15 minutes. A yet further advantage of the above-described composition is that it has very good batch-to-batch reproducibility and shelf-life stability.

In some embodiments, the composition of the invention has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, as measured using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. More preferably, the in vitro dissolution is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours.

In additional embodiments, 110 mg to 210 mg of ER amantadine in a size 1 capsule of the composition of the invention has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, as measured using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. More preferably, the in vitro dissolution is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more than 25-55% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 20% dissolution at 1 hour, (ii) about 25-45% dissolution at 2 hours, (iii) not more than 50-80% dissolution at 4 hours, and (iii) at least 80% dissolution at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

A preferred pellet-in-capsule compostion of the invention, in addition to having the above in vitro dissolution properties and any of the above-described pharmacokinetic properties (e.g. in vivo release profile, Tmax, Cmax/Cmin ratio, etc) that make the composition suitable for administration in said period before bedtime. The composition is further characterized by providing a Cmax of 1.6-2.4 ng/ml per mg of amantadine and an $AUC_{0\text{-}inf}$ of 40-75 ng*h/mL per mg of amantadine after oral administration of a single dose of the capsule to a human subject in a fasted state. A preferred pellet-in-capsule composition is further characterized by a steady state plasma concentration in which once daily oral administration of the capsule to a human subject provides a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine, a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and an $AUC_{0\text{-}24}$ of 48-73 ng*h/mL per mg of amantadine.

The above-described pellet-in-capsule compositions may be provided at a strength suitable for amantadine therapy. Typical strengths range from at least about 50 mg to about 250 mg. In a specific embodiment, the capsule strength is 70 mg, 80 mg, 90 mg, 110 mg, 120 mg, 125 mg, 130 mg, 140 mg, 150 mg, 160 mg, 160 mg, 170 mg, 180 mg, 190 mg, 210 mg, and 220 mg, that provides a single dose $AUC_{0\text{-}inf}$ per mg that is equivalent to a 100 mg tablet of an immediate release formulation of amantadine HCl (e.g. Symmetrel®, or other FDA Orange Book reference listed drug). One, two, or three, of such capsules can be administered to a subject in the period before bedtime. In a preferred embodiment, between 220 mg and 650 mg of amantadine is administered using 2 capsules of a suitable ER formulations once daily.

The invention may also be described in terms of the following numbered embodiments:

1. An extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, for use in a method of administering amantadine to a subject in need thereof, said method comprising orally administering said composition less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).
2. Use of amantadine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by the NMDA receptor to a subject in need thereof, said medicament being an extended release (ER) composition, and said treatment comprising orally administering said composition less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).
3. An extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing sleep disturbance in a human subject undergoing treatment with amantadine, said method comprising administering said composition less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).
4. Use of amantadine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing sleep disturbance in a human subject undergoing treatment with amantadine, said medicament being an extended release (ER) composition and being

adapted for administration less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).

5. The use or composition of any one of embodiments 1-4 wherein administration occurs less than 1 hour before bedtime.

6. The use or composition of any one of embodiments 1-5, wherein the patient has been diagnosed with Parkinson's disease.

7. The use or composition of any one of embodiments 1-6, wherein the composition is administered once daily.

8. The use or composition of any one of embodiments 1-7, wherein the composition is added to food prior to administration.

9. The use or composition of any one of embodiments 1-8, wherein there is no increase in plasma concentration of amantadine for at least one hour after the administration at steady state.

10. The use or composition of any one of embodiments 1-9, wherein there is no increase in plasma concentration of amantadine for at least two hours after the administration at steady state.

11. The use of composition of any one of embodiments 1-10, wherein, the amantadine has a single dose Tmax of 9 to 15 hours and/or a steady state Tmax of 7 to 13 hours after administration.

12. The use or composition of any one of embodiments 1-11, wherein the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours after administration.

13. The use of composition of any one of embodiments 1-10, wherein, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours after administration.

14. The use or composition of any one of embodiments 1-11, wherein the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours after administration.

15. The use of composition of any one of embodiments 1-10, wherein, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours after administration.

16. The use or composition of any one of embodiments 1-11, wherein the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours after administration.

17. The use or composition of any one of embodiments 1-12, wherein the amantadine has a single dose Tmax of 11 to 13 hours after administration, and or a steady state Tmax of 9 to 11 hours after administration.

18. The use or composition of any one of embodiments 1-13, wherein a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration.

19. The use or composition of any one of embodiments 1-14 having a Cmax/Cmin ratio of 1.5 to 2.0.

20. The use or composition of any one of embodiments 1-15 having a Cmax/Cmin ratio of 1.7 to 1.9.

21. The use or composition of any one of embodiments 1-16, wherein the amantadine is amantadine hydrochloride or amantadine sulfate.

22. The use or composition of any one of embodiments 1-17 wherein the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof.

23. The use or composition of embodiment 18, wherein the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof.

24. The use or composition of any one of embodiments 1-19 wherein the composition comprises 200 to 420 mg of amantadine, or a pharmaceutically acceptable salt thereof.

25. The use or composition of embodiment 20, wherein the composition is administered as two unit dosage forms each comprising 110 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof.

26. The use or composition of any one of embodiments 1 to 17, wherein the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof.

27. The use or composition of embodiment 22, wherein the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof.

28. The use or composition of embodiment 23, wherein the composition comprises 110 mg amantadine hydrochloride.

29. The use or composition of any one of embodiments 1-24, wherein oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of amantadine of 1.6 to 2.4 ng/ml per mg of amantadine and an $AUC_{0\text{-}inf}$ of 40 to 75 ng*h/mL per mg of amantadine.

30. The use or composition of any one of embodiments 1-25, wherein once daily oral administration of a dose of the composition to a human subject provides a steady state plasma amantadine concentration profile characterized by:

(i) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine,

(ii) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and

(iii) an $AUC_{0\text{-}24}$ of 44 to 83 ng*h/mL per mg of amantadine.

31. The use or composition of embodiment 26, wherein the steady state plasma concentration profile is further characterized by:

(iv) no increase in plasma concentration of amantadine for at least one hour after the administration; and

(v) a Cmax/Cmin ratio of 1.5 to 2.0.

32. The use or composition of embodiment 27, wherein the steady state plasma concentration profile is further characterized by:

(iv) no increase in concentration of amantadine for at least two hours after the administration; and

(v) a Cmax/Cmin ratio of 1.7 to 1.9.

33. The use or composition of any one of embodiments 1-28, wherein the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium.

34. The use or composition of embodiment 29, wherein the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours

35. The use or composition of any one of embodiments 1-30, wherein the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours

that is less than 5% of AUC_{0-inf}; a fractional AUC from 0 to 8 hours that is about 5 to 15% of AUC_{0-inf}; a fractional AUC from 0 to 12 hours that is about 10 to 40% of AUC_{0-inf}; a fractional AUC from 0 to 18 hours that is about 25 to 60% of AUC_{0-inf}; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of AUC_{0-inf}

36. The use or composition of any one of embodiments 1-31, wherein the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.
37. A pharmaceutical composition as embodied in any one of embodiments 1, 3, or 5 to 32, or the use of any one of embodiments 2, 4 or 5 to 32, wherein said composition is for oral administration and comprises a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising:
    (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and
    (b) an extended release coating surrounding the pellet core.
38. The use or composition of embodiment 32, wherein the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer.
39. The use or composition of any one of embodiments 33 or 34, wherein the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed.
40. The use or composition of embodiment 35, wherein, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 60 wt %, the binder is present in amounts from 8 to 25 wt %, the core seed is present in amounts from 8 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the povidone is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %.
41. The use or composition of any one of embodiments 33 to 36, further comprising a seal coating between the pellet core and the extended release coating.
42. The use or composition of any one of embodiments 35 to 37, wherein the wherein the pellet core comprises a binder, selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof.
43. The use or composition of any one of embodiments 18 to 38, wherein the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.
44. A composition of any one of embodiments 33 to 39, for use in a method of treating Parkinson's disease in a human subject in need thereof, said method comprising orally administering said composition.

Some embodiments herein provide a method of administering amantadine to a subject in need thereof, said method comprising orally administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than three hours before bedtime. In some embodiments, administration occurs less than 1 hour before bedtime. In some embodiments, the patient has been diagnosed with Parkinson's disease. In some embodiments, the composition is administered once daily. In some embodiments, the composition is added to food prior to administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least one hour after the administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least two hours after the administration. In some embodiments, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours. In some embodiments, the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours. In some embodiments, the amantadine has a single dose Tmax of 11 to 13 hours after administration, and/or a steady state Tmax of 9 to 11 hours. In some embodiments, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave night at steady state is 1.2 to 1.6. In some embodiments, the ratio of C-ave-morning/C-ave night at steady state is 1.3 to 1.5. In some embodiments, the average amantadine plasma concentration during the day (C-ave-day) at steady state is 500-2000 ng/ml. In some embodiments, the average amantadine plasma concentration in the morning (C-ave-morning) at steady state is 500-2000 ng/ml. In some embodiments, the amantadine is amantadine hydrochloride or amantadine sulfate. In some embodiments, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one or two unit dosage forms each comprising 130 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is within a capsule of capsule size #1. In some embodiments, the composition comprises 200 to 350 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 110 mg amantadine hydrochloride. In some embodiments, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine, and an AUC_{0-inf} of 40 to 75 ng*h/mL per mg of amantadine. In some embodiments, once daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by: (a) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine; (b) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (c) an AUC_{0-24} of 44 to 83 ng*h/mL per mg of amantadine. In some embodiments, the steady state plasma concentration profile is further characterized by: (d) no increase in plasma concentration of amantadine for at least one hour after the administration; and (e) a Cmax/Cmin ratio of 1.5 to 2.0. In

some embodiments, the steady state plasma concentration profile is further characterized by: (f) no increase in concentration of amantadine for at least two hours after the administration; and (g) a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 25-55% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 20% at 1 hour, 25-45% at 2 hours, 50-80% at 4 hours, and at least 80% at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours. In some embodiments, the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 8 hours that is about 5 to 15% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 12 hours that is about 10 to 40% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 18 hours that is about 25 to 60% of $AUC_{0\text{-}inf}$; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of $AUC_{0\text{-}inf}$. In some embodiments, the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

Some embodiments herein provide a method of reducing sleep disturbance in a human subject undergoing treatment with amantadine, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than three hours before bedtime. In some embodiments, administration occurs less than 1 hour before bedtime. In some embodiments, the patient has been diagnosed with Parkinson's disease. In some embodiments, the composition is administered once daily. In some embodiments, the composition is added to food prior to administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least one hour after the administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least two hours after the administration. In some embodiments, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours. In some embodiments, the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours. In some embodiments, the amantadine has a single dose Tmax of 11 to 13 hours after administration, and/or a steady state Tmax of 9 to 11 hours. In some embodiments, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave night at steady state is 1.2 to 1.6. In some embodiments, the ratio of C-ave-morning/C-ave night at steady state is 1.3 to 1.5. In some embodiments, the average amantadine plasma concentration during the day (C-ave-day) at steady state is 500-2000 ng/ml. In some embodiments, the average amantadine plasma concentration in the morning (C-ave-morning) at steady state is 500-2000 ng/ml. In some embodiments, the amantadine is amantadine hydrochloride or amantadine sulfate. In some embodiments, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one or two unit dosage forms each comprising 130 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is within a capsule of capsule size #1. In some embodiments, the composition comprises 200 to 350 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 110 mg amantadine hydrochloride. In some embodiments, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine, and an $AUC_{0\text{-}inf}$ of 40 to 75 ng*h/mL per mg of amantadine. In some embodiments, once daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by: (a) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine; (b) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (c) an $AUC_{0\text{-}24}$ of 44 to 83 ng*h/mL per mg of amantadine. In some embodiments, the steady state plasma concentration profile is further characterized by: (d) no increase in plasma concentration of amantadine for at least one hour after the administration; and (e) a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the steady state plasma concentration profile is further characterized by: (f) no increase in concentration of amantadine for at least two hours after the administration; and (g) a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 25-55% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 20% at 1 hour, 25-45% at 2 hours, 50-80% at 4 hours, and at least 80% at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours. In some

embodiments, the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of AUC_{0-inf}; a fractional AUC from 0 to 8 hours that is about 5 to 15% of AUC_{0-inf}; a fractional AUC from 0 to 12 hours that is about 10 to 40% of AUC_{0-inf}; a fractional AUC from 0 to 18 hours that is about 25 to 60% of AUC_{0-inf}; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of AUC_{0-inf}. In some embodiments, the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

Some embodiments herein provide a method of treating levodopa induced dyskinesia in a patient with Parkinson's disease, said method comprising orally administering once daily an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime. In some embodiments, administration occurs less than 1 hour before bedtime. In some embodiments, the patient has been diagnosed with Parkinson's disease. In some embodiments, the composition is administered once daily. In some embodiments, the composition is added to food prior to administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least one hour after the administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least two hours after the administration. In some embodiments, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours. In some embodiments, the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours. In some embodiments, the amantadine has a single dose Tmax of 11 to 13 hours after administration, and/or a steady state Tmax of 9 to 11 hours. In some embodiments, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave night at steady state is 1.2 to 1.6. In some embodiments, the ratio of C-ave-morning/C-ave night at steady state is 1.3 to 1.5. In some embodiments, the average amantadine plasma concentration during the day (C-ave-day) at steady state is 500-2000 ng/ml. In some embodiments, the average amantadine plasma concentration in the morning (C-ave-morning) at steady state is 500-2000 ng/ml. In some embodiments, the amantadine is amantadine hydrochloride or amantadine sulfate. In some embodiments, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one or two unit dosage forms each comprising 130 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is within a capsule of capsule size #1. In some embodiments, the composition comprises 200 to 350 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 110 mg amantadine hydrochloride. In some embodiments, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine, and an AUC_{0-inf} of 40 to 75 ng*h/mL per mg of amantadine. In some embodiments, once daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by: (a) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine; (b) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (c) an AUC_{0-24} of 44 to 83 ng*h/mL per mg of amantadine. In some embodiments, the steady state plasma concentration profile is further characterized by: (d) no increase in plasma concentration of amantadine for at least one hour after the administration; and (e) a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the steady state plasma concentration profile is further characterized by: (f) no increase in concentration of amantadine for at least two hours after the administration; and (g) a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 25-55% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 20% at 1 hour, 25-45% at 2 hours, 50-80% at 4 hours, and at least 80% at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours. In some embodiments, the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of AUC_{0-inf}; a fractional AUC from 0 to 8 hours that is about 5 to 15% of AUC_{0-inf}; a fractional AUC from 0 to 12 hours that is about 10 to 40% of AUC_{0-inf}; a fractional AUC from 0 to 18 hours that is about 25 to 60% of AUC_{0-inf}; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of AUC_{0-inf}. In some embodiments, the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

Some embodiments herein provide a pharmaceutical composition for any of the methods described herein, wherein said composition is for oral administration and comprises a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically

acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 60 wt %, the binder is present in amounts from 8 to 25 wt %, the core seed is present in amounts from 1 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the povidone is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %. In some embodiments, the composition further comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.

Some embodiments herein provide a method of administering amantadine, or a pharmaceutically acceptable salt thereof, to a human subject in need thereof, said method comprising orally administering a pharmaceutical composition comprising amantadine in a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 60 wt %, the binder is present in amounts from 8 to 25 wt %, the core seed is present in amounts from 1 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the povidone is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %. In some embodiments, the composition further comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil. Some embodiments comprise treating Parkinson's disease in a human subject in need thereof.

Some embodiments herein provide a pharmaceutical composition suitable for once daily oral administration to a patient in need thereof said composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. In some embodiments, the composition comprises 110-220 mg of amantadine or pharmaceutically acceptable salt thereof. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 40-80% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition comprises a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, the composition comprises amantadine and, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 70 wt %. In some embodiments, the pellet core comprises a core seed comprising sugar or microcrystalline cellulose that is between 100 and 500 microns in diameter. In some embodiments, the bulk density is between 0.5 and 1 gm/cm^3. In some embodiments, the composition comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.

Some embodiments herein provide a method of treating Parkinson's disease in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. In some embodiments, the composition comprises 110-220 mg of amantadine or pharmaceutically acceptable salt thereof. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 40-80% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition comprises a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, the composition comprises amantadine and, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 70 wt %. In some embodiments, the pellet core comprises a core seed comprising sugar or microcrystalline cellulose that is between 100 and 500 microns in diameter. In some embodiments, the bulk density is between 0.5 and 1 gm/cm^3. In some embodiments, the composition comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.

Some embodiments herein provide a method of treating levodopa induced dyskinesia in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. Some embodiments herein provide a method of treating traumatic brain injury in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. Some embodiments provide a method of treating traumatic brain injury in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. Some embodiments provide a method of treating fatigue in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. In some embodiments, the composition comprises 110-220 mg of amantadine or pharmaceutically acceptable salt thereof. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 40-80% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition comprises a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, the composition comprises amantadine and, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 70 wt %. In some embodiments, the pellet core comprises a core seed comprising sugar or microcrystalline cellulose that is between 100 and 500 microns in diameter. In some embodiments, the bulk density is between 0.5 and 1 gm/cm^3. In some embodiments, the composition comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil. In some embodiments, the method comprises administering the composition to a patient less than three hours before bed time.

The present invention may be better understood by reference to the following examples, which are not intended to limit the scope of the claims.

Example 1: Amantadine Extended Release Coated Pellet Formulations

Amantadine HCl extended release coated pellet compositions designed for nighttime administration were prepared using the components and relative amounts shown in Table 1 below. For each composition, the drug coating solution was prepared by adding HPMC 5 cps and Copovidone to isopropyl alcohol with continuous stirring. Purified water was added to this dispersion and stirring continued until a clear solution is formed. Drug (Amantadine HCl) was then added to this binder solution and stirring continued until the drug was completely dissolved. Finally, talc was added and dispersed uniformly by stirring.

Celphere beads (screen sizes #35 to #50 i.e. 300 to 500 micron) were loaded in a Wurster coating unit. The drug coating dispersion was sprayed onto the beads followed by a period of drying. The resulting drug coated pellets were sieved to retain the fraction between screens #18 and #24 (approximately 700 μm to 1 mm diameter).

The seal coating solution was prepared by adding HPMC 5 cps to isopropyl alcohol with continuous stirring. Purified water was added to this dispersion and stirring continued until a clear solution was formed. Talc was added and dispersed uniformly by stirring. The sieved drug coated pellets were loaded in a Wurster coating unit. The seal coating dispersion was sprayed over the drug coated pellets followed by a period of drying to remove the residual solvent and water in the pellets. The resulting seal coated pellets were sieved to retain the fraction between screens #18 and #24.

The ER coating solution was prepared by dissolving ethyl cellulose (viscosity 7 cps) in isopropyl alcohol and purified water and stirring until a clear solution was formed. Povidone K-90 was then dissolved in this clear solution followed by addition of plasticizer Miglyol 812N with continuous stirring to form a clear solution. The sieved seal coated pellets were loaded in a Wurster coating unit. The ER coating solution was sprayed over the seal coated pellets followed by a period of drying to affect the ER coat and remove the residual solvent and water in the pellets. After drying, magnesium stearate was spread on the top bed of the coated pellets in the annulus region followed by recirculation of the pellets in the Wurster unit to blend the magnesium stearate with the coated pellets. The resulting ER coated pellets were sieved to retain the fraction between screens #18 and #24.

The desired weight of the ER coated pellets containing the unit dose were filled into empty 1 hard gelatin capsule shell (size 1 for 100-140 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 1

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Pellet Core		
Amantadine Hydrochloride USP	Active	40-50%
Microcrystalline cellulose spheres (Celphere ®)	Core seeds	10-15%
Hydroxypropyl methyl cellulose 5 cps USP	Binder	10-15%
Copovidone	Binder	1-5%
Talc USP	Anti-tack	1-5%

TABLE 1-continued

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Seal Coating (optional)		
Hydroxypropyl methyl cellulose 3 cps USP	Coating polymer	5-10%
Talc USP	Anti-tack	0-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Extended Release Coating		
Ethyl cellulose	Coating polymer	10-20%
Povidone	Pore former	1-5%
Medium chain triglycerides	Plasticizer	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Magnesium Stearate NF	Lubricant	0-1%
Density of pellets		0.6-0.9 gm/cm^3

NF = National Formulary

[1]Purified water and isopropyl alcohol are removed during processing.

The in vitro dissolution of capsules prepared above was tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. Capsules meeting desired dissolution specifications released not more than 25% of the drug in 2 hours, 40-80% in 6 hours, and at least 80% at 12 hours. In an exemplary dissolution profile, there was 0% drug release at 1 hour, 12% release at 2 hours, 43% release at 4 hours, 68% release at 6 hours, 83% release at 8 hours, 92% release at 10 hours, and 97% release at 12 hours. Capsules prepared in accordance with the above method exhibited good shelf-stability, and batch-to-batch reproducibility upon scale-up.

Example 2: Amantadine Extended Release Coated Pellet Formulation with Higher Drug Loading

Amantadine HCl extended release coated pellet compositions designed for nighttime administration are prepared using the components and relative amounts shown in Table 2 below and the manufacturing process described in example 1.

The diameter of the inert cores is 200-300 microns. The diameter of the coated pellets is 600-1200 microns. The bulk density of the coated pellets is 0.7-1.2 g/cm^3.

The desired weight of the ER coated pellets containing the unit dose are filled into an empty hard gelatin capsule shell (size 1 for 170 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 2

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Pellet Core		
Amantadine Hydrochloride USP	Active	50-65%
Microcrystalline cellulose spheres (Celphere ®)	Core seeds	1-15%
Hydroxypropyl methyl cellulose USP	Binder	5-25%
Copovidone	Binder	1-5%
Talc USP	Anti-tack	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Seal Coating (optional)		
Hydroxypropyl methyl cellulose USP	Coating polymer	0-10%
Talc USP	Anti-tack	0-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Extended Release Coating		
Ethyl cellulose	Coating polymer	10-20%
Povidone	Pore former	1-5%
Medium chain triglycerides	Plasticizer	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Magnesium Stearate NF	Lubricant	0-1%

NF = National Formulary

[1]Purified water and isopropyl alcohol are removed during processing.

The in vitro dissolution of capsules prepared above are tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium and release not more than 25% of the drug in 2 hours, 40-80% in 6 hours, and at least 80% at 12 hours.

Example 3: Amantadine Extended Release Coated Pellet Formulations

Amantadine HCl extended release coated pellet compositions suitable for nighttime administration were prepared using the components and relative amounts shown in Table 3 below and the manufacturing process described in Example 1.

The desired weight of the ER coated pellets containing the unit dose was filled into empty #1 hard gelatin capsule shell (100 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 3

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule A	B	C
Pellet Core				
Amantadine Hydrochloride USP	Active	50.15%	47.94%	45.15%
Microcrystalline cellulose spheres (Celphere ®)	Core seeds	14.33%	13.70%	12.90%
Hydroxypropyl methyl cellulose USP	Binder	13.37%	12.79%	12.04%
Copovidone	Binder	3.34%	3.2%	3.01%
Talc USP	Anti-tack	2.51%	2.4%	2.26%
Isopropyl alcohol	Solvent	—[1]	—[1]	—[1]
Water	Solvent	—[1]	—[1]	—[1]
Seal Coating (optional)				
Hydroxypropyl methyl cellulose USP	Coating polymer	7.61%	7.27%	6.85%
Talc USP	Anti-tack	0.76%	0.73%	0.69%
Isopropyl alcohol	Solvent	—[1]	—[1]	—[1]
Water	Solvent	—[1]	—[1]	—[1]

TABLE 3-continued

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule A	B	C
Extended Release Coating				
Ethyl cellulose	Coating polymer	6.23%	9.46%	13.53%
Povidone	Pore former	0.85%	1.29%	1.84%
Medium chain triglycerides	Plasticizer	0.75%	1.13%	1.62%
Isopropyl alcohol	Solvent	—[1]	—[1]	—[1]
Water	Solvent	—[1]	—[1]	—[1]
Magnesium Stearate NF	Lubricant	0.1%	0.1%	0.1%

NF = National Formulary

[1]Purified water and isopropyl alcohol are removed during processing.

The in vitro dissolution of capsules prepared above were tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. The results are shown in FIG. **1**.

Example 4: Amantadine Extended Release Formulation Made by Extrusion Spheronization

Amantadine HCl extended release compositions designed for nighttime administration are prepared using the components and relative amounts shown in Table 4 below and the manufacturing process described below.

A blend of amantadine HCl, microcrystalline cellulose and lactose monohydrate was prepared and a wet mass is prepared in a high shear granulator using an aqueous solution of povidone. The wet mass is extruded using 1 mm sieve and extruded mass is spheronized using a spheronizer. The pellets are dried in a tray drier to yield core pellets. The core pellets are coated with extended release coating solution in a pan coater. The desired weight of the ER coated pellets containing the unit dose is filled into empty 1 hard gelatin capsule shell (170 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 4

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Pellet Core		
Amantadine Hydrochloride USP	Active	59.40%
Microcrystalline cellulose	Diluent	18.67%
Lactose monohydrate	Diluent	6.15%
Povidone	Binder	0.64%
Water	Solvent	—[1]
Extended Release Coating		
Ethyl cellulose	Coating polymer	12.41%
Polyethylene glycol	Pore former	1.24%
Dibutyl sebacate	Plasticizer	1.49%
Ethanol	Solvent	—[1]

The in vitro dissolution of capsules prepared above are tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium and release not more than 25% of the drug in 2 hours, 40-80% in 6 hours, and at least 80% at 12 hours.

Example 5: Pharmacokinetic Measurement of Formulations of Amantadine ER Compared to IR Amantadine

Objective: The primary objective of the study was to confirm the PK properties of extended release formulations in example 3, to determine the pharmacokinetic profiles, safety and tolerability of three prototype formulations of ER capsules of amantadine HCl described with different release properties in Example 3 relative to a 100 mg film-coated IR amantadine HCl tablet (SYMMETREL®) given as single doses to healthy adult subjects under fasting conditions.

Study design: This was a Phase 1, randomized, single dose, open-label, four-period, crossover, fasting pharmacokinetic study in which single 100 mg doses of three formulations of Amantadine ER capsules with different release properties were compared to single 100 mg doses of marketed amantadine IR tablets (SYMMETREL®). The three ER formulations differed in the amantadine release rates in vitro, as shown in FIG. **1**.

Methods: Subjects were admitted to the unit for the first period of dosing within 21 days of study screening. Subjects were dosed on the day after checking into the unit and discharged at 24 hours post dose. Subjects were asked to return after discharge for follow-up visits at 56 hours and 152 hours after dosing. Each dosing period was separated by at least 7 day washout.

After an overnight fast, the formulation was administered to the subjects while in a sitting position with 240 mL of water. Blood samples were collected at 0 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 24 (discharge), and 56 hours following each dose. Plasma samples were assayed for amantadine by a validated liquid chromatography/tandem mass spectroscopy (LC/MS/MS) method. Pharmacokinetic parameters were calculated using a non-compartmental analysis with WinNonlin software (version 4.1 or higher; Pharsight Corporation).

An analysis of variance (ANOVA) was performed on the natural logarithms of Cmax and AUC0-∞ determined from the data following a single dose of study drug using linear mixed effects model. The model included effects for subject, sequence, period, and regimen. The effects of sequence, period, and regimen were fixed, while the effect of subject was random. Ratio of ER to IR for both AUC (relative bioavailability for ER formualtions) and Cmax was calculated. (Adverse events were monitored throughout the study. Vital signs (pulse rate, blood pressure and body temperature), clinical laboratory measures (biochemistry, hematology, and urinalysis) and ECGs were collected at various times during the study.

Results: A total of 20 subjects participated in the study. The mean age was 25.5 years old (range 20-38 years). The study consisted of 8 male (40%) and 12 female (60%) subjects with a mean body mass index (BMI) of 23.6 kg/m2±2.85. The racial makeup was 100% Caucasian. Fifteen subjects received all 4 treatments.

The PK results from this study showed that all three of the Amantadine ER formulations reduced the rate of absorption, based on the reduced values of Cmax and increased Tmax, compared to SYMMETREL® (Table 5, FIGS. **5**, **6**). The IR formulation had the highest mean Cmax (277±73.9 ng/mL) and shortest median Tmax (4 h) values. Formulations A, B, and C produced progressively lower Cmax and longer Tmax values. Cmax decreased from 204±61.4 to 166±34.8 to 149±34.4 ng/mL, and median Tmax increased from 7.0, to 11.0, to 14.0 h for formulations A, B, and C, respectively. Total amantadine exposure, as measured by AUC0-∞, was

slightly lower in all three Amantadine ER formulations than SYMMETREL® but all three formulations had acceptable bioavailability (85-95%).

TABLE 5

Single Dose Pharmacokinetic Parameters of Three Formulations of Amantadine ER (Formulation A, B, and C), as Compared to SYMMETREL ® (Formulation IR)

Parameter [a]	100 mg Formulation A (n = 19)	100 mg Formulation B (n = 17)	100 mg Formulation C (n = 18)	100 mg Formulation IR (n = 18)
C_{max} (ng/mL)	204 ± 61	166 ± 35	149 ± 34	277 ± 74
T_{max} (h) [range]	7 [5-11]	11 [5-15]	14 [9-18]	4 [2-6]
$A_{UC0-last}$ (ng*h/mL)	5064 ± 1573	5028 ± 2328	4525 ± 1268	5488 ± 1730
$AUC_{0-\infty}$ (ng*h/mL)	5545 ± 1904	5724 ± 2369	5652 ± 2581	5907 ± 1907
$t_{1/2}$ (h)	13.9 ± 3.0	16.3 ± 5.2	18.3 ± 7.5	12.3 ± 3.5

[a] All parameters are reported as the mean ± standard deviation (SD), except t_{max} which is reported as a median value (min to max range)

TABLE 6

Ratio ER/IR for C_{max} and $AUC_{0-\infty}$

Comparison	Variable	ER/IR[a]
A vs. IR	C_{max} (ng/mL)	66.0%
	$AUC_{0-\infty}$ (ng*h/mL)	85.3%
B vs. IR	C_{max} (ng/mL)	60.9%
	$AUC_{0-\infty}$ (ng*h/mL)	94.6%
C vs. IR	C_{max} (ng/mL)	51.2%
	$AUC_{0-\infty}$ (ng*h/mL)	88.5%

[a]Point estimate of the geometric mean ratio (ER/IR).

Example 6: Food-Effect Evaluation of Amantadine ER

Objective:

The primary objective was to demonstrate that the amantadine ER formulations suitable for nighttime administration exhibit excellent bioavailability when administered with food. We determined the pharmacokinetics of a 100 mg capsule of an amantadine ER formulation (Example 3, Formulation B), when administered both with a high fat meal and in a fasted state.

Study Design:

This was a Phase 1, randomized, single dose, open-label, two-period, crossover, food-effect study to compare single 100 mg doses of Formulation I in healthy adult (18 to 45 years of age) male and female subjects in fed and fasted states. The study consisted of a 21-day to −2 day screening phase (prior to the scheduled dosing day) and two treatment periods, Period 1 and Period 2, with an 8-day wash-out period between treatment periods.

Methods:

After an overnight fast, the formulation was administered to the subjects while in a sitting position with 240 mL of water at ambient temperature for the fasted condition. For the fed condition, after the overnight fast, subjects were served a high fat and high calorie test meal (Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies, December 2002) as breakfast, which they were required to consume completely within 30 minutes before taking the study medication. Subjects were randomized to one of two sequences, each composed of treatment administration under fed and fasted conditions separated by an eight day wash out period.

For each period, pharmacokinetic blood samples were collected at pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 24, 28, 48, 72, 96 and 144 hours after dosing in each period. Subjects were housed in the clinical facility at least 15 hours before investigational product administration and remained in the clinical facility for at least 28 hours after administration of the investigational product in each period. Samples after 28 hours in each period were collected on an ambulatory basis. Amantadine in plasma was quantified by a validated LC/MS/MS method. The pharmacokinetic parameters were calculated from the drug concentration-time profile by non-compartmental model using WinNonlin Professional Software—Version 5.0.1 (Pharsight Corporation, USA) for amantadine. Absence of food effect was defined as met if the point estimates and 90% confidence intervals (CI) for the ln-transformed C_{max}, AUC_{last} and AUC_{∞} fed/fasting ratios of the population means were entirely within the standard accepted range of 80% to 125%. All statistical analyses for amantadine were performed using PROC MIXED of SAS® Release 9.1.3 (SAS Institute Inc., USA).

Routine safety monitoring was conducted during and after dosing in all subjects.

Results:

A total of 26 subjects participated in the study, 19 (73%) male and 7 (27%) female. The mean age was 26 years (range 19-44) and the mean BMI was 22.4 kg/m^2 (range 18.1-29.8). The racial makeup was 100% Asian. All subjects received at least one dose of study drug and were included in the safety analysis. Twenty-four (92.3%) subjects completed the study and were included in the pharmacokinetic analysis. Two subjects (7.7%) were withdrawn prior to completion of the study due protocol deviations.

The results of this study (Table 7) indicate that the single dose pharmacokinetics of Formulation B are not affected by food. The rate, as measured by C_{max}, and the extent, as measured by AUC_{0-last} and $AUC_{0-\infty}$, of absorption of amantadine, administered with and without food, were equivalent (Table 8).

TABLE 7

Mean ± SD Pharmacokinetic Parameters after Single Dose Administration of 100 mg of Formulation B in Fed and Fasted States

	Mean ± SD (Un-transformed data) n = 24	
Parameters (Units)[a]	Fasted State	Fed State
T_{max} (h)	11.9 ± 2.1 (8-15)	9.5 ± 2.4 (5-16)
C_{max} (ng/mL)	198.8 ± 34.7	219.4 ± 41.5
AUC_{0-last} (ng*h/mL)	5571.2 ± 1654.2	5394.4 ± 1581.5
$AUC_{0-\infty}$ (ng*h/mL)	5663.1 ± 1677.4	5476.6 ± 1590.7

TABLE 7-continued

Mean ± SD Pharmacokinetic Parameters after Single Dose Administration of 100 mg of Formulation B in Fed and Fasted States

	Mean ± SD (Un-transformed data) n = 24	
Parameters (Units)[a]	Fasted State	Fed State
$t_{1/2}$ (h)	11.9 ± 2.8	11.5 ± 2.0
t_{lag} (h)	1.0	2.0

[a]All parameters are reported as the mean ± standard deviation (SD). t_{max} is reported as the mean ± SD (min to max range).

TABLE 8

Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Formulation B (n = 24) in Fed and Fasted States

	ln-transformed data Geometric Least Squares Mean			90% Confidence
Parameters (Units)	Fed State	Fasted State	Ratio (Fed/Fasted)%	Interval (Parametric)
C_{max} (ng/mL)	215.6	195.8	110.1	104.4-116.2%
$AUC_{0\text{-}last}$ (ng*h/mL)	5195.9	5344.2	97.2	91.0-103.8%
$AUC_{0\text{-}\infty}$ (ng*h/mL)	5280.3	5434.7	97.2	90.9-103.8%

Conclusion:

The results of this study indicate that the single dose pharmacokinetics of amantadine ER are not affected by food. The rate, as measured by C_{max}, and the extent, as measured by $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$, of absorption of amantadine, administered with and without food, were equivalent.

Example 7: Pharmacokinetic Study Comparing Once-Daily Administration of Amantadine HCl ER Capsules with Twice-Daily Administration of Amantadine HCl IR Tablets in Healthy Adults Under Fasting Conditions

Objective: The primary objective of this study was to measure at steady state under repeat or chronic dosing the pharmacokinetics of an ER amantadine formulation suitable for nighttime administration, and enable the calculation of critical PK parameters for future safety and efficacy studies (i.e., Cave-morning, Cave-day, Cave-night) of ER amantadine formulations administered at night. We compared the single dose and repeat dose pharmacokinetics of amantadine HCl administered twice daily as a commercially available immediate release (IR) formulation to a once daily amantadine extended release (ER) formulation (Example 3, Formulation B).

Study Design:

This was a two period, multiple dose, crossover study. After a 21 day screening period, 26 healthy male and female subjects were randomized to receive one of two treatments (amantadine ER 200 mg once daily or amantadine IR 100 mg twice daily) in Period-I, then crossed over to receive the other treatment in Period-II.

Methods:

Study drug administration started on day 1. Study drug was not administered on Day 2. Multiple dosing commenced on day 3 and continued for 7 days (through day 9). A washout period of 8 days separated the dose administrations. The study drug was administered with 240 mL of drinking water. No other fluids were allowed within 1 hour of dosing. For each period, pharmacokinetic blood samples were collected at pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 24, 28, 36, and 48 hours after the first dose. The morning trough (pre-dose) blood samples were collected on Days 7 and 8. Blood samples were again collected immediately before the morning dose on Day 9 and at 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 24, 28, 48, 72, and 96 hours thereafter. Samples after 28 hours following the morning dose on day 9 were collected on an ambulatory basis in each period. Amantadine in plasma was quantified by a validated LC/MS/MS method. The pharmacokinetic parameters were calculated from the drug concentration-time profile by non-compartmental model using WinNonlin Professional Software-Version 5.0.1 (Pharsight Corporation, USA) for amantadine.

Statistical analyses were conducted to assess the pharmacokinetic profile of single dose and repeat dose amantadine HCl administered twice daily as a commercially available immediate release (IR) formulation compared to a once daily extended release (ER) formulation (Formulation B). An analysis of variance (ANOVA) was performed on the natural logarithms of C_{max}, C_{min}, and AUC_{24} determined from the data following the dose of study drug on study day 9 using linear mixed effects model. The model included the fixed effects for sequence, period, regimen and a random subject effect. The confidence intervals were used to perform the 2 one-sided tests procedure for equivalence assessment. The confidence intervals were obtained by exponentiating the endpoints of the confidence intervals for the difference of mean logarithms obtained within the framework of the ANOVA model. The upper and lower limits of confidence intervals from the natural-log transformed data were back-exponentiated to obtain the 90% confidence interval for the ratio of geometric means. Equivalence was established if the exponentiated 90% confidence interval fell entirely within the interval (80.00%, 125.00%).

Repeated measures ANOVA was carried out for comparison of C_{min} for day 7, 8 and 9 at 5% level of significance on both untransformed and ln-transformed data. Steady state was demonstrated if the repeated measures ANOVA test was found to be non-significant. The statistical analysis for amantadine was performed using PROC MIXED of SAS® Release 9.1.3 (SAS Institute Inc., USA).

Routine safety monitoring was conducted during and after dosing in all subjects, and at the end of the study.

Results:

A total of 26 subjects participated in the study, 22 (84.6%) male and 4 (15.4%) female. The mean age was 26 years (range 19-42) and the mean BMI was 22.9 kg/m^2 (range 18.1-28.8). The racial makeup was 100% Asian. All subjects received at least one dose of study drug and were included in the safety analysis. Twenty-four (92.3%) subjects completed the study and were included in the pharmacokinetic analysis. Two subjects (7.7%) were withdrawn from the PK analysis prior to completion of the study due to vomiting within 12 hours of dosing, which was a pharmacokinetic exclusion criterion.

As expected from its half-life, once daily administration of amantadine ER and twice daily dosing of amantadine IR resulted in accumulation as measured by higher C_{max} and AUC on Day 9 compared to Day 1 (Table 9 and FIG. **2**). Steady state was achieved by Day 9 for both formulations as demonstrated by similar trough levels on Days 7, 8 and 9 (data not shown). At steady state (Day 9) plasma concentrations (FIG. **2**, Table 9) and pharmacokinetic parameters (Table 9) were comparable for both formulations. Furthermore, the formulations are equivalent in terms of the extent and the rate of absorption of amantadine as measured by

steady state C_{max}, C_{min} and AUC_{0-24} (Table 9), where equivalency is defined by the 90% CIs of the ratio of the least square means of the test versus reference for steady state C_{max}, C_{min} and AUC_{0-24} of Amantadine ER to Amantadine IR falling within 80%-125%.

TABLE 9

Mean (±SD) Pharmacokinetic Parameters of Amantadine after Single and Multiple Dose Administration of IR (100 mg BID) and ER (200 mg QD) Formulations

	Formulation			
	IR (n = 24)		ER (n = 24)	
Parameter (Units)[a]	Day 1	Day 9	Day 1	Day 9
$t_{1/2}$ (h)	13.2 ± 2.8 [9.1-18.8]	12.6 ± 2.4 [9.4-18.1]	13.7 ± 3.6 [9.1-22.7]	12.8 ± 2.2 [9.2-17.4]
t_{max} (h)	14.42 ± 0.88 [13-16]	12.6 ± 4.5 [1-15]	11.4 ± 1.9 [8-18]	10.3 ± 2.0 [8-18]
C_{max} (ng/mL)	530 ± 80 [407.5-752.7]	728 ± 153 [538.4-1101.8]	431 ± 84 [313.5-559.9]	665 ± 179 [444.4-1140.0]
AUC_{0-last} (ng h/mL)	11989 ± 2224 [9243-17106]	23040 ± 8273 [13133-46446]	11171 ± 2773 [7326-16970]	21362 ± 8946 [10821-47134]
$AUC_{0-\infty}$ (ng h/mL)	13685 ± 3324 [10167-20989]	NA	12900 ± 4087 [7817-22153]	NA
AUC_{0-24} (ng h/mL)	7695 ± 1026 [5967-10171]	13752 ± 3586 [9085-22519]	7173 ± 1367 [5021-9552]	12680 ± 3879 [7896-23058]
C_{min} (ng/mL)	—	412.4 ± 142.6 [218.5-795.2]	—	374.9 ± 151.7 [172.2-767.1]

[a]All parameters are reported as the mean ± SD, [min to max range]
NA = not applicable

Certain additional PK parameters that are important in determining the suitability of the ER amantadine formulation for once daily, night time administration are also reported in Table 10.

TABLE 10

Additional Steady State PK parameters of Amantadine ER

	ER 200 mg QD	IR 100 mg BID
Cmax/Cmin	1.86	1.68
C-ave-8-16 hrs(ng/ml)	614	586
C-ave-8-12 hrs (ng/ml)	643	510
C-ave-16-24 hrs (ng/ml)	502	569
C-ave-0-8 hrs (ng/ml)	465	586
C-ave-8-16 hrs/C-ave-0-8 hrs	1.32	1.00
C-ave-8-12 hrs/C-ave-0-8 hrs	1.38	0.87
% Change in Plasma Concentration 0-3 hrs	5%	55%
% Change in Plasma Concentration 0-4 hrs	23%	48%
AUC 0-4 as % of AUC 24	12%	N/A
AUC 0-8 as % of AUC 24	30%	N/A
AUC 0-12 as % of AUC 24	51%	N/A

Conclusion: the ER amantadine formulation exhibits the desired steady state PK properties that would make the same suitable for administration at night and for achieving desired efficacy and tolerability benefits. Specifically, the ER amantadine formulation administered once daily at night results in relatively slow initial rise in amantadine plasma concentration, higher average amantadine plasma concentrations 8 to 12 hours after administration relative to 0-8 hours after administration and thus if administered at night higher ratios of average day time to night time amantadine plasma concentrations relative to IR amantadine. Thus this formulation is well suited for administration at higher doses than current practice that are expected to be relatively well tolerated and potentially provide superior efficacy in the treatment of LID, fatigue and Parkinson's disease.

Example 8: Study Comparing Administration of Amantadine HCl ER Capsules Once Nightly with Twice-Daily Administration of Amantadine HCl IR Tablets in Normal Healthy Volunteers

Objective: The primary objective is to compare the effects on sleep of amantadine extended release (ER) capsules (Formulation B) administered once daily at bedtime with amantadine immediate release (IR) tablets administered twice daily in normal healthy volunteers. This ER formulation exhibits a Cave, day/Cave, night=1.30.

Study Design:

This is a single-center, double-blind, triple-dummy, randomized, crossover study to compare the effects on sleep of amantadine ER capsules, QHS, amantadine IR tablets BID, and caffeine caplets (active comparator) in 30 normal healthy volunteers as assessed by overnight polysomnography (PSG) and standardized questionnaires (Stanford Sleepiness Scale (SSS); Modified Epworth Sleepiness Scale (m-ESS)/Karolinska Sleepiness Scale (KSS); Toronto Hospital Alertness Test (THAT)/ZOGIM Alertness Scale (ZOGIM-A); Visual analog scale of sleepiness/alertness (VAS)).

Study drugs are administered in 3 dosing periods. A single day's dosage of one drug is administered per dosing period. Each day of dosing is separated by a washout period of 1 week. A single day's dosage of amantadine ER (Formulation B) consists of one 220 mg capsule (or 2×110 mg capsule) administered at bed time (QHS; defined as 23:00 h for the purposes of this study). A single day's dosage of amantadine IR consists of one 100 mg capsule administered twice a day (BID; defined as 8:00 h and 16:00 h for the purposes of this study). A single day's dosage of caffeine consists of one 100 mg capsule administered three times a day (TID; defined as 8:00 h, 16:00 h, & 23:00 h for the purposes of this study).

All subjects are dosed three times a day, at 8:00 h, 16:00 h, & 23:00 h. At each hour of dosing, every subject receives

either the active drug or the matching placebo for each of the 3 treatments. Whether the capsule, tablet, or caplet administered at a specific hour of dosing contains active study drug or is a placebo dummy is determined according to the dosing sequence and period to which the subject is assigned.

Consented subjects who meet eligibility criteria are randomized equally to one of 3 treatment sequences (groups), each comprising 3 single-day treatment periods separated by 1 week washout periods as described above. Additionally, there is a one-day, single-blind, placebo run-in prior to each double-blind dosing day. This is to allow subjects to acclimate to sleeping in the Clinical Research Unit (CRU) under conditions of PSG recording and to establish individual baseline (BL) PSG characteristics.

For each dosing period, subjects are admitted to a CRU equipped with a sleep laboratory the day before the first day of dosing with active study drug. They stay in the CRU overnight and through the entirety of the active drug-dosing day. They again stay overnight and then are discharged from the CRU the morning of the following day. For the first dosing period, the day of admission to the CRU (Day −1) constitutes the last day of the screening phase, and the day of discharge from the CRU constitutes the first day of the first washout period (Day 2). For the second dosing period, the day of re-admission to the CRU (Day 7) constitutes the last day of the first washout period, and the day of discharge (Day 9) will constitute the first day of the second washout period. For the third dosing period, the day of re-admission to the CRU (Day 14) constitutes the last day of the second washout period, and the day of discharge (Day 16) constitutes the first day of the follow-up phase.

On the day of admission (or re-admission) to the CRU, subjects undergo routine laboratory and vital sign testing. They are administered one each of the placebo dummies (for amantadine ER, amantadine IR, & caffeine) at 16:00 h and at 23:00 h in single-blind fashion. They are questioned for adverse events (AEs) and have vital signs checked immediately prior to each dosing. Blood is drawn for routine laboratory testing and toxicology screen prior to the 16:00 h dosing. Subjects spend the night in the sleep lab under conditions of PSG recording.

On the day of dosing with active study drug, subjects are awakened at 7:00 h and fill out a battery of sleep and alertness questionnaires They receive study drug (active or placebo) at 8:00 h, 16:00, and 23:00 h. They are questioned for AEs and have vital signs checked immediately prior to each dosing. Blood is drawn to measure plasma amantadine concentrations prior to the 23:00 h dosing.

On the day after dosing with active study drug, subjects are awakened at 7:00 h and fill out a battery of sleep and alertness questionnaires Shortly before 8:00 h, i.e., 9 hours after the last dosing time, they are questioned for AEs and have vital signs checked. Also, blood is drawn to measure plasma amantadine concentrations. Instructions for contacting the site to report any AEs are reviewed with the subjects prior to their discharge from the CRU. The schedule for returning to the PSU for the next dosing period (this applies to returning for Periods 2 & 3) or for telephone contact (this applies to the follow-up after the third dosing period) is be reviewed.

All subjects receive a follow-up telephone call 3 days following discharge from the CRU (Day 19).

AEs and concomitant medications are monitored throughout the study. Blood samples for measurement of blood plasma concentrations are drawn immediately prior to the 23:00 h dosing time on Days 1, 8, and 15, and at approximately 8:00 h on Days 2, 9, and 16.

Sleep parameters and measurements of sleepiness and alertness at each time point are listed by subject. Both composite scores and scores from the individual components of the PSG and questionnaires are tabulated and analyzed. For each parameter measured, descriptive summary statistics are calculated by sequence and treatment, including means (or medians, as appropriate), ranges, and standard deviations (SDs).

Inferential statistics are performed on selected results wherein the magnitude of the differences between the means across treatment groups relative to the variance suggests a possible differential treatment effect. Continuous variable data is analyzed by parametric statistics (repeated measures analysis of variance with appropriate supplemental post-hoc analyses and/or paired t-test). Categorical data and data not conforming to a normal distribution is analyzed by non-parametric statistics (Wilcoxon signed rank test). PSG data may also be assessed by multivariate analyses and/or spectral analyses.

Results:

A lack of increase in, or reduction of, sleep disturbances with QD administration of 220 mg of amantadine ER compared to BID administration of amantadine IR, as measured by PSG and a standardized sleep questionnaire (e.g. SSS, m-ESS, KSS, THAT, ZOGIM-A, or VAS), demonstrates the suitability of amantadine ER for once daily administration at bedtime.

Example 9: Study Comparing the Effects on Sleep and Efficacy of Amantadine HCl ER Capsules Administered Once Daily at Night Relative to Amantadine HCl IR Capsules Administered Twice Daily in Parkinson's Patients

Objective:

To compare the effects on sleep and efficacy of amantadine extended release (ER) capsules.

Study Design:

This is a Multi-Center, Double-Blind, Randomized Study to Compare the Effects on Sleep and Efficacy of Amantadine Extended Release (ER) Capsules in 120 Parkinsons Patients as assessed by UPDRS (Unified Parkinson's Disease Rating Scale), UPDRS-IV (Unified Parkinson's Disease Rating Scale Part IV), AIMS (Abnormal Involuntary Movement Scale), overnight polysomnography (PSG) and standardized questionnaires (Stanford Sleepiness Scale (SSS); Modified Epworth Sleepiness Scale (m-ESS)/Karolinska Sleepiness Scale (KSS); Toronto Hospital Alertness Test (THAT)/ZOGIM Alertness Scale (ZOGIM-A); Visual analog scale of sleepiness/alertness (VAS)).

All study drugs are administered orally. Treatment A consists of a placebo capsule administered in the morning and two 110 mg capsules of Amantadine (ER) and a placebo capsule administered at bed time. Treatment B consists of a placebo capsule administered in the morning and three 110 mg capsules of Amantadine (ER) administered at bed time. Treatment C consists of a 100 mg capsule of Amantadine IR administered in the morning and a 100 mg capsule of Amantadine IR and two placebo capsules administered at bed time. Treatment D consists of a placebo capsule administered in the morning and 3 placebo capsules administered at bed time.

Consented subjects who meet eligibility criteria are randomized equally to one of 3 treatment groups, each comprising 14-day treatment periods. Additionally, there is a one-day, single-blind, placebo run-in prior to each double-blind dosing day. This is to allow subjects to acclimate to

sleeping in the Clinical Research Unit (CRU) under conditions of PSG recording and to establish individual baseline (BL) PSG characteristics.

For each dosing period, subjects are admitted to a CRU equipped with a sleep laboratory the day before the first day of dosing with active study drug. They stay in the CRU overnight and through the entirety of the active drug-dosing day. They again stay overnight and then are discharged from the CRU the morning of the following day.

Parkinson's scores are recorded in the mornings on days 1, 7 and 14 using standard scoring methods, including the UPDRS and AIM.

AEs and concomitant medications are monitored throughout the study.

Sleep parameters and measurements of sleepiness and alertness at each time point are listed by subject. Both composite scores and scores from the individual components of the PSG and questionnaires are tabulated and analyzed. For each parameter measured, descriptive summary statistics are calculated by sequence and treatment, including means (or medians, as appropriate), ranges, and standard deviations (SDs).

Inferential statistics are performed on selected results wherein the magnitude of the differences between the means across treatment groups relative to the variance suggests a possible differential treatment effect. Continuous variable data is analyzed by parametric statistics (repeated measures analysis of variance with appropriate supplemental post-hoc analyses and/or paired t-test). Categorical data and data not conforming to a normal distribution is analyzed by non-parametric statistics (Wilcoxon signed rank test). PSG data may also be assessed by multivariate analyses and/or spectral analyses.

Results:

An improvement in UPDRS, UPDRS-IV, AIM, lack of increase in, or reduction of, sleep disturbances, as measured by PSG and a standardized sleep questionnaire (e.g. SSS, m-ESS, KSS, THAT, ZOGIM-A, or VAS), demonstrates the suitability of amantadine ER for once daily administration at bedtime.

Example 10: Simulated Pharmacokinetic Characteristics of Higher Strength, Amantadine ER Formulations Administered at Nighttime

Objective: The objective is to use the data generated in the clinical study described in Example 7 to predict steady state plasma concentration-time profiles of various IR and ER amantadine regimens at different dose levels to show the benefits of higher strength amantadine ER formulations administered at nighttime.

Methodology: Plasma concentration-time profiles from healthy volunteers that received multiple doses of the ER and IR formulations of amantadine per study procedures described in Example 7 (ADS-5101-MD-104) were used to develop a pharmacokinetic model describing each of the two formulations. This study was an open-label, randomized, two-treatment, two-period, two-way crossover study comparing once-daily amantadine ER capsules and twice-daily amantadine IR tablets in 26 healthy, adult male and female volunteers. Complete data from 24 individuals were used in this exercise. Blood samples for pharmacokinetic evaluation were collected after single dosing on Day 1 and at steady state on Day 9. In the first step of the analysis, WinNonlin 5.2.1 (Pharsight Corp., Mountain View, Calif.) was used to fit a one-compartment model with first-order input and first-order output, weighted 1/y (where y is the amantadine plasma concentration), to each individual's plasma concentration-time data obtained after single (Day 1) and repeated (Day 9) dose administration of amantadine IR and ER; the fitting was done separately for both formulations, but simultaneously for both days. Modeling assumptions employed include dose proportionality and constant clearance as a function of time.

The model is described by the following equation:

$$C = \frac{FD}{V(k_a - k)}[\exp(-k(t - t_{lag})) - \exp(-k_a(t - t_{lag}))] \quad \text{Equation 1}$$

where C is the plasma concentration, F is the absolute bioavailability, D is dose, V is the volume of distribution, k_a is the absorption rate constant, k is the elimination rate constant, t is time, and t_{lag} is the lag time of absorption. The goodness of fit was verified by comparing the individual model predicted and observed concentration-time data from Study ADS-5101-MD-104. After Equation 1 was fitted to each individual's plasma concentration-time data, model parameter estimates of V/F, k_a, k, and t_{lag} were obtained for each of the 24 subjects. The goodness of the prediction at steady state was confirmed by comparing the observed data and predicted steady-state concentrations of amantadine obtained after daily dosing of 200 mg as the ER and IR formulations (Day 9).

In the second step of the analysis, individual model parameter estimates were used to simulate steady-state concentration-time profiles for each individual for both formulations by reinserting the individual parameter estimates into Equation 1, and summing the contribution of 7 sequential days of dosing, according to the following dosing regimens:

1. Once Daily (QD) dosing of 260, 340, and 420 mg of the ER formulation to steady state
2. Three times daily (TID) dosing of 100 mg of the IR formulation to steady state
3. Twice daily (BID) dosing of 100 mg of the IR formulation to steady state

Results: FIG. **4** shows the simulated steady state plasma concentration time profiles for various ER amantadine doses along with various regimes of IR amantadine. Table 11 summarizes values of the pharmacokinetic parameters that affect the efficacy and tolerability of ER amantadine when administered at night.

TABLE 11

PK parameters associated with nighttime administration - morning peak benefit measured for ER Amantadine formulation

	IR 100 mg BID	IR 100 mg TID	ER 260 mg QD	ER 340 mg QD	ER 420 mg QD
Cmax (ng/ml)	669	936	834	1091	1348
Cmin (ng/ml)	435	731	461	603	745
Cmax/Cmin	1.54	1.28	1.81	1.81	1.81
C-ave-day (6 am-4 pm) (ng/ml)	571	845	766	1002	1238
C-ave-morn (6 am-10 am) (ng/ml)	479	870	824	1078	1332
C-ave-even (4 pm-10 pm) (ng/ml)	522	852	591	773	955
C-ave-night (10 pm-6 am) (ng/ml)	596	843	616	805	995
C-ave-day/C-ave-night	0.96	1.00	1.24	1.24	1.24
C-ave-morn/C-ave-night	0.80	1.03	1.34	1.34	1.34
C-ave-day relative to 100 mg BID IR	1.00	1.48	1.34	1.76	2.17

As shown in Table 11 and in the figures, the ER amantadine formulations administered once daily at night result in higher ratios of average day time to night time amantadine plasma concentrations relative to IR amantadine and are predicted to be relatively well tolerated. The ER formulations also result in average day time amantadine plasma concentrations that are 1.3 to 2.2 fold that of IR amantadine administered at 100 mg twice daily and is predicted to result in significantly enhanced efficacy when administered to patients in the clinical study described in Example 11 below.

Example 11: A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Amantadine Extended Release Oral Capsules for the Treatment of Levodopa-Induced Dyskinesia in Parkinson's Disease

Study Objectives: This study is designed to confirm dose range of Amantadine Extended Release (ER) oral capsules dosed once daily at nighttime for the treatment of levodopa-induced dyskinesia (LID) in subjects with Parkinson's Disease (PD). In addition, the study is designed to demonstrate the safety and tolerability of Amantadine ER oral capsules dosed once daily for the treatment of LID in subjects with PD. Finally, to confirm the steady-state pharmacokinetics of the Amantadine ER dosing regimens in Parkinsons patients and to correlate C-ave-day, Cave-morning, C-ave-morning/C-ave-night and C-ave-day/C-ave-night with the efficacy and tolerability of amantadine.

Study Design:

This will be a multi-center, randomized, double-blind, placebo-controlled, 4-arm parallel group study of Amantadine ER in subjects with PD and LID/Consenting subjects who meet eligibility criteria will be randomized 1:1:1:1 to receive one of the following 4 treatments, each administered as once daily, dosed at night, for 8 weeks:

Treatment A: Placebo,

Treatment B: 260 mg Amantadine ER (ADS-5102),

Treatment C: 340 mg Amantadine ER (ADS-5102)

Treatment D: 420 mg Amantadine ER (ADS-5102)

Subjects who are randomized to Treatment C or D (higher dose amantadine groups) will receive, in double-blind fashion, 260 mg Amantadine ER once daily during week 1, with an increase to either 340 mg or 420 mg once daily at the beginning of week 2. Dosing will continue through week 8.

Following completion of the baseline visit and randomization, subjects will return to the clinic after 1, 2, 4, 6, and 8 weeks of dosing, with a follow-up visit 14 days following the last dose of study drug. Study visits and assessments will be scheduled during morning hours when possible (9 am through 1 pm). A set of two 24-hour diaries will be completed during 48 hours prior to randomization and 48 hours prior to selected study visits. The diary will be used to score five different conditions in 30-minute intervals: Sleep, OFF, ON without dyskinesias, ON with nontroublesome dyskinesias, ON with troublesome dyskinesias.

Blood samples will be collected at selected study visits for determination of amantadine plasma concentrations, and evaluation of steady-state population pharmacokinetics. Subject participation during the study will be up to 12 weeks and will include a 2-week (maximum) screening period, 8-week (maximum) treatment period, and a 2-week follow-up period. Subjects who are unable to tolerate their assigned study drug assignment will permanently discontinue study drug and continue to be followed for safety through 2 weeks following the last dose of study drug.

Patient Eligibility Criteria:

Subjects are eligible to take part in the study if they meet the inclusion and do not meet the exclusion criteria. Selected key criteria are as follows:

Inclusion Criteria:

- Male or female adults, residing in the community (i.e. not residing in an institution)
- Between 30 and 75 years of age, inclusive
- Ambulatory or ambulatory-aided (e.g. walker or cane) ability, such that the subject can come to required study visits
- Knowledgeable and reliable caregiver/study partner, if appropriate, to accompany the subject to study visits
- Signed a current IRB/IEC-approved informed consent form
- Following training, the subject is willing and able to understand and complete the 24-hour home diary (caregiver assistance allowed)
- Idiopathic Parkinson's Disease, complicated by dyskinesia (a MDS-UPDRS score will be determined during screening, but a minimum score is not required)
- On a stable regimen of antiparkinson's medications, including levodopa, for at least 30 days prior to screening, and willing to continue that regimen during study participation
- Presence of dyskinesia, defined as a minimum UDysRS score

Exclusion Criteria:

- Presence of other neurological disease that may affect cognition, including, but not limited to Alzheimer's dementia, Huntington's disease, Lewy body dementia, frontotemporal dementia, corticobasal degeneration, or motor or sensory dysfunction secondary to stroke or brain trauma.
- Presence of cognitive impairment, as evidenced by a Mini-mental State Examination (MMSE) score of less than 24 during screening.
- Presence of an acute major psychiatric disorder (e.g., Major Depressive Disorder) according to DSM-IV-TR or symptom (e.g., hallucinations, agitation, paranoia) that could affect the subject's ability to complete study assessments
- Presence of sensory impairments (e.g., hearing, vision) that would impair the subject's ability to complete study assessments
- History of alcohol or drug dependence or abuse, according to DSM-IV criteria, within 2 years prior to screening
- History of seizures (excluding febrile seizures of childhood)
- History of stroke or TIA within 2 years prior to screening
- History of myocardial infarction, NYHA Congestive Heart Failure Class 3 or 4, or atrial fibrillation within 2 years prior to screening
- History of cancer within 5 years prior to screening, with the following exceptions: adequately treated non-melanomatous skin cancers, localized bladder cancer, non-metastatic prostate cancer or in situ cervical cancer (these exceptions must be discussed with and approved by the Medical Monitor before study entry)
- Any of the following lab abnormalities; Hemoglobin <10 g/dL, WBC $<3.0\times10^9$/L, Neutrophils $<1.5\times10^9$/L, Lymphocytes $<0.5\times10^9$/L, Platelets $<100\times10^9$/L, Hemoglobin A1C >9%, or Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >2 times the upper limit of normal

Estimated GFR <50 mL/min/1.73 m^2 by Modification of Diet in Renal Disease (MDRD) or Cockcroft-Gault equation

Any clinically significant ECG abnormalities

Inability to swallow oral capsules, or a history of gastrointestinal malabsorption that would preclude the use of oral medication

Study Endpoints:

The primary efficacy endpoint will be the change from baseline to week 8 in the Unified Dyskinesia Rating Scale (UDysRS) score. Key secondary endpoints will include:

ON time without troublesome dyskinesia (ON without dyskinesia plus ON with nontroublesome dyskinesia), based on a standardized PD home diary

Unified Parkinson's Disease Rating Scale (MDS-UPDRS), overall score

Fatigue as measured by the Fatigue Severity Scale (FSS). This scale includes 9 questions that are completed by the patient using a rating scale from 1 (strongly disagree) to 7 (strongly agree). This fatigue scale is recommended by MDS for both screening and severity rating (2010)

Safety, including adverse events, safety-related study drug discontinuations, vital signs, and laboratory tests.

The following mixture of traditional and new scales have been selected for this phase 2 study:

Unified Dyskinesia Rating Scale (UDysRS) will be used for primary outcome measure. This scale has four parts, and a total possible score of 104:

I: Historical Disability (patient perceptions) of On-Dyskinesia impact

II: Historical Disability (patient perceptions) of Off-Dystonia impact

III: Objective Impairment (dyskinesia severity, anatomic distribution, and type, based on 4 observed activities)

IV: Objective Disability based on Part III activities

ON time without troublesome dyskinesia, based on a standardized Parkinson's Disease home diary (suggest Test Diary II), [33] will be a secondary outcome measure. This scale has been used in number of studies with mixed success [34]. However, most KOLs feel that subject-reported dairy data must be collected, and needs to support the primary outcome measure.

Unified Parkinson's Disease Rating Scale (UPDRS), part IV, items 32 (duration of dyskinesias: 0=none, 4=76-100% of the waking day) and 33 (disability of dyskinesias: 0=not disabling, 4=completely disabling) will be a secondary outcome measure. This scale is a traditional scale used in PD for many years and these items have been utilized in most LID studies.

Cognitive Scales: Global caregiver impression, depression and other scales will be employed to measure the mental status benefits of ER amantadine.

Statistical Methods

Efficacy Analyses: The efficacy analysis population will include all randomized and dosed subjects who provide at least one post-baseline efficacy assessment. For the efficacy endpoint of UDysRS score, the change from baseline to week 8 will be analyzed using an analysis of covariance (ANCOVA) model with treatment group as a factor and the UDysRS baseline value as a covariate. The primary analysis will compare the 260 mg ADS-5102 group to the placebo group using a two-sided test at the 5% level of significance. If the primary comparison is statistically significant ($p<0.05$), then the 340 mg and 420 mg ADS-5102 groups will be compared to placebo, also using a two-sided test at the 5% level of significance.

The secondary endpoints will be analyzed using the same types of ANCOVA models as described for the primary endpoint. All secondary comparisons between treatment groups will be performed using two-sided tests at the 5% level of significance. A last observation carried forward (LOCF) approach will be utilized for missing data. The primary efficacy analysis will be repeated for the per-protocol population, a subset of the efficacy analysis population who provide week 8 efficacy assessments.

Safety Analyses:

The safety analysis population will include all randomized subjects who receive at least one dose of study drug. All safety endpoints will be analyzed from the time of first dose through the completion of follow-up (or 2 weeks following the last dose of study drug). A safety analysis will also be done on the safety reported during the first 2 weeks of study drug treatment, in order to assess tolerability of initial dosing with ADS-5102 amantadine ER.

Results: following improvements are expected from this study are shown in the table below. Additional endpoints are described that

Significant (20-60%) reduction in dyskinesia score measured by acceptable primary endpoint (e.g., UDysRS)

Increase in ON time without troubling dyskinesia by 20-60%

Improvement in UPDRS from 5% to 20%.

Improvement in Parkinson's fatigue (FSS) from 5% to 60%.

Improvement in mood by PGI from 5% to 20%.

Instruments for Dyskinesia	% Clinical Effect (Placebo-Active/Placebo)	Range of Scores
Unified Dyskinesia Rating Scale (UDysRS)	5-60%	0-104 (4 parts, 26 items total, each 0, normal-4, severe)
Unified Parkinson's Disease Rating Scale (UPDRS, MDS revision)	5-20%	
Part IV	5-60%	0-24 (6 items, each 0, normal-4, severe)
Part IV, dyskinesia items only	5-60%	0-8 (2 dyskinesia items, 4.1 and 4.2, each 0, normal-4, severe)
Parkinson's Disease Home Diary (Hauser et al)	5-40%	0-100% (on time without dyskinesia or with nontroublesome dyskinesia)

Example 12: Simulated Pharmacokinetic Characteristics of Amantadine ER Formulations with a Delayed Release Coat Suitable for Night Time Administration

Objective: The objective is to evaluate the pharmacokinetic profile of two alternative ER formulations of amantadine suitable for nighttime administration—Formulation 1, which is the formulation tested in Example 7, and Formulation 2, which is the formulation tested in Example 7, but with a delayed release over coat on top of the extended release coat.

Plasma concentration-time profiles from healthy volunteers, who received multiple doses of the ER and IR formulations of amantadine per study procedures described in Example 7 (ADS-5101-MD-104), were used to develop a

pharmacokinetic model describing each of the two formulations. This study was an open-label, randomized, two-treatment, two-period, two-way crossover study comparing once-daily amantadine ER capsules and twice-daily amantadine IR tablets in 26 healthy, adult male and female volunteers. Complete data from 24 individuals were used in this exercise. Blood samples for pharmacokinetic evaluation were collected after single dosing on Day 1 and at steady state on Day 9. In the first step of the analysis, WinNonlin 5.2.1 (Pharsight Corp., Mountain View, Calif.) was used to fit a one-compartment model with first-order input and first-order output, weighted 1/y (where y is the amantadine plasma concentration), to each individual's plasma concentration-time data obtained after single (Day 1) and repeated (Day 9) dose administration of amantadine IR and ER; the fitting was done separately for both formulations, but simultaneously for both days. Modeling assumptions employed include dose proportionality and constant clearance as a function of time.

The model is described by the following equation

$$C = \frac{FD}{V(k_a - k)}[\exp(-k(t - t_{lag})) - \exp(-k_a(t - t_{lag}))] \quad \text{Equation 1}$$

where C is the plasma concentration, F is the absolute bioavailability, D is dose, V is the volume of distribution, k_a is the absorption rate constant, k is the elimination rate constant, t is time, and t_{lag} is the lag time of absorption. The goodness of fit was verified by comparing the individual model predicted and observed concentration-time data from Study ADS-5101-MD-104. After Equation 1 was fitted to each individual's plasma concentration-time data, model parameter estimates of V/F, k_a, k, and t_{lag} were obtained for each of the 24 subjects. The goodness of the prediction at steady state was confirmed by comparing the observed data and predicted steady-state concentrations of amantadine obtained after daily dosing of 200 mg as the ER and IR formulations (Day 9).

In the second step of the analysis, individual model parameter estimates were used to simulate steady-state concentration-time profiles for each individual for both formulations by reinserting the individual parameter estimates into Equation 1, and summing the contribution of 7 sequential days of dosing, according to the following dosing regimens:

1. Once Daily (QD) dosing of 200 mg of the ER Formulation 1 to steady state
2. Once Daily (QD) dosing of 200 mg of the ER Formulation 2 to steady state

Results: FIG. **7** shows the simulated steady state plasma concentration time profiles for the two ER amantadine formulations. (Amantadine blood plasma concentrations are shown on the y, time of day on the x-axis.) As shown in FIG. **7**, the ER amantadine formulation 2 administered once daily at night results in about a 4 hour delay in achieving peak plasma concentration at steady state relative to formulation 1. Thus, a formulation comprising a delayed release coat on top of the extended release coat has a very favorable pharmacokinetic profile in that it maximizes the daytime plasma exposure to amantadine whilst minimizing night plasma exposure at steady state.

While preferred embodiments of the present invention have been shown and described herein, such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. All references cited herein are incorporated herein by reference in their entirety.

We claim:

1. A method of administering a dose of a pharmaceutical composition of a drug, wherein the drug is selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, to a human patient in need thereof, comprising administering said dose of said pharmaceutical composition to said human patient orally, once daily 0 to 4 hours before bedtime, wherein said dose of said pharmaceutical composition comprises: (i) 220 mg to 455 mg of the drug; and (ii) one or more excipients, wherein at least one of said one or more excipients modifies the release of said drug to provide an extended release dosage form,

wherein, a unit dosage form of said pharmaceutical composition has an in vitro dissolution profile characterized by release of said drug from said pharmaceutical composition that is not more than 25% in two hours and at least 80% at 12 hours using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium, and

wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the Tmax for amantadine is 8 to 20 hours.

2. The method of claim **1**, wherein said Tmax is 9 to 18 hours.

3. The method of claim **1**, wherein said Tmax is 11 to 18 hours.

4. The method of claim **1**, wherein said in vitro dissolution profile is characterized by release of the drug from said pharmaceutical composition that is not more than 10% in one hour.

5. The method of claim **1**, wherein said in vitro dissolution profile is characterized by release of the drug from said pharmaceutical composition that is 40% to 80% in 6 hours.

6. The method of claim **4**, wherein said in vitro dissolution profile is characterized by release of the drug from said pharmaceutical composition that is 40% to 80% in 6 hours.

7. The method of claim **1**, wherein said in vitro dissolution profile is characterized by release of the drug from said pharmaceutical composition that is 25% to 55% in 6 hours.

8. The method of claim **4**, wherein said in vitro dissolution profile is characterized by release of the drug from said pharmaceutical composition that is 25% to 55% in 6 hours.

9. The method of claim **1**, wherein said in vitro dissolution profile is characterized by release of the drug from said pharmaceutical composition that is 30% to 50% in 4 hours.

10. The method of claim **4**, wherein said in vitro dissolution profile is characterized by release of the drug from said pharmaceutical composition that is 30% to 50% in 4 hours.

11. The method of claim **5**, wherein said in vitro dissolution profile is characterized by release of the drug from said pharmaceutical composition that is 30% to 50% in 4 hours.

12. The method of claim **1**, wherein said pharmaceutical composition comprises one, two, three or four unit dosage forms.

13. The method of claim **1**, wherein said pharmaceutical composition comprises one, two, or three capsules containing coated pellets.

14. The method of claim **1**, wherein said pharmaceutical composition comprises one, two, or three capsules.

15. The method of claim **1**, wherein said pharmaceutical composition is selected from the group consisting of one unit dosage form comprising 340 mg of said drug and two unit dosage forms each comprising 170 mg of said drug.

16. The method of claim **15**, wherein said drug is a pharmaceutically acceptable salt of amantadine.

17. The method of claim **15**, wherein said drug is amantadine hydrochloride.

18. The method of claim **1**, wherein said drug is a pharmaceutically acceptable salt of amantadine.

19. The method of claim **1**, wherein said drug is amantadine hydrochloride.

* * * * *

EXHIBIT L

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(12) **United States Patent**
Went et al.

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(54) **METHOD OF ADMINISTERING AMANTADINE PRIOR TO A SLEEP PERIOD**

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(57) **ABSTRACT**

Methods of nighttime administration of amantadine to reduce sleep disturbances in patient undergoing treatment with amantadine are described, as well as compositions of extended release amantadine that are suitable for nighttime administration.

43 Claims, 7 Drawing Sheets

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FIG. 1

Dissolution Profiles of Amantadine ER Formulations

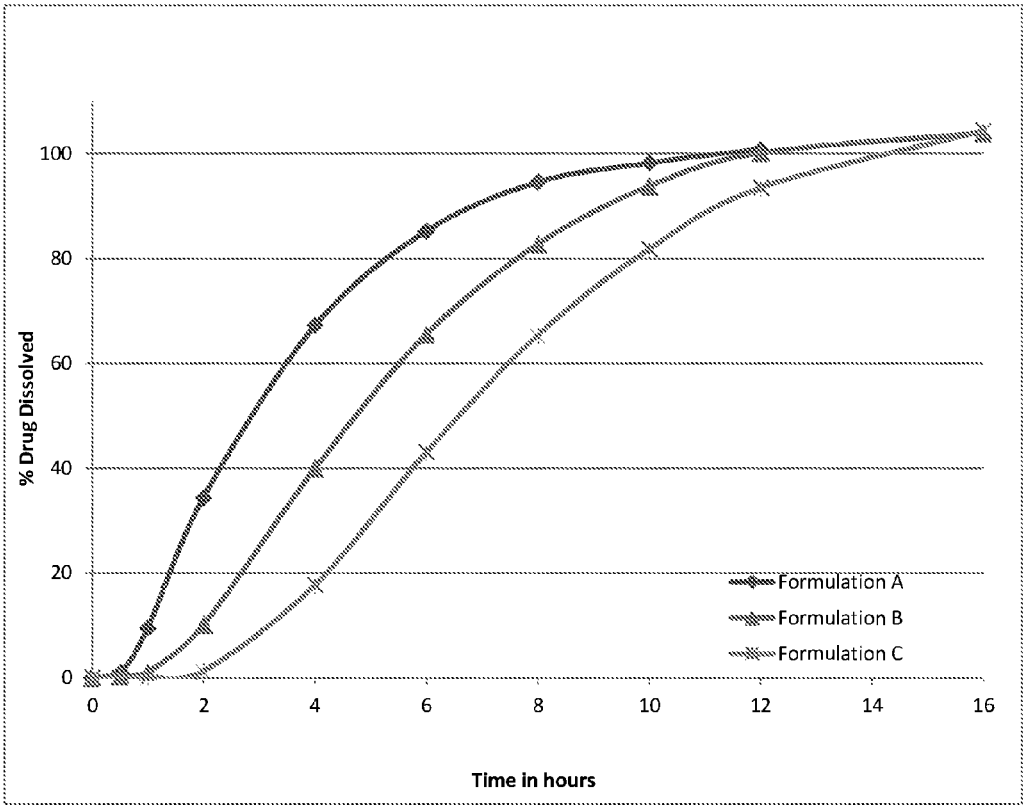


FIG. 2A

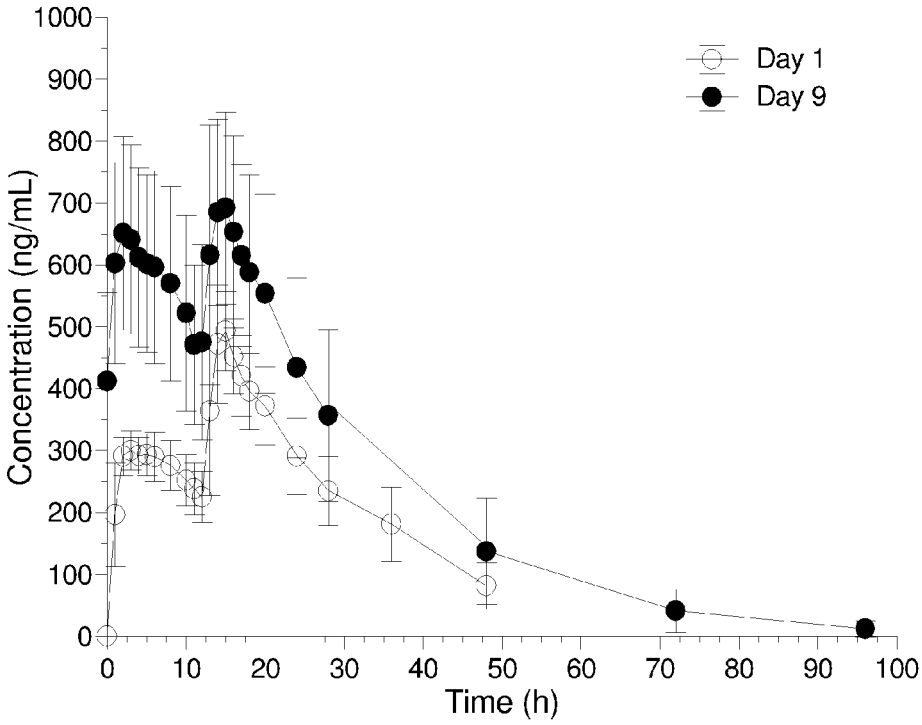

Day 1
Day 9
Concentration (ng/mL)
Time (h)
0
100
200
300
400
500
600
700
800
900
1000
0
10
20
30
40
50
60
70
80
90
100

FIG. 2B

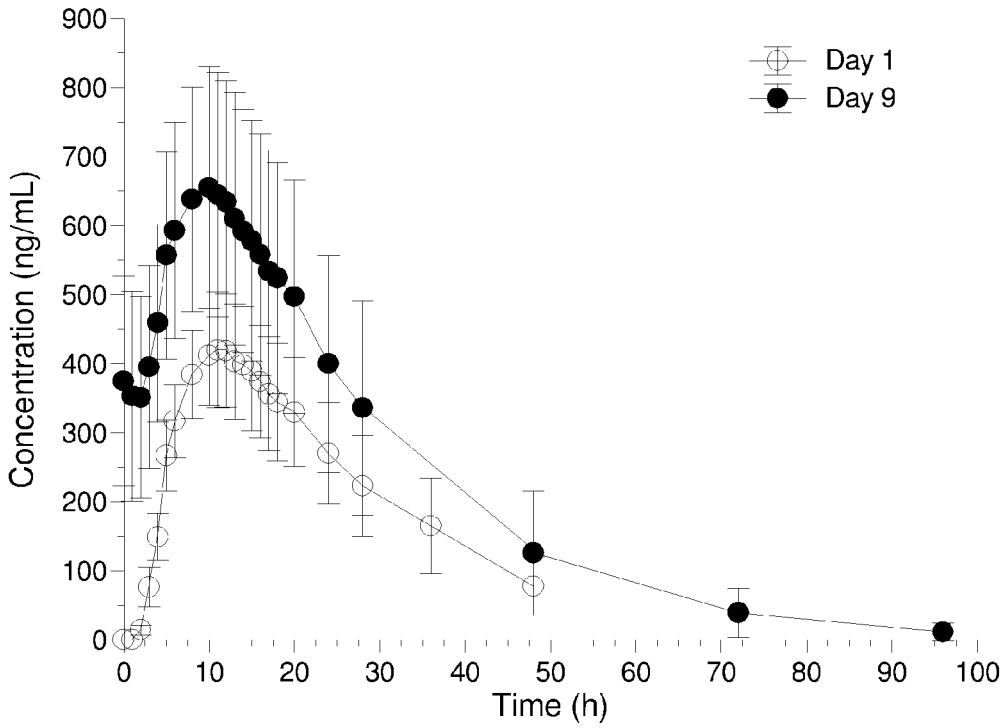

Day 1
Day 9
Concentration (ng/mL)
Time (h)
0
100
200
300
400
500
600
700
800
900
0
10
20
30
40
50
60
70
80
90
100

FIG. 3

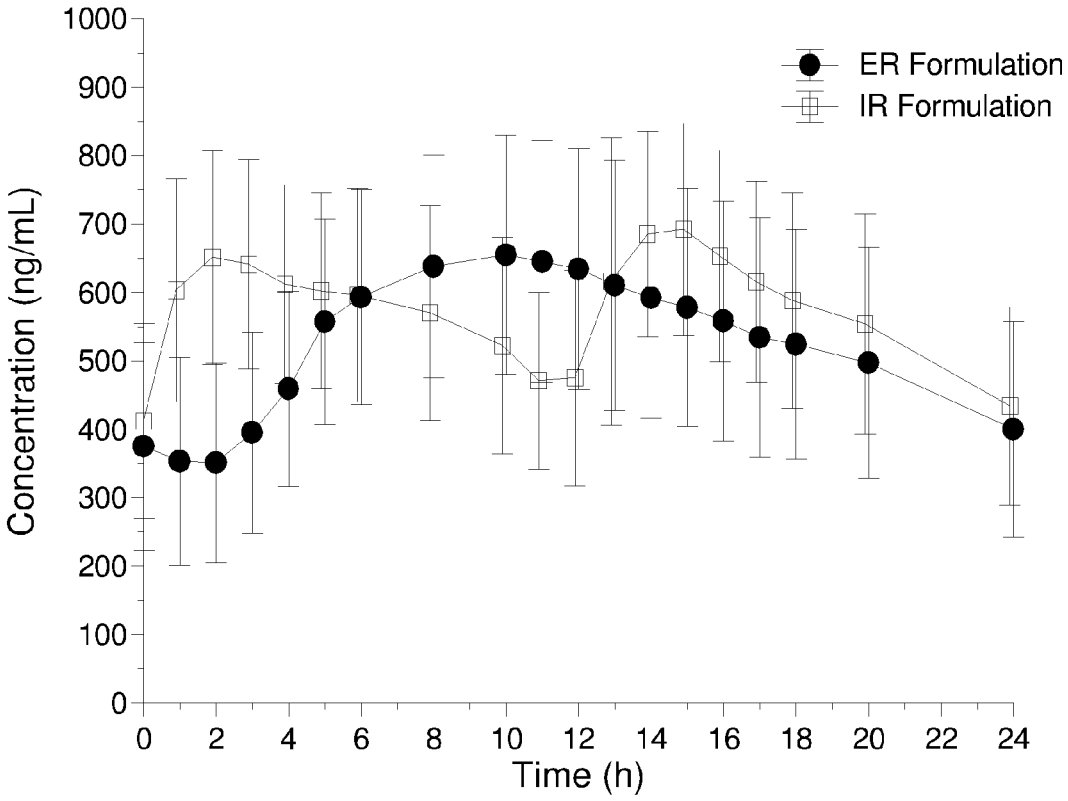
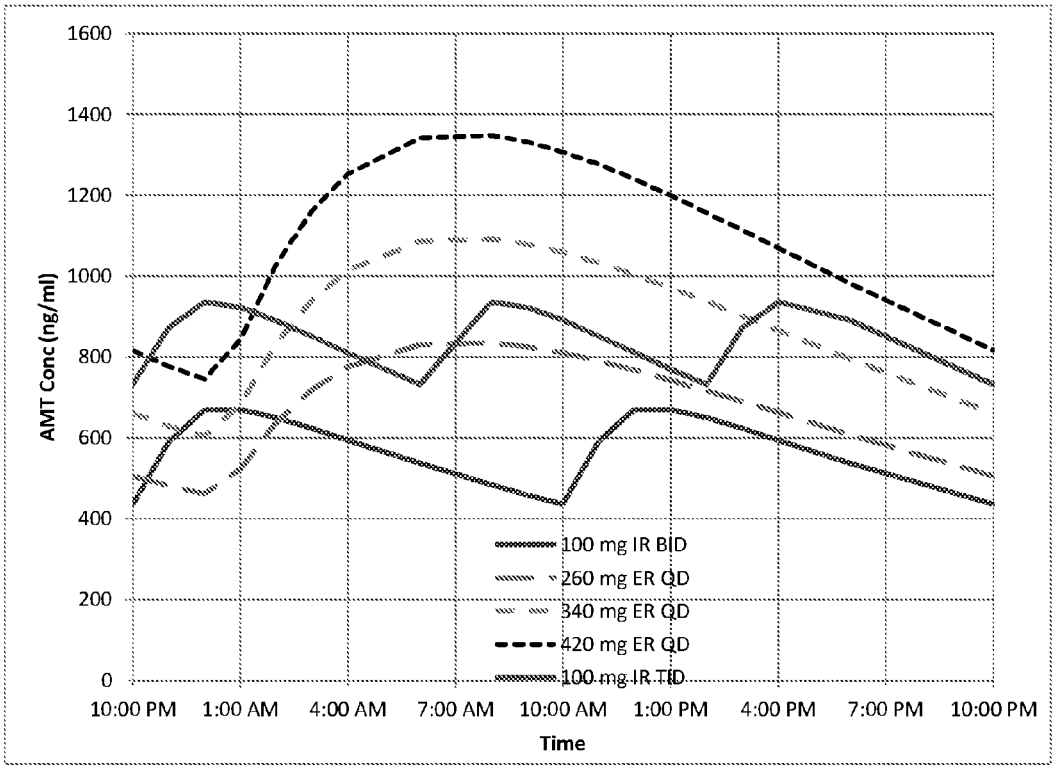

ER Formulation
IR Formulation
Concentration (ng/mL)
Time (h)
0
100
200
300
400
500
600
700
800
900
1000
0
2
4
6
8
10
12
14
16
18
20
22
24

Fig 4.



Simulation based on results of Adamas steady state PK study ADS-PD-104.

FIG. 5

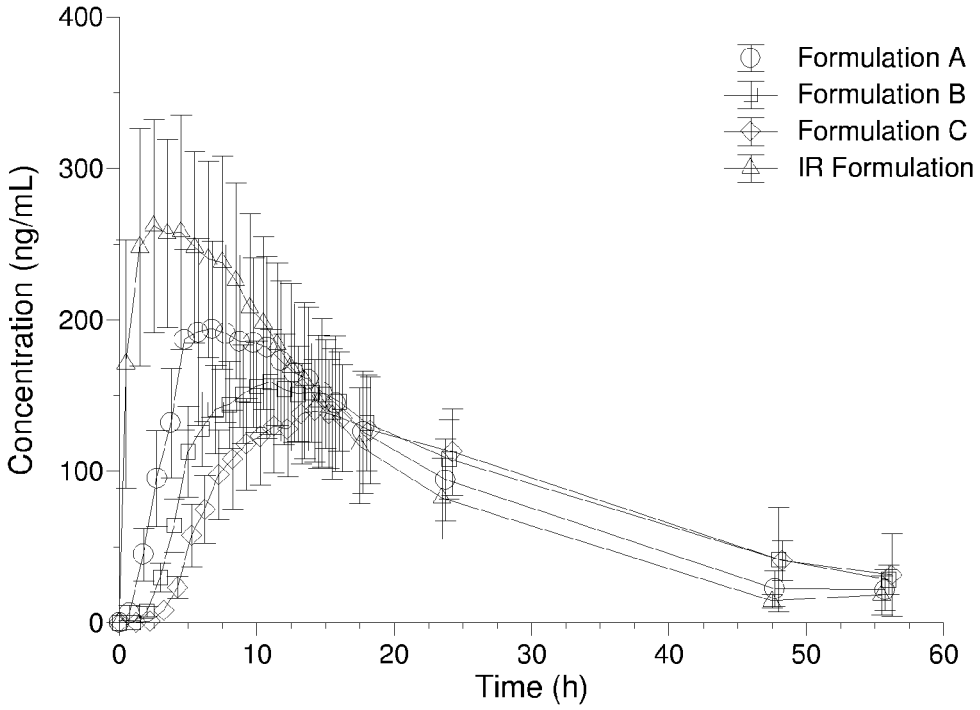

Formulation A
Formulation B
Formulation C
IR Formulation
Concentration (ng/mL)
Time (h)
0
100
200
300
400
0
10
20
30
40
50
60

FIG. 6

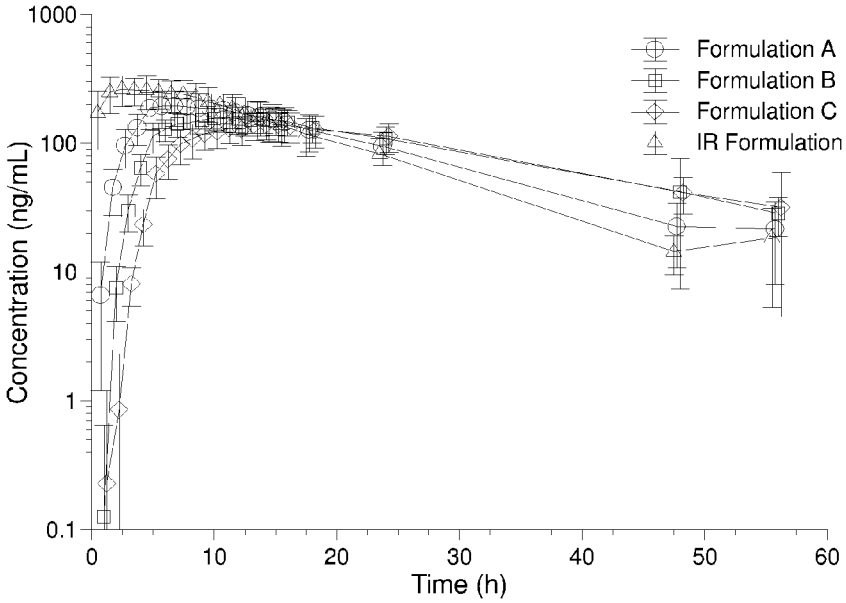
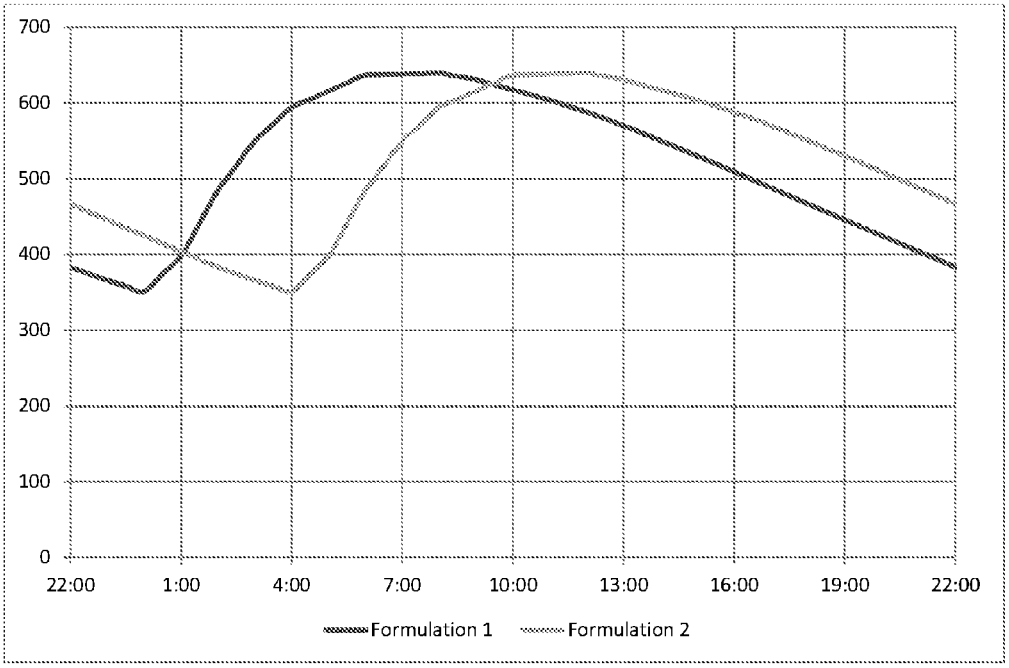

1000
100
10
1
0.1
Concentration (ng/mL)
0
10
20
30
40
50
60
Time (h)
Formulation A
Formulation B
Formulation C
IR Formulation

FIG 7.


700
600
500
400
300
200
100
0
22:00
1:00
4:00
7:00
10:00
13:00
16:00
19:00
22:00
Formulation 1
Formulation 2

METHOD OF ADMINISTERING AMANTADINE PRIOR TO A SLEEP PERIOD

CROSS-REFERENCE

This application is a continuation of U.S. patent application Ser. No. 14/863,035, filed Sep. 23, 2015, which is a continuation of U.S. patent application Ser. No. 14/523,535, filed Oct. 24, 2014, now abandoned, which is a continuation of U.S. patent application Ser. No. 14/267,597, filed May 1, 2014, now abandoned, which is a continuation of U.S. patent application Ser. No. 12/959,321, filed Dec. 2, 2010, now U.S. Pat. No. 8,741,343, which claims benefit of U.S. Provisional Application No. 61/266,053, filed Dec. 2, 2009, all of which applications are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

The field of the invention is extended release compositions of amantadine and uses thereof.

Amantadine is indicated for various conditions that can be treated by NMDA receptor antagonists including the treatment of idiopathic Parkinson's disease (Parlysis Agitans), postencephalitic Parkinsonism, and symptomatic Parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication. Amantadine also has activity as a viral M2 channel inhibitor and is used for the prophylaxis and treatment of infection of viral diseases, especially influenza A virus.

Currently marketed forms of amantadine are immediate release formulations that are typically administered two or more times a day. Amantadine's use is limited by dose related CNS side effects including dizziness, confusion, hallucinations, insomnia and nightmares (Gracies J M, Olanow C W; Current and Experimental Therapeutics of Parkinson's Disease; *Neuropsychopharmacology: the Fifth Generation of Progress*, p. 1802; American College of Neuropsychopharmacology 2002), which can be particularly exacerbated when amantadine is administered at night.

It is known that immediate release amantadine can act as a stimulant, causing insomnia and sleep disturbance. Therefore, the last dose is typically administered no later than 4 pm in order to minimize these side effects. Such dosing of amantadine results in peak plasma amantadine concentrations occurring in the evening or night, and very low plasma concentrations in the morning.

Extended release forms of amantadine have been described in the art. U.S. Pat. No. 5,358,721, to Guittard et al., and U.S. Pat. No. 6,217,905, to Edgren et al., each disclose an oral osmotic dosage form comprising an antiviral or anti-Parkinson's drug, respectively, where in each case amantadine is listed as a possible drug to be utilized in the dosage form. U.S. Pat. No. 6,194,000, to Smith et al., discloses analgesic immediate and controlled release pharmaceutical compositions utilizing NMDA receptor antagonists, such as amantadine, as the active agent. U.S. Patent Appl. Publication Nos. US 2006/0252788, US 2006/0189694, US 2006/0142398, and US 2008/0227743, all to Went et al., each disclose the administration of an NMDA receptor antagonist, such as amantadine, optionally in controlled release form.

SUMMARY OF THE INVENTION

The inventors have identified a need in the art for improved formulations of amantadine that result in a patient having higher plasma concentrations of amantadine upon waking in the morning without adversely affecting sleep. Further, the inventors have identified a need in the art for a method of administering amantadine in the late afternoon or evening, e.g. after 4 pm, which reduces side effects of insomnia and sleep disturbance and provides effective plasma concentrations of amantadine upon waking.

Therefore, there exists a need in the art for improved methods of amantadine therapy which can be administered to a patient shortly before they wish to sleep (e.g., at bedtime) without causing insomnia or sleep disturbance. In addition, there is a need for an amantadine therapy which can be taken by the patient before they go to sleep and then provides a suitable plasma concentration of amantadine when they wake up, e.g. in the morning, after a full night's sleep.

In addition, many Parkinson's disease patients have difficulty swallowing and are on multiple medications. Hence there is a need for amantadine therapy that delivers a therapeutically effective dose of the drug, can be administered once daily and is in an oral dosage form that is small in size and does not unduly increase the pill burden.

One aspect of the invention is a method of administering amantadine to a patient in need thereof, said method comprising orally administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below. Alternatively, the composition is administered less than about 4 hours before bedtime.

In a second aspect, the invention provides a method of reducing sleep disturbance in a human subject undergoing treatment with amantadine, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below. Alternatively, the composition is administered less than about 4 hours before bedtime.

In a third aspect, the invention provides a method of treating levodopa induced dyskinesia, or fatigue, or dementia, or any other symptom of Parkinson's disease, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below.

In a fourth aspect, the invention provides a method of treating brain injury, brain trauma, dementia, Alzheimer's disease, stroke, Huntington's disease, ALS, Multiple Sclerosis, neurodegenerative diseases, dementias, cerebrovascular conditions, movement disorders, cranial nerve disorders, neuropsychiatric disorders, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below.

In one embodiment of any of the above aspects, administration occurs less than two and a half, less than two, less than one and a half, less than one or less than half hour before bedtime (i. e. the time at which the subject wishes to go to sleep for the night).

In one embodiment of any of the above aspects the patient has been diagnosed with Parkinson's disease.

In one embodiment of any of the above aspects, the composition is administered once daily. In another aspect, the daily dose exceeds 200 mg, and is given in 1, 2 or 3 capsules of size 0, 1 or 2.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in levodopa induced dyskinesia (LID). In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% reduction in levodopa induced dyskinesia. In further embodiments, the reduction in levodopa induced dyskinesia is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce LID. In further specific embodiments, the scale used in measuring the reduction in LID could be UDysRS, UPDRS Part IV (subscores 32, 33), Dyskinesia Rating Scale (DRS), Abnormal Involuntary Movement Scale (AIMS), or other scales developed for this purpose.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease fatigue. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60% reduction in Parkinson's disease fatigue. In further specific embodiments, the reduction in fatigue is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce fatigue. In further specific embodiments, the scale used in measuring the reduction in fatigue could be the Fatigue Severity Scale (FSS).

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease symptoms. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's symptoms. In further specific embodiments, the reduction in Parkinson's symptoms is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce Parkinson's symptoms. In further specific embodiments, the scale used in measuring the reduction in Parkinson's symptoms could be the Unified Parkinson's Disease Rating Scale (UPDRS).

In one embodiment of any of the above aspects, the composition is added to food, and in a more specific embodiment to a small amount of soft food (e.g. applesauce or chocolate pudding), prior to administration. Addition to food may involve a capsule being opened and the contents sprinkled over the patient's food. This is advantageous if the patient is unable or unwilling to swallow the composition.

In one embodiment of any of the above aspects, there is no increase in plasma concentration of amantadine for at least one hour after the administration at steady state plasma concentrations.

In one embodiment of any of the above aspects, there is no increase in the plasma concentration of amantadine for at least two hours after the administration at steady state plasma concentrations.

In one embodiment of any of the above aspects, the administration of the composition to a human subject at steady state amantadine plasma concentrations increases the amantadine plasma concentration by less than 5%, 10%, 15%, 20% or 25% at 1, 2, 2.5 or 3 hours following such administration. For example, administration of the composition to a human subject at steady state amantadine plasma concentrations increases the amantadine plasma concentration by less than 5% at 1, 2, 2.5 or 3 hours following such administration; or by less than 10% at 1, 2, 2.5 or 3 hours following such administration; or by less than 15% at 1, 2, 2.5 or 3 hours following such administration; or by less than 20% at 1, 2, 2.5 or 3 hours following such administration; or by less than 25% at 1, 2, 2.5 or 3 hours following such administration.

In one embodiment of any of the above aspects the amantadine has a single dose Tmax of 9 to 15 hours. In a more specific embodiment, the amantadine has a single dose Tmax of 10 to 14 hours after administration. In another more specific embodiment, the amantadine has a single dose Tmax of 11 to 13 hours after administration.

In one embodiment of any of the above aspects the amantadine has a steady state Tmax of 7 to 13 hours. In a more specific embodiment, the amantadine has a steady state Tmax of 8 to 12 hours after administration. In another more specific embodiment, the amantadine has a steady state Tmax of 9 to 11 hours after administration.

In one embodiment of any of the above aspects peak plasma concentration of amantadine is achieved between 6 and 16 hours after administration of a single dose of the composition. In a more specific embodiment, peak amantadine plasma concentration is achieved 8 to 14 hours after administration of a single dose of the composition. In another more specific embodiment, peak amantadine plasma concentration is achieved 10 to 12 hours after administration of a single dose of the composition. In additional specific embodiments, peak amantadine plasma concentration is achieved between 6, 7, 8, 9, 10, 11 or 12 hours to about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 hours after administration of a single dose of the composition.

In one embodiment of any of the above aspects, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In a more specific embodiment, the steady state plasma concentration profile is characterized by a concentration increase of amantadine of less than 25% at four hours after the administration.

In one embodiment of any of the above aspects, the composition is administered once a day and the ratio of Cmax to Cmin at steady state is 1.5 to 2.0, or, more specifically, 1.7 to 1.9, or, more specifically, about 1.8.

In one embodiment of any of the above aspects, the steady state plasma concentration profile following multiple administrations to a human subject of the composition at bedtime is characterized by an average plasma concentration during the day ("C-ave-day", defined as the average day time amantadine plasma concentration as measured in a human PK study) that is 1.1 to 2.0 times the average plasma concentration during the night ("C-ave-night", defined as the average night time amantadine plasma concentration as measured in a human PK study). In more specific embodiments the C-ave-day is the average amantadine plasma concentration as measured between the hours of 5 am, 6 am, 7 am, 8 am or 9 am to the hours of 4 pm, 5 pm, 6 pm, 7 pm

or 8 pm; for example, between the hours of 6 am and 4 pm, between the hours of 7 am and 6 pm, or between the hours of 7 am and 5 pm. The C-ave-night is the average amantadine plasma concentration as measured between the hours of 4 pm, 5 pm, 6pm, 7 pm, 8 pm, 9 pm, 10 pm or 11 pm to the hours of 5 am, 6 am, 7 am, 8 am or 9 am; for example, between the hours of 10 pm and 6 am, between the hours of 7 pm and 6 am, or between the hours of 8 pm and 6 am.

In one embodiment of any of the above aspects, the steady state plasma concentration profile following multiple administrations to a human subject of the composition at bedtime is characterized by an average plasma concentration during the morning ("C-ave-morning", defined as the average amantadine plasma concentration as measured in a human PK study during the morning hours) that is 1.1 to 2.0 times the average plasma concentration during the night. In one embodiment the C-ave-morning is the average amantadine plasma concentration as measured between the hours of 5 am, 6 am, 7 am, 8 am or 9 am to the hours of 11 am, 11:30 am, 12 pm, 12:30 pm or 1:00 pm; for example, between the hours of 5 am and 11 am, or between the hours of 7 am and 12 pm. More preferably, the ratio of C-ave-morning/C-ave-night at steady state is 1.2 to 1.6.

In one embodiment of any of the above aspects, the steady state plasma concentration profile following daily administration of the composition is characterized by an average plasma concentration during the period 8 hours to 12 hours after administration ("C-ave-8-12hrs") that is 1.1 to 2.0 times the average plasma concentration during the first 8 hours after administration ("C-ave-0-8hrs"). More preferably, the ratio of C-ave-8-12hrs/C-ave-0-8hrs at steady state is 1.2 to 1.6.

In one embodiment of any of the above aspects, administration of a single dose of the composition to a human subject provides a plasma concentration profile characterized by: a fractional AUC from 0 to 4 hours that is less than 5%, and preferably less than 3% of AUC_{0-inf}; a fractional AUC from 0 to 8 hours that is about 5 to 15%, and preferably about 8 to 12% of AUC_{0-inf}; a fractional AUC from 0 to 12 hours that is about 10 to 40%, and preferably about 15 to 30% of AUC_{0-inf}; a fractional AUC from 0 to 18 hours that is about 25 to 60%, and preferably about 30 to 50% of AUC_{0-inf}; and a fractional AUC from 0 to 24 hours that is about 40 to 75%, and preferably about 50 to 70% of AUC_{0-inf}.

In one embodiment of any of the above aspects, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25%, and preferably about 5 to 20% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50%, and preferably about 20 to 40% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70%, and preferably about 40 to 60% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95%, and preferably about 75 to 90% of AUC_{24}.

In one embodiment of any of the above aspects, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by: a fractional AUC from 0 to 8 hours that is about 15 to 40%, and preferably about 20 to 32% of AUC_{24}; a fractional AUC from 8 to 16 hours that is about 30 to 50%, and preferably about 35 to 45% of AUC_{24}; and a fractional AUC from 16 to 24 hours that is about 20 to 35%, and preferably about 25 to 33% of AUC_{24}.

In one embodiment of any of the above aspects the amantadine is administered as a pharmaceutically acceptable salt. In a more specific embodiment, the amantadine is administered as hydrochloride or amantadine sulfate.

In one embodiment of any of the above aspects, a total daily dose of 50 mg to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof is administered to a patient. More specifically the daily dose of amantadine or pharmaceutically acceptable salt thereof administered may be in the range of 100 to 440 mg. In another specific embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof maybe in the range of 260 to 420 mg. In another embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof administered exceeds 300 mg per day. In various specific embodiments, the daily dose of amantadine or pharmaceutically acceptable salt thereof may be 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg.

In one embodiment of any of the above aspects, the composition comprises 50 mg to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. More specifically, the composition may comprise 100 mg to 450 mg of amantadine, or a pharmaceutically acceptable salt thereof. Still more specifically, the composition may comprise 130-210 mg of amantadine, or a pharmaceutically acceptable salt thereof. In various specific embodiments, a dosage form containing the composition comprises 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg of amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition comprises about 110, 120, 130, 140, 150, 160 170, 180, 190, 210, or 220 mg amantadine, or a pharmaceutically acceptable salt thereof. In another more specific embodiment, the composition comprises 110 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 130 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 170 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 210 mg amantadine hydrochloride.

In one embodiment of any of the above aspects, the composition is administered as one, two, three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof.

In one embodiment of any of the above aspects, the composition is administered as one, two, or three unit dosage forms each comprising 50 to 250 mg amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition is administered as one or two unit dosage forms each comprising 65 to 220 mg amantadine, or a pharmaceutically acceptable salt thereof.

In one embodiment of any of the above aspects, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma

concentration (Cmax) of 1.0 to 2.8 ng/ml per mg of amantadine. In a more specific embodiment, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine and an $AUC_{0\text{-}inf}$ (Area under the concentration-curve curve from t=0 to t=infinity) of 40 to 75 ng*h/mL per mg of amantadine.

In one embodiment of any of the above aspects, the daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by at least one of: (i) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine, (ii) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (iii) an $AUC_{0\text{-}24}$ of 44 to 83 ng*h/mL per mg of amantadine. In a more specific example, all three criteria of (i), (ii) and (iii) are met.

In a more specific embodiment, the steady state plasma concentration profile is further characterized by: (iv) no increase in concentration of amantadine for at least one hour after the administration; and (v) Cmax/Cmin ratio of 1.5 to 2.0. In a more specific embodiment, both criteria of (iv) and (v) are met.

In another more specific embodiment, the steady state plasma concentration profile is further characterized by at least one of: (iv) no increase in plasma concentration of amantadine for at least two hours after the administration; and (v) a Cmax/Cmin ratio of 1.7 to 1.9. In a more specific embodiment, both criteria of (iv) and (v) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more 55-85% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more than 25-55% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 20% dissolution at 1 hour, (ii) about 25-45% dissolution at 2 hours, (iii) not more than 50-80% dissolution at 4 hours, and (iv) at least 80% dissolution at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii), (iii) and (iv) are met. In a more specific embodiment, all four of criteria (i), (ii), (iii) and (iv) are met.

In one embodiment of any of the above aspects the in vitro dissolution profile of amantadine is further characterized by release of amantadine of: (i) not more than 10% at 1 hour, or (ii) 30-50% at 4 hours, or (iii) at least 90% at 12 hours using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three criteria of (i), (ii) and (iii) are met.

In another aspect, the present invention provides a pharmaceutical composition comprising or consisting of a pellet-in-capsule, wherein a pellet comprises a core that comprises a core seed with a mixture of amantadine and a binder coated onto the core seed, and an extended release coating surrounding the core comprising ethyl cellulose, a pore forming agent such as hydroxypropyl methyl cellulose or povidone, and a plasticizer.

In another aspect, the present invention provides a pharmaceutical composition for use in the methods of the aspects described above, wherein said composition is for oral administration and comprises a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core.

In one embodiment, the extended release coating comprises ethyl cellulose and at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In a more specific embodiment, the extended release coating comprises ethyl cellulose, povidone, and a plasticizer.

In one embodiment, the pellet core comprises amantadine and a binder coated onto a core seed. In one embodiment, the core seed is a sugar sphere (nonpareil) or microcrystalline cellulose seed (e.g. Celphere®). In a more specific embodiment, the core seed is a microcrystalline cellulose core. In another specific embodiment, the core seed has a diameter in the range of 100 microns to 1,000 microns. In additional specific embodiments, the core seed has a diameter of 100, 200, 300, 400, 500, 600 or 700 microns. In preferred specific embodiments, the core seed has a diameter of less than 500 microns.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 20 to 80 wt %, with a bulk density of 0.3 to 1.2 g/cm^3.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 40 to 60 wt %, with a bulk density of 0.5 to 1.2 g/cm^3.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 60 to 80 wt %, with a bulk density of 0.5 to 1.2 g/cm^3.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the binder is present in amounts from 8 to 25 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the core seed is present in amounts from 8 to 25 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the ethyl cellulose is present in amounts from 10 to 20 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the povidone is present in amounts from 1 to 4 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, and the plasticizer is present in amounts from 1 to 4 wt %.

In one embodiment, the coated pellet has a diameter in the range of 200 microns to 1700 micros. In additional specific embodiments, the coated pellet has a diameter of 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300 or

1500 microns. In certain specific embodiments, the coated pellet has a diameter of less than 1000 microns, e.g., from 500 to 1000 microns.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the binder is present in amounts from 5 to 25 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the core seed is present in amounts from 1 to 15 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the ethyl cellulose is present in amounts from 5 to 20 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the povidone is present in amounts from 0.25 to 4 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, and the plasticizer is present in amounts from 0.25 to 4 wt %.

In one embodiment, the pellet further comprises a seal coating between the pellet core and the extended release coating. In some embodiments, an inert coating can be applied to the inert core prior to drug coating or on drug-coated pellets or on controlled release coated pellets. In another embodiment, an enteric coating can be applied to the drug coated pellets or controlled release pellets.

In one embodiment, the pellet core comprises a binder, selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof.

In one embodiment, the above composition is provided in a size 3, size 2, size 1, size 0 or size 00 capsule.

In one embodiment, the therapeutically effective daily dose of the above composition is administered in no more than two capsules. In another embodiment, the therapeutically effective daily dose of the composition is administered in no more than three size 1 capsules. In another embodiment, the therapeutically effective daily dose of the composition is administered in no more than two size 0 capsules. In a still more preferred embodiment, the therapeutically effective daily dose of the composition is administered in no more than two size 1 capsules. In another embodiment, the therapeutically effective daily dose of the composition is administered in no more than three size 2 capsules.

In a preferred embodiment, the above composition is provided in an amount of 50 to 110 mg of amantadine or a pharmaceutically acceptable salt thereof in a size 2 capsule, and in the amount of 110 mg to 210 mg of amantadine or a pharmaceutically acceptable salt thereof in a size 1 capsule. In additional embodiments, the above composition comprises coated pellets of diameter 300 to 1000 microns, with amantadine or pharmaceutically acceptable salt thereof content of 40-80% wt % and at a bulk density of 0.5-1.2 g/cm^3. In a further preferred embodiment, the above composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more than 55-85% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, and castor oil. In a more specific embodiment, the plasticizer is medium chain triglycerides, e.g. Miglyol 812 N.

In another aspect, the present invention provides method of administering amantadine, or a pharmaceutically acceptable salt thereof, to a human subject in need thereof, said method comprising orally administering a composition of any of the above aspects.

In another aspect, the present invention provides a method of treating Parkinson's disease in a human subject in need thereof, said method comprising orally administering a composition of any of the above aspects. In a preferred aspect, the present invention provides a method of treating disease in a human subject in need thereof, said method comprising orally administering a composition of any of the above aspects once daily at nighttime, administering 1, 2 or 3 capsules.

References to administering amantadine to a subject in need thereof include treating a patient with a disease or condition which may be treated, prevented or cured by a NMDA antagonist. More specifically, administering amantadine to a subject in need thereof includes treating a patient with Parkinson's Disease, brain injury, brain trauma, dementia, Alzheimer's disease, stroke, Huntington's disease, ALS, Multiple Sclerosis, neurodegenerative diseases, dementias, cerebrovascular conditions, movement disorders, cranial nerve disorders, neuropsychiatric disorders.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the dissolution profiles for three amantadine ER formulations, A, B, C referred to in Example 3.

FIGS. **2**A and **2**B show the mean plasma concentration-time curves after administration of amantadine IR twice daily (A) and amantadine ER once daily (B) to healthy, adult, male and female subjects under fasting conditions on days 1 and 9.

FIG. **3** shows a plot of mean plasma concentration of amantadine versus time curves after administration of amantadine IR twice daily and amantadine ER once daily to healthy, adult, male and female subjects under fasting conditions on day 9.

FIG. **4** shows the simulated mean plasma concentration of amantadine versus time curves following multiple dose administration of various strengths of immediate release amantadine dosed twice or thrice daily and various strengths of amantadine ER administered once daily.

FIG. **5** shows a plot of mean (SD) plasma amantadine concentrations versus scheduled time for four (4) amantadine treatments.

FIG. **6** shows a semi-logarithmic mean (SD) plasma amantadine concentrations versus scheduled time for four (4) amantadine treatments.

FIG. **7** shows simulated steady state plasma concentration time profiles for the ER amantadine formulations as described in Example 12. The ER amantadine formulation 2, administered once daily at night, results at steady state in about 4 hour delay in achieving peak plasma concentration relative to formulation 1.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a method of reducing sleep disturbances in a patient undergoing treatment with amantadine. The method comprises administering amantadine to a patient in need thereof, such that the amantadine does not interfere with sleep, yet provides maximum benefit in morning hours when often needed most by many patients who take amantadine and further, provides nighttime coverage of

symptoms of Parkinson's disease if needed. Nighttime coverage includes providing benefit if the patient wakes up and wishes to return to sleep.

The method of the invention comprises orally administering to the patient an extended release (ER) amantadine composition designed for nighttime administration. The composition is taken less than three hours before bedtime, and preferably less than two and a half, less than two, less than one and a half, or less than one hour before bedtime. Most preferably the ER amantadine composition is taken less than half hour before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). As used herein, a reference to amantadine is intended to encompass pharmaceutically acceptable salts thereof (e.g. amantadine hydrochloride, amantadine sulfate, etc.). Alternatively, the composition is administered less than about 4 hours before bedtime.

As used herein, "extended release" includes "controlled release", "modified release", "sustained release", "timed release", "delayed release", and also mixtures of delayed release, immediate release, enteric coated, etc. with each of the above.

The patient may be diagnosed with any disease or disorder for which amantadine is prescribed, such as Parkinson's disease, multiple sclerosis, drug-induced extrapyramidal reactions, levodopa-induced dyskinesia, and viral diseases (e.g. influenza, HBV, and HCV). In a specific embodiment, the patient has Parkinson's disease, which, as used herein, also encompasses a diagnosis of parkinsonism. In one embodiment, the patient has early stage Parkinson's disease, and the amantadine is used as a monotherapy or in combination with a monoamine oxidase type B (MAO-B) inhibitor without concomitant use of levodopa. In another embodiment, the patient has late stage Parkinson's disease and the patient takes levodopa in addition to the amantadine. In another embodiment, the patient has multiple sclerosis and the amantadine is used for the treatment of fatigue. In other embodiments, the patient has a brain injury, brain injury, brain trauma, dementia, Alzheimer's disease, stroke, Huntington's disease, ALS, Multiple Sclerosis, neurodegenerative diseases, dementias, cerebrovascular conditions, movement disorders, cranial nerve disorders, neuropsychiatric disorders.

An ER amantadine composition for use in the invention is adapted for nighttime administration by providing a plasma concentration profile that does not interfere with the subject's sleep. The composition of the invention will, upon administration to a human subject, result in a gradual initial increase in plasma concentration of amantadine such that, at steady state conditions, administration of a dose of the composition results in an increase in plasma concentration of amantadine of less than 25% at three hours after the dose is administered. For example, if a subject's steady state plasma concentration of amantadine is 500 ng/ml at the time a dose of the composition is administered, three hours later the subject's plasma concentration of amantadine will be less than 625 ng/ml. Preferably, the increase in plasma concentration of amantadine is less than 15%, and most preferably, less than 10%. Particularly preferred compositions have a plasma concentration profile further characterized by no increase in amantadine plasma concentration, or even a decrease (at steady state conditions), for at least one or, in a preferred embodiment, two hours after the administration. The composition for use in the invention is further adapted for bedtime (i.e. the time at which the subject wishes to go to sleep for the night) administration by providing a maximum concentration of amantadine (Cmax) in the morning hours. The time to reach Cmax (Tmax), as measured after single dose administration in the fasted state, is at least, 8 hours and up to 13, 14, 15, or 16 hours, or at least 9 hours and up to 13, 14, 15, or 16 hours, or at least 10 hours, and up to 13, 14, 15, or 16 hours. In specific embodiments, the Tmax is 9 to 15 hours, preferably 10 to 14 hours, and most preferably 11 to 13 hours. At steady state, with once daily administration of the composition, the Tmax is 7 to 13 hours, preferably 8 to 12 hours, and most preferably 9 to 11 hours. A suitable ER amantadine composition may be further characterized by having a steady-state Cmax/Cmin ratio of 1.5 to 2.0, and preferably 1.7 to 1.9, resulting in a composition with optimal fluctuation.

In more specific, preferred embodiments, the plasma concentration profile is further characterized by having an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5%, and preferably less than 3% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 8 hours that is about 5 to 15%, and preferably about 8 to 12% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 12 hours that is about 10 to 40%, and preferably about 15 to 30% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 18 hours that is about 25 to 60%, and preferably about 30 to 50% of $AUC_{0\text{-}inf}$; and a fractional AUC from 0 to 24 hours that is about 40 to 75%, and preferably about 50 to 70% of $AUC_{0\text{-}inf}$.

In a further preferred embodiment, the plasma concentration profile is further characterized by having an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25%, and preferably about 5 to 20% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50%, and preferably about 20 to 40% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70%, and preferably about 40 to 60% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95%, and preferably about 75 to 90% of AUC_{24}.

In some embodiments of any of the above aspects, the steady state plasma concentration profile following multiple administrations to a human subject of the composition at bedtime is characterized by an average plasma concentration during the day ("C-ave-day", defined as the average day time amantadine plasma concentration as measured in a human PK study) that is 1.1 to 2.0 times the average plasma concentration during the night ("C-ave-night", defined as the average night time amantadine plasma concentration as measured in a human PK study). In some embodiments, the ratio of C-ave-day/C-ave-night at steady state is within one of the ranges 1.1 to 1.9, 1.1 to 1.8, 1.1 to 1.7, 1.1 to 1.6, 1.1 to 1.5, 1.1 to 1.4, 1.2 to 1.9, 1.2 to 1.7, 1.2 to 1.6, 1.2 to 1.5, 1.3 to 1.9, 1.3 to 1.8, 1.3 to 1.7, 1.3 to 1.6, 1.4 to 1.9, 1.4 to 1.8, 1.4 to 1.7, 1.5 to 1.9, 1.5 to 1.8, 1.5 to 1.7, 1.6 to 1.9, 1.6 to 1.8 or 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave-night at steady state is 1.1, 1.15, 1.2, 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, or 2.0. In some embodiments, the C-ave-day is the average amantadine plasma concentration as measured between the hours of 5 am, 6 am, 7 am, 8 am or 9 am to the hours of 4 pm, 5 pm, 6 pm, 7 pm or 8 pm and the C-ave-night is the average amantadine plasma concentration as measured between the hours of 4 pm, 5 pm, 6pm, 7 pm, 8 pm, 9 pm, 10 pm or 11 pm to the hours of 5 am, 6 am, 7 am, 8 am or 9 am. In some embodiments, the C-ave-day is the average amantadine plasma concentration as measured within any four to twelve hour period between the hours of 5 am and 8 pm; and the C-ave-night is the average amantadine plasma concentration as measured within any four to twelve hour

period between the hours of 8 pm and 5 am. In some embodiments, the C-ave-day is the average amantadine plasma concentration as measured within any four, five, six, seven, eight, nine, ten, eleven or twelve hour period between the hours of 5 am and 8 pm; and the C-ave-night is the average amantadine plasma concentration as measured within any four, five, six, seven, eight, nine, ten, eleven or twelve hour period between the hours of 8 pm and 5 am.

In some embodiments described herein an amantadine composition is administered to a patient from 0 to 4 hours prior to bedtime. In some embodiments, the amantadine composition is administered to a patient from 0 to 3, 0 to 2 or 0 to 1 hours prior to bedtime. In some embodiments, the amantadine composition is administered to a patient from 0 to 240 minutes, from 0 to 180 minutes, e.g. from 0 to 120 minutes, from 0 to 60 minutes, from 0 to 45 minutes, from 0 to 30 minutes, from 0 to 15 minutes or from 0 to 10 minutes prior to bedtime. In some embodiments, the amantadine composition is administered to a patient from 60 to 240 minutes, from 60 to 180 minutes, from 60 to 120 minutes or from 60 to 90 minutes prior to bedtime.

It is to be understood that administration to a patient includes administration by a healthcare professional and self administration by the patient.

Unless otherwise specified herein, the term "bedtime" has the normal meaning of a time when a person retires for the primary sleep period during a twenty-four hour period of time. While for the general populace, bedtime occurs at night, there are patients, such as those who work nights, for whom bedtime occurs during the day. Thus, in some embodiments, bedtime may be anytime during the day or night.

As used herein, unless otherwise indicated, reference to a plasma concentration profile or a specific pharmacokinetic property (e.g. Cmax, Cmin, AUC, Tmax, etc.) in a human subject refers to a mean value obtained from healthy adults s determined in a typical phase I clinical trial designed to measure pharmacokinetic properties of a drug (see e.g. Examples 5, 6 and 7, below). References herein to Tmax refer to values obtained after administration of a single dose at fasted states, unless otherwise indicated.

In some embodiments of the invention, the dose of the amantadine administered in accordance with the present invention is within or above the ranges normally prescribed for immediate release compositions of amantadine. In other embodiments, the doses of the amantadine administered with the present invention are higher than the ranges normally prescribed for immediate release compositions of amantadine. For example, the recommended dose of amantadine for the treatment of Parkinson's disease is 100 mg administered twice daily. In limited cases of the patient not deriving sufficient benefit at that dose and subject to the patient being able to tolerate such higher dose, the dose may be increased to 300 mg or 400 mg in divided doses. The most commonly prescribed doses of amantadine are 100 mg to 200 mg per day, with the latter administered in divided doses. More than 200 mg (for example 300 mg) is always given in divided doses. For the present invention, doses of 50 to 600 mg, or more preferably, 200 to 450 mg are administered for treatment of Parkinson's disease, and the methods and compositions of the invention may comprise administration of a dose as defined by any of these ranges. In specific embodiments the administration of such higher doses may be once daily. In additional embodiments the administration of such higher doses may be at night. In additional embodiments the administration of such higher doses may be in the form of 1, 2 or 3 capsules of size 0, 1 or 2 administered once daily.

In one embodiment of any of the above aspects the amantadine is administered as a pharmaceutically acceptable salt. In a more specific embodiment, the amantadine is administered as hydrochloride or amantadine sulfate.

In one embodiment of any of the above aspects, a total daily dose of 50 mg to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof is administered to a patient. More specifically the daily dose of amantadine or pharmaceutically acceptable salt thereof administered may be in the range of 100 mg to 440 mg. In another specific embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof maybe in the range of 260 mg to 420 mg. In another embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof administered exceeds 300 mg per day. In various specific embodiments, the daily dose of amantadine or pharmaceutically acceptable salt thereof may be 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg.

In one embodiment of any of the above aspects, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. More specifically, the composition may comprise 100 to 450 mg of amantadine, or a pharmaceutically acceptable salt thereof. Still more specifically, the composition may comprise 130-210 mg of amantadine, or a pharmaceutically acceptable salt thereof. In various specific embodiments, the dosage form comprises 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg of amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition comprises about 110, 120, 130, 140, 150, 160 170, 180, 190, 210, or 220 mg amantadine, or a pharmaceutically acceptable salt thereof. In another more specific embodiment, the composition comprises 110 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 130 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 170 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 210 mg amantadine hydrochloride.

In one embodiment of any of the above aspects, the composition comprises from about 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg of amantadine, or a pharmaceutically acceptable salt thereof to about 75 mg, 85 mg, 95 mg, 105 mg, 115 mg, 125 mg, 135 mg, 145 mg, 155 mg, 165 mg, 175 mg, 185 mg, 195 mg, 205 mg, 215 mg, 225 mg, 235 mg, 245 mg, 255 mg, 265 mg, 275 mg, 285 mg, 295 mg, 305 mg, 315 mg, 325 mg, 335 mg, 345 mg, 355 mg, 365 mg, 375 mg, 385 mg, 395 mg, 405 mg, 415 mg, 425 mg, 435 mg, 445 mg of amantadine, or a pharmaceutically acceptable salt thereof.

In a specific embodiment of the invention, a subject's entire daily dose of amantadine is administered once, during a period of less than about three, two or one hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). In other embodiments, at least one half of the daily dose of amantadine is taken during said period before bedtime. Preferably at least ⅔of the dose of amantadine is taken in said period before bedtime, with the remainder taken in morning or afternoon. The morning or afternoon dose of the amantadine may be provided in a conventional, immediate release dosage form, or in an extended release form.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in levodopa induced dyskinesia. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% reduction in levodopa induced dyskinesia. In further embodiments, the reduction in levodopa induced dyskinesia is measured on a numeric scale that is used by or accepted by the FDA or other regulatory agencies to evaluate the effectiveness of and to approve for licensure drugs for the treatment of LID. In further specific embodiments, the scale used in measuring the reduction in LID could be UDysRS, UPDRS Part IV (subscores 32, 33), Dyskinesia Rating Scale (DRS), Abnormal Involuntary Movement Scale (AIMS), Rush Dyskinesia Rating Scale, Parkinson Disease Dyskinesia Scale (PDYS-26), Obeso Dyskinesia Rating Scale (CAPIT), Clinical Dyskinesia Rating Scale (CDRS), Lang-Fahn Activities of Daily Living Dyskinesia or other scales developed for this purpose.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease fatigue. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, or 60% reduction in Parkinson's disease fatigue. In further specific embodiments, the reduction in fatigue is measured on a numerical scale used by or accepted by the FDA or other regulatory agencies to evaluate the effectiveness of and to approve for licensure drugs for the treatment of fatigue. In further specific embodiments, the scale used in measuring the reduction in fatigue could be the Fatigue Severity Scale (FSS), Fatigue Assessment Inventory, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue), Multidimensional Fatigue Inventory (MFI-20), Parkinson Fatigue Scale (PFS 16) and the Fatigue Severity Inventory. In other specific embodiments, the reduction in fatigue is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in fatigue is measured relative to baseline in a controlled clinical trial.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease symptoms. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's symptoms. In further specific embodiments, the reduction in Parkinson's symptoms is measured on a numerical scale used by or accepted by the FDA or other regulatory agencies to evaluate the effectiveness of and to approve for licensure drugs for the treatment of Parkinson's symptoms. In further specific embodiments, the scale used in measuring the reduction in Parkinson's symptoms could be the Unified Parkinson's Disease Rating Scale (UPDRS). Unified Parkinson's Disease Rating Scale (UPDRS, MDS revision)—Part I: non-motor aspects of experiences of daily living (13 items), Part II: motor aspects of experiences of daily living (13 items) -Part III: motor examination (33 scored items)—Part I: mental status, behavior and mood—Part II: activities of daily living—Part III: motor examination (27 scored items) Hoehn and Yahr Staging Scale (Original or Modified).

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in levodopa induced dyskinesia. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% reduction in levodopa induced dyskinesia. In further embodiments, the reduction in levodopa induced dyskinesia is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce LID. In further specific embodiments, the scale used in measuring the reduction in LID could be UDysRS, UPDRS Part IV (subscores 32, 33), Dyskinesia Rating Scale (DRS), Abnormal Involuntary Movement Scale (AIMS), or other scales developed for this purpose. In other specific embodiments, the reduction in LID is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in LID is measured relative to baseline in a controlled clinical trial.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease fatigue. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's disease fatigue. In further specific embodiments, the reduction fatigue is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce fatigue. In further specific embodiments, the scale used in measuring the reduction in fatigue could be the Fatigue Severity Scale (FSS). In other specific embodiments, the reduction in fatigue is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in fatigue is measured relative to baseline in a controlled clinical trial.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease symptoms. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's symptoms. In further specific embodiments, the reduction in Parkinson's symptoms is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce Parkinson's symptoms. In further specific embodiments, the scale used in measuring the reduction in Parkinson's symptoms could be the Unified Parkinson's Disease Rating Scale (UPDRS). In other specific embodiments, the reduction in Parkinson's disease symptoms is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in Parkinson's disease symptoms is measured relative to baseline in a controlled clinical trial.

Extended Release Formulations

Extended release amantadine compositions suitable for use in the method of the invention can be made using a variety of extended release technologies, such as those described in the patent publications referenced in the above background section, which publications are incorporated herein by reference in their entireties. In some embodiments, the invention is a pellet in capsule dosage form. In some embodiments, the pellets comprise a pellet core, which is

coated with at least one drug layer and at least one extended release coating layer. In some embodiments, the pellets are coated with at least one drug layer, an intermediate layer such as a seal coat and an extended release coating layer. In some embodiments, the pellet, the drug layer or both comprise one or more binders.

In some embodiments, the dosage unit comprises a plurality of coated pellets. In some embodiments, the pellets have a diameter of for example 300 to 1700 microns, in some cases 500 to 1200 microns. The pellets will comprise, for example, inert substrates, such as sugar spheres, microcrystalline cellulose (MCC) spheres, starch pellets. In some embodiments, pellets can be prepared by other processes such as pelletization, extrusion, spheronization, etc. or combinations thereof. The core pellets will comprise of amantadine hydrochloride and pharmaceutically acceptable excipients.

Coated Pellets

The pellet cores are coated with the active ingredient, e.g., amantadine or a pharmaceutically acceptable salt and/or polymorph thereof. In some embodiments, in addition to the active ingredient, the pellets also comprise one or more binders, such as for example hydroxypropyl methyl cellulose, copovidone, povidone, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose etc. In some embodiments, the pellets also contain one or more additional excipients, such as anti-tack agents (e.g. talc, magnesium stearate etc.)

In some embodiments, the pellets cores are coated with a drug layer comprising active ingredient, and optionally one or more binders, anti-tack agents and/or solvents by conventional coating techniques such as fluidized bed coating, pan coating.

Intermediate Layer Coating

In some embodiments, the pellets are coated with an intermediate layer, such as a seal coat. In some embodiments, the seal coat is adapted to prevent ingredients in the extended release coating from interacting with ingredients in the pellet core, to prevent migration of the ingredients in the pellet core from diffusing out of the pellet core into the extended release layer, etc. As described herein, the seal coat of the present invention can comprise one or more film forming polymers including but not limited to hydroxypropylmethyl cellulose (HPMC), copovidone, povidone, polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose or any combination thereof and the like.

The seal coat can further comprise other additives like plasticizers, such as, propylene glycol, triacetin, polyethylene glycol, tributyl citrate and optionally anti-tacking agents, such as, magnesium stearate, calcium silicate, magnesium silicate, and colloidal silicon dioxide or talc.

Apart from plasticizers and anti-tacking agents as mentioned above, the seal coat can optionally contain buffers, colorants, opacifiers, surfactants or bases, which are known to those skilled in the art.

Seal coating can be applied to the core using conventional coating techniques such as fluidized bed coating, pan coating etc. In some embodiments, the drug coated pellets cores are coated with a seal coat layer that optionally comprises one or more binders, anti-tack agents and/or solvents by fluidized bed coating or pan coating.

Binders

In some embodiments, either the pellet cores, the intermediate coating layer, or both may comprise one or more binders (e.g., film forming polymers). Suitable binders for use herein include, e.g.: alginic acid and salts thereof; cellulose derivatives such as carboxymethylcellulose, methylcellulose (e.g., Methocel®), hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose (e.g., Klucel®), ethylcellulose (e.g., Ethocel®), and microcrystalline cellulose (e.g., Avicel®); microcrystalline dextrose; amylose; magnesium aluminum silicate; polysaccharide acids; bentonites; gelatin; polyvinylpyrrolidone/vinyl acetate copolymer; crospovidone; povidone; starch; pregelatinized starch; tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitab®), and lactose; a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, polyvinylpyrrolidone (e.g., Polyvidone® CL, Kollidon® CL, Polyplasdone® XL-10), larch arabogalactan, Veegum®, polyethylene glycol, waxes, sodium alginate, and the like.

Extended Release Coating

The pellets are coated with an extended release coating. The extended release coating is adapted to delay release of the drug from the coated drug cores for a period of time after introduction of the dosage form into the use environment. In some embodiments, the extended release coating includes one or more pH-dependent or non-pH-dependent extended release excipients. Examples of non-pH dependent extended release polymers include ethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, copolymer of ethyl acrylate, methyl methacrylate (e.g. Eudgrait RS) etc. Examples of pH dependent extended release excipients include methacrylic acic copolymers, hydroxypropylmethyl cellulose acetate succinate, hydroxypropylmethyl cellulose phthalate, and cellulose acetate phthalate etc. The extended release coating may also include a pore former, such as povidone, polyethylene glycol, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, etc., sugars such as sucrose, mannitol, lactose, and salts, such as sodium chloride, sodium citrate, etc., a plasticizer, such as acetylated citrated esters, acetylated glycerides, castor oil, citrate esters, dibutylsebacate, glyceryl monostearate, diethyl phthalate, glycerol, medium chain triglycerides, propylene glycol, polyethylene glycol. The extended release coating may also include one or more additional excipients, such as lubricants (e.g., magnesium stearate, talc etc.).

Extended release coating can be applied using conventional coating techniques such as fluidized bed coating, pan coating etc. The drug coated pellets cores, which optionally comprise a seal coat, are coated with the extended release coating by fluidized bed coating.

Extended Release Excipients (Coating Polymers)

As described herein, exemplary extended release excipients include, but are not limited to, insoluble plastics, hydrophilic polymers, and fatty compounds. Plastic matrices include, but are not limited to, methyl acrylate-methyl methacrylate, polyvinyl chloride, and polyethylene. Hydrophilic polymers include, but are not limited to, cellulosic polymers such as methyl and ethyl cellulose, hydroxyalkyl celluloses such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, and cross-linked acrylic acid polymers like Carbopol® 934, polyethylene oxides and mixtures thereof. Fatty compounds include, but are not limited to, various waxes such as carnauba wax and glyceryl tristearate and wax-type substances including hydrogenated castor oil or hydrogenated vegetable oil, or mixtures thereof.

In certain embodiments, the plastic material can be a pharmaceutically acceptable acrylic polymer, including but not limited to, acrylic acid and methacrylic acid copolymers,

methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain other embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In still other embodiments, the acrylic polymer is an acrylic resin lacquer such as that which is commercially available from Rohm Pharma under the trade name Eudragit®. In further embodiments, the acrylic polymer comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the trade names Eudragit® RL3OD and Eudragit® RS30D, respectively. Eudragit® RL3OD and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit RL3OD and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. Edragit® S-100 and Eudragit® L-100 are also suitable for use herein. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, multiparticulate systems formed to include the same are swellable and permeable in aqueous solutions and digestive fluids.

The polymers described above such as Eudragit® RL/RS may be mixed together in any desired ratio in order to ultimately obtain an extended release formulation having a desirable dissolution profile. One skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L.

Pore Formers

In some embodiments, the extended release coating includes a pore former. Pore formers suitable for use in the extended release coating can be organic or inorganic agents, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. Examples of pore formers include but are not limited to organic compounds such as mono-, oligo-, and polysaccharides including sucrose, glucose, fructose, mannitol, mannose, galactose, lactose, sorbitol, pullulan, dextran; polymers soluble in the environment of use such as water-soluble hydrophilic polymers, such as povidone, crospovidone, polyethylene glycol, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyalkyl celluloses, carboxyalkyl celluloses, cellulose ethers, acrylic resins, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, polyethylene oxide, carbowaxes, Carbopol®, and the like, diols, polyols, polyhydric alcohols, polyalkylene glycols, polyethylene glycols, polypropylene glycols, or block polymers thereof, polyglycols, poly(α-Ω) alkylenediols; inorganic compounds such as alkali metal salts, lithium carbonate, sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium acetate, sodium citrate, suitable calcium salts, and the like. In certain embodiments, plasticizers can also be used as a pore former.

Capsules

The extended release pellets are introduced into a suitable capsule by using an encapsulator equipped with pellet dosing chamber. The capsule sizes may be 00, 0, 0EL, 1, 1EL, 2, 2EL, 3, 4 or 5. A particularly preferred composition that provides ideal pharmacokinetic properties and plasma concentration profiles is a pellet-in-capsule composition that comprises a plurality of pellets, typically having a diameter of about 500 μm to 1.2 mm, and preferably about 700 μm to 1000 μm, where each pellet comprises a core comprising amantadine and a binder, and an extended release coating surrounding the core that extends release of the amantadine so as to provide the desired pharmacokinetic properties and amantadine plasma concentration profiles described above.

In some embodiments, the pellets in the pellet-in-capsule are in a size 0 or smaller, preferably a size 1 or smaller capsule. Mean pellet diameters in some embodiments may be in a range of 500 μm to 1200 μm, e.g. from 500 μm to 1100 μm, from 500 μm to 1000 μm, from 500 μm to 900 μm, from 500 μm to 800 μm, from 500 μm to 700 μm, from 600 μm to 1100 μm, from 600 μm to 1000 μm, from 600 μm to 900 μm, from 600 μm to 800 μm, from 600 μm to 700 μm, from 700 μm to 1100 μm, from 700 μm to 1000 μm, from 700 μm to 900 μm, or from 700 μm to 800 μm. In some embodiments the mean particle diameters are, ±10%, e.g.: 500 μm, 550 μm, 600 μm, 650 μm, 700 μm, 750 μm, 800 μm, 850 μm, 900 μm, 950 μm, 1000 μm, 1050 μm, 1100 μm, 1150 μm or 1200 μm.

One preferred composition of the invention is a pellet-in-capsule composition wherein each pellet comprises a core that comprises a core seed with a mixture of amantadine and a binder coated onto the core seed, and an extended release coating surrounding the core comprising ethyl cellulose, a pore forming agent such as hydroxypropyl methyl cellulose or povidone, and a plasticizer. In some embodiments, the pellets may further comprise a seal coating between the pellet core and the extended release coating. The pellets are formulated using methods known in the art, such as those described in Example 1 below. In a specific embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 20-80 wt %, 45-70 wt %, 40-50 wt %, 45-55 wt %, 50-60 wt %, 55-65 wt %, 60-70 wt %, 65-75 wt %, 70-80 wt %, or 40 to 60 wt %, the binder, which is preferably hydroxypropyl methyl cellulose, copovidone, or mixtures thereof, is present in amounts from 1 to 25 wt %, the core seed, preferably a sugar sphere (nonpareil) or microcrystalline cellulose seed (e.g. Celphere®), is present in amounts from 8 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the pore forming agent, preferably povidone, is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %. In another specific embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 50 to 70 wt %, the binder, which is preferably hydroxypropyl methyl cellulose, copovidone, or mixtures thereof, is present in amounts from 1 to 25 wt %, the core seed, preferably a sugar sphere (nonpareil) or microcrystalline cellulose seed (e.g. Celphere®), is present in amounts from 5 to 15 wt %, the ethyl cellulose is present in amounts from 1 to 15 wt %, the pore forming agent, preferably povidone, is present in amounts from 0.25 to 4 wt %, and the plasticizer is present in amounts from 0.25 to 4 wt %.

Additional embodiments of the invention are illustrated in the Table, below, entitled "Various Amantadine ER Capsule Size 1 Formulations". By means of methods and compositions described herein, formulations can be made that achieve the desired dissolution characteristics and target pharmacokinetic profiles described herein. More specifi-

cally, therapeutically effective doses of amantadine can be administered once daily in no more than two size 1 (or smaller, e.g. size 2 or 3) capsules using the manufacturing methods and compositions that have been described herein to achieve these results. In particular, higher drug loading can be achieved using compositions and manufacturing methods described herein. In some embodiments, higher drug loading may be achieved, with the required dissolution profile, using smaller core pellet sizes and concomitantly increased drug layering on smaller cores, but with no change in the extended release coat. In some embodiments, using alternative manufacturing approaches described herein, e.g. extrusion and spheronization, even higher drug loads can be achieved to realize the desired dissolution profile, enabling high amantadine drug loads with suitable pharmacokinetic profiles, resulting in compositions that are therapeutically more effective, and at least as well tolerated, and can be filled in relatively small sized capsules (e.g., size 1, 2 or 3), enabling ease of administration to patients.

TABLE

Various Amantadine ER Capsule Size 1 Formulations

AMT Strength (mg)	Manufacture Method	Inert Core Pellet Size (mm)	Active Drug % w/w	Extended Release Coating % w/w	Bulk Density (g/cm^3)	% Fill in Size 1 Capsule	AMT Dissolution (%) (at T (hrs)): 2 hrs	6 hrs	12 hrs
110 mg	Fluid bed coating	0.3-0.5	40-50%	10-30%	0.6-1.0	60-70%	<25%	40-80%	>80%
140 mg	Fluid bed coating	0.3-0.5	45-50%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
150 mg	Fluid bed coating	0.3-0.5	50-55%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
170 mg	Fluid bed coating	0.2-0.3	50-55%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
170 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	65-75%	<25%		>80%
190 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	75-85%	<25%	40-80%	>80%
210 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
230 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	85-95%	<25%	40-80%	>80%

In some embodiment, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 20 to 80 wt % (based on the combined weight of the pellet core and extended release coating), with a bulk density of 0.3 to 1.2 g/cm^3. In some embodiments, the amantadine or pharmaceutically acceptable salt thereof is present in amounts from 20 to 77.5 wt %, from 20 to 75 wt %, from 20 to 72.5 wt %, from 20 to 70 wt %, from 20 to 67.5 wt %, from 20 to 65 wt %, from 20 to 62.5 wt %, from 20 to 60 wt %, from 20 to 57.5 wt %, from 20 to 55 wt %, from 20 to 52.5 wt %, from 20 to 50 wt %, from 20 to 47.5 wt %, from 20 to 45 wt %, from 20 to 42.5 wt %, from 20 to 40 wt %, from 20 to 37.5 wt %, from 20 to 35 wt %, from 20 to 32.5 wt %, from 20 to 30 wt %, from 30 to 80 wt %, from 30 to 77.5 wt %, from 30 to 75 wt %, from 30 to 72.5 wt %, from 30 to 70 wt %, from 30 to 67.5 wt %, from 30 to 65 wt %, from 30 to 62.5 wt %, from 30 to 60 wt %, from 30 to 57.5 wt %, from 30 to 55 wt %, from 30 to 52.5 wt %, from 30 to 50 wt %, from 30 to 47.5 wt %, from 30 to 45 wt %, from 30 to 42.5 wt %, from 30 to 40 wt %, from 40 to 80 wt %, from 40 to 77.5 wt %, from 40 to 75 wt %, from 40 to 72.5 wt %, from 40 to 70 wt %, from 40 to 67.5 wt %, from 40 to 65 wt %, from 40 to 62.5 wt %, from 40 to 60 wt %, from 40 to 57.5 wt %, from 40 to 55 wt %, from 40 to 52.5 wt %, from 40 to 50 wt %, from 40 to 47.5 wt %, from 40 to 45 wt %, from 50 to 80 wt %, from 50 to 77.5 wt %, from 50 to 75 wt %, from 50 to 72.5 wt %, from 50 to 70 wt %, from 50 to 67.5 wt %, from 50 to 65 wt %, from 50 to 62.5 wt %, from 50 to 60 wt %, from 50 to 57.5 wt %, from 50 to 55 wt %, from 60 to 80 wt %, from 60 to 77.5 wt %, from 60 to 75 wt %, from 60 to 72.5 wt %, from 60 to 70 wt %, from 60 to 67.5 wt %, from 60 to 65 wt %. In some embodiments, the bulk density is 0.3 to 1.2 g/cm^3, 0.3 to 1.15 g/cm^3, 0.3 to 1.1 g/cm^3, 0.3 to 1.05 g/cm^3, 0.3 to 1.0 g/cm^3, 0.3 to 0.9 g/cm^3, 0.3 to 0.8 g/cm^3, 0.3 to 0.7 g/cm^3, 0.3 to 0.6 g/cm^3, 0.3 to 0.5 g/cm^3, 0.3 to 0.4 g/cm^3, 0.4 to 1.2 g/cm^3, 0.4 to 1.15 g/cm^3, 0.4 to 1.1 g/cm^3, 0.4 to 1.05 g/cm^3, 0.4 to 1.0 g/cm^3, 0.4 to 0.9 g/cm^3, 0.4 to 0.8 g/cm^3, 0.4 to 0.7 g/cm^3, 0.4 to 0.6 g/cm^3, 0.4 to 0.5 g/cm^3, 0.5 to 1.2 g/cm^3, 0.5 to 1.15 g/cm^3, 0.5 to 1.1 g/cm^3, 0.5 to 1.05 g/cm^3, 0.5 to 1.0 g/cm^3, 0.5 to 0.9 g/cm^3, 0.5 to 0.8 g/cm^3, 0.5 to 0.7 g/cm^3, 0.5 to 0.6 g/cm^3, 0.6 to 1.2 g/cm^3, 0.6 to 1.15 g/cm^3, 0.6 to 1.1 g/cm^3, 0.6 to 1.05 g/cm^3, 0.6 to 1.0 g/cm^3, 0.6 to 0.9 g/cm^3, 0.6 to 0.8 g/cm^3, 0.6 to 0.7 g/cm^3, 0.7 to 1.2 g/cm^3, 0.7 to 1.15 g/cm^3, 0.7 to 1.1 g/cm^3, 0.7 to 1.05 g/cm^3, 0.7 to 1.0 g/cm^3, 0.7 to 0.9 g/cm^3, 0.7 to 0.8 g/cm^3, 0.5 to 1.2 g/cm^3, 0.8 to 1.15 g/cm^3, 0.8 to 1.1 g/cm^3, 0.8 to 1.05 g/cm^3, 0.8 to 1.0 g/cm^3, 0.8 to 0.9 g/cm^3, 0.9 to 1.2 g/cm^3, 0.9 to 1.15 g/cm^3, 0.9 to 1.1 g/cm^3, 0.9 to 1.05 g/cm^3, or 0.9 to 1.0 g/cm^3. In some embodiments, the composition is in a dosage unit comprising a pellet in capsule formulation, wherein the capsule size is size 00, size 0, size 1, size 2 or size 3. In some preferred embodiments, the dosage unit includes pellets

containing from 50 to 250 mg of amantadine in a size 0, 1, 2 or 3 capsule. In some embodiments, the dosage unit includes pellets containing from 100 to 250 mg, e.g. 100 to 200 mg of amantadine in a size 0, 1, 2 or 3 capsule, preferably a size 1, 2 or 3 capsule. In a more specific embodiment, the dosage unit comprises about 110, 120, 130, 140, 150, 160 170, 180, 190, 210, or 220 mg amantadine, or a pharmaceutically acceptable salt thereof. In another more specific embodiment, the dosage unit comprises 110 mg amantadine hydrochloride. In another more specific embodiment, the dosage unit comprises 130 mg amantadine hydrochloride. In another more specific embodiment, the dosage unit comprises 170 mg amantadine hydrochloride. In another more specific embodiment, the dosage unit comprises 210 mg amantadine hydrochloride.

Suitable plasticizers include medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, castor oil, and the like. The pellets are filled into capsules to provide the desired strength of amantadine. An advantage of this composition is it provides the desired release properties that make the composition suitable for administration during said period before bedtime. A further advantage is that the extended release coating is sufficiently durable so that the capsule can be opened and the pellets sprinkled onto food for administration to patients who have difficulty swallowing pills, without adversely affecting the release properties of the composition. When the composition is administered by sprinkling onto food, it is preferred to use a soft food such as applesauce or chocolate pudding, which is consumed within 30 minutes, and preferably within 15 minutes. A yet further advantage of the above-described composition is that it has very good batch-to-batch reproducibility and shelf-life stability.

In some embodiments, the composition of the invention has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, as measured using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. More preferably, the in vitro dissolution is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours.

In additional embodiments, 110 mg to 210 mg of ER amantadine in a size 1 capsule of the composition of the invention has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, as measured using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. More preferably, the in vitro dissolution is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more than 25-55% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 20% dissolution at 1 hour, (ii) about 25-45% dissolution at 2 hours, (iii) not more than 50-80% dissolution at 4 hours, and (iii) at least 80% dissolution at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

A preferred pellet-in-capsule compostion of the invention, in addition to having the above in vitro dissolution properties and any of the above-described pharmacokinetic properties (e.g. in vivo release profile, Tmax, Cmax/Cmin ratio, etc) that make the composition suitable for administration in said period before bedtime. The composition is further characterized by providing a Cmax of 1.6-2.4 ng/ml per mg of amantadine and an $AUC_{0\text{-}inf}$ of 40-75 ng*h/mL per mg of amantadine after oral administration of a single dose of the capsule to a human subject in a fasted state. A preferred pellet-in-capsule composition is further characterized by a steady state plasma concentration in which once daily oral administration of the capsule to a human subject provides a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine, a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and an $AUC_{0\text{-}24}$ of 48-73 ng*h/mL per mg of amantadine.

The above-described pellet-in-capsule compositions may be provided at a strength suitable for amantadine therapy. Typical strengths range from at least about 50 mg to about 250 mg. In a specific embodiment, the capsule strength is 70 mg, 80 mg, 90 mg, 110 mg, 120 mg, 125 mg, 130 mg, 140 mg, 150 mg, 160 mg, 160 mg, 170 mg, 180 mg, 190 mg, 210 mg, and 220 mg, that provides a single dose $AUC_{0\text{-}inf}$ per mg that is equivalent to a 100 mg tablet of an immediate release formulation of amantadine HCl (e.g. Symmetrel®, or other FDA Orange Book reference listed drug). One, two, or three, of such capsules can be administered to a subject in the period before bedtime. In a preferred embodiment, between 220 mg and 650 mg of amantadine is adminstered using 2 capsules of a suitable ER formulations once daily.

The invention may also be described in terms of the following numbered embodiments:

1. An extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, for use in a method of administering amantadine to a subject in need thereof, said method comprising orally administering said composition less than three hours before bedtime (i. e. the time at which the subject wishes to go to sleep for the night).
2. Use of amantadine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by the NMDA receptor to a subject in need thereof, said medicament being an extended release (ER) composition, and said treatment comprising orally administering said composition less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).
3. An extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing sleep disturbance in a human subject undergoing treatment with amantadine, said method comprising administering said composition less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).
4. Use of amantadine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing sleep disturbance in a human subject undergoing treatment with amantadine, said medicament being an extended release (ER) composition and being adapted for administration less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).

5. The use or composition of any one of embodiments 1-4 wherein administration occurs less than 1 hour before bedtime.
6. The use or composition of any one of embodiments 1-5, wherein the patient has been diagnosed with Parkinson's disease.
7. The use or composition of any one of embodiments 1-6, wherein the composition is administered once daily.
8. The use or composition of any one of embodiments 1-7, wherein the composition is added to food prior to administration.
9. The use or composition of any one of embodiments 1-8, wherein there is no increase in plasma concentration of amantadine for at least one hour after the administration at steady state.
10. The use or composition of any one of embodiments 1-9, wherein there is no increase in plasma concentration of amantadine for at least two hours after the administration at steady state.
11. The use of composition of any one of embodiments 1-10, wherein, the amantadine has a single dose Tmax of 9 to 15 hours and/or a steady state Tmax of 7 to 13 hours after administration.
12. The use or composition of any one of embodiments 1-11, wherein the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours after administration.
13. The use of composition of any one of embodiments 1-10, wherein, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours after administration.
14. The use or composition of any one of embodiments 1-11, wherein the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours after administration.
15. The use of composition of any one of embodiments 1-10, wherein, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours after administration.
16. The use or composition of any one of embodiments 1-11, wherein the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours after administration.
17. The use or composition of any one of embodiments 1-12, wherein the amantadine has a single dose Tmax of 11 to 13 hours after administration, and or a steady state Tmax of 9 to 11 hours after administration.
18. The use or composition of any one of embodiments 1-13, wherein a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration.
19. The use or composition of any one of embodiments 1-14 having a Cmax/Cmin ratio of 1.5 to 2.0.
20. The use or composition of any one of embodiments 1-15 having a Cmax/Cmin ratio of 1.7 to 1.9.
21. The use or composition of any one of embodiments 1-16, wherein the amantadine is amantadine hydrochloride or amantadine sulfate.
22. The use or composition of any one of embodiments 1-17 wherein the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof.
23. The use or composition of embodiment 18, wherein the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof.
24. The use or composition of any one of embodiments 1-19 wherein the composition comprises 200 to 420 mg of amantadine, or a pharmaceutically acceptable salt thereof.
25. The use or composition of embodiment 20, wherein the composition is administered as two unit dosage forms each comprising 110 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof.
26. The use or composition of any one of embodiments 1 to 17, wherein the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof.
27. The use or composition of embodiment 22, wherein the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof.
28. The use or composition of embodiment 23, wherein the composition comprises 110 mg amantadine hydrochloride.
29. The use or composition of any one of embodiments 1-24, wherein oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of amantadine of 1.6 to 2.4 ng/ml per mg of amantadine and an AUC_{0-inf} of 40 to 75 ng*h/mL per mg of amantadine.
30. The use or composition of any one of embodiments 1-25, wherein once daily oral administration of a dose of the composition to a human subject provides a steady state plasma amantadine concentration profile characterized by:
(i) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine,
(ii) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and
(iii) an AUC_{0-24} of 44 to 83 ng*h/mL per mg of amantadine.
31. The use or composition of embodiment 26, wherein the steady state plasma concentration profile is further characterized by:
(iv) no increase in plasma concentration of amantadine for at least one hour after the administration; and
(v) a Cmax/Cmin ratio of 1.5 to 2.0.
32. The use or composition of embodiment 27, wherein the steady state plasma concentration profile is further characterized by:
(iv) no increase in concentration of amantadine for at least two hours after the administration; and
(v) a Cmax/Cmin ratio of 1.7 to 1.9.
33. The use or composition of any one of embodiments 1-28, wherein the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium.
34. The use or composition of embodiment 29, wherein the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours
35. The use or composition of any one of embodiments 1-30, wherein the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of AUC_{0-inf}; a fractional AUC from 0 to 8 hours that is about 5 to 15% of AUC_{0-inf}; a fractional AUC from 0 to 12 hours that is about 10 to 40% of AUC_{0-inf}; a fractional AUC from 0 to 18 hours that is about 25 to 60% of AUC_{0-inf}; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of AUC_{0-inf}.
36. The use or composition of any one of embodiments 1-31, wherein the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that

is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

37. A pharmaceutical composition as embodied in any one of embodiments 1, 3, or 5 to 32, or the use of any one of embodiments 2, 4 or 5 to 32, wherein said composition is for oral administration and comprises a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising:
    (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and
    (b) an extended release coating surrounding the pellet core.
38. The use or composition of embodiment 32, wherein the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer.
39. The use or composition of any one of embodiments 33 or 34, wherein the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed.
40. The use or composition of embodiment 35, wherein, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 60 wt %, the binder is present in amounts from 8 to 25 wt %, the core seed is present in amounts from 8 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the povidone is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %.
41. The use or composition of any one of embodiments 33 to 36, further comprising a seal coating between the pellet core and the extended release coating.
42. The use or composition of any one of embodiments 35 to 37, wherein the wherein the pellet core comprises a binder, selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof.
43. The use or composition of any one of embodiments 18 to 38, wherein the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.
44. A composition of any one of embodiments 33 to 39, for use in a method of treating Parkinson's disease in a human subject in need thereof, said method comprising orally administering said composition.

Some embodiments herein provide a method of administering amantadine to a subject in need thereof, said method comprising orally administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than three hours before bedtime. In some embodiments, administration occurs less than 1 hour before bedtime. In some embodiments, the patient has been diagnosed with Parkinson's disease. In some embodiments, the composition is administered once daily. In some embodiments, the composition is added to food prior to administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least one hour after the administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least two hours after the administration. In some embodiments, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours. In some embodiments, the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours. In some embodiments, the amantadine has a single dose Tmax of 11 to 13 hours after administration, and/or a steady state Tmax of 9 to 11 hours. In some embodiments, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave night at steady state is 1.2 to 1.6. In some embodiments, the ratio of C-ave-morning/C-ave night at steady state is 1.3 to 1.5. In some embodiments, the average amantadine plasma concentration during the day (C-ave-day) at steady state is 500-2000 ng/ml. In some embodiments, the average amantadine plasma concentration in the morning (C-ave-morning) at steady state is 500-2000 ng/ml. In some embodiments, the amantadine is amantadine hydrochloride or amantadine sulfate. In some embodiments, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one or two unit dosage forms each comprising 130 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is within a capsule of capsule size #1. In some embodiments, the composition comprises 200 to 350 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 110 mg amantadine hydrochloride. In some embodiments, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine, and an $AUC_{0\text{-}inf}$ of 40 to 75 ng*h/mL per mg of amantadine. In some embodiments, once daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by: (a) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine; (b) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (c) an $AUC_{0\text{-}24}$ of 44 to 83 ng*h/mL per mg of amantadine. In some embodiments, the steady state plasma concentration profile is further characterized by: (d) no increase in plasma concentration of amantadine for at least one hour after the administration; and (e) a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the steady state plasma concentration profile is further characterized by: (f) no increase in concentration of amantadine for at least two hours after the administration; and (g) a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 25-55% at 6 hours, and at

least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 20% at 1 hour, 25-45% at 2 hours, 50-80% at 4 hours, and at least 80% at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours. In some embodiments, the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 8 hours that is about 5 to 15% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 12 hours that is about 10 to 40% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 18 hours that is about 25 to 60% of $AUC_{0\text{-}inf}$; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of $AUC_{0\text{-}inf}$. In some embodiments, the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}; and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

Some embodiments herein provide a method of reducing sleep disturbance in a human subject undergoing treatment with amantadine, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than three hours before bedtime. In some embodiments, administration occurs less than 1 hour before bedtime. In some embodiments, the patient has been diagnosed with Parkinson's disease. In some embodiments, the composition is administered once daily. In some embodiments, the composition is added to food prior to administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least one hour after the administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least two hours after the administration. In some embodiments, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours. In some embodiments, the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours. In some embodiments, the amantadine has a single dose Tmax of 11 to 13 hours after administration, and/or a steady state Tmax of 9 to 11 hours. In some embodiments, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave night at steady state is 1.2 to 1.6. In some embodiments, the ratio of C-ave-morning/C-ave night at steady state is 1.3 to 1.5. In some embodiments, the average amantadine plasma concentration during the day (C-ave-day) at steady state is 500-2000 ng/ml. In some embodiments, the average amantadine plasma concentration in the morning (C-ave-morning) at steady state is 500-2000 ng/ml. In some embodiments, the amantadine is amantadine hydrochloride or amantadine sulfate. In some embodiments, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one or two unit dosage forms each comprising 130 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is within a capsule of capsule size #1. In some embodiments, the composition comprises 200 to 350 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 110 mg amantadine hydrochloride. In some embodiments, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine, and an $AUC_{0\text{-}inf}$ of 40 to 75 ng*h/mL per mg of amantadine. In some embodiments, once daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by: (a) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine; (b) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (c) an $AUC_{0\text{-}24}$ of 44 to 83 ng*h/mL per mg of amantadine. In some embodiments, the steady state plasma concentration profile is further characterized by: (d) no increase in plasma concentration of amantadine for at least one hour after the administration; and (e) a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the steady state plasma concentration profile is further characterized by: (f) no increase in concentration of amantadine for at least two hours after the administration; and (g) a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 25-55% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 20% at 1 hour, 25-45% at 2 hours, 50-80% at 4 hours, and at least 80% at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours. In some embodiments, the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 8 hours that is about 5 to 15% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 12 hours that is about 10 to 40% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 18 hours that is about 25 to 60% of $AUC_{0\text{-}inf}$; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of $AUC_{0\text{-}inf}$. In some embodiments, the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional

AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

Some embodiments herein provide a method of treating levodopa induced dyskinesia in a patient with Parkinson's disease, said method comprising orally administering once daily an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime. In some embodiments, administration occurs less than 1 hour before bedtime. In some embodiments, the patient has been diagnosed with Parkinson's disease. In some embodiments, the composition is administered once daily. In some embodiments, the composition is added to food prior to administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least one hour after the administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least two hours after the administration. In some embodiments, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours. In some embodiments, the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours. In some embodiments, the amantadine has a single dose Tmax of 11 to 13 hours after administration, and/or a steady state Tmax of 9 to 11 hours. In some embodiments, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave night at steady state is 1.2 to 1.6. In some embodiments, the ratio of C-ave-morning/C-ave night at steady state is 1.3 to 1.5. In some embodiments, the average amantadine plasma concentration during the day (C-ave-day) at steady state is 500-2000 ng/ml. In some embodiments, the average amantadine plasma concentration in the morning (C-ave-morning) at steady state is 500-2000 ng/ml. In some embodiments, the amantadine is amantadine hydrochloride or amantadine sulfate. In some embodiments, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one or two unit dosage forms each comprising 130 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is within a capsule of capsule size #1. In some embodiments, the composition comprises 200 to 350 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 110 mg amantadine hydrochloride. In some embodiments, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine, and an $AUC_{0\text{-}inf}$ of 40 to 75 ng*h/mL per mg of amantadine. In some embodiments, once daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by: (a) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine; (b) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (c) an $AUC_{0\text{-}24}$ of 44 to 83 ng*h/mL per mg of amantadine. In some embodiments, the steady state plasma concentration profile is further characterized by: (d) no increase in plasma concentration of amantadine for at least one hour after the administration; and (e) a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the steady state plasma concentration profile is further characterized by: (f) no increase in concentration of amantadine for at least two hours after the administration; and (g) a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 25-55% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 20% at 1 hour, 25-45% at 2 hours, 50-80% at 4 hours, and at least 80% at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours. In some embodiments, the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 8 hours that is about 5 to 15% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 12 hours that is about 10 to 40% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 18 hours that is about 25 to 60% of $AUC_{0\text{-}inf}$; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of $AUC_{0\text{-}inf}$. In some embodiments, the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

Some embodiments herein provide a pharmaceutical composition for any of the methods described herein, wherein said composition is for oral administration and comprises a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 60 wt %, the binder is present in amounts from 8 to 25 wt %, the core seed is present in

amounts from 1 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the povidone is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %. In some embodiments, the composition further comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.

Some embodiments herein provide a method of administering amantadine, or a pharmaceutically acceptable salt thereof, to a human subject in need thereof, said method comprising orally administering a pharmaceutical composition comprising amantadine in a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 60 wt %, the binder is present in amounts from 8 to 25 wt %, the core seed is present in amounts from 1 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the povidone is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %. In some embodiments, the composition further comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil. Some embodiments comprise treating Parkinson's disease in a human subject in need thereof.

Some embodiments herein provide a pharmaceutical composition suitable for once daily oral administration to a patient in need thereof said composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. In some embodiments, the composition comprises 110-220 mg of amantadine or pharmaceutically acceptable salt thereof. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 40-80% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition comprises a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, the composition comprises amantadine and, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 70 wt %. In some embodiments, the pellet core comprises a core seed comprising sugar or microcrystalline cellulose that is between 100 and 500 microns in diameter. In some embodiments, the bulk density is between 0.5 and 1 gm/cm^3. In some embodiments, the composition comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.

Some embodiments herein provide a method of treating Parkinson's disease in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. In some embodiments, the composition comprises 110-220 mg of amantadine or pharmaceutically acceptable salt thereof. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 40-80% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition comprises a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, the composition comprises amantadine and, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 70 wt %. In some embodiments, the pellet core comprises a core seed comprising sugar or microcrystalline cellulose that is between 100 and 500 microns in diameter. In some embodiments, the bulk density is between 0.5 and 1 gm/cm^3. In some embodiments, the composition comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.

Some embodiments herein provide a method of treating levodopa induced dyskinesia in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. Some embodiments herein provide a method of treating traumatic brain injury in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a phar-

maceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. Some embodiments provide a method of treating traumatic brain injury in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. Some embodiments provide a method of treating fatigue in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. In some embodiments, the composition comprises 110-220 mg of amantadine or pharmaceutically acceptable salt thereof. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 40-80% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition comprises a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, the composition comprises amantadine and, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 70 wt %. In some embodiments, the pellet core comprises a core seed comprising sugar or microcrystalline cellulose that is between 100 and 500 microns in diameter. In some embodiments, the bulk density is between 0.5 and 1 gm/cm^3. In some embodiments, the composition comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil. In some embodiments, the method comprises administering the composition to a patient less than three hours before bed time.

The present invention may be better understood by reference to the following examples, which are not intended to limit the scope of the claims.

EXAMPLE 1

Amantadine Extended Release Coated Pellet Formulations

Amantadine HCl extended release coated pellet compositions designed for nighttime administration were prepared using the components and relative amounts shown in Table 1 below. For each composition, the drug coating solution was prepared by adding HPMC 5 cps and Copovidone to isopropyl alcohol with continuous stirring. Purified water was added to this dispersion and stirring continued until a clear solution is formed. Drug (Amantadine HCl) was then added to this binder solution and stirring continued until the drug was completely dissolved. Finally, talc was added and dispersed uniformly by stirring.

Celphere beads (screen sizes #35 to #50 i.e. 300 to 500 micron) were loaded in a Wurster coating unit. The drug coating dispersion was sprayed onto the beads followed by a period of drying. The resulting drug coated pellets were sieved to retain the fraction between screens #18 and #24 (approximately 700 μm to 1 mm diameter).

The seal coating solution was prepared by adding HPMC 5 cps to isopropyl alcohol with continuous stirring. Purified water was added to this dispersion and stirring continued until a clear solution was formed. Talc was added and dispersed uniformly by stirring. The sieved drug coated pellets were loaded in a Wurster coating unit. The seal coating dispersion was sprayed over the drug coated pellets followed by a period of drying to remove the residual solvent and water in the pellets. The resulting seal coated pellets were sieved to retain the fraction between screens #18 and #24.

The ER coating solution was prepared by dissolving ethyl cellulose (viscosity 7 cps) in isopropyl alcohol and purified water and stirring until a clear solution was formed. Povidone K-90 was then dissolved in this clear solution followed by addition of plasticizer Miglyol 812N with continuous stirring to form a clear solution. The sieved seal coated pellets were loaded in a Wurster coating unit. The ER coating solution was sprayed over the seal coated pellets followed by a period of drying to affect the ER coat and remove the residual solvent and water in the pellets. After drying, magnesium stearate was spread on the top bed of the coated pellets in the annulus region followed by recirculation of the pellets in the Wurster unit to blend the magnesium stearate with the coated pellets. The resulting ER coated pellets were sieved to retain the fraction between screens #18 and #24.

The desired weight of the ER coated pellets containing the unit dose were filled into empty 1 hard gelatin capsule shell (size 1 for 100-140 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 1

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Pellet Core		
Amantadine Hydrochloride USP	Active	40-50%
Microcrystalline cellulose spheres (Celphere ®)	Core seeds	10-15%
Hydroxypropyl methyl cellulose 5 cps USP	Binder	10-15%
Copovidone	Binder	1-5%
Talc USP	Anti-tack	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Seal Coating (optional)		
Hydroxypropyl methyl cellulose 3 cps USP	Coating polymer	5-10%
Talc USP	Anti-tack	0-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Extended Release Coating		
Ethyl cellulose	Coating polymer	10-20%
Povidone	Pore former	1-5%

TABLE 1-continued

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Medium chain triglycerides	Plasticizer	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Magnesium Stearate NF	Lubricant	0-1%
Density of pellets		0.6-0.9 gm/cm^3

NF = National Formulary
[1]Purified water and isopropyl alcohol are removed during processing.

The in vitro dissolution of capsules prepared above was tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. Capsules meeting desired dissolution specifications released not more than 25% of the drug in 2 hours, 40-80% in 6 hours, and at least 80% at 12 hours. In an exemplary dissolution profile, there was 0% drug release at 1 hour, 12% release at 2 hours, 43% release at 4 hours, 68% release at 6 hours, 83% release at 8 hours, 92% release at 10 hours, and 97% release at 12 hours. Capsules prepared in accordance with the above method exhibited good shelf-stability, and batch-to-batch reproducibility upon scale-up.

EXAMPLE 2

Amantadine Extended Release Coated Pellet Formulation With Higher Drug Loading

Amantadine HCl extended release coated pellet compositions designed for nighttime administration are prepared using the components and relative amounts shown in Table 2 below and the manufacturing process described in example 1.

The diameter of the inert cores is 200-300 microns. The diameter of the coated pellets is 600-1200 microns. The bulk density of the coated pellets is 0.7-1.2 g/cm^3.

The desired weight of the ER coated pellets containing the unit dose are filled into an empty hard gelatin capsule shell (size 1 for 170 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 2

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Pellet Core		
Amantadine Hydrochloride USP	Active	50-65%
Microcrystalline cellulose spheres (Celphere ®)	Core seeds	1-15%
Hydroxypropyl methyl cellulose USP	Binder	5-25%
Copovidone	Binder	1-5%
Talc USP	Anti-tack	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Seal Coating (optional)		
Hydroxypropyl methyl cellulose USP	Coating polymer	0-10%
Talc USP	Anti-tack	0-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Extended Release Coating		
Ethyl cellulose	Coating polymer	10-20%
Povidone	Pore former	1-5%
Medium chain triglycerides	Plasticizer	1-5%
Isopropyl alcohol	Solvent	—[1]

TABLE 2-continued

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Water	Solvent	—[1]
Magnesium Stearate NF	Lubricant	0-1%

NF = National Formulary
[1]Purified water and isopropyl alcohol are removed during processing.

The in vitro dissolution of capsules prepared above are tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium and release not more than 25% of the drug in 2 hours, 40-80% in 6 hours, and at least 80% at 12 hours.

EXAMPLE 3

Amantadine Extended Release Coated Pellet Formulations

Amantadine HCl extended release coated pellet compositions suitable for nighttime administration were prepared using the components and relative amounts shown in Table 3 below and the manufacturing process described in Example 1.

The desired weight of the ER coated pellets containing the unit dose was filled into empty #1 hard gelatin capsule shell (100 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 3

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule A	B	C
Pellet Core				
Amantadine Hydrochloride USP	Active	50.15%	47.94%	45.15%
Microcrystalline cellulose spheres (Celphere ®)	Core seeds	14.33%	13.70%	12.90%
Hydroxypropyl methyl cellulose USP	Binder	13.37%	12.79%	12.04%
Copovidone	Binder	3.34%	3.2%	3.01%
Talc USP	Anti-tack	2.51%	2.4%	2.26%
Isopropyl alcohol	Solvent	—[1]	—[1]	—[1]
Water	Solvent	—[1]	—[1]	—[1]
Seal Coating (optional)				
Hydroxypropyl methyl cellulose USP	Coating polymer	7.61%	7.27%	6.85%
Talc USP	Anti-tack	0.76%	0.73%	0.69%
Isopropyl alcohol	Solvent	—[1]	—[1]	—[1]
Water	Solvent	—[1]	—[1]	—[1]
Extended Release Coating				
Ethyl cellulose	Coating polymer	6.23%	9.46%	13.53%
Povidone	Pore former	0.85%	1.29%	1.84%
Medium chain triglycerides	Plasticizer	0.75%	1.13%	1.62%
Isopropyl alcohol	Solvent	—[1]	—[1]	—[1]
Water	Solvent	—[1]	—[1]	—[1]
Magnesium Stearate NF	Lubricant	0.1%	0.1%	0.1%

NF = National Formulary
[1]Purified water and isopropyl alcohol are removed during processing.

The in vitro dissolution of capsules prepared above were tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. The results are shown in FIG. **1**.

EXAMPLE 4

Amantadine Extended Release Formulation Made by Extrusion Spheronization

Amantadine HCl extended release compositions designed for nighttime administration are prepared using the components and relative amounts shown in Table 4 below and the manufacturing process described below.

A blend of amantadine HCl, microcrystalline cellulose and lactose monohydrate was prepared and a wet mass is prepared in a high shear granulator using an aqueous solution of povidone. The wet mass is extruded using 1 mm sieve and extruded mass is spheronized using a spheronizer. The pellets are dried in a tray drier to yield core pellets. The core pellets are coated with extended release coating solution in a pan coater. The desired weight of the ER coated pellets containing the unit dose is filled into empty 1 hard gelatin capsule shell (170 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 4

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Pellet Core		
Amantadine Hydrochloride USP	Active	59.40%
Microcrystalline cellulose	Diluent	18.67%
Lactose monohydrate	Diluent	6.15%
Povidone	Binder	0.64%
Water	Solvent	—[1]
Extended Release Coating		
Ethyl cellulose	Coating polymer	12.41%
Polyethylene glycol	Pore former	1.24%
Dibutyl sebacate	Plasticizer	1.49%
Ethanol	Solvent	—[1]

The in vitro dissolution of capsules prepared above are tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium and release not more than 25% of the drug in 2 hours, 40-80% in 6 hours, and at least 80% at 12 hours.

EXAMPLE 5

Pharmacokinetic Measurement of Formulations of Amantadine ER Compared to IR Amantadine

Objective: The primary objective of the study was to confirm the PK properties of extended release formulations in example 3, to determine the pharmacokinetic profiles, safety and tolerability of three prototype formulations of ER capsules of amantadine HCl described with different release properties in Example 3 relative to a 100 mg film-coated IR amantadine HCl tablet (SYMMETREL®) given as single doses to healthy adult subjects under fasting conditions.

Study design: This was a Phase 1, randomized, single dose, open-label, four-period, crossover, fasting pharmacokinetic study in which single 100 mg doses of three formulations of Amantadine ER capsules with different release properties were compared to single 100 mg doses of marketed amantadine IR tablets (SYMMETREL®). The three ER formulations differed in the amantadine release rates in vitro, as shown in FIG. **1**.

Methods: Subjects were admitted to the unit for the first period of dosing within 21 days of study screening. Subjects were dosed on the day after checking into the unit and discharged at 24 hours post dose. Subjects were asked to return after discharge for follow-up visits at 56 hours and 152 hours after dosing. Each dosing period was separated by at least 7 day washout.

After an overnight fast, the formulation was administered to the subjects while in a sitting position with 240 mL of water. Blood samples were collected at 0 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 24 (discharge), and 56 hours following each dose. Plasma samples were assayed for amantadine by a validated liquid chromatography/tandem mass spectroscopy (LC/MS/MS) method. Pharmacokinetic parameters were calculated using a non-compartmental analysis with WinNonlin software (version 4.1 or higher; Pharsight Corporation).

An analysis of variance (ANOVA) was performed on the natural logarithms of Cmax and AUCO-∞ determined from the data following a single dose of study drug using linear mixed effects model. The model included effects for subject, sequence, period, and regimen. The effects of sequence, period, and regimen were fixed, while the effect of subject was random. Ratio of ER to IR for both AUC (relative bioavailability for ER formualtions) and Cmax was calculated. (Adverse events were monitored throughout the study. Vital signs (pulse rate, blood pressure and body temperature), clinical laboratory measures (biochemistry, hematology, and urinalysis) and ECGs were collected at various times during the study.

Results: A total of 20 subjects participated in the study. The mean age was 25.5 years old (range 20-38 years). The study consisted of 8 male (40%) and 12 female (60%) subjects with a mean body mass index (BMI) of 23.6 kg/m2±2.85. The racial makeup was 100% Caucasian. Fifteen subjects received all 4 treatments.

The PK results from this study showed that all three of the Amantadine ER formulations reduced the rate of absorption, based on the reduced values of Cmax and increased Tmax, compared to SYMMETREL® (Table 5, FIGS. **5**, **6**). The IR formulation had the highest mean Cmax (277±73.9 ng/mL) and shortest median Tmax (4 h) values. Formulations A, B, and C produced progressively lower Cmax and longer Tmax values. Cmax decreased from 204±61.4 to 166±34.8 to 149±34.4 ng/mL, and median Tmax increased from 7.0, to 11.0, to 14.0 h for formulations A, B, and C, respectively. Total amantadine exposure, as measured by AUCO-∞, was slightly lower in all three Amantadine ER formulations than SYMMETREL® but all three formulations had acceptable bioavailability (85-95%).

TABLE 5

Single Dose Pharmacokinetic Parameters of Three Formulations of Amantadine ER (Formulation A, B, and C), as Compared to SYMMETREL ® (Formulation IR)

Parameter[a]	100 mg Formulation A (n = 19)	100 mg Formulation B (n = 17)	100 mg Formulation C (n = 18)	100 mg Formulation IR (n = 18)
C_{max} (ng/mL)	204 ± 61	166 ± 35	149 ± 34	277 ± 74
T_{max} (h) [range]	7 [5-11]	11 [5-15]	14 [9-18]	4 [2-6]
$A_{UC0\text{-}last}$ (ng * h/mL)	5064 ± 1573	5028 ± 2328	4525 ± 1268	5488 ± 1730
$AUC_{0\text{-}\infty}$ (ng * h/mL)	5545 ± 1904	5724 ± 2369	5652 ± 2581	5907 ± 1907
$t_{1/2}$ (h)	13.9 ± 3.0	16.3 ± 5.2	18.3 ± 7.5	12.3 ± 3.5

[a]All parameters are reported as the mean ± standard deviation (SD), except t_{max} which is reported as a median value (min to max range)

TABLE 6

Ratio ER/IR for C_{max} and $AUC_{0\text{-}\infty}$

Comparison	Variable	ER/IR[a]
A vs. IR	C_{max} (ng/mL)	66.0%
	$AUC_{0\text{-}\infty}$ (ng * h/mL)	85.3%
B vs. IR	C_{max} (ng/mL)	60.9%
	$AUC_{0\text{-}\infty}$ (ng * h/mL)	94.6%
C vs. IR	C_{max} (ng/mL)	51.2%
	$AUC_{0\text{-}\infty}$ (ng * h/mL)	88.5%

[a]Point estimate of the geometric mean ratio (ER/IR).

EXAMPLE 6

Food-Effect Evaluation of Amantadine ER

Objective: The primary objective was to demonstrate that the amantadine ER formulations suitable for nighttime administration exhibit excellent bioavailability when administered with food. We determined the pharmacokinetics of a 100 mg capsule of an amantadine ER formulation (Example 3, Formulation B), when administered both with a high fat meal and in a fasted state.

Study Design: This was a Phase 1, randomized, single dose, open-label, two-period, crossover, food-effect study to compare single 100 mg doses of Formulation I in healthy adult (18 to 45 years of age) male and female subjects in fed and fasted states. The study consisted of a 21-day to -2 day screening phase (prior to the scheduled dosing day) and two treatment periods, Period 1 and Period 2, with an 8-day wash-out period between treatment periods.

Methods: After an overnight fast, the formulation was administered to the subjects while in a sitting position with 240 mL of water at ambient temperature for the fasted condition. For the fed condition, after the overnight fast, subjects were served a high fat and high calorie test meal (Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies, December 2002) as breakfast, which they were required to consume completely within 30 minutes before taking the study medication. Subjects were randomized to one of two sequences, each composed of treatment administration under fed and fasted conditions separated by an eight day wash out period.

For each period, pharmacokinetic blood samples were collected at pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 24, 28, 48, 72, 96 and 144 hours after dosing in each period. Subjects were housed in the clinical facility at least 15 hours before investigational product administration and remained in the clinical facility for at least 28 hours after administration of the investigational product in each period. Samples after 28 hours in each period were collected on an ambulatory basis. Amantadine in plasma was quantified by a validated LC/MS/MS method. The pharmacokinetic parameters were calculated from the drug concentration-time profile by non-compartmental model using WinNonlin Professional Software-Version 5.0.1 (Pharsight Corporation, USA) for amantadine. Absence of food effect was defined as met if the point estimates and 90% confidence intervals (CI) for the ln-transformed C_{max}, AUC_{last} and AUC_{∞} fed/fasting ratios of the population means were entirely within the standard accepted range of 80% to 125%. All statistical analyses for amantadine were performed using PROC MIXED of SAS® Release 9.1.3 (SAS Institute Inc., USA).

Routine safety monitoring was conducted during and after dosing in all subjects.

Results: A total of 26 subjects participated in the study, 19 (73%) male and 7 (27%) female. The mean age was 26 years (range 19-44) and the mean BMI was 22.4 kg/m^2 (range 18.1-29.8). The racial makeup was 100% Asian. All subjects received at least one dose of study drug and were included in the safety analysis. Twenty-four (92.3%) subjects completed the study and were included in the pharmacokinetic analysis. Two subjects (7.7%) were withdrawn prior to completion of the study due protocol deviations.

The results of this study (Table 7) indicate that the single dose pharmacokinetics of Formulation B are not affected by food. The rate, as measured by C_{max}, and the extent, as measured by $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$, of absorption of amantadine, administered with and without food, were equivalent (Table 8).

TABLE 7

Mean ± SD Pharmacokinetic Parameters after Single Dose Administration of 100 mg of Formulation B in Fed and Fasted States

	Mean ± SD (Un-transformed data) n = 24	
Parameters (Units)[a]	Fasted State	Fed State
T_{max} (h)	11.9 ± 2.1 (8-15)	9.5 ± 2.4 (5-16)
C_{max} (ng/mL)	198.8 ± 34.7	219.4 ± 41.5
$AUC_{0\text{-}last}$ (ng * h/mL)	5571.2 ± 1654.2	5394.4 ± 1581.5
$AUC_{0\text{-}\infty}$ (ng * h/mL)	5663.1 ± 1677.4	5476.6 ± 1590.7
$t_{1/2}$ (h)	11.9 ± 2.8	11.5 ± 2.0
t_{lag} (h)	1.0	2.0

[a]All parameters are reported as the mean ± standard deviation (SD). t_{max} is reported as the mean ± SD (min to max range).

TABLE 8

Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Formulation B (n = 24) in Fed and Fasted States

Parameters (Units)	ln-transformed data Geometric Least Squares Mean Fed State	Fasted State	Ratio (Fed/Fasted) %	90% Confidence Interval (Parametric)
C_{max} (ng/mL)	215.6	195.8	110.1	104.4-116.2%
$AUC_{0\text{-}last}$ (ng * h/mL)	5195.9	5344.2	97.2	91.0-103.8%
$AUC_{0\text{-}\infty}$ (ng * h/mL)	5280.3	5434.7	97.2	90.9-103.8%

Conclusion: The results of this study indicate that the single dose pharmacokinetics of amantadine ER are not affected by food. The rate, as measured by C_{max}, and the extent, as measured by $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$, of absorption of amantadine, administered with and without food, were equivalent.

EXAMPLE 7

Pharmacokinetic study comparing once-daily administration of amantadine HCl ER capsules with twice-daily administration of amantadine HCL IR tablets in healthy adults under fasting conditions

Objective: The primary objective of this study was to measure at steady state under repeat or chronic dosing the pharmacokinetics of an ER amantadine formulation sutiable for nighttime administration, and enable the calculation of critical PK parameters for future safety and efficacy studies (i.e., Cave-morning, Cave-day, Cave-night) of ER amantadine formulations administered at night. We compared the single dose and repeat dose pharmacokinetics of amantadine HCl administered twice daily as a commercially available immediate release (IR) formulation to a once daily amantadine extended release (ER) formulation (Example 3, Formulation B).

Study Design: This was a two period, multiple dose, crossover study. After a 21 day screening period, 26 healthy male and female subjects were randomized to receive one of two treatments (amantadine ER 200 mg once daily or amantadine IR 100 mg twice daily) in Period-I, then crossed over to receive the other treatment in Period-II.

Methods: Study drug administration started on day 1. Study drug was not administered on Day 2. Multiple dosing commenced on day 3 and continued for 7 days (through day 9). A washout period of 8 days separated the dose administrations. The study drug was administered with 240 mL of drinking water. No other fluids were allowed within 1 hour of dosing. For each period, pharmacokinetic blood samples were collected at pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 24, 28, 36, and 48 hours after the first dose. The morning trough (pre-dose) blood samples were collected on Days 7 and 8. Blood samples were again collected immediately before the morning dose on Day 9 and at 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 24, 28, 48, 72, and 96 hours thereafter. Samples after 28 hours following the morning dose on day 9 were collected on an ambulatory basis in each period. Amantadine in plasma was quantified by a validated LC/MS/MS method. The pharmacokinetic parameters were calculated from the drug concentration-time profile by non-compartmental model using WinNonlin Professional Software-Version 5.0.1 (Pharsight Corporation, USA) for amantadine.

Statistical analyses were conducted to assess the pharmacokinetic profile of single dose and repeat dose amantadine HCl administered twice daily as a commercially available immediate release (IR) formulation compared to a once daily extended release (ER) formulation (Formulation B). An analysis of variance (ANOVA) was performed on the natural logarithms of C_{max}, C_{min}, and AUC_{24} determined from the data following the dose of study drug on study day 9 using linear mixed effects model. The model included the fixed effects for sequence, period, regimen and a random subject effect. The confidence intervals were used to perform the 2 one-sided tests procedure for equivalence assessment. The confidence intervals were obtained by exponentiating the endpoints of the confidence intervals for the difference of mean logarithms obtained within the framework of the ANOVA model. The upper and lower limits of confidence intervals from the natural-log transformed data were back-exponentiated to obtain the 90% confidence interval for the ratio of geometric means. Equivalence was established if the exponentiated 90% confidence interval fell entirely within the interval (80.00%, 125.00%).

Repeated measures ANOVA was carried out for comparison of C_{min} for day 7, 8 and 9 at 5% level of significance on both untransformed and ln-transformed data. Steady state was demonstrated if the repeated measures ANOVA test was found to be non-significant. The statistical analysis for amantadine was performed using PROC MIXED of SAS® Release 9.1.3 (SAS Institute Inc., USA).

Routine safety monitoring was conducted during and after dosing in all subjects, and at the end of the study.

Results: A total of 26 subjects participated in the study, 22 (84.6%) male and 4 (15.4%) female. The mean age was 26 years (range 19-42) and the mean BMI was 22.9 kg/m^2 (range 18.1-28.8). The racial makeup was 100% Asian. All subjects received at least one dose of study drug and were included in the safety analysis. Twenty-four (92.3%) subjects completed the study and were included in the pharmacokinetic analysis. Two subjects (7.7%) were withdrawn from the PK analysis prior to completion of the study due to vomiting within 12 hours of dosing, which was a pharmacokinetic exclusion criterion.

As expected from its half-life, once daily administration of amantadine ER and twice daily dosing of amantadine IR resulted in accumulation as measured by higher C_{max} and AUC on Day 9 compared to Day 1 (Table 9 and FIG. **2**). Steady state was achieved by Day 9 for both formulations as demonstrated by similar trough levels on Days 7, 8 and 9 (data not shown). At steady state (Day 9) plasma concentrations (FIG. **2**, Table 9) and pharmacokinetic parameters (Table 9) were comparable for both formulations. Furthermore, the formulations are equivalent in terms of the extent and the rate of absorption of amantadine as measured by steady state C_{max}, C_{min} and $AUC_{0\text{-}24}$ (Table 9), where equivalency is defined by the 90% CIs of the ratio of the least square means of the test versus reference for steady state C_{max}, C_{min} and $AUC_{0\text{-}24}$ of Amantadine ER to Amantadine IR falling within 80%-125%.

TABLE 9

Mean (±SD) Pharmacokinetic Parameters of Amantadine after Single and Multiple Dose Administration of IR (100 mg BID) and ER (200 mg QD) Formulations

	Formulation			
	IR (n = 24)		ER (n = 24)	
Parameter (Units)[a]	Day 1	Day 9	Day 1	Day 9
$t_{1/2}$ (h)	13.2 ± 2.8 [9.1-18.8]	12.6 ± 2.4 [9.4-18.1]	13.7 ± 3.6 [9.1-22.7]	12.8 ± 2.2 [9.2-17.4]
t_{max} (h)	14.42 ± 0.88 [13-16]	12.6 ± 4.5 [1-15]	11.4 ± 1.9 [8-18]	10.3 ± 2.0 [8-18]
C_{max} (ng/mL)	530 ± 80 [407.5-752.7]	728 ± 153 [538.4-1101.8]	431 ± 84 [313.5-559.9]	665 ± 179 [444.4-1140.0]
$AUC_{0\text{-}last}$ (ng h/mL)	11989 ± 2224 [9243-17106]	23040 ± 8273 [13133-46446]	11171 ± 2773 [7326-16970]	21362 ± 8946 [10821-47134]
$AUC_{0\text{-}\infty}$ (ng h/mL)	13685 ± 3324 [10167-20989]	NA	12900 ± 4087 [7817-22153]	NA
$AUC_{0\text{-}24}$ (ng h/mL)	7695 ± 1026 [5967-10171]	13752 ± 3586 [9085-22519]	7173 ± 1367 [5021-9552]	12680 ± 3879 [7896-23058]
C_{min} (ng/mL)	—	412.4 ± 142.6 [218.5-795.2]	—	374.9 ± 151.7 [172.2-767.1]

[a]All parameters are reported as the mean ± SD, [min to max range]
NA = not applicable

Certain additional PK parameters that are important in determining the suitability of the ER amantadine formulation for once daily, night time administration are also reported in Table 10.

TABLE 10

Additional Steady State PK parameters of Amantadine ER

	ER 200 mg QD	IR 100 mg BID
Cmax/Cmin	1.86	1.68
C-ave-8-16 hrs (ng/ml)	614	586
C-ave-8-12 hrs (ng/ml)	643	510
C-ave-16-24 hrs (ng/ml)	502	569
C-ave-0-8 hrs (ng/ml)	465	586
C-ave-8-16 hrs/C-ave-0-8 hrs	1.32	1.00
C-ave-8-12 hrs/C-ave-0-8 hrs	1.38	0.87
% Change in Plasma Concentration 0-3 hrs	5%	55%
% Change in Plasma Concentration 0-4 hrs	23%	48%
AUC 0-4 as % of AUC 24	12%	N/A
AUC 0-8 as % of AUC 24	30%	N/A
AUC 0-12 as % of AUC 24	51%	N/A

Conclusion: the ER amantadine formulation exhibits the desired steady state PK properties that would make the same suitable for administration at night and for achieving desired efficacy and tolerability benefits. Specifically, the ER amantadine formulation administered once daily at night results in relatively slow initial rise in amantadine plasma concentration, higher average amantadine plasma concentrations 8 to 12 hours after administration relative to 0-8 hours after administration and thus if administered at night higher ratios of average day time to night time amantadine plasma concentrations relative to IR amantadine. Thus this formulation is well suited for administration at higher doses than current practice that are expected to be relatively well tolerated and potentially provide superior efficacy in the treatment of LID, fatigue and Parkinson's disease.

EXAMPLE 8

Study comparing administration of amantadine HCl ER capsules once nightly with twice-daily administration of amantadine HCl IR tablets in normal healthy volunteers

Objective: The primary objective is to compare the effects on sleep of amantadine extended release (ER) capsules (Formulation B) administered once daily at bedtime with amantadine immediate release (IR) tablets administered twice daily in normal healthy volunteers. This ER formulation exhibits a Cave,day/Cave, night=1.30.

Study Design: This is a single-center, double-blind, triple-dummy, randomized, cross-over study to compare the effects on sleep of amantadine ER capsules, QHS, amantadine IR tablets BID, and caffeine caplets (active comparator) in 30 normal healthy volunteers as assessed by overnight polysomnography (PSG) and standardized questionnaires (Stanford Sleepiness Scale (SSS); Modified Epworth Sleepiness Scale (m-ESS)/Karolinska Sleepiness Scale (KSS); Toronto Hospital Alertness Test (THAT)/ZOGIM Alertness Scale (ZOGIM-A); Visual analog scale of sleepiness/alertness (VAS)).

Study drugs are administered in 3 dosing periods. A single day's dosage of one drug is administered per dosing period. Each day of dosing is separated by a washout period of 1 week. A single day's dosage of amantadine ER (Formulation B) consists of one 220 mg capsule (or 2×110 mg capsule) administered at bed time (QHS; defined as 23:00 h for the purposes of this study). A single day's dosage of amantadine IR consists of one 100 mg capsule administered twice a day (BID; defined as 8:00 h and 16:00 h for the purposes of this study). A single day's dosage of caffeine consists of one 100 mg capsule administered three times a day (TID; defined as 8:00 h, 16:00 h, & 23:00 h for the purposes of this study).

All subjects are dosed three times a day, at 8:00 h, 16:00 h, & 23:00 h. At each hour of dosing, every subject receives either the active drug or the matching placebo for each of the 3 treatments. Whether the capsule, tablet, or caplet administered at a specific hour of dosing contains active study drug

or is a placebo dummy is determined according to the dosing sequence and period to which the subject is assigned.

Consented subjects who meet eligibility criteria are randomized equally to one of 3 treatment sequences (groups), each comprising 3 single-day treatment periods separated by 1 week washout periods as described above. Additionally, there is a one-day, single-blind, placebo run-in prior to each double-blind dosing day. This is to allow subjects to acclimate to sleeping in the Clinical Research Unit (CRU) under conditions of PSG recording and to establish individual baseline (BL) PSG characteristics.

For each dosing period, subjects are admitted to a CRU equipped with a sleep laboratory the day before the first day of dosing with active study drug. They stay in the CRU overnight and through the entirety of the active drug-dosing day. They again stay overnight and then are discharged from the CRU the morning of the following day. For the first dosing period, the day of admission to the CRU (Day −1) constitutes the last day of the screening phase, and the day of discharge from the CRU constitutes the first day of the first washout period (Day 2). For the second dosing period, the day of re-admission to the CRU (Day 7) constitutes the last day of the first washout period, and the day of discharge (Day 9) will constitute the first day of the second washout period. For the third dosing period, the day of re-admission to the CRU (Day 14) constitutes the last day of the second washout period, and the day of discharge (Day 16) constitutes the first day of the follow-up phase.

On the day of admission (or re-admission) to the CRU, subjects undergo routine laboratory and vital sign testing. They are administered one each of the placebo dummies (for amantadine ER, amantadine IR, & caffeine) at 16:00h and at 23:00 h in single-blind fashion. They are questioned for adverse events (AEs) and have vital signs checked immediately prior to each dosing. Blood is drawn for routine laboratory testing and toxicology screen prior to the 16:00 h dosing. Subjects spend the night in the sleep lab under conditions of PSG recording.

On the day of dosing with active study drug, subjects are awakened at 7:00 h and fill out a battery of sleep and alertness questionnaires They receive study drug (active or placebo) at 8:00 h, 16:00, and 23:00 h. They are questioned for AEs and have vital signs checked immediately prior to each dosing. Blood is drawn to measure plasma amantadine concentrations prior to the 23:00 h dosing.

On the day after dosing with active study drug, subjects are awakened at 7:00 h and fill out a battery of sleep and alertness questionnaires Shortly before 8:00 h, i.e., 9 hours after the last dosing time, they are questioned for AEs and have vital signs checked. Also, blood is drawn to measure plasma amantadine concentrations. Instructions for contacting the site to report any AEs are reviewed with the subjects prior to their discharge from the CRU. The schedule for returning to the PSU for the next dosing period (this applies to returning for Periods 2 & 3) or for telephone contact (this applies to the follow-up after the third dosing period) is be reviewed.

All subjects receive a follow-up telephone call 3 days following discharge from the CRU (Day 19).

AEs and concomitant medications are monitored throughout the study. Blood samples for measurement of blood plasma concentrations are drawn immediately prior to the 23:00 h dosing time on Days 1, 8, and 15, and at approximately 8:00 h on Days 2, 9, and 16.

Sleep parameters and measurements of sleepiness and alertness at each time point are listed by subject. Both composite scores and scores from the individual components of the PSG and questionnaires are tabulated and analyzed. For each parameter measured, descriptive summary statistics are calculated by sequence and treatment, including means (or medians, as appropriate), ranges, and standard deviations (SDs).

Inferential statistics are performed on selected results wherein the magnitude of the differences between the means across treatment groups relative to the variance suggests a possible differential treatment effect. Continuous variable data is analyzed by parametric statistics (repeated measures analysis of variance with appropriate supplemental post-hoc analyses and/or paired t-test). Categorical data and data not conforming to a normal distribution is analyzed by non-parametric statistics (Wilcoxon signed rank test). PSG data may also be assessed by multivariate analyses and/or spectral analyses.

Results: A lack of increase in, or reduction of, sleep disturbances with QD administration of 220 mg of amantadine ER compared to BID administration of amantadine IR, as measured by PSG and a standardized sleep questionnaire (e.g. SSS, m-ESS, KSS, THAT, ZOGIM-A, or VAS), demonstrates the suitability of amantadine ER for once daily administration at bedtime.

EXAMPLE 9

Study comparing the effects on sleep and efficacy of amantadine HCl ER capsules administered once daily at night relative to amantadine HCl IR capsules administered twice daily in parkinson's patients.

Objective: To compare the effects on sleep and efficacy of amantadine extended release (ER) capsules.

Study Design: This is a Multi-Center, Double-Blind, Randomized Study to Compare the Effects on Sleep and Efficacy of Amantadine Extended Release (ER) Capsules in 120 Parkinsons Patients as assessed by UPDRS (Unified Parkinson's Disease Rating Scale), UPDRS-IV (Unified Parkinson's Disease Rating Scale Part IV), AIMS (Abnormal Involuntary Movement Scale), overnight polysomnography (PSG) and standardized questionnaires (Stanford Sleepiness Scale (SSS); Modified Epworth Sleepiness Scale (m-ESS)/Karolinska Sleepiness Scale (KSS); Toronto Hospital Alertness Test (THAT)/ZOGIM Alertness Scale (ZOGIM-A); Visual analog scale of sleepiness/alertness (VAS)).

All study drugs are administered orally. Treatment A consists of a placebo capsule administered in the morning and two 110 mg capsules of Amantadine (ER) and a placebo capsule administered at bed time. Treatment B consists of a placebo capsule administered in the morning and three 110 mg capsules of Amantadine (ER) administered at bed time. Treatment C consists of a 100 mg capsule of Amantadine IR administered in the morning and a 100 mg capsule of Amantadine IR and two placebo capsules administered at bed time. Treatment D consists of a placebo capsule administered in the morning and 3 placebo capsules administered at bed time.

Consented subjects who meet eligibility criteria are randomized equally to one of 3 treatment groups, each comprising 14-day treatment periods. Additionally, there is a one-day, single-blind, placebo run-in prior to each double-blind dosing day. This is to allow subjects to acclimate to sleeping in the Clinical Research Unit (CRU) under conditions of PSG recording and to establish individual baseline (BL) PSG characteristics.

For each dosing period, subjects are admitted to a CRU equipped with a sleep laboratory the day before the first day of dosing with active study drug. They stay in the CRU overnight and through the entirety of the active drug-dosing day. They again stay overnight and then are discharged from the CRU the morning of the following day.

Parkinson's scores are recorded in the mornings on days 1, 7 and 14 using standard scoring methods, including the UPDRS and AIM.

AEs and concomitant medications are monitored throughout the study.

Sleep parameters and measurements of sleepiness and alertness at each time point are listed by subject. Both composite scores and scores from the individual components of the PSG and questionnaires are tabulated and analyzed. For each parameter measured, descriptive summary statistics are calculated by sequence and treatment, including means (or medians, as appropriate), ranges, and standard deviations (SDs).

Inferential statistics are performed on selected results wherein the magnitude of the differences between the means across treatment groups relative to the variance suggests a possible differential treatment effect. Continuous variable data is analyzed by parametric statistics (repeated measures analysis of variance with appropriate supplemental post-hoc analyses and/or paired t-test). Categorical data and data not conforming to a normal distribution is analyzed by non-parametric statistics (Wilcoxon signed rank test). PSG data may also be assessed by multivariate analyses and/or spectral analyses.

Results: An improvement in UPDRS, UPDRS-IV, AIM, lack of increase in, or reduction of, sleep disturbances, as measured by PSG and a standardized sleep questionnaire (e.g. SSS, m-ESS, KSS, THAT, ZOGIM-A, or VAS), demonstrates the suitability of amantadine ER for once daily administration at bedtime.

EXAMPLE 10

Simulated pharmacokinetic characteristics of higher strength, amantadine ER formulations administered at nighttime

Objective: The objective is to use the data generated in the clinical study described in Example 7 to predict steady state plasma concentration-time profiles of various IR and ER amantadine regimens at different dose levels to show the benefits of higher strength amantadine ER formulations administered at nighttime.

Methodology: Plasma concentration-time profiles from healthy volunteers that received multiple doses of the ER and IR formulations of amantadine per study procedures described in Example 7 (ADS-5101-MD-104) were used to develop a pharmacokinetic model describing each of the two formulations. This study was an open-label, randomized, two-treatment, two-period, two-way crossover study comparing once-daily amantadine ER capsules and twice-daily amantadine IR tablets in 26 healthy, adult male and female volunteers. Complete data from 24 individuals were used in this exercise. Blood samples for pharmacokinetic evaluation were collected after single dosing on Day 1 and at steady state on Day 9. In the first step of the analysis, WinNonlin 5.2.1 (Pharsight Corp., Mountain View, Calif.) was used to fit a one-compartment model with first-order input and first-order output, weighted 1/y (where y is the amantadine plasma concentration), to each individual's plasma concentration-time data obtained after single (Day 1) and repeated (Day 9) dose administration of amantadine IR and ER; the fitting was done separately for both formulations, but simultaneously for both days. Modeling assumptions employed include dose proportionality and constant clearance as a function of time.

The model is described by the following equation:

$$C = \frac{FD}{V(k_a - k)}[\exp(-k(t - t_{lag})) - \exp(-k_a(t - t_{lag}))] \quad \text{Equation 1}$$

where C is the plasma concentration, F is the absolute bioavailability, D is dose, V is the volume of distribution, k_a is the absorption rate constant, k is the elimination rate constant, t is time, and t_{lag} is the lag time of absorption. The goodness of fit was verified by comparing the individual model predicted and observed concentration-time data from Study ADS-5101-MD-104. After Equation 1 was fitted to each individual's plasma concentration-time data, model parameter estimates of V/F, k_a, k, and t_{lag} were obtained for each of the 24 subjects. The goodness of the prediction at steady state was confirmed by comparing the observed data and predicted steady-state concentrations of amantadine obtained after daily dosing of 200 mg as the ER and IR formulations (Day 9).

In the second step of the analysis, individual model parameter estimates were used to simulate steady-state concentration-time profiles for each individual for both formulations by reinserting the individual parameter estimates into Equation 1, and summing the contribution of 7 sequential days of dosing, according to the following dosing regimens:

1. Once Daily (QD) dosing of 260, 340, and 420 mg of the ER formulation to steady state
2. Three times daily (TID) dosing of 100 mg of the IR formulation to steady state
3. Twice daily (BID) dosing of 100 mg of the IR formulation to steady state

Results: FIG. **4** shows the simulated steady state plasma concentration time profiles for various ER amantadine doses along with various regimes of IR amantadine. Table 11 summarizes values of the pharmacokinetic parameters that affect the efficacy and tolerability of ER amantadine when administered at night.

TABLE 11

PK parameters associated with nighttime administration - morning peak benefit measured for ER Amantadine formulation

	IR 100 mg BID	IR 100 mg TID	ER 260 mg QD	ER 340 mg QD	ER 420 mg QD
Cmax (ng/ml)	669	936	834	1091	1348
Cmin (ng/ml)	435	731	461	603	745
Cmax/Cmin	1.54	1.28	1.81	1.81	1.81

TABLE 11-continued

PK parameters associated with nighttime administration - morning peak benefit measured for ER Amantadine formulation

	IR 100 mg BID	IR 100 mg TID	ER 260 mg QD	ER 340 mg QD	ER 420 mg QD
C-ave-day (6 am-4 pm) (ng/ml)	571	845	766	1002	1238
C-ave-morn (6 am-10 am) (ng/ml)	479	870	824	1078	1332
C-ave-even (4 pm-10 pm) (ng/ml)	522	852	591	773	955
C-ave-night (10 pm-6 am) (ng/ml)	596	843	616	805	995
C-ave-day/C-ave-night	0.96	1.00	1.24	1.24	1.24
C-ave-morn/C-ave-night	0.80	1.03	1.34	1.34	1.34
C-ave-day relative to 100 mg BID IR	1.00	1.48	1.34	1.76	2.17

As shown in Table 11 and in the figures, the ER amantadine formulations administered once daily at night result in higher ratios of average day time to night time amantadine plasma concentrations relative to IR amantadine and are predicted to be relatively well tolerated. The ER formulations also result in average day time amantadine plasma concentrations that are 1.3 to 2.2 fold that of IR amantadine administered at 100 mg twice daily and is predicted to result in significantly enhanced efficacy when administered to patients in the clinical study described in Example 11 below.

EXAMPLE 11

A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Amantadine Extended Release Oral Capsules for the Treatment of Levodopa-induced Dyskinesia in Parkinson's Disease

Study Objectives: This study is designed to confirm dose range of Amantadine Extended Release (ER) oral capsules dosed once daily at nighttime for the treatment of levodopa-induced dyskinesia (LID) in subjects with Parkinson's Disease (PD). In addition, the study is designed to demonstrate the safety and tolerability of Amantadine ER oral capsules dosed once daily for the treatment of LID in subjects with PD. Finally, to confirm the steady-state pharmacokinetics of the Amantadine ER dosing regimens in Parkinsons patients and to correlate C-ave-day, Cave-morning, C-ave-morning/C-ave-night and C-ave-day/C-ave-night with the efficacy and tolerability of amantadine.

Study design: This will be a multi-center, randomized, double-blind, placebo-controlled, 4-arm parallel group study of Amantadine ER in subjects with PD and LID/Consenting subjects who meet eligibility criteria will be randomized 1:1:1:1 to receive one of the following 4 treatments, each administered as once daily, dosed at night, for 8 weeks:

Treatment A: Placebo,

Treatment B: 260 mg Amantadine ER (ADS-5102),

Treatment C: 340 mg Amantadine ER (ADS-5102)

Treatment D: 420 mg Amantadine ER (ADS-5102)

Subjects who are randomized to Treatment C or D (higher dose amantadine groups) will receive, in double-blind fashion, 260 mg Amantadine ER once daily during week 1, with an increase to either 340 mg or 420 mg once daily at the beginning of week 2. Dosing will continue through week 8.

Following completion of the baseline visit and randomization, subjects will return to the clinic after 1, 2, 4, 6, and 8 weeks of dosing, with a follow-up visit 14 days following the last dose of study drug. Study visits and assessments will be scheduled during morning hours when possible (9 am through 1 pm). A set of two 24-hour diaries will be completed during 48 hours prior to randomization and 48 hours prior to selected study visits. The diary will be used to score five different conditions in 30-minute intervals: Sleep, OFF, ON without dyskinesias, ON with nontroublesome dyskinesias, ON with troublesome dyskinesias.

Blood samples will be collected at selected study visits for determination of amantadine plasma concentrations, and evaluation of steady-state population pharmacokinetics. Subject participation during the study will be up to 12 weeks and will include a 2-week (maximum) screening period, 8-week (maximum) treatment period, and a 2-week follow-up period. Subjects who are unable to tolerate their assigned study drug assignment will permanently discontinue study drug and continue to be followed for safety through 2 weeks following the last dose of study drug.

Patient Eligibility Criteria: Subjects are eligible to take part in the study if they meet the inclusion and do not meet the exclusion criteria. Selected key criteria are as follows:

Inclusion Criteria:

- Male or female adults, residing in the community (i.e. not residing in an institution)
- Between 30 and 75 years of age, inclusive
- Ambulatory or ambulatory-aided (e.g. walker or cane) ability, such that the subject can come to required study visits
- Knowledgeable and reliable caregiver/study partner, if appropriate, to accompany the subject to study visits
- Signed a current IRB/IEC-approved informed consent form
- Following training, the subject is willing and able to understand and complete the 24-hour home diary (caregiver assistance allowed)
- Idiopathic Parkinson's Disease, complicated by dyskinesia (a MDS-UPDRS score will be determined during screening, but a minimum score is not required)
- On a stable regimen of antiparkinson's medications, including levodopa, for at least 30 days prior to screening, and willing to continue that regimen during study participation
- Presence of dyskinesia, defined as a minimum UDysRS score

Exclusion Criteria:

- Presence of other neurological disease that may affect cognition, including, but not limited to Alzheimer's dementia, Huntington's disease, Lewy body dementia, frontotemporal dementia, corticobasal degeneration, or motor or sensory dysfunction secondary to stroke or brain trauma.
- Presence of cognitive impairment, as evidenced by a Mini-mental State Examination (MMSE) score of less than 24 during screening.
- Presence of an acute major psychiatric disorder (e.g., Major Depressive Disorder) according to DSM-IV-TR or symptom (e.g., hallucinations, agitation, paranoia) that could affect the subject's ability to complete study assessments

Presence of sensory impairments (e.g., hearing, vision) that would impair the subject's ability to complete study assessments

History of alcohol or drug dependence or abuse, according to DSM-IV criteria, within 2 years prior to screening

History of seizures (excluding febrile seizures of childhood)

History of stroke or TIA within 2 years prior to screening

History of myocardial infarction, NYHA Congestive Heart Failure Class 3 or 4, or atrial fibrillation within 2 years prior to screening

History of cancer within 5 years prior to screening, with the following exceptions: adequately treated non-melanomatous skin cancers, localized bladder cancer, non-metastatic prostate cancer or in situ cervical cancer (these exceptions must be discussed with and approved by the Medical Monitor before study entry)

Any of the following lab abnormalities; Hemoglobin<10 g/dL, WBC<3.0×10^9/L, Neutrophils<1.5×10^9/L, Lymphocytes<0.5×10^9/L, Platelets<100×10^9/L, Hemoglobin AlC>9%, or Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT)>2 times the upper limit of normal

Estimated GFR<50 mL/min/1.73m^2 by Modification of Diet in Renal Disease (MDRD) or Cockcroft-Gault equation

Any clinically significant ECG abnormalities

Inability to swallow oral capsules, or a history of gastrointestinal malabsorption that would preclude the use of oral medication

Study Endpoints: The primary efficacy endpoint will be the change from baseline to week 8 in the Unified Dyskinesia Rating Scale (UDysRS) score. Key secondary endpoints will include:

ON time without troublesome dyskinesia (ON without dyskinesia plus ON with non-troublesome dyskinesia), based on a standardized PD home diary

Unified Parkinson's Disease Rating Scale (MDS-UPDRS), overall score

Fatigue as measured by the Fatigue Severity Scale (FSS). This scale includes 9 questions that are completed by the patient using a rating scale from 1 (strongly disagree) to 7 (strongly agree). This fatigue scale is recommended by MDS for both screening and severity rating (2010)

Safety, including adverse events, safety-related study drug discontinuations, vital signs, and laboratory tests.

The following mixture of traditional and new scales have been selected for this phase 2 study:

Unified Dyskinesia Rating Scale (UDysRS) will be used for primary outcome measure. This scale has four parts, and a total possible score of 104:

I: Historical Disability (patient perceptions) of On-Dyskinesia impact

II: Historical Disability (patient perceptions) of Off-Dystonia impact

III: Objective Impairment (dyskinesia severity, anatomic distribution, and type, based on 4 observed activities)

IV: Objective Disability based on Part III activities

ON time without troublesome dyskinesia, based on a standardized Parkinson's Disease home diary (suggest Test Diary II), [33] will be a secondary outcome measure. This scale has been used in number of studies with mixed success [34]. However, most KOLs feel that subject-reported dairy data must be collected, and needs to support the primary outcome measure.

Unified Parkinson's Disease Rating Scale (UPDRS), part IV, items 32 (duration of dyskinesias: 0=none, 4=76-100% of the waking day) and 33 (disability of dyskinesias: 0=not disabling, 4=completely disabling) will be a secondary outcome measure. This scale is a traditional scale used in PD for many years and these items have been utilized in most LID studies.

Cognitive Scales: Global caregiver impression, depression and other scales will be employed to measure the mental status benefits of ER amantadine.

Statistical Methods

Efficacy Analyses: The efficacy analysis population will include all randomized and dosed subjects who provide at least one post-baseline efficacy assessment. For the efficacy endpoint of UDysRS score, the change from baseline to week 8 will be analyzed using an analysis of covariance (ANCOVA) model with treatment group as a factor and the UDysRS baseline value as a covariate. The primary analysis will compare the 260 mg ADS-5102 group to the placebo group using a two-sided test at the 5% level of significance. If the primary comparison is statistically significant ($p<0.05$), then the 340 mg and 420 mg ADS-5102 groups will be compared to placebo, also using a two-sided test at the 5% level of significance.

The secondary endpoints will be analyzed using the same types of ANCOVA models as described for the primary endpoint. All secondary comparisons between treatment groups will be performed using two-sided tests at the 5% level of significance. A last observation carried forward (LOCF) approach will be utilized for missing data. The primary efficacy analysis will be repeated for the per-protocol population, a subset of the efficacy analysis population who provide week 8 efficacy assessments.

Safety Analyses: The safety analysis population will include all randomized subjects who receive at least one dose of study drug. All safety endpoints will be analyzed from the time of first dose through the completion of follow-up (or 2 weeks following the last dose of study drug). A safety analysis will also be done on the safety reported during the first 2 weeks of study drug treatment, in order to assess tolerability of initial dosing with ADS-5102 amantadine ER.

Results: following improvements are expected from this study are shown in the table below. Additional endpoints are described that

Significant (20-60%) reduction in dyskinesia score measured by acceptable primary endpoint (e.g., UDysRS)

Increase in ON time without troubling dyskinesia by 20-60%

Improvement in UPDRS from 5% to 20%.

Improvement in Parkinson's fatigue (FSS) from 5% to 60%.

Improvement in mood by PGI from 5% to 20%.

Instruments for Dyskinesia	% Clinical Effect (Placebo-Active/Placebo)	Range of Scores
Unified Dyskinesia Rating Scale (UDysRS)	5-60%	0-104 (4 parts, 26 items total, each 0, normal-4, severe)
Unified Parkinson's Disease Rating Scale (UPDRS, MDS revision)	5-20%	

-continued

Instruments for Dyskinesia	% Clinical Effect (Placebo-Active/ Placebo)	Range of Scores
Part IV	5-60%	0-24 (6 items, each 0, normal-4, severe)
Part IV, dyskinesia items only	5-60%	0-8 (2 dyskinesia items, 4.1 and 4.2, each 0, normal-4, severe)
Parkinson's Disease Home Diary (Hauser et al)	5-40%	0-100% (on time without dyskinesia or with nontroublesome dyskinesia)

EXAMPLE 12

Simulated pharmacokinetic characteristics of amantadine ER formulations with a delayed release coat suitable for night time administration

Objective: The objective is to evaluate the pharmacokinetic profile of two alternative ER formulations of amantadine suitable for nighttime administration—Formulation 1, which is the formulation tested in Example 7, and Formulation 2, which is the formulation tested in Example 7, but with a delayed release over coat on top of the extended release coat.

Plasma concentration-time profiles from healthy volunteers, who received multiple doses of the ER and IR formulations of amantadine per study procedures described in Example 7 (ADS-5101-MD-104), were used to develop a pharmacokinetic model describing each of the two formulations. This study was an open-label, randomized, two-treatment, two-period, two-way crossover study comparing once-daily amantadine ER capsules and twice-daily amantadine IR tablets in 26 healthy, adult male and female volunteers. Complete data from 24 individuals were used in this exercise. Blood samples for pharmacokinetic evaluation were collected after single dosing on Day 1 and at steady state on Day 9. In the first step of the analysis, WinNonlin 5.2.1 (Pharsight Corp., Mountain View, Calif.) was used to fit a one-compartment model with first-order input and first-order output, weighted 1/y (where y is the amantadine plasma concentration), to each individual's plasma concentration-time data obtained after single (Day 1) and repeated (Day 9) dose administration of amantadine IR and ER; the fitting was done separately for both formulations, but simultaneously for both days. Modeling assumptions employed include dose proportionality and constant clearance as a function of time.

The model is described by the following equation

$$C = \frac{FD}{V(k_a - k)}[\exp(-k(t - t_{lag})) - \exp(-k_a(t - t_{lag}))] \quad \text{Equation 1}$$

where C is the plasma concentration, F is the absolute bioavailability, D is dose, V is the volume of distribution, k_a is the absorption rate constant, k is the elimination rate constant, t is time, and t_{lag} is the lag time of absorption. The goodness of fit was verified by comparing the individual model predicted and observed concentration-time data from Study ADS-5101-MD-104. After Equation 1 was fitted to each individual's plasma concentration-time data, model parameter estimates of V/F, k_a, k, and t_{lag} were obtained for each of the 24 subjects. The goodness of the prediction at steady state was confirmed by comparing the observed data and predicted steady-state concentrations of amantadine obtained after daily dosing of 200 mg as the ER and IR formulations (Day 9).

In the second step of the analysis, individual model parameter estimates were used to simulate steady-state concentration-time profiles for each individual for both formulations by reinserting the individual parameter estimates into Equation 1, and summing the contribution of 7 sequential days of dosing, according to the following dosing regimens:

1. Once Daily (QD) dosing of 200 mg of the ER Formulation 1 to steady state
2. Once Daily (QD) dosing of 200 mg of the ER Formulation 2 to steady state

Results: FIG. **7** shows the simulated steady state plasma concentration time profiles for the two ER amantadine formulations. (Amantadine blood plasma concentrations are shown on the y, time of day on the x-axis.) As shown in FIG. **7**, the ER amantadine formulation 2 administered once daily at night results in about a 4 hour delay in achieving peak plasma concentration at steady state relative to formulation 1. Thus, a formulation comprising a delayed release coat on top of the extended release coat has a very favorable pharmacokinetic profile in that it maximizes the daytime plasma exposure to amantadine whilst minimizing night plasma exposure at steady state.

While preferred embodiments of the present invention have been shown and described herein, such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention.

It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. All references cited herein are incorporated herein by reference in their entirety.

What is claimed is:

1. A method of treating levodopa-induced dyskinesia (LID) in a human patient with Parkinson's disease, comprising orally administering to said human patient with Parkinson's disease and levodopa-induced dyskinesia, once daily 0 to 4 hours before bedtime, a pharmaceutical composition comprising 220 mg to 455 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, in an extended release dosage form,

wherein said extended release dosage form comprises one or more capsules each containing one or more pellets wherein each of said one or more pellets comprises: a) a pellet core comprising said drug; and b) surrounding the pellet core, an extended release coating layer comprising an extended release coating polymer, a pore former, and a plasticizer,

wherein said drug is present at a weight percent of from 40% to 80% based on the combined weight of said pellet core and said extended release coating layer,

wherein said extended release coating layer is present at a weight percent from 10% to 30% based on the combined weight of said pellet core and said extended release coating layer,

wherein said one or more capsules have an in vitro dissolution profile of said drug of not more than 10% at 1 hour, not more than 25% at 2 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml of water at 37° C. as the dissolution medium, and

wherein the extended release dosage form has a Tmax for amantadine of 8 hours to 18 hours when the Tmax of the extended release form is determined in a fasted single dose human pharmacokinetic study.

2. A method of administering amantadine, or a pharmaceutically acceptable salt thereof, to a patient in need thereof, comprising orally administering to said patient in need thereof, once daily 0 to 4 hours before bedtime, a pharmaceutical composition comprising 220 mg to 455 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, in an extended release dosage form,

wherein said extended release dosage form comprises one or more capsules each containing one or more pellets, wherein each of said one or more pellets comprises: a) a pellet core comprising said drug; and b) surrounding the pellet core, an extended release coating layer comprising an extended release coating polymer, a pore former, and a plasticizer,

wherein said drug is present at a weight percent of from 40% to 80% based on the combined weight of said pellet core and said extended release coating layer,

wherein said extended release coating layer is present at a weight percent from 10% to 30% based on the combined weight of said pellet core and said extended release coating layer,

wherein the one or more capsules have an in vitro dissolution profile of said drug of not more than 10% at 1 hour, not more than 25% at 2 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles at 50 rpm with 500 ml of water at 37° C. as the dissolution medium, and

wherein the extended release dosage form has a Tmax for amantadine of 8 hours to 18 hours when the Tmax of the extended release form is determined in a fasted single dose human pharmacokinetic study.

3. A method of reducing sleep disturbances in a subject taking amantadine, comprising orally administering to said subject taking amantadine a pharmaceutical composition once daily 0 to 4 hours before bedtime, the pharmaceutical composition comprising 220 mg to 455 mg of a drug selected from the group consisting of amantadine and pharmaceutically acceptable salts thereof, in an extended release dosage form,

wherein said extended release dosage form comprises one or more capsules each containing one or more pellets wherein each of said one or more pellets comprises: a) a pellet core comprising said drug; and b) surrounding the pellet core, an extended release coating layer comprising an extended release coating polymer, a pore former, and a plasticizer,

wherein said drug is present at a weight percent of from 40% to 80% based on the combined weight of said pellet core and said extended release coating layer,

wherein said extended release coating layer is present at a weight percent from 10% to 30% based on the combined weight of said pellet core and said extended release coating layer,

wherein the one or more capsules have an in vitro dissolution profile of said drug of not more than 10% at 1 hour, not more than 25% at 2 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml of water at 37° C. as the dissolution medium, and

wherein the extended release dosage form has a Tmax for amantadine of 8 hours to 18 hours when the Tmax of the extended release form is determined in a fasted single dose human pharmacokinetic study.

4. The method of claim **1**, wherein the one or more capsules have an in vitro dissolution profile of said drug of 25% to 55% at 6 hours.

5. The method of claim **1**, wherein said extended release coating polymer comprises ethyl cellulose.

6. The method of claim **5**, wherein said ethyl cellulose is present in an amount of 5 to 20% based on the combined weight of said pellet core and said extended release coating layer.

7. The method of claim **1**, wherein the pharmaceutical composition comprises 260 mg to 420 mg of amantadine or a pharmaceutically acceptable salt thereof.

8. The method of claim **1**, wherein the method reduces the severity or frequency of dyskinesia.

9. The method of claim **1**, wherein said Tmax for amantadine is 12 hours to 18 hours.

10. The method of claim **1**, wherein said pellet core further comprises a seed core and a binder.

11. The method of claim **10**, wherein said seed core is a cellulose sphere.

12. The method of claim **10**, wherein said binder comprises hydroxypropyl methylcellulose.

13. The method of claim **1**, wherein said extended release dosage form comprises one, two,. or three capsules.

14. The method of claim **2**, wherein the one or more capsules have an in vitro dissolution profile of said drug of 25% to 55% at 6 hours.

15. The method of claim **2**, wherein said extended release coating polymer comprises ethyl cellulose.

16. The method of claim **15**, wherein said ethyl cellulose is present in an amount of 5 to 20% based on the combined weight of said pellet core and said extended release coating layer.

17. The method of claim **2**, wherein the pharmaceutical composition comprises 260 mg to 420 mg of amantadine or a pharmaceutically acceptable salt thereof.

18. The method of claim **2**, wherein the said Tmax for amantadine is 12 hours to 18 hours.

19. The method of claim **2**, wherein said pellet core further comprises a seed core and a binder.

20. The method of claim **19**, wherein said seed core is a cellulose sphere.

21. The method of claim **20**, wherein said binder comprises hydroxypropyl methylcellulose.

22. The method of claim **2**, wherein the extended release dosage form comprises one, two, or three capsules.

23. The method of claim **3**, wherein the one or more capsules have an in vitro dissolution profile of said drug of 25% to 55% at 6 hours.

24. The method of claim **3**, wherein said extended release coating polymer comprises ethyl cellulose.

25. The method of claim **24**, wherein said ethyl cellulose is present in an amount of 5 to 20% based on the combined weight of said pellet core and said extended release coating layer.

26. The method of claim **3**, wherein the pharmaceutical composition comprises 260 mg to 420 mg of amantadine or a pharmaceutically acceptable salt thereof.

27. The method of claim **3**, wherein said Tmax for amantadine is 12 hours to 18 hours.

28. The method of claim **3**, wherein said pellet core further comprises a seed core and a binder.

29. The method of claim **28**, wherein said seed core is a cellulose sphere.

30. The method of claim **28**, wherein said binder comprises hydroxypropyl methylcellulose.

31. The method of claim **3**, wherein said extended release dosage form comprises one, two, or three capsules.

32. The method of claim **1**, wherein said extended release dosage form is selected from the group consisting of one capsule comprising 340 mg of said drug and two capsules each comprising 170 mg of said drug.

33. The method of claim **32**, wherein said drug is a pharmaceutically acceptable salt of amantadine.

34. The method of claim **32**, wherein said drug is amantadine hydrochloride.

35. The method of claim **2**, wherein said extended release dosage form is selected from the group consisting of one capsule comprising 340 mg of said drug and two capsules each comprising 170 mg of said drug.

36. The method of claim **35**, wherein said drug is a pharmaceutically acceptable salt of amantadine.

37. The method of claim **35**, wherein said drug is amantadine hydrochloride.

38. The method of claim **3**, wherein said extended release dosage form is selected from the group consisting of one capsule comprising 340 mg of said drug and two capsules each comprising 170 mg of said drug.

39. The method of claim **38**, wherein said drug is a pharmaceutically acceptable salt of amantadine.

40. The method of claim **38**, wherein said drug is amantadine hydrochloride.

41. The method of claim **1**, wherein said drug is present at a weight percent of from 40% to 65% based on the combined weight of said pellet core and said extended release coating layer.

42. The method of claim **2**, wherein said drug is present at a weight percent of from 40% to 65% based on the combined weight of said pellet core and said extended release coating layer.

43. The method of claim **3**, wherein said drug is present at a weight percent of from 40% to 65% based on the combined weight of said pellet core and said extended release coating layer.

* * * * *

EXHIBIT M

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(12) **United States Patent**
Went et al.

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(45) **Date of Patent: *Jan. 30, 2018**

(54) **METHOD OF ADMINISTERING AMANTADINE PRIOR TO A SLEEP PERIOD**

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Methods of nighttime administration of amantadine to reduce sleep disturbances in patient undergoing treatment with amantadine are described, as well as compositions of extended release amantadine that are suitable for nighttime administration.

31 Claims, 7 Drawing Sheets

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FIG. 1

Dissolution Profiles of Amantadine ER Formulations

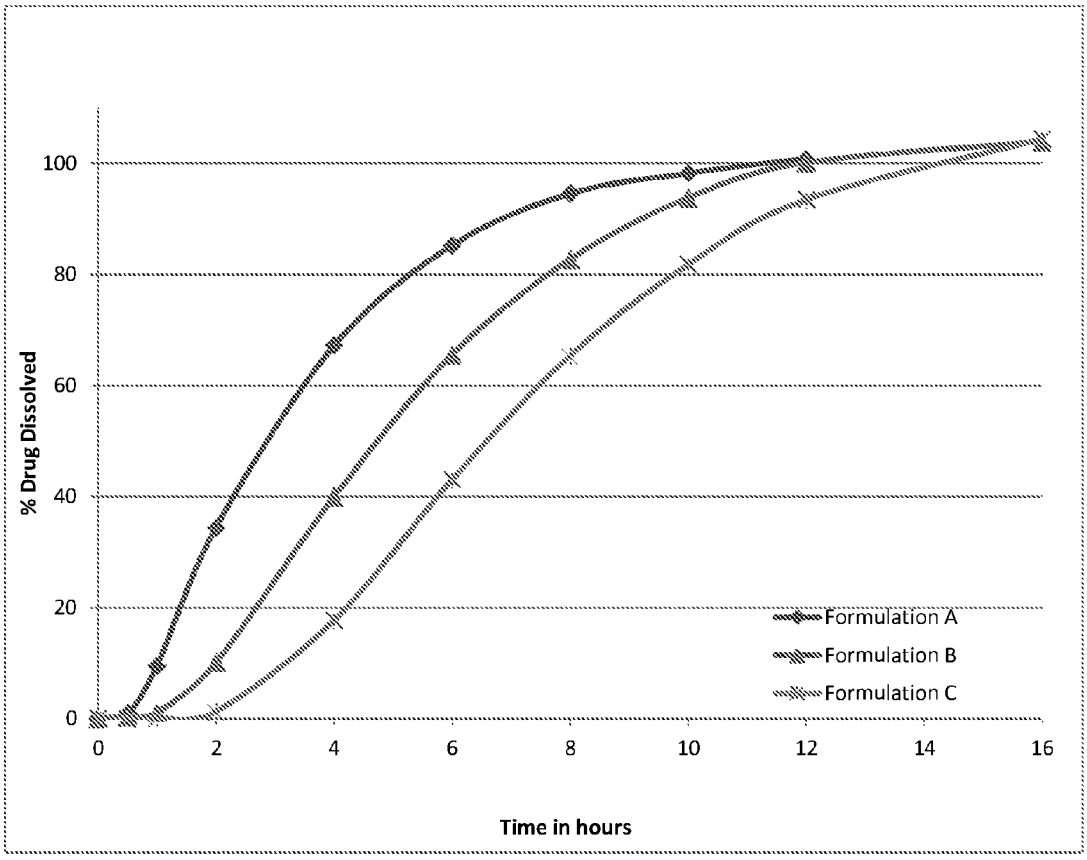


FIG. 2A

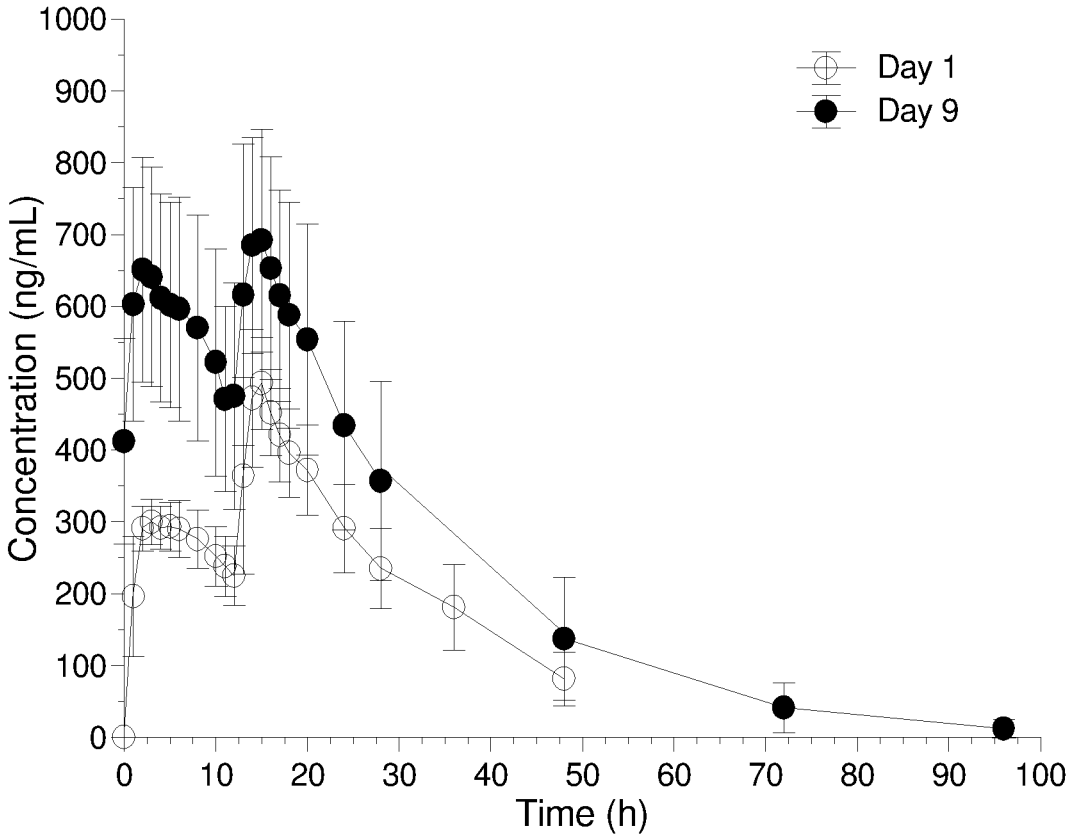

Day 1
Day 9
Concentration (ng/mL)
Time (h)
0
100
200
300
400
500
600
700
800
900
1000
0
10
20
30
40
50
60
70
80
90
100

FIG. 2B

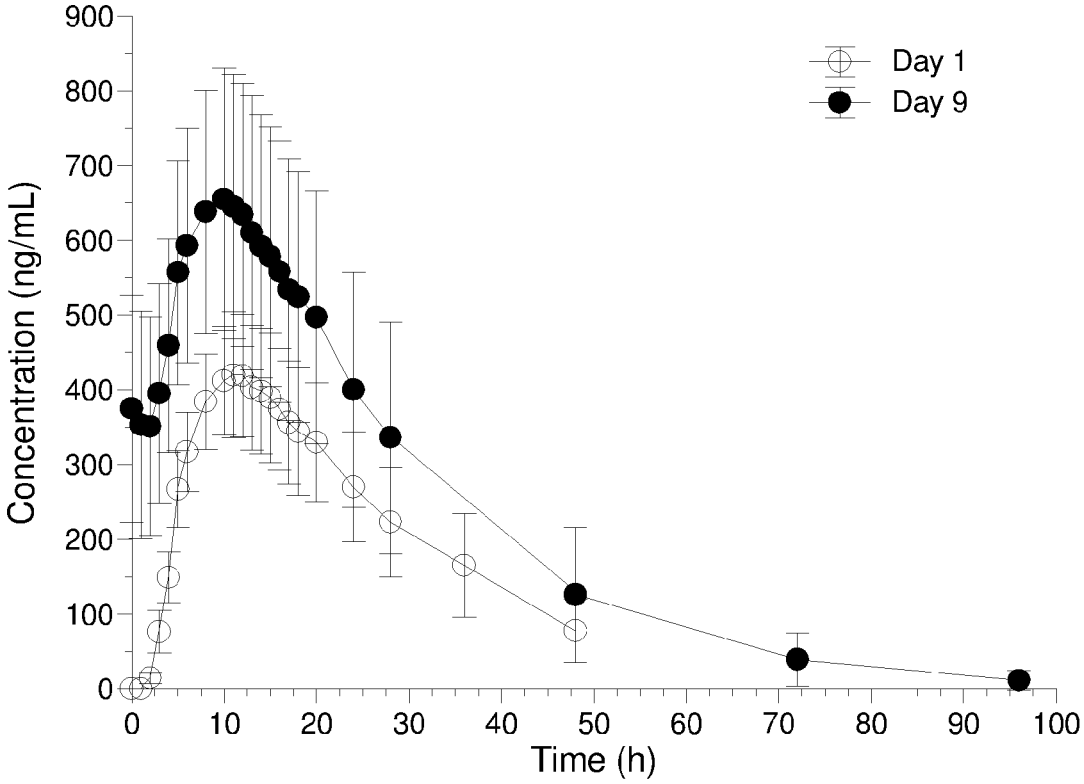

Day 1
Day 9
Concentration (ng/mL)
Time (h)
0
100
200
300
400
500
600
700
800
900
0
10
20
30
40
50
60
70
80
90
100

FIG. 3

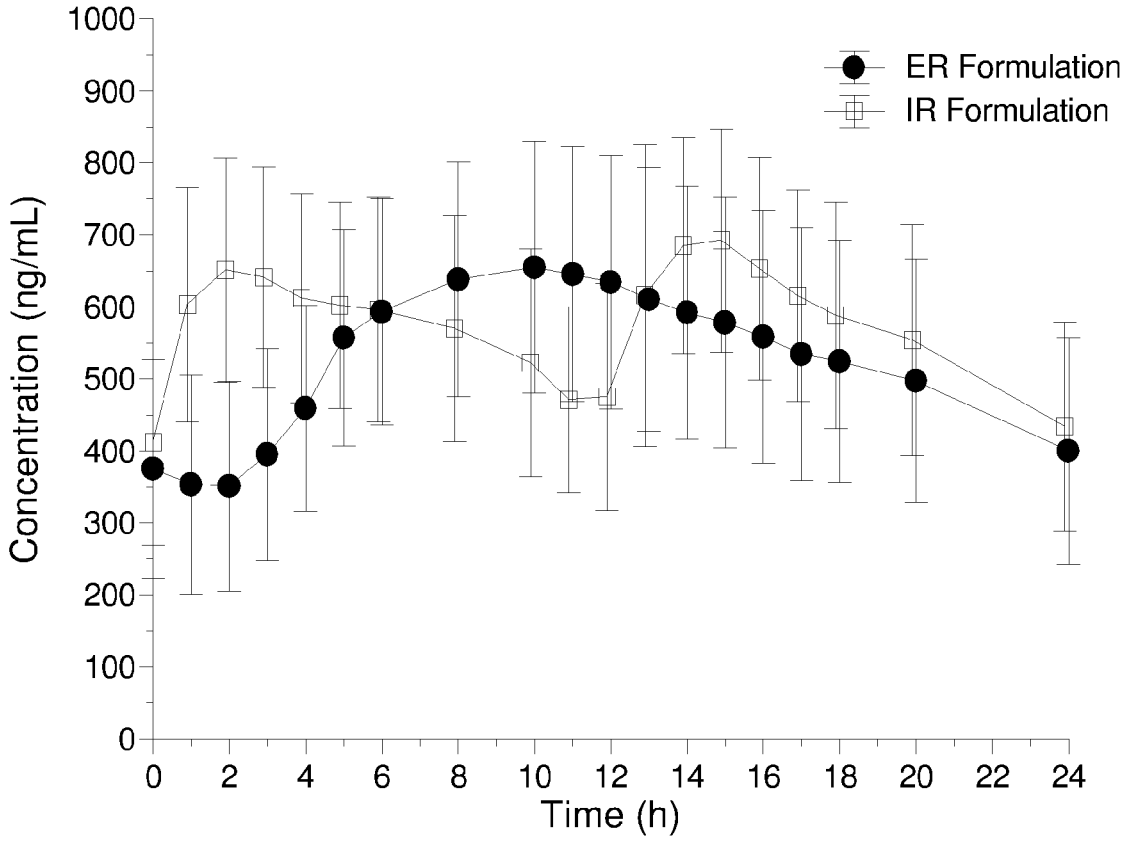
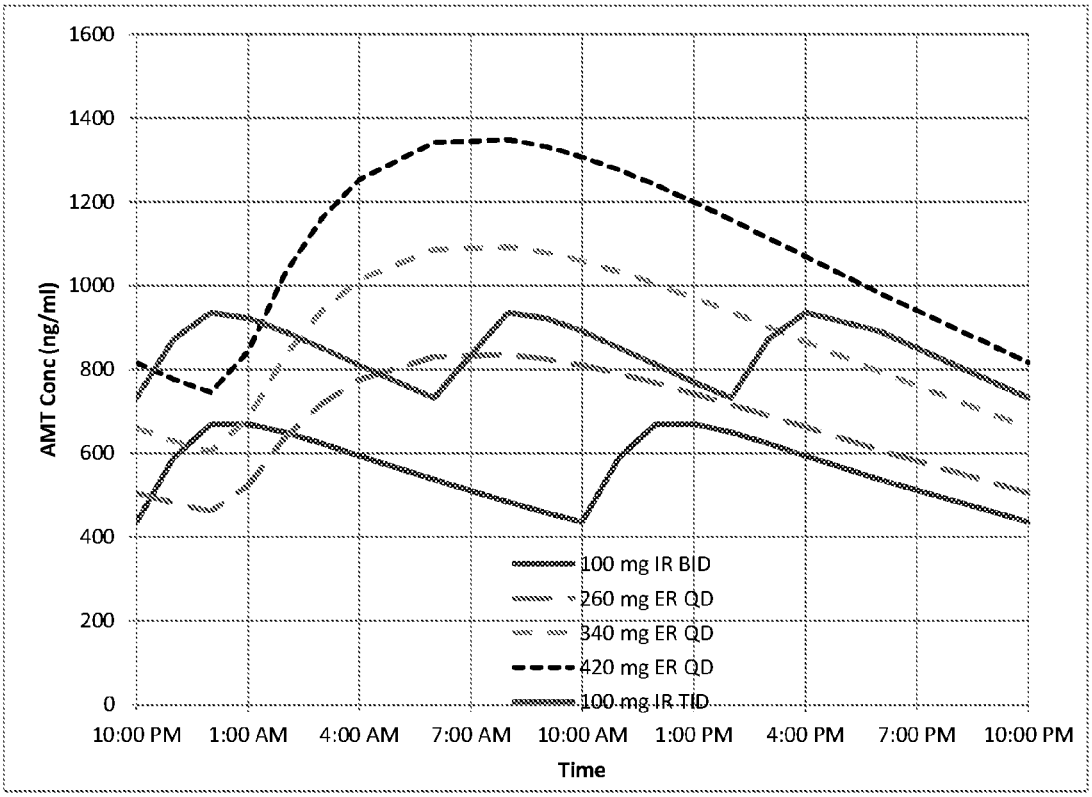

ER Formulation
IR Formulation
Concentration (ng/mL)
Time (h)
0
100
200
300
400
500
600
700
800
900
1000
0
2
4
6
8
10
12
14
16
18
20
22
24

Fig 4.



Simulation based on results of Adamas steady state PK study ADS-PD-104.

FIG. 5

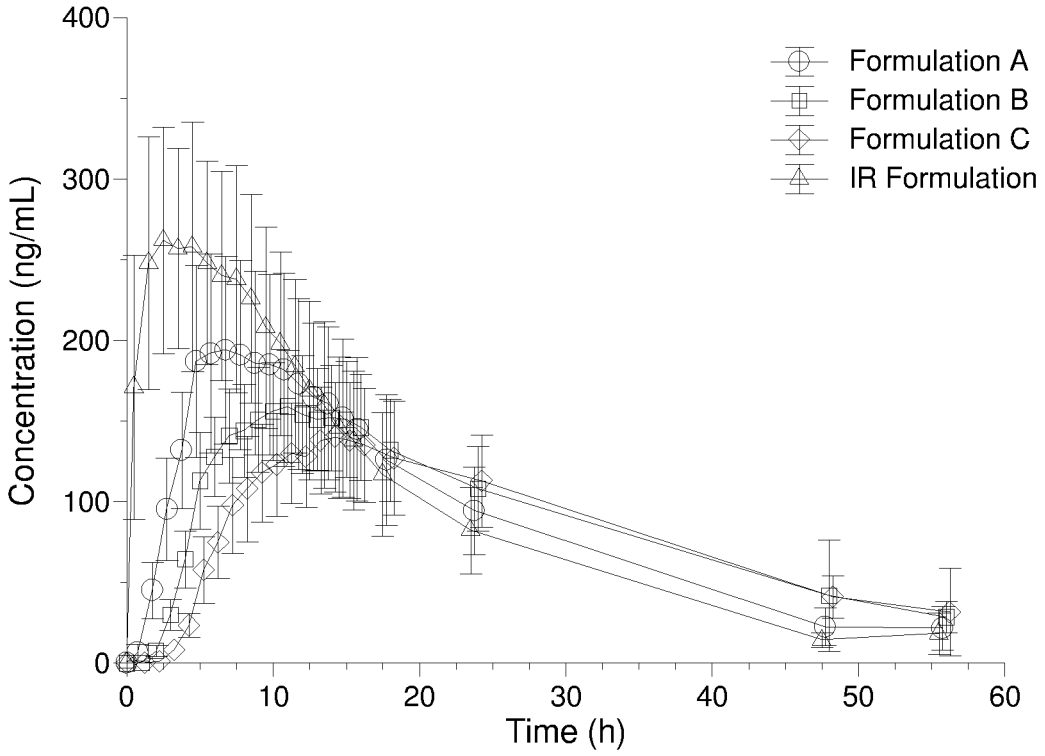

Formulation A
Formulation B
Formulation C
IR Formulation
Concentration (ng/mL)
Time (h)
0
100
200
300
400
0
10
20
30
40
50
60

FIG. 6

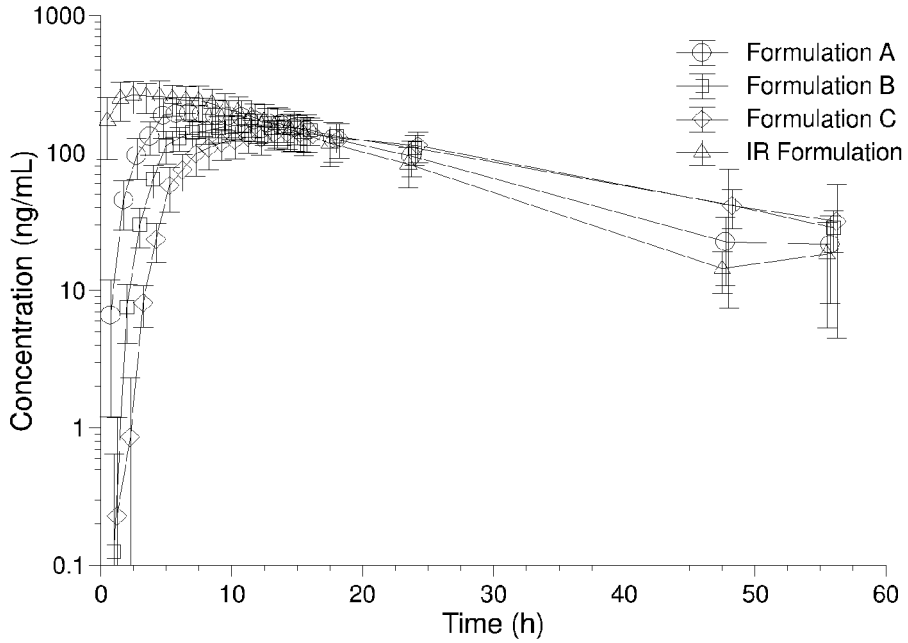
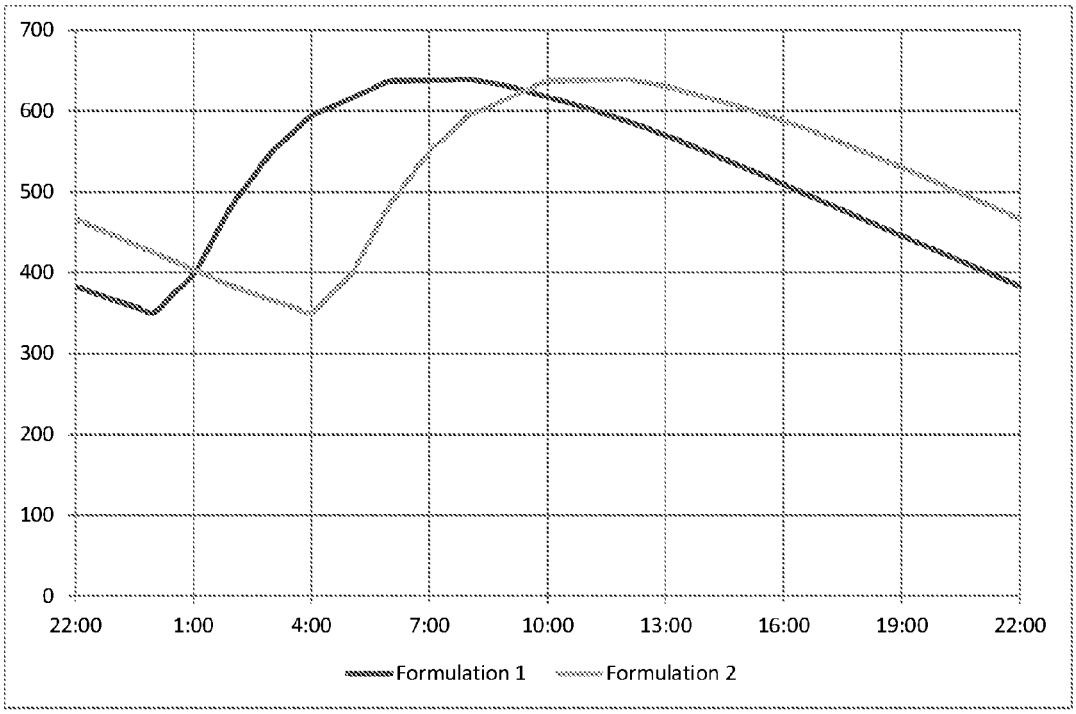

1000
100
10
1
0.1
Concentration (ng/mL)
0
10
20
30
40
50
60
Time (h)
Formulation A
Formulation B
Formulation C
IR Formulation

FIG 7.


700
600
500
400
300
200
100
0
22:00
1:00
4:00
7:00
10:00
13:00
16:00
19:00
22:00
Formulation 1
Formulation 2

METHOD OF ADMINISTERING AMANTADINE PRIOR TO A SLEEP PERIOD

CROSS-REFERENCE

This application is a continuation of U.S. patent application Ser. No. 14/863,035, filed Sep. 23, 2015, which is a continuation of U.S. patent application Ser. No. 14/523,535, filed Oct. 24, 2014, now abandoned, which is a continuation of U.S. patent application Ser. No. 14/267,597, filed May 1, 2014, now abandoned, which is a continuation of U.S. patent application Ser. No. 12/959,321, filed Dec. 2, 2010, now U.S. Pat. No. 8,741,343, which claims benefit of U.S. Provisional Application No. 61/266,053, filed Dec. 2, 2009, all of which applications are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

The field of the invention is extended release compositions of amantadine and uses thereof.

Amantadine is indicated for various conditions that can be treated by NMDA receptor antagonists including the treatment of idiopathic Parkinson's disease (Parlysis Agitans), postencephalitic Parkinsonism, and symptomatic Parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication. Amantadine also has activity as a viral M2 channel inhibitor and is used for the prophylaxis and treatment of infection of viral diseases, especially influenza A virus.

Currently marketed forms of amantadine are immediate release formulations that are typically administered two or more times a day. Amantadine's use is limited by dose related CNS side effects including dizziness, confusion, hallucinations, insomnia and nightmares (Gracies J M, Olanow C W; Current and Experimental Therapeutics of Parkinson's Disease; *Neuropsychopharmacology: the Fifth Generation of Progress*, p. 1802; American College of Neuropsychopharmacology 2002), which can be particularly exacerbated when amantadine is administered at night.

It is known that immediate release amantadine can act as a stimulant, causing insomnia and sleep disturbance. Therefore, the last dose is typically administered no later than 4 pm in order to minimize these side effects. Such dosing of amantadine results in peak plasma amantadine concentrations occurring in the evening or night, and very low plasma concentrations in the morning.

Extended release forms of amantadine have been described in the art. U.S. Pat. No. 5,358,721, to Guittard et al., and U.S. Pat. No. 6,217,905, to Edgren et al., each disclose an oral osmotic dosage form comprising an antiviral or anti-Parkinson's drug, respectively, where in each case amantadine is listed as a possible drug to be utilized in the dosage form. U.S. Pat. No. 6,194,000, to Smith et al., discloses analgesic immediate and controlled release pharmaceutical compositions utilizing NMDA receptor antagonists, such as amantadine, as the active agent. U.S. Patent Appl. Publication Nos. US 2006/0252788, US 2006/0189694, US 2006/0142398, and US 2008/0227743, all to Went et al., each disclose the administration of an NMDA receptor antagonist, such as amantadine, optionally in controlled release form.

SUMMARY OF THE INVENTION

The inventors have identified a need in the art for improved formulations of amantadine that result in a patient having higher plasma concentrations of amantadine upon waking in the morning without adversely affecting sleep. Further, the inventors have identified a need in the art for a method of administering amantadine in the late afternoon or evening, e.g. after 4 pm, which reduces side effects of insomnia and sleep disturbance and provides effective plasma concentrations of amantadine upon waking.

Therefore, there exists a need in the art for improved methods of amantadine therapy which can be administered to a patient shortly before they wish to sleep (e.g., at bedtime) without causing insomnia or sleep disturbance. In addition, there is a need for an amantadine therapy which can be taken by the patient before they go to sleep and then provides a suitable plasma concentration of amantadine when they wake up, e.g. in the morning, after a full night's sleep.

In addition, many Parkinson's disease patients have difficulty swallowing and are on multiple medications. Hence there is a need for amantadine therapy that delivers a therapeutically effective dose of the drug, can be administered once daily and is in an oral dosage form that is small in size and does not unduly increase the pill burden.

One aspect of the invention is a method of administering amantadine to a patient in need thereof, said method comprising orally administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below. Alternatively, the composition is administered less than about 4 hours before bedtime.

In a second aspect, the invention provides a method of reducing sleep disturbance in a human subject undergoing treatment with amantadine, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below. Alternatively, the composition is administered less than about 4 hours before bedtime.

In a third aspect, the invention provides a method of treating levodopa induced dyskinesia, or fatigue, or dementia, or any other symptom of Parkinson's disease, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below.

In a fourth aspect, the invention provides a method of treating brain injury, brain trauma, dementia, Alzheimer's disease, stroke, Huntington's disease, ALS, Multiple Sclerosis, neurodegenerative diseases, dementias, cerebrovascular conditions, movement disorders, cranial nerve disorders, neuropsychiatric disorders, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). This aspect also includes the use of such compositions and the use of amantadine for the manufacture of a medicament as described below.

In one embodiment of any of the above aspects, administration occurs less than two and a half, less than two, less than one and a half, less than one or less than half hour before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).

In one embodiment of any of the above aspects the patient has been diagnosed with Parkinson's disease.

In one embodiment of any of the above aspects, the composition is administered once daily. In another aspect, the daily dose exceeds 200 mg, and is given in 1, 2 or 3 capsules of size 0, 1 or 2.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in levodopa induced dyskinesia (LID). In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% reduction in levodopa induced dyskinesia. In further embodiments, the reduction in levodopa induced dyskinesia is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce LID. In further specific embodiments, the scale used in measuring the reduction in LID could be UDysRS, UPDRS Part IV (subscores 32, 33), Dyskinesia Rating Scale (DRS), Abnormal Involuntary Movement Scale (AIMS), or other scales developed for this purpose.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease fatigue. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60% reduction in Parkinson's disease fatigue. In further specific embodiments, the reduction in fatigue is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce fatigue. In further specific embodiments, the scale used in measuring the reduction in fatigue could be the Fatigue Severity Scale (FSS).

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease symptoms. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's symptoms. In further specific embodiments, the reduction in Parkinson's symptoms is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce Parkinson's symptoms. In further specific embodiments, the scale used in measuring the reduction in Parkinson's symptoms could be the Unified Parkinson's Disease Rating Scale (UPDRS).

In one embodiment of any of the above aspects, the composition is added to food, and in a more specific embodiment to a small amount of soft food (e.g. applesauce or chocolate pudding), prior to administration. Addition to food may involve a capsule being opened and the contents sprinkled over the patient's food. This is advantageous if the patient is unable or unwilling to swallow the composition.

In one embodiment of any of the above aspects, there is no increase in plasma concentration of amantadine for at least one hour after the administration at steady state plasma concentrations.

In one embodiment of any of the above aspects, there is no increase in the plasma concentration of amantadine for at least two hours after the administration at steady state plasma concentrations.

In one embodiment of any of the above aspects, the administration of the composition to a human subject at steady state amantadine plasma concentrations increases the amantadine plasma concentration by less than 5%, 10%, 15%, 20% or 25% at 1, 2, 2.5 or 3 hours following such administration. For example, administration of the composition to a human subject at steady state amantadine plasma concentrations increases the amantadine plasma concentration by less than 5% at 1, 2, 2.5 or 3 hours following such administration; or by less than 10% at 1, 2, 2.5 or 3 hours following such administration; or by less than 15% at 1, 2, 2.5 or 3 hours following such administration; or by less than 20% at 1, 2, 2.5 or 3 hours following such administration; or by less than 25% at 1, 2, 2.5 or 3 hours following such administration.

In one embodiment of any of the above aspects the amantadine has a single dose Tmax of 9 to 15 hours. In a more specific embodiment, the amantadine has a single dose Tmax of 10 to 14 hours after administration. In another more specific embodiment, the amantadine has a single dose Tmax of 11 to 13 hours after administration.

In one embodiment of any of the above aspects the amantadine has a steady state Tmax of 7 to 13 hours. In a more specific embodiment, the amantadine has a steady state Tmax of 8 to 12 hours after administration. In another more specific embodiment, the amantadine has a steady state Tmax of 9 to 11 hours after administration.

In one embodiment of any of the above aspects peak plasma concentration of amantadine is achieved between 6 and 16 hours after administration of a single dose of the composition. In a more specific embodiment, peak amantadine plasma concentration is achieved 8 to 14 hours after administration of a single dose of the composition. In another more specific embodiment, peak amantadine plasma concentration is achieved 10 to 12 hours after administration of a single dose of the composition. In additional specific embodiments, peak amantadine plasma concentration is achieved between 6, 7, 8, 9, 10, 11 or 12 hours to about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 hours after administration of a single dose of the composition.

In one embodiment of any of the above aspects, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In a more specific embodiment, the steady state plasma concentration profile is characterized by a concentration increase of amantadine of less than 25% at four hours after the administration.

In one embodiment of any of the above aspects, the composition is administered once a day and the ratio of Cmax to Cmin at steady state is 1.5 to 2.0, or, more specifically, 1.7 to 1.9, or, more specifically, about 1.8.

In one embodiment of any of the above aspects, the steady state plasma concentration profile following multiple administrations to a human subject of the composition at bedtime is characterized by an average plasma concentration during the day ("C-ave-day", defined as the average day time amantadine plasma concentration as measured in a human PK study) that is 1.1 to 2.0 times the average plasma concentration during the night ("C-ave-night", defined as the average night time amantadine plasma concentration as measured in a human PK study). In more specific embodiments the C-ave-day is the average amantadine plasma concentration as measured between the hours of 5 am, 6 am, 7 am, 8 am or 9 am to the hours of 4 pm, 5 pm, 6 pm, 7 pm

or 8 pm; for example, between the hours of 6 am and 4 pm, between the hours of 7 am and 6 pm, or between the hours of 7 am and 5 pm. The C-ave-night is the average amantadine plasma concentration as measured between the hours of 4 pm, 5 pm, 6 pm, 7 pm, 8 pm, 9 pm, 10 pm or 11 pm to the hours of 5 am, 6 am, 7 am, 8 am or 9 am; for example, between the hours of 10 pm and 6 am, between the hours of 7 pm and 6 am, or between the hours of 8 pm and 6 am.

In one embodiment of any of the above aspects, the steady state plasma concentration profile following multiple administrations to a human subject of the composition at bedtime is characterized by an average plasma concentration during the morning ("C-ave-morning", defined as the average amantadine plasma concentration as measured in a human PK study during the morning hours) that is 1.1 to 2.0 times the average plasma concentration during the night. In one embodiment the C-ave-morning is the average amantadine plasma concentration as measured between the hours of 5 am, 6 am, 7 am, 8 am or 9 am to the hours of 11 am, 11:30 am, 12 pm, 12:30 pm or 1:00 pm; for example, between the hours of 5 am and 11 am, or between the hours of 7 am and 12 pm. More preferably, the ratio of C-ave-morning/C-ave-night at steady state is 1.2 to 1.6.

In one embodiment of any of the above aspects, the steady state plasma concentration profile following daily administration of the composition is characterized by an average plasma concentration during the period 8 hours to 12 hours after administration ("C-ave-8-12 hrs") that is 1.1 to 2.0 times the average plasma concentration during the first 8 hours after administration ("C-ave-0-8 hrs"). More preferably, the ratio of C-ave-8-12 hrs/C-ave-0-8 hrs at steady state is 1.2 to 1.6.

In one embodiment of any of the above aspects, administration of a single dose of the composition to a human subject provides a plasma concentration profile characterized by: a fractional AUC from 0 to 4 hours that is less than 5%, and preferably less than 3% of AUC_{0-inf}; a fractional AUC from 0 to 8 hours that is about 5 to 15%, and preferably about 8 to 12% of AUC_{0-inf}; a fractional AUC from 0 to 12 hours that is about 10 to 40%, and preferably about 15 to 30% of AUC_{0-inf}; a fractional AUC from 0 to 18 hours that is about 25 to 60%, and preferably about 30 to 50% of AUC_{0-inf}; and a fractional AUC from 0 to 24 hours that is about 40 to 75%, and preferably about 50 to 70% of AUC_{0-inf}.

In one embodiment of any of the above aspects, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25%, and preferably about 5 to 20% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50%, and preferably about 20 to 40% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70%, and preferably about 40 to 60% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95%, and preferably about 75 to 90% of AUC_{24}.

In one embodiment of any of the above aspects, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by: a fractional AUC from 0 to 8 hours that is about 15 to 40%, and preferably about 20 to 32% of AUC_{24}; a fractional AUC from 8 to 16 hours that is about 30 to 50%, and preferably about 35 to 45% of AUC_{24}; and a fractional AUC from 16 to 24 hours that is about 20 to 35%, and preferably about 25 to 33% of AUC_{24}.

In one embodiment of any of the above aspects the amantadine is administered as a pharmaceutically acceptable salt. In a more specific embodiment, the amantadine is administered as hydrochloride or amantadine sulfate.

In one embodiment of any of the above aspects, a total daily dose of 50 mg to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof is administered to a patient. More specifically the daily dose of amantadine or pharmaceutically acceptable salt thereof administered may be in the range of 100 to 440 mg. In another specific embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof maybe in the range of 260 to 420 mg. In another embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof administered exceeds 300 mg per day. In various specific embodiments, the daily dose of amantadine or pharmaceutically acceptable salt thereof may be 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg.

In one embodiment of any of the above aspects, the composition comprises 50 mg to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. More specifically, the composition may comprise 100 mg to 450 mg of amantadine, or a pharmaceutically acceptable salt thereof. Still more specifically, the composition may comprise 130-210 mg of amantadine, or a pharmaceutically acceptable salt thereof. In various specific embodiments, a dosage form containing the composition comprises 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg of amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition comprises about 110, 120, 130, 140, 150, 160 170, 180, 190, 210, or 220 mg amantadine, or a pharmaceutically acceptable salt thereof. In another more specific embodiment, the composition comprises 110 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 130 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 170 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 210 mg amantadine hydrochloride.

In one embodiment of any of the above aspects, the composition is administered as one, two, three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof.

In one embodiment of any of the above aspects, the composition is administered as one, two, or three unit dosage forms each comprising 50 to 250 mg amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition is administered as one or two unit dosage forms each comprising 65 to 220 mg amantadine, or a pharmaceutically acceptable salt thereof.

In one embodiment of any of the above aspects, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma

concentration (Cmax) of 1.0 to 2.8 ng/ml per mg of amantadine. In a more specific embodiment, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine and an $AUC_{0\text{-}inf}$ (Area under the concentration-curve curve from t=0 to t=infinity) of 40 to 75 ng*h/mL per mg of amantadine.

In one embodiment of any of the above aspects, the daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by at least one of: (i) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine, (ii) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (iii) an $AUC_{0\text{-}24}$ of 44 to 83 ng*h/mL per mg of amantadine. In a more specific example, all three criteria of (i), (ii) and (iii) are met.

In a more specific embodiment, the steady state plasma concentration profile is further characterized by: (iv) no increase in concentration of amantadine for at least one hour after the administration; and (v) Cmax/Cmin ratio of 1.5 to 2.0. In a more specific embodiment, both criteria of (iv) and (v) are met.

In another more specific embodiment, the steady state plasma concentration profile is further characterized by at least one of: (iv) no increase in plasma concentration of amantadine for at least two hours after the administration; and (v) a Cmax/Cmin ratio of 1.7 to 1.9. In a more specific embodiment, both criteria of (iv) and (v) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more 55-85% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more than 25-55% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 20% dissolution at 1 hour, (ii) about 25-45% dissolution at 2 hours, (iii) not more than 50-80% dissolution at 4 hours, and (iv) at least 80% dissolution at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii), (iii) and (iv) are met. In a more specific embodiment, all four of criteria (i), (ii), (iii) and (iv) are met.

In one embodiment of any of the above aspects the in vitro dissolution profile of amantadine is further characterized by release of amantadine of: (i) not more than 10% at 1 hour, or (ii) 30-50% at 4 hours, or (iii) at least 90% at 12 hours using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three criteria of (i), (ii) and (iii) are met.

In another aspect, the present invention provides a pharmaceutical composition comprising or consisting of a pellet-in-capsule, wherein a pellet comprises a core that comprises a core seed with a mixture of amantadine and a binder coated onto the core seed, and an extended release coating surrounding the core comprising ethyl cellulose, a pore forming agent such as hydroxypropyl methyl cellulose or povidone, and a plasticizer.

In another aspect, the present invention provides a pharmaceutical composition for use in the methods of the aspects described above, wherein said composition is for oral administration and comprises a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core.

In one embodiment, the extended release coating comprises ethyl cellulose and at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In a more specific embodiment, the extended release coating comprises ethyl cellulose, povidone, and a plasticizer.

In one embodiment, the pellet core comprises amantadine and a binder coated onto a core seed. In one embodiment, the core seed is a sugar sphere (nonpareil) or microcrystalline cellulose seed (e.g. Celphere®). In a more specific embodiment, the core seed is a microcrystalline cellulose core. In another specific embodiment, the core seed has a diameter in the range of 100 microns to 1,000 microns. In additional specific embodiments, the core seed has a diameter of 100, 200, 300, 400, 500, 600 or 700 microns. In preferred specific embodiments, the core seed has a diameter of less than 500 microns.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 20 to 80 wt %, with a bulk density of 0.3 to 1.2 g/cm^3.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 40 to 60 wt %, with a bulk density of 0.5 to 1.2 g/cm^3.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 60 to 80 wt %, with a bulk density of 0.5 to 1.2 g/cm^3.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the binder is present in amounts from 8 to 25 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the core seed is present in amounts from 8 to 25 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the ethyl cellulose is present in amounts from 10 to 20 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the povidone is present in amounts from 1 to 4 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, and the plasticizer is present in amounts from 1 to 4 wt %.

In one embodiment, the coated pellet has a diameter in the range of 200 microns to 1700 micros. In additional specific embodiments, the coated pellet has a diameter of 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300 or

1500 microns. In certain specific embodiments, the coated pellet has a diameter of less than 1000 microns, e.g., from 500 to 1000 microns.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the binder is present in amounts from 5 to 25 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the core seed is present in amounts from 1 to 15 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the ethyl cellulose is present in amounts from 5 to 20 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, the povidone is present in amounts from 0.25 to 4 wt %.

In one embodiment, based on the combined weight of the pellet core and extended release coating, and the plasticizer is present in amounts from 0.25 to 4 wt %.

In one embodiment, the pellet further comprises a seal coating between the pellet core and the extended release coating. In some embodiments, an inert coating can be applied to the inert core prior to drug coating or on drug-coated pellets or on controlled release coated pellets. In another embodiment, an enteric coating can be applied to the drug coated pellets or controlled release pellets.

In one embodiment, the pellet core comprises a binder, selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof.

In one embodiment, the above composition is provided in a size 3, size 2, size 1, size 0 or size 00 capsule.

In one embodiment, the therapeutically effective daily dose of the above composition is administered in no more than two capsules. In another embodiment, the therapeutically effective daily dose of the composition is administered in no more than three size 1 capsules. In another embodiment, the therapeutically effective daily dose of the composition is administered in no more than two size 0 capsules. In a still more preferred embodiment, the therapeutically effective daily dose of the composition is administered in no more than two size 1 capsules. In another embodiment, the therapeutically effective daily dose of the composition is administered in no more than three size 2 capsules.

In a preferred embodiment, the above composition is provided in an amount of 50 to 110 mg of amantadine or a pharmaceutically acceptable salt thereof in a size 2 capsule, and in the amount of 110 mg to 210 mg of amantadine or a pharmaceutically acceptable salt thereof in a size 1 capsule. In additional embodiments, the above composition comprises coated pellets of diameter 300 to 1000 microns, with amantadine or pharmaceutically acceptable salt thereof content of 40-80% wt % and at a bulk density of 0.5-1.2 g/cm^3. In a further preferred embodiment, the above composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more than 55-85% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, and castor oil. In a more specific embodiment, the plasticizer is medium chain triglycerides, e.g. Miglyol 812 N.

In another aspect, the present invention provides method of administering amantadine, or a pharmaceutically acceptable salt thereof, to a human subject in need thereof, said method comprising orally administering a composition of any of the above aspects.

In another aspect, the present invention provides a method of treating Parkinson's disease in a human subject in need thereof, said method comprising orally administering a composition of any of the above aspects. In a preferred aspect, the present invention provides a method of treating disease in a human subject in need thereof, said method comprising orally administering a composition of any of the above aspects once daily at nighttime, administering 1, 2 or 3 capsules.

References to administering amantadine to a subject in need thereof include treating a patient with a disease or condition which may be treated, prevented or cured by a NMDA antagonist. More specifically, administering amantadine to a subject in need thereof includes treating a patient with Parkinson's Disease, brain injury, brain trauma, dementia, Alzheimer's disease, stroke, Huntington's disease, ALS, Multiple Sclerosis, neurodegenerative diseases, dementias, cerebrovascular conditions, movement disorders, cranial nerve disorders, neuropsychiatric disorders.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the dissolution profiles for three amantadine ER formulations, A, B, C referred to in Example 3.

FIGS. **2**A and **2**B show the mean plasma concentration-time curves after administration of amantadine IR twice daily (A) and amantadine ER once daily (B) to healthy, adult, male and female subjects under fasting conditions on days 1 and 9.

FIG. **3** shows a plot of mean plasma concentration of amantadine versus time curves after administration of amantadine IR twice daily and amantadine ER once daily to healthy, adult, male and female subjects under fasting conditions on day 9.

FIG. **4** shows the simulated mean plasma concentration of amantadine versus time curves following multiple dose administration of various strengths of immediate release amantadine dosed twice or thrice daily and various strengths of amantadine ER administered once daily.

FIG. **5** shows a plot of mean (SD) plasma amantadine concentrations versus scheduled time for four (4) amantadine treatments.

FIG. **6** shows a semi-logarithmic mean (SD) plasma amantadine concentrations versus scheduled time for four (4) amantadine treatments.

FIG. **7** shows simulated steady state plasma concentration time profiles for the ER amantadine formulations as described in Example 12. The ER amantadine formulation 2, administered once daily at night, results at steady state in about 4 hour delay in achieving peak plasma concentration relative to formulation 1.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a method of reducing sleep disturbances in a patient undergoing treatment with amantadine. The method comprises administering amantadine to a patient in need thereof, such that the amantadine does not interfere with sleep, yet provides maximum benefit in morning hours when often needed most by many patients who take amantadine and further, provides nighttime coverage of

symptoms of Parkinson's disease if needed. Nighttime coverage includes providing benefit if the patient wakes up and wishes to return to sleep.

The method of the invention comprises orally administering to the patient an extended release (ER) amantadine composition designed for nighttime administration. The composition is taken less than three hours before bedtime, and preferably less than two and a half, less than two, less than one and a half, or less than one hour before bedtime. Most preferably the ER amantadine composition is taken less than half hour before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). As used herein, a reference to amantadine is intended to encompass pharmaceutically acceptable salts thereof (e.g. amantadine hydrochloride, amantadine sulfate, etc.). Alternatively, the composition is administered less than about 4 hours before bedtime.

As used herein, "extended release" includes "controlled release", "modified release", "sustained release", "timed release", "delayed release", and also mixtures of delayed release, immediate release, enteric coated, etc. with each of the above.

The patient may be diagnosed with any disease or disorder for which amantadine is prescribed, such as Parkinson's disease, multiple sclerosis, drug-induced extrapyramidal reactions, levodopa-induced dyskinesia, and viral diseases (e.g. influenza, HBV, and HCV). In a specific embodiment, the patient has Parkinson's disease, which, as used herein, also encompasses a diagnosis of parkinsonism. In one embodiment, the patient has early stage Parkinson's disease, and the amantadine is used as a monotherapy or in combination with a monoamine oxidase type B (MAO-B) inhibitor without concomitant use of levodopa. In another embodiment, the patient has late stage Parkinson's disease and the patient takes levodopa in addition to the amantadine. In another embodiment, the patient has multiple sclerosis and the amantadine is used for the treatment of fatigue. In other embodiments, the patient has a brain injury, brain injury, brain trauma, dementia, Alzheimer's disease, stroke, Huntington's disease, ALS, Multiple Sclerosis, neurodegenerative diseases, dementias, cerebrovascular conditions, movement disorders, cranial nerve disorders, neuropsychiatric disorders.

An ER amantadine composition for use in the invention is adapted for nighttime administration by providing a plasma concentration profile that does not interfere with the subject's sleep. The composition of the invention will, upon administration to a human subject, result in a gradual initial increase in plasma concentration of amantadine such that, at steady state conditions, administration of a dose of the composition results in an increase in plasma concentration of amantadine of less than 25% at three hours after the dose is administered. For example, if a subject's steady state plasma concentration of amantadine is 500 ng/ml at the time a dose of the composition is administered, three hours later the subject's plasma concentration of amantadine will be less than 625 ng/ml. Preferably, the increase in plasma concentration of amantadine is less than 15%, and most preferably, less than 10%. Particularly preferred compositions have a plasma concentration profile further characterized by no increase in amantadine plasma concentration, or even a decrease (at steady state conditions), for at least one or, in a preferred embodiment, two hours after the administration. The composition for use in the invention is further adapted for bedtime (i.e. the time at which the subject wishes to go to sleep for the night) administration by providing a maximum concentration of amantadine (Cmax) in the morning hours. The time to reach Cmax (Tmax), as measured after single dose administration in the fasted state, is at least, 8 hours and up to 13, 14, 15, or 16 hours, or at least 9 hours and up to 13, 14, 15, or 16 hours, or at least 10 hours, and up to 13, 14, 15, or 16 hours. In specific embodiments, the Tmax is 9 to 15 hours, preferably 10 to 14 hours, and most preferably 11 to 13 hours. At steady state, with once daily administration of the composition, the Tmax is 7 to 13 hours, preferably 8 to 12 hours, and most preferably 9 to 11 hours. A suitable ER amantadine composition may be further characterized by having a steady-state Cmax/Cmin ratio of 1.5 to 2.0, and preferably 1.7 to 1.9, resulting in a composition with optimal fluctuation.

In more specific, preferred embodiments, the plasma concentration profile is further characterized by having an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5%, and preferably less than 3% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 8 hours that is about 5 to 15%, and preferably about 8 to 12% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 12 hours that is about 10 to 40%, and preferably about 15 to 30% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 18 hours that is about 25 to 60%, and preferably about 30 to 50% of $AUC_{0\text{-}inf}$; and a fractional AUC from 0 to 24 hours that is about 40 to 75%, and preferably about 50 to 70% of $AUC_{0\text{-}inf}$.

In a further preferred embodiment, the plasma concentration profile is further characterized by having an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25%, and preferably about 5 to 20% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50%, and preferably about 20 to 40% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70%, and preferably about 40 to 60% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95%, and preferably about 75 to 90% of AUC_{24}.

In some embodiments of any of the above aspects, the steady state plasma concentration profile following multiple administrations to a human subject of the composition at bedtime is characterized by an average plasma concentration during the day ("C-ave-day", defined as the average day time amantadine plasma concentration as measured in a human PK study) that is 1.1 to 2.0 times the average plasma concentration during the night ("C-ave-night", defined as the average night time amantadine plasma concentration as measured in a human PK study). In some embodiments, the ratio of C-ave-day/C-ave-night at steady state is within one of the ranges 1.1 to 1.9, 1.1 to 1.8, 1.1 to 1.7, 1.1 to 1.6, 1.1 to 1.5, 1.1 to 1.4, 1.2 to 1.9, 1.2 to 1.7, 1.2 to 1.6, 1.2 to 1.5, 1.3 to 1.9, 1.3 to 1.8, 1.3 to 1.7, 1.3 to 1.6, 1.4 to 1.9, 1.4 to 1.8, 1.4 to 1.7, 1.5 to 1.9, 1.5 to 1.8, 1.5 to 1.7, 1.6 to 1.9, 1.6 to 1.8 or 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave-night at steady state is 1.1, 1.15, 1.2, 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, or 2.0. In some embodiments, the C-ave-day is the average amantadine plasma concentration as measured between the hours of 5 am, 6 am, 7 am, 8 am or 9 am to the hours of 4 pm, 5 pm, 6 pm, 7 pm or 8 pm and the C-ave-night is the average amantadine plasma concentration as measured between the hours of 4 pm, 5 pm, 6 pm, 7 pm, 8 pm, 9 pm, 10 pm or 11 pm to the hours of 5 am, 6 am, 7 am, 8 am or 9 am. In some embodiments, the C-ave-day is the average amantadine plasma concentration as measured within any four to twelve hour period between the hours of 5 am and 8 pm; and the C-ave-night is the average amantadine plasma concentration as measured within any four to twelve hour

period between the hours of 8 pm and 5 am. In some embodiments, the C-ave-day is the average amantadine plasma concentration as measured within any four, five, six, seven, eight, nine, ten, eleven or twelve hour period between the hours of 5 am and 8 pm; and the C-ave-night is the average amantadine plasma concentration as measured within any four, five, six, seven, eight, nine, ten, eleven or twelve hour period between the hours of 8 pm and 5 am.

In some embodiments described herein an amantadine composition is administered to a patient from 0 to 4 hours prior to bedtime. In some embodiments, the amantadine composition is administered to a patient from 0 to 3, 0 to 2 or 0 to 1 hours prior to bedtime. In some embodiments, the amantadine composition is administered to a patient from 0 to 240 minutes, from 0 to 180 minutes, e.g. from 0 to 120 minutes, from 0 to 60 minutes, from 0 to 45 minutes, from 0 to 30 minutes, from 0 to 15 minutes or from 0 to 10 minutes prior to bedtime. In some embodiments, the amantadine composition is administered to a patient from 60 to 240 minutes, from 60 to 180 minutes, from 60 to 120 minutes or from 60 to 90 minutes prior to bedtime.

It is to be understood that administration to a patient includes administration by a healthcare professional and self administration by the patient.

Unless otherwise specified herein, the term "bedtime" has the normal meaning of a time when a person retires for the primary sleep period during a twenty-four hour period of time. While for the general populace, bedtime occurs at night, there are patients, such as those who work nights, for whom bedtime occurs during the day. Thus, in some embodiments, bedtime may be anytime during the day or night.

As used herein, unless otherwise indicated, reference to a plasma concentration profile or a specific pharmacokinetic property (e.g. Cmax, Cmin, AUC, Tmax, etc.) in a human subject refers to a mean value obtained from healthy adults s determined in a typical phase I clinical trial designed to measure pharmacokinetic properties of a drug (see e.g. Examples 5, 6 and 7, below). References herein to Tmax refer to values obtained after administration of a single dose at fasted states, unless otherwise indicated.

In some embodiments of the invention, the dose of the amantadine administered in accordance with the present invention is within or above the ranges normally prescribed for immediate release compositions of amantadine. In other embodiments, the doses of the amantadine administered with the present invention are higher than the ranges normally prescribed for immediate release compositions of amantadine. For example, the recommended dose of amantadine for the treatment of Parkinson's disease is 100 mg administered twice daily. In limited cases of the patient not deriving sufficient benefit at that dose and subject to the patient being able to tolerate such higher dose, the dose may be increased to 300 mg or 400 mg in divided doses. The most commonly prescribed doses of amantadine are 100 mg to 200 mg per day, with the latter administered in divided doses. More than 200 mg (for example 300 mg) is always given in divided doses. For the present invention, doses of 50 to 600 mg, or more preferably, 200 to 450 mg are administered for treatment of Parkinson's disease, and the methods and compositions of the invention may comprise administration of a dose as defined by any of these ranges. In specific embodiments the administration of such higher doses may be once daily. In additional embodiments the administration of such higher doses may be at night. In additional embodiments the administration of such higher doses may be in the form of 1, 2 or 3 capsules of size 0, 1 or 2 administered once daily.

In one embodiment of any of the above aspects the amantadine is administered as a pharmaceutically acceptable salt. In a more specific embodiment, the amantadine is administered as hydrochloride or amantadine sulfate.

In one embodiment of any of the above aspects, a total daily dose of 50 mg to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof is administered to a patient. More specifically the daily dose of amantadine or pharmaceutically acceptable salt thereof administered may be in the range of 100 mg to 440 mg. In another specific embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof maybe in the range of 260 mg to 420 mg. In another embodiment, the daily dose of amantadine or pharmaceutically acceptable salt thereof administered exceeds 300 mg per day. In various specific embodiments, the daily dose of amantadine or pharmaceutically acceptable salt thereof may be 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg.

In one embodiment of any of the above aspects, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. More specifically, the composition may comprise 100 to 450 mg of amantadine, or a pharmaceutically acceptable salt thereof. Still more specifically, the composition may comprise 130-210 mg of amantadine, or a pharmaceutically acceptable salt thereof. In various specific embodiments, the dosage form comprises 50 to 75 mg, 70 to 95 mg, 90 to 115 mg, 110 to 135 mg, 130 to 155 mg, 150 to 175 mg, 170 to 195 mg, 190 to 215 mg, 210 to 235 mg, 230 to 255 mg, 250 to 275 mg, 270 to 295 mg, 290 to 305 mg, 300 to 315 mg, 310 to 325 mg, 320 to 335 mg, 330 to 345 mg, 340 to 355 mg, 350 to 365 mg, 360 to 375 mg, 370 to 385 mg, 380 to 395 mg, 390 to 405 mg, 400 to 415 mg, 410 to 425 mg, 420 to 435 mg, 430 to 445 mg or 440 to 455 mg of amantadine, or a pharmaceutically acceptable salt thereof. In a more specific embodiment, the composition comprises about 110, 120, 130, 140, 150, 160 170, 180, 190, 210, or 220 mg amantadine, or a pharmaceutically acceptable salt thereof. In another more specific embodiment, the composition comprises 110 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 130 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 170 mg amantadine hydrochloride. In another more specific embodiment, the composition comprises 210 mg amantadine hydrochloride.

In one embodiment of any of the above aspects, the composition comprises from about 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg of amantadine, or a pharmaceutically acceptable salt thereof to about 75 mg, 85 mg, 95 mg, 105 mg, 115 mg, 125 mg, 135 mg, 145 mg, 155 mg, 165 mg, 175 mg, 185 mg, 195 mg, 205 mg, 215 mg, 225 mg, 235 mg, 245 mg, 255 mg, 265 mg, 275 mg, 285 mg, 295 mg, 305 mg, 315 mg, 325 mg, 335 mg, 345 mg, 355 mg, 365 mg, 375 mg, 385 mg, 395 mg, 405 mg, 415 mg, 425 mg, 435 mg, 445 mg of amantadine, or a pharmaceutically acceptable salt thereof.

In a specific embodiment of the invention, a subject's entire daily dose of amantadine is administered once, during a period of less than about three, two or one hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night). In other embodiments, at least one half of the daily dose of amantadine is taken during said period before bedtime. Preferably at least ⅔ of the dose of amantadine is taken in said period before bedtime, with the remainder taken in morning or afternoon. The morning or afternoon dose of the amantadine may be provided in a conventional, immediate release dosage form, or in an extended release form.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in levodopa induced dyskinesia. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% reduction in levodopa induced dyskinesia. In further embodiments, the reduction in levodopa induced dyskinesia is measured on a numeric scale that is used by or accepted by the FDA or other regulatory agencies to evaluate the effectiveness of and to approve for licensure drugs for the treatment of LID. In further specific embodiments, the scale used in measuring the reduction in LID could be UDysRS, UPDRS Part IV (subscores 32, 33), Dyskinesia Rating Scale (DRS), Abnormal Involuntary Movement Scale (AIMS), Rush Dyskinesia Rating Scale, Parkinson Disease Dyskinesia Scale (PDYS-26), Obeso Dyskinesia Rating Scale (CAPIT), Clinical Dyskinesia Rating Scale (CDRS), Lang-Fahn Activities of Daily Living Dyskinesia or other scales developed for this purpose.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease fatigue. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, or 60% reduction in Parkinson's disease fatigue. In further specific embodiments, the reduction in fatigue is measured on a numerical scale used by or accepted by the FDA or other regulatory agencies to evaluate the effectiveness of and to approve for licensure drugs for the treatment of fatigue. In further specific embodiments, the scale used in measuring the reduction in fatigue could be the Fatigue Severity Scale (FSS), Fatigue Assessment Inventory, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue), Multidimensional Fatigue Inventory (MFI-20), Parkinson Fatigue Scale (PFS-16) and the Fatigue Severity Inventory. In other specific embodiments, the reduction in fatigue is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in fatigue is measured relative to baseline in a controlled clinical trial.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease symptoms. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's symptoms. In further specific embodiments, the reduction in Parkinson's symptoms is measured on a numerical scale used by or accepted by the FDA or other regulatory agencies to evaluate the effectiveness of and to approve for licensure drugs for the treatment of Parkinson's symptoms. In further specific embodiments, the scale used in measuring the reduction in Parkinson's symptoms could be the Unified Parkinson's Disease Rating Scale (UPDRS). Unified Parkinson's Disease Rating Scale (UPDRS, MDS revision)—Part I: non-motor aspects of experiences of daily living (13 items), Part II: motor aspects of experiences of daily living (13 items)—Part III: motor examination (33 scored items)—Part I: mental status, behavior and mood—Part II: activities of daily living—Part III: motor examination (27 scored items) Hoehn and Yahr Staging Scale (Original or Modified).

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in levodopa induced dyskinesia. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% reduction in levodopa induced dyskinesia. In further embodiments, the reduction in levodopa induced dyskinesia is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce LID. In further specific embodiments, the scale used in measuring the reduction in LID could be UDysRS, UPDRS Part IV (subscores 32, 33), Dyskinesia Rating Scale (DRS), Abnormal Involuntary Movement Scale (AIMS), or other scales developed for this purpose. In other specific embodiments, the reduction in LID is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in LID is measured relative to baseline in a controlled clinical trial.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease fatigue. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's disease fatigue. In further specific embodiments, the reduction fatigue is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce fatigue. In further specific embodiments, the scale used in measuring the reduction in fatigue could be the Fatigue Severity Scale (FSS). In other specific embodiments, the reduction in fatigue is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in fatigue is measured relative to baseline in a controlled clinical trial.

In one embodiment of any of the above aspects, administration of the composition to a Parkinson's disease patients results in a significant reduction in Parkinson's disease symptoms. In a specific embodiment, administration of the composition results in about 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% reduction in Parkinson's symptoms. In further specific embodiments, the reduction in Parkinson's symptoms is measured on a numeric scale that is used by the FDA to evaluate effectiveness of drugs indicated to reduce Parkinson's symptoms. In further specific embodiments, the scale used in measuring the reduction in Parkinson's symptoms could be the Unified Parkinson's Disease Rating Scale (UPDRS). In other specific embodiments, the reduction in Parkinson's disease symptoms is measured relative to placebo in a controlled clinical trial. In other embodiments, the reduction in Parkinson's disease symptoms is measured relative to baseline in a controlled clinical trial.

Extended Release Formulations

Extended release amantadine compositions suitable for use in the method of the invention can be made using a variety of extended release technologies, such as those described in the patent publications referenced in the above background section, which publications are incorporated herein by reference in their entireties. In some embodiments, the invention is a pellet in capsule dosage form. In some embodiments, the pellets comprise a pellet core, which is

coated with at least one drug layer and at least one extended release coating layer. In some embodiments, the pellets are coated with at least one drug layer, an intermediate layer such as a seal coat and an extended release coating layer. In some embodiments, the pellet, the drug layer or both comprise one or more binders.

In some embodiments, the dosage unit comprises a plurality of coated pellets. In some embodiments, the pellets have a diameter of for example 300 to 1700 microns, in some cases 500 to 1200 microns. The pellets will comprise, for example, inert substrates, such as sugar spheres, microcrystalline cellulose (MCC) spheres, starch pellets. In some embodiments, pellets can be prepared by other processes such as pelletization, extrusion, spheronization, etc. or combinations thereof. The core pellets will comprise of amantadine hydrochloride and pharmaceutically acceptable excipients.

Coated Pellets

The pellet cores are coated with the active ingredient, e.g., amantadine or a pharmaceutically acceptable salt and/or polymorph thereof. In some embodiments, in addition to the active ingredient, the pellets also comprise one or more binders, such as for example hydroxypropyl methyl cellulose, copovidone, povidone, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose etc. In some embodiments, the pellets also contain one or more additional excipients, such as anti-tack agents (e.g. talc, magnesium stearate etc.)

In some embodiments, the pellets cores are coated with a drug layer comprising active ingredient, and optionally one or more binders, anti-tack agents and/or solvents by conventional coating techniques such as fluidized bed coating, pan coating.

Intermediate Layer Coating

In some embodiments, the pellets are coated with an intermediate layer, such as a seal coat. In some embodiments, the seal coat is adapted to prevent ingredients in the extended release coating from interacting with ingredients in the pellet core, to prevent migration of the ingredients in the pellet core from diffusing out of the pellet core into the extended release layer, etc. As described herein, the seal coat of the present invention can comprise one or more film forming polymers including but not limited to hydroxypropylmethyl cellulose (HPMC), copovidone, povidone, polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose or any combination thereof and the like.

The seal coat can further comprise other additives like plasticizers, such as, propylene glycol, triacetin, polyethylene glycol, tributyl citrate and optionally anti-tacking agents, such as, magnesium stearate, calcium silicate, magnesium silicate, and colloidal silicon dioxide or talc.

Apart from plasticizers and anti-tacking agents as mentioned above, the seal coat can optionally contain buffers, colorants, opacifiers, surfactants or bases, which are known to those skilled in the art.

Seal coating can be applied to the core using conventional coating techniques such as fluidized bed coating, pan coating etc. In some embodiments, the drug coated pellets cores are coated with a seal coat layer that optionally comprises one or more binders, anti-tack agents and/or solvents by fluidized bed coating or pan coating.

Binders

In some embodiments, either the pellet cores, the intermediate coating layer, or both may comprise one or more binders (e.g., film forming polymers). Suitable binders for use herein include, e.g.: alginic acid and salts thereof; cellulose derivatives such as carboxymethylcellulose, methylcellulose (e.g., Methocel®), hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose (e.g., Klucel®), ethylcellulose (e.g., Ethocel®), and microcrystalline cellulose (e.g., Avicel®); microcrystalline dextrose; amylose; magnesium aluminum silicate; polysaccharide acids; bentonites; gelatin; polyvinylpyrrolidone/vinyl acetate copolymer; crospovidone; povidone; starch; pregelatinized starch; tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitab®), and lactose; a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, polyvinylpyrrolidone (e.g., Polyvidone® CL, Kollidon® CL, Polyplasdone® XL-10), larch arabogalactan, Veegum®, polyethylene glycol, waxes, sodium alginate, and the like.

Extended Release Coating

The pellets are coated with an extended release coating. The extended release coating is adapted to delay release of the drug from the coated drug cores for a period of time after introduction of the dosage form into the use environment. In some embodiments, the extended release coating includes one or more pH-dependent or non-pH-dependent extended release excipients. Examples of non-pH dependent extended release polymers include ethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, copolymer of ethyl acrylate, methyl methacrylate (e.g. Eudgrait RS) etc. Examples of pH dependent extended release excipients include methacrylic acic copolymers, hydroxypropylmethyl cellulose acetate succinate, hydroxypropylmethyl cellulose phthalate, and cellulose acetate phthalate etc. The extended release coating may also include a pore former, such as povidone, polyethylene glycol, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, etc., sugars such as sucrose, mannitol, lactose, and salts, such as sodium chloride, sodium citrate, etc., a plasticizer, such as acetylated citrated esters, acetylated glycerides, castor oil, citrate esters, dibutylsebacate, glyceryl monostearate, diethyl phthalate, glycerol, medium chain triglycerides, propylene glycol, polyethylene glycol. The extended release coating may also include one or more additional excipients, such as lubricants (e.g., magnesium stearate, talc etc.).

Extended release coating can be applied using conventional coating techniques such as fluidized bed coating, pan coating etc. The drug coated pellets cores, which optionally comprise a seal coat, are coated with the extended release coating by fluidized bed coating.

Extended Release Excipients (Coating Polymers)

As described herein, exemplary extended release excipients include, but are not limited to, insoluble plastics, hydrophilic polymers, and fatty compounds. Plastic matrices include, but are not limited to, methyl acrylate-methyl methacrylate, polyvinyl chloride, and polyethylene. Hydrophilic polymers include, but are not limited to, cellulosic polymers such as methyl and ethyl cellulose, hydroxyalkyl celluloses such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, and cross-linked acrylic acid polymers like Carbopol® 934, polyethylene oxides and mixtures thereof. Fatty compounds include, but are not limited to, various waxes such as carnauba wax and glyceryl tristearate and wax-type substances including hydrogenated castor oil or hydrogenated vegetable oil, or mixtures thereof.

In certain embodiments, the plastic material can be a pharmaceutically acceptable acrylic polymer, including but not limited to, acrylic acid and methacrylic acid copolymers,

methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain other embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In still other embodiments, the acrylic polymer is an acrylic resin lacquer such as that which is commercially available from Rohm Pharma under the trade name Eudragit®. In further embodiments, the acrylic polymer comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the trade names Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. Edragit® S-100 and Eudragit® L-100 are also suitable for use herein. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, multiparticulate systems formed to include the same are swellable and permeable in aqueous solutions and digestive fluids.

The polymers described above such as Eudragit® RL/RS may be mixed together in any desired ratio in order to ultimately obtain an extended release formulation having a desirable dissolution profile. One skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L.

Pore Formers

In some embodiments, the extended release coating includes a pore former. Pore formers suitable for use in the extended release coating can be organic or inorganic agents, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. Examples of pore formers include but are not limited to organic compounds such as mono-, oligo-, and polysaccharides including sucrose, glucose, fructose, mannitol, mannose, galactose, lactose, sorbitol, pullulan, dextran; polymers soluble in the environment of use such as water-soluble hydrophilic polymers, such as povidone, crospovidone, polyethylene glycol, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyalkyl celluloses, carboxyalkyl celluloses, cellulose ethers, acrylic resins, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, polyethylene oxide, carbowaxes, Carbopol®, and the like, diols, polyols, polyhydric alcohols, polyalkylene glycols, polyethylene glycols, polypropylene glycols, or block polymers thereof, polyglycols, poly(α-Ω) alkylenediols; inorganic compounds such as alkali metal salts, lithium carbonate, sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium acetate, sodium citrate, suitable calcium salts, and the like. In certain embodiments, plasticizers can also be used as a pore former.

Capsules

The extended release pellets are introduced into a suitable capsule by using an encapsulator equipped with pellet dosing chamber. The capsule sizes may be 00, 0, 0EL, 1, 1EL, 2, 2EL, 3, 4 or 5. A particularly preferred composition that provides ideal pharmacokinetic properties and plasma concentration profiles is a pellet-in-capsule composition that comprises a plurality of pellets, typically having a diameter of about 500 μm to 1.2 mm, and preferably about 700 μm to 1000 μm, where each pellet comprises a core comprising amantadine and a binder, and an extended release coating surrounding the core that extends release of the amantadine so as to provide the desired pharmacokinetic properties and amantadine plasma concentration profiles described above.

In some embodiments, the pellets in the pellet-in-capsule are in a size 0 or smaller, preferably a size 1 or smaller capsule. Mean pellet diameters in some embodiments may be in a range of 500 μm to 1200 μm, e.g. from 500 μm to 1100 μm, from 500 μm to 1000 μm, from 500 μm to 900 μm, from 500 μm to 800 μm, from 500 μm to 700 μm, from 600 μm to 1100 μm, from 600 μm to 1000 μm, from 600 μm to 900 μm, from 600 μm to 800 μm, from 600 μm to 700 μm, from 700 μm to 1100 μm, from 700 μm to 1000 μm, from 700 μm to 900 μm, or from 700 μm to 800 μm. In some embodiments the mean particle diameters are, ±10%, e.g.: 500 μm, 550 μm, 600 μm, 650 μm, 700 μm, 750 μm, 800 μm, 850 μm, 900 μm, 950 μm, 1000 μm, 1050 μm, 1100 μm, 1150 μm or 1200 μm.

One preferred composition of the invention is a pellet-in-capsule composition wherein each pellet comprises a core that comprises a core seed with a mixture of amantadine and a binder coated onto the core seed, and an extended release coating surrounding the core comprising ethyl cellulose, a pore forming agent such as hydroxypropyl methyl cellulose or povidone, and a plasticizer. In some embodiments, the pellets may further comprise a seal coating between the pellet core and the extended release coating. The pellets are formulated using methods known in the art, such as those described in Example 1 below. In a specific embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 20-80 wt %, 45-70 wt %, 40-50 wt %, 45-55 wt %, 50-60 wt %, 55-65 wt %, 60-70 wt %, 65-75 wt %, 70-80 wt %, or 40 to 60 wt %, the binder, which is preferably hydroxypropyl methyl cellulose, copovidone, or mixtures thereof, is present in amounts from 1 to 25 wt %, the core seed, preferably a sugar sphere (nonpareil) or microcrystalline cellulose seed (e.g. Celphere®), is present in amounts from 8 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the pore forming agent, preferably povidone, is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %. In another specific embodiment, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 50 to 70 wt %, the binder, which is preferably hydroxypropyl methyl cellulose, copovidone, or mixtures thereof, is present in amounts from 1 to 25 wt %, the core seed, preferably a sugar sphere (nonpareil) or microcrystalline cellulose seed (e.g. Celphere®), is present in amounts from 5 to 15 wt %, the ethyl cellulose is present in amounts from 1 to 15 wt %, the pore forming agent, preferably povidone, is present in amounts from 0.25 to 4 wt %, and the plasticizer is present in amounts from 0.25 to 4 wt %.

Additional embodiments of the invention are illustrated in the Table, below, entitled "Various Amantadine ER Capsule Size 1 Formulations". By means of methods and compositions described herein, formulations can be made that achieve the desired dissolution characteristics and target pharmacokinetic profiles described herein. More specifi-

cally, therapeutically effective doses of amantadine can be administered once daily in no more than two size 1 (or smaller, e.g. size 2 or 3) capsules using the manufacturing methods and compositions that have been described herein to achieve these results. In particular, higher drug loading can be achieved using compositions and manufacturing methods described herein. In some embodiments, higher drug loading may be achieved, with the required dissolution profile, using smaller core pellet sizes and concomitantly increased drug layering on smaller cores, but with no change in the extended release coat. In some embodiments, using alternative manufacturing approaches described herein, e.g. extrusion and spheronization, even higher drug loads can be achieved to realize the desired dissolution profile, enabling high amantadine drug loads with suitable pharmacokinetic profiles, resulting in compositions that are therapeutically more effective, and at least as well tolerated, and can be filled in relatively small sized capsules (e.g., size 1, 2 or 3), enabling ease of administration to patients.

TABLE

Various Amantadine ER Capsule Size 1 Formulations

AMT Strength (mg)	Manufacture Method	Inert Core Pellet Size (mm)	Active Drug % w/w	Extended Release Coating % w/w	Bulk Density (g/cm^3)	% Fill in Size 1 Capsule	AMT Dissolution (%) (at T (hrs)): 2 hrs	6 hrs	12 hrs
110 mg	Fluid bed coating	0.3-0.5	40-50%	10-30%	0.6-1.0	60-70%	<25%	40-80%	>80%
140 mg	Fluid bed coating	0.3-0.5	45-50%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
150 mg	Fluid bed coating	0.3-0.5	50-55%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
170 mg	Fluid bed coating	0.2-0.3	50-55%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
170 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	65-75%	<25%		>80%
190 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	75-85%	<25%	40-80%	>80%
210 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	80-90%	<25%	40-80%	>80%
230 mg	Extrusion spheronization, pan or fluidized bed coating	N/A	55-75%	10-30%	0.6-1.0	85-95%	<25%	40-80%	>80%

In some embodiment, the amantadine, or a pharmaceutically acceptable salt thereof, is present in amounts from 20 to 80 wt (based on the combined weight of the pellet core and extended release coating), with a bulk density of 0.3 to 1.2 g/cm^3. In some embodiments, the amantadine or pharmaceutically acceptable salt thereof is present in amounts from 20 to 77.5 wt %, from 20 to 75 wt %, from 20 to 72.5 wt %, from 20 to 70 wt %, from 20 to 67.5 wt %, from 20 to 65 wt %, from 20 to 62.5 wt %, from 20 to 60 wt %, from 20 to 57.5 wt %, from 20 to 55 wt %, from 20 to 52.5 wt %, from 20 to 50 wt %, from 20 to 47.5 wt %, from 20 to 45 wt %, from 20 to 42.5 wt %, from 20 to 40 wt %, from 20 to 37.5 wt %, from 20 to 35 wt %, from 20 to 32.5 wt %, from 20 to 30 wt %, from 30 to 80 wt %, from 30 to 77.5 wt %, from 30 to 75 wt %, from 30 to 72.5 wt %, from 30 to 70 wt %, from 30 to 67.5 wt %, from 30 to 65 wt %, from 30 to 62.5 wt %, from 30 to 60 wt %, from 30 to 57.5 wt %, from 30 to 55 wt %, from 30 to 52.5 wt %, from 30 to 50 wt %, from 30 to 47.5 wt %, from 30 to 45 wt %, from 30 to 42.5 wt %, from 30 to 40 wt %, from 40 to 80 wt %, from 40 to 77.5 wt %, from 40 to 75 wt %, from 40 to 72.5 wt %, from 40 to 70 wt %, from 40 to 67.5 wt %, from 40 to 65 wt %, from 40 to 62.5 wt %, from 40 to 60 wt %, from 40 to 57.5 wt %, from 40 to 55 wt %, from 40 to 52.5 wt %, from 40 to 50 wt %, from 40 to 47.5 wt %, from 40 to 45 wt %, from 50 to 80 wt %, from 50 to 77.5 wt %, from 50 to 75 wt %, from 50 to 72.5 wt %, from 50 to 70 wt %, from 50 to 67.5 wt %, from 50 to 65 wt %, from 50 to 62.5 wt %, from 50 to 60 wt %, from 50 to 57.5 wt %, from 50 to 55 wt %, from 60 to 80 wt %, from 60 to 77.5 wt %, from 60 to 75 wt %, from 60 to 72.5 wt %, from 60 to 70 wt %, from 60 to 67.5 wt %, from 60 to 65 wt %. In some embodiments, the bulk density is 0.3 to 1.2 g/cm^3, 0.3 to 1.15 g/cm^3, 0.3 to 1.1 g/cm^3, 0.3 to 1.05 g/cm^3, 0.3 to 1.0 g/cm^3, 0.3 to 0.9 g/cm^3, 0.3 to 0.8 g/cm^3, 0.3 to 0.7 g/cm^3, 0.3 to 0.6 g/cm^3, 0.3 to 0.5 g/cm^3, 0.3 to 0.4 g/cm^3, 0.4 to 1.2 g/cm^3, 0.4 to 1.15 g/cm^3, 0.4 to 1.1 g/cm^3, 0.4 to 1.05 g/cm^3, 0.4 to 1.0 g/cm^3, 0.4 to 0.9 g/cm^3, 0.4 to 0.8 g/cm^3, 0.4 to 0.7 g/cm^3, 0.4 to 0.6 g/cm^3, 0.4 to 0.5 g/cm^3, 0.5 to 1.2 g/cm^3, 0.5 to 1.15 g/cm^3, 0.5 to 1.1 g/cm^3, 0.5 to 1.05 g/cm^3, 0.5 to 1.0 g/cm^3, 0.5 to 0.9 g/cm^3, 0.5 to 0.8 g/cm^3, 0.5 to 0.7 g/cm^3, 0.5 to 0.6 g/cm^3, 0.6 to 1.2 g/cm^3, 0.6 to 1.15 g/cm^3, 0.6 to 1.1 g/cm^3, 0.6 to 1.05 g/cm^3, 0.6 to 1.0 g/cm^3, 0.6 to 0.9 g/cm^3, 0.6 to 0.8 g/cm^3, 0.6 to 0.7 g/cm^3, 0.7 to 1.2 g/cm^3, 0.7 to 1.15 g/cm^3, 0.7 to 1.1 g/cm^3, 0.7 to 1.05 g/cm^3, 0.7 to 1.0 g/cm^3, 0.7 to 0.9 g/cm^3, 0.7 to 0.8 g/cm^3, 0.5 to 1.2 g/cm^3, 0.8 to 1.15 g/cm^3, 0.8 to 1.1 g/cm^3, 0.8 to 1.05 g/cm^3, 0.8 to 1.0 g/cm^3, 0.8 to 0.9 g/cm^3, 0.9 to 1.2 g/cm^3, 0.9 to 1.15 g/cm^3, 0.9 to 1.1 g/cm^3, 0.9 to 1.05 g/cm^3, or 0.9 to 1.0 g/cm^3. In some embodiments, the composition is in a dosage unit comprising a pellet in capsule formulation, wherein the capsule size is size 00, size 0, size 1, size 2 or size 3. In some preferred embodiments, the dosage unit includes pellets

containing from 50 to 250 mg of amantadine in a size 0, 1, 2 or 3 capsule. In some embodiments, the dosage unit includes pellets containing from 100 to 250 mg, e.g. 100 to 200 mg of amantadine in a size 0, 1, 2 or 3 capsule, preferably a size 1, 2 or 3 capsule. In a more specific embodiment, the dosage unit comprises about 110, 120, 130, 140, 150, 160 170, 180, 190, 210, or 220 mg amantadine, or a pharmaceutically acceptable salt thereof. In another more specific embodiment, the dosage unit comprises 110 mg amantadine hydrochloride. In another more specific embodiment, the dosage unit comprises 130 mg amantadine hydrochloride. In another more specific embodiment, the dosage unit comprises 170 mg amantadine hydrochloride. In another more specific embodiment, the dosage unit comprises 210 mg amantadine hydrochloride.

Suitable plasticizers include medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, castor oil, and the like. The pellets are filled into capsules to provide the desired strength of amantadine. An advantage of this composition is it provides the desired release properties that make the composition suitable for administration during said period before bedtime. A further advantage is that the extended release coating is sufficiently durable so that the capsule can be opened and the pellets sprinkled onto food for administration to patients who have difficulty swallowing pills, without adversely affecting the release properties of the composition. When the composition is administered by sprinkling onto food, it is preferred to use a soft food such as applesauce or chocolate pudding, which is consumed within 30 minutes, and preferably within 15 minutes. A yet further advantage of the above-described composition is that it has very good batch-to-batch reproducibility and shelf-life stability.

In some embodiments, the composition of the invention has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, as measured using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. More preferably, the in vitro dissolution is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours.

In additional embodiments, 110 mg to 210 mg of ER amantadine in a size 1 capsule of the composition of the invention has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, as measured using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. More preferably, the in vitro dissolution is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 25% dissolution at 2 hours, (ii) not more than 25-55% dissolution at 6 hours, and (iii) at least 80% dissolution at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

In one embodiment of any of the above aspects the composition has an in vitro dissolution profile of amantadine which shows at least one of (i) not more than 20% dissolution at 1 hour, (ii) about 25-45% dissolution at 2 hours, (iii) not more than 50-80% dissolution at 4 hours, and (iii) at least 80% dissolution at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In a more specific embodiment two of criteria (i), (ii) and (iii) are met. In a more specific embodiment, all three of criteria (i), (ii) and (iii) are met.

A preferred pellet-in-capsule composition of the invention, in addition to having the above in vitro dissolution properties and any of the above-described pharmacokinetic properties (e.g. in vivo release profile, Tmax, Cmax/Cmin ratio, etc) that make the composition suitable for administration in said period before bedtime. The composition is further characterized by providing a Cmax of 1.6-2.4 ng/ml per mg of amantadine and an $AUC_{0\text{-}inf}$ of 40-75 ng*h/mL per mg of amantadine after oral administration of a single dose of the capsule to a human subject in a fasted state. A preferred pellet-in-capsule composition is further characterized by a steady state plasma concentration in which once daily oral administration of the capsule to a human subject provides a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine, a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and an $AUC_{0\text{-}24}$ of 48-73 ng*h/mL per mg of amantadine.

The above-described pellet-in-capsule compositions may be provided at a strength suitable for amantadine therapy. Typical strengths range from at least about 50 mg to about 250 mg. In a specific embodiment, the capsule strength is 70 mg, 80 mg, 90 mg, 110 mg, 120 mg, 125 mg, 130 mg, 140 mg, 150 mg, 160 mg, 160 mg, 170 mg, 180 mg, 190 mg, 210 mg, and 220 mg, that provides a single dose $AUC_{0\text{-}inf}$ per mg that is equivalent to a 100 mg tablet of an immediate release formulation of amantadine HCl (e.g. Symmetrel®, or other FDA Orange Book reference listed drug). One, two, or three, of such capsules can be administered to a subject in the period before bedtime. In a preferred embodiment, between 220 mg and 650 mg of amantadine is adminstered using 2 capsules of a suitable ER formulations once daily.

The invention may also be described in terms of the following numbered embodiments:

1. An extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, for use in a method of administering amantadine to a subject in need thereof, said method comprising orally administering said composition less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).
2. Use of amantadine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by the NMDA receptor to a subject in need thereof, said medicament being an extended release (ER) composition, and said treatment comprising orally administering said composition less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).
3. An extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing sleep disturbance in a human subject undergoing treatment with amantadine, said method comprising administering said composition less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).
4. Use of amantadine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing sleep disturbance in a human subject undergoing treatment with amantadine, said medicament being an extended release (ER) composition and being adapted for administration less than three hours before bedtime (i.e. the time at which the subject wishes to go to sleep for the night).

5. The use or composition of any one of embodiments 1-4 wherein administration occurs less than 1 hour before bedtime.
6. The use or composition of any one of embodiments 1-5, wherein the patient has been diagnosed with Parkinson's disease.
7. The use or composition of any one of embodiments 1-6, wherein the composition is administered once daily.
8. The use or composition of any one of embodiments 1-7, wherein the composition is added to food prior to administration.
9. The use or composition of any one of embodiments 1-8, wherein there is no increase in plasma concentration of amantadine for at least one hour after the administration at steady state.
10. The use or composition of any one of embodiments 1-9, wherein there is no increase in plasma concentration of amantadine for at least two hours after the administration at steady state.
11. The use of composition of any one of embodiments 1-10, wherein, the amantadine has a single dose Tmax of 9 to 15 hours and/or a steady state Tmax of 7 to 13 hours after administration.
12. The use or composition of any one of embodiments 1-11, wherein the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours after administration.
13. The use of composition of any one of embodiments 1-10, wherein, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours after administration.
14. The use or composition of any one of embodiments 1-11, wherein the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours after administration.
15. The use of composition of any one of embodiments 1-10, wherein, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours after administration.
16. The use or composition of any one of embodiments 1-11, wherein the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours after administration.
17. The use or composition of any one of embodiments 1-12, wherein the amantadine has a single dose Tmax of 11 to 13 hours after administration, and or a steady state Tmax of 9 to 11 hours after administration.
18. The use or composition of any one of embodiments 1-13, wherein a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration.
19. The use or composition of any one of embodiments 1-14 having a Cmax/Cmin ratio of 1.5 to 2.0.
20. The use or composition of any one of embodiments 1-15 having a Cmax/Cmin ratio of 1.7 to 1.9.
21. The use or composition of any one of embodiments 1-16, wherein the amantadine is amantadine hydrochloride or amantadine sulfate.
22. The use or composition of any one of embodiments 1-17 wherein the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof.
23. The use or composition of embodiment 18, wherein the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof.
24. The use or composition of any one of embodiments 1-19 wherein the composition comprises 200 to 420 mg of amantadine, or a pharmaceutically acceptable salt thereof.
25. The use or composition of embodiment 20, wherein the composition is administered as two unit dosage forms each comprising 110 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof.
26. The use or composition of any one of embodiments 1 to 17, wherein the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof.
27. The use or composition of embodiment 22, wherein the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof.
28. The use or composition of embodiment 23, wherein the composition comprises 110 mg amantadine hydrochloride.
29. The use or composition of any one of embodiments 1-24, wherein oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of amantadine of 1.6 to 2.4 ng/ml per mg of amantadine and an $AUC_{0\text{-}inf}$ of 40 to 75 ng*h/mL per mg of amantadine.
30. The use or composition of any one of embodiments 1-25, wherein once daily oral administration of a dose of the composition to a human subject provides a steady state plasma amantadine concentration profile characterized by:
(i) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine,
(ii) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and
(iii) an $AUC_{0\text{-}24}$ of 44 to 83 ng*h/mL per mg of amantadine.
31. The use or composition of embodiment 26, wherein the steady state plasma concentration profile is further characterized by:
(iv) no increase in plasma concentration of amantadine for at least one hour after the administration; and
(v) a Cmax/Cmin ratio of 1.5 to 2.0.
32. The use or composition of embodiment 27, wherein the steady state plasma concentration profile is further characterized by:
(iv) no increase in concentration of amantadine for at least two hours after the administration; and
(v) a Cmax/Cmin ratio of 1.7 to 1.9.
33. The use or composition of any one of embodiments 1-28, wherein the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium.
34. The use or composition of embodiment 29, wherein the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours
35. The use or composition of any one of embodiments 1-30, wherein the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 8 hours that is about 5 to 15% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 12 hours that is about 10 to 40% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 18 hours that is about 25 to 60% of $AUC_{0\text{-}inf}$; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of $AUC_{0\text{-}inf}$
36. The use or composition of any one of embodiments 1-31, wherein the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that

is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

37. A pharmaceutical composition as embodied in any one of embodiments 1, 3, or 5 to 32, or the use of any one of embodiments 2, 4 or 5 to 32, wherein said composition is for oral administration and comprises a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising:
    (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and
    (b) an extended release coating surrounding the pellet core.
38. The use or composition of embodiment 32, wherein the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer.
39. The use or composition of any one of embodiments 33 or 34, wherein the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed.
40. The use or composition of embodiment 35, wherein, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 60 wt %, the binder is present in amounts from 8 to 25 wt %, the core seed is present in amounts from 8 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the povidone is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %.
41. The use or composition of any one of embodiments 33 to 36, further comprising a seal coating between the pellet core and the extended release coating.
42. The use or composition of any one of embodiments 35 to 37, wherein the wherein the pellet core comprises a binder, selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof.
43. The use or composition of any one of embodiments 18 to 38, wherein the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.
44. A composition of any one of embodiments 33 to 39, for use in a method of treating Parkinson's disease in a human subject in need thereof, said method comprising orally administering said composition.

Some embodiments herein provide a method of administering amantadine to a subject in need thereof, said method comprising orally administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than three hours before bedtime. In some embodiments, administration occurs less than 1 hour before bedtime. In some embodiments, the patient has been diagnosed with Parkinson's disease. In some embodiments, the composition is administered once daily. In some embodiments, the composition is added to food prior to administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least one hour after the administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least two hours after the administration. In some embodiments, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours. In some embodiments, the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours. In some embodiments, the amantadine has a single dose Tmax of 11 to 13 hours after administration, and/or a steady state Tmax of 9 to 11 hours. In some embodiments, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave night at steady state is 1.2 to 1.6. In some embodiments, the ratio of C-ave-morning/C-ave night at steady state is 1.3 to 1.5. In some embodiments, the average amantadine plasma concentration during the day (C-ave-day) at steady state is 500-2000 ng/ml. In some embodiments, the average amantadine plasma concentration in the morning (C-ave-morning) at steady state is 500-2000 ng/ml. In some embodiments, the amantadine is amantadine hydrochloride or amantadine sulfate. In some embodiments, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one or two unit dosage forms each comprising 130 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is within a capsule of capsule size #1. In some embodiments, the composition comprises 200 to 350 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 110 mg amantadine hydrochloride. In some embodiments, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine, and an $AUC_{0\text{-}inf}$ of 40 to 75 ng*h/mL per mg of amantadine. In some embodiments, once daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by: (a) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine; (b) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (c) an $AUC_{0\text{-}24}$ of 44 to 83 ng*h/mL per mg of amantadine. In some embodiments, the steady state plasma concentration profile is further characterized by: (d) no increase in plasma concentration of amantadine for at least one hour after the administration; and (e) a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the steady state plasma concentration profile is further characterized by: (f) no increase in concentration of amantadine for at least two hours after the administration; and (g) a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 25-55% at 6 hours, and at

least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 20% at 1 hour, 25-45% at 2 hours, 50-80% at 4 hours, and at least 80% at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours. In some embodiments, the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 8 hours that is about 5 to 15% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 12 hours that is about 10 to 40% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 18 hours that is about 25 to 60% of $AUC_{0\text{-}inf}$; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of $AUC_{0\text{-}inf}$. In some embodiments, the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}; and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

Some embodiments herein provide a method of reducing sleep disturbance in a human subject undergoing treatment with amantadine, said method comprising administering an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than three hours before bedtime. In some embodiments, administration occurs less than 1 hour before bedtime. In some embodiments, the patient has been diagnosed with Parkinson's disease. In some embodiments, the composition is administered once daily. In some embodiments, the composition is added to food prior to administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least one hour after the administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least two hours after the administration. In some embodiments, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours. In some embodiments, the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours. In some embodiments, the amantadine has a single dose Tmax of 11 to 13 hours after administration, and/or a steady state Tmax of 9 to 11 hours. In some embodiments, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave night at steady state is 1.2 to 1.6. In some embodiments, the ratio of C-ave-morning/C-ave night at steady state is 1.3 to 1.5. In some embodiments, the average amantadine plasma concentration during the day (C-ave-day) at steady state is 500-2000 ng/ml. In some embodiments, the average amantadine plasma concentration in the morning (C-ave-morning) at steady state is 500-2000 ng/ml. In some embodiments, the amantadine is amantadine hydrochloride or amantadine sulfate. In some embodiments, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one or two unit dosage forms each comprising 130 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is within a capsule of capsule size #1. In some embodiments, the composition comprises 200 to 350 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 110 mg amantadine hydrochloride. In some embodiments, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine, and an $AUC_{0\text{-}inf}$ of 40 to 75 ng*h/mL per mg of amantadine. In some embodiments, once daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by: (a) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine; (b) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (c) an $AUC_{0\text{-}24}$ of 44 to 83 ng*h/mL per mg of amantadine. In some embodiments, the steady state plasma concentration profile is further characterized by: (d) no increase in plasma concentration of amantadine for at least one hour after the administration; and (e) a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the steady state plasma concentration profile is further characterized by: (f) no increase in concentration of amantadine for at least two hours after the administration; and (g) a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 25-55% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 20% at 1 hour, 25-45% at 2 hours, 50-80% at 4 hours, and at least 80% at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours. In some embodiments, the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 8 hours that is about 5 to 15% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 12 hours that is about 10 to 40% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 18 hours that is about 25 to 60% of $AUC_{0\text{-}inf}$; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of $AUC_{0\text{-}inf}$. In some embodiments, the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional

AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

Some embodiments herein provide a method of treating levodopa induced dyskinesia in a patient with Parkinson's disease, said method comprising orally administering once daily an extended release (ER) composition comprising amantadine, or a pharmaceutically acceptable salt thereof, less than about three hours before bedtime. In some embodiments, administration occurs less than 1 hour before bedtime. In some embodiments, the patient has been diagnosed with Parkinson's disease. In some embodiments, the composition is administered once daily. In some embodiments, the composition is added to food prior to administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least one hour after the administration. In some embodiments, there is no increase in plasma concentration of amantadine for at least two hours after the administration. In some embodiments, the amantadine has a single dose Tmax of 9 to 15 hours, and/or a steady state Tmax of 7 to 13 hours. In some embodiments, the amantadine has a single dose Tmax of 10 to 14 hours after administration, and/or a steady state Tmax of 8 to 12 hours. In some embodiments, the amantadine has a single dose Tmax of 11 to 13 hours after administration, and/or a steady state Tmax of 9 to 11 hours. In some embodiments, a once daily oral administration of the composition to a human subject provides a steady state plasma concentration profile characterized by a concentration increase of amantadine of less than 25% at three hours after the administration. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the PK curve has a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the ratio of C-ave-day/C-ave night at steady state is 1.2 to 1.6. In some embodiments, the ratio of C-ave-morning/C-ave night at steady state is 1.3 to 1.5. In some embodiments, the average amantadine plasma concentration during the day (C-ave-day) at steady state is 500-2000 ng/ml. In some embodiments, the average amantadine plasma concentration in the morning (C-ave-morning) at steady state is 500-2000 ng/ml. In some embodiments, the amantadine is amantadine hydrochloride or amantadine sulfate. In some embodiments, the composition comprises 50 to 600 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one, two, or three or four unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as one or two unit dosage forms each comprising 130 to 210 mg of extended release amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is within a capsule of capsule size #1. In some embodiments, the composition comprises 200 to 350 mg of amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered as two unit dosage forms each comprising 100 to 175 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 50 to 200 mg amantadine or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 100 to 125 mg amantadine, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises 110 mg amantadine hydrochloride. In some embodiments, oral administration of a single dose of the composition to a human subject in a fasted state provides a maximum plasma concentration (Cmax) of 1.6 to 2.4 ng/ml per mg of amantadine, and an $AUC_{0\text{-}inf}$ of 40 to 75 ng*h/mL per mg of amantadine. In some embodiments, once daily oral administration of a dose of the composition to a human subject provides a steady state plasma concentration profile characterized by: (a) a Cmax of 2.4 to 4.2 ng/ml per mg of amantadine; (b) a Cmin of 1.1 to 2.6 ng/ml per mg of amantadine, and (c) an $AUC_{0\text{-}24}$ of 44 to 83 ng*h/mL per mg of amantadine. In some embodiments, the steady state plasma concentration profile is further characterized by: (d) no increase in plasma concentration of amantadine for at least one hour after the administration; and (e) a Cmax/Cmin ratio of 1.5 to 2.0. In some embodiments, the steady state plasma concentration profile is further characterized by: (f) no increase in concentration of amantadine for at least two hours after the administration; and (g) a Cmax/Cmin ratio of 1.7 to 1.9. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 55-85% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 25-55% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 20% at 1 hour, 25-45% at 2 hours, 50-80% at 4 hours, and at least 80% at 8 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the in vitro dissolution profile of amantadine is further characterized by release of amantadine of not more than 10% at 1 hour, 30-50% at 4 hours, and at least 90% at 12 hours. In some embodiments, the composition has an AUC profile after administration of a single dose of the composition characterized by: a fractional AUC from 0 to 4 hours that is less than 5% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 8 hours that is about 5 to 15% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 12 hours that is about 10 to 40% of $AUC_{0\text{-}inf}$; a fractional AUC from 0 to 18 hours that is about 25 to 60% of $AUC_{0\text{-}inf}$; and a fractional AUC from 0 to 24 hours that is about 40 to 75% of $AUC_{0\text{-}inf}$. In some embodiments, the composition has an AUC profile after once daily dosing of the composition at steady state conditions characterized by: a fractional AUC from 0 to 4 hours that is about 2 to 25% of AUC_{24}; a fractional AUC from 0 to 8 hours that is about 15 to 50% of AUC_{24}; a fractional AUC from 0 to 12 hours that is about 30 to 70% of AUC_{24}: and a fractional AUC from 0 to 18 hours that is about 60 to 95% of AUC_{24}.

Some embodiments herein provide a pharmaceutical composition for any of the methods described herein, wherein said composition is for oral administration and comprises a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 60 wt %, the binder is present in amounts from 8 to 25 wt %, the core seed is present in

amounts from 1 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the povidone is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %. In some embodiments, the composition further comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.

Some embodiments herein provide a method of administering amantadine, or a pharmaceutically acceptable salt thereof, to a human subject in need thereof, said method comprising orally administering a pharmaceutical composition comprising amantadine in a capsule for oral administration, said capsule comprising a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 60 wt %, the binder is present in amounts from 8 to 25 wt %, the core seed is present in amounts from 1 to 25 wt %, the ethyl cellulose is present in amounts from 10 to 20 wt %, the povidone is present in amounts from 1 to 4 wt %, and the plasticizer is present in amounts from 1 to 4 wt %. In some embodiments, the composition further comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil. Some embodiments comprise treating Parkinson's disease in a human subject in need thereof.

Some embodiments herein provide a pharmaceutical composition suitable for once daily oral administration to a patient in need thereof said composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. In some embodiments, the composition comprises 110-220 mg of amantadine or pharmaceutically acceptable salt thereof. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 40-80% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition comprises a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, the composition comprises amantadine and, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 70 wt %. In some embodiments, the pellet core comprises a core seed comprising sugar or microcrystalline cellulose that is between 100 and 500 microns in diameter. In some embodiments, the bulk density is between 0.5 and 1 gm/cm^3. In some embodiments, the composition comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.

Some embodiments herein provide a method of treating Parkinson's disease in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. In some embodiments, the composition comprises 110-220 mg of amantadine or pharmaceutically acceptable salt thereof. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 40-80% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition comprises a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, the composition comprises amantadine and, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 70 wt %. In some embodiments, the pellet core comprises a core seed comprising sugar or microcrystalline cellulose that is between 100 and 500 microns in diameter. In some embodiments, the bulk density is between 0.5 and 1 gm/cm^3. In some embodiments, the composition comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil.

Some embodiments herein provide a method of treating levodopa induced dyskinesia in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. Some embodiments herein provide a method of treating traumatic brain injury in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a phar-

maceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. Some embodiments provide a method of treating traumatic brain injury in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. Some embodiments provide a method of treating fatigue in a human subject, said method comprising orally administering a composition comprising a therapeutically effective amount of amantadine or a pharmaceutically acceptable salt thereof in an extended release form which can be administered as not more than two size 0 or smaller capsules in a single daily administration. In some embodiments, the composition comprises 110-220 mg of amantadine or pharmaceutically acceptable salt thereof. In some embodiments, the composition has an in vitro dissolution profile of amantadine of not more than 25% at 2 hours, 40-80% at 6 hours, and at least 80% at 12 hours, using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. In some embodiments, the composition comprises a plurality of pellets, each pellet comprising: (a) a pellet core comprising amantadine, or a pharmaceutically acceptable salt thereof, and (b) an extended release coating surrounding the pellet core. In some embodiments, the extended release coating comprises ethyl cellulose, at least one of povidone and hydroxypropyl methyl cellulose, and a plasticizer. In some embodiments, the pellet core comprises amantadine, or a pharmaceutically acceptable salt thereof, and a binder coated onto a core seed. In some embodiments, the composition comprises amantadine and, based on the combined weight of the pellet core and extended release coating, the amantadine is present in amounts from 40 to 70 wt %. In some embodiments, the pellet core comprises a core seed comprising sugar or microcrystalline cellulose that is between 100 and 500 microns in diameter. In some embodiments, the bulk density is between 0.5 and 1 gm/cm^3. In some embodiments, the composition comprises a seal coating between the pellet core and the extended release coating. In some embodiments, the pellet core comprises a binder selected from the group consisting of hydroxypropyl methyl cellulose, copovidone, and mixtures thereof. In some embodiments, the plasticizer is selected from the group consisting of medium chain triglycerides, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides and castor oil. In some embodiments, the method comprises administering the composition to a patient less than three hours before bed time.

The present invention may be better understood by reference to the following examples, which are not intended to limit the scope of the claims.

EXAMPLE 1

Amantadine Extended Release Coated Pellet Formulations

Amantadine HCl extended release coated pellet compositions designed for nighttime administration were prepared using the components and relative amounts shown in Table 1 below. For each composition, the drug coating solution was prepared by adding HPMC 5 cps and Copovidone to isopropyl alcohol with continuous stirring. Purified water was added to this dispersion and stirring continued until a clear solution is formed. Drug (Amantadine HCl) was then added to this binder solution and stirring continued until the drug was completely dissolved. Finally, talc was added and dispersed uniformly by stirring.

Celphere beads (screen sizes #35 to #50 i.e. 300 to 500 micron) were loaded in a Wurster coating unit. The drug coating dispersion was sprayed onto the beads followed by a period of drying. The resulting drug coated pellets were sieved to retain the fraction between screens #18 and #24 (approximately 700 μm to 1 mm diameter).

The seal coating solution was prepared by adding HPMC 5 cps to isopropyl alcohol with continuous stirring. Purified water was added to this dispersion and stirring continued until a clear solution was formed. Talc was added and dispersed uniformly by stirring. The sieved drug coated pellets were loaded in a Wurster coating unit. The seal coating dispersion was sprayed over the drug coated pellets followed by a period of drying to remove the residual solvent and water in the pellets. The resulting seal coated pellets were sieved to retain the fraction between screens #18 and #24.

The ER coating solution was prepared by dissolving ethyl cellulose (viscosity 7 cps) in isopropyl alcohol and purified water and stirring until a clear solution was formed. Povidone K-90 was then dissolved in this clear solution followed by addition of plasticizer Miglyol 812N with continuous stirring to form a clear solution. The sieved seal coated pellets were loaded in a Wurster coating unit. The ER coating solution was sprayed over the seal coated pellets followed by a period of drying to affect the ER coat and remove the residual solvent and water in the pellets. After drying, magnesium stearate was spread on the top bed of the coated pellets in the annulus region followed by recirculation of the pellets in the Wurster unit to blend the magnesium stearate with the coated pellets. The resulting ER coated pellets were sieved to retain the fraction between screens #18 and #24.

The desired weight of the ER coated pellets containing the unit dose were filled into empty 1 hard gelatin capsule shell (size 1 for 100-140 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 1

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Pellet Core		
Amantadine Hydrochloride USP	Active	40-50%
Microcrystalline cellulose spheres (Celphere ®)	Core seeds	10-15%
Hydroxypropyl methyl cellulose 5 cps USP	Binder	10-15%
Copovidone	Binder	1-5%
Talc USP	Anti-tack	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Seal Coating (optional)		
Hydroxypropyl methyl cellulose 3 cps USP	Coating polymer	5-10%
Talc USP	Anti-tack	0-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]

TABLE 1-continued

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Extended Release Coating		
Ethyl cellulose	Coating polymer	10-20%
Povidone	Pore former	1-5%
Medium chain triglycerides	Plasticizer	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Magnesium Stearate NF	Lubricant	0-1%
Density of pellets		0.6-0.9 gm/cm^3

NF = National Formulary

[1]Purified water and isopropyl alcohol are removed during processing.

The in vitro dissolution of capsules prepared above was tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. Capsules meeting desired dissolution specifications released not more than 25% of the drug in 2 hours, 40-80% in 6 hours, and at least 80% at 12 hours. In an exemplary dissolution profile, there was 0% drug release at 1 hour, 12% release at 2 hours, 43% release at 4 hours, 68% release at 6 hours, 83% release at 8 hours, 92% release at 10 hours, and 97% release at 12 hours. Capsules prepared in accordance with the above method exhibited good shelf-stability, and batch-to-batch reproducibility upon scale-up.

EXAMPLE 2

Amantadine Extended Release Coated Pellet Formulation with Higher Drug Loading

Amantadine HCl extended release coated pellet compositions designed for nighttime administration are prepared using the components and relative amounts shown in Table 2 below and the manufacturing process described in example 1.

The diameter of the inert cores is 200-300 microns. The diameter of the coated pellets is 600-1200 microns. The bulk density of the coated pellets is 0.7-1.2 g/cm^3.

The desired weight of the ER coated pellets containing the unit dose are filled into an empty hard gelatin capsule shell (size 1 for 170 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 2

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Pellet Core		
Amantadine Hydrochloride USP	Active	50-65%
Microcrystalline cellulose spheres (Celphere ®)	Core seeds	1-15%
Hydroxypropyl methyl cellulose USP	Binder	5-25%
Copovidone	Binder	1-5%
Talc USP	Anti-tack	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Seal Coating (optional)		
Hydroxypropyl methyl cellulose USP	Coating polymer	0-10%
Talc USP	Anti-tack	0-5%

TABLE 2-continued

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Extended Release Coating		
Ethyl cellulose	Coating polymer	10-20%
Povidone	Pore former	1-5%
Medium chain triglycerides	Plasticizer	1-5%
Isopropyl alcohol	Solvent	—[1]
Water	Solvent	—[1]
Magnesium Stearate NF	Lubricant	0-1%

NF = National Formulary

[1]Purified water and isopropyl alcohol are removed during processing.

The in vitro dissolution of capsules prepared above are tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium and release not more than 25% of the drug in 2 hours, 40-80% in 6 hours, and at least 80% at 12 hours.

EXAMPLE 3

Amantadine Extended Release Coated Pellet Formulations

Amantadine HCl extended release coated pellet compositions suitable for nighttime administration were prepared using the components and relative amounts shown in Table 3 below and the manufacturing process described in Example 1.

The desired weight of the ER coated pellets containing the unit dose was filled into empty #1 hard gelatin capsule shell (100 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 3

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule A	B	C
Pellet Core				
Amantadine Hydrochloride USP	Active	50.15%	47.94%	45.15%
Microcrystalline cellulose spheres (Celphere ®)	Core seeds	14.33%	13.70%	12.90%
Hydroxypropyl methyl cellulose USP	Binder	13.37%	12.79%	12.04%
Copovidone	Binder	3.34%	3.2%	3.01%
Talc USP	Anti-tack	2.51%	2.4%	2.26%
Isopropyl alcohol	Solvent	—[1]	—[1]	—[1]
Water	Solvent	—[1]	—[1]	—[1]
Seal Coating (optional)				
Hydroxypropyl methyl cellulose USP	Coating polymer	7.61%	7.27%	6.85%
Talc USP	Anti-tack	0.76%	0.73%	0.69%
Isopropyl alcohol	Solvent	—[1]	—[1]	—[1]
Water	Solvent	—[1]	—[1]	—[1]
Extended Release Coating				
Ethyl cellulose	Coating polymer	6.23%	9.46%	13.53%
Povidone	Pore former	0.85%	1.29%	1.84%
Medium chain triglycerides	Plasticizer	0.75%	1.13%	1.62%

TABLE 3-continued

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule A	B	C
Isopropyl alcohol	Solvent	—[1]	—[1]	—[1]
Water	Solvent	—[1]	—[1]	—[1]
Magnesium Stearate NF	Lubricant	0.1%	0.1%	0.1%

NF = National Formulary

[1]Purified water and isopropyl alcohol are removed during processing.

The in vitro dissolution of capsules prepared above were tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium. The results are shown in FIG. **1**.

EXAMPLE 4

Amantadine Extended Release Formulation Made by Extrusion Spheronization

Amantadine HCl extended release compositions designed for nighttime administration are prepared using the components and relative amounts shown in Table 4 below and the manufacturing process described below.

A blend of amantadine HCl, microcrystalline cellulose and lactose monohydrate was prepared and a wet mass is prepared in a high shear granulator using an aqueous solution of povidone. The wet mass is extruded using 1 mm sieve and extruded mass is spheronized using a spheronizer. The pellets are dried in a tray drier to yield core pellets. The core pellets are coated with extended release coating solution in a pan coater. The desired weight of the ER coated pellets containing the unit dose is filled into empty 1 hard gelatin capsule shell (170 mg strength) using an encapsulator equipped with pellet dosing chamber.

TABLE 4

Composition of amantadine HCl ER capsules

Component	Function	combined w/w of capsule
Pellet Core		
Amantadine Hydrochloride USP	Active	59.40%
Microcrystalline cellulose	Diluent	18.67%
Lactose monohydrate	Diluent	6.15%
Povidone	Binder	0.64%
Water	Solvent	—[1]
Extended Release Coating		
Ethyl cellulose	Coating polymer	12.41%
Polyethylene glycol	Pore former	1.24%
Dibutyl sebacate	Plasticizer	1.49%
Ethanol	Solvent	—[1]

The in vitro dissolution of capsules prepared above are tested using a USP Apparatus II (Paddles) at 50 rpm with 500 ml water at 37° C. as the dissolution medium and release not more than 25% of the drug in 2 hours, 40-80% in 6 hours, and at least 80% at 12 hours.

EXAMPLE 5

Pharmacokinetic Measurement of Formulations of Amantadine ER Compared to IR Amantadine

Objective: The primary objective of the study was to confirm the PK properties of extended release formulations in example 3, to determine the pharmacokinetic profiles, safety and tolerability of three prototype formulations of ER capsules of amantadine HCl described with different release properties in Example 3 relative to a 100 mg film-coated IR amantadine HCl tablet (SYMMETREL®) given as single doses to healthy adult subjects under fasting conditions.

Study design: This was a Phase 1, randomized, single dose, open-label, four-period, crossover, fasting pharmacokinetic study in which single 100 mg doses of three formulations of Amantadine ER capsules with different release properties were compared to single 100 mg doses of marketed amantadine IR tablets (SYMMETREL®). The three ER formulations differed in the amantadine release rates in vitro, as shown in FIG. **1**.

Methods: Subjects were admitted to the unit for the first period of dosing within 21 days of study screening. Subjects were dosed on the day after checking into the unit and discharged at 24 hours post dose. Subjects were asked to return after discharge for follow-up visits at 56 hours and 152 hours after dosing. Each dosing period was separated by at least 7 day washout.

After an overnight fast, the formulation was administered to the subjects while in a sitting position with 240 mL of water. Blood samples were collected at 0 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 24 (discharge), and 56 hours following each dose. Plasma samples were assayed for amantadine by a validated liquid chromatography/tandem mass spectroscopy (LC/MS/MS) method. Pharmacokinetic parameters were calculated using a non-compartmental analysis with WinNonlin software (version 4.1 or higher; Pharsight Corporation).

An analysis of variance (ANOVA) was performed on the natural logarithms of Cmax and AUC0-∞ determined from the data following a single dose of study drug using linear mixed effects model. The model included effects for subject, sequence, period, and regimen. The effects of sequence, period, and regimen were fixed, while the effect of subject was random. Ratio of ER to IR for both AUC (relative bioavailability for ER formulations) and Cmax was calculated. (Adverse events were monitored throughout the study. Vital signs (pulse rate, blood pressure and body temperature), clinical laboratory measures (biochemistry, hematology, and urinalysis) and ECGs were collected at various times during the study.

Results: A total of 20 subjects participated in the study. The mean age was 25.5 years old (range 20-38 years). The study consisted of 8 male (40%) and 12 female (60%) subjects with a mean body mass index (BMI) of 23.6 kg/m2±2.85. The racial makeup was 100% Caucasian. Fifteen subjects received all 4 treatments.

The PK results from this study showed that all three of the Amantadine ER formulations reduced the rate of absorption, based on the reduced values of Cmax and increased Tmax, compared to SYMMETREL® (Table 5, FIGS. **5**, **6**). The IR formulation had the highest mean Cmax (277±73.9 ng/mL) and shortest median Tmax (4 h) values. Formulations A, B, and C produced progressively lower Cmax and longer Tmax values. Cmax decreased from 204±61.4 to 166±34.8 to 149±34.4 ng/mL, and median Tmax increased from 7.0, to 11.0, to 14.0 h for formulations A, B, and C, respectively. Total amantadine exposure, as measured by AUC0-∞, was slightly lower in all three Amantadine ER formulations than SYMMETREL® but all three formulations had acceptable bioavailability (85-95%).

TABLE 5

Single Dose Pharmacokinetic Parameters of Three Formulations of Amantadine ER (Formulation A, B, and C), as Compared to SYMMETREL ® (Formulation IR)

Parameter[a]	100 mg Formulation A (n = 19)	100 mg Formulation B (n = 17)	100 mg Formulation C (n = 18)	100 mg Formulation IR (n = 18)
C_{max} (ng/mL)	204 ± 61	166 ± 35	149 ± 34	277 ± 74
T_{max} (h) [range]	7 [5-11]	11 [5-15]	14 [9-18]	4 [2-6]
$A_{UC0\text{-}last}$ (ng * h/mL)	5064 ± 1573	5028 ± 2328	4525 ± 1268	5488 ± 1730
$AUC_{0\text{-}\infty}$ (ng * h/mL)	5545 ± 1904	5724 ± 2369	5652 ± 2581	5907 ± 1907
$t_{1/2}$ (h)	13.9 ± 3.0	16.3 ± 5.2	18.3 ± 7.5	12.3 ± 3.5

[a]All parameters are reported as the mean ± standard deviation (SD), except t_{max} which is reported as a median value (min to max range)

TABLE 6

Ratio ER/IR for C_{max} and $AUC_{0\text{-}\infty}$

Comparison	Variable	ER/IR[a]
A vs. IR	C_{max} (ng/mL)	66.0%
	$AUC_{0\text{-}\infty}$ (ng * h/mL)	85.3%
B vs. IR	C_{max} (ng/mL)	60.9%
	$AUC_{0\text{-}\infty}$ (ng * h/mL)	94.6%
C vs. IR	C_{max} (ng/mL)	51.2%
	$AUC_{0\text{-}\infty}$ (ng * h/mL)	88.5%

[a]Point estimate of the geometric mean ratio (ER/IR).

EXAMPLE 6

Food-Effect Evaluation of Amantadine ER

Objective: The primary objective was to demonstrate that the amantadine ER formulations suitable for nighttime administration exhibit excellent bioavailability when administered with food. We determined the pharmacokinetics of a 100 mg capsule of an amantadine ER formulation (Example 3, Formulation B), when administered both with a high fat meal and in a fasted state.

Study Design: This was a Phase 1, randomized, single dose, open-label, two-period, crossover, food-effect study to compare single 100 mg doses of Formulation I in healthy adult (18 to 45 years of age) male and female subjects in fed and fasted states. The study consisted of a 21-day to −2 day screening phase (prior to the scheduled dosing day) and two treatment periods, Period 1 and Period 2, with an 8-day wash-out period between treatment periods.

Methods: After an overnight fast, the formulation was administered to the subjects while in a sitting position with 240 mL of water at ambient temperature for the fasted condition. For the fed condition, after the overnight fast, subjects were served a high fat and high calorie test meal (Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies, December 2002) as breakfast, which they were required to consume completely within 30 minutes before taking the study medication. Subjects were randomized to one of two sequences, each composed of treatment administration under fed and fasted conditions separated by an eight day wash out period.

For each period, pharmacokinetic blood samples were collected at pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 24, 28, 48, 72, 96 and 144 hours after dosing in each period. Subjects were housed in the clinical facility at least 15 hours before investigational product administration and remained in the clinical facility for at least 28 hours after administration of the investigational product in each period. Samples after 28 hours in each period were collected on an ambulatory basis. Amantadine in plasma was quantified by a validated LC/MS/MS method. The pharmacokinetic parameters were calculated from the drug concentration-time profile by non-compartmental model using WinNonlin Professional Software-Version 5.0.1 (Pharsight Corporation, USA) for amantadine. Absence of food effect was defined as met if the point estimates and 90% confidence intervals (CI) for the ln-transformed C_{max}, AUC_{last} and AUG, fed/fasting ratios of the population means were entirely within the standard accepted range of 80% to 125%. All statistical analyses for amantadine were performed using PROC MIXED of SAS® Release 9.1.3 (SAS Institute Inc., USA).

Routine safety monitoring was conducted during and after dosing in all subjects.

Results: A total of 26 subjects participated in the study, 19 (73%) male and 7 (27%) female. The mean age was 26 years (range 19-44) and the mean BMI was 22.4 kg/m^2 (range 18.1-29.8). The racial makeup was 100% Asian. All subjects received at least one dose of study drug and were included in the safety analysis. Twenty-four (92.3%) subjects completed the study and were included in the pharmacokinetic analysis. Two subjects (7.7%) were withdrawn prior to completion of the study due protocol deviations.

The results of this study (Table 7) indicate that the single dose pharmacokinetics of Formulation B are not affected by food. The rate, as measured by C_{max}, and the extent, as measured by $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$, of absorption of amantadine, administered with and without food, were equivalent (Table 8).

TABLE 7

Mean ± SD Pharmacokinetic Parameters after Single Dose Administration of 100 mg of Formulation B in Fed and Fasted States

	Mean ± SD (Un-transformed data) n = 24	
Parameters (Units)[a]	Fasted State	Fed State
T_{max} (h)	11.9 ± 2.1 (8-15)	9.5 ± 2.4 (5-16)
C_{max} (ng/mL)	198.8 ± 34.7	219.4 ± 41.5
$AUC_{0\text{-}last}$ (ng * h/mL)	5571.2 ± 1654.2	5394.4 ± 1581.5
$AUC_{0\text{-}\infty}$ (ng * h/mL)	5663.1 ± 1677.4	5476.6 ± 1590.7
$t_{1/2}$ (h)	11.9 ± 2.8	11.5 ± 2.0
t_{lag} (h)	1.0	2.0

[a]All parameters are reported as the mean ± standard deviation (SD).

t_{max} is reported as the mean ± SD (min to max range).

TABLE 8

Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Formulation B (n = 24) in Fed and Fasted States

Parameters (Units)	ln-transformed data Geometric Least Squares Mean Fed State	Fasted State	Ratio (Fed/Fasted)%	90% Confidence Interval (Parametric)
C_{max} (ng/mL)	215.6	195.8	110.1	104.4-116.2%
$AUC_{0\text{-}last}$ (ng * h/mL)	5195.9	5344.2	97.2	91.0-103.8%
$AUC_{0\text{-}\infty}$ (ng * h/mL)	5280.3	5434.7	97.2	90.9-103.8%

Conclusion: The results of this study indicate that the single dose pharmacokinetics of amantadine ER are not affected by food. The rate, as measured by C_{max}, and the extent, as measured by $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$, of absorption of amantadine, administered with and without food, were equivalent.

EXAMPLE 7

Pharmacokinetic Study Comparing Once-daily Administration of Amantadine HCl ER Capsules with Twice-daily Administration of Amantadine HCl IR Tablets in Healthy Adults Under Fasting Conditions

Objective: The primary objective of this study was to measure at steady state under repeat or chronic dosing the pharmacokinetics of an ER amantadine formulation suitable for nighttime administration, and enable the calculation of critical PK parameters for future safety and efficacy studies (i.e., Cave-morning, Cave-day, Cave-night) of ER amantadine formulations administered at night. We compared the single dose and repeat dose pharmacokinetics of amantadine HCl administered twice daily as a commercially available immediate release (IR) formulation to a once daily amantadine extended release (ER) formulation (Example 3, Formulation B).

Study Design: This was a two period, multiple dose, crossover study. After a 21 day screening period, 26 healthy male and female subjects were randomized to receive one of two treatments (amantadine ER 200 mg once daily or amantadine IR 100 mg twice daily) in Period-I, then crossed over to receive the other treatment in Period-II.

Methods: Study drug administration started on day 1. Study drug was not administered on Day 2. Multiple dosing commenced on day 3 and continued for 7 days (through day 9). A washout period of 8 days separated the dose administrations. The study drug was administered with 240 mL of drinking water. No other fluids were allowed within 1 hour of dosing. For each period, pharmacokinetic blood samples were collected at pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 24, 28, 36, and 48 hours after the first dose. The morning trough (pre-dose) blood samples were collected on Days 7 and 8. Blood samples were again collected immediately before the morning dose on Day 9 and at 1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 24, 28, 48, 72, and 96 hours thereafter. Samples after 28 hours following the morning dose on day 9 were collected on an ambulatory basis in each period. Amantadine in plasma was quantified by a validated LC/MS/MS method. The pharmacokinetic parameters were calculated from the drug concentration-time profile by non-compartmental model using WinNonlin Professional Software-Version 5.0.1 (Pharsight Corporation, USA) for amantadine.

Statistical analyses were conducted to assess the pharmacokinetic profile of single dose and repeat dose amantadine HCl administered twice daily as a commercially available immediate release (IR) formulation compared to a once daily extended release (ER) formulation (Formulation B). An analysis of variance (ANOVA) was performed on the natural logarithms of C_{max}, C_{min}, and AUC_{24} determined from the data following the dose of study drug on study day 9 using linear mixed effects model. The model included the fixed effects for sequence, period, regimen and a random subject effect. The confidence intervals were used to perform the 2 one-sided tests procedure for equivalence assessment. The confidence intervals were obtained by exponentiating the endpoints of the confidence intervals for the difference of mean logarithms obtained within the framework of the ANOVA model. The upper and lower limits of confidence intervals from the natural-log transformed data were back-exponentiated to obtain the 90% confidence interval for the ratio of geometric means. Equivalence was established if the exponentiated 90% confidence interval fell entirely within the interval (80.00%, 125.00%).

Repeated measures ANOVA was carried out for comparison of C_{min} for day 7, 8 and 9 at 5% level of significance on both untransformed and ln-transformed data. Steady state was demonstrated if the repeated measures ANOVA test was found to be non-significant. The statistical analysis for amantadine was performed using PROC MIXED of SAS® Release 9.1.3 (SAS Institute Inc., USA).

Routine safety monitoring was conducted during and after dosing in all subjects, and at the end of the study.

Results: A total of 26 subjects participated in the study, 22 (84.6%) male and 4 (15.4%) female. The mean age was 26 years (range 19-42) and the mean BMI was 22.9 kg/m^2 (range 18.1-28.8). The racial makeup was 100% Asian. All subjects received at least one dose of study drug and were included in the safety analysis. Twenty-four (92.3%) subjects completed the study and were included in the pharmacokinetic analysis. Two subjects (7.7%) were withdrawn from the PK analysis prior to completion of the study due to vomiting within 12 hours of dosing, which was a pharmacokinetic exclusion criterion.

As expected from its half-life, once daily administration of amantadine ER and twice daily dosing of amantadine IR resulted in accumulation as measured by higher C_{max} and AUC on Day 9 compared to Day 1 (Table 9 and FIG. **2**). Steady state was achieved by Day 9 for both formulations as demonstrated by similar trough levels on Days 7, 8 and 9 (data not shown). At steady state (Day 9) plasma concentrations (FIG. **2**, Table 9) and pharmacokinetic parameters (Table 9) were comparable for both formulations. Furthermore, the formulations are equivalent in terms of the extent and the rate of absorption of amantadine as measured by steady state C_{max}, C_{min} and $AUC_{0\text{-}24}$ (Table 9), where equivalency is defined by the 90% CIs of the ratio of the least square means of the test versus reference for steady state C_{max}, C_{min} and $AUC_{0\text{-}24}$ of Amantadine ER to Amantadine IR falling within 80%-125%.

TABLE 9

Mean (±SD) Pharmacokinetic Parameters of Amantadine after Single and Multiple Dose Administration of IR (100 mg BID) and ER (200 mg QD) Formulations

	Formulation			
	IR (n = 24)		ER (n = 24)	
Parameter (Units)[a]	Day 1	Day 9	Day 1	Day 9
$t_{1/2}$ (h)	13.2 ± 2.8 [9.1-18.8]	12.6 ± 2.4 [9.4-18.1]	13.7 ± 3.6 [9.1-22.7]	12.8 ± 2.2 [9.2-17.4]
t_{max} (h)	14.42 ± 0.88 [13-16]	12.6 ± 4.5 [1-15]	11.4 ± 1.9 [8-18]	10.3 ± 2.0 [8-18]
C_{max} (ng/mL)	530 ± 80 [407.5-752.7]	728 ± 153 [538.4-1101.8]	431 ± 84 [313.5-559.9]	665 ± 179 [444.4-1140.0]
$AUC_{0\text{-}last}$ (ng h/mL)	11989 ± 2224 [9243-17106]	23040 ± 8273 [13133-46446]	11171 ± 2773 [7326-16970]	21362 ± 8946 [10821-47134]
$AUC_{0\text{-}\infty}$ (ng h/mL)	13685 ± 3324 [10167-20989]	NA	12900 ± 4087 [7817-22153]	NA
$AUC_{0\text{-}24}$ (ng h/mL)	7695 ± 1026 [5967-10171]	13752 ± 3586 [9085-22519]	7173 ± 1367 [5021-9552]	12680 ± 3879 [7896-23058]
C_{min} (ng/mL)	—	412.4 ± 142.6 [218.5-795.2]	—	374.9 ± 151.7 [172.2-767.1]

[a]All parameters are reported as the mean ± SD, [min to max range]
NA = not applicable

Certain additional PK parameters that are important in determining the suitability of the ER amantadine formulation for once daily, night time administration are also reported in Table 10.

TABLE 10

Additional Steady State PK parameters of Amantadine ER

	ER 200 mg QD	IR 100 mg BID
Cmax/Cmin	1.86	1.68
C-ave-8-16 hrs (ng/ml)	614	586
C-ave-8-12 hrs (ng/ml)	643	510
C-ave-16-24 hrs (ng/ml)	502	569
C-ave-0-8 hrs (ng/ml)	465	586
C-ave-8-16 hrs/C-ave-0-8 hrs	1.32	1.00
C-ave-8-12 hrs/C-ave-0-8 hrs	1.38	0.87
% Change in Plasma Concentration 0-3 hrs	5%	55%
% Change in Plasma Concentration 0-4 hrs	23%	48%
AUC 0-4 as % of AUC 24	12%	N/A
AUC 0-8 as % of AUC 24	30%	N/A
AUC 0-12 as % of AUC 24	51%	N/A

Conclusion: the ER amantadine formulation exhibits the desired steady state PK properties that would make the same suitable for administration at night and for achieving desired efficacy and tolerability benefits. Specifically, the ER amantadine formulation administered once daily at night results in relatively slow initial rise in amantadine plasma concentration, higher average amantadine plasma concentrations 8 to 12 hours after administration relative to 0-8 hours after administration and thus if administered at night higher ratios of average day time to night time amantadine plasma concentrations relative to IR amantadine. Thus this formulation is well suited for administration at higher doses than current practice that are expected to be relatively well tolerated and potentially provide superior efficacy in the treatment of LID, fatigue and Parkinson's disease.

EXAMPLE 8

Study Comparing Administration of Amantadine HCl ER Capsules Once Nightly with Twice-daily Administration of Amantadine HCl IR Tablets in Normal Healthy Volunteers

Objective: The primary objective is to compare the effects on sleep of amantadine extended release (ER) capsules (Formulation B) administered once daily at bedtime with amantadine immediate release (IR) tablets administered twice daily in normal healthy volunteers. This ER formulation exhibits a Cave,day/Cave,night=1.30.

Study Design: This is a single-center, double-blind, triple-dummy, randomized, cross-over study to compare the effects on sleep of amantadine ER capsules, QHS, amantadine IR tablets BID, and caffeine caplets (active comparator) in 30 normal healthy volunteers as assessed by overnight polysomnography (PSG) and standardized questionnaires (Stanford Sleepiness Scale (SSS); Modified Epworth Sleepiness Scale (m-ESS)/Karolinska Sleepiness Scale (KSS); Toronto Hospital Alertness Test (THAT)/ZOGIM Alertness Scale (ZOGIM-A); Visual analog scale of sleepiness/alertness (VAS)).

Study drugs are administered in 3 dosing periods. A single day's dosage of one drug is administered per dosing period. Each day of dosing is separated by a washout period of 1 week. A single day's dosage of amantadine ER (Formulation B) consists of one 220 mg capsule (or 2×110 mg capsule) administered at bed time (QHS; defined as 23:00 h for the purposes of this study). A single day's dosage of amantadine IR consists of one 100 mg capsule administered twice a day (BID; defined as 8:00 h and 16:00 h for the purposes of this study). A single day's dosage of caffeine consists of one 100 mg capsule administered three times a day (TID; defined as 8:00 h, 16:00 h, & 23:00 h for the purposes of this study).

All subjects are dosed three times a day, at 8:00 h, 16:00 h, & 23:00 h. At each hour of dosing, every subject receives either the active drug or the matching placebo for each of the 3 treatments. Whether the capsule, tablet, or caplet administered at a specific hour of dosing contains active study drug

or is a placebo dummy is determined according to the dosing sequence and period to which the subject is assigned.

Consented subjects who meet eligibility criteria are randomized equally to one of 3 treatment sequences (groups), each comprising 3 single-day treatment periods separated by 1 week washout periods as described above. Additionally, there is a one-day, single-blind, placebo run-in prior to each double-blind dosing day. This is to allow subjects to acclimate to sleeping in the Clinical Research Unit (CRU) under conditions of PSG recording and to establish individual baseline (BL) PSG characteristics.

For each dosing period, subjects are admitted to a CRU equipped with a sleep laboratory the day before the first day of dosing with active study drug. They stay in the CRU overnight and through the entirety of the active drug-dosing day. They again stay overnight and then are discharged from the CRU the morning of the following day. For the first dosing period, the day of admission to the CRU (Day −1) constitutes the last day of the screening phase, and the day of discharge from the CRU constitutes the first day of the first washout period (Day 2). For the second dosing period, the day of re-admission to the CRU (Day 7) constitutes the last day of the first washout period, and the day of discharge (Day 9) will constitute the first day of the second washout period. For the third dosing period, the day of re-admission to the CRU (Day 14) constitutes the last day of the second washout period, and the day of discharge (Day 16) constitutes the first day of the follow-up phase.

On the day of admission (or re-admission) to the CRU, subjects undergo routine laboratory and vital sign testing. They are administered one each of the placebo dummies (for amantadine ER, amantadine IR, & caffeine) at 16:00 h and at 23:00 h in single-blind fashion. They are questioned for adverse events (AEs) and have vital signs checked immediately prior to each dosing. Blood is drawn for routine laboratory testing and toxicology screen prior to the 16:00 h dosing. Subjects spend the night in the sleep lab under conditions of PSG recording.

On the day of dosing with active study drug, subjects are awakened at 7:00 h and fill out a battery of sleep and alertness questionnaires They receive study drug (active or placebo) at 8:00 h, 16:00, and 23:00 h. They are questioned for AEs and have vital signs checked immediately prior to each dosing. Blood is drawn to measure plasma amantadine concentrations prior to the 23:00 h dosing.

On the day after dosing with active study drug, subjects are awakened at 7:00 h and fill out a battery of sleep and alertness questionnaires Shortly before 8:00 h, i.e., 9 hours after the last dosing time, they are questioned for AEs and have vital signs checked. Also, blood is drawn to measure plasma amantadine concentrations. Instructions for contacting the site to report any AEs are reviewed with the subjects prior to their discharge from the CRU. The schedule for returning to the PSU for the next dosing period (this applies to returning for Periods 2 & 3) or for telephone contact (this applies to the follow-up after the third dosing period) is be reviewed.

All subjects receive a follow-up telephone call 3 days following discharge from the CRU (Day 19).

AEs and concomitant medications are monitored throughout the study. Blood samples for measurement of blood plasma concentrations are drawn immediately prior to the 23:00 h dosing time on Days 1, 8, and 15, and at approximately 8:00 h on Days 2, 9, and 16.

Sleep parameters and measurements of sleepiness and alertness at each time point are listed by subject. Both composite scores and scores from the individual components of the PSG and questionnaires are tabulated and analyzed. For each parameter measured, descriptive summary statistics are calculated by sequence and treatment, including means (or medians, as appropriate), ranges, and standard deviations (SDs).

Inferential statistics are performed on selected results wherein the magnitude of the differences between the means across treatment groups relative to the variance suggests a possible differential treatment effect. Continuous variable data is analyzed by parametric statistics (repeated measures analysis of variance with appropriate supplemental post-hoc analyses and/or paired t-test). Categorical data and data not conforming to a normal distribution is analyzed by non-parametric statistics (Wilcoxon signed rank test). PSG data may also be assessed by multivariate analyses and/or spectral analyses.

Results: A lack of increase in, or reduction of, sleep disturbances with QD administration of 220 mg of amantadine ER compared to BID administration of amantadine IR, as measured by PSG and a standardized sleep questionnaire (e.g. SSS, m-ESS, KSS, THAT, ZOGIM-A, or VAS), demonstrates the suitability of amantadine ER for once daily administration at bedtime.

EXAMPLE 9

Study Comparing the Effects on Sleep and Efficacy of Amantadine HCl ER Capsules Administered Once Daily at Night Relative to Amantadine HCl IR Capsules Administered Twice Daily in Parkinson's Patients

Objective: To compare the effects on sleep and efficacy of amantadine extended release (ER) capsules.

Study Design: This is a Multi-Center, Double-Blind, Randomized Study to Compare the Effects on Sleep and Efficacy of Amantadine Extended Release (ER) Capsules in 120 Parkinsons Patients as assessed by UPDRS (Unified Parkinson's Disease Rating Scale), UPDRS-IV (Unified Parkinson's Disease Rating Scale Part IV), AIMS (Abnormal Involuntary Movement Scale), overnight polysomnography (PSG) and standardized questionnaires (Stanford Sleepiness Scale (SSS); Modified Epworth Sleepiness Scale (m-ESS)/Karolinska Sleepiness Scale (KSS); Toronto Hospital Alertness Test (THAT)/ZOGIM Alertness Scale (ZOGIM-A); Visual analog scale of sleepiness/alertness (VAS)).

All study drugs are administered orally. Treatment A consists of a placebo capsule administered in the morning and two 110 mg capsules of Amantadine (ER) and a placebo capsule administered at bed time. Treatment B consists of a placebo capsule administered in the morning and three 110 mg capsules of Amantadine (ER) administered at bed time. Treatment C consists of a 100 mg capsule of Amantadine IR administered in the morning and a 100 mg capsule of Amantadine IR and two placebo capsules administered at bed time. Treatment D consists of a placebo capsule administered in the morning and 3 placebo capsules administered at bed time.

Consented subjects who meet eligibility criteria are randomized equally to one of 3 treatment groups, each comprising 14-day treatment periods. Additionally, there is a one-day, single-blind, placebo run-in prior to each double-blind dosing day. This is to allow subjects to acclimate to sleeping in the Clinical Research Unit (CRU) under conditions of PSG recording and to establish individual baseline (BL) PSG characteristics.

For each dosing period, subjects are admitted to a CRU equipped with a sleep laboratory the day before the first day of dosing with active study drug. They stay in the CRU overnight and through the entirety of the active drug-dosing day. They again stay overnight and then are discharged from the CRU the morning of the following day.

Parkinson's scores are recorded in the mornings on days 1, 7 and 14 using standard scoring methods, including the UPDRS and AIM.

AEs and concomitant medications are monitored throughout the study.

Sleep parameters and measurements of sleepiness and alertness at each time point are listed by subject. Both composite scores and scores from the individual components of the PSG and questionnaires are tabulated and analyzed. For each parameter measured, descriptive summary statistics are calculated by sequence and treatment, including means (or medians, as appropriate), ranges, and standard deviations (SDs).

Inferential statistics are performed on selected results wherein the magnitude of the differences between the means across treatment groups relative to the variance suggests a possible differential treatment effect. Continuous variable data is analyzed by parametric statistics (repeated measures analysis of variance with appropriate supplemental post-hoc analyses and/or paired t-test). Categorical data and data not conforming to a normal distribution is analyzed by non-parametric statistics (Wilcoxon signed rank test). PSG data may also be assessed by multivariate analyses and/or spectral analyses.

Results: An improvement in UPDRS, UPDRS-IV, AIM, lack of increase in, or reduction of, sleep disturbances, as measured by PSG and a standardized sleep questionnaire (e.g. SSS, m-ESS, KSS, THAT, ZOGIM-A, or VAS), demonstrates the suitability of amantadine ER for once daily administration at bedtime.

EXAMPLE 10

Simulated Pharmacokinetic Characteristics of Higher Strength, Amantadine ER Formulations Administered at Nighttime

Objective: The objective is to use the data generated in the clinical study described in Example 7 to predict steady state plasma concentration-time profiles of various IR and ER amantadine regimens at different dose levels to show the benefits of higher strength amantadine ER formulations administered at nighttime.

Methodology: Plasma concentration-time profiles from healthy volunteers that received multiple doses of the ER and IR formulations of amantadine per study procedures described in Example 7 (ADS-5101-MD-104) were used to develop a pharmacokinetic model describing each of the two formulations. This study was an open-label, randomized, two-treatment, two-period, two-way crossover study comparing once-daily amantadine ER capsules and twice-daily amantadine IR tablets in 26 healthy, adult male and female volunteers. Complete data from 24 individuals were used in this exercise. Blood samples for pharmacokinetic evaluation were collected after single dosing on Day 1 and at steady state on Day 9. In the first step of the analysis, WinNonlin 5.2.1 (Pharsight Corp., Mountain View, Calif.) was used to fit a one-compartment model with first-order input and first-order output, weighted 1/y (where y is the amantadine plasma concentration), to each individual's plasma concentration-time data obtained after single (Day 1) and repeated (Day 9) dose administration of amantadine IR and ER; the fitting was done separately for both formulations, but simultaneously for both days. Modeling assumptions employed include dose proportionality and constant clearance as a function of time.

The model is described by the following equation:

$$C = \frac{FD}{V(k_a - k)}[\exp(-k(t - t_{lag})) - \exp(-k_a(t - t_{lag}))] \quad \text{Equation 1}$$

where C is the plasma concentration, F is the absolute bioavailability, D is dose, V is the volume of distribution, k_a is the absorption rate constant, k is the elimination rate constant, t is time, and t_{lag} is the lag time of absorption. The goodness of fit was verified by comparing the individual model predicted and observed concentration-time data from Study ADS-5101-MD-104. After Equation 1 was fitted to each individual's plasma concentration-time data, model parameter estimates of V/F, k_a, k, and t_{lag} were obtained for each of the 24 subjects. The goodness of the prediction at steady state was confirmed by comparing the observed data and predicted steady-state concentrations of amantadine obtained after daily dosing of 200 mg as the ER and IR formulations (Day 9).

In the second step of the analysis, individual model parameter estimates were used to simulate steady-state concentration-time profiles for each individual for both formulations by reinserting the individual parameter estimates into Equation 1, and summing the contribution of 7 sequential days of dosing, according to the following dosing regimens:

1. Once Daily (QD) dosing of 260, 340, and 420 mg of the ER formulation to steady state
2. Three times daily (TID) dosing of 100 mg of the IR formulation to steady state
3. Twice daily (BID) dosing of 100 mg of the IR formulation to steady state

Results: FIG. **4** shows the simulated steady state plasma concentration time profiles for various ER amantadine doses along with various regimes of IR amantadine. Table 11 summarizes values of the pharmacokinetic parameters that affect the efficacy and tolerability of ER amantadine when administered at night.

TABLE 11

PK parameters associated with nighttime administration - morning peak benefit measured for ER Amantadine formulation

	IR 100 mg BID	IR 100 mg TID	ER 260 mg QD	ER 340 mg QD	ER 420 mg QD
Cmax (ng/ml)	669	936	834	1091	1348
Cmin (ng/ml)	435	731	461	603	745
Cmax/Cmin	1.54	1.28	1.81	1.81	1.81

TABLE 11-continued

PK parameters associated with nighttime administration - morning peak benefit measured for ER Amantadine formulation

	IR 100 mg BID	IR 100 mg TID	ER 260 mg QD	ER 340 mg QD	ER 420 mg QD
C-ave-day (6am-4pm) (ng/ml)	571	845	766	1002	1238
C-ave-morn (6am-10am) (ng/ml)	479	870	824	1078	1332
C-ave-even (4pm-10pm) (ng/ml)	522	852	591	773	955
C-ave-night (10pm-6am) (ng/ml)	596	843	616	805	995
C-ave-day/C-ave-night	0.96	1.00	1.24	1.24	1.24
C-ave-morn/C-ave-night	0.80	1.03	1.34	1.34	1.34
C-ave-day relative to 100 mg BID IR	1.00	1.48	1.34	1.76	2.17

As shown in Table 11 and in the figures, the ER amantadine formulations administered once daily at night result in higher ratios of average day time to night time amantadine plasma concentrations relative to IR amantadine and are predicted to be relatively well tolerated. The ER formulations also result in average day time amantadine plasma concentrations that are 1.3 to 2.2 fold that of IR amantadine administered at 100 mg twice daily and is predicted to result in significantly enhanced efficacy when administered to patients in the clinical study described in Example 11 below.

EXAMPLE 11

A Randomized, Double-blind, Placebo-controlled Study of the Efficacy and Safety of Amantadine Extended Release Oral Capsules for the Treatment of Levodopa-induced Dyskinesia in Parkinson's Disease

Study Objectives: This study is designed to confirm dose range of Amantadine Extended Release (ER) oral capsules dosed once daily at nighttime for the treatment of levodopa-induced dyskinesia (LID) in subjects with Parkinson's Disease (PD). In addition, the study is designed to demonstrate the safety and tolerability of Amantadine ER oral capsules dosed once daily for the treatment of LID in subjects with PD. Finally, to confirm the steady-state pharmacokinetics of the Amantadine ER dosing regimens in Parkinsons patients and to correlate C-ave-day, Cave-morning, C-ave-morning/C-ave-night and C-ave-day/C-ave-night with the efficacy and tolerability of amantadine.

Study Design: This will be a multi-center, randomized, double-blind, placebo-controlled, 4-arm parallel group study of Amantadine ER in subjects with PD and LID/Consenting subjects who meet eligibility criteria will be randomized 1:1:1:1 to receive one of the following 4 treatments, each administered as once daily, dosed at night, for 8 weeks:

Treatment A: Placebo,

Treatment B: 260 mg Amantadine ER (ADS-5102),

Treatment C: 340 mg Amantadine ER (ADS-5102)

Treatment D: 420 mg Amantadine ER (ADS-5102)

Subjects who are randomized to Treatment C or D (higher dose amantadine groups) will receive, in double-blind fashion, 260 mg Amantadine ER once daily during week 1, with an increase to either 340 mg or 420 mg once daily at the beginning of week 2. Dosing will continue through week 8.

Following completion of the baseline visit and randomization, subjects will return to the clinic after 1, 2, 4, 6, and 8 weeks of dosing, with a follow-up visit 14 days following the last dose of study drug. Study visits and assessments will be scheduled during morning hours when possible (9 am through 1 pm). A set of two 24-hour diaries will be completed during 48 hours prior to randomization and 48 hours prior to selected study visits. The diary will be used to score five different conditions in 30-minute intervals: Sleep, OFF, ON without dyskinesias, ON with nontroublesome dyskinesias, ON with troublesome dyskinesias.

Blood samples will be collected at selected study visits for determination of amantadine plasma concentrations, and evaluation of steady-state population pharmacokinetics. Subject participation during the study will be up to 12 weeks and will include a 2-week (maximum) screening period, 8-week (maximum) treatment period, and a 2-week follow-up period. Subjects who are unable to tolerate their assigned study drug assignment will permanently discontinue study drug and continue to be followed for safety through 2 weeks following the last dose of study drug.

Patient Eligibility Criteria: Subjects are eligible to take part in the study if they meet the inclusion and do not meet the exclusion criteria. Selected key criteria are as follows:

Inclusion Criteria:

- Male or female adults, residing in the community (i.e. not residing in an institution)
- Between 30 and 75 years of age, inclusive
- Ambulatory or ambulatory-aided (e.g. walker or cane) ability, such that the subject can come to required study visits
- Knowledgeable and reliable caregiver/study partner, if appropriate, to accompany the subject to study visits
- Signed a current IRB/IEC-approved informed consent form
- Following training, the subject is willing and able to understand and complete the 24-hour home diary (caregiver assistance allowed)
- Idiopathic Parkinson's Disease, complicated by dyskinesia (a MDS-UPDRS score will be determined during screening, but a minimum score is not required)
- On a stable regimen of antiparkinson's medications, including levodopa, for at least 30 days prior to screening, and willing to continue that regimen during study participation
- Presence of dyskinesia, defined as a minimum UDysRS score

Exclusion Criteria:

- Presence of other neurological disease that may affect cognition, including, but not limited to Alzheimer's dementia, Huntington's disease, Lewy body dementia, frontotemporal dementia, corticobasal degeneration, or motor or sensory dysfunction secondary to stroke or brain trauma.
- Presence of cognitive impairment, as evidenced by a Mini-mental State Examination (MMSE) score of less than 24 during screening.

- Presence of an acute major psychiatric disorder (e.g., Major Depressive Disorder) according to DSM-IV-TR or symptom (e.g., hallucinations, agitation, paranoia) that could affect the subject's ability to complete study assessments
- Presence of sensory impairments (e.g., hearing, vision) that would impair the subject's ability to complete study assessments
- History of alcohol or drug dependence or abuse, according to DSM-IV criteria, within 2 years prior to screening
- History of seizures (excluding febrile seizures of childhood)
- History of stroke or TIA within 2 years prior to screening
- History of myocardial infarction, NYHA Congestive Heart Failure Class 3 or 4, or atrial fibrillation within 2 years prior to screening
- History of cancer within 5 years prior to screening, with the following exceptions: adequately treated non-melanomatous skin cancers, localized bladder cancer, non-metastatic prostate cancer or in situ cervical cancer (these exceptions must be discussed with and approved by the Medical Monitor before study entry)
- Any of the following lab abnormalities; Hemoglobin <10 g/dL, WBC $<3.0\times10^9$/L, Neutrophils $<1.5\times10^9$/L, Lymphocytes $<0.5\times10^9$/L, Platelets $<100\times10^9$/L, Hemoglobin A1C >9%, or Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >2 times the upper limit of normal
- Estimated GFR <50 mL/min/1.73 m^2 by Modification of Diet in Renal Disease (MDRD) or Cockcroft-Gault equation
- Any clinically significant ECG abnormalities
- Inability to swallow oral capsules, or a history of gastrointestinal malabsorption that would preclude the use of oral medication

Study Endpoints: The primary efficacy endpoint will be the change from baseline to week 8 in the Unified Dyskinesia Rating Scale (UDysRS) score. Key secondary endpoints will include:

- ON time without troublesome dyskinesia (ON without dyskinesia plus ON with non-troublesome dyskinesia), based on a standardized PD home diary
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), overall score
- Fatigue as measured by the Fatigue Severity Scale (FSS). This scale includes 9 questions that are completed by the patient using a rating scale from 1 (strongly disagree) to 7 (strongly agree). This fatigue scale is recommended by MDS for both screening and severity rating (2010)
- Safety, including adverse events, safety-related study drug discontinuations, vital signs, and laboratory tests.

The following mixture of traditional and new scales have been selected for this phase 2 study:

- Unified Dyskinesia Rating Scale (UDysRS) will be used for primary outcome measure. This scale has four parts, and a total possible score of 104:
  - I: Historical Disability (patient perceptions) of On-Dyskinesia impact
  - II: Historical Disability (patient perceptions) of Off-Dystonia impact
  - III: Objective Impairment (dyskinesia severity, anatomic distribution, and type, based on 4 observed activities)
  - IV: Objective Disability based on Part III activities
- ON time without troublesome dyskinesia, based on a standardized Parkinson's Disease home diary (suggest Test Diary II), [33] will be a secondary outcome measure. This scale has been used in number of studies with mixed success [34]. However, most KOLs feel that subject-reported dairy data must be collected, and needs to support the primary outcome measure.
- Unified Parkinson's Disease Rating Scale (UPDRS), part IV, items 32 (duration of dyskinesias: 0=none, 4=76-100% of the waking day) and 33 (disability of dyskinesias: 0=not disabling, 4=completely disabling) will be a secondary outcome measure. This scale is a traditional scale used in PD for many years and these items have been utilized in most LID studies.
- Cognitive Scales: Global caregiver impression, depression and other scales will be employed to measure the mental status benefits of ER amantadine.

Statistical Methods

Efficacy Analyses: The efficacy analysis population will include all randomized and dosed subjects who provide at least one post-baseline efficacy assessment. For the efficacy endpoint of UDysRS score, the change from baseline to week 8 will be analyzed using an analysis of covariance (ANCOVA) model with treatment group as a factor and the UDysRS baseline value as a covariate. The primary analysis will compare the 260 mg ADS-5102 group to the placebo group using a two-sided test at the 5% level of significance. If the primary comparison is statistically significant ($p<0.05$), then the 340 mg and 420 mg ADS-5102 groups will be compared to placebo, also using a two-sided test at the 5% level of significance.

The secondary endpoints will be analyzed using the same types of ANCOVA models as described for the primary endpoint. All secondary comparisons between treatment groups will be performed using two-sided tests at the 5% level of significance. A last observation carried forward (LOCF) approach will be utilized for missing data. The primary efficacy analysis will be repeated for the per-protocol population, a subset of the efficacy analysis population who provide week 8 efficacy assessments.

Safety Analyses: The safety analysis population will include all randomized subjects who receive at least one dose of study drug. All safety endpoints will be analyzed from the time of first dose through the completion of follow-up (or 2 weeks following the last dose of study drug). A safety analysis will also be done on the safety reported during the first 2 weeks of study drug treatment, in order to assess tolerability of initial dosing with ADS-5102 amantadine ER.

Results: following improvements are expected from this study are shown in the table below. Additional endpoints are described that

- Significant (20-60%) reduction in dyskinesia score measured by acceptable primary endpoint (e.g., UDysRS)
- Increase in ON time without troubling dyskinesia by 20-60%
- Improvement in UPDRS from 5% to 20%.
- Improvement in Parkinson's fatigue (FSS) from 5% to 60%.
- Improvement in mood by PGI from 5% to 20%.

Instruments for Dyskinesia	% Clinical Effect (Placebo-Active/ Placebo)	Range of Scores
Unified Dyskinesia Rating Scale (UDysRS)	5-60%	0-104 (4 parts, 26 items total, each 0, normal-4, severe)
Unified Parkinson's Disease Rating Scale (UPDRS, MDS revision)	5-20%	
Part IV	5-60%	0-24 (6 items, each 0, normal-4, severe)
Part IV, dyskinesia items only	5-60%	0-8 (2 dyskinesia items, 4.1 and 4.2, each 0, normal-4, severe)
Parkinson's Disease Home Diary (Hauser et al)	5-40%	0-100% (on time without dyskinesia or with nontroublesome dyskinesia)

EXAMPLE 12

Simulated Pharmacokinetic Characteristics of Amantadine ER Formulations with a Delayed Release Coat Suitable for Night Time Administration

Objective: The objective is to evaluate the pharmacokinetic profile of two alternative ER formulations of amantadine suitable for nighttime administration—Formulation 1, which is the formulation tested in Example 7, and Formulation 2, which is the formulation tested in Example 7, but with a delayed release over coat on top of the extended release coat.

Plasma concentration-time profiles from healthy volunteers, who received multiple doses of the ER and IR formulations of amantadine per study procedures described in Example 7 (ADS-5101-MD-104), were used to develop a pharmacokinetic model describing each of the two formulations. This study was an open-label, randomized, two-treatment, two-period, two-way crossover study comparing once-daily amantadine ER capsules and twice-daily amantadine IR tablets in 26 healthy, adult male and female volunteers. Complete data from 24 individuals were used in this exercise. Blood samples for pharmacokinetic evaluation were collected after single dosing on Day 1 and at steady state on Day 9. In the first step of the analysis, WinNonlin 5.2.1 (Pharsight Corp., Mountain View, Calif.) was used to fit a one-compartment model with first-order input and first-order output, weighted 1/y (where y is the amantadine plasma concentration), to each individual's plasma concentration-time data obtained after single (Day 1) and repeated (Day 9) dose administration of amantadine IR and ER; the fitting was done separately for both formulations, but simultaneously for both days. Modeling assumptions employed include dose proportionality and constant clearance as a function of time.

The model is described by the following equation

$$C = \frac{FD}{V(k_a - k)}[\exp(-k(t - t_{lag})) - \exp(-k_a(t - t_{lag}))] \quad \text{Equation 1}$$

where C is the plasma concentration, F is the absolute bioavailability, D is dose, V is the volume of distribution, k_a is the absorption rate constant, k is the elimination rate constant, t is time, and t_{lag} is the lag time of absorption. The goodness of fit was verified by comparing the individual model predicted and observed concentration-time data from Study ADS-5101-MD-104. After Equation 1 was fitted to each individual's plasma concentration-time data, model parameter estimates of V/F, k_a, k, and t_{lag} were obtained for each of the 24 subjects. The goodness of the prediction at steady state was confirmed by comparing the observed data and predicted steady-state concentrations of amantadine obtained after daily dosing of 200 mg as the ER and IR formulations (Day 9).

In the second step of the analysis, individual model parameter estimates were used to simulate steady-state concentration-time profiles for each individual for both formulations by reinserting the individual parameter estimates into Equation 1, and summing the contribution of 7 sequential days of dosing, according to the following dosing regimens:

1. Once Daily (QD) dosing of 200 mg of the ER Formulation 1 to steady state
2. Once Daily (QD) dosing of 200 mg of the ER Formulation 2 to steady state

Results: FIG. **7** shows the simulated steady state plasma concentration time profiles for the two ER amantadine formulations. (Amantadine blood plasma concentrations are shown on the y, time of day on the x-axis.) As shown in FIG. **7**, the ER amantadine formulation 2 administered once daily at night results in about a 4 hour delay in achieving peak plasma concentration at steady state relative to formulation 1. Thus, a formulation comprising a delayed release coat on top of the extended release coat has a very favorable pharmacokinetic profile in that it maximizes the daytime plasma exposure to amantadine whilst minimizing night plasma exposure at steady state.

While preferred embodiments of the present invention have been shown and described herein, such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. All references cited herein are incorporated herein by reference in their entirety.

What is claimed is:

1. A method of treating a patient with Parkinson's disease, comprising administering once daily, 0 to 4 hours before bedtime, to said patient with Parkinson's disease, a pharmaceutical composition comprising: (i) 220 mg to 455 mg of a drug selected from the group consisting of amantadine and a pharmaceutically acceptable salt thereof; and (ii) one or more excipients, wherein at least one of said one or more excipients modifies the release of said drug to provide an extended release dosage form,

wherein ON time without troublesome dyskinesia is increased in said patient with Parkinson's disease, and

wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the Tmax for the drug is 8 to 20 hours.

2. The method of claim **1**, wherein said increased ON time without troublesome dyskinesia is determined from a Parkinson's disease home diary.

3. The method of claim **1**, wherein said Tmax is 9 to 18 hours.

4. The method of claim **1**, wherein said Tmax is 11 to 18 hours.

5. The method of claim **1**, wherein when said pharmaceutical composition is dosed in a single dose, fasted, human

pharmacokinetic study in healthy subjects, the $AUC_{0\text{-}inf}$ for the drug is 40 to 75 ng*hr/ml per mg of the drug.

6. The method of claim **1**, wherein when said pharmaceutical composition is dosed in a multiple dose, fasted, human pharmacokinetic study in healthy subjects, the steady state $AUC_{0\text{-}24}$ for the drug is 44 to 83 ng*hr/ml per mg of the drug.

7. The method of claim **1**, wherein said pharmaceutical composition is administered to said patient once daily, 0 to 3 hours before bedtime.

8. The method of claim **1**, wherein said pharmaceutical composition comprises 1 or 2 unit dosage forms.

9. The method of claim **1**, wherein said pharmaceutical composition comprises one, two, or three capsules.

10. A method of treating a patient with Parkinson's disease, comprising administering once daily, 0 to 4 hours before bedtime, to said patient with Parkinson's disease, a pharmaceutical composition comprising: (i) 220 mg to 445 mg of a drug selected from the group consisting of amantadine and a pharmaceutically acceptable salt thereof; and (ii) one or more excipients, wherein at least one of said one or more excipients modifies the release of said drug to provide an extended release dosage form,

wherein ON time without troublesome dyskinesia is increased in said patient with Parkinson's disease, and

wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the Cmax for the drug is 1.0 to 2.8 ng/ml per mg of the drug and the $AUC_{0\text{-}inf}$ for the drug is 40 to 75 ng*h/ml per mg of the drug.

11. The method of claim **10**, wherein said increased ON time without troublesome dyskinesia is determined from a Parkinson's disease home diary.

12. The method of claim **10**, wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the Tmax for the drug is 8 to 18 hours.

13. The method of claim **10**, wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the Tmax for the drug is 9 to 18 hours.

14. The method of claim **10**, wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the Tmax for the drug is 11 to 18 hours.

15. The method of claim **10**, wherein when said pharmaceutical composition is dosed in a multiple dose, fasted, human pharmacokinetic study in healthy subjects, the steady state $AUC_{0\text{-}24}$ for the drug is 44 to 83 ng*hr/ml per mg of the drug.

16. The method of claim **10**, wherein said pharmaceutical composition is administered to said patient once daily, 0 to 3 hours before bedtime.

17. The method of claim **10**, wherein said pharmaceutical composition comprises 1 or 2 unit dosage forms.

18. The method of claim **10**, wherein said pharmaceutical composition comprises one, two, or three capsules.

19. The method of claim **10**, wherein said drug is a pharmaceutically acceptable salt of amantadine.

20. The method of claim **10**, wherein said drug is amantadine hydrochloride.

21. The method of claim **10**, wherein said pharmaceutical composition is selected from the group consisting of one unit dosage form comprising 340 mg of said drug and two unit dosage forms each comprising 170 mg of said drug.

22. The method of claim **21**, wherein said drug is a pharmaceutically acceptable salt of amantadine.

23. The method of claim **21**, wherein said drug is amantadine hydrochloride.

24. The method of claim **1**, wherein said drug is a pharmaceutically acceptable salt of amantadine.

25. The method of claim **1**, wherein said drug is amantadine hydrochloride.

26. The method of claim **1**, wherein said pharmaceutical composition is selected from the group consisting of one unit dosage form comprising 340 mg of said drug and two unit dosage forms each comprising 170 mg of said drug.

27. The method of claim **26**, wherein said drug is a pharmaceutically acceptable salt of amantadine.

28. The method of claim **26**, wherein said drug is amantadine hydrochloride.

29. The method of claim **1**, wherein when said pharmaceutical composition is dosed in a single dose, fasted, human pharmacokinetic study in healthy subjects, the Cmax for the drug is 1.0 to 2.8 ng/ml per mg of the drug.

30. The method of claim **29**, wherein the Cmax for the drug is 1.0 to 2.4 ng/ml per mg of the drug.

31. The method of claim **10**, wherein the Cmax for the drug is 1.0 to 2.4 ng/ml per mg of the drug.

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