01/2008:1411

COCOYL CAPRYLOCAPRATE

Cocoylis caprylocapras

DEFINITION

Mixture of esters of saturated C_{12} - C_{18} alcohols with caprylic (octanoic) and capric (decanoic) acids obtained by the reaction of these acids with vegetable saturated fatty alcohols.

CHARACTERS

Appearance: slightly yellowish liquid.

Solubility: practically insoluble in water, miscible with ethanol (96 per cent) and with liquid paraffin.

Relative density: about 0.86.

Refractive index: about 1.445.

Viscosity: about 11 mPa·s.

IDENTIFICATION

A. Freezing point (*2.2.18*): maximum 15 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *cocoyl caprylocaprate CRS*.

C. Composition of fatty acids and fatty alcohols (see Tests).

TESTS

Appearance. The substance to be examined is not more intensely coloured than reference solution Y_5 (*2.2.2, Method I*).

Acid value (*2.5.1*): maximum 0.5, determined on 5.00 g.

Hydroxyl value (*2.5.3, Method A*): maximum 5.0.

Iodine value (*2.5.4, Method A*): maximum 1.0.

Saponification value (*2.5.6*): 160 to 173.

Composition of fatty acids and fatty alcohols (*2.4.22, Method C*). Use the chromatogram obtained with the following reference solution for identification of the peaks due to the fatty alcohols.

Reference solution. Dissolve the amounts of the substances listed in the following table in 10 mL of *heptane R*.

Substance	Amount (mg)
Methyl caproate R	10
Methyl caprylate R	90
Methyl caprate R	50
Methyl laurate R	20
Methyl myristate R	10
Methyl palmitate R	10
Methyl stearate R	10
Capric alcohol R	10
Lauryl alcohol R	100
Myristyl alcohol R	40
Cetyl alcohol CRS	30
Stearyl alcohol CRS	20

Consider the sum of the areas of the peaks due to the fatty acids listed below to be equal to 100 and the sum of the areas of the peaks due to the fatty alcohols listed below to be equal to 100.

Composition of the fatty acid fraction of the substance:
- *caproic acid*: maximum 2.0 per cent,
- *caprylic acid*: 50.0 per cent to 80.0 per cent,
- *capric acid*: 20.0 per cent to 50.0 per cent,
- *lauric acid*: maximum 3.0 per cent,
- *myristic acid*: maximum 2.0 per cent.

Composition of the fatty alcohol fraction of the substance:
- *capric alcohol*: maximum 3.0 per cent,
- *lauryl alcohol*: 48.0 per cent to 63.0 per cent,
- *myristyl alcohol*: 18.0 per cent to 27.0 per cent,
- *cetyl alcohol*: 6.0 per cent to 13.0 per cent,
- *stearyl alcohol*: 9.0 per cent to 16.0 per cent.

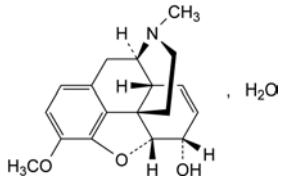
Water (*2.5.12*): maximum 0.1 per cent, determined on 5.00 g.

Total ash (*2.4.16*): maximum 0.1 per cent, determined on 1.0 g.

04/2008:0076
corrected 7.0

CODEINE

Codeinum



$C_{18}H_{21}NO_3,H_2O$ M_r 317.4
[6059-47-8]

DEFINITION

7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol monohydrate.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals.

Solubility: soluble in boiling water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C.

Second identification: A, B, D, E.

A. Melting point (*2.2.14*): 155 °C to 159 °C.

B. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).
Test solution. To 2.0 mL of solution S (see Tests) add 50 mL of *water R* then 10 mL of *1 M sodium hydroxide* and dilute to 100.0 mL with *water R*.
Spectral range: 250-350 nm.
Absorption maximum: at 284 nm.
Specific absorbance at the absorption maximum: about 50 (dried substance).

C. Infrared absorption spectrophotometry (*2.2.24*).
Preparation: dried substance prepared as a disc of *potassium bromide R*.
Comparison: *codeine CRS*.

D. To about 10 mg add 1 mL of *sulfuric acid R* and 0.05 mL of *ferric chloride solution R2* and heat on a water-bath. A blue colour develops. Add 0.05 mL of *nitric acid R*. The colour changes to red.

E. It gives the reaction of alkaloids (*2.3.1*).

TESTS

Solution S. Dissolve 50 mg in *carbon dioxide-free water R* and dilute to 10.0 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Specific optical rotation (*2.2.7*): – 142 to – 146 (dried substance).

Dissolve 0.50 g in *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined and 0.100 g of *sodium octanesulfonate R* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a). Dissolve 5.0 mg of *codeine impurity A CRS* in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (b). Dilute 1.0 mL of reference solution (a) to 20.0 mL with the mobile phase.

Reference solution (c). Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (d). To 0.25 mL of the test solution, add 2.5 mL of reference solution (a).

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

– *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: dissolve 1.08 g of *sodium octanesulfonate R* in a mixture of 20 mL of *glacial acetic acid R* and 250 mL of *acetonitrile R* and dilute to 1000 mL with *water R*.

Flow rate: 2 mL/min.

Detection: spectrophotometer at 245 nm.

Injection: 10 µL.

Run time: 10 times the retention time of codeine.

Relative retention with reference to codeine (retention time = about 6 min): impurity B = about 0.6; impurity E = about 0.7; impurity A = about 2.0; impurity C = about 2.3; impurity D = about 3.6.

System suitability: reference solution (d):

– *resolution*: minimum 3 between the peaks due to codeine and impurity A.

Limits:

– *correction factor*: for the calculation of content, multiply the peak area of impurity C by 0.25;

– *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

– *impurities B, C, D, E*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);

– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);

– *sum of impurities other than A*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);

– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Loss on drying (*2.2.32*): 4.0 per cent to 6.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in 10 mL of *anhydrous acetic acid R*. Add 20 mL of *dioxan R*. Titrate with *0.1 M perchloric acid*, using 0.05 mL of *crystal violet solution R* as indicator.

1 mL of *0.1 M perchloric acid* is equivalent to 29.94 mg of $C_{18}H_{21}NO_3$.

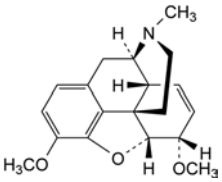
STORAGE

Protected from light.

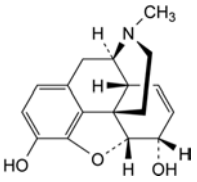
IMPURITIES

Specified impurities: A, B, C, D, E.

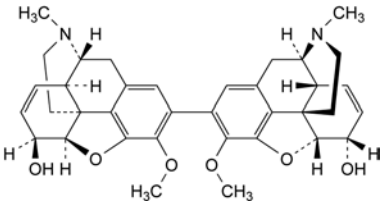
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034)*. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *F, G.*



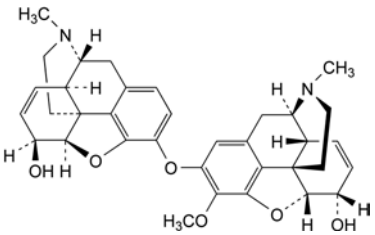
A. 7,8-didehydro-4,5α-epoxy-3,6α-dimethoxy-17-methylmorphinan (methylcodeine),



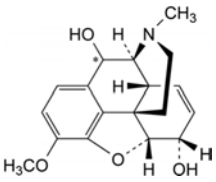
B. 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol (morphine),



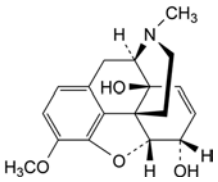
C. 7,7′,8,8′-tetradehydro-4,5α:4′,5′α-diepoxy-3,3′-dimethoxy-17,17′-dimethyl-2,2′-bimorphinanyl-6α,6′α-diol (codeine dimer),



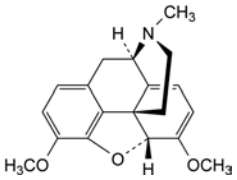
D. 7,8-didehydro-2-[(7,8-didehydro-4,5α-epoxy-6α-hydroxy-17-methylmorphinan-3-yl)oxy]-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol (3-*O*-(codein-2-yl)morphine),



E. 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α,10-diol,



F. 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α,14-diol,

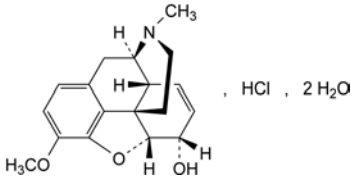


G. 6,7,8,14-tetradehydro-4,5α-epoxy-3,6-dimethoxy-17-methylmorphinan (thebaine).

01/2008:1412

CODEINE HYDROCHLORIDE DIHYDRATE

Codeini hydrochloridum dihydricum



$C_{18}H_{22}ClNO_3,2H_2O$ M_r 371.9

DEFINITION

7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol hydrochloride dihydrate.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder or small, colourless crystals.

Solubility: soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in cyclohexane.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D, E.

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *Ph. Eur. reference spectrum of codeine hydrochloride dihydrate.*

B. To 5 mL of solution S (see Tests) add 1 mL of a mixture of equal volumes of *strong sodium hydroxide solution R* and *water R* and initiate crystallisation, if necessary, by scratching the wall of the tube with a glass rod and cooling in iced water. Wash the precipitate with *water R* and dry at 100-105 °C. It melts (*2.2.15*) at 155 °C to 159 °C.

C. To about 10 mg add 1 mL of *sulfuric acid R* and 0.05 mL of *ferric chloride solution R2* and heat on a water-bath. A blue colour develops. Add 0.05 mL of *nitric acid R*. The colour changes to red.

D. Solution S gives reaction (a) of chlorides (*2.3.1*).

E. It gives the reaction of alkaloids (*2.3.1*).

TESTS

Solution S. Dissolve 2.00 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Acidity or alkalinity. To 5 mL of solution S add 5 mL of *carbon dioxide-free water R*. Add 0.05 mL of *methyl red solution R* and 0.2 mL of *0.02 M hydrochloric acid*; the solution is red. Add 0.4 mL of *0.02 M sodium hydroxide*; the solution becomes yellow.

Specific optical rotation (*2.2.7*): – 117 to – 121 (anhydrous substance).

Dilute 5.0 mL of solution S to 10.0 mL with *water R*.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined and 0.100 g of *sodium octanesulfonate R* in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a). Dissolve 5.0 mg of *codeine impurity A CRS* in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (b). Dilute 1.0 mL of reference solution (a) to 20.0 mL with the mobile phase.

Reference solution (c). Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (d). To 0.25 mL of the test solution add 2.5 mL of reference solution (a).

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 μm).

Mobile phase: dissolve 1.08 g of *sodium octanesulfonate R* in a mixture of 20 mL of *glacial acetic acid R* and 250 mL of *acetonitrile R* and dilute to 1000 mL with *water R*.

Flow rate: 2 mL/min.

Detection: spectrophotometer at 245 nm.

Injection: 10 μL.

Run time: 10 times the retention time of codeine.

Relative retention with reference to codeine (retention time = about 6 min): impurity B = about 0.6; impurity E = about 0.7; impurity A = about 2.0; impurity C = about 2.3; impurity D = about 3.6.

System suitability: reference solution (d):

– *resolution*: minimum 3 between the peaks due to codeine and impurity A.

Limits:

– *correction factor*: for the calculation of content, multiply the peak area of impurity C by 0.25;
– *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);
– *impurities B, C, D, E*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);
– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent);
– *sum of impurities other than A*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);
– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Sulfates (*2.4.13*): maximum 0.1 per cent.

Dilute 5 mL of solution S to 20 mL with *distilled water R*.

Water (*2.5.12*): 8.0 per cent to 10.5 per cent, determined on 0.250 g.