

Extrusion- Spheronization, Engineered for Today's Controlled Release Forms

Synchronizing and controlling API delivery, extrusion-spheronization offers pharmaceutical companies a robust technique to manufacture today's most complex therapeutics.

Manufacturing oral solid dose (OSD) APIs into spheres via extrusion-spheronization (E-S) is not new. What is new is that in the right hands, with the right capabilities, this well-understood process stands ready to help lead the development and manufacturing of both today's and tomorrow's complex OSD therapeutics.



Spheronization's Expanding Influence As a Drug Manufacturing Driver

Widely acknowledged as a predictable vehicle for the control, distribution and transportation of therapeutic agents around the body, E-S engineered formulations make a variety of common and emerging controlled release dose forms possible. These include fixed-dose combinations (FDCs), combined, modified release single-capsule forms and emerging multi-unit particulate system (MUPS) tablet designs.

Ultimately E-S spheres offer a variety of physical attributes that innovators can leverage to control drug delivery, enhance therapeutic performance and the patient-centricity of today's complex, combined and modified release OSDs.

Extrusion-Spheronization is extremely viable for complex OSD development

E-S is proving to be an extremely versatile manufacturing technique and a viable route for many of today's most attractive but often complex OSD development paths, including New Molecular Entities (NMEs) and life-cycle management (LCM) extensions.

Because of its broad utility in OSD engineering, E-S also supports emerging (505(b)²) development pathways – tailoring

compounds for pediatric/geriatric applications or developing FDCs to create a new best-in-class product.

Done correctly with best-practice techniques and technology, pharmaceutical companies can leverage a better process and take advantage of its many benefits, including high-throughput manufacturing, less waste in process and better yield.

Mighty sphere of influence

Development of E-S over the past decade has been accelerated by pharmaceutical science's more comprehensive understanding of the raw materials, active ingredients, processes and controls behind the methodology, as well as how to manage and manipulate those inputs to increase therapeutic performance or modify API release - without compromising the integrity of the compound or molecule.

The dynamics of extrusion and subsequent spheronization can be managed closely

to control solubility and bioavailability characteristics, including manipulating the blending of size and density to attain different release patterns over time.

The modified release dose control E-S allows can also be used to help diminish or eliminate side effects, manage irritation or discomfort in the gastro-intestinal (GI) tract or to target release in the lower intestine to avoid acidic environments.

Patient-based outcomes driving all drug development

Medicines and therapeutics of all kinds are in increasing demand as more of the world adopts western-style pharmaceutical-based healthcare. This will prompt even more development and exploration of new techniques, materials and excipients to ensure the safety and efficacy of today's drug substances in manufacture and development.

On the innovator side, pharma's development pipeline is being filled with complex compounds that require sophisticated delivery strategies to administer doses correctly. This expertise is in high demand as drug developers seek outsourced solutions to commercialize their products.

Where drug technology meets drug strategy

A first-in-class route

For one prospective drug owner, the API in formulation of their first-in-class⁴ oncology treatment had both solubility and bioavailability issues. Single fixed-release forms would require a three times daily dosing regimen that simply was not feasible from a dose-compliance and overall therapeutic value standpoint.

These challenges were overcome by leveraging the unique flexibility of spheronization to modify and control the release of API over an extended period within a MUPS form. The result - an easy to swallow coated tablet that via a single dose provided for the controlled release of highly potent active ingredients over a 24-hour period.

A best-in-class FDC strategy

Facing the patent expiry of a popular and lucrative therapeutic, another drug developer was seeking to explore a 505(b)² life-cycle management strategy that involved integrating two proven but highly incompatible APIs into a single dose, controlled-release capsule. The challenge for this company's development team was to create a best-in-class⁴ therapy that built on the therapeutic performance of the individual drugs but improved patient outcomes and therapeutic performance better than multiple doses of two medications. Spheronization's ability to segregate and control previously incompatible APIs and combine other functional ingredients in cohesive pellets within a single OSD form offered a solution.

Focus on patient value

For the past 10 years or more, pharma and the life-sciences sector has slowly shifted its emphasis from treating disease in abstract to a more patient-centric, holistic approach.

According to an industry whitepaper on patient centricity, the shift is primarily due to pharma's growing focus on value-based care.¹ Now prioritizing quality over quantity, the health care industry and its payers are rejecting fee-for-service models and adopting approaches that are centered on improved patient health outcomes, better patient experiences and ultimately, lower overall healthcare costs.

Regulators have also been playing a greater role in driving the patient's voice into drug research and development. For instance, under the Prescription Drug User Fee Act (PDUFA V), the Food and Drug

Administration (FDA) conducted 24 disease-specific Patient-Focused Drug Development (PFDD) meetings to systematically gather patients' perspectives on their condition and available therapies to treat their condition. The report covering all 24 meetings was released at the end of 2019.²

Similarly, the European Medicines Agency (EMA) maintains its Patient Engagement Framework for guidance and thought leadership, with support from the European Patients' Academy (EUPATI).³

For the most part, regulators are looking for more effective ways to incorporate patient-reported outcomes in understanding the value that new or redeveloped therapies can bring to a specific modality or treatment area.

Harnessing Extrusion-Spheronization horsepower to accelerate therapeutic performance

Delivering therapeutic performance and better health outcomes to patients are central drivers of contemporary drug development. Genetic profiling and advanced analytical techniques for example, are assisting the personalized/precision medicine approach by providing deep insight into different patient populations and better transparency into the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of drugs under development.

Patient centricity is manifesting itself across the life sciences industry in many fundamental ways, but where the movement is being realized most profoundly is in the formulation and manufacture of OSD medications.

Extrusion-Spheronization means extra strength to pursue patient-centric OSD drug strategies

Increasingly, pharma is turning to outsourcing partners to deliver the API processing and manufacturing capabilities they need.

Tailoring dose forms to better suit a given patient population's special needs and treat disease more effectively – in principle – are all patient centric.

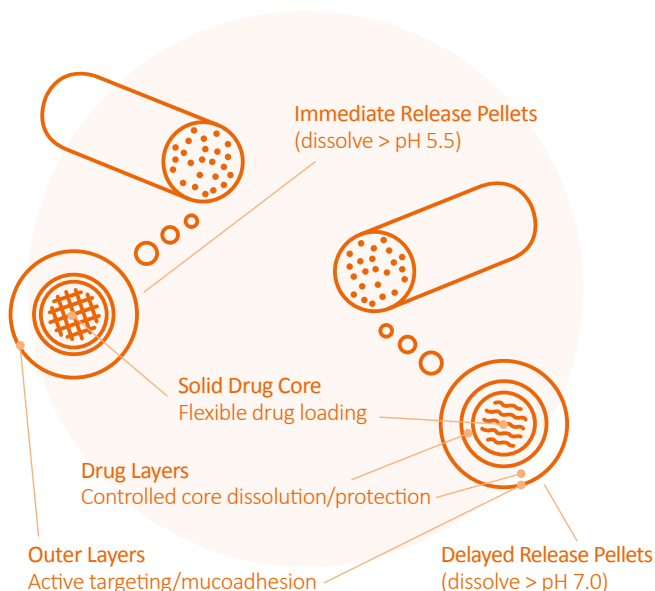
Modified release formulations, for example, can be effective for delivering drug substances that have a narrow therapeutic index or need to be in an OSD form to assure dose compliance. Orally administered drugs are by far the preferred dose form. Most patient groups respond well to taking oral medications that are easy to swallow,

require fewer doses to be effective (for longer periods) and that reduce or eliminate unpleasant side effects.

Multi-particle, multi-sphere finished-dose forms offer drug developers economic ways to explore and exploit complex patient-centric OSD drug strategies. Multi-particle systems are proving to demonstrate higher levels of desired reproducible PK and PD behaviours (including insoluble potent APIs) resulting in improved therapeutic effect in patients.

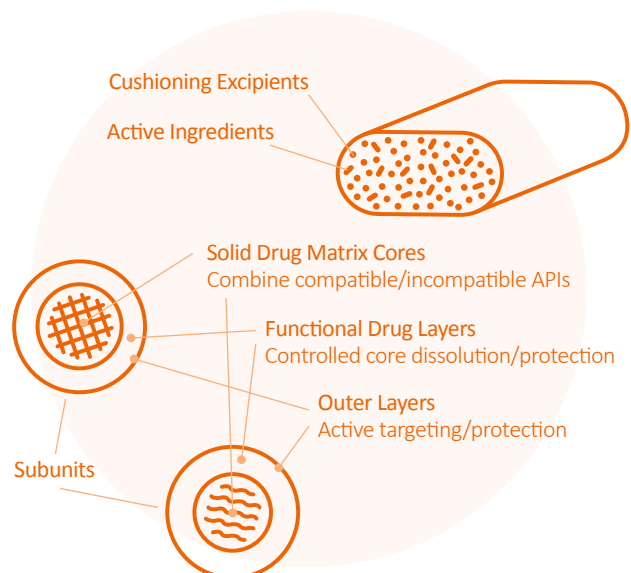
For drug designers looking to develop patient centric OSDs, these finished dose forms are offering new flexibility and utility.

Modified Release Capsules



- Highly flexible, reliable form
- Efficient delivery of potent, complex drugs
- Allows for incompatible FDCs

Multiple-Unit Pellet System (MUPS)



- Ultimate modified-release and delivery
- Patient-centric dose form flexibility
- Proven multi-API combination system

Controlling release; spheronization's key benefit

Study after study has made it clear that the method's over-arching benefit is its ability to control all important aspects of dosing APIs. The controlled, modified release of APIs provides pharmacologists and drug designers truly effective and reliable alternatives to managing dose delivery in single-unit dose forms.

Why Extrusion-Spheronization is such a handy tool

Offering processing accuracy and quality control, spheronization offers inherent efficiency, reliability and minimum variability. Because of the efficiencies related to drug loading and similar characteristics in formulation, the process generates economies on all fronts without diminishing quality.

For example, single APIs often require dispersion throughout a solid matrix to control release. These matrices can limit the rate at which active ingredients are dispersed into the body. The process also offers a reliable, flexible alternative to other spheronization or pellet agglomeration manufacturing techniques like coating or layering. Further, drug pelleting via E-S is acknowledged as a much faster process than drug layering.

A practical best practice

Extruded-spheronized pellets offer distinct physical and therapeutic advantages to drug designers including:

Physical advantages:

- Narrow particle size distribution
- Smooth, coatable surface
- Low friability
- Uniform packing characteristics
- Fewer inert ingredients and excipients
- Improved flow properties
- Precise drug release
 - API core can be integrated with release excipients
 - Can mitigate subsequent dose-controlling coatings

Therapeutic advantages:

- Permits high drug loading
 - 90% API spheres possible
 - Fewer doses, better compliance
- Disperses freely in the GI tract
 - Minimizes dose-dumping side effects
 - Manages dispersion/concentration issues
- Facilitates maximum drug absorption
 - Minimum peak plasma fluctuations
- Combines incompatible APIs

Focus on Extrusion-Spheronization in manufacturing

In the 1970s Reynolds demonstrated that the ability of E-S to produce spheres with higher drug loading was one of the primary advantages of the process.

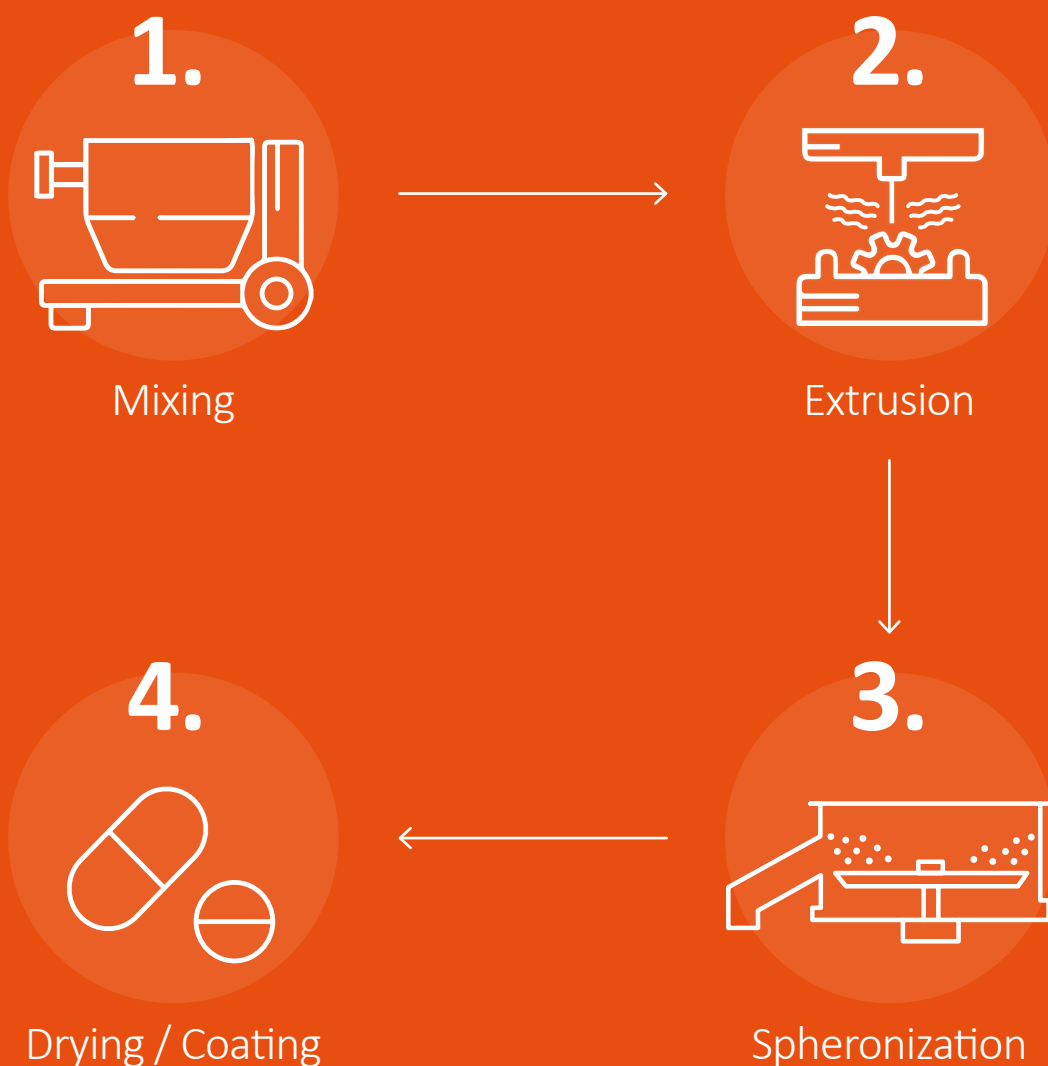
At present, it is possible to achieve upwards of 95% drug loading with this technique, depending on the API. The process is easily scalable and repeatable, as well

as capable of providing a consistent and uniform product.

Since its introduction, E-S has experienced significant development as the industry has come to understand how well the technique can be engineered to support controlled API delivery in OSD forms.

Spheronization's four simple steps

E-S consists of four steps: mixing, extrusion, spheronization and drying / coating.



Step 1: Mixing

E-S begins with mixing a combination of API, excipients or binders (plus sterile water) in desired ratios to create the wet granulation batch ready for extrusion. Depending on desired density, mix homogeneity and flow needs, processors can manipulate mixer shear loading, speed and other variables to achieve desired properties.

Ultimately the goal of mixing is to create a soft, wet, homogenous mass that can hold its shape under low pressure with enough gliding properties to keep extrusion flowing and pressures low.

There are several methodologies available to make wet, granulated formulations.

One popular technique is the use of modified microcrystalline cellulose (MCC) to suspend active ingredients and API. A mature, well understood technology, seminal studies revealed that MCC has the ability to hold higher levels of water within its structure, restrict the migration of water in the wet mass under pressure, and allow for higher levels of API loading in each sphere.

For drug developers, MCC's ability to suspend and disperse API in a stable and reliable way and perform well under the pressures and thermal loads relative to extrusion, make it a valuable tool.

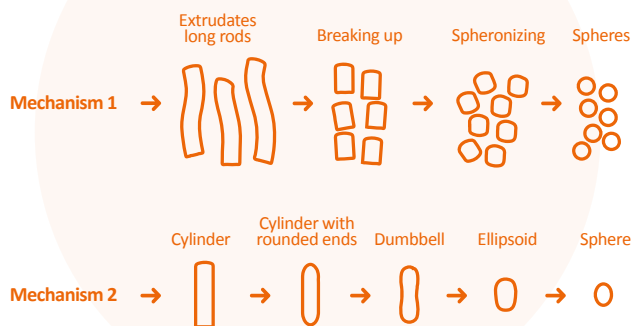


Image: Extrusion Dome

Step 2: Extrusion

The primary mission of extrusion is to produce extrudates suitable for spheronization. The process consists of forcing the mass of wet cake from a large diameter through a small diameter. Extrusion can be accomplished through a number of specific technological routes and equipment manufacturers currently offer a broad range of systems to meet formulation and manufacturing needs.

Spheronization Mechanism



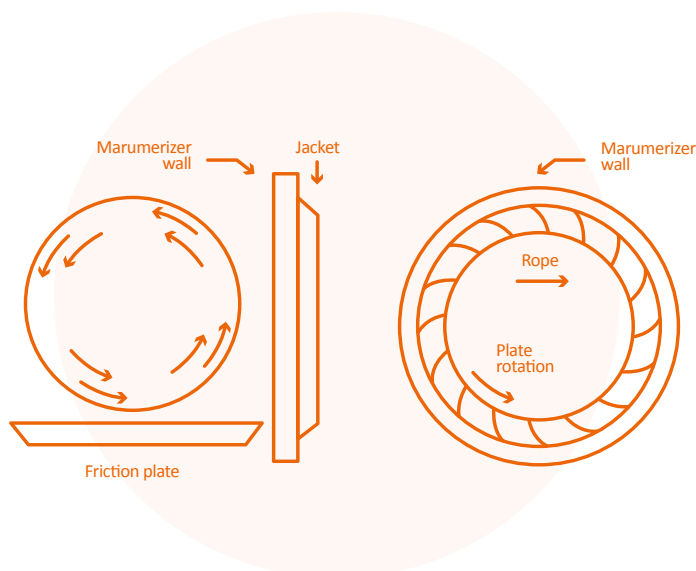
Step 3: Spheronization

Spheronization is essentially a rotating / milling operation that tumbles the wet cake extrudates into uniform spherical shapes. A straightforward physical process, spheronizer's employ a spinning friction plate that, through centrifugal force and friction, generate the micro-collisions that eventually shape the cylindrical extrudates into spheres.

The mechanism of spheronization depends on three types of collisions:

1. Particles with the plate
2. Particles against the wall
3. Particle to particle

By manipulating the variables of processing time and moisture content, friction plate speed and configuration, technicians can produce uniform spherical particles (aspect ratio closest to 1.0), control particle size distribution (PSD) and particle density.



Size matters

Dose control is accomplished in a variety of ways. One way to modify release is related to the size of the sphere and its API loading. Fortunately spheres can be spheronized into a range of sizes. For most applications the smallest practical size possible about 0.6mm. It is possible to go down to 0.4mm but this can be accompanied by technical challenges and is tough to accomplish with economic reliability.

Step 4: Coating/drying

Completing the spheronization process, the uniform, homogenous spheres (if necessary) can be dried and/or subjected to coating processes to manage dose delivery goals like controlling API release in the gut or taste masking.

Equipment suppliers now offer the industry a variety of coating and drying systems capable of finishing E-S spheres to meet a broad range of OSD API delivery goals and the therapeutic performance of the finished drug product.

Continuous flow Extrusion-Spheronization manufacturing is here, now

In the context of pharma manufacturing quality, current GMP thinking in E-S means incorporating quality-by-design (QBD) chemistry, state-of-the-art mixing, extruding and spheronizing equipment and entraining it in continuous flow.

Commercial E-S processing can be either batch or continuous. But E-S is proving quite adaptable and a significant portion of the process can be run continuously.

Technically, from beginning to end E-S is semi-continuous but the configuration is proving it can be a real game changer when scaling to commercial output. It's been demonstrated throughput can reach upwards of 200-300 Kg/hour, depending on formulation and other variables.

Twin-dome extrusion, no waiting

Extrusion, as described previously, is accomplished through a number of preferred equipment formats. One solution, a twin-dome design, is proving to be an important element in commercial-scale continuous E-S because it helps speed throughput while managing the thermal deltas of the product being extruded.

Offering shorter residence times in transit through the extruder, the twin dome design can be fed continuously while providing for a consistent pressure profile across the extruder die, plus the capacity and throughput control needed to adequately feed downstream processes. This creates uniform high-quality extrudates that are ready to be flowed to spheronization in process.



Image: Extrusion Dome

Bora's center of continuous Extrusion-Spheronization excellence and capabilities

To deliver E-S to pharma's drug developers, Bora's investing in its global facilities, introducing a continuous processing line engineered and commissioned by LCI Corporation. Certified by all leading international regulators, Bora's E-S capabilities comply with PIC/S, GMP and GDP guidance for all drug products.

All production activities related to E-S processing are conducted in temperature and relative humidity-monitored areas. Process rooms have individual temperature and humidity recorders installed to tightly control optimal conditions.

It's well known that the more experience project teams have can help accelerate go-to-market schedules and technical/operational mastery is a prerequisite. However, to unlock spheronization's commercial potential the process requires both experience and the investment operationally to do it well and meet all commercial, financial and regulatory expectations.

Bora's formulation skills and experience with the mechanisms of continuous-flow E-S continue to support and optimize customers' OSD commercialization plans.

A well rounded technology perfected by the Japanese

Spheronization in a continuous flow process is likely to be accomplished by patented “Marumerizer,” technology innovated and developed in Japan. Maru, means “round” in Japanese, hence Marumerizer. Spheronizing mills can be automatically fed to maintain continuous process flow without intermediate steps.

As noted, the spheronizer’s mission is to produce the most spherical product (aspect ratio closest to 1.0) and ensure PSD meets specifications.

To assure product quality and all physical aspects of the spheres, technicians calibrate all controls precisely, including friction plate speed, processing time, moisture content and the configuration of the friction plate itself.



Image: Extrusion Dome

Downstream pellet drying and finishing

After spheronizing comes subsequent drying and coating operations. Adept technicians can tailor these operations to accomplish several therapeutic and drug delivery tasks and prepare the spheres for introduction and integration into final dose forms and drug-product finishing steps.

Summary

Pharma's development pipeline is being filled with more sophisticated, harder to make compounds. To achieve therapeutic goals and patient value, these formulations require complex delivery strategies to administer doses correctly. Demand for specialist expertise in this area has soared, and drug developers are increasingly seeking specialized outsourcing partners and solutions to manufacture and commercialize products.

E-S has demonstrated tremendous success improving quality, safety, therapeutic efficacy and dose compliance across a diverse range of therapeutic areas. Delivering therapeutic compounds and molecules via spherized forms will continue to offer pharma the utility and functionality they need to meet their most visionary drug product manufacturing goals.



A culture apart: Three reasons to choose Bora

What makes Bora's E-S offering unique among contract development and manufacturing suppliers? Here are three reasons why Bora is a culture apart from its peers in the space:



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Reason 1: Bora's historical quality-centered culture

Especially relevant to successful outsourced drug development and commercialization is how well culture and quality support successful therapeutic development, and above all, achieve better patient-based outcomes.

Quality has deep roots in Asia. Bora's culture of quality is not just a commercial mandate, it is a cultural imperative that our people apply to their professional roles and personal lives every day. Since its inception, Bora's commitment to quality has been central to its growth, the development of its OSD manufacturing expertise and above all demonstrated by an outstanding compliance record with the world's regulators.

Reason 2: The right technology at the right time

It's increasingly clear that matching particular manufacturing and operational strengths to specific drug development plans is a straighter path to successful drug development. It's also a sound strategy when choosing strategic outsourcing partners. Whether seeking Best-in-Class or First-in-Class goals***, Bora's spherization experience provides a proven way for drug sponsors and designers to engineer better dose control and therapeutic performance.

Bora's decades of experience spherizing actives to achieve a drug's precise delivery goals within a reliable, high-quality production environment may offer strategic advantage and accelerate drug development to meet time-to-market goals.

Reason 3: We are passionate about our customers' products

From both a cultural and professional standpoint, Bora offers a way of working that our customers enjoy and truly benefit from—something they experience from the very beginning of their drug programs to the very end.

Few commercial relationships are as intensive; the stakes are extremely high. It's a marriage that requires commitment, but it also requires equal measures of passion and compassion. At Bora, collaboration is almost inadequate to describe how our teams approach and manage each customer program.

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