DESIGN AND APPLICATIONS OF EXTRUDER-SPHERONIZER

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Extrusion-spheronization

- Extrusion-spheronization is a pelletization technique that was developed in the early 1960s, and this process is commonly used in the pharmaceutical industry to make uniformly sized spheroids.

- It is especially useful for making dense granules for controlled-release solid oral dosage forms with a minimum amount of excipients.
Extrusion

- Extrusion is a necessary first step in the extrusion-spheronization process.
- It is the process of forming a raw material into a product of uniform shape and density by forming it through an orifice or die under controlled conditions.
Spheronization

- The spheronization technology was introduced by Nakahara in 1964.

- Spheronization (or) marumerization, is a rapid and flexible process where pharmaceutical products are made into small spheres, (or) spheroids.
Spheronized products are relatively dense, of a uniform in size and shape and have defined surface characteristics.
Advantages of spheronization

✓ Optimum flow and handling characteristics.
✓ More reproducible packing into small containers.
✓ Minimum surface area to volume ratio.
✓ Optimum shape for coating and for controlled release.
✓ Easy mixing of non-compatible products.
✓ Elimination of dust.
✓ Improved hardness and friability.
EQUIPMENTS

- Many types of equipments are utilized in the extrusion-spheronization process such as blenders, granulators, sieve sizers.
- Extrusion-spheronization is a multistep process involving a number of unit operations and equipment.
- The most critical pieces of processing equipments are the extruders and the spheronizers.
EXTRUDERS

An extruder consists of two distinct parts

1. A delivery system – which transports the material and sometimes imparts a degree of distributive mixing, and
2. A die system – which forms the material into the required shape.

Extrusion may be broadly classified into

1. molten systems under temperature control (or)
2. semisolid viscous systems
Types of extruders

✓ Screw extruders
  ✓ a) radial extruder
  ✓ b) axial extruder
✓ Gravity-fed extruders
  ✓ a) rotary cylinder extruders
  ✓ b) rotary gear extruders
✓ Ram extruder
✓ Screen (or) Basket extruder
✓ Roll extruder
Screw extruder

- A screw extruder, utilizes a screw to develop the necessary pressure to force the material to flow through uniform openings, producing uniform strands (or) extrudates.

- It utilizes a screw-fed mechanism consisting of single (or) twin helical screws rotating in a barrel to convey the damp mass from a feed hopper to the die zone.
- The die consists of a thin steel plate perforated with numerous holes, which is positioned radially (or) axially to the screw feed, they are called radial (or) axial screw extruders respectively.
Advantages

- The advantage of this arrangement are high continuous throughput rates, from 5 kg/h of wet mass for a laboratory-scale single-screw extruder, upto 800 kg/h for a larger twin-screw design.
- The screens are easily cleaned and interchanged, they have holes of varying diameter beginning at 0.5 mm and are available commercially.

Disadvantages

- Screw mechanism can exert a high pressure on the material, generating excessive friction and heat as the wet mass passes between the screw and barrel.
Gravity-fed extruders

- It include the rotary cylinder and rotary gear extruders, which differ mainly in the design of the two-counterrotating cylinders.

Rotary cylinder extruder

- In this extruder, one of the two counter-rotating cylinders is hollow and perforated, where as the other cylinder is solid and acts as a pressure roller.
- The material to be extruded is fed into the area above the two cylinders. Pressure is built up in the perforations, which compacts the wet mass and forces the extrudate to the interior of the cylinder.
The temperature increase in the extrudate is minimized by circulating cool water through the pressure cylinder.
Advantages

- Laboratory-scale extruders with a throughput range of 30-50 kg/h use granulation cylinders 70mm in diameter.
- Production-scale equipment with a larger granulating cylinder (186 mm diameter) can achieve an output of 100-105 kg/h.

Disadvantages

- Cleaning of the granulating cylinder can be troublesome.
- Granulating cylinders are expensive because of the high cost of drilling stainless steel.
Rotary gear extruder

- It consist of two hollow counter-rotating gear cylinders with counterbored dies as nozzles, they are drilled into the cylinders between the teeth.

- The material, gravity fed from a hopper, is drawn in by the toothed cylinders and pushed through nozzles into the cylinders, where scrapers cut off the extrudate.

- The product is compacted as it passes through the nozzles, and thereby forms a dense extrudate.
The diameter of the holes can be varied from 1-10 mm to produce a range of pellet sizes.
Advantages

- Produces a relatively higher density extrudate.

- Throughput capacity ranges from 20 kg/h for the small scale laboratory extruders to approximately 1000 kg/h for production equipment.
Ram extruder

- it is the oldest type of extruder, a piston displaces and forces the material through a die at the end.
Screen (or) Basket extruder

Sieve or Screen extruders - They have a chamber that contains the materials to be extruded and a plate or screen. A rotating/oscillating arm passes the damp material through a sieve or perforated screen to form short or long extrudates, depending on the moisture content.
Basket-type extruders are similar to sieve extruders except that the sieve/screen is part of a vertical, cylindrical wall.

The extrudate falls vertically from the sieve plate of a sieve type extruder, while in a basket extruder, the extrudate is formed in the horizontal plane as it is formed through the vertical holes.
Roll extruder

- Roll extruder, which are also known as “pellets mills”, operate by feeding material between a roller and a perforated plate or ring die.
  - The basic designs are

**Type-1:** A ring die plate rotates around one or more rollers installed inside the cylindrical die chamber, each of which rotates on its stationary axis.

- All rotating components turn in the same direction.
Feed material is introduced onto the inside surface of the ring die and pressed outward by the rollers.
Type-2: The rollers are mounted on the outside of the die and material is fed from a hopper, occasionally with a screw, into the region between the roller and the die.

- Material is extruded into the center of the ring die and flows out one end. The roller and the die move in opposite directions.
Which extruder is suitable for your needs?

<table>
<thead>
<tr>
<th>Machine</th>
<th>Mini screw extruder</th>
<th>Extruder 20</th>
<th>Extruder 35</th>
<th>Extruder 40C M</th>
<th>Extruder 40C A</th>
<th>Extruder 100 or larger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Special suitability</td>
<td>For the screw extrusion of very small amounts of material.</td>
<td>A bench top extruder for research and small scale development batch production.</td>
<td>A floor standing screen extruder.</td>
<td>A manually operated gear extruder for small scale production and production trials.</td>
<td>Similar to the 40C M but with automatic controls.</td>
<td>A larger production machines ideally suited for materials that should not be excessively “worked” during extrusion.</td>
</tr>
<tr>
<td></td>
<td>Extraduce very small amounts of material.</td>
<td>Low pressure extrusion of experimental materials where the product is not worked excessively.</td>
<td>Designed as a low cost and efficient screen extruder for production use.</td>
<td>Specially suitable when high quality wet extrusion is required.</td>
<td>Can be custom designed and built to fit existing operations.</td>
<td></td>
</tr>
<tr>
<td>GMP compatible</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum load</td>
<td>6g</td>
<td>100g</td>
<td>1kg</td>
<td>20–180kg/hr</td>
<td>40kg/hr</td>
<td>&gt; 100kg/hr</td>
</tr>
<tr>
<td>Maximum capacity</td>
<td>Approx 30g in 5 min</td>
<td>Approx 1kg in 3 min</td>
<td>20–180kg/hr</td>
<td>40kg/hr</td>
<td>&gt; 100kg/hr</td>
<td></td>
</tr>
<tr>
<td>Companion equipment</td>
<td>Spheronizer 120</td>
<td>Spheronizer 123.</td>
<td>Spheronizer 380</td>
<td>Spheronizer 500</td>
<td>Spheronizer 700 or 700 Twin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multi bowl spheronizer optional with inserts</td>
<td>Multi bowl spheronizer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical extrudate size</td>
<td>Variable to customer needs but a typical range would be from 0.7 to 3.0 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Construction material</td>
<td>304/316 stainless steel and polypropylene</td>
<td>304/316 stainless steel and polypropylene</td>
<td>Cabinet in 304 stainless steel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact parts material</td>
<td>316 stainless steel and FDA approved plastics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor power</td>
<td>180W</td>
<td>180W</td>
<td>2.2 kW</td>
<td>7.5 kW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimensions</td>
<td>300x530x350mm</td>
<td>300x530x350mm</td>
<td>500x700x1000mm</td>
<td>1000x480x1000mm</td>
<td>Depends upon configuration</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>25kg</td>
<td>25kg</td>
<td>120kg</td>
<td>230kg</td>
<td>Approx 1000kg</td>
<td></td>
</tr>
<tr>
<td>Available certification</td>
<td>Technical Construction File and CE sticker are supplied with each machine. Full pharmaceutical documentation package available if required.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speed control</td>
<td>User set between 20 and 150 rpm</td>
<td></td>
<td>Variable set by user, approx 100rpm</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Spheronizing equipment

- A Spheronizer known as Marumerizer, consists of a static cylinder or stator and a rotating friction plate or disk at the base.
- The stator can be jacketed for temperature control.
- The friction plate, a rotating disk which has a grooved surface, is the most important part of the equipment that initiates the spheronization process.
- A standard friction plate has a cross-hatch pattern, where the grooves intersect at a 90° angle.
- The groove width is selected based on the desired pellet diameter. Usually groove diameter 1.5-2 times the target pellet diameter are used.
- The diameter of the friction plate is approximately 20 cm for laboratory-scale equipment or up to 1m for production-scale units.
Air-assisted spheronizers.

- The new variation of spheronizers that was introduced into the market are the so called Air-assisted spheronizers.

- It is similar to the standard spheronizer except that they are designed to permit a conditioned air stream is introduced into the product from underneath the rotating disk and passes through the gap or slit between the cylindrical wall and the rotating friction plate.
A Brief Description of the Spheronization Process

- The basic spheronization machine consists of a rotating friction disk designed to impart friction to the extrudate by spinning at the bottom of a fixed cylindrical drum. The spinning friction disc has variety of groove patterns on the processing surface to chose from.

- Extrudates are charged into the spheronizer and fall onto the spinning disc and are immediately thrown to the drum wall.

- The cylindrical extrudate segments are cut into segments after a certain amount of time which then, as time progresses, collide with the bowl wall as well as each other and the disc and are then thrown back to the inside of the disc.
The ongoing action of particles colliding with the drum wall and the disc and each other creates a "rope-like" movement of product along the bowl wall. The cylindrical segments are gradually rounded into spheres by the collisions.

When the particles have obtained the desired spherical shape, the discharge valve of the chamber is opened and the granules are discharged by the centrifugal force. This process usually takes somewhere between 1 to 6 minutes.
<table>
<thead>
<tr>
<th>Machine</th>
<th>Spheronizer 120</th>
<th>Multi Bowl Spheronizer</th>
<th>Spheronizer 380</th>
<th>Spheronizer 500</th>
<th>Spheronizer 700</th>
<th>Spheronizer 700 Twin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Special suitability</td>
<td>For general R&amp;D or teaching work with small quantities rare and expensive development compounds.</td>
<td>For R&amp;D with the capacity for small scale batch production. Suitable for scale up studies.</td>
<td>Pilot plant or production machine tailored to individual requirements. Manual or automatic control available.</td>
<td>Production machine tailored to individual requirements. Manual or automatic control available.</td>
<td>Production machine tailored to individual requirements. Manual or automatic control available.</td>
<td>Large scale production machine. Custom designed and built in collaboration with the customer.</td>
</tr>
<tr>
<td>Minimum load</td>
<td>10g</td>
<td>1g</td>
<td>0.5kg</td>
<td>1kg</td>
<td>2kg</td>
<td></td>
</tr>
<tr>
<td>Maximum load</td>
<td>150g</td>
<td>5kg</td>
<td>4kg</td>
<td>10kg</td>
<td>20kg</td>
<td></td>
</tr>
<tr>
<td>Oyster (only guide)</td>
<td>N/A</td>
<td>10kg/hour</td>
<td>50kg/hour</td>
<td>100kg/hour</td>
<td>150kg/hour</td>
<td>300-600kg/hr</td>
</tr>
<tr>
<td>Ideal equipment</td>
<td>• Mixer Torque Rheometer,</td>
<td><strong>Extruder model 20 with reduced height screens</strong></td>
<td><strong>Extruder model 20</strong></td>
<td><strong>Mini screw extruder</strong></td>
<td><strong>Mixer Torque Rheometer.</strong></td>
<td><strong>Extruder model 40 or model 35 depending on material specification and characteristics</strong></td>
</tr>
<tr>
<td>Discs available</td>
<td>• Cross hatch patterns available from 1x1 to 6x6 mm pattern available in 1mm increments.</td>
<td>• Redlist disc available.</td>
<td>• PTFE and other coatings are available on request.</td>
<td>Controlled by the extrusion process and equipment. Typical range 0.0 to 3.0 mm (0.6mm is possible)</td>
<td>316 stainless steel and FDA approved plastics</td>
<td></td>
</tr>
<tr>
<td>Construction material</td>
<td>Cabinet in 304 stainless steel</td>
<td>316 stainless steel and FDA approved plastics</td>
<td></td>
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</tr>
<tr>
<td>Contact parts construction material</td>
<td>316 stainless steel and FDA approved plastics</td>
<td>316 stainless steel and FDA approved plastics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disc speed range</td>
<td>To 1800 rpm</td>
<td>200 – 3000 rpm</td>
<td>200 – 1500 rpm</td>
<td>0200 – 1000 rpm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor power</td>
<td>95W</td>
<td>150W</td>
<td>2.2kW</td>
<td>3.5kW</td>
<td>7.5kW</td>
<td></td>
</tr>
<tr>
<td>Dimensions</td>
<td>250x200x450 mm</td>
<td>500x300x520 mm</td>
<td>950x700x1150 mm</td>
<td>800x1340x1350 mm</td>
<td>Custom design</td>
<td>Custom design</td>
</tr>
<tr>
<td>Weight</td>
<td>Approx 10kg</td>
<td>Approx 45kg</td>
<td>Approx 300kg depending on specification</td>
<td>Approx 1090kg depending on specification</td>
<td>Custom design</td>
<td>Custom design</td>
</tr>
<tr>
<td>Electricity supply</td>
<td>Single phase, voltage to customer requirement</td>
<td>3 phase, voltage to customer requirement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timing control</td>
<td>Manually set and controlled by the user</td>
<td>Manually and automatic according to customer requirement at time of order</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speed control</td>
<td>Manually set and controlled by the user</td>
<td>Manually and automatic according to customer requirement at time of order</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comment</td>
<td>Our lowest cost spherizer</td>
<td>The ideal R&amp;D machine</td>
<td>Built to specific customer requirement regarding bowl placement, control placements, level of automation etc.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Extrusion and Spheronization

PROCESS

1. Mixing

- The pre-mixed dry ingredients, mostly composed of the API and Avicel, are wetted with water or organic solvent and mixed in a high shear granulator or double planetary mixer to form a homogeneous wet mass suitable for wet extrusion.

2. Extrusion

- The wet mass is metered by a special feeder into the extruder where it is continuously formed into cylindrical extrudates of uniform shape and size.
3. Spheronization

- The wet extrudates are placed in a spheronizer where a gridded, fast spinning disc, breaks them into smaller particles and rounds them to form spheres.

Extrudates  After 5 seconds  After 15 seconds  After 120 seconds
4. Coating/Drying

- These wet spheres (sometimes referred to as "beads" or "beadlets") are then transferred to a coating column where they are coated with a slow-release polymer matrix, then dried. The finished spheres are then tableted or encapsulated. In some cases, the extrudates are dried and tableted without going through a spheronizer.
Applications

- The process of wet extrusion, followed by extrusion-spheronization, is used to produce a wide variety of engineered, controlled release drugs. These solid dosage forms are mostly in the form of tablets or capsules containing high levels of an Active Pharmaceutical Ingredient (API).

- Ram extruders are preferred during formulation development because they are designed to allow for measurement of the rheological properties of formulations.

- The twin-screw extrusion used for the continuous production of solid dosage forms, i.e., useful for the wet granulation of alpha-lactose monohydrate or microcrystalline cellulose and produces high shear granulation.
Pharmaceutical Applications for Extruders and Spheronizers

- Controlled release pellets for encapsulation
- Delayed release enteric coated pellets
- Sustained release pellets
- Multi-particulate systems
- Multi-unit erosion matrix pellets
- Pellets for special tabletting applications
- Immediate release pellets for sachets
Multi-particulates

Extrusion/Spheronization

Extrusion spheronization offers an attractive alternative to traditional drug-layering on pellets. This highly specialized process results in unique spherical, drug-loaded pellets. The formulator can achieve higher drug loading with this approach over that possible with layering. We recommend Avicel® PH-101 or PH-102 for this application because they produce:

- Reduced spheroid friability
- Prevents overwetting and lessens the process sensitivity
- Improved sphericity of pellets

**Recommended Products:**
Avicel PH 101, PH-102
To develop an enteric-coated multiunit dosage form containing aceclofenac, a nonsteroidal anti-inflammatory drug. The pellets were prepared by using extrusion/spheronization method, and the core pellets were coated with a pH-sensitive poly(metha)acrylate copolymer to achieve site-specific drug release.

In vitro Release Kinetics Study of Ambroxol Hydrochloride Pellets Developed by Extrusion-Spheronization Technique Followed by Acrylic Polymer Coating for the controlled release.

To develop monodimensional, spherical particles of 400 µm by extrusion-spheronization. An Alexanderwerk GA65 cylinder extruder with two counter-rotating rollers associated with a Caleva model 15 spheronizer were used. The study was made with an auxiliary substance of fatty consistency and with amphiphilic properties: Gelucire 50/02.
To investigate the phase transitions occurring in nitrofurantoin and theophylline formulations during pelletization by extrusion-spheronization. An at-line process analytical technology (PAT) approach was used to increase the understanding of the solid-state behavior of the active pharmaceutical ingredients (APIs) during pelletization. Raman spectroscopy, near-infrared (NIR) spectroscopy, and X-ray powder diffraction (XRPD) were used in the characterization of polymorphic changes during the process.

**Formulation, Characterization of Pellets of Duloxetine Hydrochloride by Extrusion and Spheronization.**

**Formulation of palatable ‘Melt in Mouth’ pellets of Ferrous fumarate that would improve the compliance of the acceptance of medicines in pediatrics for the treatment of iron deficiency.**
**Preparation of Controlled Release Spheronized Beads by a Simple Extrusion and Modified Spheronization Process**

- Beads loaded with the water-soluble drug, phenylpropanolamine HCl (PPA), were prepared using an extruder and double arm counter-rotating roller modified from a traditional pill machine.

- The mean diameter of the cylindrical rod-like extrudate from the ram extruder was 3mm; that of the uncoated bead after cutting and spheronization by the modified double arm counter-rotating roller was 3.26-3.28 mm.
Conclusion

- The extrusion and spheronization process can be used to prepare pellets that can be used as granulations for solid dosage forms compression and as specially formulated or coated controlled-release matrices.
- The pellets produced by this process can be considered as any other pharmaceutical drug delivery system and can be subjected to the same study and analysis.
References


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• By: Jittima Chatchawalsaisin, Suzanne Boute, J Michael Newton, Fridrun Podczeck; The Preparation of Spherical Granules by Extrusion/ Spheronization without Microcrystalline Cellulose, Oct 1, 2004 Pharmaceutical Technology Europe.


• Sibeum Lee, Min-Soo Kim, Seoung Wook Jun, Jeong-Sook Park, and Sung-Joo Hwang National Research Lab of Pharmaceutical Technology, College of Pharmacy, Chungnam National University, Dae-jeon 305-764, Korea http://apr.psk.or.kr
International Journal of Pharmaceutics
Volume 369, Issues 1-2, 18 March 2009, Pages 96-104.

info@calveva.co.uk
www.spheronization.com
www.pharmagateway.net
www.glatt.com

A novel aid for the preparation of pellets by extrusion-spheronization (www.pharmatech.com)
THANK YOU