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SPECIAL EMPHASIS GIVEN ON SPHERONIZATION: A REVIEW

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ABSTRACT

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Extrusion-spheronization is a pelletization process for making pellets that are amenable for immediate and controlled release preparations. It includes the processes of blending, granulation, extrusion, spheronisation, drying, screening and encapsulation or compression into tablets. The major advantages in formulating drugs as pellets includes the ability to incorporate a high drug loading, improved homogeneity from uniform distribution of ingredients and improved wetting/dissolution because of larger surface area than a single unit such as a tablet. The established mechanisms only consider deformation of the initially fractured particles but do not account for mass transfer between the particles as a factor in achieving spherical particles. Moreover, it is evident that there are regional distinctions in the amount of mass transfer at the particle surface. Therefore, the commonly espoused pelletization mechanisms need to be extended to account for material transfer between pellet particles, which has not been considered before.

INTRODUCTION

Pellets are systematically produced, geometrically defined agglomerates of bulk drugs and excipients. They are small, free-flowing, and spherical or semi-spherical solid units which are in the size range of 0.5-2.0 mm.

Spheronisation is a process in which the wetted extrudates are converted into spherical micropellets. Hence, spheronisation is the essential step in the production, where collision of particles occurs due to the generated force of the spinning friction plate. Therefore, the extrudates must show a combination of cohesiveness, firmness and plasticity to go through the various states of forming ^[1].

A Spheronizer consists of a vertical hollow cylinder with an inner horizontal rotating disc (friction plate) ^[2] Spheronizer may vary in the friction plate diameter and its features as well as additional process variables. The surface texture of the friction plate can be designed with different grooves from which the 'cross-hatched' pattern is commonly used. Furthermore, differences in additional Spheronizer process variables such as a double jacket wall or an inlet air pressure can also exist ^[3]. The mechanism of spheronisation is complex and the process is affected by mechanical stress and by the temperature. Besides the requirements of the extrudates, the spheronisation process is mainly dependent on three different factors: spheronisation speed, residence time and loading ^[4-5] Therefore, the mutual effects between the extrusion and spheronisation process, especially with regard to the moisture content of the extrudates, have been investigated ^[6]

General description of spheronisation processes: - ^[7,8]

The extrusion of the product is a required step prior to spheronisation. The size of the spheres are determined by the diameter of the extrudates used for the spheronisation process. For example, in order to obtain spheres with a diameter of 1 mm, a 1 mm screen is used on the extruder, although spheres with a slighter bigger diameter will sometimes be obtained. In a Spheronizer, it is possible to obtain spheres with a diameter ranging from about 0.5 mm to about 10 mm but in practical terms the range 0.7 to 3 mm is considered normal. Larger sizes would have a poor product appearance (not round) and a low yield of product and smaller sizes would be difficult to extrude.

These are the basic steps in converting a pharmaceutical formulation into a spheronized product:

1. The Powder Mix
2. The Plastic Mass
3. Wet Sphere
4. Coated Sphere

In principle the basic machine consists of a rotating friction disk, designed to increase friction with the product, which spins at high speed at the bottom of a cylindrical bowl. The spinning friction disc has a carefully designed groove pattern on the processing surface. This is most often crosshatched, but several sizes and other types are available. Extrudates are charged to the spheronizer and fall on the spinning disc. At first, the cylindrical extrudate segments are cut into segments with a length ranging from 1 to 1.2 times the diameter. These segments then collide with the bowl wall and they are thrown back to the inside of the friction plate. Centrifugal force sends the material to the outside of the disc. The action of the material being moved causes the extrudate to be broken down into pieces of approximately equal length relative to the diameter of the extrudates. These cylindrical segments are gradually rounded by the collisions with the bowl wall, the plate and each other. The ongoing action of particles colliding with the wall and being thrown back to the inside of the plate creates a "rope-like" movement of product along the bowl wall.

The continuous collision of the particles with the wall and with the friction plate gradually turn the cylindrical segments into spheres, provided that the granules are plastic enough to allow the deformation without being destroyed. It is essential that this rope movement is present for an optimal spheronisation

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.

The design principle of the Spheronizer is relatively simple but additions and adaptations are available have widened the range of applications and greatly improved the flexibility of the machines. For example, the Caleva "Twin" incorporates two Spheronizer which allow continuous productions of spheroids.

Equipment used in spheronisation process: -

There are various type of equipments used for the process of spheronisation. Different types of equipments posses different qualities and capabilities. Following is a brief description of these equipments.

1. **Multi bowl Spheronizer 250:** - The Multi-Bowl Spheronizer has four different interchangeable Spheronizer bowls which can be used on the same base to Spheronizer a wide range of batch sizes with a single apparatus. By using the appropriate bowls, it may be possible to process batches ranging in size from 1g to 1kg.^[9]
2. **Model 380 Spheronizer:** - The **Spheronizer 380** is a floor standing production machine that can be customized to your requirements. It is small enough to be moved on the fitted castors yet sturdy enough to be considered as production equipment.^[10, 11]
Others model includes 500 Spheronizer, 700 Spheronizer, Model 700 twin Spheronizer having specific capabilities and efficiencies.^[12]

Specific parameters of Spheronizer Model 120.^[13, 14]

Pharmex 35T-Spheromat extrusion-spheronization equipment, Spheronizer Model 120 (Caleva Process Solutions Ltd., UK.

Rotation number of spheronisation plate: 1000 rpm

Spheronisation time: 2 min

Rotation number of the screw: 75-80 1/min.

Diameter of the sieve: 800 μm .

Table 1: - An overview of Spheronizer of varying scales and capacities: -^[15]

Company	Model	Typical operating capacity	Maximum plate speed
LCI	QJ-230, QJ-400, QJ-700, QJ-1000.	0.1-0.4, 0.2-3.0, 1.0-15, 2.5-35	1800, 1280, 690, 790
Caleva	Spheronizer 120, 250, 380, 500, 700.	0.03-0.15, 0.1-1.0, 0.5-4, 1-11, 5-20	
Gabler	R 250, 400, 600, 900	0.15-0.6, 1-3, 2-6, up to 20	
NICA	S 320, 450, 700	0.2-1, 0.4-2, 2-10	600, 450, 300

Mechanisms of pellet formation by spheronisation process: - ^[16]

Two models have been proposed to describe the mechanism as shown graphically in Figure 1.

One model was proposed by **Baert and Remon** (1993) who suggested that, the initial cylindrical particles (Fig.1.2: 1a) are deformed into a bent, rope-shaped particle (Fig.1.2: 1b), then form a dumbbell with a twisted middle (Fig.1.2: 1c). The twisting action causes the dumbbell to break into two spherical particles, with a flat side having a hollow cavity (Fig.1.2: 1d). Continued action in the spheronizer causes the particles to round off into spheres (Fig.1.2: 1e).

The second model proposed by **Rowe** (1985), describes a transition whereby the cylindrical particles (Fig.1.2: 2a) are first rounded off into cylindrical particles with rounded ends (Fig.1.2: 2b), then form dumbbell-shaped particles (Fig.1.2: 2c), ellipsoids (Fig.1.2: 2d), and finally, spheres (Fig.1.2: 2e) (**Erkoboni**, 2003).

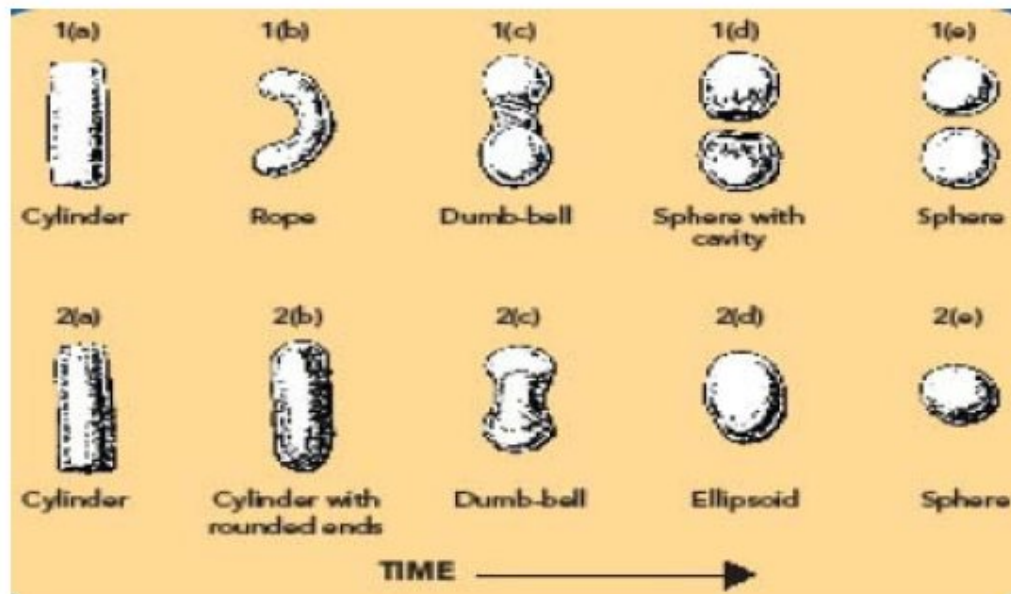


Figure 1: Pellet-forming mechanisms by spheronization process.

Spheronisation technique: -**Extrusion/spheronization process: -**

Extrusion spheronisation follows mainly five steps that is mixing or blending, extrusion, spheronisation, Coating and finally drying, which can be explained/described as Dry mixing of ingredient to achieve homogenous powder dispersion.

1. Wet massing to produce a sufficient plastic mass.
2. Extrusion to form rod shaped particles of uniform diameter.
3. Spheronisation to round off these rod shaped particles into spherical particles with narrow size distribution.
4. Drying to achieve desired final moisture content.
5. And screening to obtain desired size of spheres/pellets.^[17]

Extrusion involves forcing the wet powder mass through a restricted crosssection. Extruders of different sizes and type can be used depending on the load they can handle and the extrudates quality. To control the extrudate and subsequently the final pellet properties, various types of extruders like screw feed (axial/end and dome/radial), sieve, basket, ram/piston feed, gravity feed and roll extruders can be used.

In **spheronisation** process, the extrudates break into small cylinders with a length equal to their diameter. Two mechanisms are proposed for the formation of the spheres; these plastic cylinders are rounded due to frictional forces into cylinder with rounded edges, dumbbells and elliptical particles to eventually form perfect spheres. Another mechanism suggested that a twisting of the cylinder occurs after the formation of cylinders with rounded edges, finally resulting in the breaking of the cylinder into two distinct parts having a round and a flat side. Due to the rotational and the frictional forces involved in the spheronization process, the edges of the flat side fold together like a flower forming the cavity. At the end of the spheronization process, wet pellets must be dried to adjust pellet size, density, hardness etc.^[18]

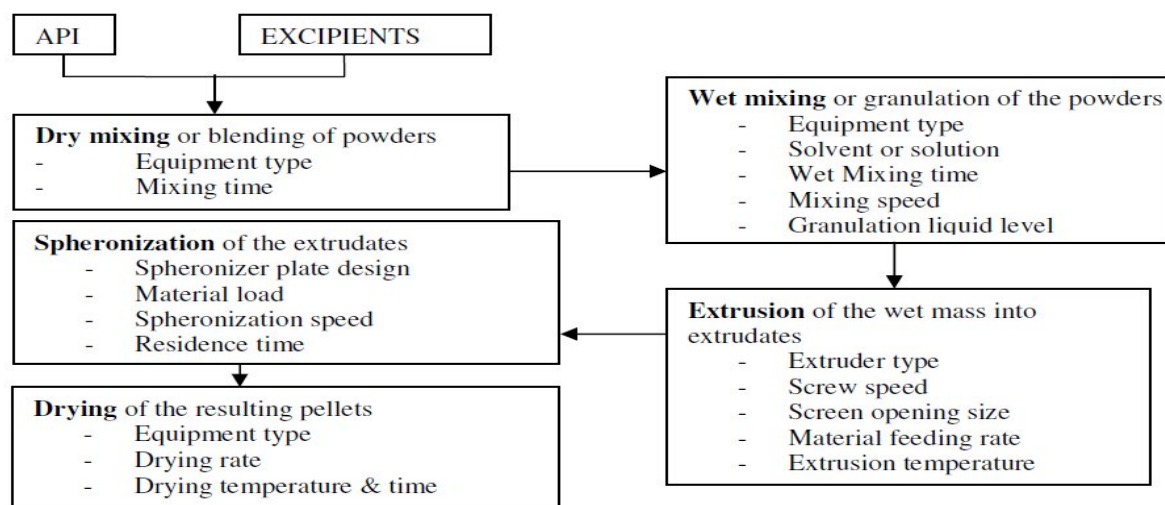


Figure 2 Extrusion/spheronisation process flow chart with individual processing variables.^[19]

CHARACTERIZATION OF PELLETS: -**1. Particle size distribution:**

It is done to ensure minimum variation in coating thickness, facilitating blending of pellets if required. Sizing of pellets is necessary as it has substantial influence on the release kinetics. It must be as narrow as possible. The pellets are polydispersal. Hence it is more sensible to determine the size distribution in the batch rather than size of the pellets.

Particle size is determined by simple sieve analysis using sieve shaker. It is the most widely used method for determining particle size distribution. It is inexpensive, rapid and simple. Sieves are arranged with the coarsest at top. Dried pellets were placed on top sieve and are mechanically agitated for certain time. The pellets retained on each sieve are weighed. Particle size of the pellets can also be determined by optical microscopy. In this method, the diameter of pellets is measured using calibrated micrometers.^[20]

2. Surface morphology:

Scanning electron microscopy is used to examine the surface characteristics or the microstructure of the pellets. The pellets are mounted on the aluminum stub, sputter-coated with thin layer of platinum under argon atmosphere and examined using SEM. SEM is also examined to ascertain influence of fillers on the quality of pellets.^[21]

3. Surface area:

Surface area of pellets depends on the size, shape, porosity and surface roughness. It is important to determine surface area when film coating is desired as thickness of coating depends on surface area. It is also important in case of uncoated pellets as drug release depends on surface area of the pellet. It is determined by 2 methods: -

1. Gas adsorption method
2. Air permeation method⁽²²⁻²⁴⁾.

1. Gas adsorption method:

It is commonly known as BET method (Brunauer, Emmett & Teller). In this method, volume of nitrogen adsorbed by the substrate in an evacuated glass bulb is measured at different pressure. The results are interpreted using linear point of BET equation for the adsorption of nitrogen on the surface.

2. Air permeability method:

It is most widely used method of determining surface area especially to control batch-to-batch variations. A column packed with powder is subjected to air stream. The system is then

sealed off and the drop in the pressure is measured across the bed. The principle resistance to the air flow through a plug of Compacted material is the surface area of the material. The commercially available instrument used for this method is Fischer sub-sieve sizer ⁽²⁵⁾.

4. Sphericity: - Pellets of optimum size were taken, stained with dye solution in a Petri- dish and dried on a hot air oven. Each pellet is recorded using camera lucida fixed to an optical microscope and circulatory factor(S) was calculated using the equation: -

$$S = P^2/12.56 * A \quad (1)$$

Where A is the area and P is the perimeter of circular tracing. Visual inspection of pellets by microscope and stereomicroscope are another method to determine shape of pellets.

5. Porosity: - Porosity influences the dissolution characteristics of drug by affecting capillary action of the dissolved drug. The porosity can be determined qualitatively by SEM with an image. It can be determined quantitatively by mercury porosimetry or by using optical microscopy and SEM together. The sample is introduced into the chamber, degassed, and then completely covered with mercury. Pressure is applied and the volume of mercury that penetrates into the pores is recorded.

Pore radius is given by Washburn equation: -

$$R = 2 g [\cos q] / P(2)$$

Where; g = 480 ergs/cm³, q= 140°, r = pore radius, p = mercury-intrusion pressure.

6. Density: Bulk and tap densities of the pellets are determined to ensure the homogeneity of the particle size distribution. Density of the pellets depends on the change in formulation or process factors such as capsule filling, coating, and mixing. Bulk density can be measured using automated tapper while true density can be determined by air-comparison pycnometer or by solvent displacement method. Bulk density indicates the packing properties of the pellets whereas true density indicates the extent of compaction. Bulk density is greatly influenced by sphericity of the pellets.

7. Hardness and friability: Hardness and friability determination is necessary in order to check the mechanical strength of the pellets during handling, shipping, storage, coating process and other unit processes which result in formation of dust. Relative hardness of the pellets is determined by using Kaul pellet hardness tester. Friability of the pellets is determined using Erkewa type tablet friabilator or by using fluidized bed with Wurster insert by using stream of air. Friabilator involves the use of glass beads which increases the mechanical stress on the pellets.

8. Tensile strength: - Tensile strength of the pellets can be determined by using tensile apparatus with a 5 kg load cell. Pellets have to be strained until failure occurs. Further load is recorded and the tensile strength is calculated by applying the value for the failure load and the radius of the pellets as already reported. ^[26]

Concept of Mass Transfer in Spheronisation: - ^[27]

Since the water content of the extrudates is a crucial parameter in spheronisation, its influence on this mechanism has been investigated further. Mass transfer between pellets has been observed for all water contents. The extent of the mass transfer increased in correlation with an increasing amount of water used. The higher extent of the mass transfer is also demonstrated by the larger pellet diameter because smaller pellets disappeared in the fine fraction and combined with larger particles, provoking pellet growth. A higher mass transfer was found for higher water contents, which could be explained with lower rigidity of the extrudates. This results in a higher fine fraction and higher capillary forces, which attach more fine particles to the surface of the pellets.

Table 2: - Examples of Multilithic Drug Products (Pellets, Spheroids, Granules) ^[28]

Brand name	Drug	Company	Product form	Market form
Xenical®	Orlistat	Roche	Uncoated pellets	Capsule
Nexium®	Esomeprazole Mg	Astrazenaca LP	Delayed-release pellets	Capsule
Toprol-XL®	Metoprolol succinate	Astrazeneca LP	EXR coated pellets	Tablet
Verelan PM®	Verapamil HCl	Schwarz	EXR pellets with controlled onset	Capsule
Singulair®	Montelukast sodium	Merck	Oral granules	Granule
Prevpac® and Prevacid®	Lansoprazole	TAP	Enteric granules	Capsule
Paser®	Aminosalicic acid	Jacobus	Enteric granules	Granule
Effexor XR®	Venlafaxine	Wyeth	EXR spheroids	Capsule

ADVANTAGES OF EXTRUSION-SPHERONIZATION

Today extrusion spheronisation (wet mass extrusion) and melt extrusion spheronisation represents an efficient pathway for novel drug delivery system. The potential of this technology lies in the scope for different oral controlled delivery systems including oral and topical delivery systems. Because of its simple design, high efficiency of producing spheres and fast processing, extrusion spheronisation has found a special position in pharmaceutical industry and especially in case of production of multiparticulate oral controlled release dosage forms. Pellet formation by this technique produces more spherical pellets and offers more advantages than other pelletization process. Other advantages include large surface area coverage, prevention of dose-dumping and less variation in bioavailability. In addition, hot melt extrusion method has provided a new platform to produce spherical particles of drugs which are not stable or having compatibility problem in presence of solvents. [29]

CONCLUSION

Granulation or the manufacture of pellets using the extrusion spheronisation technique includes several process stages (blending of the dry mass, wet granulation of the mass, extrusion of the moist mass, rotation of the extrudates by spheronisation, and drying). The amount of wetting liquid in the powder mass in pelletization by extrusion spheronisation is relatively high compared with fluidized bed granulation. Consequently, depending on the drug substance and excipients processed, solution-mediated polymorphic transformations probably take place. Pelletization processes have also been studied in terms of the phase transformations of APIs. From a bioavailability standpoint, pellets minimize inter and intraindividual variability and food effects as they undergo gradual but continuous and uniform gastric emptying. While pellets have been confined to formulation of small molecules, they also offer a convenient mode of dosing for large molecules typically administered by parenteral route. In addition, pellets are less prone to dose dumping that is commonly associated with single unit such as a tablet. Other advantages include improved flow properties, dust control and marketing appeal. Mass transfer between particles must be considered in addition to plastic deformation in order to capture the mechanism.

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