



## MULTIPARTICULATE DRUG DELIVERY SYSTEM: PELLETIZATION THROUGH EXTRUSION AND SPHERONIZATION

Anshuli Sharma<sup>1\*</sup>, Sandhya Chaurasia<sup>2</sup>

<sup>1</sup>Noida Institute of Engineering and Technology, Greater Noida, India

<sup>2</sup>Sagar Institute of Research and Technology, Bhopal, India

Article Received on: 17/12/12 Revised on: 01/01/13 Approved for publication: 10/02/13

\*Email: anshulisharma.024@gmail.com

### ABSTRACT

Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimising side effects. Recent trends indicate that multiparticulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. Pelletization is a technique used to prepare fine powders into pellets used as multiparticulate drug delivery systems. There are different pelletization techniques used to prepare pellets. Extrusion and spheronization is one of them used to prepare pellets drug loaded beads/pellets for extended release or sustained release oral formulations such as tablets and capsules.

**Keywords:** Pellets, Pelletization, Extrusion and spheronization.

### INTRODUCTION

The concept of the multiple unit dosage form (MUDF) was initially introduced in the early 1950.<sup>1</sup> Multiparticulate drug delivery systems are the most accepted and extensively used dosage form as they offer numerous advantages over unit dosage forms like improved bioavailability because of increased surface area, reduced inter-subject variation, more even and predictable distribution and transportation and reduced chances of dose dumping.<sup>2</sup> Multiparticulates are discrete particles that make up a multiple unit system. They provide many advantages over single-unit systems because of their small size. Multiparticulates are less dependent on gastric emptying, resulting in less inter and intra-subject variability in gastrointestinal transit time. They are also better distributed and less likely to cause local irritation.<sup>3</sup> There are many reasons for formulating a drug as a multiparticulate system for example, to facilitate disintegration in the stomach, or to provide a convenient, fast disintegrating tablet that dissolves in water before swallowing which can aid compliance in older patients and children. Multiparticulate systems show better reproducible pharmacokinetic behaviour than conventional (monolithic) formulations. After disintegration which occurs within a few minutes often even within seconds, the individual subunit particles pass rapidly through the GI tract.<sup>4</sup>

### PELLETIZATION

Pelletization is referred to as an agglomeration process, that converts fine powders or granules of bulk drugs or excipients into small, free flowing, spherical or semi-spherical units, referred to as pellets. Traditionally, the word 'pellet' has been used to describe a variety of systematically produced, geometrically defined agglomerates obtained from diverse starting materials utilizing different processing conditions. These are oral dosage forms consisting of multiplicity of small discrete units, each exhibiting some desired characteristics. They are produced by agglomerating fine powder with a binder solution. The size of pellets varies from formulation to formulation, but usually ranges in size from 0.5-1.5 mm.<sup>5</sup>

### Advantages of pelletization

There are various advantages associated with pelletization listed below:

- When formulated as modified release dosage forms, pellets are less susceptible to dose dumping than reservoir type single unit formulations.
- Pellets are recommended for patients with difficulty in swallowing and dysphagia like in case of children and aged people.
- Pelletization reduces intra and inter-subject variability of plasma profiles by reducing variations in gastric emptying rates and overall transit times.
- Pelletization produces spheroids with high loading capacity of active ingredient without producing extensively large particles.
- Pellets exhibit better roundness than the commercial non-pareil seeds and have excellent flow and packing properties.
- Pellets composed of different drugs can be blended and formulated in single unit dosage form that facilitates delivery of two or more chemically compatible or incompatible drugs at the same or different site in GI tract.
- Incompatible drugs processed separately and mixed later, or pellets with different release mechanisms can be mixed to give a new modified release profile.
- Pellets reduce peak plasma fluctuations and minimize potential side-effects without appreciably lowering the drug bioavailability.
- Pellets disperse freely in the GI tract and hence greater absorption of the active drug occurs.
- Particles less than 2-3 mm rapidly pass the pylorus regardless of the filling level of the stomach or the size and density of chyme. Also, GI irritations are limited spread as the particles spread in the intestine.

### Factors affecting pelletization

There are various factors affecting pelletization such as:

- Type of excipient used
- Solubility of excipients and drug in the granulating fluid
- Type of extruder used
- Type and diameter of the spheronizer plate

- Time, load and speed of spheronization
- Drying technique and drying temperature.

#### Purpose of Pelletization

Pelletization is one of the most promising technique of Multiunit particulate drug delivery system. The various purpose of pelletization are:

- To improve flow, dispersion, solubility, stability and compaction.
- To have less variance in transit time through the gastrointestinal tract than single-unit dosage forms like tablets prepared by granulation and compression.
- To produce pellets of uniform size with high drug loading capacity.
- To prevent segregation and dust.
- Pellets can be compressed into tablets called as "pelltabs" and can also be filled into capsules.<sup>6,7,8</sup>

#### EXTRUSION AND SPHERONIZATION

It is the most widely used pelletization technique in the pharmaceutical industry as it is a robust, simple, fast processing and reproducible pellet production process. Extrusion-spheronization is widely used in formulation of immediate release; extended release and controlled release delivery systems.<sup>9</sup>

Pelletization by **Extrusion-spheronization** is a process where pellets are produced from mixtures of solids and liquids by the involvement of forming and shaping forces.

**Extrusion and Spheronization** involves four steps:

Preparation of the wet mass (Granulation) → Shaping the wet mass into cylinders (Extrusion) → Breaking up the extrudates and rounding of the particles into spheres (spheronization) → Drying of Pellets

Extrusion involves forcing the wet powder mass through a restricted cross-section. 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.

During the Spheronization process, the extrudates break into small cylinders with a length equal to their diameter. Two mechanisms are proposed for the formation of spheres; these plastic cylinders are rounded due to frictional forces into cylinder with rounded, 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 edges cavity.<sup>10</sup>

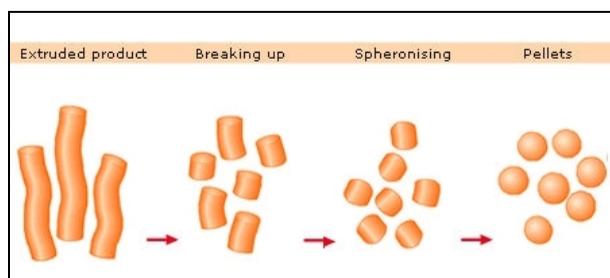


Figure 1: Schematic diagram showing spheronization

At the end of the spheronization process, the wet pellets must be dried to adjust pellet size, density, hardness etc.

#### EXTRUSION AND SPHERONIZING EQUIPMENT

##### Extrusion

Extrusion is a method of applying pressure to a mass until it flows through an orifice or defined opening, is a technique that determines two dimensions of an agglomeration of particles. Because the cross sectional geometry is defined by the orifice, extrudate length is usually the only one dimensional variable. The extrudate length may vary depending upon physical characteristics of the material to be extruded, the method of extrusion, and how the particles are manipulated after extrusion. In general, the extrusion operation is the major contributing factor in the final particle size of the pellets. The diameter of the extruder-screen openings directly controls the diameter of the extrudate, which is related to mean particle size of the pellets. The relationship between the diameter of the extruder-screen openings and the mean diameter of final pellets has been reported unity.

Various types of extrusion devices have been grouped into the following general classifications:

**1. Screw Extruder:** As the name implies, utilizes a screw to develop the necessary pressure to force material to flow through uniform openings, producing uniform strands or extrudates. The screw extruder has three major zones that are defined by the principle mechanical operation being performed: **Feed zone;** **Transport Compression zone;** and **Extrusion zone.**

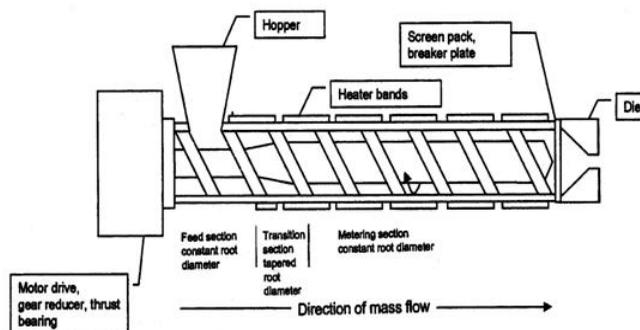


Figure 2: Detailed parts of screw extruder

Two fundamentally different mechanisms for screw extrusion are possible:

- a) Radial screw feed extruder
- b.) Axial screw feed extruder

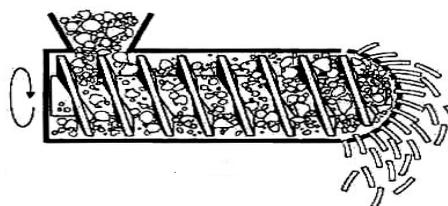


Figure 3: Radial screw extruder

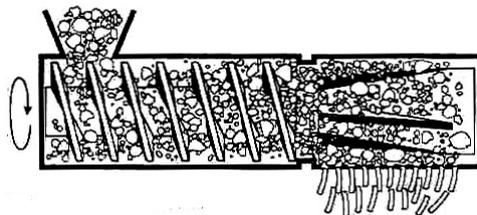


Figure 4: Axial screw feed extruder

**2. Sieve & Basket Type Extruder**

Sieve extruders are constructed like a flour sifter used in baking. That is, they have a chamber that contains the material to be extruded and a plate or screen. Some sieve extruders used with moist materials to form granules suitable for feeding to tablet presses. Basket type extruders are similar to sieve extruders except that the sieve or 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 formed in the horizontal plane as it is forced through the vertical holes.

**3. Roll Extruder**

Also known as “pellet mills” to operate by feeding material between a roller and a perforated plate or a ring die, a method that forces moist formulation through the die.

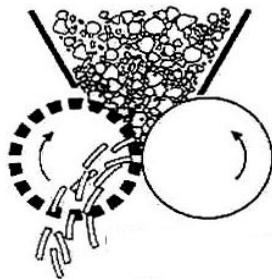


Figure 5: Roll extruder

**4. RAM Extruders**

It is the oldest type of extruder, a piston riding inside a cylinder or channel is used to compress material and force it through an orifice on the forward stroke. Each return stroke allows material to fall into the chamber. The back pressure, due to friction in the die and from the compression of material against the walls, compresses the material, and a dense extrudate is formed.<sup>10,11</sup>

**SPHERONIZING EQUIPMENT**

Spheronization technology was first introduced by Nakahara in 1964. A spheronizer also known as marumerizer consists of a static cylinder and a rotating

friction plate where the extrudate is broken up into smaller cylinders with a length equal to their diameter and these plastic cylinders are rounded due to frictional forces. During spheronization process different stages can be distinguished depending upon the shape. The friction plate, a rotating disk with a characteristically grooved surface to increase the frictional forces, is the most important component of the equipment. Two geometric patterns are generally used. It includes a cross-hatched pattern with grooves running at right angle to one another, a radial pattern with grooves running radially from the center of the disc. The rotational speed of the friction plate varies from 100-2000 rpm. Spheronization process involves transition from rods to spheres that might occur in various stages which usually take 5 to 30 minutes provided mass should not be too dry wherein no more spheres are formed and the rods will transform as far as dumbbells only.

A spheronizer is a device consisting of a vertical hollow bowl with a horizontal rotating disk (friction plate) located inside. Extrudate is charged onto the rotating plate and broken into short segments by contact with the friction plate, by collisions between the particles and by collisions with the wall. Mechanical energy introduced by the spinning friction plate is transmitted into kinetic energy in the form of a “mechanically fluidized bed” a more-or-less random mixture of air-borne particles moving at high velocities.

The most important component is friction plate which can have variety of surface textures designed for various purposes. The cross-hatch pattern is most common where the grooves intersect each other at 90° angles. A possibly more efficient pattern is radial groove plate, where grooves emanate from the centre like spokes of a bicycle wheel. The spheronization operation has been divided into three stages: (a) breaking of cylindrical segments or extrudates, (b) agglomeration of broken segments, (c) smoothing of particles. The breaking stage has been attributed to the interaction of the extrudate with the rotating plate, the stationary wall and the extrudate particles. Agglomeration occurs when small fragments produced during the breaking stage are picked up by larger particles during smoothing. The smoothing stage creates spherical pellets by generating rotational motion of each granule about its axis in constantly changing planes. The friction plate is responsible for providing the energy necessary to produce pellets and for controlling the extent of pellet growth. The energy required for spheronization is provided in the form of interparticulate friction.<sup>12,13,14</sup>

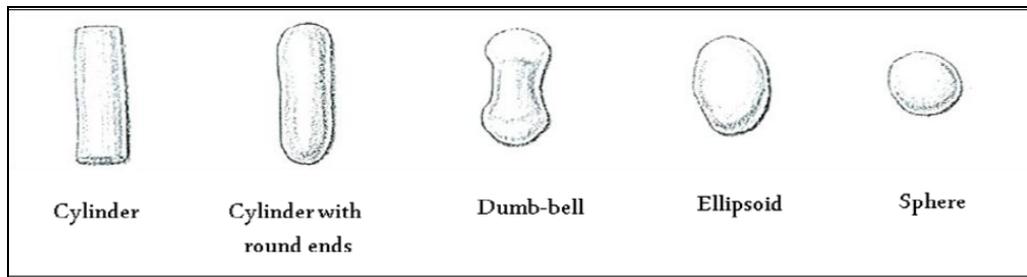


Figure 6: Schematic representation of different pellet formation stages during spheronization

## PROCESS PARAMETERS FOR EXTRUSION AND SPHERONIZATION

There are various process parameters for extrusion and spheronization that has to be considered during processing. They are:

**Starting Material:** The nature of the starting material influences the size, hardness and sphericity of the particle, as well as the release rate of the loaded drug. The material used in the formulation causes difference in pellet quality produced from different compositions. The use of similar products manufactured by different suppliers also showed changes in the characteristics of the pellet produced.

**Extruders:** According to Reynolds and Rowe an axial screw extruder produces a denser material than a radial screw extruder. The latter has a higher output but also produces but shows greater heat production during the processing. Pellet quality is dependent on the thickness of the screen and the diameter of the perforations. A thinner screen produced a rough and loosely bound extrudate, whereas a thicker screen forms smooth and well-bound extrudate because of the higher densification of the wet mass. Similarly, the diameter of the perforations determines the size of pellets- a larger diameter in the perforations will produce pellets with a larger diameter under similar processing conditions.

**Extrusion Speed:** The output from the extruder depends on the extrusion speed. The increasing speed causes at surface impairments, such as roughness and shark-skinning which leads to pellets with lower quality because the extrudate will break up unevenly during the initial stages of the spheronization process, resulting in a number of fines and a wide particle-size distribution.

**Extrusion Temperature:** The extrusion cycle during the operation may lead to rise in the temperature which could cause the granulating liquid to evaporate from the granules which causes difference in the quality of the extrudate right in the beginning of the batch itself. Extrusion temperature control is especially taken into the consideration when processing a thermolabile drug formulation.

**Spheronizer Specifications:** Pellet quality is also dependent on spheronizer load which affects the particle size distribution, bulk and tapped density of final pellets. The increase in the spheronizer speed and a low spheronizer load will result in wider particle size distribution with less yield of pellets, whereas it increases with extended spheronization time at a higher spheronizer load. It was also reported that an increasing spheronizer load decreased the roundness and increased the

hardness of pellets. Hellen et al. reported that the bulk and tap density increased as the size of the pellets decreased with an increasing spheronizer load.<sup>15</sup>

## CONCLUSION

This brief review on Multiunit particulate drug delivery system hereby concludes with a note that they are considered as most promising drug delivery system today which is catching up with the fast pace of pharmaceutical industry. This system has gained popularity due to its easy portability, improved patient compliance and better bioavailability. Extrusion and spheronization is thus one of the most promising techniques to prepare pellets/beads. This is one of the most fast, robust and easy techniques to prepare MUPS. Many leading pharmaceutical companies are adopting this technique to prepare MUPS to prepare much better and more effective dosage forms.

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Source of support: Nil, Conflict of interest: None Declared