PELLETS AND PELLETIZATION TECHNIQUES: A CRITICAL REVIEW

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ABSTRACT

In the pharmaceutical industry, pellets can be defined as small, free-flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment. Pelletization has gained a great interest in recent years due to its various advantages over other similar techniques; such as uniformity of dose and flexibility in dosage form design. There are a number of pelletization techniques currently used by pharmaceutical industry. Among them Extrusion-spheronization and solution/suspension layering are most commonly used in pharmaceutical industries. Other novel techniques include balling, compression, cryopelletization, dry powder layering, hot melt extrusion etc. In this review, a brief account of all the important techniques with special reference to extrusion-spheronization and solution layering is included. Extrusion-spheronization is a multistep process involving dry mixing, wet granulation, extrusion, spheronization, drying, and screening; whereas solution or suspension layering involves deposition of successive layers of drug and binder solution/ suspension on started seeds, which can be either an inert material or granules of same drug. Every technique has their own advantages and limitations, therefore a thorough understanding of the process variables is important before choosing a pelletization method.

Keywords: Pelletization techniques, extrusion, spheronization, solution layering, suspension layering, spray drying, congealing, cryopelletization.

INTRODUCTION

In the pharmaceutical industry, pellets can be defined as small, free-flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment¹.

The general terms “granulation” and “pelletization” are sometimes used synonymously, the units obtained are referred to as granules, pellets, agglomerates or spheroids without making any clear distinction among them. However, there are more specific definitions available in various literatures.

Generally, if a size-enlargement process produces agglomerates of a size distribution within the range of 0.1 mm to 2.0 mm and a high porosity (about 20-50%), the process may be called “granulation”, and the resulting agglomerates are called “granulates”. “Pelletization” is often referred to as a size-enlargement process that involves the manufacture of agglomerates with a relatively narrow size range, usually with mean size from 0.5 to 2.0 mm, named “pellets”. Pellets have free-flowing properties and a low porosity (about 10 %). The term “spheronization” is usually associated with spherical units formed by a special process that includes a spheronization step where extrudates or agglomerates are rounded as they tumble on a rotating frictional base plate².

Pelletization is one of the most promising technique for the multiparticulate drug delivery systems. The interest in pellets as dosage forms (filled into hard gelatin capsules or compressed into disintegrating tablets) has been increasing continuously, since their multiparticulate nature offers many important pharmacological as well as technological advantages over conventional single-unit solid dosage forms. They can be divided into desired dose strengths without formulation or process changes and also can be blended to deliver incompatible bioactive agents simultaneously and/or to provide different release profiles at the same or different sites in the gastrointestinal (GI) tract. When taken orally, they disperse freely in the GI tract, maximize drug absorption,

minimize local irritation of the mucosa by certain irritant drugs, and reduce inter- and intra-patient variability.

Because of these enormous advantages, pelletization has become focus of extensive research, on refining & optimizing the existing techniques, as well as on the development of novel manufacturing approaches.

History of Pellets

The term pellet has been used by a number of industries to describe a variety of agglomerates produced from diverse raw materials, using different pieces of manufacturing equipment. These agglomerates include fertilizers, animal feeds, iron ores, and pharmaceutical dosage units and thus do not only differ in composition but also encompass different sizes and shapes. As a result, pellets meant different things for different industries¹.

When it comes to pharmaceutical industry, it was only in the early 1950's, in response to a desire to sustain the release of drugs over an extended period of time, that the pharmaceutical industry developed a keen interest in the technology. And it's been since the late 1970's, the advantages of pellets over single-unit dosage forms have been realized².

In time, extensive research was conducted to develop pelletization techniques and major resources were allocated towards exploring methods that were faster, cheaper and more efficient, both in terms of formulation and processing equipment. The trend is expected to continue in the foreseeable future^{2,3}.

Advantages & Limitations

Pellets offer a significant number of advantages over conventional unit-dose systems^{2,5}.

Technological Advantages

1. **Uniformity of dose.** Layering techniques and extrusion-spheronization technique offers great accuracy with uniform drug delivery to the pellets.

2. Spheres have **excellent flow properties**. This becomes very useful in automated processes or in processes where exact dosing is required, e.g. tableting, moulding operations, capsule filling, and packaging.
3. **Prevention of dust formation**, resulting in an improvement of the process safety, as fine powders can cause dust explosions and the respiration of fines can cause health problems.
4. Controlled release application of pellets due to the ideal **low surface area-to-volume ratio** that provides an ideal shape for the application of film coatings.
5. They can be blended to **deliver incompatible bioactive agents simultaneously** and/or to provide different release profiles at the same or different sites in the gastrointestinal (GI) tract.

Therapeutic Advantages

6. Pellets **can disperse freely throughout the GIT** after administration and consequently the drug **absorption is maximized**.
7. The wide distribution of spherical particles in the gastrointestinal tract **limits localized build-up of the drug**, avoiding the irritant effect of some drugs on the gastric mucosa;
8. **Reduce inter- and intra-patient variability**.
9. Modified-release multiparticulate delivery systems **are less susceptible to dose dumping** than single-unit dosage forms.

However, there are some disadvantages associated with pellet & pelletization.

1. It is difficult to compress pellets into tablets as they are too rigid. Therefore, they are often delivered encapsulated in hard gelatin capsule shells.
2. Pelletization demands highly sophisticated and specialized equipment, thereby increasing the cost of manufacturing.
3. The control of manufacturing process is complicated with too many process variables as well as formulation variables.

Requirements for good pellets

- Spherical shape and smooth surface is considered as desired characteristics for uniform film coating.
- The particle size of pellets should be in range of 600-1000µm.
- The quantity of the active ingredient in pellets should be maximum in order to maintain size of pellet^{5,6}.

Pelletization Techniques

The most commonly used and intensively investigated pelletization technique include extrusion-spheronization, powder layering and solution/suspension layering. There are other methods available which can be used for preparing pellets. Some of them are listed below (Figure 1). However, practical applicability of these methods are often very limited.

Extrusion-Spheronization

Extrusion / spheronization is a multistage process for obtaining pellets with uniform size from wet granulates (extrudates). The method involves the following main steps¹

- The dry mixing of the ingredients, in order to achieve homogenous powder dispersions;

- Wet massing, in which the powders are wet mixed to form a sufficiently plastic mass.
- An extrusion stage, in which the wet mass is shaped into cylindrical segments with a uniform diameter;
- The spheronization stage, in which the small cylinders are rolled into solid spheres (spheroids);
- The drying of the spheroids, in order to achieve the desired final moisture content;
- Screening (optional), to achieve the desired narrow size distribution.

Extrusion consists in applying pressure to a wet mass until it passes through the calibrated openings of a screen or die plate of the extruder and further shaped into small extrudate segments. The extrudates must have enough plasticity in order to deform, but an excessive plasticity may lead to extrudates which stick to each other. The diameter of the segments and the final size of the spheroids depend on the diameter of the openings in the extruder screen^{6,7}.

Spheronization refers to the formation of spherical particles from the small rods produced by extrusion. The essential part of the spheronizer is the friction plate (Figure 2). The indentation pattern on the plate can have various designs, which correspond to specific purposes. The most common design is the cross-hatch pattern with grooves intersecting each other at 90° angles.

In order to form spheroids, the extrudates are brought onto the rotating friction plate of the spheronizer, which imparts a rolling motion to the material. Following the collisions between the extrudates with each other and with the friction plate and the stationary walls of the spheronization chamber, the cylindrical segments change their shape and size. The movement of the product along the chamber and transition from the almost cylindrical segments to spheres during the spheronization process occurs in several stages shown in figure 3 & figure 4.

Extrusion/spheronization is a versatile process for producing pellets with useful properties. Microcrystalline cellulose (MCC) is extensively used for preparing the above-mentioned 'wet mass' from which the pellets are to be prepared. MCC is considered as golden standard for extrusion-spheronization. Based on its good binding properties, it is able to provide the appropriate rheological conditions the process needs. Moreover, by controlling the movement of water through the plastic mass, it prevents phase separation during extrusion or spheronization⁶. However, some limitations of MCC as excipient for production of pellets by spheronization has been reported in various literature⁷.

- Drug adsorption onto the surface of MCC fibers has been reported⁸.
- Chemical incompatibility of MCC with a number of drugs⁹.
- Lack of disintegration of MCC-based pellets was reported in some literatures¹⁰.

O'Connor et al.^{11, 12} studied the behavior of some common excipients in extrusion/ spheronization. They also investigated the effect of varying drug, excipient, and excipient:drug ratios. They found that, for low dose applications, MCC was the best excipient to use since it formed the most spherical particles. At moderate drug loading (50%), MCC as well as the two products consisting of MCC co-processed with Na-CMC (Avicel RC-581 and

Avicel CL-611) resulted in acceptable spheres. At higher loading levels, however, the MCC did not yield acceptable spheres and the coprocessed materials did. The spheres produced using Avicel CL-611 were the most spherical.

Hot Melt Extrusion

This is a newly modified variation of extrusion-spheronization method. Here a drug substance and excipients are converted into a molten or semi-molten state and subsequently shaped using appropriate equipment to provide solid spheres or pellets. This is a simple, efficient and continuous process which requires fewer processing stages. It does not require a lengthy drying stage since it does not involve addition of water or other solvent, in disparity to granulation process¹³.

Layering Techniques

Solution & Suspension Layering

Layering a solution/suspension of a drug on a 'starter seed' material (usually, a coarse crystal or nonpareil) can produce pellets that are uniform in size distribution and generally possess very good surface morphology. These characteristics are especially desirable when pellets will be coated for the purpose of achieving a controlled release¹⁴.

The Wurster coating process, which was invented about 30 years ago, had evolved through elaborate design modifications and refinement into ideal equipment for the manufacture of pellets by solution and suspension layering.

The primary features that distinguish Wurster equipment from other fluid-bed equipment are the cylindrical partition located in the product chamber and the configuration of the air distributor plate, also known as the orifice plate. This plate is configured to allow most of the fluidization or drying air to pass at high velocity around the nozzle and through the partition, carrying with it the particles to the expansion chamber (figure 3). In the large expansion chamber, the velocity of air becomes slower, thereby causing the particles to fall back again to area surrounding the partition (down bed). The down bed is kept aerated by the small fraction of air that passes through the small holes on the periphery of the orifice plate. The particles in the down bed are transported horizontally through the gap between the air distributor plate and the partition by suction generated by the high air velocity that prevails around the nozzle and immediately below the partition. Thus, a constant and well-organized motion of particles is formed inside the chamber, helping a uniform coating on the particles to form.

The disadvantage of the Wurster process is the inaccessibility of the nozzles. If the nozzles are clogged at any time during the layering process, the operation has to be interrupted, and the spray guns must be removed for cleaning. The problem can be minimized by screening the formulation or by using a spray gun with a bigger nozzle^{15,16}.

The importance of various process parameters are very high while layering with Wurster technique. It is important to identify and optimize various formulation characteristics like solubility, concentration of binder, viscosity of solution/suspension etc. When suspensions are used, the size of particles must be very carefully optimized; as smooth and potent pellets can only be obtained by using small (micron-sized) particles, otherwise the surface of pellets tends to be rough, which may adversely affect the coating process.

Solution/suspension layering is usually used when the desired drug loading of the pellets is low because production of high-potency pellets from a low solids content formulation is not

economically feasible. In case of suspensions, another important factor comes into play i.e. the particle size of the drug. Micronized drug particles provide smooth pellets, and therefore are preferable for controlled-release formulations, where subsequent film coating is required. A drug with larger particle size requires higher amount of binder solution. As a result, potency of prepared pellets is reduced, and their surface also tend to be rough^{16,17}.

Dry Powder Layering

Powder layering is similar to the solution or suspension layering. Instead of these dispersions, the layering is performed using a drug powder. The process involves the deposition of successive layers of dry powder of drug or excipients or both on preformed nuclei or cores with the help of a binding liquid. Usually, the process is carried out in conventional coating pans.

Initially, the nonpareils or starter seeds are charged into a rotating pan, and then wetted by spraying an adhesive solution. As the wet seeds reach the front end of the pan, the powder added in the vortex adheres to them¹⁸.

Claudio Nastruzziet al¹⁹ investigated the Influence of formulation and process parameters on pellet production by powder layering technique. Inert cores were intermittently treated with micronized drug powder and adhesive solution. This treatment led to the formation of multiple layers of drug particles around an inert core resulting in the production of pellets that can further be coated by different polymers to obtain modified release formulations. During its preparation, the formulation showed no degradation of the drug. This study showed the good performance of the GS automated pan-coating system in obtaining enteric coated pellets prepared by powder layering technique using aqueous solutions.

Golam Kibria et al²⁰ formulated pellets of domperidone by powder layering on sugar cores in conventional coating pans and evaluated the prepared pellets for various in-vitro parameters. The results showed that the pan coating system is efficient for manufacturing highly stable instant release pellets.

Balling

Balling, otherwise known as spherical agglomeration, is a pelletization technique in which powders are converted into spherical pellets by a continuous rolling or tumbling motion. This can be done either by adding an appropriate amount of liquid into the powder, or subjecting it to high temperature.

Spherical agglomeration can be divided into two categories—liquid-induced agglomerations and melt-induced agglomerations. Various instruments are used ranging from conventional horizontal drum pelletizers, inclined dish pelletizers or tumbling blenders to more advanced rotary fluid-bed granulators and high-shear mixers. This technique is popularly used in iron ore and fertilizer industries, but its use in pharmaceutical industries are still very limited²¹.

During liquid-induced agglomeration, liquid is added to the powder before or during the agitation step. As powders come in contact with a liquid phase, they form agglomerates or nuclei. Melt-induced agglomeration processes are similar to liquid-induced processes except that the binding material is a melt. The rate and extent of agglomerate formation depend on formulation variables such as particle size and solubility of the powder, the degree of liquid saturation, and the viscosity of the liquid phase²².

Compression

Compression is one type of compaction technique for preparing pellets. Pellets of definite sizes and shapes are prepared by compacting mixtures or blends of active ingredients and excipients under pressure. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablet manufacturing.

Kadar et al²³ prepared sustained release pellets of poly (lactic acid) with increasing bovine serum albumin (BSA) load and studied the in-vitro release pattern of theophylline from prepared pellets. They reported that theophylline release was driven by leaching through channels and not by polymer degradation. The release rate was found to be dependent on BSA loading and annealing.

Globulation

Globulation, or droplet formation, consists of two related processes, spray drying and spray congealing. They involve atomization of hot melts, solutions, or suspensions to generate spherical particles or pellets.

Spray Drying

During spray drying, drug entities in solution or suspension are sprayed, with or without excipients, into a hot stream of air to generate dry and highly spherical particles. As the atomized droplets come in contact with hot air, evaporation of the application medium occurs. This drying process continues through a series of stages whereby the viscosity of the droplets constantly increases until finally almost the entire application medium is evaporated and solid particles are obtained.

Though the technique is suitable for the development of controlled-release pellets, it is generally employed to improve the dissolution rates and the bioavailability of poorly soluble drugs. Also, this method is applied for processing heat sensitive pharmaceuticals, such as: amino acids, antibiotics, ascorbic acid, liver extracts, pepsin and similar enzymes.

The spray-dried powder particles are homogenous, approximately spherical and nearly uniform in size. The design and operation of the spray drier can influence a great number of the characteristics of the final product, such as particle size and size distribution, bulk density, porosity, moisture content, flow ability and friability²⁴.

Spray Congealing

Spray-congealing is a process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes, fatty acids or other melting solids. The dispersion is then sprayed into a stream of air and other gases with a temperature below the melting point of the formulation components. Under appropriate processing conditions, spherical congealed pellets are obtained²⁵.

Cryopelletization

Cryopelletization is a process whereby droplets of a liquid formulation are converted into solid spherical particles or pellets by using liquid nitrogen as the fixing medium at -160°C. The procedure permits instantaneous and uniform freezing of the material. The rapid heat transfer that occurs between the droplets and liquid nitrogen is responsible for the same. The pellets are dried in conventional freeze dryers. Generally, 3-5 kg of liquid nitrogen is required for preparation of 1 kg pellets²⁵.

Compression of pellets into tablets

Typically, pellets are produced for administering in a capsule dosage form after manufacturing with desired modified release properties. However, they can be compressed into tablets as well. One challenge in the production of such tablets is maintaining the desired drug release after compaction. There are a number of investigations reported on compaction of pellets, both coated and uncoated²⁶.

Wang et al.²⁶ reported compression of various lactose/microcrystalline cellulose compositions in powder or pellet form. Schwartz et al.²⁷ demonstrated the compaction characteristics of MCC processed into spheres are significantly different than the original powder. The powder material forms hard compacts at low compression forces, while the spheres are not compressible and form soft compacts, even at high forces. Nicklasson²⁸ investigated the compression behavior of pellets consisting of MCC, with or without other excipients such as polyethylene glycol and DCP. Deformation of the aggregates was found to depend on three deformation characteristics, namely, the capacity for, the mode of and the resistance to deformation.

Figure 1: Schematic presentation of various pelletization techniques

Figure 2: Schematic representation of a spheronizer friction plate with a cross-hatch pattern indentation

Figure 3: The movement of the product along the chamber

Figure 4: Shape transitions during a spheronization process

Figure 5: Schematic representation of the Wurster product chamber and process. (A) Product chamber, (B) Partition, (C) Orifice plate, (D) Nozzle, and (E) Expansion chamber¹

CONCLUSION

This review focused on various pelletization techniques, especially emphasizing on Extrusion-Spheronization and Solution/suspension layering. Some other novel techniques were also discussed. In recent times, growing interest in pelletization is observed, owing to its advantages over conventional granulation methods. Each pelletization technique have their own advantages and limitations. Therefore the technique to be used has to be chosen very carefully, considering all the variables of that particular technique that may affect the product.

It can be concluded that due to their good technological and biopharmaceutical advantages, pelletization has gained an importance in modern pharmaceutical science; and pellets are expected to play a major role in design and fabrication of many novel drug delivery systems in the future.

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