Multiple Unit Particulate System: Pelletization Techniques: An Overview

Bharkatiya Meenakshi *, Siyal Harsha
B.N. Institute of Pharmaceutical Sciences, Udaipur (Raj.) 313001 India

In today scenario multiple unit dosage forms are of great concern as an alternative system for oral drug delivery due to their advantages over single unit dosage form. The present review outlines the manufacturing of pellets by various pelletization techniques and characterization of pellets. There are various types of pelletization techniques like powder layering, solution/suspension layering, extrusion-spheronization, hot-melt extrusion, freeze pelletization, cryopelletization, spray drying and spray congealing and spherical agglomeration. These techniques have been discussed along with the parameters affecting pelletization.

Key words: Pelletization, extrusion-spheronization, cryopelletization, spray drying

INTRODUCTION
Pelletization is referred to as an agglomeration process of size enlargement, that converts fine powders or granules of bulk drugs or excipients into small, free flowing, spherical or semi-spherical units of size 0.5-2.0mm, referred to as pellets. These multiple unit dosage form was initially introduced in early 1950s. They are intended mostly for oral administration. The use of pellets as vehicle for drug delivery at a controlled rate has recently received significant attention. Pellets are not only useful in pharmaceutical industries but also used in different industries as fertilizers, animal feeds, iron ores etc.1 In pharmaceutical Industries pellets offer a high degree of flexibility in the design and development of oral dosage form. Besides offering therapeutic advantages such as enhanced absorption due to involvement of large GI surface in absorption process, less gastric irritation by limiting localized buildup and reduced inter- and intrapatient variability pellets also provide many technical advantages such as good flowability due to uniform size and spherical shape, high physical integrity of spherical agglomerates, high strength, low friability, narrow particle size distribution, superior quality for coating application due to spherical shape and a low surface area-to-volume ratio and uniform packing characteristics. They can be divided into desired dose strengths without formulation or process changes and also can be blended to deliver incompatible bioactive

*Address for correspondence
meenakshibharkatiya@rediffmail.com
agents simultaneously and/or to provide different release profiles at the same or different sites in the gastrointestinal (GI) tract. Extensive research has focused recently on refining and optimizing existing pelletization techniques as well as on the development of novel manufacturing approaches that use innovative formulations and processing equipment.²⁻⁴

Regardless of which manufacturing process is used, pellets have to meet the following requirements: ⁵⁻⁶

Spherical shape, low surface area to volume ratio 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.

Stages of Pellet Growth

The mechanism of pellet formation has traditionally been subdivided into nucleation, coalescence, layering, abrasion transfer, crushing, and other concomitant events such as snow balling and onion skinning, based mainly on the elementary growth mechanism suggested by Sastry and Fuerstenau (Fig. 1)⁷

Nucleation is the initial phase of agglomeration in which nuclei or small agglomerates of loose and porous structure are formed after the primary particles are wetted by a binding liquid droplet. The primary particles are bound by liquid bridges in the pendular state.

The nucleation phase is characterized by the disappearance of fines as a consequence of coalescence between the wetted primary particles or the primary particles with the formed nuclei. The resultant nuclei would undergo consolidation under the impact of the externally applied mechanical forces and acquire sufficient strength to resist further breakdown by impact forces and will be able to grow into bigger agglomerates.

Nucleation is followed by a transition phase for progression in the size of the formed nuclei, and the growth mechanisms
affecting the transition region are coalescence and layering. Coalescence is defined as the formation of large-sized particles by random collision of well-formed nuclei, and the mechanism requires slight excess moisture on the nuclear surface. Although the number of nuclei is progressively reduced, the total mass of the system remains unchanged during this step. Layering is a slow growth mechanism and involves the successive addition of fragments and fines on an already formed nucleus. In the layering step, the number of particles remains the same, but the total mass in the system increases due to increasing particle size as a function of time. The layering growth stage generally takes place after the agglomerates have attained a certain size and rigidity and is associated with the reduced rate of coalescence. In the ball growth phase the main mechanism affecting the slow growth of agglomeration is the abrasion transfer which involves the transfer of materials from one granule formed to another without any preference in either direction. The particles, however, undergo a continuous change in size as long as the conditions that leads to the transfer of material exist.

**Methods of Pellet Preparation:**
The most commonly used and intensely investigated pelletization processes are powder layering, solution/suspension layering, and extrusion–spheronization. Other pelletization processes that either have limited application include spherical agglomeration or balling, spray congealing/ drying, and emerging technologies such as cryopelletization and melt spheronization.

**Powder Layering:** In powder drug layering, successive layers of dry powder of drug or excipients or both are deposited on preformed nuclei or cores with the help of a binding liquid. Because of simultaneous application of the binding liquid and dry powder, powder layering generally requires specialized equipment. The primary equipment-related requirement in a powder-layering process is that the product container should have solid walls with no perforations to avoid powder loss beneath the product chamber before the powder is picked up by the wet mass of pellets that is being layered on.

During powder layering, a binding solution and a finely milled powder are added simultaneously to a bed of starter seeds at a controlled rate. In the initial stages, the drug particles are bound to the starter seeds and subsequently to the forming pellets with the help of liquid bridges originated from the sprayed liquid. These liquid bridges are eventually
replaced by solid bridges derived either from a binder in the application medium or from any material, including the drug substance, that is soluble in the liquid. Successive layering of the drug and binder solution continues until the desired pellet size is reached. It is extremely important to deliver the powder accurately at a predetermined rate throughout the process and in a manner that maintains equilibrium between the binder liquid addition rate and the powder addition rate. If the powder addition rate is high, dust generation may occur, and if the liquid addition rate is high, over wetting of the pellets may take place and neither the quality nor the yield of the product can be maximized. Powder layering can be carried out in a coating pan or a tangential spray or centrifugal fluid bed granulator.\textsuperscript{12}

**Solution/Suspension Layering:**

Solution/suspension layering involves the deposition of successive layers of solutions and/or suspensions of drug substances and binders on starter seeds, which may be inert materials or crystals/granules of the same drug.

During processing, all the components of the formulation are first dissolved or suspended in an appropriate quantity of application medium to provide a formulation with the desired viscosity and is then sprayed onto the product bed. The sprayed droplets immediately impinge on the starter seeds and spread evenly on the surface, provided the drying conditions and fluid dynamics are favorable. This is followed by a drying phase that renders dissolved materials to precipitate and form solid bridges that would hold the formulation components together as successive layers on the starter seeds. The process continues until the desired quantity of drug substance and thus the target potency of the pellets are achieved. Ideally, no new nuclei are formed, and the particle population remains the same; however, the sizes of the pellets increase as a function of time, and as a result, the total mass of the system also increases. For suspension layering, particle size of the drug plays an important role. If the particle size is large, a higher quantity of binder may be necessary to ensure adherence of the drug particles on the pellet surfaces. Use of high viscosity binders and stirring of the suspensions during applications, are recommended in order to avoid any settling of the drug particles. Use of very large particle may block the spraying gun or may settle in the tubing if the diameter of the tube is too large. For suspension layering process, the particle size of the API should be less than 10 - 50 μm. In principle, the factors that control coating processes apply to solution or suspension
layering and, as a result, require basically the same processing equipment. Consequently, conventional coating pans, fluid bed centrifugal granulators, and wurster coaters have been used successfully to manufacture pellets.\textsuperscript{13-14}

**Extrusion–Spheronization:**

The extrusion-spheronization process is commonly used in the pharmaceutical industry to make uniformly sized spheroids. The main objective of the extrusion spheronization is to produce pellets/spheroids of uniform size with high drug loading capacity. Extrusion–spheronization is a multistep process involving dry mixing, wet granulation, extrusion, spheronization, drying, and screening. The first step is dry mixing of the drug and excipients in suitable mixers followed by wet granulation, in which the powder is converted into a plastic mass that, can be easily extruded. The wet mass is extruded through cylindrical dies or perforated screens with circular holes, typical 0.5 - 2.0 mm in diameter to form cylindrical extrudates. These may be further processed, by cutting and drying to yield cylindrical granules. The extruded strands are transferred into a sphonizer, where they are instantaneously broken into short cylindrical rods on contact with the rotating friction plate and are pushed outward and up the stationary wall of the processing chamber by centrifugal force. Finally, owing to gravity, the particles fall back to the friction plate, and the cycle is repeated until the desired sphericity is achieved. At the end of the spheronization process, the wet pellets must be dried at room temperature or at an elevated temperature to adjust pellet size, density, hardness etc. High shear mixers, screw-fed extruders, gravity-fed extruders, ram extruders, spheronizer or merumerizer, air assisted sphonizer, fluid bed dryer, microwave oven, force circulation oven are used for different processes.\textsuperscript{15-17}

**Hot Melt Extrusion:**

A novel hot-melt extrusion and spheronization process has been recently reported to produce spherical pellets without the use of water or other solvents. This method eliminates instability problems during processing due to water. Furthermore, pellets produced by melt extrusion do not require additional film coating since the drug release is diffusion controlled. It has been widely used technique in plastic industries and now it is used in pharmaceutical industries for formulation of sustained release, controlled release and transdermal as well as transmucosal drug delivery system. Melt extrusion process consists of three basic steps: melting or plasticating a solid material, shaping the molten material and
solidification of the material into the desired shape. A hot melt extrusion line consists of a material feed hopper, extruder inside a heated barrel, having three different sections, and spheronizer. The hopper holds the material and continuously feeds it into the extruder, which has a heated barrel containing the rotating screw. The extrudate is cut into uniform cylindrical segments, which are spheronized in a jacketed spheronizer or one with a heat source to generate uniform sized pellets. The spheronization temperature should be high enough so that it partially softens the extrudate to facilitate its deformation and eventual spheronization. 18, 19

**Spherical Agglomeration:**
Spherical agglomeration, or balling, is a pelletization process in which powders, on addition of an appropriate quantity of liquid or when subjected to high temperatures, are converted to spherical particles by a continuous rolling or tumbling motion in pans, discs, drums or mixers. 20

**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. These pellets are then freeze dried or lyophilized to remove water or organic solvents. Solid content and temperature of the liquid formulation determine the amount of liquid nitrogen used in the whole process. This technology was first developed to lyophilize bacterial suspension in the nutrition industry and now a days it is used in the pharmaceutical industry to produce drug loaded pellets for immediate as well as controlled release formulations. 21

Immediate release formulation typically consists of drugs, fillers (lactose and mannitol) and binders (gelatin and PVP) while cross-linked polymers of collagen derivatives are used in the sustained release formulation. The equipment consists of a perforated plate below which a reservoir of liquid nitrogen having conveyer belt of varying speed with transport baffle is dipped. The varying speed of the conveyer belt can be adjusted to provide the residence time required for freezing the pellets. The frozen pellets are transported into storage container at -60°C before drying and are finally dried into the freeze dryer. Droplet formation is the most critical step in this technique and is influenced by formulation related variables, such as solid content, viscosity, surface tension, equipment design and process variables.

**Spray Drying and Spray Congealing**
Spray drying and spray congealing, known
as globulation processes, involve atomization of hot melts, solutions, or suspensions to generate spherical particles or pellets. Spray drying is a process in which, the drug entities in solution or suspension are sprayed, with or without excipients, into a hot air stream to generate dry and highly spherical particles. This process is commonly used for improving the dissolution rates, hence bioavailability of poorly soluble drugs. Spray congealing is the process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes or fatty acids, and is sprayed into an air chamber where the temperature is kept below the melting point of the formulation components, to produce spherical congealed pellets under appropriate processing conditions.  

**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.

**Freeze Pelletization:**
Freeze pelletization technique is a novel technique for producing spherical matrix pellets containing active ingredients. In this technique, a molten solid carrier along with a dispersed active ingredient is introduced as droplets into an inert and immiscible column of liquid. These droplets can move either in upward or downward directions, depending on their density with respect to the liquid in the column and solidify into spherical pellets. The technique involves less process variables and also offers several advantages over other pelletization methods, in terms of quality of pellets and process cost. The pellets produced by this technique are spherical in shape with narrow size distribution. Since the pellets are solid at room temperature, they do not require drying.

**Characterization of Pellets**

1) Particle size distribution
The sizing of pellets is necessary because it has significant influence on the release kinetics. Particle size distribution, mean ferret diameter, geometric mean diameter, mean particle width and length, are the parameters by which size of pellets can be determined. Particle size distribution should be as narrow as possible to ensure minimum variation in coating thickness and to facilitate blending process if blending of different types of pellets is required. Sieve analysis using sieve shaker is the most widely used method for
measuring particle size distribution. Microscopy is a direct method for determining particle size distribution. Optical microscopy and scanning electron microscopy are used to measure the diameter of pellets.27-28

2) Surface area
The characteristics of pellets, those controlling the surface area, are mainly size, shape, porosity and surface roughness. There are three methods of measuring the surface area of pellets. It can be calculated from the particle-size distribution by measuring/using the mean diameter. Two other techniques, i.e. gas adsorption and air permeability, permit direct calculation of surface area. Air permeability methods are widely used pharmaceutically for specific surface measurement, especially to control batch to batch variations. The principal resistance to the flow of a fluid - such as air – through a plug of compacted material is the surface area of the material.29 The gas adsorption method (commonly known as the BET method) was developed by Brunauer, Emmett and Teller (1937). Gas adsorption is carried out by placing a powder sample in a chamber and evacuating the air within. The volume of nitrogen that is adsorbed by the substrate contained in an evacuated glass bulb is measured at different pressures. From the knowledge of pressures and temperatures before and after introduction of the adsorbing gas, calculations of total sample surface area can be made.30

3) Porosity
The porosity of pellets influences the rate of release of drugs from the pellets by affecting the capillary action of the dissolved drug. The porosity of the pellets can be measured quantitatively by mercury porosimetry.31 The porosity of pellets can be determined qualitatively as well as quantitatively by using optical microscopy and scanning electron microscopy together with image analysis.32

4) Density
The density of pellets can be affected by changes in the formulation and/or process, which may affects other processes or factors, such as capsule filling, coating, and mixing. The bulk density of the pellets can be measured by an automated tapper. True density indicates the extent of densification or compactness of substances. The true density of pellets can be determined by an air-comparison pycnometer, a helium pycnometer or by the solvent displacement method.33-34

5) Hardness and Friability
As the pellets have to withstand during handling, shipping, storage and other processing such as coating, hardness and friability determination of pellets is
necessary. The instrument such as the Kaul pellet hardness tester provide relative hardness values and friability of pellets are determined by using Erkewa type tablet friabilator or turbula mixer for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion. Friability can also be determined using fluidized bed with wurster insert by using stream of air.\textsuperscript{35,36}

6) Tensile Strength

The tensile strength of the pellets is determined by using tensile apparatus with a 5 kg load cell, the pellets are strained until failure occurs. The load is recorded and the tensile strength is calculated applying the value for the failure load and the radius of the pellets.

7) Disintegration Time

Disintegration of pellets is one of the main characteristics for immediate release pellets. Huyghebaert et al., 2005 reported disintegration test using the reciprocating cylinder method (USP Apparatus 3).\textsuperscript{38} While Thommes and kleinbudde, 2006 performed it in a tablet disintegration tester specially designed by inserting special transparent tubes of certain diameter and length with sieve of 710 μm mesh size at the top and bottom of the tube.

8) \textit{In Vitro} Dissolution Studies

\textit{In vitro} dissolution has been recognized as an important element both in drug development and quality assessment, especially in controlled released formulation. Drug release from pellets mainly depends on the composition, hardness and size of pellets and it is determined by using USP Apparatus I or by USP Apparatus II. The drug release profiles from pellets also depended on the nature of the carrier solid, aqueous solubility of the drug, physical state of the drug in the matrix, drug load and the presence of additives such as surfactants. In case of wax based freeze dried pellets, the drug release decreased as the hydrophobicity of wax increased and the drug release increased as the aqueous drug solubility increased.\textsuperscript{38-39}

CONCLUSION:

Multiparticulate drug delivery system is an efficient pathway for novel drug delivery system. The potential of this technology lies in the scope for different oral drug delivery systems whether it is immediate release or controlled one. In recent years pelletization has occupied a special space in pharmaceutical industries mainly for controlled release formulation. All techniques of pelletization accommodate several advantages within. The novel approaches are carried out for drugs that are instable at certain levels of existing pelletization techniques. Hot-melt
extrusion method has provided a new, wider platform to produce spherical pellets of drugs which are not stable or have compatibility problems in presence of solvents. Freeze pelletization technique involves fewer steps and less process variables are involved which offers several advantages over other pelletization methods in terms of quality of pellets and process cost.

REFERENCE


27. Santosh H, Veiga F, Pina M, Sousa JJ. A study on the effect of drying techniques on the mechanical properties of pellets and


