

# Recent Advances in Pelletization Technique for Oral Drug Delivery: A Review

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**Abstract:** Multiparticulate dosage forms are receiving a great deal of attention as alternative system for oral drug delivery. The present review outlines the recent findings on the manufacturing and evaluation of spherical pellets published over the past decade. The techniques namely extrusion-spheronization, hot melt extrusion, freeze pelletization, cryopelletization have been discussed along with parameters affecting pelletization. Evaluation of quality of the pellets is discussed with reference to the size distribution, shape, surface morphology, specific surface area, friability, tensile strength, density, porosity, disintegration time and *in vitro* dissolution studies of pellets. The use of multiparticulate dosage forms as a promising system for the oral delivery of many therapeutic agents has also been examined in the current review.

**Keywords:** Pelletization, extrusion spheronization, freeze pelletization, cryopelletization, hot melt extrusion.

## INTRODUCTION

Pelletization is referred to as a size enlargement process and if the final agglomerates are spherical with a size of 0.5-2.0 mm and low intra-agglomerate porosity (about 10%), they are called pellets. The pellets 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 dose dumping [1,2] 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 and uniform packing characteristics [2-4].

The pellets are filled into hard gelatin capsule and can also be compressed into tablets [4-6]. The compression of pellets into tablets is a modern technological process, and is much more ideal than enclosing them in a hard gelatin capsule [7-10]. Modified release pellets have several therapeutic advantages over single unit dosage form such as powder filled capsule dosage form like uniform distribution of drug as compared to local build up [2,11].

Manufacturing of pellets using layering process such as solution layering, suspension layering or powder layering has been used over the years. These processes have limitations such as non-uniformity in the size of pellets and less drug loading. Most of the pharmaceutical scientists till date have focused mainly on the preparation of uniform size pellets with high drug loading using extrusion spheronization process. In recent years freeze pelletization; cryopelletization and hot melt extrusion have also been used to produce spherical pellets. This article reviews the recent development in preparation of pellets.

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## EXTRUSION- SPHERONIZATION

Wet mass extrusion spheronization also called cold-mass extrusion spheronization has become the method of choice when one is desirous of having dense spherical pellets of uniform size and shape. It involves the following steps;

### (a) Dry Mixing

Dry mixing of ingredients is done to achieve homogeneous powder dispersion using twin shell blender [12], planetary mixer [9], high speed mixer [13] and tumbler mixer [14].

### (b) Wet Massing

Wet massing is done to produce a sufficient plastic mass for extrusion, by employing normal equipment and processes as employed in wet granulation for compaction. The most commonly used granulator is planetary mixer or Hobart mixer [9,15-17] or sigma blade mixer [18] and high shear mixer [19,20]. Evaporation of the fluid phase is a major problem with high shear mixers as they introduce a high amount of energy into the wet mass which is partly transformed into heat and induces evaporation of the granulation liquid [21] thus changing the extrusion behavior of the wet mass. Cooling of the granulation bowl may avoid this problem.

### (c) Extrusion

This is the third step in the process, which produces rod shaped particles of uniform diameter from the wet mass. The wet mass is forced through dies and shaped into small cylindrical particles with uniform diameter. The extrudate particles break at similar length under their own weight. Thus, the extrudate must have enough plasticity to deform but not so much that the extrudate particles adhere to other particles when rolled during spheronization process.

Extruders are classified into three categories namely, Screw feed extruder (axial or end plate, dome and radial), Gravity feed extruder (cylinder roll or gear roll) and Piston feed extruder (ram).

The screw extruder consists of one or two (twin -screw) feeding the wet mass to an axial or radial extrusion screen [3,22]. In the axial type, the screen is placed at the end of the screw, while in radial type the screen is placed around the screw, discharging the extrudate perpendicularly to the axis of the screw.

Gravity feed extruders include rotary cylinder and rotary gear extruders, which differ mainly in the design of the two counter rotating cylinders. In the rotary cylinder extruder, one of the two counter rotating cylinders is hollow and perforated, whereas the other cylinder is solid and acts as a pressure roller. In the rotary gear extruders there are two hollow counter rotating gear cylinders with counter board holes.

In ram extruders which are probably the oldest type of extruders, a piston displaces and forces the material through a die at the end. Ram extruders are preferentially used in the development phase, because they can also be used to measure the rheological properties of the formulations [23, 24].

#### (d) Spheronization

The spheronization technology was first introduced by Nakahara in 1964 [25]. A spheronizer also known as merumerizer 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 [26] and these plastic cylinders are rounded due to frictional forces [27]. 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.

A cross-hatched pattern with grooves running at right angle to one another and 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. According to West and Rowe, 1988 [28] a rotational speed in the range of 200-400 rpm would be satisfactory to obtain highly spherical pellets. Spheronization of a product usually takes 2-10 minutes [29]. The transition from rods to spheres during spheronization occurs in various stages. If the mass is too dry, spheres will not be formed and the rods will only transform as far as dumbbells.

#### (e) Drying

A drying stage is required in order to achieve the desired moisture content. The pellets can be dried at room temperature [30,31] or at elevated temperature in a tray drier/ oven [1,32-34] or in a fluidized bed drier [15,20,21,35].

Bataille *et al.*, 1993 [36] reported the use of microwave oven in the final phase of the production process of pellets to evaporate the slurry of the extruded mass during drying process. Huyghebaert *et al.*, 2005 [37] reported the use of freeze dryer in order to maintain viability of living bacterial

spores. If solute migration occurs during drying of the wet mass, this may result in an increased initial rate of dissolution, stronger pellets with modified surfaces, which might reduce adhesion of any added film coats.

#### (f) Screening

Screening may be necessary to achieve the desired size distribution, and for this purpose sieves are used. In case of pellets prepared by extrusion-spheronization, screening is essentially required after manufacture, in order to avoid pellets having high size polydispersity index [38].

### PARAMETERS AFFECTING QUALITY OF PELLETS IN EXTRUSION-SPHERONIZATION PROCESS

#### Amount of Granulation Liquid

Moisture content of the wet mass is the most critical variable for pellet growth in the extrusion spheronization process because it provides the required plasticity and cohesiveness to the powder to extrude the wet mass and spheronize it to give a spherical shape. An optimum quantity of moisture content should be there to obtain pellet of acceptable quality [39, 40]. Moisture content exceeding the optimum quantity leads to agglomeration of pellets during spheronization due to excess of water on the surface of pellets while less quantity leads to generation of fines with large size distribution of pellets. The effect of moisture content on pellet quality has been shown by Baert and Remon, Kleinbudde, Ku, Pinto, Wan, Mezreb [1,15,17,20,32,40].

The rheological characteristics of the wet mass are important for extrusion spheronization process [41]. Elbert *et al.*, 1992 [19] showed that, optimum conditions for extrusion spheronization process could be determined by measuring the plasticity of the drug-excipients mixture as a function of the granulation liquid added.

A soluble drug gets dissolved by the granulation liquid. Thus, increasing the volume of the liquid phase could lead to over wetting of the system and agglomeration of pellets [42]. An increase in wetting liquid increases plasticity if there is a plastic substance like Gelucire 50/02 in the mass but after a certain extent it induces stickiness [43].

#### Composition of Granulation Liquid

Besides the use of water as a granulation liquid, use of alcohol or water/alcohol mixture [19,33,44], ethyl ether [45], dilute acetic acid [46], isopropyl alcohol [47] has also been reported. Millili and Schwartz, 1990 [44] reported that a minimum of 5% of granulation liquid had to be water in order to produce pellets containing Avicel PH 101 and theophyllin (90:10 w/w). Steckel and Mindermann-Nogly, 2004 [46] used water and dilute acetic acid in different powder to liquid ratios in order to increase the mass fraction of chitosan within the pellets and concluded that mass fraction can be increased to 100% by using dilute acetic acid for granulation step in place of demineralized water. Binders are usually not incorporated, as the addition of binders [Micro Crystalline Cellulose (MCC)] provides more cohesiveness. However, researchers have attempted to incorporate various binders in the moistening liquid. Aqueous polymer dispersion/ suspension containing Eudragit NE 30D, HPMC, PVP and Gelatin

have been used in the moistening liquid [48]. PVP was reported to produce pellets of higher sphericity as compared to gelatin.

### Physical Properties of Starting Material

Extrusion-spheronization has been found to be affected by formulation variables such as type and content of MCC, type of fillers and particle size of constituents. Most widely used base excipient for pellet formulation is MCC [3,26]. Unique properties of MCC make it a very efficient spheronization aid for pellet formation. Quality of pellets depend not only on the composition but also on different grades of the same product [1,14].

Shettigar and Damle, 1996 [1] demonstrated the effect of Avicel type on the quality of pellets (size, shape and release rate). Sodium CMC present in Avicel RC-581 acts as a swelling polymer, which in the presence of dissolution fluid forms a gel around each pellet and slows the release rate, whereas the pellets containing Avicel PH 101 remain unchanged in the dissolution medium resulting in greater release rate. Souto *et al.*, 2005 [33] described the effect of two superdisintegrants [Crosscarmellose Sodium and Sodium starch Glycolate (SSG)] on the quality of pellets. Neither disintegrant had significant effect on the pellet morphology and flow properties. Drug dissolution rate was slightly higher in pellets prepared with SSG, probably because of higher swelling capacity.

The MCC content had the most significant impact on spheronization efficiency and the amount required was dependent on the other components in the formulation. Increased MCC content lead to narrowing of size distribution and increased mean size and sphericity. Not only the type and composition of pellets affect the quality of pellets but also same product from different suppliers could have different characteristics. The formulation prepared with MCC and corn-starch as excipients result in best quality pellets with smooth surface, while the pellets with lactose and calcium hydrogen phosphate as excipients result in pellets of lesser quality with a much rougher surface [1].

### Spheronizer Speed

The speed of the spheronizer plate should be kept constant during the whole process. It has been found that speed affects the size [20], hardness, sphericity [32] and density of the pellets [49]. High speed has been reported to give higher sphericity, lower friability, smooth surface and higher crushing strength. The speed of the plate was also found to have a major influence on the overall dissolution rate, which is linked to pellet size.

### Spheronization Time and Load

Pellet size was found to be related to the time of spheronization [32]. An extended spheronization time resulted in pellets with narrow size distribution, higher sphericity, lower friability, smooth surface, reduced pore volume and higher tensile strength. Besides spheronization speed and time, the load of the spheronizer also has significant effect on quality of pellets. With an increase in spheronizer load, the size of the pellet decreases while their density increases

[31]. Pellets with wide size distribution are produced with an increase in speed at low spheronizer load while those with narrow size distribution are produced with increased spheronization time at higher load [50].

### Extrusion Screen

The quality of the extrudate/ pellets is greatly influenced by the characteristics of the orifice of the screen. An increase in orifice dimension resulted in increased mean pellet size [49]. For ibuprofen/MCC/Lactose mixture, Bianchini and Vecchio, 1989 [51] obtained a more homogenous granulometric distribution with 0.8 mm diameter orifice than with 1.0 mm. The increase in orifice depth decreased with the presence of water at the extrudate surface, increasing the extrusion force, and then had a negative effect on granulometric distribution and on shape [15]. The critical parameter is the L/R ratio, L being the orifice depth and R its radius [41]. When L/R decreases, extrudate density decreases [52], and flakes appear on the extrudate surface [53]. According to Harrison, Newton, and Rowe who worked on piston extruder, L/R ratio must be greater than 4 to avoid appearance of flakes [53].

In addition to these factors, there are some other factors such as type of extruder, extruder speed, extrusion temperature and drying methods, which affect the quality of pellets to a certain extent.

### HOT-MELT EXTRUSION

Wet mass extrusion is the most frequently used method for producing spherical pellets, which utilizes a granulating liquid such as water and requires drying phase that is time consuming. Many drugs exhibit stability problems due to the presence of water during processing and residual water during storage. In addition to this, pellets exhibit a rapid drug release and require a film coating to provide the controlled release properties. 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. Hot melt-extrusion is widely used in the plastic industry, and is also becoming popular in the pharmaceutical industry for the production of pellets; immediate and sustained release tablets and transdermal drug delivery systems [54-56]. It is a fast, simple, continuous, solvent-free process requiring fewer processing steps. Pharmaceutical products manufactured using melt-extrusion techniques have been approved in the USA, Europe and Asia [57]. 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. The single screw extruder is the most important type of extruder used due to its advantages of relatively low cost, ruggedness and reliability [58]. The design of the extruder die is influenced by several variables such as composition of the extrudate as well as the operating parameters of the extruder [59]. Melt spheronization can be carried out in a single piece of equipment, such as a jacketed, high shear mixer where certain components of the formulation are melted to generate spherical particles. The process is similar to wet granulation, except that the binder is in the molten state and hence does not require water or other solvents to liquefy it.

In pharmaceuticals, melt extrusion technique is used to disperse an active ingredient in a carrier material which must exhibit thermal stability during processing. Most raw materials used in this technique have also been employed in conventional techniques.

The material in which the drug is dispersed is called the thermal carrier. During extrusion, the carrier is usually transformed into a molten state. The carrier substance is usually a polymer or low melting point wax. Heat generated due to friction by the screw is sufficient to melt wax. The physical and chemical properties of the carriers have significant effect on the drug release characteristics. The mechanism of drug release is primarily diffusion controlled from the dosage form containing water-insoluble polymers and waxes such as ethyl cellulose [60] or carnauba wax [61] and both diffusion as well as erosion from water-soluble polymers such as hydroxypropyl cellulose [62,63]. Low porosity of the melt extruded dosage forms can result in incomplete drug release [64].

The incorporation of plasticizers into pharmaceutical polymer facilitates thermal processing, modifies drug release properties and improves surface appearance of dosage forms. Upon addition of plasticizers, thermal processing time is reduced which diminishes the degradation of heat sensitive components [55]. Plasticizers improve the flexibility of polymers by reducing the tensile strength and glass transition temperature of the material. Sometimes drugs and other excipients are employed as plasticizers. Wu and McGinity, 1999 [65] reported that non-traditional plasticizers including methyl paraben and drugs such as ibuprofen were able to lower the glass transition temperature of polymeric films prepared from aqueous latex dispersion of Eudragit RS 30 D.

Functional excipients used in hot melt extrusion include release modifying agents which are added to improve the bulk and processing agents which can impart specific properties to the dosage form produced by hot melt extrusion in a manner similar to those in traditional dosage forms.

### **FREEZE PELLETIZATION**

Freeze pelletization technique is a simple and novel technique for producing spherical matrix pellets containing active ingredients [6]. 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 [66]. Since the pellets are solid at room temperature, they do not require drying.

Two types of equipments are used and the selection depends upon the density of the molten solid carrier. Molten solid carriers are introduced as droplets into the column of liquid in which the molten solid is immiscible. Carriers may be hydrophilic or hydrophobic in nature and are melted at a temperature 5-10°C higher than the melting point of the carrier solids. The active constituent and excipients are mixed with the molten carrier to form solution or dispersion. In case of freeze pelletizer I, solution or dispersion is introduced as droplets using needles or nozzles into the inlet column of liquid and dropped from a certain height, so that droplets remain intact as they fall into the liquid column. Size of needle gauge can range from 16-31 depending on the size of the pellets desired.

The column of both the apparatus is divided into two parts, initial portion from which the molten solid carrier is introduced and is maintained between 25-100°C, and the cooling portion in which droplets solidification occurs and is maintained between 0 to -40°C using cooling mixtures of acetone and dry ice.

The molten solid droplets move in upward or downward direction which depends on the density of droplets with respect to the liquid in the column. In case of freeze pelletizer I, the molten solid carrier are introduced from the upper portion of the column because density of the solid carriers is more than the density of the liquid used in the column and the carriers solidify in the bottom portion, while in case of freeze pelletizer II, the molten solid carrier is introduced from the bottom of the column because density of the solid carrier is low as compared to the liquid used in the column and the carriers solidify at the top [66]. Suitable carriers for freeze pelletization are those, which are solid at room temperature and have melting point below 100°C in order to minimize degradation of the active constituent.

For freeze pelletizer I, hydrophilic carriers such as polyvinyl alcohol, polyethylene glycol and low melting point sugars (dextrose, maltose) are used. Suitable liquids for column are low-density oil such as mineral oil, vegetable oil and silicone oil. Silicone oil having a wide range of viscosity is most suitable as the liquid in the column.

For freeze pelletizer II, hydrophobic carriers of low density such as glyceryl palmitostearate, glyceryl behenate and glyceryl monostearate are used as solid carriers. Suitable liquids for column are high-density hydrophilic liquids such as liquid polyethylene glycol, ethyl alcohol, glycerin and water. For sustained release pellets containing mixture of hydrophilic and hydrophobic solids, liquids that are immiscible with both hydrophilic and hydrophobic molten solids are used as cooling liquid in the column [66, 67].

### **CRYOPELLETIZATION**

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. 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. In this technique, droplets of liquid formulation such as aqueous- organic solutions, suspensions or emulsions are converted into solid spherical pellets by using liquid nitrogen as the solidifying medium. These pellets are then freeze dried or lyophilized to remove water or organic solvents [68-70]. Solid content and temperature of the liquid formulation determine the amount of liquid nitrogen used in the whole process.

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 provides the required residence time to freeze the pellets. The frozen pellets are transported into storage container at  $-60^{\circ}\text{C}$  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. Size and shape of the pellets is influenced by diameter of the perforated plate, as smaller the diameter of the perforation, smaller is the size of the pellets produced. The distance between the perforated plate and the reservoir of liquid nitrogen should be such that it allows the drops to become spherical before contacting liquid nitrogen, because shape of the pellets largely depends on this distance but it should not be so much that it leads to deformation of the pellets. When it is desirable to have pellets with diameter less than 2 mm, then liquid nitrogen should be stirred continuously to prevent agglomeration. By the addition of surfactant to the formulation, surface tension of the liquid can be reduced in order to obtain pellets of smaller size. In addition to that pellets produced by freeze-drying are highly porous.

#### FACTORS AFFECTING THE PELLET CHARACTERISTICS IN DROPLET FREEZING TECHNIQUES

A mathematical model was derived by Cheboyina *et al* in 2006 [71] which was based on the various forces acting on the droplets at the time of droplet formation to predict the size of the pellets formed in the freeze pelletization process. In this study a molten solid carrier (without any actives/excipients) was slowly injected in such a way that individual droplets were formed at the tip of the needle. An equation for predicting the size of the wax pellets formed in apparatus II was given as

$$D_p = [12 r_N \gamma_{LL} \rho_{PL} \phi(r_N/a) / \Delta \rho g \rho_p]^{1/3}$$

where  $D_p$  is the diameter of the pellet at room temperature,  $r_N$  is the inner or outer radius of the circular needle tip depending on the wetting characteristics between the molten carrier and the material of construction of the needle tip,  $\gamma_{LL}$  and  $\Delta \rho$  are interfacial tension and density difference between the column liquid and the molten solid carrier at the initial column temperature, respectively,  $\rho_{PL}$  and  $\rho_p$  are the densities of molten solid carrier at the initial column and room temperatures, respectively,  $\phi(r_N/a)$  is the Harkins and Brown's droplet correction factor,  $a$  is the capillary constant of the molten

solid carrier and is defined as  $(2\gamma_{LL}/\Delta \rho g)^{1/2}$  and  $g$  is the acceleration due to gravity.

Following conclusions were also drawn with respect to the parameters affecting pellet size; the viscosity of neither the column liquids nor the molten waxes affected the pellet size in the range of viscosities studied, the shape and wetting characteristics of the needle tips were found to have a significant effect on the pellet size in addition to the gauge size of the needle, and the pellet size slightly decreased as the temperature maintained in the initial column increased. However, the viscosity of the aqueous glycerol solutions significantly affected the shape of the wax pellets formed in apparatus II. Based on the conclusions further studies were conducted to determine the most suitable viscosity to produce spherically shaped pellets [6, 66, 67].

### EVALUATION OF PELLETS

#### Size Distribution

The sizing of pellets is necessary because it has significant influence on the release kinetics [38]. 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. In most of the cases particle size determination is carried out by simple sieve analysis using sieve shaker [9,6,14,15,17,32]. Wiwattaapatapee, 2004 [72] reported the use of vernier calipers to determine the size of pellets.

#### Pellets Shape

Sphericity of the pellets is the most important characteristics and various methods have been used to determine it. The shape factor estimates the amount by which the projected image of particles deviate from a circle and it is calculated by means of the projected area of the pellets and its circumference [17,32]. For acceptable quality of pellets the roundness index/shape factor should be between 1 and 1.2 [70]. For perfectly circular projected image, the shape factor should be 1 while a value of 0.6 describes a particle of good sphericity [9,48]. Visual inspection of pellets by microscope and stereomicroscope is another method to determine shape of pellets [33,35,43,73,74].

One plane critical stability, which an angle at which a plane has to be tilted before a particle begins to roll, is one of the important methods used for determining shape [15,75,76]. The angle of repose is an indirect indication of the circularity of pellets [45,77] and is calculated by the ratio of double the pile height and pile radius by fixed funnel method measured after a certain amount of pellets are allowed to fall from a given height through a specific orifice.

#### Surface Morphology

Scanning electron microscopy is used to examine the surface morphology and cross section of pellets [4,12,33,46,78,79]. Sood *et al.*, 2004 [4] reported the use of optical microscopy to examine the microstructure of pellet surface. Eurrkainea and Lindqvist, 1991 [80] took SEM pictures to observe the influence of different fillers and concluded that MCC and corn- starch gives best quality pellets with smooth surface. Prieto *et al.*, 2005 [81] took SEM pic-

tures of pellets to show the influence of Starch-Dextrin mixtures, a base excipient for extrusion spherization technique while Wiwaattarataptee and Pengno, 2003 [72] took SEM pictures to detect antagonistic bacteria both on the surface and inside of the pellets. Santosh *et al.*, 2004 [9] analyzed surface roughness of pellets by applying a non-contracting laser profilometer.

### Specific Surface Area

Surface area of pellets is directly related with size and shape of the pellets. Knowledge of the surface area is desirable especially if film coating is considered. Knowledge about the surface area is important even in case of uncoated pellets, since drug release is influenced by the surface area (Husson *et al.*, 1992). Specific surface area of pellets is determined by gas adsorption technique (Santosh *et al.*, 2004).

### Friability

The mechanical properties of pellets are important for processing. Pellets flake off during handling and coating process resulting in formation of dust. In the case of subsequent coating it is desirable to have pellets with low friability. Friability of pellets are determined by using Erkewa type tablet friabilator [6,9,72,82,83] or turbula mixer [84] 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 [12,46].

### Tensile Strength

The tensile strength of the pellets are 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 [9,85].

### Density

Density of pellets (bulk and tapped) can be affected by change in the formulation or process which may affect other process or factors such as filling and packaging characteristic during capsule manufacture and tablet compression, and is determined simply by USP density apparatus [1, 13, 17, 49, 75].

### Porosity

The porosity of the pellets influences the 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 [9,12, 46, 33, 35]. The porosity of the pellets can also be determined quantitatively by using optical microscopy and SEM together with image analysis [86].

### Disintegration Time

Disintegration of pellets is one of the main characteristics for immediate release pellets. Huyghebaert *et al.*, 2005 [37] reported disintegration test using the reciprocating cylinder method (USP Apparatus 3). While Thommes and Klein-

budde, 2006 [35] performed it in a tablet disintegration tester specially designed by inserting special transparent tubes of certain diameter and length with sieve of 710  $\mu\text{m}$  mesh size at the top and bottom of the tube.

### In Vitro Dissolution Studies

*In vitro* dissolution has been recognized for the past four decades as an important element both in drug development and quality assessment, especially in controlled released formulation [87]. Release of drug from solid dosage form often constitute a determining step in the *in vivo/in vitro* absorption process and used in conjunction with *in vivo/in vitro* correlation to establish quality control parameter. Release of the drug from pellet mainly depends on the composition, hardness and size of pellets and it is determined by using USP Apparatus I [4, 43, 67, 73, 87]) or by USP Apparatus II [12, 33-35, 88, 89]. 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 [67]. The influence of pellet composition by incorporating citric acid in the formulation on retarding the release of highly water soluble drug from enteric coated pellets in 0.1 N HCl was investigated by Bruce *et al.*, 2003 [12].

### SUMMARY

This review focused on extrusion spherization technique as well as some novel techniques to produce spherical pellets. Each technique has its own advantages and disadvantages. Extrusion spherization is frequently used method for producing spherical pellets with high drug loading but major disadvantage is that it utilizes granulating liquid such as water and requires drying phase that is time consuming process. Many drugs exhibit stability problem due to presence of water. Cryopelletization is a novel pelletization technique, which involves freeze-drying or lyophilization to remove water or organic solvents. A major limitation of this process is that it requires liquid nitrogen that has a temperature of  $-196^{\circ}\text{C}$  and the impact of liquid or semisolid droplets on the surface of the liquid nitrogen can create surface irregularities in the pellets. In addition to that pellets produced by freeze drying are highly porous.

A novel hot-melt extrusion and spherization process produces spherical pellets without the use of water or other solvents. This method eliminates instability problem during processing due to water. 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. The pellets produced by this technique are spherical in shape with narrow size distribution and solid at room temperature.

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