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# 6. Pellets

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## 6.1 Introduction:

Pellets are spherical or nearly spherical, free- flowing granules with a narrow size distribution, typically varying between 500 and 1500 µm for pharmaceutical applications. They are generally produced via a pelletization process whereby a powder blend consisting of an API and excipient particles is agglomerated into spherical granules. After being processed, pellets are usually filled into hard gelatin capsules or compressed into tablets. Furthermore, they can be formulated as immediate release dosage form or in sustain drug release over a long duration time or can be coated also to deliver a drug to a specific site of action in the gastrointestinal tract. Pellets provide the development scientist with a high degree of flexibility during the design and development of oral dosage forms. They can be divided into desired dose strengths without formulation or process changes, and also be blended to deliver incompatible bioactive agents. simultaneously or particles with different release profiles at the same site or at different sites within gastrointestinal tract. Pellets provide development of formulation with high degree of flexibility due to free- flowing characteristic. So, they are packed easily without any difficulties. The spherical shape and a low surface area to volume ratio of pellets made uniform film coating. Pellets eliminate the dose dumping effect, which gives smoother plasma concentration profile and gradual. absorption of drug than tablet, which further decrease the adverse effect of drugs.

## Advantages:

- Uniformity of dose Layering techniques and extrusion- spheronization offers great accuracy with drug delivery the pellets.
- Spheres have excellent flow properties, and this becomes very useful in automated processes or in processes where exact dosing is required, e.g, tableting, capsule filling, and packaging.
- Prevention of dust formation: fine powders can cause dust explosions and the respiration of fines can cause health problems and these can be reduced by using pellets.
- 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.
- 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:

- Pellets can disperse freely throughout the GIT after administration and consequently the drug absorption is maximized,
- 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,

- Reduce inter- and intra-patient variability.
- Modified-release multi-particulate delivery systems are less susceptible to dose dumping than single-unit dosage forms.

## Disadvantages:

- Pellets filling involve capsule filling which can increase the costs.
- Tableting of pellets destroy film coating on the pellets.
- The size of the pellets may vary formulation to formulation but usually is in range of 0.05 mm and 2 mm.
- It is difficult to compress pellets into tablets as they are too rigid. Therefore, they are often delivered encapsulated in hard gelatin capsule shells,
- Pelletization demands highly sophisticated and specialized equipment, thereby increasing the cost of manufacturing.

## Desirable Properties of Pellets:

### A. For Uncoated pellets

- Uniform spherical size
- Narrow particle size distribution.
- Good flow property
- Low friability
- Even surface
- Low dust formation
- Reproducible packing

### B. For Coated pellet

- Maintain all above properties.
- Desirable drug release characteristics

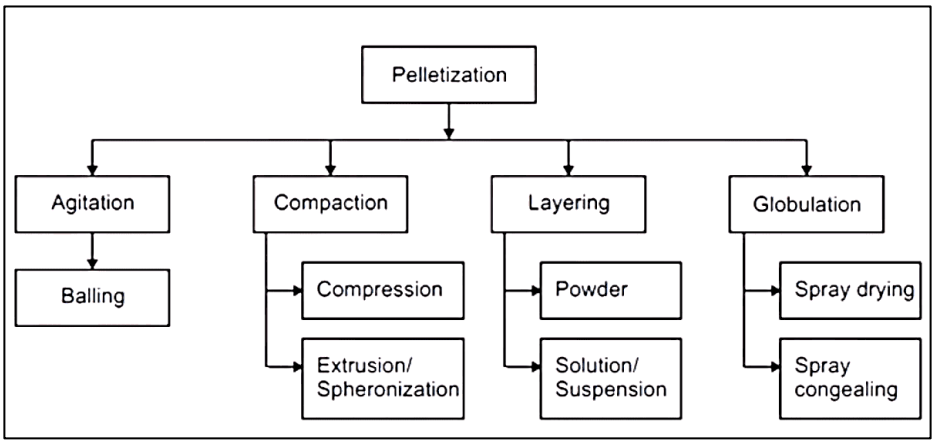


**Figure 6.1: Pelletization Process**

## 6.2 Different Techniques of Pelletization:

### 6.2.1 Pelletization Techniques:

#### A. Drug Layering:

It includes deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of the same material. In solution/suspension layering, drug particles are dissolved or suspended in the binding liquid. In powder drug layering, a binder solution is first sprayed onto previously prepared inert seeds, followed by the addition of powder.

#### B. 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 them. 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.

#### C. Solution and Suspension Layering:

Layering a solution/suspension of a drug on a 'starter seed material (usually, a coarse crystal or nonpareil) nonpare 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 release. The Wurster ster coating process had evolved through elaborate design modifications and refinement into ideal equipment for the manufacture of pellets by solution. and suspension layering.

#### D. Extrusion-Spheronization:

Extrusion / spheronization is a multistage process for obtaining pellets with uniform size from wet granulates (extrudates).

- 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.

**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. 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.

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 spheronization.

### E. Cryopelletization:

Pellets here can be produced by allowing droplets of liquid formulation such as solution, suspension or emulsion to come in contact with liquid nitrogen at -160°C in which liquid nitrogen used as solidifying medium.

The procedure permits freezing of the material being processed due to rapid heat transfer that occurs between the droplets and the liquid nitrogen for manufacturing a given quantity depends on the solid content and temperature of solution or suspension being processed. The pellets are dried in conventional freeze dryers to remove water or organic solvents.

### F. 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.

### G. 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.

## H. Hot-Melt Extrusion Technology (HME):

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.

## I. Freeze Pelletization:

In this technique, a molten-solid carrier/matrix is introduced as droplets into an inert column of liquid in which the molten solid is immiscible. The molten solid moves in the liquid column as droplets. and solidifies into spherical pellets. The molten solid droplets can move upward or downward in the liquid column depending on the droplet's density with respect to the liquid in the column. If the density of the molten-solid carrier/matrix is less than that of the liquid in the column, then droplets are introduced from top of the column and pellets solidify in the bottom portion of the column.

## J. Spray-drying and Spray-congealing:

**a. 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.

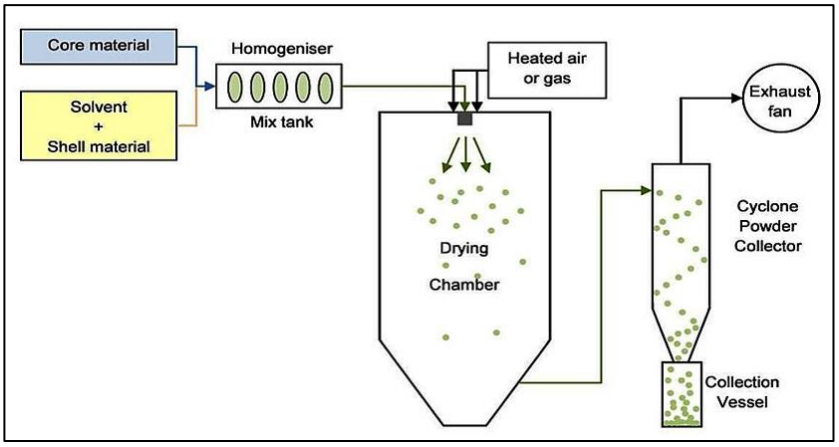


**Figure 6.2: Spray-Drying**

**b. Spray-Congealing (Spray-Chilling):** 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 obtained,

## 6.3 Factors Affecting Pelletization Technique:

**A. Moisture Content:** Moisture in the wet mass brings cohesiveness to powder so that the wet mass can be extracted and spheronizer to give spherical shape. High moisture contents lead to agglomeration of pellets during the process of spheronization.

**B. Rheological Characteristics:** The optimum rheological condition leads to good flow ability in order to extrudate the wet mass. The rheological variations make improper and non- uniform extrudate.

**C. Solubility of excipients and drug in granulating fluid:** Soluble drug get dissolve in a granulating liquid. Thus, increasing the volume of liquid phase leads to over wetting of pellets. But increase in wetting liquid increases plasticity but includes sticky mass.

**D. Composition of Granulating Fluid:** Besides water, alcohol, water/alcohol mixture, ethyl ether, dilute acetic acid, isopropyl alcoholis used as a granulating liquid. Aqueous polymer dispersion containing HPMC, PVP, etc can also be used as granulating fluid.

**E. Physical Properties of Starting Material:** Quality of pellets depend not only composition but also on different grades of the same product. The swelling property of material used in pelletization technique decides the release rate of drug in pellets.

**F. Speed of Spheronizer:** It affects the size, hardness, sphericity and density of pellets. The high speed gives high sphericity, lower friability, smooth surface and higher crushing strength.

**G. Extrusion Screen:** The quality of pellets is greatly influenced by the characteristics of orifice of the screen. And increase in orifice dimension resulted in increased mean pellet size. The increase in orifice depth. decreased with the presence of water at the extrudate surface.

## 6.4 Evaluation Parameters:

### A. Particle Size Distribution:

- Particle size should be as narrow as possible. This will ensure minimum variation in coating, thickness, facilitate blending process if blending of different types is requires.
- Sieve analysis using sieve shaker is most widely used method for measuring particle size distribution.

- 100 gm of pellets are weighed using electronic weighing balance. Pellets are then transferred to set of sieves having different mesh size for particle size analysis, Calculate the % retained on each sieve.

**B. 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 particle-size distribution by measuring the mean diameter, gas adsorption, and air permeability.
- Mean diameter- This calculation does not account for the contributions of the surface area arising from other morphologic characteristics such as porosity, surface roughness and shape of pellets.
- Air permeability method- It is widely used pharmaceutically for specific surface measurement, for controlling batch to batch variations. The principle for resistance to flow of a fluid such as air through a plug of compacted material is the surface area of material.
- Gas adsorption method- In this method the volume of nitrogen that is absorbed by the substrate contained in an evacuated glass blub is measured at different pressures.

**C. Porosity:**

- The porosity of pellets influences the rate of release of drugs from pellets by affecting the capillary action of the dissolved drug.
- The porosity of pellets can be measured qualitatively by scanning electron microscopy (SEM) and quantitatively by mercury porosimetry; optical microscopy and scanning electron microscopy together with image.

**D. Density:**

- The density of pellets can be affected by changes in the formulation or process, which may affect other processes or factors, such as capsule filling, coating and mixing.
- The bulk density of pellets can be measured by an automated tapper. True density indicates the extent of densification or compactness of substances.
- Bulk Density Weight of powder/ Bulk volume
- Tapped density Weight of powder/ Tapped volume.

**E. Hardness and Friability:**

- Hardness and friability determination of pellets is necessary because the pellets have to withstand during handling, shipping, storage and other processes such as coating.
- The instrument such as Kaul pellet hardness tester provides relative hardness values.
- 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.

**F. Tensile Strength:** The tensile strength of 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 pellets.

## 6.5 Formulation Aids for Pellets:

**A. Fillers:** add bulk to the product are water soluble/insoluble substances selection depends on physical property of drug, desired dose and method of preparation. Examples MCC, starch, sucrose, lactose.
**B. Binders:** used to bind, provide integrity to product selection depends on solubility and physical property of drug. Examples HPMC, Gelatin, Methyl cellulose, starch, sucrose, lactose.
**C. Lubricant:** used to reduce friction between particles and surface of equipment maintain consistency of pellets Examples Glycerin, PEG, magnesium stearate, calcium stearate.
**D. Seperating Agent**: to prevent attraction between particles of pellets prevent charge development in particles Examples Talc, Silicon dioxide, kaolin.
**E. Disintegrating Agent**: to promote disintegration in g.i.t. required in small quantity Examples Alginate.
**F. Surfactant**: improve wettability lowers the interfacial tension between solvent and drug particles. Examples SLS, polysorbate.
**G. pH Adjuster maintain pH for absorption in g.i.t** Examples citrate, phosphate.
**H. Spheronization Enhancer**: impart plasticity to pellets provide strength Maintain integrity Examples MCC (Micro crystalline cellulose), sodium carboxy methyl cellulose.
**I. Glidant**: reduce friction between die wall and material matrix during compression or ejection Examples Talc, starch, Magnesium stearate.
**J. Miscellaneous agents** coloring, flavoring, sweetning, preservatives, release modifier (Ethyl cellulose, shellac, carnuba Wax).

## 6.6 Mechanism of Drug Release from Multi-Particulates:

- **Diffusion**: On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.
- **Erosion**: Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle
- **Osmosis**: In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating. Advantages of Pellets

## 6.7 Resons for Pelletization:

- Prevention of segregation of co-agglomerated
- Improvement of the process safety, as fine powders can cause dust explosions and the respiration of fines can cause health problems.
- The defined shape and weight improve the appearance of the product.

- 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.
- pellets can disperse freely throughout an area of the gastrointestinal tract after administration and consequently the drug absorbtion is maximized as a large gastrointestinal surface can be involved in this process.
- peak plasma level of the drug can be reduced by the use of spherical particles with different release rates.
- potential side effects are minimized without markedly lowering drug bioavailability.
- the wide distribution of spherical particles in the gastrointestinal tract limits localized build-up of the drug avoiding the irritand effect of some drugs on the gastric mucosa.

## 6.8 Equipments for Manufacture of Pellets:

- A pelleting system is made up of different machines designed to efficiently complete the task of pelletisation.
- An arrangement of a pelleting system showing all the equipments is represented in figure.
- The process of pelleting starts in the bin storing the mixture of mash, which flows into the pellet mill under gravity.
- The hot, extruded mash (now called pellets) from the pellet mill now flows into a cooler under gravity. Here it is cooled and dried by a flow of air for 3-6 minutes.
- This air is drawn through the mass of pellets and passed into a dust collecting device, such as a cyclone collector.
- The dust from the outlet of the collector is returned to the pellet mill to be compacted again into a pellet.
- The pellets from the cooler are passed through a pair of crumble rolls to be crushed to a smaller size so that a relatively fine product is obtained.
- If the full pellet size is to be obtained, the pellets from the cooler are flowed around the crumble rolls.
- The product from the crumble rolls flows into a bucket elevator to be raised to a higher point, where the shaker separates the product into various sizes by passing the material through a number of screens, each of a different opening size.
- This step allows the separation of the desired product from the larger or smaller particles and then delivering the finished product to the bin.
- The remnants are returned to the pellet mill for re-pelleting, or, in case of crumbles, they are returned to the cooler, and then through the crumble rolls for re-crumbling.
- The fines or smaller materials are routed back to the pellet premix bin and reprocessed through the pelleting system.

### 6.8.1 Supply Bins:

The supply bins located ahead of the pellet mill, should store a sufficient quantity of feed to provide a continuous operation of the pelleting unit and also a continuous operation of the mixer which provides mash to the pelleting unit. The supply bin constructed from stainless steel should have at least two bins, results in an efficient mixing as well as pelleting.

### 6.8.2 Pellet Mills:

The thoroughly mixed ingredients (now called mash or meal) flow into a flow rate regulator called a feeder under gravity.

It is equipped with speed controlling devices, provides a constant, controlled and uniform flow of feed to the mixing and pelleting operation, and variation in this flow leads to poor conditioning and a variable product.

The feeder delivers a constant and prescribed amount of the mash to a conditioning chamber in the pellet mill to be thoroughly mixed with steam (heat and water) and other desirable liquids, such as molasses.

### 6.8.3 Coolers:

The pellets from the pellet mill flow under gravity into a device for cooling and drying.

When the pellets leave the pellet mill, they are at very high temperatures (190°F) and also have high moisture content (17- 18%).

Proper storage and handling of the pellets demand their moisture content to be reduced to 10-12% and their temperature to be maintained at 15°F above atmospheric temperature.

This can be accomplished by passing an air stream through a bed of pellets, which evaporates the excess moisture and cools down the pellets (by evaporating the water from the pellets and also by contact with them).

The capacity of air to hold water increases two folds with every 20° rise in temperature.

Thus, warmer the air, the more moisture it should remove from the pellets.

### 6.8.4 Crumble Rolls:

A crumbling process should be used for producing small, pelleted feed particles.

In this process, small pellets are broken between two powered corrugated rolls, placed below the cooler. A crumbling roll has heavy steel frame and housing.

The corrugated rolls are 8-12 inches in diameter and 72 inches long.

Each corrugation is spaced at 6-12 inches.

This controls the sizing or degree of crumbling of the product.

A by-pass valve directs the pellets around the outside of the rolls when the product is not required to be crumbled.

### 6.8.5 Shaker:

The product (either whole or crumblised) from the crumbling device is passed to a shaker (screening device) that extracts the undesirable undersized portions of the product from the correctly sized material. The undersized product is returned to the pellet mill for repelletisation and is termed recycle or fines. When a product is being crumblised, some pellets may not properly break to a specific size and remain oversized. These particles are removed by screening and returned to the original crumbler roll for reprocessing and are again screened. Around 25-30% of fine materials are returned through the crumbling. process for reworking. The screening devices used today are mainly oscillating, vibrating, or gyrating wire or metal screens with appropriate opening sizes.

An oscillating pellet screen has a steel or wood frame from which the screens are supported or suspended. The screen frames are oscillated by an eccentrically weighed drive unit powered by an electric motor.

### 6.8.6 Pellet Elevating Systems:

The correct sized product in its finished form is obtained from the shaker and is ready for packaging or shipment.

In many mills, the pellet shaker is located on the upper floors of the unit so that the screened product, the oversize crumbles, and the fines flow under gravity to their correct destination.

This requires that the unscreened pellets are conveyed vertically (elevated) from the cooler to the shaker. In other mills, the shaker is located below the cooler and the sized finished product is conveyed to the packaging or bulk shipping point.

In both the cases, an elevating system (vertical conveyor) is required. This can be done either mechanically by using a bucket elevator or pneumatically by using an air conveying system.

Air systems are used for conveying the hot pellets because they are not as subject to the build-up of hot, wet material as is a bucket elevator. Bucket elevators are used as they are less expensive, and their installation, maintenance and working are easy.

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