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# Review on pelletization techniques

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## ABSTRACT

Pellets are multiparticulate dosage form consisting of a multiplicity of small discrete units each exhibit some desired characteristics. Pellets are small free flowing, Spherical or semi spherical units with size and diameter ranging from 0.5-1.5mm. The present review deals with the outline of the pellets, pellets growth mechanism and various types of pelletization techniques like extrusion/spheronization, layering, Cryopelletization, freeze pelletization, spray congealing, spray drying. Among various techniques now-a-days fluid bed processor is most widely used in the pharmaceutical industry due to its uniform coating and highly efficiency. Fluid bed processor involves different spray process i.e top spray, bottom spray and tangential spray. Fluid bed processor has wide range of applications such as drying, particle coating and pelletizing.

**Keywords:** Mutliparticulates, Pellets, Pelletization, Techniques, fluid bed processor, top spray, bottom spray, tangential spray

## INTRODUCTION

Pelletization can be defined as an agglomeration process that converts fine powder or particles of the bulk drug and excipients into small, free-flowing, more or less spherical units, called pellets.

Pellets are agglomerates of fine powder or granules of bulk drug and excipients. They consist of small, free flowing, spherical or semi -spherical solid units typically form about 0.5-2mm.

Pellets can be defined as a small free flowing spherical particulates manufactured by the agglomeration of fine powder or granules of the drug substance and excipients using appropriate processing equipment.

In recent years pelletization dosage form is widely used since these dosage form have gained considerable popularity because of their distinct advantages such as sustained, delayed, controlled delivery of drug; free flowing properties due to its spherical shape; maximum drug absorption and reduce peak plasma fluctuation as they get uniformly distributed in the gastrointestinal tract as subunits; less susceptible to dose dumping.

Pharmaceutical pellets are multiparticulate solid dosage forms that can be filled in the hard gelatin

capsules or compressed into tablets. Multiple-unit dosage forms (e.g., pellets, granules or microspheres, microcapsules) are becoming more important than single-unit dosage forms (e.g., tablet, capsule) forms as multiple-unit dosage form provide several advantages compared to single unit dosage forms.

## ADVANTAGES OF PELLETS

- Pellets have better flow due to uniform size and spherical shape
- Uniform coating for each pellet and also for the batch to batch due to the smooth surface and uniform size of the pellets
- When pellets are administrated orally they pass evenly throughout the gastrointestinal tract and maximize the drug absorption
- Pellets can be designed and developed into different dosage forms like tablets, capsules, suspensions
- These are used as taste masking of the bitter drugs
- Provides less risk of dose dumping
- Improves safety and efficacy of a drug
- Minimize the local irritation
- These can be divided into desired dosage strength without formulation or process changes

## DISADVANTAGES OF PELLETS

- Difficulty in filling into the capsules, when different subunits are involved
- The manufacturing of pellets is expensive and required specialized equipments

## ELEMENTARY GROWTH MECHANISM OF PELLETS

The most classified pelletization process involves three consecutive stages

- Nucleation
- Coalescence
- Layering
- Abrasion transfer

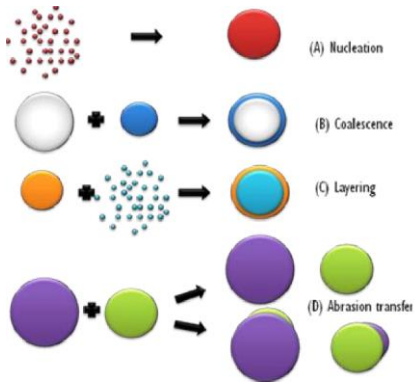



**Figure: 1 Pellets growth mechanism**

### Nucleation

It occurs whenever a powder is wetted with liquid and it is the first stage of pellets growth. The primary particles are drawn together to form three phase air-water-liquid nuclei and together by a liquid bridge which are pendular in nature. The Size of primary particles, the viscosity, moisture content, wettability of subtract and the processing conditions influence the size, rate and extent of nuclear formation.

### Coalescence

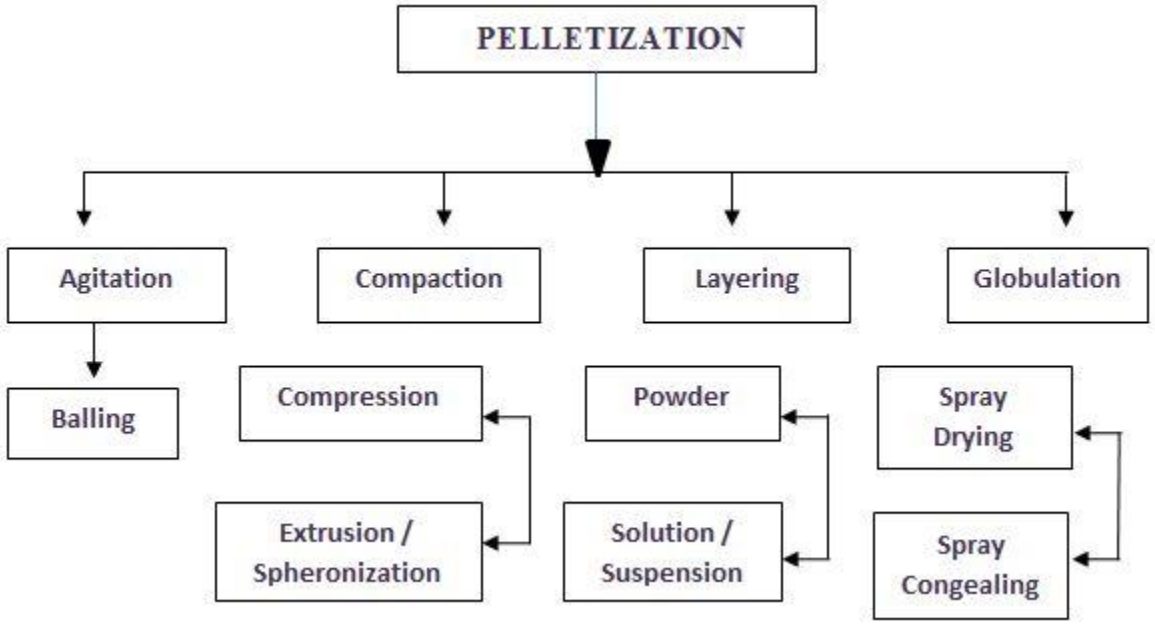
Nucleation is followed by coalescence, formation of large size particles by random collision of nuclei with each other. Although the number of nuclei is reduced but the total mass of the system remains unchanged. During collision, fines and fragments of particle are produced due to size reduction by breakage, attrition and shatter.

### Layering

This stage involves successive addition of fines and fragments on the surface of nuclei. Due to this number of nuclei remains constant, but total mass of nuclei in the system increases due to increasing particle size at this stage ball growth is reached.

## Abrasion transfer

This is the final step of pellet formation, which involves transfer of materials form one granule formed to another without any preference in either direction. Particles will experience a change in size as long as the conditions that leads to the transfer of material but no change in the total number or mass of the particles.




**Different Pelletization Techniques**

## Agitation

## Balling

Finely divided particles are converted upon the addition of appropriate quantities of liquid, to spherical particles by a continuous rolling or tumbling motion. Pans, discs, drums, or mixtures may be used to produce pellets by balling.

## Compaction

## Compression

Mixtures or blends of active ingredients and excipients are compacted under pressure to generate pellets of defined shape and size.

## Extrusion-spheronization

It is a multi-step process involves extrusion of the mass and transfer of the mass to spheronizer to produce spherical particles.

## Extrusion

Extrusion may be a standard process technology that has been developed over the last century. The unit operation of pelletization takes place in three steps-

- Feed preparation
- Pellet production
- Pellet curing

Feed preparation constitutes mixing of drug-excipient with desired additives such as solutions of binding agents. The second and most important step, agglomeration, is taken place in a pelletizer, where desired size pellets are formed. The final step is where wet pellets are cured either by thermal drying or by simple stockpiling. An extrusion spheronization process takes place in the following steps- Formation of plastic mass; Formation of extrudates; calling it quits of extrudates; Spheronization.

## Spheronization

Spheronization means formation of spherical particles from the small rods produced by extrusion. The pelletization operation begins with the dispensing of powder feed material beside binder resolution to the granulator to make a plasticized wet

mass. The plasticized mass thus fashioned is then allowed to fall into the screening chamber of extruder. Here, extrusion or pressure blades give adequate compression to the plasticized wet mass against the exteriors of screen.

The extruded material is firstly discharged into the discharge unit through the scrapper blade and then finally it is introduced into the spheronizer. Pelletizer disk makes to rotate extrudates at high speed to the vessel wall in the direction of rotation. This is similar to the formation of helix like structure as the rolling movement of the extrudates takes place in two dimensions. In short time duration the extrudate surface becomes smooth due to the intense rolling action. Finally pellets are discharged at the discharge unit.

## Layering

In this technique drug is layered on to starter materials in powder, solution or suspension form and leads to heterogeneous pellets, which consist of inner core region and outer shell region of different composition. Layering is of three type's namely direct pelletization, powder layering and solution or suspension layering.

## Direct pelletizing

A process that leads to formation of homogeneous pellets which have uniform spherical structure and no core can be detected. It is mainly performed in high shear mixtures and fluidized bed equipment.

## Powder layering

Powder layering involves the deposition of successive layers of dry powders of drug and excipients on preformed nuclei or cores with the assistance of binding liquids. Equipment used is tangential spray/centrifugal/rotary fluidized bed granulator.

## Solution/suspension layering

This process involves deposition of successive layers of solution/suspension of drug substance and binder on the existing nuclei, which may be inert seed, crystal or granule.

Layering is done by using **fluid bed processor**. It is a unique process for uniform, continuous coating of granulation, drug layering and drying of particulate material. The most commonly known fluid bed process for coating in the pharmaceutical industry is bottom spray process (Wurster). The principle involved in the fluid bed processor is a bed of solid particulates through which hot air is passed at high pressure through air distribution plate then the particles are lifted from the bottom and suspended in the air stream (fluidized state). With the help of spray nozzle coating solution is sprayed to produce granules and then dried with hot air.

Depending on the location of the spray nozzle position three types of sprays in fluid bed processor they are

- Top spray
- Bottom spray
- Tangential spray

## Top spray

- Top spraying is most accepted method for the wet granulation.
- The main parts of the top spray system are product container/expansion chamber, an exhaust and air handling system.
- Spray nozzle is located above expansion chamber.
- The coating liquid is sprayed down onto a bed of fluidized particles.

Desired granules were achieved by adjusting process variables. Some of the process variables are inlet air temperature, atomization air pressure, fluidization air volume. As increasing the inlet air temperature there is a decreasing in average granule size. Increasing atomization pressure decreases size of granules. Faster the addition of binding solution causes less friable granules and larger than the average granule size. The critical parameters in top spray are liquid addition and atomization air pressure.

This process is mostly used when a taste masking coating is applied. Additionally it is appropriate for the applying of hot melt coating.

## Bottom spray

The bottom spray is also known as **wurster process** the most popular method in the pharmaceutical industry for drug layering. This process was developed by Dr.Dale Wuster in late 1950s.

The spray nozzle is located at the bottom of the fluidization chamber. The hot air passed through fluidized bed, particulate materials are lifted in air

stream, solution sprayed on fluid bed for granulating and coating.

This process is used for the application of modified release coating and also suitable for layering of drug when drug dose is low to medium range.

### Tangential spray

- The nozzle is introduced at the side of the product container/ expansion chamber.
- During process, three mechanical forces cause particle movement, mixing, granulating and compounding.
- Centrifugal force is generated by the spinning of the disk.
- The gravitational force causes material to fall down onto the disk
- These forces provide good mixing and results in granules drying, coating with good content uniformity.
- This process is used for modified release film coating. And also for drug layering when drug dose is medium to high.

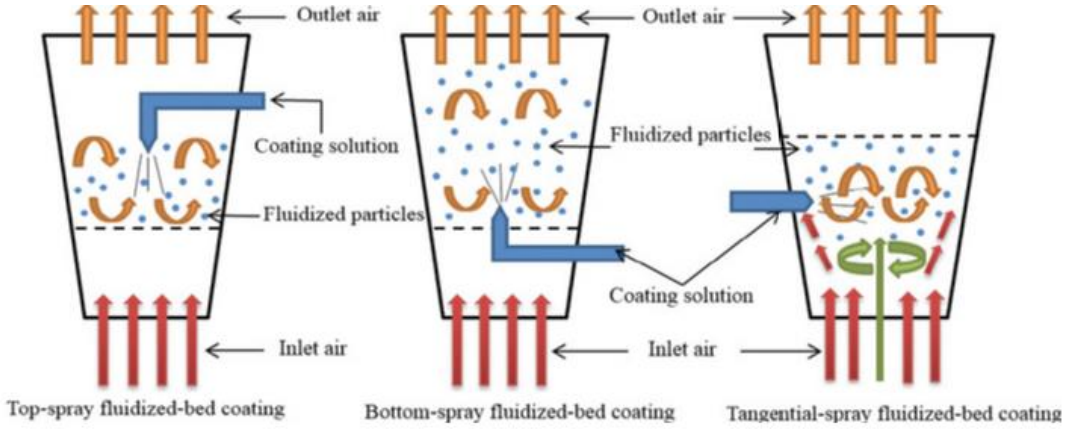



**Figure: 2 a. Top spray fluid bed coating**

- Bottom spray fluid bed coating
- Tangential spray fluid bed coating

## RECENT ADVANCES IN PELLETIZATION TECHNIQUES

### Cryopelletization

In this method the droplets of liquid formulations are converted into solid spherical particles or pellets by using liquid nitrogen as fixing medium. This technology used to produce drug loaded pellets in liquid nitrogen at -160$^{o}$c. The equipment consists of following parts they are; perforated plates, reservoir, conveyor belt with transport baffles, storage container. The perforated plates generate droplets that fall and freeze as they come into contact with liquid nitrogen then the frozen pellets are transported out from the nitrogen bath into the storage container at -60$^{0}$c.

### Hot melt extrusion

It's a method whereby a drug substance and excipients are converted into a liquified or semi liquified state and later shaped using appropriate equipment to provide solid spheres or pellets. The drug is blended with the excipients, polymers, and waxes and extruded at predetermined temperature. It consists of a material feed hopper, extruder inside a heated barrel and spheronizer.

### Freeze pelletization

In this technique, a molten-solid carrier in which the drug is uniformly dispersed is allowed to enter as tiny droplets into an inert column of liquid in which the molten solid carrier is totally immiscible. This droplet gets solidifies into spherical pellets. These pellets can move in either direction i.e. upward or downward depending upon the density of the molten solid carrier with respect to the liquid in the column. If the density of the molten-solid carrier is less than that of the liquid in the column then droplets are introduced from the bottom of the column, which then gets converted into solid pellets at the top portion of the column. Conversely, if the density of the molten-solid carrier is more than of the liquid in the column then the droplets are introduced from the top of the

column, and that gets solidify in the bottom portion of the column.

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