PELLETS: A GENERAL OVERVIEW

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Abstract:

Traditionally, the word "Pellet" has been used to describe a variety of systematically produced, geometrically defined agglomerates obtained from diverse starting materials utilizing different processing conditions. Pellets range in size, typically, between 0.5 – 1.5 mm, though other sizes could be prepared. Pellets are for pharmaceutical purposes and are produced primarily for the purpose of oral controlled-release dosage forms having gastro resistant or sustained-release properties or the capability of site-specific drug delivery. For such purposes, coated pellets are administered in the form of hard gelatin capsules or disintegrating tablets that quickly liberate their contents of pellets in the stomach. As drug-delivery systems become more sophisticated, the role of pellets in the design and development of dosage forms is increasing. Formulation of drugs in multiple-unit dosage forms, such as coated pellets filled in capsules or compressed into tablets, offers flexibility as to target-release properties. The safety and efficacy of the formulation is higher than that of other dosage forms.

Keywords: pellets, coating, pelletization process, controlled release pellets

Introduction

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 can also be blended to deliver incompatible bioactive agents simultaneously or particles with different release profiles at the same site or at different sites within the gastrointestinal tract.

Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free flowing, spherical or semi spherical units, referred to as pellets [1]. In addition, pellets have numerous therapeutic advantages over traditional single units, such as tablets and powder-filled capsules. Taken orally, pellets generally disperse freely in the gastrointes-tinal tract, and consequently maximize the drug absorption, minimize local irritation of the mucosa by certain irritant drugs because of the small quantity of drug available in a single pellet, and reduce inter- and intrapatient variability [2].

As the advantages of pellets over single units became clear, the pharmaceutical industry as a whole started to devote

resources to conduct research in pellet technology and, whenever possible, acquire advanced equipment suitable for the manufacture of pellets.

Pellets may be manufactured by using different methods according to the application and the choice of producer. The methods used for Pelletization are essentially the same as the granulation methods. The most widely used processes are extrusion and spheronization and solution or suspension layering, and powder layering. Other processes with limited application in the development of pharmaceutical palletized products include globulation, balling, and compression.

Advantages of pellets:

- They can be divided in to desired dosage strength without process or formulation changes.
- When pellets containing the active ingredient are in the form of suspension, capsules, or disintegrating tablets, they offer significant therapeutic advantages over single unit dosage forms [3-5].
- They can also be blended to deliver incompatible bioactive agents.
- They can also be used to provide different release profile at the same or different sites in the gastrointestinal tract.
- Pellets offer high degree of flexibility (figure 1) in the design and development of oral dosage form like suspension, sachet, tablet and capsule [6 -8].
- Pellets disperse freely in GI tract, maximize drug absorption, and minimize local irritation of the mucosa by certain irritant drugs.
- ***Improved flow characteristics:*** Spheres have excellent flow properties which can be used in automated processes or in processes where exact dosing is required, e.g. tabletting, moulding operations, capsule filling, and packaging.
- ***Coating:*** Coating of granules is often applied for stabilizing active ingredients in the granule or to control the release of these active ingredients. Typical applications in the pharmaceutical industry are the controlled release medicines. The easiest shape to coat is the sphere due to the absence of edges. It is also the most economical one to coat as no extra coating material is required to fill irregularities in the surface of the granules [9-11].
- ***Packing of beds and columns*** [12]***:*** In certain processes, porous beds or columns are used as chemical reactors. Spherical particles allow the reproduction of beds with always the same void volume, surface area and permeability. Calculations and predictions of the process characteristics also become easier when round particles are used as many equations are based on flows around symmetrical bodies.
- ***Density increase:*** Both the true and the bulk density of granules are increased by spheronising. This can

improve the process and the packaging.

- ***Marketing:*** For consumer products, spheronising is sometimes only applied for improved product appearance and marketing reasons.
- ***Hardness and friability:*** Hardness and friability depend on the internal cohesive forces and surface characteristics. Spheronization increases the hardness and reduces the friability of granules. This will reduce the amount of fines generated during handling or transportation.

Disadvantages of pellets [13]:

- Dosing by volume rather than number and splitting into single dose units as required.
- Involves capsule filling which can increase the costs or tabletting which destroy film coatings on the pellets.
- The size of pellets varies from formulation to formulation but usually lies between 1 to 2mm.

Desirable properties of pellets: [14, 15]

- **Uncoated pellets:**
  - Uniform spherical shape,
  - Uniform size,
  - Good flow properties,
  - Reproducible packing,
  - High strength,
  - Low friability, Low dust,
  - Smooth surface,
  - Ease of coating.
- **Once coated:**
  - Maintain all of the above properties,
  - Have desired drug release characteristics.

The photographical representations of different pellets are given in figure 2.

Pelletization techniques [16, 17, 18]:

The preparation of spherical agglomerates can be approached by several techniques which can be subdivided into the basic types of systems shown in figure 3.

Direct pelletizing [19]:

Means Manufacturing of pellets directly from powder.

- **Effective process:** Pellets are manufactured directly from powder with a binder or solvent, fast process. Low usage of auxiliary materials.
- **Product advantages:** Compact, round pellets - ideal for automatic dosing and even coating and Pellet diameter also obtained between 0.2 m m and 1.2 m m.
- **Comparison:** Pellets have a higher density than spray granulates and agglomerates.
- **Process principles:** Powder is mixed and moistened. A solvent or binder can also be added. The powder bed is set into a centrifugal motion. (Fluid Bed Pelletizing in the rotor). The impact and acceleration forces that occur in this process result in the formation of agglomerates, which become rounded out into uniform and dense pellets. The speed of rotation has a direct influence on the density and size of the pellets. The moist pellets are subsequently

dried in the fluid bed. If required, the systems can be made inert for applications with organic solvents. Another alternative for direct pelletizing is Spray Granulation.

- With suitable additives, pellets can be made into tablets or used to fill capsules. The round shape is ideal for uniform coating. Pellets are good for automatic dosing. The various steps of process principle are given in figure 4.

Powder layering [19]

Powder layering involves the deposition of successive layers of dry powder of drug or excipients or both on performed nuclei or cores with the help of a binding liquid. Because powder layering involves the simultaneous application of the liquid and dry powder, it generally requires specialized equipment. Pieces of equipments revolutionized powder layering processing as a pelletizing techniques are- tangential spray or centrifugal fluid bed granulators. In case of tangential spray the rotating disk and fluidization air provides proper mixing. With a double wall centrifugal granulator, the process is carried out in the open and closed position. With powder layering, the inner wall is closed so that simultaneous application of liquid and powder could proceed until the pellets have reached the desired size. The inner wall is then raised, and the spheres enter the drying zone. The pellets are lifted by the fluidization air up and over the inner wall back in to forming zone. The cycle is repeated until the desired residual moisture level in the pellets is achieved. The principle of powder layering process with different steps is completely illustrated in figure 5.

The other requirements which formulation are suppose to meet are [19]

- Binder solution must have a high binder capacity.
- Micronizing or finely milling the drug before layering improves the efficiency of the layering process.
- The rheological properties of binding liquid, the liquid application rate, and drying air temperature should be optimized.
- In addition, the powder should be delivered at a rate that maintains a balance between the surface wetness of the cores and powder adhesion.

Fluid bed coating for layering of pellets [20]

- Innovative processes for coating our products.
- Film coating; lipid hot melt coating, Coating of granules, pellets, tablets.
- Specific manipulation of the particle surface characteristics. Protection of the product against moisture, light, air.
- Specific manipulation of the way in which the particle dissolves the decomposition or the release of active ingredients.
- **Process advantages:** Uniform, continuous product coating. Aqueous or organic coatings can be applied. Coating and drying take place in one machine. In terms of Total Containment, the coating process and the filling and emptying of the

machine can be carried out in complete isolation and without product spreading into the environment.

Principle of operation of fluid bed coating [20]

With fluid bed coating, particles are fluidized and the coating fluid sprayed on and dried. Small droplets and a low viscosity of the spray medium ensure an even product coating. Glatt offers Batch Fluid Bed Systems in different batch sizes with:

a. Top Spray Coating
b. Bottom Spray Coating (Wurster Coating)
c. Tangential Spray Coating (Rotor Pellet Coating)

A. Top spray coating:

This process is used for general coatings right up to enteric coating. With top spray coating in the fluid bed (batch and continuous), particles are fluidized in the flow of heated air, which is introduced into the product container via a base plate. The coating liquid is sprayed into the fluid bed from above against the air flow (countercurrent) by means of a nozzle. Drying takes place as the particles continue to move upwards in the air flow. Small droplets and a low viscosity of the spray medium ensure that the distribution is uniform. Coating in the continuous fluid bed is particularly suitable for protective coatings/color coatings where the product throughput rates are high. The product is continuously fed into one side of the machine and is transported onwards via the sieve bottom by means of the air flow. Depending on the application, the system is sub-divided into pre-heating zones, spray zones and drying zones. The dry, coated particles are continuously extracted.

B. Bottom spray coating (Wurster coating): This process is particularly suitable for a controlled release of active ingredients. In the Wurster process, a complete sealing of the surface can be achieved with a low usage of coating substance. The spray nozzle is fitted in the base plate resulting in a spray pattern that is concurrent with the air feed. By using a Wurster cylinder and a base plate with different perforations, the particles to be coated are accelerated inside the Wurster tube and fed through the spray cone concurrently. As the particles continue traveling upwards, they dry and fall outside the Wurster tube back towards the base plate. They are guided from the outside back to the inside of the tube where they are once again accelerated by the spray. This produces an extremely even film. Particles of different sizes are evenly coated.

Bottom spray coating (Continuous fluid bed): Particularly suitable for protective coatings/color coatings where the product throughput rates are high.
The product is continuously fed into one side of the machine and is transported onwards via the sieve bottom by means of the air flow. Depending on the application, the system is sub-divided into pre-heating zones, spray zones and drying zones whereby spraying can take place from below in the form of a bottom spray. The dry, coated particles are continuously extracted.

C. Tangential spray coating (Rotor pellet coating): Ideal for coatings with high solid content. The product is set into a spiral motion by means of a rotating base plate, which has air fed into the powder bed at its edge. The spray nozzle is arranged tangentially to the rotor disc and also sprays concurrently into the powder bed. Very thick film layers can be applied by means of the rotor method. The photographical representation of top spray coating, bottom spray coating and tangential coating are displayed in figure 6.

Equipment description: A GPCG (Glatt-Powder-Coater-Granulator) [30] from Glatt are used for processes those are uniform, reproducible and gentle on the product using fluid bed techniques. Batch sizes from **5 k** g to 1.**5 t** /batch.

It offers advantages such as:

- **All-in-one:** From demanding powder coating to simple drying. Whether granulation/ agglomeration, particle coating or pelletizing. Whether spraying from above (Top Spray), from below (Bottom Spray) or from the side (Tangential Spray): simply anything is possible with a GPCG. In this way, you are just as flexible as your machine.
- **Unique technology:** All GPCGs provide an optimum ratio of air volume flow to quantity of product used. The conical pressure relief zone and the resulting reduced flow speed allow even very fine products to be processed. At the centre of granulation is the legendary Glatt single pipe nozzle. This combines outstanding spray behavior with optimum media delivery and easy cleaning.
- **Simple handling:** Both horizontal and vertical product flow can be realized with all sizes. Contained feed systems using gravity or suction can be provided. The container is emptied by rotating it in the moving carriage (up to certain batch sizes). Dust-free tipping and feeding into the container on one lifting column. Emptying can likewise be carried out from the side by means of suction or by gravity or - as the fastest and most effective method of all - vertically with the unique Glatt rotating bottom.
- **Innovative ABC-technology:** The unique ABC-technology (Anti-Bearding-Cap) allows spraying without bearding. The perfect supplement to the ABC-technology: The unique nano-coating to the nozzle prevents the deposit of coating material on the nozzle cap.
    - No process downtime due to cleaning of the nozzle
    - No blocked liquid inserts

  No interference of spray pattern

Pharmaceutical applications [20, 26]

The process of FBP is used to produce a wide variety of engineered, controlled release drugs. These solid dosage forms are mostly in the form of tablets or capsules containing high levels of an Active Pharmaceutical Ingredient (API). Product characteristics include:

- Dense pellets

- Smooth coatable pellets
- Narrow particle size distributions, and
- High yield and flow ability.

Important pharmaceutical applications include:

- Controlled release pellets for encapsulations
- Sustained release pellets / Delayed release enteric coated pellets
- Multi-particulate systems
- Multi-unit erosion matrix pellets
- Pellets for special tableting applications
- Immediate release pellets for sachets

Conclusion:

The challenges in preparing tablets from coated pellets are evident. Various formulation and process parameters have to be optimized in order to obtain tableted reservoir-type pellets having the same properties, and, in particular, release properties as the original, uncompacted pellets. The most important variable is the type of polymer selected for the coating of the pellets. The polymer coating must remain intact during compaction in order to extend the drug release. Traditionally used polymers for the coating of solid dosage forms which do not resist the mechanical stress during compaction (e.g. ethyl cellulose) are not suitable for the preparation of compacted pellets. The polymers have to be flexible enough to not rupture. The formulations of the pellet core and the final tablet have to be carefully selected in order to prevent the rupture of the coating, and to obtain tablets with proper content uniformity, hardness and rapid disintegration. Key variables include the pellet: excipient ratio and the compression force. Microcrystalline cellulose appears to be the excipient of choice because of its good compaction and disintegration properties.

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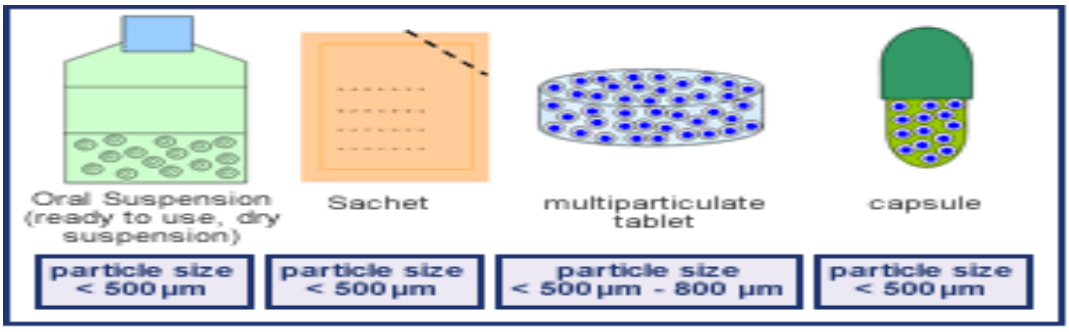
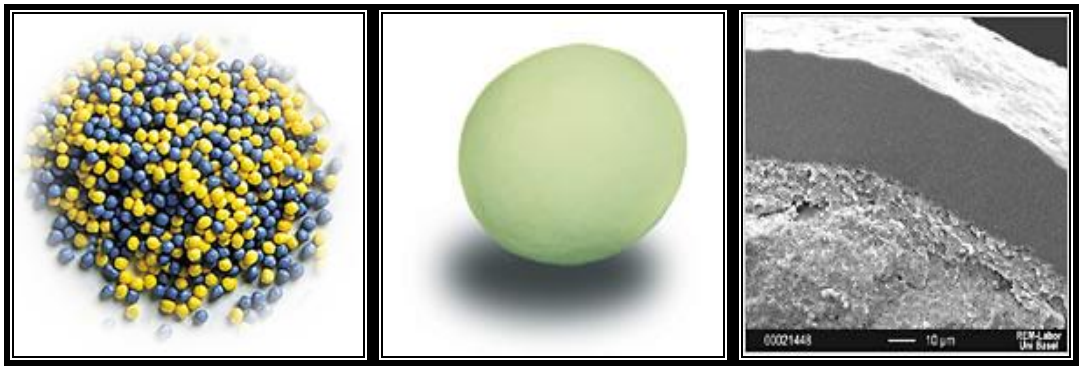


Figure: 1 Flexibility of pellets in development of dosage form



(a) (b) (c)

Figure: 2. (a) Pellets, (b) Perfect pellet, (c) Coated pellet

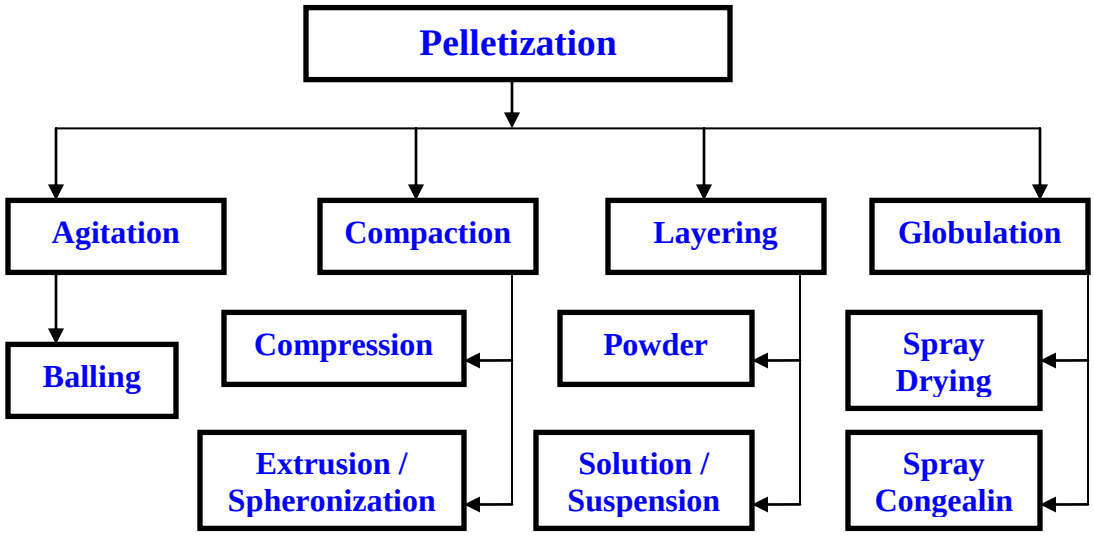


Figure 3 Different pelletization techniques

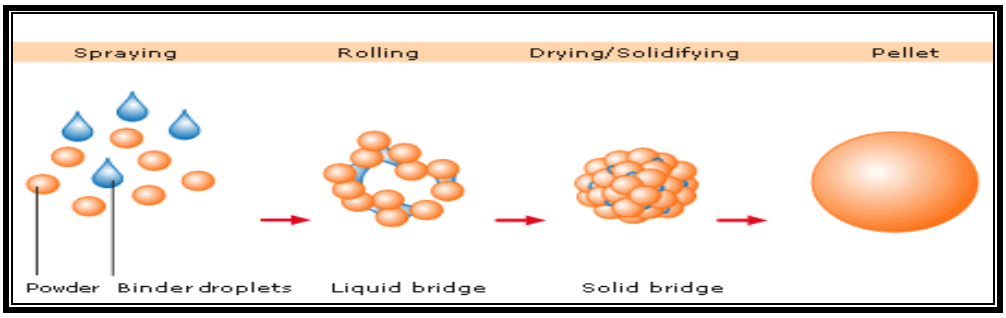


Figure 4: Process principles of Direct pelletizing

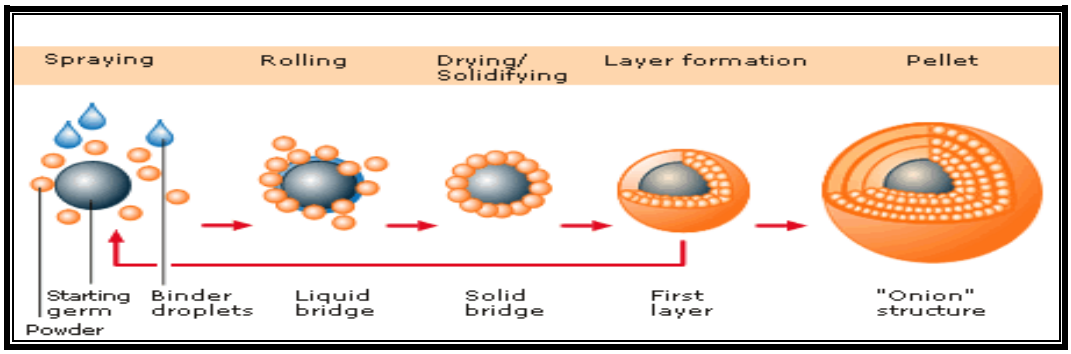
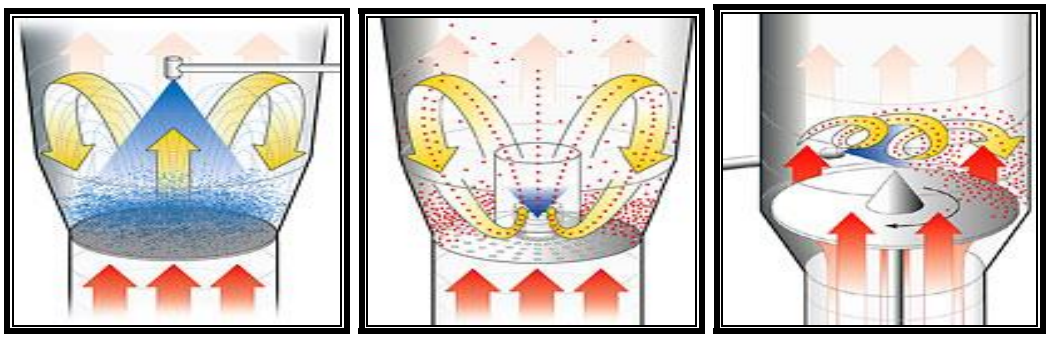


Figure 5: Principle of Powder layering process



(a) ***(b)*** ***(c)***

Figure 6: (a) Principle of Top spray, (b)Bottom spray, & (C) tangential spray coating