PELLETIZATION: A MOST SIGNIFICANT TECHNOLOGY IN THE PHARMACEUTICALS

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ABSTRACT

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. Pelletization is a technique that enables the formation of spherical beads or pellets with a mean diameter usually ranging from 0.5 to 2.0 mm. These pellets can eventually be coated and very often used in controlled-release dosage forms. In present times, the Pelletization technologies are giving much attention as they represent an efficient pathway for manufacture of new drug delivery system. It has good advantage over the conventional dosage form as it leads to an improvement in flow ability, appearance and mixing properties thus avoiding for generation of excessive dust and reduces segregation and remove the undesirable properties and improve the physical and chemical properties of fine powder. The aim of this paper is to review some general aspects about pellets and Pelletization and some common techniques used in the pharmaceutical industry. Pellets are prepared by different techniques, such as extrusion and spherization, rotogranulation, solution, suspension or powder layering, spray-drying or spray-congealing. Several other alternative methods are currently being developed, such as: hot-melt extrusion, freeze Pelletization, emulsion / solvent evaporation, granulation using foamed aqueous binders.

KEY WORDS: Pellets, Pelletization, Granulator, extrusion spherization, Spray Dryer.
1. INTRODUCTION

Historical Development

Although various industries have routinely utilized pelletization processes since the turn of the century to manufacture particles with defined size and shapes, it was only in the early 1950s in response to a desire to sustain the release of drugs over extended periods of time that the pharmaceutical industry developed a keen interest in the technology. A major breakthrough occurred in 1949 when a pharmaceutical scientist at SmithKline and French (SKF) realized the potential application of candy seed in sustained-release preparations and embarked on the development of tiny drug pellets that could be loaded into capsules. The candy seeds were nothing but small sugar particles. The process utilized standard coating pans and involved successive layering of powder and binder on sugar granules until spherical seed of the desired size were obtained. The process was lengthy and required days to be completed. In 1964, a new pelletization technique that provided sustained-release pellets ranging in size between 0.25-2.0 mm was patented by SKF. It comprised a spray congealing process in which the drugs were dissolved or dispersed in a lipid material in the molten state to form a slurry, followed by atomization of the slurry into a low temperature gas chamber until spherical congealed pellets were produced. The size of the pellets obtained from a given formulation and a set of processing conditions were determined by the nozzle orifice. The pellets were manufactured in a spray dryer, a piece of equipment that already had a wide application in the industry. At about the same time, the Marumerizer was commercially introduced. This new machine was developed in Japan and could produce large quantities of spherical pellets in a relatively short time. The process is capable of producing pellets containing more than 90% active, provided that the physicochemical properties of the drug and other formulation constituents are optimum. As drug delivery systems became more sophisticated, the role of pellets in drug dosage from design and development increased substantially, and both manufacturers of processing equipment and private investigators have intensified their search for highly efficient processing equipment in order to accommodate the increased demand.

Pellets

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration. Implants of small, sterile cylinders formed by compression from medicated masses are also defined as pellets in
pharmacy. Pellets can be prepared by many methods, the compaction and drug-layering techniques being the most widely used today. Regardless of which manufacturing process is used, pellets have to meet the following requirements:

1. They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating.

2. The particle size range should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 600 and 1000 µm.

3. The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.

In the last two decades, pellets have established their position for many reasons. Pellets offer a great flexibility in pharmaceutical solid dosage form design and development. They flow freely and pack easily without significant difficulties, resulting in uniform and reproducible fill weight of capsules and tablets. Successful film coating can be applied onto pellets due to their ideal spherical shape and a low surface area-to-volume ratio. Pellets composed of different drugs can be blended and formulated in a single dosage form. This approach facilitates the delivery of two or more drugs, chemically compatible or incompatible, at the same sites or different sites in the gastrointestinal tract. Even pellets with different release rates of the same drug can be supplied in a single dosage form. The palletized products can improve the safety and efficacy of the active agent. These multiple-unit doses are usually formulated in the form of suspensions, capsules or disintegrating tablets, showing a number of advantages over the single-unit dosage system. The palletized product can freely disperse in the gastrointestinal tract as a subunit, thus maximizing drug absorption and reducing peak plasma fluctuation. Consequently, potential side effects can be minimized without impairing drug bioavailability. Local irritation derived from high local concentrations of a drug from a single-unit dose, can be avoided.

The most important reason for the wide acceptance of multiple-unit products is the rapid increase in popularity of oral controlled-release dosage forms. Controlled-release oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time. With pellets, the above mentioned goals can be obtained through the application of coating materials (mainly different polymers), providing the desired function or through the formulation of matrix pellets to provide the desired effect. The advantage of multiple-unit products as a controlled-release dosage form is believed to be their behaviour in vivo because
of their advantageous dispersion pattern in the gastrointestinal tract and their special size characteristics. The transit time of a gastrointestinal drug delivery system along the gastrointestinal tract is the most limiting physiological factor in the development of a controlled-release gastrointestinal drug delivery system targeted to once-a-day medication. Gastro-intestinal transit time, greatly affects the bioavailability of a drug from an orally administered controlled release preparation. Gastric transit of both single and multiple-unit solid dosage forms is prolonged in a fed stomach compared to a fasting one. Plastic spheres of 7 mm remained in the food-filled stomach even as food itself expelled steadily. Once the stomach had emptied, the spheres began to transit in clusters. It has been reported that pellets smaller than about 2.4 mm in diameter, are free from the digestive function of the stomach and the closing system of the pyloric sphincter to be emptied from the stomach. A maximum pellet diameter of 1.5 mm has been recommended for an optimal multiple-unit formulation. Kelly 1981 and Devereux 1987 clearly showed that the threshold size must be below 1 mm. According to Khosla et al. (1989), there is no actual cut-off size for gastric emptying, but as the size of the pellets increase, predictable emptying from the fed stomach becomes uncertain and highly variable. However, it has been demonstrated that gastric emptying is not only dependent on the size but also on some other important factors, such as density of pellets, nature of food and inter-subject variation. Clarke et al. 1993 and Tuleu et al. 1999 showed that both density and size of the pellets affect the gastrointestinal transit time. The higher density of the pellets prolonged the gastric transit time, while the larger size slightly prolonged the small gut transit time but not the gastric transit time. Controversial results have also been reported to the effect of pellets densities on the transit times through the gastrointestinal tract.

2. Desirable properties of pellets \(^{[2,3]}\)

**Uncoated pellets:**

1. Uniform spherical shape,
2. Uniform size,
3. Good flow properties,
4. Reproducible packing,
5. High strength,
6. Low friability, Low dust,
7. Smooth surface,
8. Ease of coating.
Once coated

Maintain all of the above properties,
Have desired drug release characteristics

Figure: 1. (a) Pellets, (b) Perfect pellet, (c) Coated pellet
3. Theory of pellet formation and growth$^{[1]}$

In order to judiciously select and optimize any pelletization/granulation process, it is important to understand the fundamental mechanisms of granule formation and growth. Different theories have been postulated related to the mechanism of formation and growth of pellets. Some of these theories are derived from experimental results while others are confined to visual observations. Results obtained from the experiments with some form of tracer technique are regarded as acceptable and convincing. As the conventional Granulation, the most thoroughly studied, most classified pelletization process, which involves a rotating drum, a pan or a disc, has been divided into three consecutive regions: nucleation, transition and ball growth. However, based on the experiments on the mechanism of pellet formation and growth, the following steps were proposed:

1. Nucleation
2. Coalescence
3. Layering
4. Abrasion transfer.

**Nucleation (Figure 2A)** is a common stage in all pelletization/granulation processes and occurs whenever a powder is wetted with liquid. The primary particles are drawn together to form three-phase air-water-liquid nuclei and are attached together by liquid bridges which are pendular in nature. The bonding strength is improved by reduction of particle size. The sizes of the primary particles, the moisture content, the viscosity of the binding particles, the wettability of the substrate and the processing conditions, such as tumbling and drying rates, influence the size, the rate and the extent of nuclear formation. Both the mass and the number of nuclei in the system change as a function of time, which is an important feature of nucleation. Nucleation is followed by a transition phase, and the growth mechanisms affecting the transition region are coalescence and layering.

**Coalescence (Figure 2B)** is defined as the formation of large-sized particles by random collision of well-formed nuclei, and the mechanism requires slight excess moisture on the nuclear surface. Although the number of nuclei is progressively reduced, the total mass of the system remains unchanged during this step.
Layering (Figure 2C) is a slow growth mechanism and involves the successive addition of fragments and fines on an already formed nucleus. In the layering step, the number of particles remains the same, but the total mass in the system increases due to increasing particle size as a function of time. The fragments or fine particles can be formed by particle size reduction that occurs due to attrition, breakage and shatter. The fines and the fragments
that are produced through size reduction are picked up by large pellets. Production of fines and subsequent coalescence and layering continues until the number of favourable collisions declines rapidly, thereby leading to a reduction in the rate of growth of the pellets. At this point the third phase, the ball growth region, is reached. In the ball growth phase the main mechanism affecting the slow growth of agglomeration is the abrasion transfer (Figure 2D) which involves the transfer of materials from one granule formed to another without any preference in either direction. This situation does not result in a change in the total number or mass of the particles. The particles, however, undergo a continuous change in size as long as the conditions that lead to the transfer of material exist.

4. Characterization of pellets

Pellets with rapid drug release are seldom delivered (supplied) as a finished product without using an extra coating. The pellets are mainly coated for aesthetic, taste masking, stability, enteric-release or controlled-release purposes. The coating thickness of the pellets must be uniform in order to achieve any of these end product performances. For uniform coating thickness, the formulation, equipment and process variables are usually selected based on the reproducibility of the size distribution, surface area, shape, surface roughness, density and friability, including the reproducibility of morphologic properties of the pellets.

4.1 Size distribution

The size distribution of the pellets should be as narrow as possible due to the following reasons:
1. For acceptable film coating, a narrow size distribution of pellets is a prerequisite (in addition to spherical shape and smooth surface). The size distribution affects both the performance of the coating and the release rate of the drug. A narrow size distribution will ensure minimum variation in coating thickness throughout the batch of pellets and therefore result in a uniform performance of pellets within the batch.
2. Segregation is a common occurrence in capsule-filling and tablet compression due to the wide size distribution of pellets and thus results in variations in content uniformity and/or dosage form performance.
3. A narrow particle size-distribution improves (facilitates) the blending process in blending different types of pellets or different batches of pellets.
The size distributions of pellets are determined by different methods. The most common and widely used method is sieve analysis. The reasons for its extensive use are simplicity, lower costs, low time consumption and low turnover of operators. Sieve loading, type of motion (vibratory or tap), intensity and duration of intensity are recognized critical variables. In spite of the simple and easy technique, sieving has some disadvantages, such as the screen skewing particle size data due to the inability of the sieve to detect variation in the shapes of particles.

Another widely used method of measuring the size distribution of pellets is microscopy. The main advantage of this method over most other methods of size analysis is that the particle profile itself is measured rather than some property which is dependent on the particle size. Optical microscopy has been developed for particles size analysis from simple eye piece graticules to fast device projectors and comparators, and the latest popular computerized method of image analysis. Scanning electron microscopy can also be used for measuring the size of the pellets. Both types of microscopic techniques are tedious and time consuming, since a large number of particles need to be measured individually to make a size-frequency distribution plot. In addition, variation in the generated data is possible among operators.

Another method developed for the measurements of pellet size distribution is laser diffraction. This method is most suitable for spherical particles.

**4.2 Shape and surface roughness**

One of the important objects of pellet preparation (pelletisation) is to produce spherical and smooth particles, suitable for subsequent successful coating, i.e., optimal for controlled-release products. Moreover, spherical particles help the transfer of materials due to their good flow characteristics. And, last but not least, good spherical properties are useful in processes that require an exact metering of granules such as capsule filling. Different methods have been proposed for measuring the shape and surface roughness of the pellets. The commonly used method is the analysis of microscopic or non-microscopic pictures of objects of interest. However, the most widely accepted advanced technique is optical microscopy with image analysis. The direct measurement of surface roughness/smoothness by the image analysis method is not sensitive enough. Instead, fractal geometry of particle obtained by microscopy with image analysis is used for the measurement of surface smoothness of pellets. In the pharmaceutical field, fractal geometry has mainly been used in the study of surface roughness of powders, either excipient or drugs. Since it has been revealed that powder or granule characteristics like flow and packing properties, are also related to the smoothness of the
particle surface, knowledge about the smoothness of the pellet surface is important. Electron microscopy (SEM) is the technique of choice for measuring the shape and surface smoothness of the pellets to support visually the other qualitative and quantitative results.

4.3 Surface area

The characteristics of pellets, those controlling the surface area, are mainly size, shape, porosity and surface roughness. Knowledge of the surface area of pellets is desirable especially if film coating is considered. Because the thickness of the film applied to pellets in a sustained-release-type dosage form dictates the rate at which drug is released, knowledge about the surface area is important even in case of uncoated pellets, since drug release is influenced by the surface area available.

There are three methods of measuring the surface area of pellets. It can be calculated from the particle-size distribution by measuring/using the mean diameter, since the surface area is equal to \( \pi d^2 \). However, 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 the pellets. Therefore, two techniques, i.e. gas adsorption and air permeability, permit direct calculation of surface area.

Quick and simple, air permeability methods are widely used pharmaceutically for specific surface measurement, especially to control batch to batch variations. The principal resistance to the flow of a fluid - such as air – through a plug of compacted material is the surface area of the material. The applicability of air permeability methods for pellets is not highly acceptable since the flow rate through the plug or bed is also affected by the degree of compression of the material.

The gas adsorption method (commonly known as the BET method) was developed by Brunauer, Emmett and Teller (1937). In this method the volume of nitrogen that is adsorbed by the substrate contained in an evacuated glass bulb is measured at different pressures, and the results are plotted as \( P/V \) (\( p_0-p \)) versus \( p/p_0 \) to generate a linear plot where \( V \) is the volume of gas in cm\(^3\) adsorbed per gram of substrate at pressure \( p \) and \( p_0 \) is the saturation vapour pressure of liquefied nitrogen at the temperature of the experiment. The slope and intercept of the plot yield the values \( b \) and \( Vm \). The specific surface (\( sw \)) of the pellets is then obtained by using the following equation:

\[
SW = 4.35 \times Vm
\]
4.4 Porosity
The porosity of pellets influences the rate of release of drugs from the pellets by affecting the capillary action of the dissolved drug. It also affects film deposition and formation during coating. The porosity of the pellets can be measured qualitatively by scanning electron microscopy (SEM) and quantitatively by mercury porosimetry. The porosity of pellets can be determined quantitatively also by using optical microscopy and scanning electron microscopy together with image analysis.

4.5 Density
The density of pellets can be affected by changes in the formulation and/or process, which may affects other process or factors, such as capsule filling, coating, and mixing. Variation of density from batch to batch affects the potency of the finished capsule, causes problems in batch size determination during coating and produces segregation during mixing. The bulk density of the pellets can be measured by an automated tapper. It is indicative of the packing properties of particles and, therefore, is greatly influenced by the diameter and the size distribution of the pellets. True density indicates the extent of densification or compactness of substances. The true density of pellets can be determined by an air-comparison pycnometer, a helium pycnometer or by the solvent displacement method.

4.6 Friability
The essential requirement of pellets is to have an acceptable friability to withstand further processing, especially the subsequent coating. A high amount of attrition during the coating procedure could modify the release behaviour due to the incorporation of small particles in the film. A friability of less than 0.08% is generally accepted for tablets, but for pellets this value could be higher due to the higher surface area/unit and subsequent involvement of frictional force. A number of different methods for the determination of pellet friability have been described in the literature and an overview of the present methods is shown in Table 1.

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erweka Friabilator, Roche Friabilator</td>
<td>Rotating drum like Friability testing apparatus</td>
</tr>
<tr>
<td>Turbula</td>
<td>Turbula blender (closed test system)</td>
</tr>
<tr>
<td>Born Friabimat</td>
<td>Horizontal shaker (closed system)</td>
</tr>
<tr>
<td>Laboratory coating apparatus</td>
<td>Fluid bed device (open system)</td>
</tr>
</tbody>
</table>
5. Advantages of pellets:[7]

1. They can be divided into desired dosage strength without process or formulation changes.
2. 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. They can also be blended to deliver incompatible bioactive agents.
4. They can also be used to provide different release profile at the same or different sites in the gastrointestinal tract.
5. Pellets offer high degree of flexibility in the design and development of oral dosage form like suspension, sachet, tablet and capsule[4-6].

![Diagram of dosage forms](image)

Figure: 3. Flexibility of pellets in development of dosage form

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.
Packing of beds and columns
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.

6. Disadvantages of pellets: [8]
1. The volume per dose is usually higher than for tablets because of the lower bulk densities of pellets compared to compressed tablets.
2. Compared to larger single unit dosage forms, the specific surface area per dose is higher and more coating material is necessary to obtain coatings of the same thickness and the same functionality.
3. The preparation of pellets and the subsequent filling into capsules and the compaction of pellet containing tablets is more complicated and time-consuming than the production of compressed tablets made from granules or Powder mixtures.

7. INTRODUCTION OF PELLETIZATION
7.1 Definition: [9]
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.
7.2 Rationale for Pelletization
1. Flexibility in dosage form design & development
2. Improve the safety & efficacy of bioactive agents
3. Disperse freely in the GIT
4. Reduce variation in gastric emptying rates
5. Reduce the inter- & intra-subject variability
6. Avoid High local concentrations
7. Controlled release pellets an be manufactured
8. Pellets have a low surface area-to-volume ratio & provide an ideal shape for the application of film coating
9. Reproducible & uniform fill weights in capsules
10. Pellets can be made aesthetically appealing
11. Average transit time of pellets in the intestine can be increased
12. Pellets are less susceptible to dose dumping

8. Pelletization methods
1. Direct pelletization
2. Extrusion/spheronization
3. Pelletizing by Layering
4. Other pelletisation methods
   1. Agitation (Balling )
   2. Compaction (compression)
   3. Globulation

8.1 Direct pelleting [10]
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.

Figure: 4. Principles of Direct Pelletizing

Example
1. Pelletization Disc
2. High Shear mixer/granulator
3. (Rotor-)Fluid Bed granulator

8.1.1 Pelletization disc
The use of a pelletization disc is one of the oldest methods for the preparation of pharmaceutical pellets. Köhler (1969) and later Wan et al. (1985) described the agglomeration of pharmaceutical powders on a cylindrical disc rotating around an inclined axis by spraying a binding solution onto the agitated powder bed. The resulting agglomerates
were spherical in shape because of the rolling motion on the disc. After pelletization, the wet pellets have to be dried in an oven or a fluidized bed dryer. The method could not be established in the pharmaceutical industry even though it has been used in other industries like the fertilizer or iron ore industries for a long time.

Figure: 5. Mars Mineral Disc Pelletizer is equipped with binder spray system for use in micro-pelletizing.

8.1.2 High-shear mixer/granulatɔr[8]

High-shear mixers or granulators are commonly used in the pharmaceutical industry to prepare granules. The powder material is placed in the mixer and agitated by an impeller. Agglomerates are formed when a liquid binder is added by pouring or spraying into the mixer. The formation of oversized agglomerates is avoided by using a rapidly rotating device called a chopper. Under optimized process conditions, pellets can be obtained that of course have to be dried in separate equipment. The process is sensitive to changes in formulation variables e.g. the particle size of the starting material and process variables such as impeller speed. The addition of a meltable substance such as polyethylene glycol, lipids or waxes can lead to the formation of granules or pellets without the addition of a liquid binder. The walls of the high-shear mixer are heated or the impeller itself generates heat of friction which causes the melting of the binder and subsequent agglomeration. Pellets are obtained on cooling. One important issue is the adhesion of material to the impeller or to the wall of the mixer bowl. The pellets formed are usually dense.
8.1.3 (Rotor) Fluidized bed granulator[8]

In a fluidized bed granulator, powders are fluidized by a hot air stream and a binder solution is sprayed simultaneously onto the particles. The binder solution wets the particles which then stick together to form larger agglomerates. Part of the drying step takes place even during granule formation; the final drying process is completed in the same equipment once the binder solution has been added. Usually, the fluidized bed granulation process produces granules; however, under optimized conditions, the preparation of pellets is also possible. The use of a rotary fluidized bed processor (figure 3) increases the shear forces during agglomeration. The rotating friction plate at the bottom of the container induces a so-called spiral rope-like movement which is the result of three forces: the centrifugal force from the rotating plate, the fluidizing force from the air stream through the orifice and the force of gravity. The higher shear forces lead to stronger densification and more spherical agglomerates.

![Figure: 6. Rotary fluidized bed processor](image)

Melt Pelletization is also possible in the rotor fluidized bed granulator. Initially, the powders are fluidized with the powdered binder particles using cold air. The fluidized air is then heated and the binder melts and forms agglomerates with the other powder particles. It is also possible to spray the binder in molten form onto the fluidized particles during the process. On cooling to room temperature, the binder solidifies and pellets are formed. For this process, neither the addition of liquid nor a drying step is necessary.
8.2 Extrusion/spheronization\textsuperscript{[10]}

Extrusion-spheronization is a multiple step process capable of making uniformly sized spherical particles. Although the process is more efficient than other techniques for producing spheres, it is more labor and time-intensive than the more common granulation techniques. Therefore, it should be considered as a granulating technique when the desired particle properties are essential and cannot be produced using more conventional techniques.

![Figure: 7. Principle of the Extruded product spheronising process](image)

Irregular particles can be spheronized with the help of a pelletizer/spheronizer. The moist granulates or extruded products are fed onto the rotating pelletizing plate. The surface is smoothed due to the intensive rolling movement and spherical pellets are produced. Spheronization is a process invented by Nakahara, in 1964. The patent describes a Method and Apparatus for Making Spherical Granules from wet powder mixtures\textsuperscript{[12]}. And described the steps involved in the process, including\textsuperscript{[13,14]}

![Figure: 8. The extrusion-spheronization process\textsuperscript{[15]}](image)
(A) Dry Mixing
During the first step, powders are dry mixed to achieve a uniform dispersion before wet granulation. It is generally carried out in the same mixer used for the granulation; however, if a continuous granulator is used, a separate mixer is required for the dry mix. This step is typically taken for granted because wet massing follows. The uniformity of the dry mix, however, can have a significant effect on the quality of the granulation and, in turn, on the spherical particles produced.

(B) Granulation
The second step is granulation, during which a wet mass, having the requisite plasticity or deformation characteristics, is prepared. With a few exceptions, this step is similar to conventional granulation techniques used to produce products for compression. It is typically carried out in a batch-type mixer-granulator; however, any equipment capable of producing a wet mass, including the continuous type, can be used.

(C) Extrusion
Extrusion is the third step of the process and consists of shaping the wet mass into long rods, which are more commonly termed ‘extrudate’. The extrusion process is used not only in the pharmaceutical industry but also in the food, ceramic and polymer industries. The extrusion process is currently used as an alternative method for the manufacture of completely water-soluble tablets. The wet mass is forced through dies and shaped into small cylindrical particles having a uniform diameter. The extrudate particles break at similar lengths under their own weight. The extrudate must have enough plasticity to deform, but not so much that it adheres to other particles when collected or rolled in the spheronizer.

Classification of Extruders
Extruders come in many varieties, but can generally be divided into three classes, based on their feed mechanism as given in table 2.

Table: 2 Type of pharmaceutical extruders

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Extruder</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Screw fed extruders</td>
<td>Axial or End Plate, Dome, Radial</td>
</tr>
<tr>
<td>2</td>
<td>Gravity feed extruders</td>
<td>Cylinder Roll, Gear roll, Radial</td>
</tr>
<tr>
<td>3</td>
<td>Piston feed extruders</td>
<td>Ram</td>
</tr>
</tbody>
</table>
Screw Extruders
Commonly used in industrial applications
Higher pressure and heat can degrade pharmaceutical products

Screen, or Basket, Extruders
1. Commonly used in pharmaceutical industry
2. Lower density extrudate
3. Relatively high throughput

Gear Extruders
1. Commonly used in pharmaceutical industry
2. Produces a relatively higher density extrudate
3. Gentler on product
4. Gears are robust and last longer
(D) Spheronization [7]

The fourth step in the extrusion-spheronization process is the spheronization step.

Basic Configuration

(1)

In principle the basic machine consists of a rotating friction disk, designed to increase friction with the product, which spins at high speed at the bottom of a cylindrical bowl. The spinning friction disc has a carefully designed groove pattern on the processing surface. This is most often crosshatched, but several sizes and other types are available.
Extrudates are charged to the spherizer and fall on the spinning disc. At first, the cylindrical extrudate segments are cut into segments with a length ranging from 1 to 1.2 times the diameter. These segments then collide with the bowl wall and they are thrown back to the inside of the friction plate. Centrifugal force sends the material to the outside of the disc. The action of the material being moved causes the extrudate to be broken down into pieces of approximately equal length relative to the diameter of the extrudate. These cylindrical segments are gradually rounded by the collisions with the bowl wall, the plate and each other.

The ongoing action of particles colliding with the wall and being thrown back to the inside of the plate creates a "rope-like" movement of product along the bowl wall. The continuous collision of the particles with the wall and with the friction plate gradually turns the cylindrical segments into spheres, provided that the granules are plastic enough to allow the
deformation without being destroyed. It is essential that this rope movement is present for an optimal spheronization. When the particles have obtained the desired spherical shape, the discharge valve of the chamber is opened and the granules are discharged by the centrifugal force.

(E) Drying

Drying is the final step in the process. This can be accomplished in any dryer that can be used for conventional type granulations, including tray dryers, column-type fluid beds, and deck-type vibratory fluid beds. Fluidized bed dryers result in a much more rapid drying rate because of the higher air volumes and the potential use of higher inlet temperatures.

Product characteristics of the granulates and pellets

| Top: Spheronized extruded product | Dust free |
| Bottom: spheronized wet granulate | Round, uniform shape |
|                                      | Good flow behaviour |
|                                      | Easy to dose |
|                                      | Good dispersibility |
|                                      | Good solubility |
|                                      | Compact structure |
|                                      | Low hygroscopicity |
|                                      | High bulk density |
|                                      | Dense surface |
|                                      | Narrow grain size distribution |
|                                      | Low abrasion |
|                                      | Visual attractiveness |
|                                      | Optimum starting shape for subsequent coating |

Spheronization Advantages

1. Manufacture of modified or controlled release formulations.
2. To enable uniform coating and accurate free flow filling into capsules.
3. Esthetics - Small spheres can be an important marketing and product feature for pharmaceutical products.
4. Elimination of airborne dust. Spheroids reduce risks due to toxic, environmental, and explosive hazards.
5. Improved processing consistency and productivity by using consistent free flowing spheres.
8.3 Pelletizing by Layering

The layering process comprises the 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 or inert starter seeds. In solution/suspension layering, drug particles are dissolved or suspended in the binding liquid. In powder layering, complete dissolution does not occur, due to low liquid saturation, irrespective of the solubility of the active agent in the binding liquid. In powder drug layering, a binder solution is first sprayed onto the previously prepared inert seeds, followed by the addition of powder

1. Powder layering
2. Suspension and solution layering

8.3.1 Powder layering\(^{[18]}\)

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.

![Diagram of Powder Layering Process](image)

**Figure: 9. Principle of Powder layering process**

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 other requirements which formulation are suppose to meet are**\(^{[19]}\)

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

### 8.3.2 Solution or suspension layering \(^{[18]}\)

Involves the deposition of successive layers of solution and/or suspension of drug substances and binder on starter seeds, which may be inert materials or crystal/granules of the same drug. The primary features that distinguish wurster equipment from other fluid bed equipment are the cylindrical partition located in the product chamber and the configuration of the air distribution plate, also known as the orifice plate. The latter is configured to allow most of the fluidization or drying air to pass at high velocity around nozzle and through the partition, carrying with it the particles that are being layered on. Once the particles are exiting the partition, they enter the expansion chamber, where the velocity of the air is reduced below the entrainment velocity, and the particles fall back to the area surrounding the partition. The down bed is kept aerated by the small fraction of air that passes through the small holes on the periphery of the orifice plate. The spray direction is concurrent with the particle movement. The disadvantages of the wurster process are the inaccessibility of the nozzles. If the nozzles are clogged at any time during the layering process, the operation has to be interrupted, and the spray guns must be removed for cleaning. The problem can be alleviated by screening the formulation or by using a spray gun with a bigger nozzle. Suspension layering is usually used when the desired drug loading of the pellets is low because production of pellets from low solids content formulation is not economically feasible.
An important factor that needs to be considered when suspensions are used as opposed to solutions is the particle size of the drug. If the size of the drug in suspension is large, the amount of binder required to immobilize the particles on to cores will be high, and consequently pellets of low potency are produced.

**Product characteristics**

| Layered pellet | Dust free  |
|               | Round pellets |
|               | Good flow behaviour |
|               | Easy to dose |
|               | Compact structure |
|               | Low hygroscopicity |
|               | High bulk density |
|               | Dense, uniform surface |
|               | Narrow grain size distribution |
|               | Low abrasion |
|               | High active ingredient content possible |
|               | Optimum starting shape for subsequent coating |

8.4 Other Pelletization methods: [1]

1. Agitation (Balling )
2. Compaction (compression)
3. Globulation

8.4.1 Balling

Describes a Pelletization process in which finely divided particles are converted, upon the addition of appropriate quantities of liquid, to spherical particles by a continuous rolling or
tumbling motion. The liquid may be added prior to or during the agitation stage. Pans, discs, drums, or mixers may be used to produce pellets by the balling process.

8.4.2 Compression
Is a pelletization process in which mixtures or blends of active ingredients and excipients are compacted under pressure to generate pellets of defined shape and size. The pellets are small enough to be filled into capsules. The formulation and processing variables that govern the production of pellets during compression are similar to those that are routinely employed in tablet manufacturing. In fact, pellets produced by compression are nothing but small tablets that are approximately spheroidal in shape.

8.4.3 Globulation
Globulation or droplet formations describe the two related processes of spray drying and spray congealing.

8.4.3.1 Spray drying
During Spray drying, drug entities in solution or in suspension form are sprayed, with or without excipients, into a hot air stream to generate dry and highly spherical particles. Though the technique is suitable for the development of controlled release pellets, it is generally employed to improve the dissolution rates and hence, bioavailability of poorly soluble drugs. Spray drying has been used for a variety of reasons. Consequently, the literature is replete with description of both process and equipment.
8.4.3.2 Spray congealing
Spray congealing is a process in which a drug is allowed to melt, disperse, or dissolve in hot melts of guns, waxes, fatty acids, etc., and is sprayed into an air chamber where the temperature is below the melting points of the formulation components, to provide, under appropriate processing conditions, spherical congealed pellets. Depending on the physicochemical properties of the ingredients and other formulation variables, pellets with immediate or controlled release behavior can be produced.

9. Dosage form design of pellets
With regard to the final dosage form, the multiparticulates can be filled into hard gelatin capsules or be compressed into tablets. The compression of multiparticulates into tablets is becoming more popular, especially in the USA, where hard gelatin capsules have been tampered (Tylenol").

![Diagram of dosage form design of pellets]

Figure: 12. Dosage form design of pellets

The advantages of Tableting multiparticulates include a reduced risk of tampering and less difficulty in esophageal transport when compared with capsules. Large volume tablets generally have a higher patient compliance than capsules; higher dose strength could be administered with tablets. Tablets from pellets can be prepared at lower cost when compared to pellet-filled capsules because of the higher production rate of tablet presses. The expensive control of capsule integrity after filling is also eliminated. In addition, tablets containing multiparticulates could be scored without losing the controlled release properties. Scored
tablets allow a more flexible dosing regimen. Compaction of coated multiparticulates into tablets could either result in disintegrating tablets providing a multiparticulate system during GI-transit or in intact tablets due to the fusion of the multiparticulates in a larger compact. Ideally, the compacted pellets should disintegrate rapidly in the individual pellets in gastrointestinal fluids \cite{22, 23}. The pellets should not fuse into a non-disintegrating matrix during compaction. The drug release should not be affected by the compaction process With reservoir type coated pellet dosage forms, the polymeric coating must be able to withstand the compression force; it can deform, but should not rupture.

So, the aim of most studies on the compaction of pellets is to convert a multiple unit dosage form into a single unit dosage form containing the multiparticulates, with this single unit dosage form having the same properties, in particular drug release properties, as the individual multiparticulates. But, problem encountered duringtabletting of pellets. Those are rupture of coating and demixing with other excipients. Demixing is solved by increasing the mixing time but rupture of coating is solved by showing in figure 12.
Market products of Pellets

Table: 3 Marketed products of pellets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Active Components</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bontril SR</td>
<td>Not found</td>
<td>Carnrick lab, Inc.</td>
</tr>
<tr>
<td>Hispril</td>
<td>Not found</td>
<td>Smith Kline &amp; French</td>
</tr>
<tr>
<td>Betacap TR</td>
<td>Propranolol HCL</td>
<td>Natco Pharma</td>
</tr>
<tr>
<td>Coldact TR</td>
<td>Phenylpropanolamine HCL and Chlorpheniramine Maleate</td>
<td>Natco Pharma</td>
</tr>
<tr>
<td>Dilgard XL ER</td>
<td>Diltiazem HCL</td>
<td>Cipla</td>
</tr>
<tr>
<td>FEFOL- Z SR</td>
<td>Zn + iron + Folic acid</td>
<td>Smithkline Beecham Pharmaceuticals</td>
</tr>
<tr>
<td>Ibubid TR</td>
<td>Ibuprofen</td>
<td>Natco Pharma</td>
</tr>
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<td>Indacap</td>
<td>Indomethacin</td>
<td>Jagsonpal Pharma</td>
</tr>
<tr>
<td>Sudafed SA</td>
<td>Pseudoephedrine HCL</td>
<td>Borroughs- Wellcome</td>
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<tr>
<td>Tuss – ornade</td>
<td>Not Found</td>
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<tr>
<td>Theolong SR</td>
<td>Theophylline</td>
<td>SOL Pharma</td>
</tr>
<tr>
<td>Ventorlin CR</td>
<td>Salbutamol</td>
<td>Glaxo India</td>
</tr>
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<td>Glaxo</td>
</tr>
<tr>
<td>Theo- 24 SR</td>
<td>Anhydrous Theophylline</td>
<td>Searle Pharmaceuticals</td>
</tr>
</tbody>
</table>

10. Pharmaceutical applications\![24, 25]

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:

1. Dense pellets
2. Smooth coatable pellets
3. Narrow particle size distributions, and
4. High yield and flow ability.

Important pharmaceutical applications include

1. Controlled release pellets for encapsulations
2. Sustained release pellets / Delayed release enteric coated pellets
3. Multi-particulate systems
4. Recent application of Pelletization technology is Innoherb formulation. Which is made up of many micro pellets or small beads containing active herbal compounds, The special coating for each plant extract contains top quality standardized extract which assures efficacy and safety of the semi permeable membrane, improves stability, mask taste/smell and affords gastro protection as well as promote controlled release of actives, optimal availability and better absorption  Example: Innoherb
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