PELLETIZATION TECHNIQUES USED IN PHARMACEUTICAL FIELDS

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ABSTRACT

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 evantually be coated and very often used in controlled-release dosage forms. The use of pelletization and pellets leads to an improvement in the flowability, appearance and mixing properties, thus avoiding excessive dust and reducing segregation and, generally, eliminating undesirable properties and improving the physical or chemical properties of fine powders. Pellets are prepared by different techniques, such as extrusion and spheronisation, rotogranulation, solution, suspension or powder layering, spray-drying or spray-congealing. The aim of this paper is to review some general aspects about pellets and pelletization and some common techniques used in the pharmaceutical industry. Several alternative methods are currently being developed, such as: hot-melt extrusion, freeze pelletization, emulsion / solvent evaporation, granulation using foamed aqueous binders, etc. (1-7).

Key words: Pelletization, pellets

Introduction

Pelletization can be defined as an agglomeration (size-enlargment) process that converts fine powders or particles of bulk drugs and excipients into small, free-flowing, more or less spherical units, called pellets (7).

Granulation is also known as pelletization, agglomeration or spheronization, and the units obtained are referred to as granules, pellets, agglomerates or spheroids (8).

The general terms "granulation" and "pelletization" are sometimes used synonymously and no clear distinction is made between them.

Generally, if a size-enlargement process produces agglomerates of a size distribution within the range of 0.1 to 2.0 mm and a high porosity (about 20-50%), the process may be called "granulation", and the resulting agglomerates are called "granulates".

"Pelletization" is often referred to as a size-enlargement process that involves the manufacture of agglomerates with a relatively narrow size range, usually with mean size from 0.5 to 2.0 mm, named "pellets". Pellets have free-flowing properties and a low porosity (about 10 %).

The term "spheronization" is more specific, usually associated with spherical units formed by a size-enlargement process that includes a spheronization step where extrudates or agglomerates are rounded as they tumble on a rotating frictional base plate, being named "spheroids" (9).

A short history of pellets

Although various industries have routinely utilized pelletization processes since the turn of the XXth century in order to manufacture particles with defined sizes and shapes, it was only in the early 1950's, in response to a desire to sustain the release

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of drugs over an extended period of time, that the pharmaceutical industry developed a keen interest in the technology.

In 1949, pharmaceutical scientists at Smith Kline & French (SKF) realised the potential of candy seeds in developing sustained-release preparations and began the development of tiny drug pellets that could be loaded into capsules.

In time, extensive research was conducted to develop pelletization techniques and major ressources were allocated towards exploring methods that were faster, cheaper and more efficient, both in terms of formulation and processing equipment (8).

The trend is expected to continue in the forseeable future.

Also, the role of pellets, especially of spheroids, in oral dosage form design and development has increased substantially during recent decades.

Currently, pellets containing the active ingredients are administered in the form of suspensions, capsules or tablets, a great number of this kinds of pharmaceutical products being available on the market.

Also, pelletization is used in various industries, such as agriculture (fertilizers and herbicides), mineral processing (iron ore pelletization), food and detergent industry.

Reasons for pelletization

The pharmaceutical industry has developed a great interest in pelletization due to a variety of reasons (10):

- prevention of segregation of co-agglomerated components, resulting in an improvement of the uniformity of the content;
- prevention of dust formation, resulting in an improvement of the process safety, as fine powders can cause dust explosions and the respiration of fines can cause health problems;
- increasing bulk density and decreasing bulk volume;
- the defined shape and weight improves the appearance of the product;
- improvement of the handling properties, due to the free-flowing properties;
- improvement of the hardness and friability of 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.

All these aspects can be considered as technological advantages of pelletization.

Aditionally, the production of controlled-release multiparticulate oral dosage forms using spheroids, designed to deliver drugs at a specific site within the gastrointestinal tract or over an extended period of time, leads to a series of therapeutic advantages over conventional oral dosage forms (tablets or capsules) (11), such as:

- 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;
- modified-release multiparticulate delivery systems are less susceptible to dose dumping than single-unit dosage forms.

But pellets also present some disadvantages:

- often pellets can not be pressed into tablets because they are too rigid. In that case, pellets have to be encapsulated into capsules.
- the production of pellets is often an expensive process and / or requires highly specialised equipment.
- the control of the production process is difficult (e.g. the amount of water to be added is critical for the quality of the pellets and overwetting can occur very easily).

Methods of pelletization

Pelletization methods used in the pharmaceutical industry can be grouped by various criteria, e.g. by the type of equipment used, the intensity of the mechanical forces involved or the techniques employed for the production of pellets.

The success of these methods depends on the complex relations between the equipment, the formulation and process variables (12 – 14).

Extrusion / Spheronisation

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

The method involves the following main steps:

- 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 spheronisation 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

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.

As the mass passes through the extruder screen, the resulting extrudates eventually break under their own weight. Usually the extrudates have the same length. The extrudates must have enough plasticity in order to deform, but an excessive plasticity may lead to extrudates which stick to each other as they are collected and further processed in the spheroniser. The diameter of the segments and the final size of the spheroids depend on the diameter of the openings in the extruder screen.

In order to obtain reproductible results, it is recommended to monitor extrusion parameters such as: feed rate, powder consumption, die temperature and compression chamber pressure.

Spheronisation

Spheronisation reffers to the formation of spherical particles from the small rods produced by extrusion. The essential part of the spheronizer is the friction plate. The indentation pattern on the plate can have various designs, which correspond to specific purposes. The most common design is the cross-hatch pattern with grooves intersecting each other at 90° angles. 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.

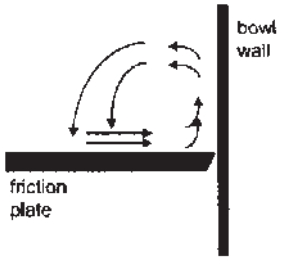

Figure 1. The whirling movement of the particles at the chamber wall

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 transition from the almost cylindrical segments to spheres during the spheronisation process occurs in several stages.

The resulting spherical shape of the pellets is correlated to the peripheral velocity of the plate. As the spheronisation process begins, the processed material begins to move inside the spheroniser on a trajectory which resembles a woven rope.

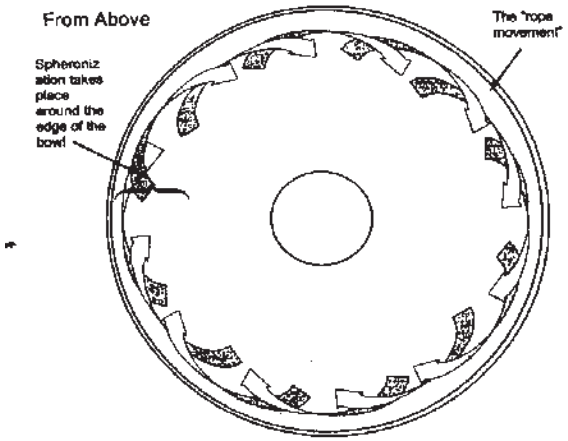

Figure 2. The movement of the product along the chamber wall

In addition, in order to obtain a high yield of spherical pellets, it is essential that the extrudates are non-friable and that they have suitable plastic properties which allow them to take a spherical shape.

The process of spheroid formation by extrusion / spheronization is similar to the wet granulation process, claiming the presence of a moistening liquid.

However, there are two major differences in the granulation steps:

- the amount of granlation fluid required to obtain pellets with uniform size and sphericity is likely to be higher than for a similar wet granulation;
- uniform dispersion of the granulation fluid leads to a product with a good quality.

Extrusion/spheronisation is a versatile process for producing pellets with useful properties. However, the process is more labour-intensive and more expensive than the conventional wet-granulation technique, as its use should be limited only to the production of spherical pellets for controlled release of drugs.

Technological advances now allow the production of spherical pellets by new processes, such as fluid-bed granulation and rotary granulation.

In these cases, specialized equipments allow the whole cycle of wet spheronization, drying and coating of the pellets to be performed in one closed system.

Fluid-bed Granulation

The process is carried out continuously in a fluid-bed granulator.

It consists in the spraying of a granulation solution onto the suspended particles, which then are dried rapidly in the hot air stream.

The fluid-bed granulation is performed following these steps (2):

- the preblending of the formulation powder, including the active ingredients, fillers, disintegrants, in a flow of air;
- the granulation of the mixture by spraying a suitable liquid binder onto the fluidized (suspended) powder bed;
- the drying of the granulated product to the desired moisture content.

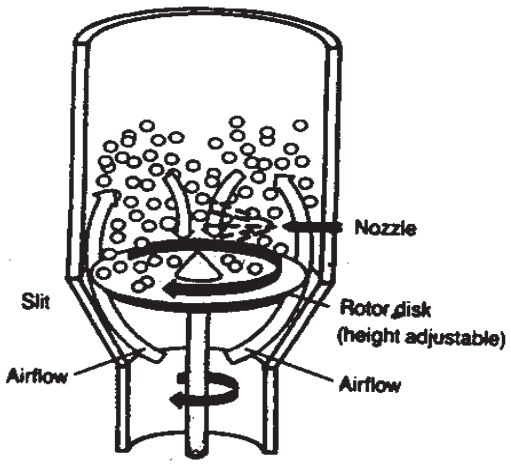

Figure 3. The schematic representation of a fluid-bed granulator

There are numerous equipment, processes and product parameters that can influence the quality of the final granules, such as:

- equipment parameters:
- the shape of the granulator body,
- the air distribution plate,
- the nozzle height,
- positive or negative pressure operation.
- product parameters:
- the type and quantity of the binder,
- the concentration and temperature of the granulating solution,
- the properties of the starting materials (fluidization, hydrophobicity).
- process parameters:
- bed load,
- rate of adition of binder,
- temperature in the fluid bed of particles,
- fluidizing air flow rate,
- temperature, volume and humidity of the air,
- nozzle type and spray angle,
- droplet size.

Fluid-bed granulation has several advantages over traditional wet granulation: the process is automated, performed in one unit, thus saving costs, transfer losses and time. On the other side, the process requires extensive efforts in the initial formulation and in the scale-up from development to production.

Rotogranulation

Rotogranulation is one of the most recent methods for the production of spheroids.

The single-unit spheronizing system can be described using terms like centrifugal granulator, rotary fluidized-bed granulator, rotary fluid bed, rotary processor or rotor granulator.

Regardless the name of the equipment, they all have the same main piece, a rotating disc. When the equipment is operating, this disk provides a centrifugal force which throws the pellets towards the wall of the processing chamber.

Air via a slit between the disc and the wall of the chamber moves the particles in a vertical direction. As the fluidizing force decreases with the distance above the slit, the pellets fall towards the bottom of the disc.

The centrifugal force is in relation with the rotation speed of the disc, while the vertical distance for which the particles move is dependent on the air velocity and volume.

The combined action of the three forces generates a spiral, twisted, rope-like motion of the material (7).

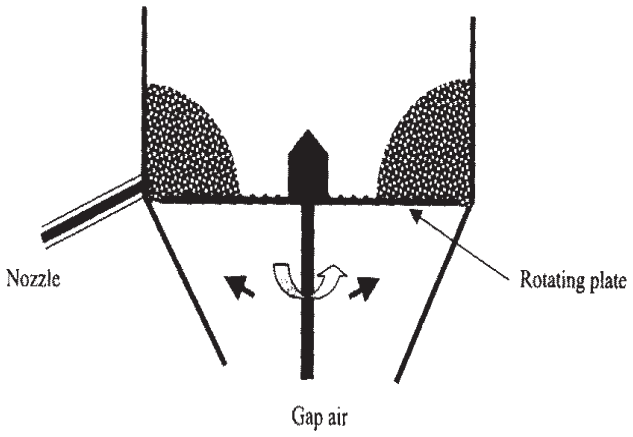

Figure 4. The schematic diagram of a rotary processor

Subsequent to the granulation, the coating of the pellets by spraying them with a coating solution or a dispersion is possible in any of the all-in-one glanulation equipments described above.

Solution and Suspension Layering

Layering a suspension or a solution of a drug on a seed material (usually, a coarse crystal or nonpareil) can produce pellets that are uniform in size distribution and generally posess very good surphace morphology (15).

These characteristics are especially desirable when pellets will be coated for the purpose of achieving a controlled release.

The equipment employed for this kind of processes consists of custom modified conventional coating pans (perforated pans) and various configurations of fluid-bed equipment.

There are many factors that determine the economic and performance feasability of pellet coating.

Besides the process variables mentioned before, there are other formulation variables, such as the drug solubility in the media used for solution layering, or the suspension concentration in solid particles for the suspension layering of the pellets, which need to be taken into account.

Dry Powder Layering

This process is similar to the solution or suspension layering. Instead of these dispersions, the layering is performed using a drug powder.

Usually, the process is carried out in conventional coating pans.

Initially, the nonpareils or starter seeds (neutral or innert pellets, beads, spheres) are charged into a rotating pan, 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 (16).

A baffle inserted into the rolling bed enhances the vortex action, which in turn intensifies the mixing and shear, improving the adhesion of the of the powder to the wet seeds. After the wet seeds pick up the powder, they are directed back into the upward moving bed and the entire process is repeated. In an intermitent powder layering process, the layering solution is added until the bed is wet and tacky. The drug powder is then added, until the bed is dry. Warm drying air may be used after each cycle. The process continues untill all of the drug powder has been added. In a continuous process, the layering solution and the drug powder are added simultaneously.

When using a centrifugal granulator, as the pellets rotate in a rope-like fashion, they are first wetted by the adhesive solution and the powder is added to the wet pellets immediately afterwards. This cycle continues until the desired pellet size is obtained (17).

Spray-drying

Spray-drying represents another process with limited application in the development of pharmaceutical pelletized products, based on globulation.

During spray-drying, a drug solution or suspension is sprayed, with or without excipients, into a hot-air stream, generating dry and highly spherical particles.

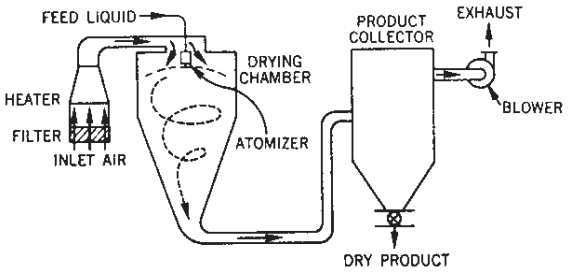

Figure 5. The schematic diagram of a spray-drier

Though the technique is suitable for the development of controlled-release pellets, it is generally employed to improve the dissolution rates and, hence, 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 enzimes, protein hydrolysate and thiamine (2).

The spray-dried powder particles are homogenous, approximately spherical, nearly uniform in size. The design and operation of the spray drier can influence a great number of the characteristics of the final product, such as particle size and size distribution, bulk density, porosity, moisture content, flowability and friability.

Spray-congealing

Spray-congealing (spray-chilling) is a technique similar to spray-drying.

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.

The resultant material can be used for the production of prolonged-release dosage forms (2, 8).

Conclusions

In the later decades, pelletization has gained an increased interest, especially due to the posibilities to use pellets in the development of modified-release solid oral dosage forms.

Currently there are several pelletization methods, the most widely used being etxrusion / spheronization.

Due to the good technological, pharmacokinetic and biopharmaceutic characteristics of the pellets and the flexibility of the maufacturing processes involved, pellets are expected to continue to play a major role in design and fabrication of solid dosage forms.

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