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A REVIEW ON : PELLETIZATION AN ADVANCEMENT IN SOLID ORALS

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ABSTRACT

The pelletization is a technique in which free flowing spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipient. Pelletization involves size enlargement process and if the final agglomerates are spherical in shape in the size range of 0.5-2.0 mm pellets. By pelletization technique enhanced drug absorption process, less gastric irritation by limiting localized build up and dose dumping good flowability due to uniform size and shape, high tensile strength, low friability, narrow particle size distribution, and uniform packing characteristics. Pellets are directly filled into capsule and can also be compressed into tablets. The preparation of spherical agglomerates can be approached by several techniques such as a powder/solution layering, Extrusion, Melt spheronization, cryopelletization. Pellets containing the active ingredients are administered in the form of suspensions, capsules or tablets, a great number of these kinds of pharmaceutical products being available on the market. Pelletization technique used in various approach modified release multiple dosage, taste masking, self-emulsification, gastro retentive floating technique.

INTRODUCTION

Pelletization can be defined as an agglomeration (size-enlargement) process that converts fine powders or particles of bulk drugs and excipient 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 term "granulation" and "pelletization" are sometimes used synonymously and no clear distinction is made between them.

"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 %).

Pellets are prepared using different technologies such as layering of the drug solution, suspension or powder on the inactive cores, extrusion, spheronization and agglomeration in roto-granulators or rot processors, compression, spray drying and spray congealing. Pellets have numerous therapeutic as well as technical advantages such as enhanced drug absorption due to involvement of large GI surface in absorption process, less gastric irritation by limiting localized build up and dose dumping good flowability due to uniform size and shape, high tensile strength, low friability, narrow particle size distribution, and uniform packing characteristics.

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 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 resources were allocated towards exploring methods that were faster, cheaper and more efficient, both in terms of formulation and processing equipment [8].

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.

ADVANTAGES OF PELLETIZATION TECHNIQUE

1. When formulated as modified release dosage forms, pellets are less susceptible to dose dumping than reservoir type single unit formulations.
2. Pellets are recommended for patients with difficulty in swallowing and dysphagia like in case of children and aged people.
3. Pelletization reduces intra and inter subject variability of plasma profiles by reducing variations in gastric emptying rates and overall transit times.
4. Pelletization produces spheroids with high loading capacity of active ingredient without producing extensively large particles.
5. Pellets exhibit better roundness than the commercial nonpareil seeds and have excellent flow and packing properties.
6. Pellets composed of different drugs can be blended and formulated in single unit dosage form that facilitates delivery of two or more chemically compatible or incompatible drugs at the same or different site in GI tract.
7. Pellets reduce peak plasma fluctuations and minimize potential side effects without appreciably lowering the drug bioavailability.
8. Incompatible drugs processed separately and mixed later, or pellets with different release mechanisms can be mixed to give a new modified release profile.
9. Pellets disperse freely in the GI tract and hence greater absorption of the active drug occurs.
10. Particles less than 2-3 mm rapidly pass the pylorus regardless of the filling level of the stomach or the size and density of chyme. Also, GI irritations are limited spread as the particles spread in the intestine.

DISADVANTAGES OF PELLETIZATION TECHNIQUE

1. Capsule filling which can increase the costs or tableting which destroy film coatings on the pellets.
2. Often pellets can not be pressed into tablets because they are too rigid. In that case, pellets have to be encapsulated into capsules.
3. The production of pellets is often an expensive process and / or requires highly specialised equipment.

PELLETIZATION TECHNIQUE

1) Powder Layering technique

Layering processes are probably the most well controlled and straight forward pelletization techniques. 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. They are classified into two categories: solution/suspension layering and powder layering.

In solution/suspension layering drug particles and other components are dissolved or suspended in the application medium. The droplets impinge on the starter seed or cores and spread evenly as the solution or suspension is sprayed on the cores. Followed by drying phase allows dissolved material to crystallize and form solid bridges between the cores and initial layer of the drug substance and among the successive layers of drug substance or polymer. Continue this process until the desired layers of drug or polymer formed[4].

In powder layering the binding liquid helps to form successive layers of dry powder of drug and other components on starting cores. In this technique the drug particles are bound to the starter seeds and subsequently to the forming pellets with the help of liquid bridges originated from the sprayed binding liquid. These liquid bridges are eventually replaced by solid bridges derived either from a binder in the liquid medium or from any material. Successive layering of the drug and binder solution continues until the desired pellet size is reached. The most commonly used equipments for layering are the standard or conventional coating pans and fluidized bed granulators (bottom spray, top spray and tangential spray) [2].

2) Suspension / Solution layering technique

This technique involves the deposition of successive layer of solution and /or suspension of drug substances and binders on starter seeds which may be inert material or crystal of granules of the same drug. In this technique drug particles and others component are dissolved or suspended in the application medium. The droplets impinge on the starter seeds or cores and spread evenly as the solution or suspension is sprayed on the cores. Followed by drying phase allows dissolved material to crystallize and form solid bridges between the cores and initial layer of the drug substances and among the successive layer of drug substances or polymer. Continue this process until the desired layer of drug or polymer formed. Consequently conventional coating press, fluidized bed centrifugal granulator of Wurster coater has been used successfully to manufacture pellets.

The most common configuration for bottom spray coating is known as the Wurster system. In this study solution/ layering of neutral pellets has been conducted applying novel fluidized bed technology from .This technology claims to improve the product movement in defined direction in all the equipment by the Disk jet gas distribution plate. Furthermore, a 3 component spray nozzle is used in order to improve the film formation on the pellets due to constant and reproducible drop size distribution.

Accessibility of clogged nozzles without stopping and interrupting the process makes the equipment advantageous in respect to Wurster system. Hüettlin's three component nozzle is an air nozzle with an additional channel through which a second gas or component can be introduced to create a special microclimate around the nozzle which prevents excessive spray drying or clogging of the nozzle.

Such microclimates near nozzle apertures are very useful when a film former with a relatively high minimum film-forming temperature (MFT) issued. The MFT of aqueous shellac suspensions, for example, lies between 35 and 55°C, depending on the plasticizer selected[5].

3) Extrusion

The extrusion operation can be considered to be a specialized wet granulation technique as well as an integral part of the overall spheronization process. Extrusion a method of applying pressure to a mass until it flows through an opening is a technique that determines two dimensions of an agglomeration of particles. Because the cross sectional geometry is defined by the orifice, extrudate length is usually the only dimensional variable. This operation is the major contributing factor in the final particle size of the pellets. The diameter of the extruder screen opening directly controls the diameter of the extrudate.

In this process the wetted mass is passed through the extruder to form rod shaped particles of uniform diameter. The extrudate must have enough plasticity to deform but not so much that the extrudate particles adheres to other particles when rolled during spheronization process. The granulation solvent serves as the binding agent to form the granules and as the lubricating during the extrusion operation**.**

4) Spheronization

The spheronization technology was first introduced by Nakahara in 1964. The formation of pellets during the spheronization operation depends on the formulation of extrudates. The extruded granulation must have the combined characteristics of cohesiveness, firmness and plasticity. This operation has been divided into three stages such as breaking of the cylindrical segments or extrudate, agglomeration of the broken segments and smoothing of the particles.

Breaking of the cylindrical segments occurs due to the interaction of the extrudate with the rotating plate, stationary wall and other extrudate particles. Agglomeration occurs when the small fragments produced during the breaking stage are picked up by the larger granules during smoothing. Spherical particles are created during smoothing stage by generating rotational motion of each granule about its axis in constantly changing planes[6].

5) Melt Spheronization

Melt Spheronization is a process whereby a drug substance and excipients are converted into a molten or semi molten state and subsequently shaped using appropriate equipment to provide solid spheres or pellets. The drug substance is first blended with the appropriate pharmaceutical excipients, such as polymers and waxes, and extruded at a predetermined temperature. The extrusion temperature must be high enough to melt at least one or more of the formulation components. The extrudate is cut into uniform cylindrical segments with a cutter. The segments are spheronized in a jacketed Spheronizer to generate uniformly sized pellets[9].

Advantages

- Neither solvent nor water used in this process. Fewer processing steps needed thus time consuming drying steps eliminated. Uniform dispersion of fine particle occurs.
- There are no requirements on the compressibility of active ingredients and the entire procedure simple, continuous and efficient.
- Good stability at varying pH and moisture levels, do not require additional film coating since the drug release is diffusion controlled. Safe application in humans due to their non-swellable and water insoluble nature.

Disadvantages

- Requires high energy input. The melt technique is that the process cannot be applied to heat-sensitive materials owing to the elevated temperatures involved.
- Lower-melting-point binder risks situations where melting or softening of the binder occurs during handling and storage of the agglomerates.
- Higher-melting-point binders require high melting temperatures and can contribute to Instability problems especially for heat-labile materials.

6) Spherical Agglomeration

Spherical agglomeration, or balling, is a pelletization process in which powders, on addition of an appropriate quantity of liquid or when subjected to high temperatures, are converted to spherical particles by a continuous rolling or tumbling action. Spherical agglomeration can be divided into two categories— Liquid-induced and Melt-induced agglomerations.

Liquid-induced agglomeration

During liquid-induced agglomeration, liquid is added to the powder before or during the agitation step. As powders come in contact with a liquid phase, they form agglomerates or nuclei, which initially are bound together by liquid bridges. These are subsequently replaced by solid bridges, which are derived from the hardening binder or any other dissolved material within the liquid phase. The nuclei formed collide with other adjacent nuclei and coalesce to form larger nuclei or pellets. At this point, coalescence is replaced by layering, whereby small particles adhere on much larger particles and increase the size of the latter until pelletization is completed.

Melt-induced agglomeration

Melt-induced agglomeration processes are similar to liquid-induced processes except that the binding material is a melt. Therefore, the pellets are formed with the help of congealed material without having to go through the formation of solvent-based liquid bridges. If the surface moisture is not optimum, some particles may undergo nucleation and coalescence at different rates and form different sizes of nuclei admixed with the larger pellets. As a result, spherical agglomeration tends to produce pellets with a wide particle size distribution.

7) Spray Drying and Spray Congealing

Spray Drying and Spray Congealing, also known as globulation process, involve atomization of hot melts, solutions, or suspensions to generate spherical particles or pellets. The droplet size in both processes is kept small to maximize the rate of evaporation or congealing, and consequently the particle size of the pellets produced is usually very small.

Spray Drying

The drug entities in solution or suspension are sprayed, with or without excipients, into a hot air stream to generate dry and highly spherical particles. As the atomized droplets come in contact with hot air, evaporation of the application medium is initiated. This drying process continues through a series of stages whereby the viscosity of the droplets constantly increases until finally almost the entire application medium is driven off and solid particles are formed. Generally, spray-dried pellets tend to be porous.

Spray Congealing

This process consists of suspending the particles in a molten coating material and pumping the resultant slurry into a spray dryer in which cold air is circulated. The slurry droplets congeal on contact with the air. The coating agents normally employed is low melting materials such as waxes. The congealing process require higher ratio of coating agents to active material than does the spray drying, because only the molten coating agent constitutes the liquid phase**.**

8) Cryopelletization

Cryopelletization is a process whereby droplets of a liquid formulation are converted into solid spherical particles or pellets by using liquid nitrogen as the fixing medium. The technology, which was initially developed for lyophilization of viscous bacterial suspensions, can be used to produce drug-loaded pellets in liquid nitrogen at -1600°C. The procedure permits instantaneous and uniform freezing of the processed material Owing to the rapid heat transfer that occurs between the droplets and liquid nitrogen. The amount of liquid nitrogen required for manufacturing a given quantity depends on the solids content and temperature of the solution or suspension being processed. The equipment consists of a container equipped with: Perforated Plates A Reservoir Conveyor belt with Transport baffles Storage Container .The perforated plates generate droplets that fall and freeze instantaneously as they come in contact with the liquid nitrogen below. The frozen pellets are transported out of the nitrogen bath into a storage container at - 600°C before drying[9].

RECENT NOVEL TRENDS OF PELLETS

1. They help in preparation of modified release multiple dosage form with different release patterns like immediate and sustained release pattern.
2. They help in taste masking of the drugs which are bitter in taste.
3. They are available as mouth melt pellets.
4. Polymer based pellets for control release pattern of drug.
5. As fast dissolving tablets containing micro pellets.
6. As a self-emulsifying pellets.
7. Gastro retentive floating pellets etc.

This trend of pellets has increased patient acceptance. This novel trends helps in giving the information about the releasing pattern of the drug and its bioavailability of the drug to the systemic circulation of the and how it as increased the patient acceptance of pH sensitive drugs releasing pattern of drugs, taste mask of the drugs, self-emulsification of pellets, and polymer based control release of the drugs, mouth melt pellets etc.

CHARACTERIZATION OF PELLETS

1. Particle size distribution

Particle size distribution should be as narrow as possible. That will ensure minimum variation in coating thickness; facilitate blending process if blending of different of pellets is required. Sieve analysis using sieve shaker is the most widely used method for measuring particle size distribution. Microscopy is direct method for determining particle size distribution. Optical

microscopy and scanning electron microscope are used to measure the diameter of pellets. Patappee.W. 2004 reported the use of vernier callipers to determine the size of pellets.

2. Surface area

The characteristics of pellets, those controlling the surface area, are mainly size, shape, porosity and surface roughness. There are three methods of measuring the surface area of pellets. It can be calculated from the particle-size distribution by measuring/using the mean diameter, since the surface area is equal to πd^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[10].

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 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 (p0-p) versus p/p0 to generate a linear plot where V is the volume of gas in cm^3 adsorbed per gram of substrate at pressure p and p0 is the saturation vapour pressure of liquefied nitrogen at the temperature of the experiment.

3. Porosity

The porosity of pellets influences the rate of release of drugs from the pellets by affecting the capillary action of the dissolved drug. 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.

4. Density

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

5. Hardness and Friability

Hardness and friability determination of pellets is necessary because the pellets have to withstand during handling, shipping, storage and other processing such as coating. The instrument such as

the Kaul pellet hardness tester provide relative harness values and friability of pellets are determined by using Erkewa type tablet friabilator or turbula mixer for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion. Friability can also be determined using fluidized bed with Wurster insert by using stream of air [10].

6. Tensile strength

The tensile strength of the pellets is determined by using tensile apparatus with a 5 kg load cell, the pellets are strained until failure occurs. The load is recorded and the tensile strength is calculated applying the value for the failure load and the radius of the pellets.

CONCLUSION

Development of pelletization has acquired the market of novel drug delivery involving both the controlled as well as immediate release. Due to its simple design, greater flexibility, efficiency of producing spherical pellets and fast processing; it has found a special place in the Pharmaceutical industry. Due to their good technological and biopharmaceutical advantages, pelletization has gained an importance in modern pharmaceutical science.

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