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Emerging Trend in Pelletization Techniques

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Spherical dosage form such as pellets have been used in the pharmaceutical industries for a long time. The manufacturing of pellets has been the subject of intensive research in term of innovative formulation and processing equipment in current scenario. Various advantages of pelletization systems over single-unit oral dosage forms has been proved. More extensive research has focused recently on refining and optimization of pelletization techniques as well as on the development of novel manufacturing approaches that use innovative formulations and processing equipment.

Key Words: Pelletization, Techniques.

INTRODUCTION

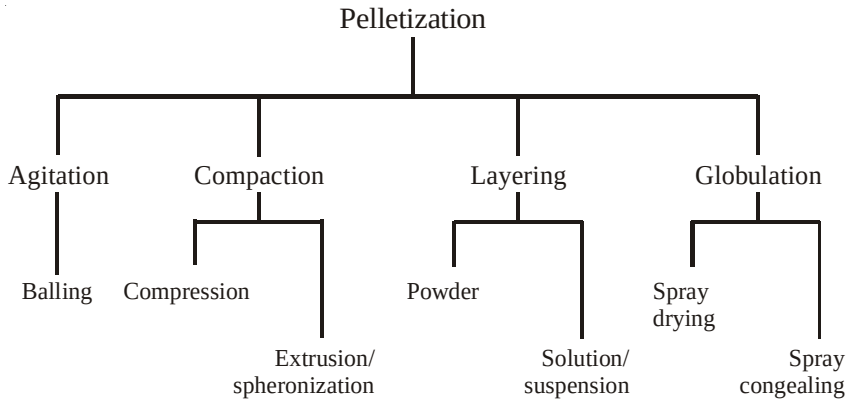
In pharmaceutical sense, pellets can be defined as small, free-flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment. Although pellets have been used in the pharmaceutical industry for more than four decades, it has only been since the late 1970s, with the advent of controlled-release technology, that the advantages of pellets over single-unit dosage forms have been realized.

Pellets offer a high degree of flexibility in the design and development of oral dosage forms. They can be divided into desired dose strengths without formulation or process changes and can also be blended to deliver incompatible bioactive agents simultaneously and/or to provide different release profiles at the same or different sites in the gastrointestinal (GI) tract. In addition, pellets, taken orally, disperse freely in the GI tract, maximize drug absorption, minimize local irritation of the mucosa by certain irritant drugs and reduce inter- and intra-patient variability.

The enormous advantages of multiparticulate systems over single-unit oral dosage forms, extensive research has focused recently on refining and optimizing existing pelletization techniques as well as on the development of novel manufacturing approaches that use innovative formulations and processing equipment[1].

Pelletization processes

The most commonly used and intensely investigated pelletization processes are powder layering, solution/suspension layering and extrusion-spheronization. Other pelletization processes includes spherical agglomeration or balling, spray congealing/drying and emerging technologies such as cryopelletization and melt spheronization[2].



Classification of pelletization process

Powder layering: Powder layering involves the deposition of successive layers of dry powder of drug or excipients or both on preformed nuclei or cores with the help of a binding liquid. Because powder layering involves the simultaneous application of the binding liquid and dry powder and requires specialized equipment. The primary equipment-related requirement in a powder-layering process is that the product container should have solid walls with no perforations to avoid powder loss beneath the product chamber before the powder is picked up by the wet mass of pellets that is being layered on[2].

Solution/suspension layering: Solution/suspension layering involves the deposition of successive layers of solutions and/or suspensions of drug substances and binders on starter seeds, which may be inert materials or crystals/granules of the same drug. In principle, the factors that control coating processes apply to solution or suspension layering and as a result, require basically the same processing equipment. Consequently, conventional coating pans, fluid-bed centrifugal granulators and Wurster coaters have been used successfully to manufacture pellets. The efficiency of the process and the quality of pellets produced are in part related to the type of equipment used[2].

Extrusion-spheronization: Extrusion-spheronization is a multistep process involving dry mixing, wet granulation, extrusion, spheronization, drying and screening. The first step is dry mixing of the drug and excipi-

ents in suitable mixers followed by wet granulation, in which the powder is converted into a plastic mass that can be easily extruded. The extruded strands are transferred into a spheronizer, where they are instantaneously broken into short cylindrical rods on contact with the rotating friction plate and are pushed outward and up the stationary wall of the processing chamber by centrifugal force. Finally, owing to gravity, the particles fall back to the friction plate, and the cycle is repeated until the desired sphericity is achieved[2].

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 temperature, are converted to spherical particles by continuous rolling or tumbling action. Spherical agglomeration can be divided into two categories *i.e.* liquid induced and melt induced agglomeration

Liquid induced agglomeration: In this process liquid is added to the powder before or during the agitation step. As powder comes 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 bridge, 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 coalesces to form larger nuclei or pellets. The coalescence process continues until a condition arises in which bonding forces are overcome by breaking forces. At this point, coalescence is replaced by layering. Whereby small particals adhere on much larger particals and increase the size of the later until pelletization is completed. If the surface moisture is not optimum, some particals may undergo nucleation and coalescences at different rates and form different size of nuclei admixed with the larger pellets. As a result, spherical agglomeration tends to produce pellets with a wide particle size distribution.

Melt-induced agglomeration: It is similar to liquid-induced process except that the binding material is melt. Therefore, the pellets are formed with the help of congealed material without having to go through the formation of solvent-base liquid bridges.

Spray drying and spray congealing: Spray drying and congealing, known as gloubulation processes, involved atomization of hot melts, solution or suspension to generate spherical particle 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 pellets produced is usually very small. During spray drying, 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 automized 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 droplets constantly increased until finally almost the entire application medium is driven off and solid particles are formed. During spray congealing, a drug substance is allow to melt, dispersed, or dissolved in hot melts of waxes, fatty acids, *etc.* and sprayed into an air chamber, where the temperature is below the melting temperatures of the formulations components, to provide spherical congealed pellets under appropriate processing conditions. Because the process dose not involved evaporation of solvents, the pellets produced are dense and non porous.

Cryopelletization: It is a process whereby droplets of 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 liophilization of viscous bacterial suspension, can be used to produce drug-loaded pellets in liquid nitrogen at -160ºC. 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 pellets are dried in conventional freeze driers. The small size of droplets and thus the large surface area facilitate the drying process. The amount of liquid nitrogen required for manufacturing a given quantity depends on the solids contents and temperature of the solution or the suspension being processed. It is usually between 3 and 5 kg per kilogram of finished pellets[2].

Melt spheronization: It is the process whereby a drug substance and excipients are converted into a molten or semimolten state and subsequently shaped using appropriate equipment to provide solid spheres or pellets. The process requires several pieces of equipment such as blenders, extruders, cutters (known as pelletizers in the plastics industry) and spheronizer. The drug substance is first blended with the appropriate pharmaceutical excipients, such as polymers and waxes and extruded at predetermined temperatures. 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 jacked spheronizer to generate uniformly sized pellets.

The spheronizer temperature needs to be high to partially soften the extrudate and facilitate deformation and eventual spheronization. Depending on the characteristics of the formulation ingredients pellets that exhibit immediate or sustained release characteristics can be manufactured in a single step. The pellets produced are unique in that they are monosize, a property unmatched by any other pelletization technique. However, the process is still in the development stage and additional work is needed before the process become a viable pelletization technique[2].

Equipments used in pelletization techniques

The first equipment used to manufacture pellets on a commercial scale was the conventional coating pan, a machine that has been used by pharmaceutical firms. Conventional coating pan, however have significant limitations as pelletization equipment. There are various functions *viz.*, pan shape tilt angle, baffle arrangement and rotation speed, *etc*. must be optimized to provide uniform pellets.

Therefore many new types of equipment have been developed to overcome the limitation of coating pans and revolutionized pelletization. Some of them, which are commonly used, are discussed below.

Tangential spray or centrifugal fluid bed granulator: This equipment was originally developed to perform granulation processes and was later expanded to cover other unit operations including the manufacturing and coating of pellets and is used in powder layering and solution/suspension layering pelletization technique. The basic operational principle includes centrifugal force, fluidization air velocity and gravitational force. During a layering process, three forces act to generate a spiral rope like motion of the particles in the product bed. It contains rotating disc, which create centrifugal force that pushes the particle outward to the vertical wall of the product chamber or stator. The fluidization air generates a force that carries the particle to vertical along the wall of the product container into the expansion chamber. The particle lose their momentum and cascade down towards the center of the rotating disc owing to gravitational force. Aside from the rotating disc, the other unique feature of the centrifugal equipment is the spray method. During layering the liquid is sprayed tangentially to and concurrent with particle movement.

The degree of mixing depends on the fluidization air volume and velocity, the slit width, the bed size and the disc speed. These variables, as well as liquid and powder application rate, atomization air pressure, fluidization air temperature and degree of moisture saturation determine the yield and quality of pellets[3].

Double-walled centrifugal granulator: It is more or less similar to tangential spray or centrifugal fluid bed granulator in terms of principle and design. The only difference is that it is double walled and the process is carried out with the inner wall in the open or closed position. For example 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 into the forming zone. The cycle is repeated until the desired residual moisture level in the pellet is achieved.

Wurster coating process equipment: It is invented about three decades ago, and had evolved through elaborated design modifications and refinements into ideal equipment for the manufacture of pellets by solution/suspension layering. The high drying efficiency inherent in fluid-bed equipment, coupled with the innovative and efficient design feature of the Wurster process, proved to be predictable and economically feasible pelletization equipment.

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 distributor 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 the nozzle and through the partition, carrying with it the particles that are being layered on. Once the particle exits the partition, they enter the expansion chamber, where the velocity of the air is reduced below the entrainment velocity, and the particle fall back to the area surrounding the partition (down bed). The down bed is kept aerated and the particle from the down bed are then transported horizontally through the gap between the air distributor plate and the partition by the suction generated by the high air velocity that prevails around the nozzle and immediately below the partition. Because the spray direction is concurrent with the particle movement and particle motion is well organized under optimum conditions, uniform layering of the drug substance is consistently achieved[2].

Extruder and spherodizer: Extruders are used for converting the powder material into extrudes/granules which subsequently can be converted to spheroids or uniform pellets with the help of spherodizer. A variety of extruders, which differ in design features and operational principles, are currently on the market and can be classified as Screws-fed extruder, gravity-fed extruder and ram extruder.

Screw-fed extruders: It includes screws that rotate along the horizontal axis and hence transport the material horizontally. They may be axial or radial screw extruders. Axial extruders, which have a die plate that is positioned axially, consist of a feeding zone, a compression zone, and an extrusion zone. The product temperature is controlled during extrusion by jacket barrels. In radial extruders, the transport zone is short and the material is extruded radically through screens mounted around the horizontal axis of the screw.

Gravity fed extruders: It includes the rotary cylinder and rotary gear extruders, which differ primarily in the design of the two counter rotating cylinders. In the rotary cylinder extruder, one of the two counter-rotating cylinders is hollow and perforated, whereas the other cylinder is solid and

acts as a pressure roller. In rotary-gear extruder, there are two hollow counter-rotating gear cylinders with counter bored holes.

Ram extruder: In this a piston displaces and forces the material through a die at the end. Ram extruders are preferred during formulation development because they are designed to allow for measurement of the rheological properties of formulation[2].

Future prospectus: Pellets offer a high degree of flexibility in the design and development of oral dosage forms. They can be divided into desired dose strengths without formulation or process changes and also can be blended to deliver incompatible bioactive agents simultaneously and/or to provide different release profiles at the same or different sites in the gastrointestinal (GI) tract.

Conclusion

Pelletization techniques are recent developed techniques for the development of variable drug delivery systems[4]. It is concluded that these techniques will be successful development of multiple-unit tablets for controlled drug delivery of a variety of drugs ranging from good to poor aqueous solubility. As follows: (i) Preparation of multiple-unit tablets of drugs for delayed release extended release, colon release and/or pulsed release[5]. (ii) Production of multiple-unit controlled release tablets such as bilayer or trilayer tablets (iii) Putting together incompatible substances in a single dosage form.

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