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Review Article

PELLETIZATION TECHNIQUES: A LITERATURE REVIEW

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ABSTRACT
In present times, the pelletization technologies are gaining much attention as they represent an efficient pathway for manufacture of oral drug delivery systems. This is due to the reason that pellets offer many therapeutic, technological as well as biopharmaceutical advantages over the conventional oral dosage forms. Pelletization technique enables the formation of spherical beads or pellets with a mean diameter usually ranging from 0.5-2.0 mm which can be eventually coated for preparation of modified release dosage forms. Pelletization leads to an improvement in flowability, appearance and mixing properties thus avoiding generation of excessive dust and reducing segregation, and, generally, eliminating undesirable properties and improving the physical and chemical properties of fine powders. Pellets are produced by various techniques, such as, extrusion/ spheronization, layering, cryopelletization, freeze pelletization, spray congealing, spray drying and compression. Amongst various techniques, Extrusion/Spheronization technique is the most widely utilized technique due to its high efficiency and simple and fast processing. The aim of this paper is to review some general aspects about pellets and pelletization and some common techniques being utilized in the pharmaceutical industry.
KEYWORDS: Pelletization, extrusion, spheronization, cryopelletization.

INTRODUCTION

Pellets

Historically, the word pellet has been used by various industries to describe a variety of agglomerates produced from different and diverse raw materials. Many industries have been utilizing pelletization techniques since the turn of 20th century but pharmaceutical industry started showing keen interest in this technology only in the early 1950s due to increased demand of sustained release preparations. The research scientists of Smith Kline & French realized in 1949, about the potential and developed tiny drug pellets for capsule filling. With the extensive research, more and more faster, efficient and cheaper pelletization techniques were developed[1].

Pellets for pharmaceutical applications are defined as spherical/ semi-spherical, free flowing solid units with a narrow size distribution, typically varying in diameter between 500 and 1500 µm. Due to their various advantages, pellets have gained considerable attention in development of both immediate release and modified release dosage form[2]. The commercially available pellet formulations are mainly coated with a polymer film to obtain a controlled release effect. In the pelletization process there is agglomeration of fine powders of drug and excipients into small spherical units[3-5]. Applications are found in pharmaceutical industry as well as agrochemicals, polymer industry, detergent additives, food industry, sweeteners.

Pellets should possess these ideal properties:

- Spherical shape and smooth surface texture.
- Particle size in range of 500-1500µm.
- The quantity of the active ingredient should be maximum so as to maintain the pellet size.

Advantages of pellets[6-11]

- Improved appearance of product.
- Improved flow properties and ease of packing resulting in uniform and reproducible fill weight of tablets and capsules.
- Improved safety and efficacy of active ingredient.
- Decreased handling hazards and easier transport.
- No crystallization or precipitation of solution and suspensions.
- Decreased hygroscopicity.
- High bulk density.
- Little abrasion and decreased friability.
- Uniform size with narrow size distribution.
- High drug loading capacity without producing extensively large particles.
- When formulated as modified release preparation ,pellets are less susceptible to dose dumping thus lowering the risk of side effects.
- They also reduce accumulation of drugs(irritant to GI mucosa)
- Pellets disperse freely in GIT fluids due to their small size, providing larger surface area for drug absorption and also reduce peak plasma level fluctuations.
- Pellets offer reduced variations in gastric emptying rate and intestinal transit time thus reducing inter and intra subject variability.
- Pelletization can be used for taste masking of unpalatable drugs.
- It can also be used for separation of incompatible drugs and/or excipients. Such ingredients can be formed into pellets and delivered in a single dose after encapsulation.
- In chemical industries, pelletization provides an effective method of avoiding powder dust.

Disadvantages of pellets

- Pellets are rigid and so cannot be pressed into tablets. So they have to be encapsulated into capsules.
- The production of pellets is quite an expensive process due to the requirement of highly specialized equipment and trained personnel.
- The control of production process is difficult. (e.g. the amount of water added and time is critical for the quality of pellets as over-wetting can occur very easily.)

Pelletization

Sometimes, granulation and pelletization terms are used synonymously. If a size-enlargement process produces agglomerates in size range of 0.1-2.0 mm and about 20-50%

porosity, such process may be called granulation. Whereas, Pelletization is a size enlargement process of manufacturing agglomerates with a relatively narrow size range of 0.5-2 mm called pellets.

Pelletization can be defined as an agglomeration process for converting fine powders or granules of bulk drugs or excipients into small, free flowing, spherical or semi-spherical units, referred to as pellets. Pellets are oral dosage forms consisting of multiplicity of small, discrete units, each exhibiting their desired characteristics[12].

Pelletization Techniques

1. Pelletization by extrusion spheronization
2.Drug layering (dry powder layering & solution and suspension layering)
3. Cryopelletization
4. Freeze pelletization
5. Globulation
6. Compression
7. Balling

Extrusion - Spheronisation

Extrusion spheronization technique was developed as a pelletization technique in the early 1960s. For the purpose of formulating controlled or modified release, a consistent smooth surface is required with a narrow size distribution in order to ensure uniform coating and free flowing property. Extrusion spheronization technique can be used to achieve this. The main objective of this technique is to produce pellets/spheroids of uniform size with high drug loading capacity. Extrusion spheronization is a multiple process involving a pre-consolidation stage by extrusion followed by spheronization to produce uniform size spherical particles, called as spheroids, pellets, beads or matrix pellets depending upon material as well as process used. These days this technology has gained attention because of its simple and fast processing and high efficiency. Hence good extrudates will have to possess the desirable attributes to be broken down into regular fragments that can be rounded into pellets of a narrow size distribution.

The method involves the following main steps[2]: (Fig. 1)

Dry mixing of ingredients, to obtain homogenous powder dispersions, using different type of mixers like twin shell blender, high shear mixer, tumbler mixer and planetry mixer[13].

Wet massing, in which powders are mixed to form a sufficiently plastic mass. Mostly planetry mixer is used routinely for both mixing and granulation operations.

Extrusion stage, in which wet mass is shaped into cylindrical segments with a uniform diameter. This stage forms an integral part of overall spheronization process and is the major contributing factor in the final particle size of pellets, the diameter being directly controlled by diameter of extruder screen[14,15]. The extrusion of a suitable moistened powder mass is important to produce plastic yet brittle extrudates which can be broken down by moderate shear forces into regular fragments in the spheroniser. Extrusion process involves applying pressure to a wet mass until it passes through the calibrated openings of a screen or die plate of extruder and further shaped into small extrudate segments which eventually break under their own weight. The extrudates must have enough plasticity in order to deform, but an excessive plasticity may lead to extrudates which stick to each other while collecting and further processing. In order to obtain reproducible results, monitoring of extrusion parameters is necessary, such as: feed rate, powder consumption, die temperature and compression chamber pressure.

Spheronisation stage, in which the small cylinders are rolled into solid spheres. Nakahara was the first to introduce this technology in 1964. The three stages of this operation are breaking of cylindrical segments or extrudate, agglomeration of broken segments and smoothing of particles. The breaking of cylindrical segments takes place due to interaction of extrudate with rotating grooved or smooth plate, stationary wall or other extrudate particles. Spherical particles are created during smoothing stage by generation of rotational motion of each granule about its axis in constantly changing planes. These fragments will subsequently be rounded into pellets as there is adequate surface plasticity under stress for remodeling and yet, the mass is sufficiently cohesive to remain as an entity under the frictional stress during spheronization[14, 15].

Drying of spheroids, to achieve the desired final moisture content. The pellets can be dried at room temperature or elevated temperature in a tray drier/oven or in a fluidized bed drier.

Screening, to achieve the desired narrow size distribution. It is required essentially after manufacturing to avoid pellets having high size polydispersity index[16].

Extrusion And Spheronising Equipments

Extruders

There are many different types of extruders available these days but generally they can be divided into three classes based on their feed mechanisms:

a) Screw-feed extruders (axial or end-plate, dome and radial)
b) Gravity-feed extruders (cylinder roll, gear roll and radial)
c) Piston-feed extruders (ram)

Screw-fed extruders have screws that rotate along the horizontal axis transporting the material horizontally. Axial extruders (Fig.2) have an axially-placed die-plate, consisting of feeding zone, compression zone and an extrusion zone. Radial extruders (Fig.3) have a short transport zone and the screens are mounted around the horizontal axis of the screws.

Gravity –feed extruders consist of rotary cylinder and gear extruders. In the rotary cylinder, (Fig.4) one of the two counter-rotating cylinder is hollow and perforated and the other solid cylinder acts as a pressure roller. The rotary gear extruder (Fig.5) consists of two hollow counter-rotating cylinders with counter bored holes.

Ram extruder (Fig.6) has pistons which displaces and force the material through a die at the end. These can also be used to measure the rheological properties of the formulation so preferentially used in the development phase[17].

Spheroniser

A spheroniser also known as marumizer consist of a static vertical hollow cylinder or stator with a horizontal rotating disk or friction plate at the base. The stator can be jacketed for temperature control. The friction plate acts as the energy provider in the form of interparticulate friction for producing pellets and for controlling the extent of pellet growth. The friction plate has a characteristically grooved surface to increase the frictional forces. The two geometric patterns generally used are, a cross-hatched pattern with groove running at right angle to one another and a radial pattern with grove running radially from the center of the disk[18]. The width of grooves is in general 1.5-2 times the target pellet diameter. The diameter of friction plate is about 20cm in the lab scale equipments and is about 1m in production scale units. The rotational speed can range from 100-2000 rpm but speed in the range of 200-400 rpm is considered optimum.

The spheroniser provides main advantage over other methods of producing pellets due to its capacity to produce spherical pellets of uniform size and high drug content upto 90%.

Drug Layering

The layering process is one of the most well-controlled and straight forward pelletization technique. The process comprises of deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of same material or inert starter seeds. The process of solution/suspension layering consists of preparing a solution or suspension of drug particles and other components in application medium. The dissolved material crystallizes forming solid bridges between the cores and initial layers of drug substance and among successive layers of drug substance and polymer. Process is continued until desired layer of drug or polymer is formed[19]. An important factor that needs to be considered when suspensions are used as opposed to solutions is the particle size of the drug. Micronized drug particles tend to provide pellets that are smooth in appearance, a property that is extremely desirable during subsequent film coating, particularly for controlled-release applications. If the particle size of the drug in the suspension is large, the amount of binder required to immobilize the particles onto the cores will be high, and, consequently, pellets of low potency are produced. The morphology of the finished pellets also tends to be rough and may adversely affect the coating process and the coated product. Moreover, because particles detach easily from the core they are being layered on owing to frictional forces, yield is usually low.

In powder layering method, the binding liquid helps in forming successive layers of dry powder of drug and other components on starting cores by forming liquid bridges which are eventually replaced by solid bridges. In order to achieve the desired pellet size, successive layering of drug and binder solution is continued[20]. The first equipment used to manufacture pellets on a commercial scale was the conventional coating pan, but it has significant limitations as pelletization equipment. The degree of mixing is very poor, and the drying process is not efficient. Other equipments used for powder layering process are: Tangential Spray granulator Centrifugal Fluid Bed granulator.

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 by allowing droplets of liquid formulation such as solution, suspension or emulsion to come in contact with 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 pellets are dried in conventional freeze dryers to remove water or organic solvent. 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. The critical step is droplet formation and is influenced by formulation related variables like viscosity, surface tension and solid content, equipment design and process variables[21]. When it is desirable to have pellets with diameter less than 2 mm the liquid nitrogen should be stirred continuously to prevent agglomeration. This technique may be used to produce drug loaded pellets for immediate as well as controlled release formulation.

Freeze Pelletization

Freeze pelletization is a novel and simple technique in which a molten solid carrier along with a dispersed active ingredient is introduced as droplets into an inert and immiscible column of liquid. There are less process variables involved and also various advantages over other pelletization techniques in terms of quality of pellets and process cost. Pellets with a narrow size distribution can be produced with this technique. Drying is not required as pellets are solid at room temperature. The solid carriers are introduced as droplets in molten state into the immiscible liquid column. Depending on their density with respect to the liquid in the column, the droplets can move either in upward or downward direction and solidify into spherical pellets. The hydrophilic or hydrophobic carriers are melted at a temperature 5-10°C higher than the melting point of carrier solids[22]. Suitable carriers for pelletization are such, which are solid at room temperature having melting point below 100°C so that degradation of active constituent is minimized. Two types of equipments are used. In case of freeze pelletizer I the molten solid carrier are introduced from the upper portion of the column because density of the solid carriers is more than the density of the liquid used in the column and the carriers solidify in the bottom portion, while in case of freeze pelletizer II the molten solid carrier is introduced from the bottom of the column because density of the solid carrier is low as compared to the liquid used in the column and the carrier solidify at the top. For freeze pelletizer I, hydrophilic carrier such as polyvinyl alcohol, polyethylene glycol and low melting point sugars (dextrose, maltose) are used. Suitable liquids for column are low density oil such as mineral oil, vegetable oil, and silicone oil. For freeze pelletizer II, hydrophobic carriers of low density such as glyceryl palmitostearate, glyceryl behenate and glyceryl monostearate are used as solid carriers. Suitable liquids for column are high density hydrophilic liquids such as liquid polyethylene glycol, ethyl alcohol, glycerine and water. For sustained release pellets containing mixture of hydrophilic and hydrophobic solids, liquids that are immiscible with both hydrophilic and hydrophobic molten solids are used as cooling liquid in the column[23].

Globulation

Globulation or droplet formation, consists of two related processes, spray drying and spray congealing, 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 is the process in which drugs in the suspension or solution without excipient are sprayed into a hot stream to produce dry and more spherical particles. This process is commonly used for improving the dissolution rates, hence bioavailability of poorly soluble drugs. 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[1].

Spray congealing is the process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes or fatty acids, and is sprayed into an air chamber where the temperature is kept below the melting point of the formulation components, to produce spherical congealed pellets. 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 are 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. Both immediate- and controlled-release pellets can be prepared in this process depending on the physicochemical properties of the ingredients and other formulation variables[1].

Compression

Compression is one of type of compaction technique for preparing pellets. Pellets of definite sizes and shapes are prepared by compacting mixtures or blends of active ingredients and excipients under pressure. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablet manufacturing[24].

Balling

Balling is the pelletization process in which pellets are formed by a continuous rolling and tumbling motion in pans, discs, drums or mixers. The process consists of conversion of finely divided particles into spherical particles upon addition of appropriate amounts of liquid[24].

CONCLUSION

Though the concept of multiparticulate dosage forms was introduced in the 1950's, but in the past few decades pelletization technology has gained an increased interest within the pharmaceutical industry because of its simple design, high efficiency of producing spherical pellets and fast processing, especially in case of production of multiparticulate oral controlled release dosage forms as compared to granulation. Given 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 equipments. This technology is growing at a fast pace thus creating a challenge for most of the pharmaceutical companies to focus their research on pelletized dosage forms for a wide range of active pharmaceutical ingredients. Extrusion/Spheronization is the most widely used technique as it is a versatile process for producing pellets with useful properties and it also offers various advantages over other pelletization techniques in terms of efficiency, product quality, simple and fast processing. In this review attempt has been done to outline general techniques of pelletization and to assess its importance in the development of multiparticulate drug delivery system.

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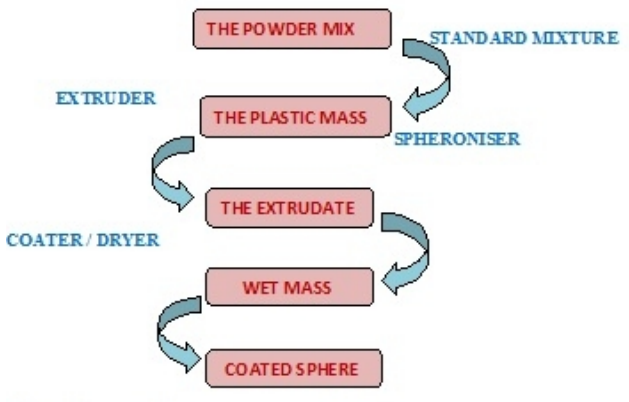

Fig. 1 : Extrusion Spheronization process Layout

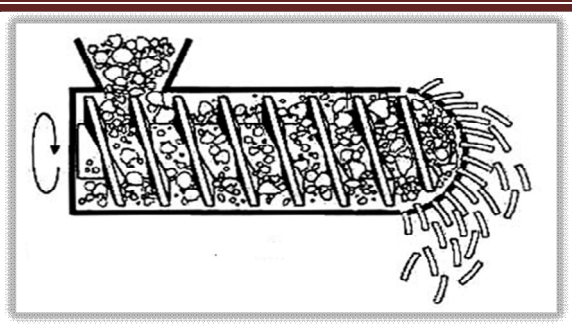

Fig. 2 : Axial - Screw Feed Extruder

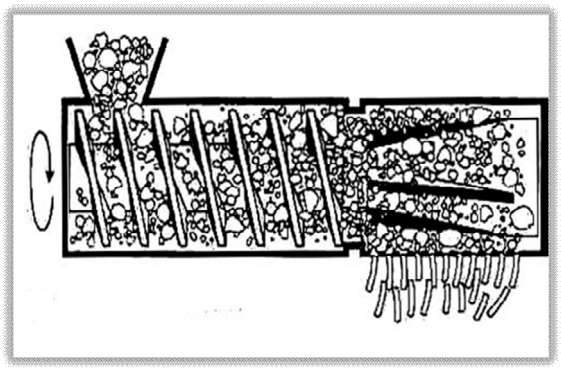

Fig. 3 : Radial – Screw Feed Extruder

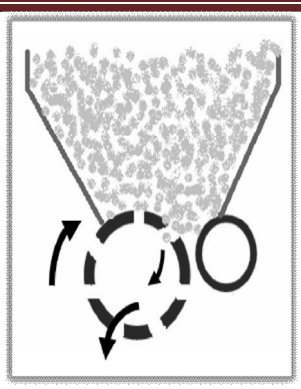

Fig. 4 : Rotary Cylinder Extruder

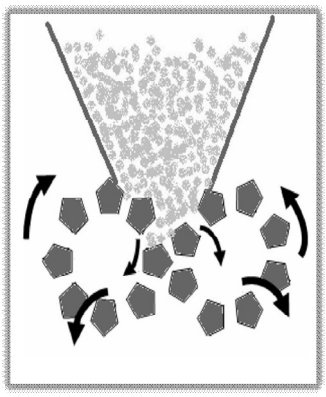

Fig. 5 : Rotary gear Extruder

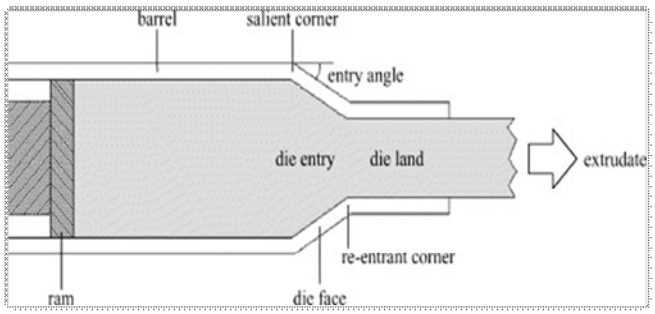

Fig. 6 : Ram Extruder