A Review on The Techniques of Pelletization

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***Abstract*- Over the years, there's a significant rise in the popularity and usage of novel and controlled drug delivery systems. Among them, pellets emerged as a versatile delivery system. Pelletization is an agglomeration technique that converts fine powders or granules of bulk drugs and excipients into small, free flowing, spherical or semi-spherical units, referred to as pellets. This review provides an insight of the techniques used for pelletization which include Extrusion-spheronization, Drug layering, Cryopelletization, Freeze pelletization, Globulation, Compression & Balling along with outlining several advantages & disadvantages of pellets and the factors that affect the pelletization process.**

Keywords: **Pellets, Pelletization, Controlled drug delivery systems.**

INTRODUCTION:

A pellet can be defined as a solid dosage form, agglomerated from various starting materials, which functions as a multiparticulate controlled drug delivery system.

Pelletization is a process of size enlargement wherein the final product obtained has a spherical appearance, with dimensions of 0.5-2 mm and has a reduced intra-agglomerate porosity.[1]

The terms granulation and pelletization are often used synonymously but granules differ from pellets by having a size range of 0.1-2.0 mm and about 20-50 % porosity.

Since the 20th century, technique of pelletization was known. Pharmaceutical industries showed an interest in pelletization in the early 1950s, due to increased requirement for sustained release preparations.[2]

Pellets offer high degree of flexibility throughout design and development of oral dosage forms. They can be divided into different dose strengths without any change in the process.[3]

Pellets can be designed over a long period of time as an immediate release delivery form or in continuous drug release or can also be coated to deliver a drug to a particular gastrointestinal tract site of action.[4]

These can be separated into different dosage strengths without components or process changes and can also be combined to provide incompatible bioactive markers with separate release profiles on the same site or at different sites within the gastrointestinal tract.[5]

In recent years, the popularity of controlled drug delivery systems has risen over conventional dosage forms. Amidst the broad classification of CDDS, multiple unit dosage form poses several advantages over the single unit CDDS.[6]

ADVANTAGES: [7-13]

- Increased aesthetical value.
- Improvement in the Rheological properties (flow properties).
- Uniformity in tablet weight & capsule fill weight is achieved
- Increase in the safety & efficacy of API.
- Handling of powders during the production in the industry is hazardous to the personnel due to the powder dust that is generated which can be eliminated with the usage of pellets
- Transportation is easier
- Decrease in Hygroscopic properties of the contents. (Hygroscopicity refers to the tendency of a substance to absorb moisture).
- Increase in the bulk density.
- Reduced abrasive property.
- Decreased friability.
- Narrow size distribution is achieved.
- High drug loading capability without the production of extensively large particles.
- Pellets are less prone to dose dumping when formulated as a modified release preparation, reducing the likelihood of side effects.
- They also lessen drug accumulation which might cause irritation to Gastro intestinal mucosa.
- Due to their smaller size, pellets are freely distributed in the fluids of GIT, offering more surface area for drug absorption and reducing variations in peak plasma levels.
- Pellets provide reduced inter and intra subject variability by minimising variances in gastric emptying rate and intestinal transit time.
- Pelletization helps in increasing the palatability of unpalatable drugs by masking their actual taste.
- Drugs and/or excipients that are incompatible can be separated with the process of pelletization which are then be encapsulated and administered in a single dose.

DISADVANTAGES:

- The production of pellets requires highly specialized equipment and trained personnel. So it is an expensive process.
- The production process is highly complicated making it difficult to control
- Pellets are rigid and cannot be compressed into tablets. So they have to be encapsulated into capsules.

FACTORS AFFECTING PELLETIZATION:

The process of pelletization is affected by certain factors such as,

1. Moisture content:
   moisture content in the manufacturing system should be properly controlled as the increase in moisture leads to pellet agglomeration.[14]
2. Solubility of API & additives in the granulating fluid:
   The solubility of API & Additives in the granulating fluid that is being used affects the process of pelletization.
3. Composition of granulating fluid:
   For the production of pellets having appropriate quality, 5% of granulating fluid must be water. Isopropyl alcohol is also often used as granulating fluid.[15]
4. Speed of spheronizer & drying temperature:
   The rotational speed of the spheronizer affects the pellet characteristics. High rotational speeds offer excessive sphericity which leads to the decrease in friability. In order to produce a therapeutically efficient product, all the aspects of the process must be strictly monitored including drying.[16]

THE TECHNIQUES OF PELLETIZATION:

Different techniques employed for pelletization are

1. Pelletization by extrusion-spheronization
2. Drug layering (Dry powder layering, Solution & Suspension layering)
3. Cryopelletization
4. Freeze Pelletization
5. Globulation
6. Compression
7. Balling

1. EXTRUSION-SPHERONIZATION

This technique was developed for pelletization in the early 1960s. To achieve uniform coating and free flowing properties while creating controlled or modified release dosage forms, a consistent smooth surface with a small size distribution of pellets is necessary. To do this, extrusion spheronization can be used. This method's primary goal is to create uniformly sized pellets or spheroids with high drug loading capacities.

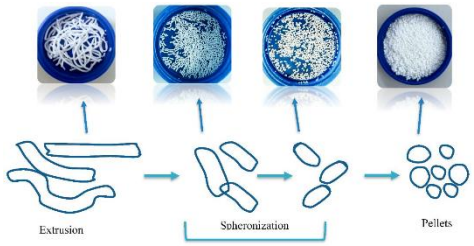

Fig.1: Principle of pellet formation[32]

Extrusion spheronization is a multi - step procedure that involves a pre-consolidation stage by extrusion, followed by spheronization to generate uniform sized spherical particles. Depending on the material and process employed, these particles are referred to as pellets, matrix pellets, spheroids or beads. This technology has recently attracted interest due to its straightforward and quick processing capacity with great efficiency. The character of being broken down into regular fragments that may be shaped into pellets with a narrow size distribution must be present in good extrudates.

The Following are the main steps involved in the method[17]

- Dry mixing

Dry blending of materials with various types of mixers, such as high shear mixers, planetary mixers, twin shell blenders and tumbler mixers to produce homogeneous powder dispersions.[18]

- Wet mixing

In this stage, a sufficiently plastic mass is formed by mixing of powders mostly with the use of planetary mixer which can also be used for granulating operations.

- Extrusion stage

In this stage, cylindrical segments having a uniform diameter are formed from a wet mass of contents. The diameter of the pellets to be prepared is directly influenced by the diameter of the screen of extruder making this stage an integral part of the whole process.[19,20] In order to make plastic yet brittle extrudates that can be broken down into regular fragments by moderate shear pressures in the spheronizer, it is crucial to extrude a properly moistened powder mass. The procedure involves application of pressure onto the wet mass inside the extruder to make it pass through calibrated openings present on the extruder screen to form extrudate segments. The formed extrudates must possess enough plasticity to be able to deform but not in excess which might result

in extrudates sticking to each other while further processing them. It is necessary to monitor several parameters of extrusion such as consumption of powder, feed rate, pressure in the compression chamber & die temperature to get reproducible results.

- Spheronization stage

1964 is the year in which the technology of small cylinders being rolled into solid spheres was introduced by Nakahara. This is called as spheronization. Spheronization includes 3 different stages which are, breaking of cylindrical segments, agglomeration of segments that are broken, particle smoothing. The cylindrical segments break down in the spheronizer by them colliding with the rotating grooved/smooth plate, wall of the spheronizer or surrounding extrudate particles. During the smoothing stage, spherical particles are produced by the rotational motion of each granule about its axis in continuously shifting planes. Then, these particles will be shaped into pellets as under stress, sufficient surface plasticity is present for remodelling them. Yet, the mass possesses adequate cohesiveness to maintain its integrity under frictional stress which is applied onto them while the procedure is being carried out.[19,20]

- Drying of spheroids

In a tray dryer/oven or a fluidized bed dryer, the pellets are dried either at room temperature or at an increased temperature.

- Screening

It is done to attain preferred narrow size distribution. Essentially screening is required after manufacturing to avoid pellets with high size polydispersity index.[21]

Extrusion and spheronization equipment:

- Extruders

Although a wide variety of extruders are available in the market right now, based on the feed mechanisms, extruders can be classified into three groups:

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 huge horizontally aligned screws that rotate along the same axis transporting the material towards the screen/die plate.

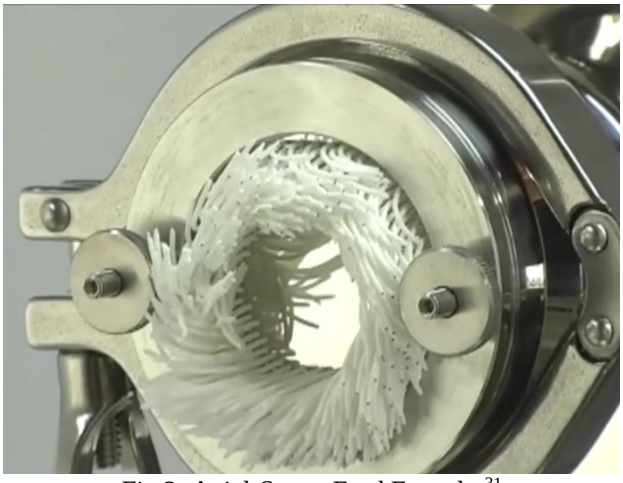

Fig.2: Axial-Screw Feed Extruder[31]

Axial-Screw feed extruders consist an axially-placed die-plate, an extrusion zone, a compression zone, and a feeding zone.

Fig.3: Radial-Screw Feed Extruder[31]

Radial extruders will be having shorter transport zones and screens will be mounted around horizontal axis of screws.
Gravity-fed extruders contain gear extruders and rotary cylinders. Among the two counter rotating cylinders, one is hollow with perforations while the other cylinder is solid and acts as a pressure roller.

Rotary Gear extruder has two counter-rotating hollow cylinders which bear counter bored holes. Ram extruders which consist of pistons forcing the mass out of the die plate at the end are preferential during the development phase because of their ability to measure the rheological/flow properties of the formulation.[22]

- Spheroniser

A spheroniser/marumerizer comprises of a stator (a stator is a vertical hollow cylinder) which can be jacketed for controlling the temperature with a horizontally aligned friction plate present at the base which acts by providing the energy in the form of inter-particulate friction to produce pellets and control the extent of their growth.

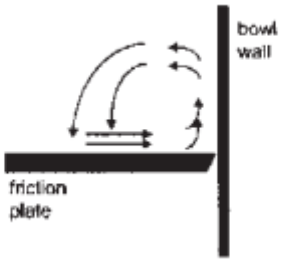

Fig.4: The whirling movement of the particles at the chamber wall

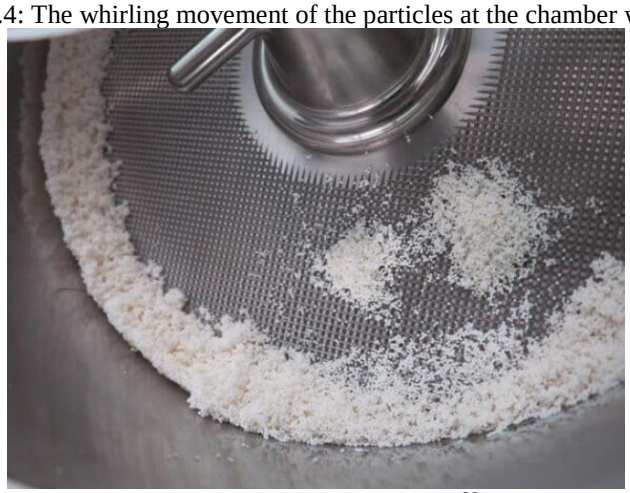

Fig.5: Spheronizing chamber[33]

The friction plates used in the spheronizers consist of characteristic geometrically patterned grooves to increase the frictional forces. Two patters that are used most often are, the cross-hatched pattern, which consists of grooves running at right angles to each other and the radial pattern, in which the grooves run radially on the plate from the centre.[23.] Although these patterns are generally used, none of them have been proved to be better over the other. Usually, the grooves will be having a width of 1.5-2 times the desired diameter of Pellets. About 20cm is the diameter of friction plate in laboratory scale equipment while 1m is their diameter in the production scale equipment. The Rotational speed of the friction plate can vary from 100-2000 rotations per minute but the optimum speed range is considered to be 200-400. Due to the capability of the spheronizer to produce pellets having size uniformity and high drug loading capacity (up to 90%), it is considered advantageous over the other methods available.

2. DRUG LAYERING

Drug layering is one among the most straight forward & well-controlled Technique of Pelletization. The procedure involves depositing successive layers of medicinal substances from solutions, suspensions, or dry powders onto nuclei that could be granules or crystals of same material or inert starter seeds.

The process of solution/suspension layering involves preparation of suspensions/solutions of drugs and other required components in medium of application.

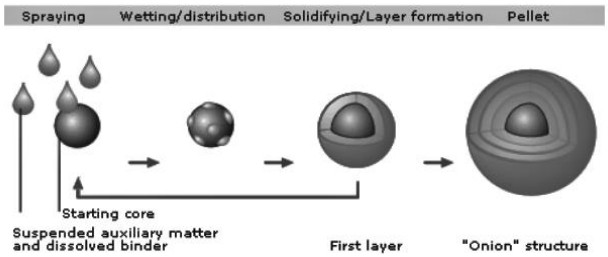

Fig.6: Principle of solution/suspension layering

Between succeeding layers of drug substance and polymer as well as between the cores and first layers of the drug substance, the dissolved material crystallises to form solid bridges. Until the desired layer of drug or polymer is created, the process is repeated.[24.] The Drug's particle size is an important factor that must be considered when suspensions are used rather than solutions. Especially for controlled release, smooth pellets produced by micronized drug particles are highly desired during the subsequent film coating

process. High amounts of binders are required in order to immobilize the particles onto cores if large sized particles are present in the suspensions, which results in productions of pellets that have low potency. The resulting pellets' morphology also has a tendency to be rough, which could have a negative impact on the coating procedure and also the coated product. Additionally, yield is typically low because, due to frictional forces particles easily detach from the core they are being placed on.

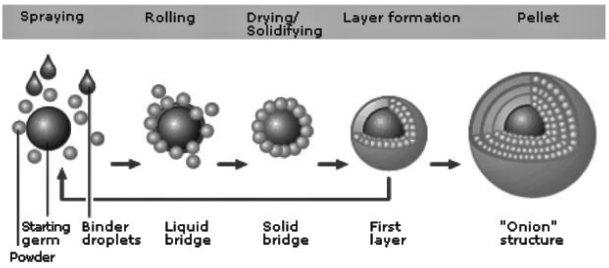

Fig.7: Principle of powder layering

In the method of powder layering, the binder solution creates liquid bridges that are subsequently replaced by solid bridges, assisting in the formation of additional layers of dry drug powder and other components on the initial cores. The drug & binder are successively layered until the required pellet size is obtained.[25]

The equipment often used for the powder layering process of pellets are Tangential Spray granulator & Centrifugal Fluid Bed granulator. Earlier, conventional coating pan was used in the manufacture of pellets on commercial scale but had very significant limitations for their use in pelletization such as poor degree of mixing and inefficient drying process.

3. CRYOPELLETIZATION

Using liquid nitrogen as the fixing medium, cryopelletization is the process by which liquid formulation droplets are transformed into solid spheres or pellets. When droplets of a liquid formulation, such as a solution, suspension, or emulsion, come into contact with liquid nitrogen at a temperature of -1600°C, drug loaded pellets are produced. This technology was originally developed for the lyophilization of viscous bacterial suspensions.

Due to the quick heat transfer that takes place between droplets and liquid nitrogen during the technique, the processed material is frozen instantly and uniformly. To eliminate any remaining water or organic solvent, conventional freeze dryers are used to dry the pellets. A container equipped with perforated plates, a reservoir, a conveyor belt with transport baffles, and a storage container make up the equipment.

Droplets are created by the perforated plates and descend to the liquid nitrogen below, where they instantly freeze upon contact. After being removed from the nitrogen bath and placed in a storage container at -600°C, the frozen pellets are dried. The crucial stage is droplet formation, which is governed by equipment design, process variables, and formulation-related factors like viscosity, surface tension, and solid content.[26]

When pellets with a diameter of less than 2 mm are desired, liquid nitrogen must be continuously agitated to avoid agglomeration. Using this method, drug-loaded pellets for both controlled and quick release formulations can be produced.

4. FREEZE PELLETIZATION

Freeze pelletization process is a novel and straightforward process that involves introducing melted solid carriers and dispersed active ingredients as droplets into an immiscible, inert column of liquid.

In comparison to other pelletization procedures, there are fewer process variables and numerous advantages in terms of pellet quality and process expense. With this method, pellets having a narrow size distribution can be made. Since pellets are solid at room temperature, drying is not necessary.

The solid carriers are added to the immiscible liquid column as molten droplets. The droplets can travel upward or downward depending on their density in relation to the liquid in the column and harden into spherical pellets. At a temperature that is 5–10 °C higher than the melting point of the carrier solids, the hydrophilic or hydrophobic carriers are melted.[27]

The degradation of the active ingredient is minimised by using carriers that are solid at room temperature and have a melting point below 100°C. There are two different kinds of equipment. When using freeze pelletizer I, molten solid carriers are introduced from the top of the column because they have a higher density than the liquid used in the column and solidify at the bottom, whereas when using a freeze pelletizer II, they are introduced from the bottom of the column because they have a lower density than the liquid used in the column and solidify at the top.

Low melting point sugars (maltose, dextrose) and hydrophilic carriers like polyvinyl alcohol and polyethylene glycol are utilised in the freeze pelletizer I. Low density oils including silicone oil, vegetable oil, and mineral oil are appropriate for use in columns.

Hydrophobic low density solid carriers used for the freeze pelletizer II include glyceryl palmitostearate, glyceryl behenate, and glyceryl monostearate. High density hydrophilic liquids such liquid polyethylene glycol, ethyl alcohol, glycerine, and water are suitable for use in columns. Liquids that are immiscible with both hydrophilic and hydrophobic molten solids are employed as the cooling liquid in the column for sustained release pellets with those mixtures.[28]

5. GLOBULATION

Globulation also known as droplet formation, consists two related processes, spray congealing & spray drying. They involves atomization of hot melts, suspensions or solutions to generate small sized spherical particles or pellets. To maximise the rate of evaporation or congealing, the size of the droplet in both of the processes is kept small, and as a result, the particle size of the pellets generated is often quite small.

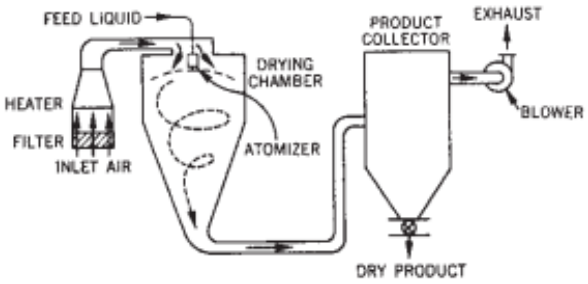

Fig.8: The schematic diagram of a spray-dryer

In spray congealing process, for the production of spherical, congealed pellets, the drug is sprayed into an air chamber having a temperature that is lower than the melting points of the components of the formulation after it is dissolved, melted or dispersed in hot melts of gums, fatty acids, or waxes. In this method, the particles are suspended in molten coating material & the resulting slurry is pumped into a spray dryer with cool air circulating through it. Upon coming into touch with the air, the slurry droplets congeal. Low melting-point substances like waxes are typically used as coating agents. Compared to spray drying, the congealing method requires a larger ratio of coating agents to active material since only the molten coating agent is a liquid phase. Depending on the physicochemical characteristics of the components and other formulation factors, both immediate- and controlled-release pellets can be created using this approach.[29]

6. COMPRESSION

One form of compaction technique for creating pellets is compression. By compacting different mixtures or blends of active substances and excipients under pressure, pellets of specific sizes and forms are produced. The formulations and process factors governing the quality of the resulting pellets are comparable to those employed in the production of tablets.[24]

7. BALLING

When pellets are generated by a continuous rolling & tumbling movement in pans, discs, drums, or mixers, the process is known as balling. When the right amount of liquid is added, the process transforms the finely divided particles into spherical particles.[30]

CONCLUSION:

Pelletization technology is used in producing pellets - a multiparticulate delivery system that possess several advantages over single-unit oral dosage forms. It involves the use of different techniques based on requirements and availability among which extrusion spheronization is the most widely used technique for its ability to produce pellets having good quality in a simple & efficient manner whilst still consuming relatively less time. This review provides you with an outline of the several commonly used pelletization techniques.

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