Review Article

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A REVIEW ON PELLETIZATION TECHNIQUES

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ABSTRACT

Pelletization is novel drug delivery system which converts fine powder particles into pellets. Pelletization has gained great interest in recent years due to various advantages with respect to conventional dosage form, such as dose uniformity, flexibility in dosage form, prevention of dust formation. This review gives information about advantages, disadvantages, desirable properties of pellets, drug selection criteria and growth mechanism and will provide insight about different methods of pelletization, production process which includes granulation, extrusion and spheronization and drying and also discussed about parameters which influences the quality of the pellets followed by coating of pellets. It also gives brief idea about characterization of pellets like particle size distribution, surface area, shape and sphericity, porosity, density, friability, flow property, disintegration, and dissolution of the pellets are explained with various applications of mentioned techniques.

Keywords: Pellets, Pelletization, Parameters, Coating of pellets, Characterization of pellets, Applications.

INTRODUCTION

Pellets are the small; free flowing, spherical or semi-spherical particles and intended typically for oral management by using the agglomerates of fine powders or granules of bulk drugs and excipients using appropriate processing equipment.¹

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.² 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.³ These can be separated into different dosage strengths without components or process changes and can also be combined to provide incompatible bioactive marketers with separate release profiles on the same site or at different sites within the gastrointestinal tract.⁴

Multi particulate dosage forms (MUPS) has gained lots of advantages over single unit dosage form due to their predictable gastric emptying, decrease in dose dumping. Higher distributed and much less possibly to motive neighbourhood irritation.⁵ Pellets are physicochemically and microbiologically stable because of their entrapment of drug into matrix. The MUPS dosage forms are noticeably tamper-evidence. Due to pellets, dust problems can be reduced which may be discovered in tablet production.⁶

Advantages

- Flexibility to the dosage form design and development offered by pelletization.
- Pellets are having less chance to dose dumping.
- Products which are having a fine pharmaceutical elegance those products appearance can be improved.
- In the case of irritating drugs pelletization helps to reduces accumulation of drugs.

- Safety and efficacy of a drug can be improved.
- Pellets reduce changes in gastric emptying rate and intestinal transit time.
- Pellets invariably increase drug absorption, also minimize peak plasma fluctuation and disperse freely in gastrointestinal tract.
- Taste masking problem can be solved by pelletization technique.
- Chemically incompatible products can be fashioned into pellets.⁷

Disadvantages

- Expensive process of production because of highly specialized equipment and trained personnel are required.
- Difficult to control production process.
- Pellets are filled in to a capsule which in turn increases cost.⁸
- Film coating of pellets was destroyed by tableting of pellets.
- The size of pellets varies from formulation to formulation but usually lies between 0.5 – 1.5 millimeter.⁹

Factors affecting Pelletization

• Moisture content

Moisture content within the system of manufacturing of pellets should be nicely maintained growth in moisture contents lead to agglomeration of pellets because of excess of water gift on the floor of pellets.¹⁰

• Solubility of additives and Drug in granulating fluid

Over wetting of device of agglomeration of pellets are due to increase inside the extent of liquid phase. With an increase in wetting liquid boom the plasticity in turn induces sticky mass.

- **Composition of Granulating Fluid**

As a way to produce pellets of appropriate quality it should be 5% of granulating liquid should be water. Isopropyl alcohol is also used as a granulating liquid.¹¹

- **Spheronizer speed and drying temperature**

The speed of the spheronizer impacts the characteristics of pellets, high speed offers excessive sphericity leads to decrease in friability. Variation in pellets length, form and go with the flow will result in distinction physicochemical properties of optimized dosage form like weight variation, mistaken filling and many others, in order to similarly have an effect on the therapeutic efficiency of the delivery gadget. So, proper drying is essential to gain ideal pellets.¹²

Selection criteria for Polymers

Polymers selected for the pelletization should be water insoluble have longer water absorption and retention capability. They have got sufficiently large surface area with cohesiveness for water interplay and formula aspect.¹³ Polymers must have ability to enhance drug release in immediate release pellets.¹⁴ The choice of polymers is purely based on proper dose and production technique.¹⁵ Binders like sucrose, starch, Hydroxypropyl methylcellulose (HPMC) are used to control the sticking of drug on seal coated pellets and give uniform coating on it. Talc is used as a glidant for decreasing the static charges to avoid sticking film coating process.¹⁶ about 2-5% concentration of HPMC is used in total weight of API for immediate release pellets in order to get high quality pellets.¹⁷ Microcrystalline cellulose (MCC) is most widely used excipient for pellets. It provides good plasticity to wet well binding property.

Methods of preparation of Pellets

Agitation

Balling

Balling is also known as spherical agglomeration, bulk powders were converted into spherical pellets by a continuous rolling motion. This process can be performed by addition of proper volume of liquid in to the powder or by exposing it to elevated temperature.¹⁸

Compaction

Compression

Compression comes under the compaction technique used for preparing pellets. Definite size and shaped pellets were prepared by blend of an active ingredients and excipient under pressure or by compacting mixtures.¹⁹

Extrusion / Spheronization

Extrusion, Spheronization was first reported by Reynolds, Connie and Hadley in 1970. It is the most convenient and effective method used in the pharmaceutical industry to obtain uniform sized pellets.²⁰

It is a multistep process which involves four steps as follows

- Granulation (Preparation of wet mass)
- Extrusion (Shaping of wet mass into cylinder)

- Spheronization (Breaking of the extrudates into spheres)
- Drying of pellets.²¹

- **Granulation**

Preparations of the wet mass of the material, most commonly used granulators are planetary mixer and sigma blade mixer.

- **Extrusion**

Wet mass prepared was converted into cylinder force is applied to a mass until it flows out through an orifice to produce the extrudates. Different size and type of extrudates can be used based on the load they can withstand and extrudates quality.²²

- **Spheronization**

The extrudates obtained has to be chopped into pieces and transfer to spheronizer. In spheronization, the cylindrical extrudates obtained are shaped into spherical pellets with uniform length, the shaping process is due to plastic deformation formed debris are damaged into uniform lengths.²³

- **Drying**

Final step is the drying of pellets in an oven or fluidized bed drier to adjust the size, density of the pellets.²⁴

Layering

It is well-controlled pelletization technique. In this process, on the nuclei starter seeds, drug entities from solution, suspension or dry powder are deposited into layers that may be inert materials or crystals of the same substance. They are classified into two categories: Solution or suspension layering and Powder layering. Through solution / suspension layering, the product medium dissolves or suspends drug particles. The droplets impinge on the cores and disperse like poured on the cores uniformly as a solution or suspension. The dissolved material is then crystallized to form bridges between the cores and the drug content. Process has to be carried out until desired layers of drug or polymers are formed.²⁵ In powder layering, formation of successive layers of drug powder and excipient on core with the help of binding liquid. For application of dry powder and liquid simultaneously it requires specialized equipments.²⁶

Globulation

This method consists of spray drying and spray congealing, it involves automation of hot melts, solutions or suspensions to form spherical particle. Droplet length in each approach is kept small to enhance the rate of evaporation.²⁷

- **Spray Drying**

This method is widely used to enhance dissolution rate, it also increases the bioavailability of medications that are poorly soluble. Evaporation of the application medium is caused as the atomized droplets come into contact with hot air. Through a number of stages, the drying system continues until the medium is fully used. Commonly spray-dried pellets have a tendency to be porous.

- **Spray Congealing**

Spray congealing is the process in which drug is allowed to melt, disperse or dissolve in holt melts of gums, waxes or fatty acids

and is sprayed in to air chamber where the temperature is saved to supply round congealed pellets. This process consists of suspending the particles in a molten coating material and pumping the resultant slurry into a spray dryer. Both immediately and control release pellets may be formulated in this process depending on the physiochemical nature of the components.

Cryopelletization

In this method, liquid formulation has kept into liquid nitrogen at -160°C to get frozen particles. At that temperature, Liquid nitrogen behaves as solidifying agent. By using conventional freeze dryers' frozen particles are dried to remove the solvents. Advantage of this method is as it allows instantaneous and even freezing due to rapid heat transfer between droplets and liquid nitrogen.²⁸

Freeze Pelletization

It is the basic and modern production technique of spherical pellets. In this method, solid particles in the molten state are introduced into the liquid medium in which molten solid is immiscible so that it forms droplets in the liquid medium. The droplets then convert into solid spherical pellets at room temperature. This technique offers several advantages than other methods with respect to cost and quality of pellets.^{29,30}

Coating of Pellets

It is a method in which the application of the coating agent by spraying coating solution onto the moving bed of pellets with the simultaneous use of heated air increases solvent evaporation.

The main goals of pellets coating are as follows

- In order to mask the taste, odor and colour of the drug.
- It bypasses the inactivation of drugs in stomach.
- Break in activity of dosing can be elongated.
- It enhances the patient's compliance.
- It enhances the shape and consistency of the dosage form.^{31,32}

Seal Coating

It is one of the methods of coating that is added to the center of the pellets to separate the pellets from the humidity to ensure good product stability. Due to the fact that sealing coat produces sometimes a degree of tackiness during the drying process to avoid using this dusting powder.³³

Film Coating

Surrounding pellets by means of a thin sheet of polymeric material is a present-day process mile. The coating solution is sprayed onto the pellet movement bed followed by drying, which makes it easier to extract the solvent leaving the thin film of coating material around each pellet behind.³⁴

Characterization of Pellets

Particle size distribution

Particle size is determined by simple sieve analysis with use sieve shaker. It is inexpensive, rapid and simple. Sieves are arranged with the course at top. Dried pellets were arranged on top sieve and are mechanically agitated for certain time. The pellets retained on each sieve are weighed. Particle size of the pellets can

also be resolved by optical microscopy. In this method, the diameter of pellets is measured using calibrated micrometers.³⁵

Surface morphology

Scanning electron microscopy determined the surface characteristics of the pellets. The pellets are attached to the aluminum stub, sputter-coated under the argon atmosphere with a thin layer of platinum and screened with SEM (Scanning Electron Microscopy). SEM is also investigated to assess the effect of fillers on pellet quality.³⁶

Surface area

Size, shape, porosity and surface roughness was mainly influenced by surface area of pellets. It is important to determine surface area when film coating is desired as thickness of coating depends on surface area. It is calculated by two methods: method of Gas adsorption and Air permeation method.³⁷

• Gas adsorption method

It is commonly known as BET method (Brunauer, Emmett and Teller). In this method, volume of nitrogen takes up by the substrate in an empty glass bulb is measured at different pressure.

• Air permeation method

It is most commonly used in pharmaceutical industries for specific surface determinations, particularly when the purpose is to monitor batch-to-batch variation. The Fisher sub-sieve sizer is a commercially available tool. Resistance to air flow into a lightweight material plug is the material's surface area. The compression level of the material also affects the flow rate through a plug or bed; it is questionable whether pellet air permeability methods are applicable.³⁸

Pellets Shape

The pellets sphericity is the most important feature. Measuring the bulk by which the particle image projected is diverted from a circle and is determined by the estimated area of the pellets and their circumference 0.5 to 1.5 millimeter must be roundness index for satisfactory grade of pellets. Microscope and stereomicroscope visual inspection of pellets is any other technique by using equation mentioned below shape of pellets can be determined.³⁹

$$S = P^2/12.56 * A$$

A is the area and P is the perimeter of circular tracing.

Porosity

Porosity influences the dissolution characteristics of drug by Influencing dissolved drug capillary activity. It can be determined quantitatively by mercury porosimetry or by using optical microscopy and SEM simultaneously. The sample is placed in the container, degassed, and then completely covered with mercury.

Density

Density of the pellets depends on the change in formulation or process parameters like capsule filling, coating and mixing. Bulk density can be measured using automated tapper while true density can be determined by air-comparison pycnometer. Bulk density indicates the packing characteristics of the pellets

whereas true density shows the effect of compaction. Bulk density is greatly influenced by sphericity of the pellets.⁴⁰

Friability

Friability determination is necessary to check the mechanical strength of the pellets while handling, shipping which result in formation of dust.⁴¹

Tensile strength

This is measured by the use of a 5-kilogram load cell tensile device. Pellets will be squeezed before there is a failure. Additional load is reported, and the tensile strength is determined by adding the value for the pellets loss load and radius.

Crushing strength

The crushing force is the estimate of the load needed to break the pellets while the elastic element is the measurement load needed to start plastic deformation.⁴²

In vitro Dissolution Studies

This test is used to measure the drug release at given time under certain conditions from the given formulation and to determine the relationship between *in vitro* release and *in vivo* absorption. The release process from the dosage form is determined by its polymer and binder structure, the amount of granulating material, the properties of the product and other additives. *In vitro* dissolution studies were performed by using USP Apparatus I or USP Apparatus II.⁴³

Applications of Pelletization techniques

Pellets have varied applications in a number of industries and a progressive use of its may want to acquire maximum profitability.^{44,45}

Taste masking

Pellets are the best product for which an ideal flavour reduction is required. While different techniques were used to mask a drug's bitter taste, such as adding Sweeteners and aromas, filled containers, water-insoluble polymer coating, ion-exchange resin complexing, micro-coating of different polymers. Taste masking problem was solved without affecting the degree of bioavailability with their high surface area.

Immediate release

Pellets are the potential candidate for rapidly dispersible tablets by administration of drugs in pellet form creates an increase in surface area over traditional compressed tablets.

Varying dosage without reformulation

Varied dosage from can be administered without performing reformulation of the product because these pellets are having excellent flow properties, so conveniently used for filling capsules by varying the capsule size.

Pharmaceutical applications

- Controlled release pellets for encapsulation.
- Sustain release pellets / delayed release enteric coated pellets.
- Multi-particulate system.

- Multi- unit erosion system.
- Chemically incompatible formulation can be administered.⁴⁶

Figure 1: Principle of Pellet Formation

CONCLUSION

In Recent years pelletization shows an Active path to the delivery of new drugs for administration of Immediate or managed method of delivery of drugs with both oral and buccal routes. The major disadvantage of pellets is it is time consuming process. Microcrystalline based pellets shows lack of disintegration and prolong drug release. So, different alternatives are used to change drug diffusion and release kinetics. Extrusion spheronization techniques challenge most pharmaceutical companies to develop pelletized dosage forms that are fast growing for a wide range of pharmaceutical active ingredients. There is also a scope for developing new methodologies for characterization of the pellets.

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