Recently used technologies in Pellet Formulation - A Review

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ABSTRACT

Now a day's medication systems that need frequent dosing are always with problems. So there is thrust in the area of pharmaceutical research to develop novel formulations, which will enhance the therapeutic efficacy of the existing drug. The goal of this study is to provide detailed and different techniques of pelletization such as powder layering, suspension and solution layering, globulation, freeze, extrusion - spheronization, cryopelletization etc. It has some merits, demerits and its characterization as a tool in the multipariculate drug delivery system etc. It also gives brief idea about the evaluation of pellets and application of pelletization technique. Evaluation of quality of the pellets is discussed with reference to the size distribution, shape, surface morphology, specific surface area, friability and tensile strength.

Keywords: Pellets, pelletization technique, powder layering, droplet formation, extrusion-spheronization, cryopelletization.

INTRODUCTION

Incorporation of old era medicine into a novel drug delivery system helps to improve its performance in terms of efficacy, safety and improved patient compliance. Existing drug molecule can get new life, thereby increasing its market value. Oral drug administration has been one of the most convenient and widely accepted routes of delivery for most therapeutic agents. It has various merits over other dosage forms as it can be self administered is one of the most important one. Recently and traditionally, oral dosage forms are classified as single unit and multiple unit dosage forms. Multiparticulate dosage forms are receiving an immense attention as alternative drug delivery system for oral drug delivery even though single unit dosage forms have been widely used for decades. The most commonly used pharmaceutical solid dosage forms today include suspension, emulsion, solution, powders, dentifrices, granules, pellets, tablets and capsules, out of which pellets being the most popular dosage form, accounting majorly for all ethical pharmaceutical preparations produced [1, 2].

Pellet is systematically produced, geometrically defined agglomerate obtained from diverse starting materials utilizing different processing conditions. Pellets contain multiples of free flowing, spherical or semispherical solid units which are smaller in size, and are intended mostly for oral administration [3]. The small sterile masses which are obtained from the compression of implants or sterile cylinders are termed as pellets. For the past two decades, pellets made their use promising for are ideal characteristics[4]. Due to free-flowing character of Pellets they are packed easily without any difficulties and hence flexibility in design and development a uniform solid dosage form. The radial shape and a low surface area to volume ratio of pellets made uniform film coating [5,6].

1. POWDER LAYERING TECHNIQUE

It involves the deposition of successive layer of powdered drug and excipient or both on preformed nuclei or core with the help of a binding liquid. During powder layering the binding solution and finely milled powder are added simultaneously to a bed of starter seeds at a pre-determined controlled rate. In initial stages the drug particle are bound to the starter seeds of subsequently to the forming pellets with the help of a liquid bridges originated from sprayed binding liquid. These liquid bridges are replaced by solid bridges derived either from a binder in the liquid medium or from any material. Successive layering of a drug and the binder solution continuous until desired pellet size are reached. The first equipment used to manufacture pellets on commercial scale was the conventional coating pan but it has significant limitation that is the degree of

mixing is very poor and the drying process is not efficient. Throughout the processes it is extremely important to deliver the powder accurately at a predetermine rate and in a manner that maintains equilibrium between the binder liquid application rate and powder delivery rate is not maintained ,over wetting or dust generation may occur and neither the quality nor the yield of the product can be maximized . More over the fines may be generated by inter particle and wall to particle friction and appear in the yield. The above problem can be overcome if the application medium is sprayed on the cascading pellets at the end to increase the moisture level at the pellets surface and facilitate layering of fines on to the pellets. For this purpose now it is equipment like tangential spray granulator and centrifugal bed granulator are used [7].

2. SUSPENSION / SOLUTION LAYERING TECHNIQUE

It involves the deposition of successive layer of solution 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 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. Huettlin'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 issued [8].

3. FREEZE PELLETIZATION

It is a technique in which the droplets are introduced using needles or nozzles or atomizer into the inlet column of liquid and dropped from a certain height, so that droplets remain intact as they fall into the liquid column. The process can be scaled-up by increasing the number of nozzles based on the desired rate of production and they can be static or vibrated electrically. Size of needle gauge ranges from 16-31 depending on the size of the pellets desired. These droplets move either to the top or bottom of the column depending on their density with respect to liquid in the column. Based on the movement of molten-solid droplets, two apparatus are designed. The former Freeze pelletizer I, with an inlet at the top for introducing droplets and these droplets settle at the bottom of the column as the density of the matrix droplet is more than the liquid column. Freeze pelletizer II is used when the carrier droplet density is less than the liquid column which has an inlet at the bottom and the droplets solidify at the top. The column is 24 inches long and made of borosilicate glass. It is divided into two portions; initial portion with a temperature of 25^0C to 100^0C, a region where the droplets are introduced. The second is cooling portion at which the droplets solidify and form spherical pellets; having a temperature 0^0C to -40^0C maintained using cooling mixture such as acetonitrile which is either dry ice or salt-ice. The carriers used should be solid at room temperature and have melting point below 100°C in order to minimize degradation of the active constituent. The molten solid matrices may be hydrophilic or hydrophobic. For freeze pelletizer I, hydrophilic carrier matrices used are polyethylene glycol; polyvinyl alcohol; low melting point sugars like xylitol, dextrose, sorbitol, maltose; water soluble polyoxyethylene derivatives; polyethylenepropylene glycol copolymers; polyethylene oxide derivatives; PEG-PEO derivatives. For freeze pelletizer II, hydrophobic solid carrier matrices used are ; glyceryl dibehenate; ethylene glycol palmitostearate;

cetostearyl alcohol; stearyl alcohol; cholesterol; hydrogenated vegetable oils; phospholipids; lanolin; triglycerides; long chain fatty acids or hydrocarbons and hard fat . In case of hydrophilic carriers, hydrophobic liquid column and for hydrophobic carriers, hydrophilic column is used. For freeze pelletizer I, hydrophobic liquid columns used are low density oils such as silicone oils, mineral oils, vegetable oils, aliphatic long chain hydrocarbons and for freeze pelletizer II, hydrophilic columns such as liquid propylene glycol, glycerin, ethyl alcohol, water are used. These carriers are melted at a temperature 5-10°C higher than the melting point of the carrier solids. 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 18-20. This technique involves less process variables and also offers several advantages like production of non-porous spherical pellets with narrow particle size range which are feasible for further coatings like delayed; colon targeted and sustained release coatings. Since the pellets are solid at room temperature, they do not require drying [9].

4. DROPLET FORMATION

It is also called as globulation. It consists of two related processes, spray drying and spray congealing. Spray drying is the process in which drugs in the suspension or solution without excipients are sprayed into a hot stream to produce dry and more spherical particles. 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. Both immediate- and controlled-release pellets can be prepared in this process depending on the physicochemical properties of the ingredients and other formulation variables [10].

5. EXTRUSION - SPHERONIZATION

The extrusion-spheronization process is commonly used in the pharmaceutical industry to make uniformly sized spheroids. It is especially useful for making dense granules with high drug loading for controlled-release oral solid dosage forms with a minimum amount of excipients. Extrusion spheronization is comprising of following steps.

1) Dry mixing

Dry mixing of all ingredients is done to get homogeneous powder dispersion or mixer using different types of mixers like twin shell blender, high shear mixer, tumbler mixer and planetary mixer [11].

2) Wet massing

Wet massing of powder dispersion is done to produce a sufficient plastic mass for extrusion. This granulation is similar to a conventional wet granulation with the exception of the granulation endpoint. The granulation endpoint is determined by the behavior of the wetted mass during the extrusion operation. The most commonly used granulator is planetary mixer or sigma blade mixer or high shear mixer and Hobart mixer. Typically, planetary mixer is used routinely for both blending and granulation operation. High shear mixer introduces a high amount of energy into the wet mass which is transformed into heat and induces evaporation of granulation fluid. This changes the extrusion behavior of the wet mass. By cooling the granulation bowl may avoid this problem [12].

3) Extrusion

The extrusion operation can be considered to be a specialized wet granulation spheronization process. Extrusion is 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 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 [13].

5) Drying

To get desired moisture content in pellets a drying stage is required. The pellets can be dried at room temperature or at elevated temperature in a tray drier/ oven or in a fluidized bed drier. D.I. Wilson *et.al,.* 2006 studied the effect of mode of drying upon the physical appearance and compaction characteristics of the extrusion–spheronization granules of a microcrystalline cellulose/propyl gallate/water paste. According to their study freeze-drying retained the shape and size of the granules, whereas oven-drying produced roughened granules due to the uneven shrinkage of the wet powders. Compaction of one size fraction indicated that the granule strength differed noticeably, with the oven-dried samples producing tablets of lower void age for a given applied compaction pressure. There was a reasonable correlation between tablet crushing strength and voidage [14]. Major differences were observed in tablet dissolution, with the freeze-dried material exhibiting two-regime behavior and an initial dissolution rate constant an order of magnitude greater than the oven-dried form.

6) Screening

It may be necessary to achieve the desired size distribution, and for this purpose sieves are used. In case of pellets prepared by extrusion spheronization, screening is essentially required after manufacturing, in order to avoid pellets having high size polydispersity index [15].

6. AGGLOMERATION/ AGITATION/ BALLING

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 [16].

a. 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.

b. 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.

7. CRYOPELLETIZATION

It is a process whereby droplets of a liquid formulation are converted into 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 -160^{0}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 - 60^{0}C before drying [17].

8. COMPRESSION/COMPACTION

It is one type of compression technique for preparing pellets. Pellets of definite sizes and shapes are prepared by compacting mixtures or blends of active ingredients and excipients under pressure 48. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablets manufacturing. Influence of formulation and compression parameters on the properties of tablets containing enteric coated pellets and on the integrity of the enteric polymer of the individual pellets often compression [18].

MERITS

Pellets and pelletization techniques has some advantages which are mentioned bellow.

1. Safety and efficacy is more.
2. Development of the appearance of the product which has fine pharmaceutical elegance.
3. It offers flexibility into the dosage form design and development.
4. Pellets improve the flow properties in formulation development.
5. It is used in separation of incompatible drugs.
6. They flow freely and are easy to pack without significant difficulties.
7. Pellets are less susceptible to dose dumping.
8. It reduces accumulation of drugs especially proven advantageous in the case of irritating drugs.
9. It offers reduced variation in gastric emptying rate and intestinal transit time.
10. It disperses freely in alimentary tract and invariably maximizes drug absorption and also reduces peak plasma fluctuation.
11. It solves the problem of taste masking.
12. Coating of pellets can be done with different drugs to enable a pellets release rate.
13. The coating material may be colored with a dye material so that the beads of different coating thickness will be darker in color and distinguishable from those having fewer coats.
14. Surface area of pellets enables better distribution.
15. Chemically incompatible products can be formed into pellets & delivered in a single dose by encapsulating them.
16. It reduces inter and intra patient variability.
17. Help to avoid powder dusting [19].

DEMERITS

1. Controlling the production is difficult process.
2. The production is an expensive process.
3. It requires highly specialized equipment and trained personnel.
4. Due to the rigidity of pellets they cannot be pressed into tablets.
5. Encapsulation is one of time consuming process.

IDEAL PROPERTIES OF THE PELLETS

Pellets have some ideal properties which are beneficial for the human body as far as the dosing concern.

1. Particle size should be in range of 600-1000µm.
2. Good dispensability.
3. Self administration can be done by the patient with fixed dose.
4. Easy to administered.
5. Good flow behavior.
6. Shape should be dumbbell, spherical, cylindrical and smooth and dense surface.
7. The quantity of the active ingredient in pellets should be maximum in order to maintain size of pellet.
8. Compact structure.
9. High bulk density.

PHYSICAL CHARACTRISTICS OF PELLETS

Various physical characteristics of the pellets are a follows;

• Particle size distribution of pellets

The particle size is one of the important characteristics. The sizing of pellets is necessary because it has significant influence on the release kinetics and the compactivity. Particle size determination can be done by following methods.
Simple sieve analysis using sieve shaker.
Vernier caliper.

• Weight distribution of pellets

Sieving method is used to estimate the weight distribution. Sieves were arranged in a nest with the coarsest at the top. A 5 gm sample of the dried pellets is to be placed on the top sieve and subjected to mechanical agitation. The sieve set has to fixed and shaken for 10 mins. The pellets retained on each sieve should be weighed. Frequently, the pellets were assigned the mesh number of the screen through which it passed or on which it was retained. It is expressed in terms of arithmetic mean of the two sieves [20].

• Shape of Pellets

Radial shape of the pellets is the most important characteristics and various methods have been used to determine it. The pellets were mounted on a light microscope fitted to a Camera Lucida and the images of the pellets were drawn manually on a graph paper. The shape factor estimates the amount by which the projected image of particles deviate from a circle and it is calculated by means of the projected area of the pellets and its circumference. For acceptable quality of pellets the roundness index/shape factor should be between 1 and 1.2. For perfectly circular projected image, the shape factor should be 1 while a value of 0.6 describes a particle of good sphericity. Visual inspection of pellets by microscope and stereomicroscope are another method to determine shape of pellets. An angle at which a plane has to be tilted before a particle begins to roll is called to be one plane critical stability, is one of the important methods used for determining shape [21]. The angle of repose is an indirect indication of the circularity of pellets and is calculated by the ratio of double the pile height and pile radius by fixed funnel method measured after a certain amount of pellets are allowed to flow through a specific orifice from a given height.

• Surface morphology

Scanning electron microscopy is used to examine the surface morphology and cross section of pellets. The sampling pellets are mounted onto the aluminum stub, sputter-coated with a thin layer of Platinum using sputter coater under Argon atmosphere, and then examined using SEM. The use of optical microscopy to examine the microstructure of pellet surface. While the SEM pictures collected to observe the influence of different fillers and concluded that MCC and corn-starch gives best quality pellets with smooth surface [22].

•Specific surface area of pellets

Surface area of pellets is directly related with size and shape of the pellets. It is important in the absorption and the diffusion of the excipients and the active constituents too. The knowledge of the surface area is desirable especially if film coating is considered. Knowledge about the surface area is important even in case of uncoated pellets, since drug release is influenced by the surface area.

•Hardness of pellets

The mechanical properties of pellets are important for processing of pelletization. Pellets flake off during handling, shipping, storage coating process and

other unit operations thereby resulting in formation of dust. Variations in the formulation and/or process of pellets, as well as variability in the raw materials, can potentially result in significant variations with hardness of pellets. Hardness of pellets can be determined using Kahl pellet-hardness tester but might not be accurate.

Friability of pellets

Friability of pellets are determined by using Erkewa type tablet friabiliator or turbula mixer for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion and to generate friability index. Friability can also be determined using fluidized bed with Wurster insert by using stream of air [23].

MECHANICAL TESTS

• Tensile Strength

The strength required to give the tense to the pellet is called as tensile strength. It can be determined by using tensile apparatus with a 5 kg load cell, the pellets are strained until failure occurs [24]. The load is recorded and the tensile strength is calculated applying the value for the failure load and the radius of the pellets.

• Crushing strength

The strength or load required to break the pellets is called as crushing strength and elastic modulus of 15 pellets were determined using a Material Testing Machine. The speed of the upper mobile platen fitted with a 1 kN load cell was set at 1 mm/min. Elastic modulus and force–displacement graphs were obtained by a computer system attached to the apparatus [25].

• Density of pellets

Density of pellets can be affected by change in the formulation or process which may affect other process or factors such as filling and packaging characteristic during capsule manufacture and tablet compression, and is determined simply by USP density apparatus. The bulk density of pellets can be measured by using an automated tapper, while the true density of pellets can be determined by an air-comparison pycnometer or by solvent displacement method. Bulk density is indicates the packing properties of pellets or spherical seeds which provide higher bulk densities due to small intraparticle porosities. True density indicates the extent of densification or compactness of pellets [26].

• Porosity of the pellets

The porosity of the pellets influences the release of drugs from the pellets by affecting the capillary action of the dissolved drug. The porosity of the pellets can be measured quantitatively by mercury porositimetry.

• Roughness of the pellet surface

The surface roughness measurements were carried out on the same samples of pellets as those used to measure the diameter. Samples were mounted on a non-reflective black plate, which was placed on an air -bearing table and the surface roughness measured with a laser profilometer [27].

FACTORS AFFECTING PELLETIZATION TECHNIQUE

1. Moisture Content

It is one of the critical parameter for pellet growth in pelletization technique .Moisture in the wet mass bring cohesiveness to the powder so that the wet mass can be extracted and spheronize to give spherical shape[28]. High moisture contents lead to agglomeration of pellets during the process of spheronization which is one of the technique of pelletization due to excess of water in the surface of pellets and low moisture content lead to generation of fines with large variation in size distribution .

2. Rheological characteristics

The rheological condition of the wet mass determines the flow ability in extruder optimum rheological condition leads to good flow ability in order to extrude the wet mass variation in rheology make improper and non-uniform extrusion[29].

3. Solubility of excipients and drug in granulating fluid

A soluble drug get dissolve in a granulating liquid. Thus increasing the volume of liquid phase lead to over wetting of system of agglomeration of pellet sand increase in wetting liquid increases plasticity but induces sticky mass.

4. Speed of the spheronizer

The speed of the spheronizer affects the size, hardness, sphericity and density of pellets, high speed gives high sphericity, lower friability, smooth surface and higher crushing strength.

5. Composition of granulating fluid

Besides water, alcohol, water / alcohol mixture, Ethyl Ether, Dilute Acetic Acid, Isopropyl alcohol is also used as a granulating liquid. According to researcher like Millili and Schwartz, a minimum of 5 % of granulation liquid have to be water in order to produce pellets be water in order to produce pellets containing Avicel pH (101) and theophylline. Some researchers used water and dilute acetic acid in different powder to liquid ratio and concluded that mass fraction can be increased up to 100% by using dilute acetic acid for granulation step in place of demineralized water. Aqueous polymer dispersion containing Eudragit, Hydroxy Propyl Methylcellulose (HPMC), Poly vinyl pyrrilodine (PVP) and Gelatin is used in the moistening liquid [30].

6. Physical properties of starting material

Formulation variable such as type and content of starting material, type of filler and particle size of constituent have the effect on the pelletization process. Quality of pellets depends not only upon composition but also on different grades of the same product. The swelling property of material used in pelletization technique decides the release rate of the drug in pellets [31].

7. Extrusion screen

The quality of the extrudate / pellets is greatly influenced by the characteristics of the orifice of the screen. An increase in orifice dimension resulted in increased mean pellet size. The increase in orifice depth decreased with the presence of water at the extrudate surface, increasing the extrusion force, and then had a negative effect on granulometric distribution and on shape [32].

8. Drying technique and drying temperature

It is important to get proper size, shape and flow of pellets and it must be reproducible and consistent in all the batches. Variation in pellet's size, shape and flow will lead to difference in physicochemical properties of final dosage form like weight variation, improper filling etc, which will further affect the therapeutic efficiency of the delivery system. Wider particle size distribution may lead to variation in the dose of drug delivery. Variation in shape may lead to variation in flow and compressibility.

CONCLUSION

Presented review on the pelletization technology hereby concludes that they are considered as a most promising drug delivery system to have a high existence in the Pharma world. It has scope for different oral immediate or controlled delivery systems. Because of its simple design, high efficiency of producing spherical pellets and fast processing, pelletization has found a special position in pharmaceutical industry and especially in case of production of multiparticulate oral controlled release dosage forms as compared to granulation. This system gain more popularity because of their easy portability improved patience compliance and ease of administration and flexibility in the fabrication as tablets or capsules or packed simply as a single dose packets. They can be applied by both oral and buccal routes. This technology is growing in fast pace challenging most of the pharmaceuticals companies to develop pelletized dosage forms for wide range of active pharmaceuticals ingredients.

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