AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Pelletization Technique In Drug Delivery System-A Review

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ABSTRACT

In present times, the pelletization technologies are giving much attention as they represent an efficient pathway for manufacture of new drug delivery system .It has good advantage over the conventional dosage form. Pelletization technique help in the formation of spherical beads or pellets having a diameter 0.5 -1.5 mm which can be eventually coated for preparation of modified release dosage form . It leads to an improvement in flow ability, appearance and mixing properties thus avoiding for generation of excessive dust and reduces segregation and remove the undesirable properties and improve the physical and chemical properties of fine powder. The aim of this study is to provide detailed and different techniques of pelletization such as powder layering, suspension /solution layering, extrusion and spheronization, cryopelletization, etc. It also gives a brief idea about the evaluation of pellets and application of pelletization technique.

Keywords : Pelletization, Extrusion, Spheronization, Cryopelletization

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Received 11 March 2014, Accepted 15 March 2014

Please cite this article in press as: Chandak R.. *et al.*, Pelletization Technique In Drug Delivery System-A Review. American Journal of PharmTech Research 2014.

INTRODUCTION

Traditionally, pellets have been described as agglomerates that are produced from different types of raw materials. Specifically, with respect to pharmaceutical sector, pellets can be defined as agglomerates of fine powders or granules made up of drugs and pharmaceutical excipients. Pellets range in size typically between 0.5 to 1.5mm and are mostly preferred for oral route of drug delivery. [1-5]

Pellets are the multiple unit dosage forms which can be formulated in the form of suspensions, capsules or disintegrating tablets. The pelletized products can improve the safety and efficacy of the active agent. Pellets have excellent flow and packing properties, resulting in uniform and reproducible fill weight of capsules and tablets [6-11].

Need for pelletization[12]:

- To improve flow, dispersion, solubility, stability and compaction.
- To have less variation in transit time through the GIT than single-unit dosage forms like tablets prepared by granulation and compression.
- To produce pellets of uniform size with high drug loading capacity.
- To prevent segregation and dust.
- Pellets can be compressed into tablets called ‘pelltabs’ and can also be filled into capsules.

Advantages of pellets [13—14]:

- Improved appearance of the product which is having fine pharmaceutical elegance.
- Pelletization offers flexibility into the dosage form design and development.
- Pellets improve the flow properties in formulation development.
- They flow freely and are easy to pack without significant difficulties (resulting in uniform and reproducible fill weight of capsules).
- Pellets are less susceptible to dose dumping.
- It reduces accumulation of drugs especially proven advantageous in the case of irritating drugs
- It improves safety and efficacy of a drug.
- Pelletization is a convenient way to manage the separation of incompatible drugs.
- Pellets offer reduced variation in gastric emptying rate and intestinal transit time.
- Pellets disperse freely in G.I.T. and invariably maximize drug absorption and also reduce peak plasma fluctuation.
- Pelletization solves the problem of taste masking.

- Coating of pellets can be done with different drugs to enable a pellets release rate.
- 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
- In case of immediate Release Products larger surface area of pellets enables better distribution.
- Chemically incompatible products can be formed into pellets & delivered in a single dose by encapsulating them.
- In the chemical industries it is used to avoid powder dusting.
- The most important reason for the wide acceptance of multiple unit products is the rapid increase in popularity of oral pellets dosage forms, Pellets oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time.

Disadvantages of pellets[15]:

- Dosing by volume rather than number and splitting into single dose units as required.
- Involves capsule filling which can increase the costs or tabletting which destroy film coatings on the pellets.
- The size of pellets varies from formulation to formulation but usually lies between 1 to 2mm.

PELLETIZATION TECHNIQUES :

1. Extrusion-spheronization technique or wet mass extrusion.
2. Hot melt extrusion.
3. Layering.
4. Cryopelletization.
5. Balling.
6. Compression
7. Globulation or droplet formation
8. Freeze Pelletization

1.EXTRUSION AND SPHERONIZATION OR WET MASS EXTRUSION[16]:

Extrusion spheronization was developed in the early 1960s as a pelletization technique. 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 a multi-step compaction process comprising of following steps.

I. 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.

II. Wet massing:

This process of powder dispersion is done to produce a sufficient plastic mass for Extrusion. It is similar to the wet granulation method but the granulation and point is determined by the behaviour of the wetted mass during the extrusion operation .The most commonly used granulator is Planetory mixer or sigma blade mixer or high shear mixer and Horbat mixer.

III. Extrusion:

This is a method of applying pressure to a mass until it flows through an opening and determine two dimension of an agglomeration of particles .This operation is the major contributing factor in the final particle size of the pellets. 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.

IV. Spheronization:

This process is used to round up these rod shaped particles in to spherical particle in to spherical particle with narrow size distribution. The instrument used is called Spheronizer where the extrudate is rotated at higher speed by friction plate that breaks the rod shaped particles in to smaller particles and rounded them to form spheres.

V. Drying:

In order to get desired moisture content in pellets a drying stage is required the pellets are dried at room temperature or at a elevated temperature in a tray dryer or in a fluidized bed dryer, according to DI. Wilsom et. Al, 2006 freeze drying method retains the shape and size and the granules whereas the oven drying produce rough granules.

VI. Screening:

It is necessary to achieve the desired size distribution and for this purpose sieves are used. Based on the type of feed mechanism and to transfer the mass towards the die, Variety of extruders is used in the above mentioned technique. These extruders are classified in to following classes

Screw fed extruders:

The screw rotates along the horizontal axis and hence transports the material horizontally.

They may be of two types:

Axial screw extruders

These have a die plate that is positioned axially, consist of a feeding zone, a compression zone, and an extrusion zone.

Radial screw extruders

The transport zone is short, and the material is extruded radially through screens mounted around the horizontal axis of the screws.

Gravity-fed extruders:

These are of two types, which differ primarily in the design of the two counter-rotating cylinders.

The Rotary Cylinder

One of the two counter-rotating cylinders is hollow and perforated, Where as the other cylinder is solid and acts as a pressure roller.

Rotary-Gear Extruder

There are two hollow counter-rotating gear cylinders with counter bored holes.

Ram Extruders:

This is probably the oldest type of extruders; a piston displaces and forces the material through a die at the end. These extruders are preferentially used in the development phase, because they can also measure the rheological properties of formulations.

Marumerizer:

It consists of a two parts:

Static cylinder or stator

Rotating friction plate.

A typical friction plate has a crosshatch pattern, where the grooves intersect at a 900 angle. The rotational speed of the friction plate is variable and ranges from 100 to 2000 rpm; depending on the diameter of the unit. Spheronizer friction plate with a crosshatch pattern.

2. HOT MELT EXTRUSION:

Hot melt extrusion is most widely used processing technique in plastic, rubber and food industry. It is used in pharmaceutical industry for developing formulation of sustained release, controlled release, transdermal and transmucosal drug delivery systems[17-21].

This method was developed in order to eliminate the stability problems associated with extrusion-spheronization process and during storage due to presence of water. Extrusion is a method of converting raw material into a product of uniform shape and density. It is done by forcing the raw materials through the die under controlled conditions of temperature, mixing, feed rate and pressure[22-24].

Hot melt extrusion process consists of three basic steps: melting or plasticizing of solid material, shaping of melted material and finally solidification into desired shape. Hot melt extrusion equipment consists of material feed hopper, extruder inside a heated barrel, and a spheronizer. The hopper stores the material and feeds into the extruder containing heated barrel and a rotating screw. Jacketed, high shear mixer is used to perform spheronization where in certain components of formulation are melted to obtain spherical particles.

This method is similar to wet granulating except that the binder will be in molten state. Hence it does not require any solvent to liquefy it [25-26].At first, drug substance is mixed with suitable excipients like polymers and it is extruded at predetermined temperature. Then, the extruded material is spheronized at a temperature high enough to soften it partially facilitating its deformation and eventual spheronization.

Single screw extruder is most often used due to its low cost, ruggedness and reliability. The material which is used to disperse the drug is called as thermal carrier or binder. Polymers or low melting point wax like polyethylene glycol, poloxamer 188, gelucire 50/13,beeswax, carnauba wax, paraffin wax, and microcrystalline wax can be used as a thermal carrier. Carrier gets transform into molten state in the course of processing. The heat generated by the screw due to friction is sufficient to melt the carrier. The physico-chemical characteristics of the carrier hold a major cause on the drug release characteristics. Mechanism of drug release is by diffusion of drug from the dosage form containing water insoluble polymers and waxes like ethyl cellulose or carnauba wax and it is both diffusion and erosion for water soluble polymers like hydroxyl propyl cellulose[27-32].

3. LAYERING [33-39]:

Layering process is the most well-controlled pelletization technique. In this method, drug entities from solution, suspension or dry powder are deposited into layers on the nuclei/ starter seeds which may be inert materials or crystals of same material. They are classified into two categories: solution or suspension layering, and powder layering.

In solution/suspension layering:

Drug particles and other suitable excipients are dissolved or suspended in the application medium. The droplets impinge on the cores and evenly spread as solution or suspension as sprayed on the cores. Then it is dried to crystallize the dissolved material to form bridges between the cores and initial layer of drug substance and among successive layers of drug or polymer. The process is continued until the desired layers of drug or polymers are formed.

In powder layering :

Binding liquid helps to form successive layers of drug powder and other excipients on starting cores. It generally requires specialized equipment as it involves application of dry powder and liquid simultaneously. Micronizing or fine milling or drug before layering improves the efficiency. The equipments which are used in powder layering process for pellets formation are tangential spray (rotor pellet coating) or centrifugal fluid bed granulators.

At the beginning, conventional pan coaters were used for drug layering pelletization process. But the use of conventional pan coaters is not economical as it involves high labor costs and time consumption.

Fluidized bed processors are recently used for pelletization. It performs various processes like coating, drying, granulation and pelletization. It has highly efficient drying system and continuous coating is achieved. It is an ideal method for control release film coating, pellet granulation and hot melt coating. In this method, particles are fluidized and are coated by spraying the coating fluid on the particles and dried. There are different types fluidized bed processors: top spray coating, bottom spray coating (wurster coating), and tangential spray coating (rotor pellet coating).

4. CRYOPELLETIZATION [40-41]:

This technique was initially developed to lyophilize viscous bacterial suspensions. In this method, liquid formulation such as solution, suspension or emulsionis dropped into liquid nitrogen at -1600c to get frozen particles. At that temperature, Liquid nitrogen behaves as solidifying agent. The frozen particles are then freeze dried in conventional freeze dryers to remove water and organic solvents. The amount of liquid nitrogen required depends on the solid content and temperature being processed. This method is advantageous as it allows instantaneous and even freezing due to rapid heat transfer between droplets and liquid nitrogen.

The equipment consists of container filled with liquid nitrogen reservoir above which perforated plate is placed. The conveyor belt of variable speed is immersed in the reservoir. The most critical step in this process is droplet formation which depends on the formulation variables like viscosity, surface tension, solid content, equipment design and other processing variablesx.

5. 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 the addition of appropriate amounts of liquid.

6. COMPRESSION [42]:

Compression is one 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.

7. GLOBULATION OR DROPLET FORMATION:

Globulation or droplet formation involves two related processes namely, spray drying and spray congealing.

Spray drying:

In this method, drugs in suspension or solution form are sprayed into hot stream of air to generate dry spherical particles. It is usually applied in development of controlled release systems, in the improvement of bioavailability of poorly soluble drugs.

Spray congealing:

In this process, the drug is allowed to melt and it is then dispersed or dissolved in hot melt of waxes, gums or fatty acids etc. The resultant dispersion is then sprayed into air chamber, whose temperature is lower than the melting point of formulation components, to get spherical congealed pellets. It is employed in development of both immediate release and sustained release pellets.

8. FREEZE PELLETIZATION [43-44]:

It is the simple and new method of producing spherical matrix 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 method offer several advantages than other methods in terms of cost and quality of pellets and it involve less process variables. Since pellets are solid at room temperature, it does not require drying.

EXCIPIENTS FOR PELLETS[45-49]:

Active pharmaceutical ingredient:

The different drugs can be used to develop immediate release, sustained release pellets with diversified applications in different areas. Pellets can be formulated with the drugs that can be delivery even subcutaneously and intramuscularly depending on the size variations where the size range is maintained below 600 microns and are called as micropellets.

Binder:

Binder are adhesive materials that can be incorporated into pellet formulations to bind powders and maintain integrity on pellet formation and the addition of the binder may be as a solution than the dry form. The binders are commonly used in the range of 2-10%w/w or v/v.

Spheronizing Enhancer:

Spheronization enhancers are formulation aids that improve the production of spherical pellets, mainly during spheronization and balling processes. They not only impart plasticity onto the formulation, but also impart binding properties that are essential for pellet strength and integrity.

Filler:

These are the excipients used to form the bulk of the material, in the process of pelletization 70 to 80% of the excipients is formed by fillers. Generally microcrystalline cellulose is used for this purpose. Avicel PH 101 is considered to be the pelletization aiding excipient in this process. Glyceryl mono stearate, Starch RX1500, spray dried lactose.

Plasticizer:

Plasticizers improve the flexibility of polymers by reducing the tensile strength and glass transition temperature of the material. The flow of polymer will be improved with the use of plasticizer that enhances the strength of the polymer. Glycerol, Propylene glycol, polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate are some of the commonly used plasticizer excipients.

Lubricant:

Lubricants are use reduces the friction between the die wall and material mix either during the compression process or in ejection phase. They also play a significant role in smooth discharge of the pellets from the Spheronizer.

Separating Agents:

Separating agents are materials which are adsorbed on the surface and promote the separation of pellets into individual units during a pelletization process, which are incorporated initially in the formulation or externally during processing to prevent pellets attracting one another due to surface charge development during the process..

Surfactant:

Surfactants are added to the liquid to improve wettability by lowering the interfacial tension between the liquid and drug particles60. Surfactants help to weaken the liquid bridges and results in more friable pellets.

pH adjusters:

The pH adjusters are substances that are incorporated in pellet formulations which influence the microenvironment of drug molecules used for many reasons. Generally acid-labile drugs are protected from the pH conditions of the GIT by giving an enteric coating. Buffer systems may also be added to the core formulation to maintain the stability of core in a favorable range.

Release modifiers:

These are the substances, used in preparation of cores, which modify the release of drug from pellets in dissolution process. Generally, water soluble low molecular weight substances, surfactants and disintegrants may be incorporated to enhance the release rate of drugs, while water insoluble polymers, hydrophobic substances and hydrophilic polymers, which swell and form gel are used to retard the release

FACTOR AFFECTING PELLETIZATION TECHNIQUE[50-55]:

1) **Moisture Content :**

It is one of the critical parameter for pellet growth in pelletization technique. 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) **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.

3) **Composition of Granulating Fluid :**

Besides water, alcohol, water / alcohol mixture, Ethyl Ether, Dilute Acetic Acid, Isopropyl alcohol is also used as a granulating liquid. 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.

4) **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 composition but also on different grades of the same product .

5) **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.

6) **Drying technique and drying temperature :**

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. Variation in shape may lead to variation in flow and compressibility.

7) Extrusion Screen :

The quality of the 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.

EVALUATION OF PELLETS [56-60]:

Particle size distribution:

Particle size distribution should be as narrow as possible. That will ensure minimum variation in coating thickness. Sieve analysis using sieve shaker is the most widely used method for measuring particle size distribution. Microscopy is direct method for determining particle size distribution. Optical microscopy and scanning electron microscope are used to measure the diameter of pellets.

Surface area:

Surface area of pellets depends on the size, shape, porosity and surface roughness. It is important to determine surface area when film coating is desired as thickness of coating depends on surface area. It is also important in case of uncoated pellets as drug release depends on surface area of the pellet. It is determined by 2 methods: gas adsorption method and air permeation method.

Air permeability methods are widely used pharmaceutically for specific surface measurement, especially to control batch to batch variations. The principal resistance to the flow of a fluid such as air through a plug of compacted material is the surface area of the material

Gas adsorption method (commonly known as the BET method) was developed by Brunauer, Emmett and Teller (1937). In this method the volume of nitrogen that is adsorbed by the substrate contained in an evacuated glass bulb is measured at different pressures.

Porosity:

The porosity of pellets influences the rate of release of drugs from the pellets by affecting the capillary action of the dissolved drug. The porosity of the pellets can be measured qualitatively by scanning electron microscopy (SEM) and quantitatively by mercury porosimetry ,optical microscopy and scanning electron microscopy together with image.

Density:

The density of pellets can be affected by changes in the formulation and/or process, which may affects other processes or factors, such as capsule filling, coating, and mixing. The bulk density of the pellets can be measured by an automated tapper. The true density of pellets can be determined by an air-comparison pycnometer, a helium pycnometer or by the solvent displacement method.

Hardness and Friability:

Hardness and friability determination of pellets is necessary because the pellets have to withstand during handling, shipping, storage and other processing such as coating. The instrument such as the Kaul pellet hardness tester provide relative harness values and friability of pellets are determined by using Erkewa type tablet friabilator or turbula mixer for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion.

Tensile strength:

The tensile strength of the pellets is determined by using tensile apparatus with a 5 kg load cell, the pellets are strained until failure occurs. The load is recorded and the tensile strength is calculated applying the value for the failure load and the radius of the pellets.

Sphericity:

Pellets of optimum size are taken, stained with dye solution in a petridish and dried on a hot air oven. Each pellet is recorded using camera lucida fixed to an optical microscope.

Cushing strength:

The crushing strength (the load needed to break the pellets) and elastic modulus pellets (850–1000mm size fraction) are determined using a Material Testing Machine. Elastic modulus and force–displacement graphs are obtained by a computer system attached to the apparatus.

APPLICATIONS[61-62]:

Taste masking:

The pelletization technique solves difficult taste masking problem while maintaining a high degree of bioavailability due to their high surface area, especially for oral products.Many products, such as antibiotics (clarithromycin, roxithromycin and cephelexin) and anti-inflammatory drugs with a bitter taste, can now be formulated in products with high patient compliance,

Immediate release:

Administering drugs in pellet form leads to an increased surface area as compared to traditional compressed tablets and capsules which would considerably reduce the disintegration time and

have the potential for use in rapidly dispersible tablets.

Sustained release:

The pellet form provides a smoother absorption profile from the gastrointestinal tract as the beads pass gradually through the stomach into the small intestine at a steady rate

Chemically Incompatible Product:

In the compressed tablet dosage form separate tablets would have to be administered, but the pellets can be administered in a single capsule.

Varying dosage without reformulation:

Pellets have excellent flow properties, due to this, they can be conveniently used for filling capsules and the manufacturer can vary the dosage by varying the capsule size without reformulating the product.

CONCLUSION:

Pelletization lays the scope for different oral immediate or controlled delivery system. Due to its simple design, efficiency of producing spherical pellets and fast processing; it has found a special place in the Pharmaceutical industry. Also Pelletization technique produces more spherical pellets and offers more advantages than granulation process. In addition, hot-melt extrusion method has provided a new, wider platform to produce spherical pellets of drugs which are not stable or have compatibility problems in presence of solvents.

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