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Pelletization Techniques for Oral Drug Delivery

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ABSTRACT
Multiparticulates are discrete particles that make up a multiple unit system. Although pellets have been used in the pharmaceutical industry for more than four decades, with the advent of controlled release technology, that the full impact of the inherent advantages of pellets over single unit dosage forms have been realized, not only has focused on refining and optimizing existing pelletization techniques, but also focused on the development of novel approaches and procedures for manufacturing of pellets. The present review outlines the manufacturing and evaluation of pellets. The manufacturing techniques include layering, cryopelletization, freeze pelletization, extrusion spheronization and hot melt extrusion have been discussed. Characterization of pellets is discussed with reference to the particle size distribution, surface area, porosity, density, hardness, friability and tensile strength of pellets.

Keywords: Multiparticulates, pelletization, freeze pelletization, cryopelletization, extrusion spheronization.

INTRODUCTION

Historically, the word pellet has been used by a number of industries to describe a variety of agglomerates produced from diverse raw materials. In the pharmaceutical industry, pellets can be defined as agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration. [4, 8, 10, 12]

The pelletized products can improve the safety and efficacy of the active agent. These multiple-unit doses are usually formulated in the form of suspensions, capsules or disintegrating tablets, showing a number of advantages over the single-unit dosage system. [3, 12, 13, 15] In multiple-unit systems, the total drug dose is divided over many units. Failure of a few units may not be as consequential as failure of a single-unit system. This is apparent in sustained release (SR) single-unit dosage forms, where a failure may lead to dose-dumping of the drug. [4, 6]

When multiple-unit systems are taken orally, multiparticulates are released into the gastrointestinal tract and are less dependent on gastric emptying than single-unit systems. [11] Their small size allows them to pass through the pyloric sphincter easily. This reduces intra- and inter- subject variation in gastrointestinal transit time. [5-6] Their small size also enables them to be well distributed along the gastrointestinal tract, improving absorption and reducing the irritant effect that single-unit systems may cause to the mucosal lining, especially if lodged for a prolonged period at a particular site. [7]

Pellets offer a great flexibility in pharmaceutical solid dosage form design and development. They flow freely and pack easily without significant difficulties, resulting in uniform and reproducible fill weight of capsules and tablets. [2, 4, 9, 14, 17] Successful film coating can be applied onto pellets due to their ideal spherical shape and a low surface area-to-volume ratio. [15] Pellets composed of different drugs can be blended and formulated in a single dosage form. This approach facilitates the delivery of two or more drugs, chemically compatible or incompatible, at the same sites or different sites in the gastrointestinal tract. Even pellets with different release rates of the same drug can be supplied in a single dosage form. [4, 12]

Variety of techniques is available for pellet manufacturing. Layering processes have been used over the years. Those processes have some limitations such as non-uniformity in the size of the pellets and less drug loading. In recent year's extrusion-spheronization, cryopelletization, freeze pelletization and hot melt extrusion have been used to produce spherical pellets. This article reviews these pelletization techniques in detail.

LAYERING

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Layering processes are probably the most well controlled and straight forward pelletization techniques. The layering process comprises the deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of the same material or inert starter seeds. They are classified into two categories: solution/suspension layering and powder layering. [4, 20]

In solution/suspension layering drug particles and other components are dissolved or suspended in the application medium. The droplets impinge on the started seed 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 substance and among the successive layers of drug substance or polymer. Continue this process until the desired layers of drug or polymer formed. [4, 12, 16, 20] [Fig. 1] depicts principle of solution and suspension layering process.

In powder layering the binding liquid helps to form successive layers of dry powder of drug and other components on starting cores. In this technique the drug particles are bound to the starter seeds and subsequently to the forming pellets with the help of liquid bridges originated from the sprayed binding liquid. These liquid bridges are eventually replaced by solid bridges derived either from a binder in the liquid medium or from any material. Successive layering of the drug and binder solution continues until the desired pellet size is reached. [4, 13, 16, 18] Fig. 2 depicts principle of powder layering process.

The most commonly used equipments for layering are the standard or conventional coating pans and fluidized bed granulators (bottom spray, top spray and tangential spray). [4]

Conventional pan coaters have been used from the very beginning of the history of drug layering pelletisation. From the economic point of view, however, use of conventional pan coaters is not very reasonable due to the higher labour costs and time consumption, and lower yield. An important disadvantage of pan coaters is the shortage of process control. [12, 17] More recently modified forms of pan coaters have been developed, which resolves many of the drawbacks related to the old system. [21]

Fluidized bed processor

Fluidized bed processor is a equipment that can perform multiple functions like coating, drying, granulation and pelletizing. It has highly efficient drying system and uniform, continuous product coating achieved. [21] Ideal for a wide range of process applications includes coating, heating, drying, agglomeration and granulation. [19] Protects product against moisture, light, air. [19] Ideal for control release film coating, pellet granulation and hot melt coating. Applied to Specific manipulation of the particle surface characteristics.

With fluid bed coating, particles are fluidized and the coating fluid sprayed on and dried. Small droplets and a low viscosity of the spray medium ensure an even product coating.[19,23,24] Different types of fluidized bed processors include top spray coating, bottoms spray coating (Wurster coating) and tangential spray coating (Rotor pellet coating). [Figure 4] depicts the types fluid bed processors.

Top spray coating

This process is used to spray binder solution for powder granulation. Particles are fluidized in the flow of heated air, which is introduced into the product container via a base plate. The binder solution is sprayed into the fluid bed from above against the air flow (counter current) by using nozzle. Air volume is adjusted to have the center of the particle stream very close to the nozzle. Drying takes place as the particles to move upwards in the air flow. It is preferred when a taste masking coating is applied, additionally suitable for the application of hot melt coating. Continuous spray coater is particularly suitable for protective coatings/ color coatings. [19, 23, 24]

Bottom spray coating

The process is suitable for pellet suspension coating or film/sugar coating, particularly useful for a control release active ingredients. In this process, a complete sealing of the surface can be achieved with a low usage of coating substance. When the hot air flows through the bottom screen of container and coating column, it will generate the siphonage principle. Convection is created through the strong force from bottom toward top. The granules will then fall down and will be sucked into the coating column again, while the bottom spray gun will spray towards top to achieve coating purpose. As the particles continue traveling upwards, they dry and fall outside the Wurster tube back towards the base plate. Preferred for the application of modified release coatings to a wide variety of multi particulates and also suitable for drug layering when the drug dose is in the low to medium range. [19, 23]

Tangential spray coating (Rotor pellet coating)

This process is particularly suitable for pellet powder coating, suspension coating or film/sugar coating. In this process the cores are placed on the turntables and hot air is blown upward between the turntables and the granulation area. The passage of air causes the cores to roll on the turntables. At the same time, the coating solution is sprayed on the rolling cores through the pump and spray gun. The process involves simultaneous coating and drying of the cores, layer after layer, until the repeated actions achieve the desired coating thickness or granule size. It is suitable for the application of modified release film coatings to a wide range of multi particulate products, ideal for drug layering when the dose is medium to high and also useful as a spheronizing process for producing spheres from powders. [19, 22, 23]

Formulation

Optimization of process variables is critical for the successful development of a pelletized product. During development phase formulation characteristics are carefully identified and optimized both qualitatively and quantitatively. Solution layering is usually employed when the potency of the desired pellets is low, since production of high potency pellets is not possible economically by using solution layering from a low solid content formulation. [4, 16, 22]

Particle size of the drug is most important factor during suspension layering. Since micronized particles produces smooth pellets and allows subsequent film coating particularly for controlled release applications. If particle size is high, high quantity of binder required immobilizing the particles onto the core; consequently pellets of low potency and rough surface are produced. The yield is usually low. [16]

Binder usually imparts strength to the pellets. They should not increase the viscosity of the formulations appreciably and should not modify the release characteristics of the pellets. Usually low molecular weight polymers are compatible with the drug substance. [1, 4, 25]

During powder layering it is essential that the powder delivery rate be as precise as the liquid application rate to

avoid over-wetting or under-wetting. The powder should have excellent flow characteristics, should not adhere to the sides and feed screw, may not form rat holes with in the hopper. Glidants may improve the flow properties. [22]

CRYOPELLETIZATION

This technology was initially developed for the nutrition industry to lyophilize viscous bacterial suspension, can be used to produce drug loaded pellets. In cryopelletization the pellets can be produced by allowing droplets of liquid formulation such as solution, suspension or emulsion to come in contact with liquid nitrogen at -160°C in which liquid nitrogen used as solidifying medium. The procedure permits instantaneous and even freezing of the material being processed due to the rapid heat transfer that occurs between the droplets and the liquid nitrogen. The required amount of liquid nitrogen for manufacturing a given quantity depends on the solids content and temperature of the solution or suspension being processed. The pellets are dried in conventional freeze dryers to remove water or organic solvents. [26]

The equipment consists of a container equipped with perforated plate below which a reservoir of liquid nitrogen in which a conveyer belt with transport baffles is immersed. The variable speed of conveyer belt provides the required residence time required for freezing the pellets. The frozen pellets are transported into storage container at -60°C before drying in freeze dryer. Equipments of different sizes like laboratory and production size available. Droplet formation is a critical step in cryopelletization and is influenced by formulation related variables, equipment design and the corresponding processing variables. Formulation related variables include viscosity, surface tension and solids content. [27]

Viscosity and solid content of the liquid formulation should be high enough and not exceed a critical limit which depends on the formulation. Surface tension of the liquid formulation also influences droplet formation and size. Addition of a surfactant reduces the surface tension and produces smaller particle.

The diameter and design of the shearing edge of the holes of the perforated plate influences the size and shape of the pellets. As smaller the nozzle diameter, the smaller the pellets produced. The distance between the perforated plate and the reservoir of liquid nitrogen should be such that it allows the drops to become spherical before contacting liquid nitrogen, because shape of the pellets largely depends on this distance but it should not be so much that it leads to deformation of the pellets. When it is desirable to have pellets with diameter less than 2 mm. the liquid nitrogen should be stirred continuously to prevent agglomeration. [26]

This technique may be used to produce drug loaded pellets for immediate as well as controlled release formulation.

FREEZE PELLETIZATION

Freeze pelletization is a simple and novel technique for producing spherical matrix pellets containing active ingredients. In this technique a molten solid carrier along with a dispersed active ingredient is introduced as droplets into an inert and immiscible column of liquid. The technique involves less process variables and also offers several advantages over other pelletization methods, In terms of quality of pellets and process cost. The pellets produced by this technique are spherical in shape with narrow size distribution. Since the pellets are solid at room temperature, they do not require drying. [30]

Molten solid carriers are introduced as droplets into the column of liquid in which the molten solid is immiscible. These droplets can move either in upward or downward directions depending on their density with respect to the liquid in the column and solidify into spherical pellets. Carrier may be hydrophilic or hydrophobic in nature and are melted at a temperature 5-10°C higher than the melting point of the carrier solids. [29]

Two types of equipments are used and the selection of equipment depends upon the density of the molten solid carrier. The column of both the apparatus is divided into two parts, initial portion from which the molten solid carrier is introduced and is maintained between 25-100°C, and the cooling portion in which droplets solidification occurs and is maintained between 0 to -40°C using cooling mixture of acetone and dry ice.

The active constituent and other excipients are mixed with the molten carrier to form solution or dispersion. This solution or dispersion is introduced as droplets using needles or nozzles into the inlet column of liquid and dropped from a certain height, so that droplets remain intact as they fall into the liquid column. Size of needle gauge from 16-31 depending on the size of the pellets desired. In case of freeze pelletizer I the molten solid carrier are introduced from the upper portion of the column because density of the solid carriers is more than the density of the liquid used in the column and the carriers solidify in the bottom portion, while in case of freeze pelletizer II the molten solid carrier is introduced from the bottom of the column because density of the solid carrier is low as compared to the liquid used in the column and the carrier solidify at the top.

Suitable carrier for freeze pelletization are those, which are solid at room temperature and have melting point below 100°C in order to minimize degradation of the active constituent. For freeze pelletizer I, hydrophilic carrier such as polyvinyl alcohol, polyethylene glycol and low melting point sugars (dextrose, maltose) are used. Suitable liquids for column are low density oil such as mineral oil, vegetable oil, and silicone oil. [30]

For freeze pelletizer II, hydrophobic carriers of low density such as glyceryl palmitostearate, glyceryl behenate and glyceryl monostearate are used as solid carriers. Suitable liquids for column are high density hydrophilic liquids such as liquid polyethylene glycol, ethyl alcohol, glycerine and water. For sustained release pellets containing mixture of hydrophilic and hydrophobic solids, liquids that are immiscible with both hydrophilic and hydrophobic molten solids are used as cooling liquid in the column. [32]

Christy M. Wyandt, et. al., studied drug release from Wax-based sustained release matrix pellets prepared by a novel freeze pelletization technique II. They examined the drug release significantly depended on the wax type used and the aqueous drug solubility. The drug release decreased as the hydrophobicity of wax increased and the drug release increased as the aqueous drug solubility increased. In glyceryl monostearate (GMS) pellets, drug release rate decreased as the loading of theophylline increased. On the contrary, the release rate increased as the drug loading of diltiazem HCl increased in Precirol pellets. Theophylline at low drug loads existed in a dissolved state in GMS pellets and the release followed desorption kinetics. At higher loads,

theophylline existed in a crystalline state and the release followed dissolution-controlled constant release for all the waxes studied.

EXTRUSION AND SPHERONIZATION

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. [4] 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.

Advantages of spheronization

- The flow characteristics of spheres make them suitable for transportation by most systems found in the pharmaceutical industry, including vacuum transfer.
- The packing of small sphere into small containers, such as hard gelatine capsules, or larger packages is much more convenient than other dry forms such as powders or granules. Eliminate quality problems with variable dosage due to packaging problems with powder. [4]
- Spheres are a dense material and provide the lowest surface area to volume ratio and thus pharmaceutical compounds can be coated with a minimum of coating material. Important for effective release of some drugs.
- Coating can provide controlled, targeted release at different locations within the body. Important for effective release of some drugs.
- Spherical particles are easily mixed. Smooth spheres are an ideal base on which to apply a coating. Minimum coating time and coating material used. [4]
- Spheres will reduce production of fines and dust during transportation, handling and packaging.
- Dependent upon adhesive forces and surface characteristics spheronization increases the hardness and reduces friability of granules.

Extrusion spheronization is a multi step compaction process 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. [4]

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. [4] The most commonly used granulator is planetary mixer or sigma blade mixer or high shear mixer and Hobart mixer. [35] 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. [37]

3) Extrusion

This is the third step in the process. The extrusion operation can be considered to be a specialized wet granulation technique as well as an integral part of the overall spheronization process. Extrusion 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.[4,35,37]

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.

3) Spheronization

The spheronization technology was first introduced by Nakahara in 1964. 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. [4] 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. [1, 31, 37]

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. [Fig. 3] explains principle of spheronization.

Extrusion and spheronizing equipment

Extruders for the extrusion process have been classified generally as screw, sieve and basket, roll and ram extruders. Screw extruders are the only strictly continuous extrusion devices, since product can exit in a smooth continuous flow. The remainder of the extrusion devices produce surge of material. Based on the type of feed mechanism used to transport the mass towards the die, they have been broadly classified as screw, gravity or piston-type extruders.[4, 31]

Screw fed extruders have screws that rotates along the horizontal axis that transport the material horizontally, they may be axial or radial. Die plate positioned axially in axial type extruder. In radial extruder the transport zone is short; the material is extruded radially through screens mounted around the horizontal axis of the screw. [4, 31]

Gravity fed extruder includes the rotary cylinder and rotary gear extruders, which differ mainly in the design of the two counterrotating cylinders. In the rotary cylinder extruder one of the two counterrotating cylinders is hollow and perforated, whereas the other cylinder acts as a pressure roller. Rotary gear extruders have two hollow counterrotating gear cylinders with counterbored holes.

In ram extruders a piston displaces and forces the material through a die at the end. Ram extruders are preferentially used in the development phase because they can also be used to measure the rheological properties of formulations. [31]

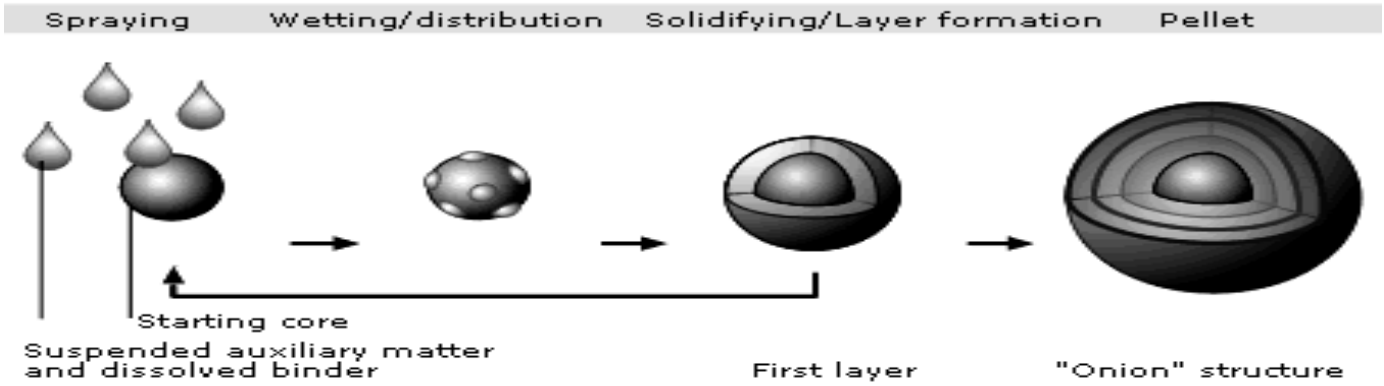


Fig. 1: Principle of solution and suspension layering

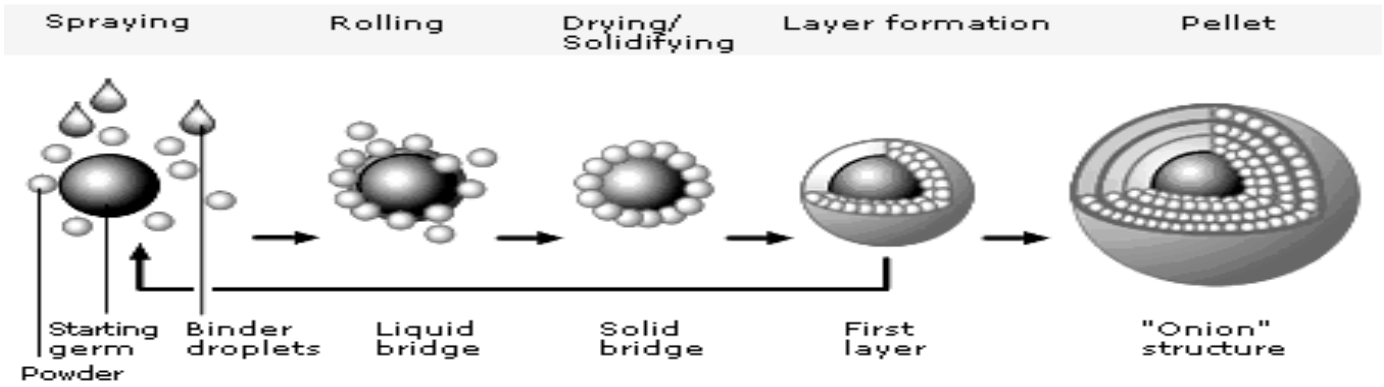


Fig. 2: Principle of powder layering

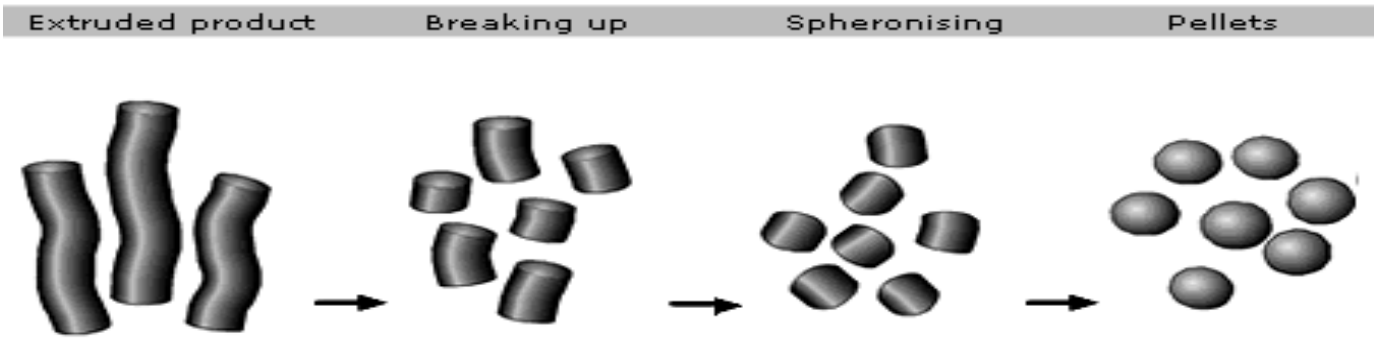
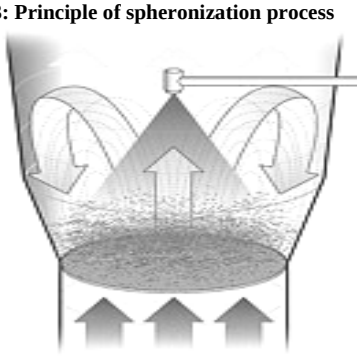
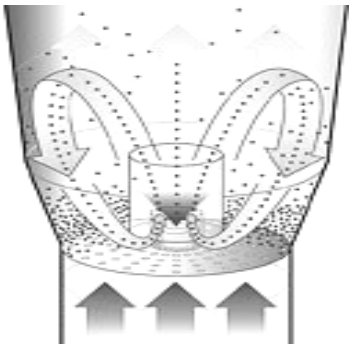


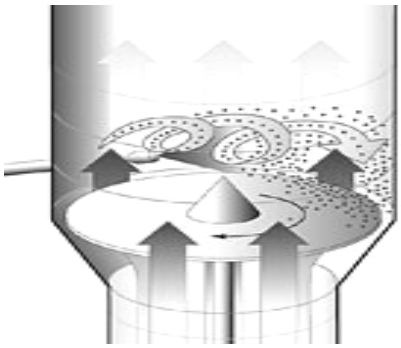
Fig. 3: Principle of spheronization process



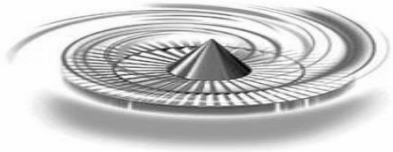
Top spray



Bottom spray



Tangential spray



Spin flow of rotation plate in tangential spray coating

A spheronizer also known as merumerizer consists of a vertical hollow cylinder with a horizontal rotating disk (friction plate) where the extrudate is broken up into smaller segments by contact with friction plate or other particle or with wall. The friction plate is responsible for providing the energy necessary to produce pellets and for controlling the extent of pellet growth and is provided in the form of interparticulate friction.

The friction plate, a rotating disk with a characteristically grooved surface to increase the frictional forces is the most important component of the equipment. Two geometric patterns are generally used. A cross hatched pattern with grooved running at right angle to one another and a radial pattern with grooved running radially from the center of the disc. [4, 31, 35]

In air assisted spheronizer the small amount of dry air allows the granules to slide across each other more easily and facilitates the mechanically induces fluidization. The friction plate looks rather similar to a plate a standard merumerizer, except for what appears to be a propeller like device that is mounted on top. The base is perforated so that air can be distributed throughout the product.

Recently, different types of fluidised bed rotary processors have been developed more successfully for preparing compaction-type pellets such as the extrusion spheronization process in a one-step process. This technique has solved many problems related to the multi-step extrusion and spheronization process; it consumes less time, requires lower labour costs and less space. [15]

4) 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. [4, 9] 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 voidage for a given applied compaction pressure. There was a reasonable correlation between tablet crushing strength and voidage. Major differences were observed in tablet dissolution, with the freeze-dried material exhibiting two-regime behaviour and an initial dissolution rate constant an order of magnitude greater than the oven-dried form.

5) Screening

Screening 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. [1, 4]

HOT MELT EXTRUSION

Industrial application of the extrusion process dates back to 1930's. Wet mass extrusion is the most frequently used method for producing spherical pellets. Hot-melt extrusion is one of the most widely applied processing technologies in the plastic, rubber and food industry. Currently, more than half of all plastic products, including plastic bags, sheets and pipes are manufactured by this process. Recently melt extrusion has found its place in the array of the pharmaceutical manufacturing operations. This process is currently applied in the pharmaceutical for the manufacture of variety of dosage forms and formulation to modify drug release such as immediate and sustained release pellets, granules and tablets, transdermal passage of the drug and enhancing dissolution rates for poor water soluble drugs. [28, 36]

Advantages:

- Neither solvent nor water used in this process. Fewer processing steps needed thus time consuming drying steps eliminated. Uniform dispersion of fine particle occurs.
- There are no requirements on the compressibility of active ingredients and the entire procedure simple, continuous and efficient.
- Good stability at varying pH and moisture levels, do not require additional film coating since the drug release is diffusion controlled. Safe application in humans due to their non-swellable and water insoluble nature.[34]

Disadvantages:

- Requires high energy input. The melt technique is that the process cannot be applied to heat-sensitive materials owing to the elevated temperatures involved.
- Lower-melting-point binder risks situations where melting or softening of the binder occurs during handling and storage of the agglomerates.
- Higher-melting-point binders require high melting temperatures and can contribute to instability problems especially for heat-labile materials.

Applications: In pharmaceutical industry the melt extrusion has been used for various purposes, such as

- Improving the dissolution rate and bioavailability of the drug by forming a solid dispersion or solid solution.
- Controlling or modifying the release of the drug by preparing different release pellets and granules. Useful in masking the bitter taste of an active drug, enhancing dissolution rates for poorly water soluble drugs. [34]

Extrusion Technology:

Pharmaceutical products manufactured using melt extrusion techniques have been approved in the USA, Europe and Asia. Melt extrusion process consists of three basic steps: melting or plasticating a solid material, shaping the molten material and solidification of the material in to the desired shape. A hot melt extrusion line consists of a material feed hopper, extruder inside a heated barrel, having three different sections, and spheronizer. [28]

The hopper holds the material and continuously feeds it into the extruder, which has a heated barrel containing the rotating screw. Spheronization can be carried out in a single piece of equipment, such as a jacketed, high shear mixer where certain components of a formulation are melted to generate spherical particles. The process is similar to wet granulation, except that the binder is in the molten state and hence does not require water or other solvents to liquefy it[34].

The drug substance is first blended with the appropriate pharmaceutical excipients, such as polymer and waxes, and

extruded at a predetermined temperature. The spheronization temperature should be high enough so that it partially softens the extrudate to facilitate its deformation and eventual spheronization. The extrudate is cut into uniform cylindrical segments with pelletizer. The segments are spheronized in a jacketed spheronizer to generate uniform sized pellets.

The single screw extruder is the most important type of extruder used due to its advantages of relatively low cost, ruggedness and reliability. The design of the extruder die is influenced by several variables such as composition of the extrudate and the operating parameters of the extruder.

Most of the raw materials used in this technique have also been employed in conventional techniques. The material in which the drug is dispersed is called thermal carrier. During processing the carrier is usually transformed into a molten state. The carrier substance is usually a polymer or low melting point wax like polyethylene glycol, poloxamer 188, gelucire 50/13, bees wax, carnauba wax, paraffin wax and microcrystalline wax. [34] In 1994 Follonier and co-workers investigated hot-melt extrusion technology to produce sustained-release pellets of diltiazem hydrochloride; a relatively stable, freely soluble drug was incorporated into polymer-based pellets for sustained-release capsules. Four polymers were considered for extrusion trials, namely ethylcellulose, cellulose acetate butyrate (CAB), poly (ethylene-co-vinyl acetate) (EVAC) and polymethacrylate derivative (Eudragit® RSPM). The plasticizers included triacetin and diethyl phthalate. The pellets produced, exhibited a smooth surface and low porosity. The in-vitro release of the drug was biphasic, with the CAB and EVAC pellets giving the lowest release rate. [28]

The incorporation of plasticizers into pharmaceutical polymers modifies drug release properties and improves surface appearance of dosage forms. Plasticizer improves the flexibility of polymers by reducing the tensile strength and glass transition temperature of the material and also diminishes the degradation of heat sensitive components.

An application of hot-melt extrusion was described by Miyagawa, Sato, and coworkers in 1996 and 1997. They studied the controlled release and mechanism of release of diclofenac. These researchers utilized a twin-screw compounding extruder, carnauba wax, the model drug, and other rate controlling agents to prepare granules. Their first investigation showed that a wax matrix with high mechanical strength could be obtained even at temperatures below the melting point of the wax. Dissolution release profiles of diclofenac from wax matrix granules were strongly influenced by the formulation of the granules. The rate controlling additives that were varied in the formulations included hydroxypropyl cellulose, methacrylic acid copolymer (Eudragit L-100), and sodium chloride. The authors emphasized the advantages of using twin-screw extruder for wax matrix tablets, such as low temperatures, high kneading and dispersing ability and low residence time of the material in extruder.

Paul Wan Sia Heng. et.al. was studied the control of the melt pelletization process in an 8-l high shear mixer using specific energy consumption of the impeller motor. They used lactose as the bulk material and polyethylene glycol 3000 as a meltable binder. They examined the effects of binder concentration, mean particle size of bulk material and post-melt impeller speed on the relationship of specific energy consumption and pellet growth. Specific energy consumption was found to be a suitable tool for monitoring the melt pelletization process, and specific energy consumption correlated well with pellet growth. The mean size of the pellets formed becomes correspondingly larger with increasing specific energy consumption.

CHARACTERIZATION OF PELLETS

1) Particle size distribution

Particle size distribution should be as narrow as possible. That will ensure minimum variation in coating thickness; facilitate blending process if blending of different types of pellets is required. 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. Patappee.W. 2004 reported the use of vernier callipers to determine the size of pellets. [1, 4, 16]

2) Surface area

The characteristics of pellets, those controlling the surface area, are mainly size, shape, porosity and surface roughness. There are three methods of measuring the surface area of pellets. It can be calculated from the particle-size distribution by measuring/using the mean diameter, since the surface area is equal to $\pi d2$. However, this calculation does not account for the contributions of the surface area arising from other morphologic characteristics, such as porosity, surface roughness and shape of the pellets. Therefore, two techniques, i.e. gas adsorption and air permeability, permit direct calculation of surface area. [4, 33]

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. [1, 4, 16]

The 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, and the results are plotted as P/V (p0-p) versus p/p0 to generate a linear plot where V is the volume of gas in cm3 adsorbed per gram of substrate at pressure p and p0 is the saturation vapour pressure of liquefied nitrogen at the temperature of the experiment. The slope and intercept of the plot yield the values b and Vm. The specific surface (sw) of the pellets is then obtained by using the following equation:

$SW = 4.35 * Vm$

3) 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. The porosity of pellets can be determined quantitatively also by using optical microscopy and scanning electron microscopy together with image. [1, 15, 16]

4) 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. True density indicates the extent of densification or compactness of substances. The true density

of pellets can be determined by an air-comparison pycnometer, a helium pycnometer or by the solvent displacement method. [1, 4]

5) 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. Friability can also be determined using fluidized bed with Wurster insert by using stream of air. [4, 12, 33]

6) 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. [4, 16]

Today pelletization technology represents an efficient pathway for manufacture of drug delivery system. This review focused on frequently used pelletization techniques for producing pellets for oral drug delivery. Each technique has its own advantages and disadvantages. Layering processes have been used over the years for manufacturing of pellets. Most of the scientists have focused research on refining and optimizing existing pelletization techniques and also focused on the development of novel approaches and procedures of manufacturing pellets employing innovative formulation and processing equipment. These pelletization techniques have great impact on the development of different types novel drug delivery systems. A number of pelletized products are being designed to maximize the in vivo performance of medications already in the market and to meet all regulatory requirements.

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