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MULTIPLE UNIT DOSAGE FORM - PELLET AND PELLETIZATION TECHNIQUES: AN OVERVIEW

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ABSTRACT
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. There are various types of pelletization techniques like spheronization and extrusion, pelletization by layering, pelletization by solution layering & direct pelletization. The techniques namely extrusion-spheronization, hot melt extrusion, freeze pelletization, cryopelletization have been discussed along with parameters affecting pelletization.
KEYWORDS: - Pellets, Spheronization, Cryopelletization, Extrusion.

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INTRODUCTION

The concept of the multiple unit dosage form (MUDF) was initially introduced in the early 1950. These forms can be defined as oral dosage form consisting of a multiplicity of small discrete unit, each exhibiting some desired characteristics. Together each unit provide the overall desired control release of dose. These multiple units are also referred to as pellets, spherical granules or spheroids. Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipient into small, free flowing, spherical or semi-spherical units referred to as pellets. Pellets range in size, typically, between 0.5-1.5 mm, though other size could be prepared, depending on the processing technologies employed. The use of pellets as a vehicle for drug delivery at a controlled rate has recently received significant attention. Applications are found not only in the pharmaceutical industry but also in the agribusiness (such as in fertilizer and fish food) and in the polymer industry. Like other MUDFs, several mini tablets can either be filled in to hard capsules or compacted in to bigger tablets. Then after disintegration, they release these sub-units as multiple dosage forms. There has been increasing interest in the development of MUDF'S incorporated into tablets instead of hard gelatine capsules in order to overcome the higher production costs of capsules. In contrast to Monolithic dosage forms multiple unit dosage forms offer several advantages[1].

Rationale for Pelletization

The use of pellets as a vehicle for drug delivery at a controlled rate has recently received significant attention, pellets disperse freely in gastrointestinal tract, so they invariably maximize drug absorption, reduce peak plasma fluctuation, and minimize potential side effects without appreciably lowering drug bioavailability, pellets also reduce variation in gastric emptying rates and overall transit times, which is common with single unit regimens, is minimized, high local concentration of bioactive agent, which may inherently be irrigative or anaesthetic, can be avoided, when formulated as modified release dosage form, pellets are less susceptible to dose dumping than the reservoir type single unit formulation, better flow properties, narrow particle size distribution, less friable dosage form and uniform packaging[2, 3].

Methods for Pellet Preparation

The most widely used pelletization processes in the pharmaceutical industry are[4]: -

Extrusion and Spheronization

Extrusion/spheronization is currently one of the techniques used to produce pharmaceutical pellets. With each production techniques pellets with specific characteristics are obtained. The preparation of spherical granules or pellets by extrusion and spheronization is now a more established method because of its advantages over the other methods. Extrusion is the second step of the process and consists of shaping the wet mass into long rods, which are commonly termed extrudate. The extrusion process is currently used as an alternative method for the manufacture of completely water soluble tablets. The third step of extrusion and spheronization process involves the dumping of the cylinders onto spheronizer's spinning plate, known as friction plate, upon which extricate is broken up into smaller cylinders with a length equal to their diameter. A spheronizer is a device that consists of a vertical hollow cylinder (bowl) with a horizontal rotating disk (friction plate) located inside. The fourth and final step of the process is the drying of the pellets. The pellets can be dried at room temperature or at an elevated temperature in the fluidized-bed drier, in a forced circulation oven or in a microwave oven. Pellets quality is dependent on the type of dryer used.

Process and equipment

In basic terms extrusion and spheronization process involves four steps:

Granulation- Preparation of wet mass

Extrusion-shaping the wet mass into cylinder

Spheronization- breaking up the extrudate and rounding off the particles into sphere;

Drying- drying of pellets

Advantages

Ease of operation, High throughput with low wastage, Narrower particle size distribution, Production of pellets with low friability, Production of pellets that are suited for film coating, More sustained and better controlled drug release profile when compared with other techniques[5-7].

Layering

Layering process are probably the most well- controlled and straight forward pelletization techniques that have been used over the years. They are classified into three categories: solution layering, suspension layering and powder layering. Solution and suspension layering involves the deposition of successive layers of solution and substances, respectively, on the other started seeds that may be inert materials or crystals or granules of the same drug. In principle, the factors that control coating processes applying directly to solution or suspension layering, and as a result, require basically the same process equipment. Over the years, conventional coating pans, fluid- bed centrifugal granulators, and wurster coaters have been used manufacture pellets by solution and suspension layering.

Process

During solution and suspension layering, all the components of the formulation are dissolved or suspended in the application medium and hence determine the solid content and the viscosity of the liquid sprayed. As the solution or suspension is sprayed on the product bed, the droplets impinge on the starter seeds or cores and sprayed evenly on the surface, provided that the drying conditions and fluid dynamics are favourable. This is followed by a drying phase which allows dissolved materials to crystallize and form solid bridges between the core and initial layer of the drug substance as well as among the successive layers of drug substance. The process continues until the desired layers of drug and hence the target potency of the pellets is achieved. The rate of particle growth is rather slow due to the particle population remains the same, the size of the pellets increases as a function of time and, as a result, the total mass of the system increases[8, 9].

Powder layering

Powder layering involves the deposition of successive layers of dry powder of drug or excipients on performed nuclei or cores with the help of a binding liquid, because powder layering involves the simultaneous application of the binding liquid and dry powder, not all the pelletization equipment that is routinely used to prepare pellets by solution or suspension layering can be employed, although the reserve is true. The main equipment –related requirement in a powder layering process is that the product container should have solid walls with no perforation in order to avoid powder loss underneath the product chamber before the powder is picked up by the wet mass of pellets that is being layered upon.

Process

During powder layering, a binding solution and a finely milled powder are added, simultaneously, to a bed of starter seeds at a controlled rate. In the initial stages, the drug particles are bound to the starter seeds the 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 application medium or from any material, including the drug substance, that is soluble in the binding liquid. Successive layering of drug and binder solution continues until the desired pellets size is reached. If the powder delivery rate is not maintained at predetermined

levels, over-wetting or dust generation, as the case may be occurring, and neither the quality nor the yield of product can be maximized[8, 9].

Other processes with limited application in the development of pharmaceutical pelletized product include: -

Globulation and Droplet formation

It describes the two related processes of spray drying and spray congealing. During spray drying, drug entities in solution or in suspension form are sprayed, with or without Excipient, into a hot air stream to generate dry and highly spherical particles. Though the techniques is suitable for the development of controlled- release pellets, it is generally employed to improve the dissolution rates and, hence bioavailability of poorly soluble drugs. Spray drying has been used for years for a variety of reasons[10].

Balling

Balling describes a pelletization process in which finely divided particles are converted, upon the addition of appropriate quantities of liquid, to spherical particles by a continuous rolling and tumbling motion. The liquid may be added prior to or during the agitation stage. Pans, discs, drums or mixers may be used to produce pellets by the balling process[11].

Compression

Compression is a pelletization process in which a mixtures or blends of active ingredients and excipients are compacted under pressure to generate pellets of defined shape and size. The pellets are small enough to be filled into capsules. The formulation and processing variables that govern the production of pellets during compression are similarly to those that are routinely employed in tablet manufacturing. In fact pellets produced by compression are nothing but small tablets that are approximately spheroidal in shape[12].

Spray congealing

Spray congealing is a process in which a drug is allowed to melt, disperse or dissolves in hot melts of gums, waxes, fatty acids, etc. and is sprayed into an air chamber where the temperature is below the melting point of the formulation components, to provide, under appropriate processing condition, spherical congealed pellets. Depending on the physicochemical properties of the ingredients and other formulation variables, pellets with immediate or controlled release behaviour can be produced[13].

And emerging technology used is: -

Cryopelletization

In cryopelletization droplets of a liquid formulation are converted into solid spherical particles or pellets by employing liquid nitrogen as the fixing medium. The pellets are dried in conventional freeze dryers. The small size of the droplets, and hence the large surface area, facilitating the drying process. The most critical step in cryopelletization in droplet formation, which is influenced not only by formulation related variables such as viscosity, surface tension and solid content, but also by equipment design and the corresponding processing variables. The diameter and design of the shearing edge of the holes on the container plates are critical[14, 15].

Melt Spheronization

In melt spheronization drug substance and excipients are converted into a molten and semi molten state and subsequently shaped using appropriate equipment to provide solid spheres or pellets. Melt spheronization can be carried out in a single piece of equipment, such as 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 molten state and hence does not require water or other solvent to liquefy it. Due to the randomness of the interparticle collisions that occurs during the process, the particle size distribution of the pellets tends to be wide as is commonly observed with balling. In fact the process is considered a variation of the balling process[16].

Wurster Equipment

The wurster coating equipment was invented by D. wurster. The wurster equipment is a circulating fluid bed specially designed for the coating process. It consists of a container with one or more wurster partition inserts (called the partitions). The product movement in the wurster process is called a circulating fluid bed in the chemical engineering literature. Another name for the wurster process is a spouted bed. The circulating fluid bed process contains four distinct zones: a riser, a solid recycle part, a stand pipe and a feeder. The four zones are: the up bed region, the deacceration region (in expansion chamber), the down bed region and the horizontal transport region[17, 18].

Parameter to be controlled in fluid bed system

The parameters that affect the final product processed through fluidized bed system can be enumerated as below: -

Air distribution plate: position of the air distribution plate influences the airflow pattern inside the body.

Shape of instrument body: annular base gives better product and fluidization.

Nozzle height in case of coater and granulator: it plays vital role as in coating, the atomized coating solution should not get dried before reaching the tablet surface.

Positive and negative operation.

Process parameter - Temperature, Humidity and Airflow rate.

In granulation process - Related to spray nozzle- Spray rate and Spray pressure.

In coating process - Related to spray nozzle, Distance of spray nozzle, Droplet size, Spray rate and Spray pressure), **Product parameters i.e. In drying process (**Initial moisture content of material, Batch size).

In granulation process (Granulating agent and Starting material)**, in coating process (**Coating agent and Starting material)[19].

Formulation variable

Formulation aids or Excipient are added to pharmaceutical dosage forms mainly to produced satisfactory delivery of the drug to the intended site, to impart favourable characteristics to the dosage form, and to facilitate the manufacturer of the product. Hard drug entities processed all of the necessary attributes to accomplish these tasks; there would be no need to add excipients to pharmaceutical products. Unfortunately, drugs do not, in general, posses many of the properties that are required for the fabrication of dosage forms. Consequently, formation and subsequent manufacture of drug product invariably involves the incorporation of one or more Excipient that has different functions. Since pellets are intended to be administered orally, the Excipient used in pellets dosage forms is typically the same as those used in tablet or capsule formulations. Their primary functions also are not significantly different. Excipients vary widely in their chemical composition and physical properties and are classified mainly in terms of their functional role during the development and manufacture of dosage forms. The physicochemical properties of both excipient and drugs are crucial to the successful development of pelletized product and should be thoroughly understood[19-27].

Formulation aids

Filler

Fillers are water soluble or insoluble substances that are incorporated into pellet formulations, mainly to add bulk. Selection of filler should be based on the intended overall properties of the pellets. Some of the fillers used in pellets Depending on the desired dose, the physical properties of drug, and manufacturing process involved, the amount of filler in the formulation can be as high as 99% or as low as 1%. If the filler component is the main ingredient of pellet formulation, its properties essentially determine the properties of the pellets. It is apparent, therefore in some cases; the presence of filler in formulation may supersede the intended diluents function and contribute largely to the rate and extent of drug availability from pellets.

Two factors that impact heavily on the selection of filler are physicochemical and pharmacological inertness. The physicochemical stability of the filler also figures the stability of the pellets.

Binder

Binder is adhesive materials that are incorporated in pellets formulations to bind powder and maintain pellet integrity. They are essential components of pellet formulations, regardless of the manufacturing process..

Lubricants

Lubricants are substances that are incorporated in pellet formulations to reduce the coefficient of friction between individual particles or between the particles and the surface of processing equipment.

Separating agent

Separating agent are materials that absorb on surfaces and promote the separation of pellets into distinct units during a pelletization process. Pellets can develop surface charge during manufacture and may tend to attract one another.

Disintegrants

Disintegrant are substances which in the presence of liquid, promote the disruption of solid dosage form, such as tablets, pellets, granules, capsules plugs or any other agglomerated materials to regenerate the primary particles that were originally compacted or agglomerated to produce the dosage form.

pH adjuster

pH adjuster are substances that are incorporated in pellets formulation to influence the microenvironment of drug molecules for a variety of reasons. Generally, acid labile compounds are protected from the acidic regions of the gastrointestinal tract through the application of an enteric film coat. Buffer systems may also be added to the core formulation to maintain the pH of the core in the favourable range for drug stability

Surfactants

Surfactants are used in pellet formulation mainly for the same reasons that they are used in any other solid dosage form. They are employed to improve wet ability and enhance dissolution rates of poorly soluble and hydrophobic drugs. In most pelletization processes, the initial formation and subsequent growth of pellets depends, to some extent, on the liquid bridges that hold the primary particles together. Therefore it is important that the liquid (water in most cases) wet the particles effectively. That is, by lowering the surface tension of the binding liquid, surfactants tends to weaken the liquid bridges and make the forming pellets friable.

Spheronization enhancers

Spheronization enhancers are formulation aids that facilitate the production of spherical pellets, mainly

during spheronization the balling. These substances not only confer plasticity on the formulation, but also impart binding properties that are essential for pellet strength and integrity.

Glidants

Flow characteristics play an important role during powder layering. Because the process require a well controlled powder feed rate to the balance the simultaneous application of binder solution, it is imperative that the powder does not adhere to the sides of the hopper and form bridges or rat holes[28-36].

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