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MULTIPARTICULATE DRUG DELIVERY SYSTEM AND THEIR PROCESSING TECHNIQUES

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ABSTRACT

Multiparticulates are discrete particles that make a multiple unit system. In pharmaceutical industry pellets can be defined as small, free flowing, spherical particulate manufactured through the cluster of fine powder or granules of drug substances and excipients using appropriate handling equipment. A present review outlines the transient account of all important manufacturing and evaluation technique of pellets. The manufacturing techniques are as spheronization and exctrusion, pelletization by solution layering, hot-melt exctrusion, cryopelletization, freeze pelletization have been deliberated

KEYWORD: pellets, spheronization, extrusion, cryopelletization, freeze pelletization.

INTRODUCTION

Orally modified drug delivery systems can be classified in to two extensive group single unit dosage forms & multiple unit dosage forms. Multiple unit dosage forms (MUDF's), such as granules, pellets. The insight of MUDF's was initially presented in 1950s. The production of MUDF's is a common policy to control the release of drug as shown by their reducibility of the release profiles when compared to the ones obtained with single unit dosage form (SUDF's).The progress of mini matrices is a hopeful area in pharmaceutical research concerned with a high control over the release rate of the drug combined with a high flexibility on the adjustment of both the dose and the release of drugs and has attracted some attention in the 1990s. Similar too their MUDF's several mini tablets can either be filled in to hard capsules or compacted in to bigger tablets. Then after disintegration, they may 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 reduction costs of capsules. In contrast to Monolithic dosage forms a multiple unit dosage forms offer several advantages.[1]

HISTORY OF PELLETS

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 proposed usually for oral administration.

The pelletized products can expand 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. 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.[2,3,4,5]

When it comes to pharmaceutical industry, it was early in the 1950's, in response to a desire to sustained the release of drug over an extended period of time, that the pharmaceutical industry develop a keen interest in the technology. And it's been from 1970's advantages of pellets over single unit dosage form have been recognized.

In time further research was conducted to develop a pelletization technique and major experiment allocated toward exploring method that were faster, cheaper and more efficient both in term of formulation and processing equipment.[6.,7]

Therapeutic advantages of pellets over single unit dose system

When taken orally

- Disperse freely in gastro intestinal tract.
- Maximise drug absorption, reduced peak plasma fluctuation, minimise irritation of mucosa by certain irritation of drug and minimise potential side effect appreciably lowering drug bioavailability.
- No risk of dose dumping.
- Improves safety and efficacy of drug.
- More suitable for fabrication of formulation with acid sensitive drug.

ADVANTAGES OF PELLETS

- In case of immediate release products larger surface area of pellets produce better distribution.
- The smooth surface and uniform size of pellets permit uniform coating not only each pellets but also from batch to batch.
- Chemically incompatible product formed into pellets and deliver in a single dose by encapsulating them.
- The thickness of coat on the pellets dictates the rate at which the drug or content released from coated particles.
- By selecting the proper formulation, processing conditions and processing equipment, it is possible to get smooth surface and uniform pellets.
- They offer a great degree of flexibility in design and development of oral dosage form like tablet, capsule, suspension.

Disadvantages of pellets

- The manufacturing of multiple unit dosage form is more expensive and complicated.
- The filling into gelatine capsule is difficult to accomplish especially in case where different subunit are involve.

Methods for pellets preparation

The most widely used pelletization processes in the pharmaceutical industry are-

EXTRUSION AND SPHERONIZATION [9]

Extrusion-Spheronization was developed in 1960^{s} as pelletization technique. The extrusion-spheronization process is usually used in pharmaceutical industry to make uniform sized spheroids. It is valuable for making dense granules with a high drug loading for controlled release oral solid dosage form with a minimum amount of excipient. An extrusion is a second step of process and consists of shaping the wet mass into long rod, which is commonly termed extrude. The third step of extrusion and spheronization including dumping of cylinder onto spheronizers spinning plate, known as friction plate upon which the extract broken up into smaller cylinder with a length is equal to diameter. A spheronizer is a device that consists of vertical hollow cylinder with a horizontal rotating disc located inside. The fourth and final step of pellets includes drying of pellets. The pellets can be dried at room temperature or at elevated temperature or at elevated temperature in the fluidised bed dryer,

in a forced circulation in oven or in microwave oven. Pellets quality can be depend on the type of dryer used. [8]

EQUIPMENT

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

Screw feed extruder have screws that rotate along horizontal axis that transport the material horizontally, they may be radial or axial. Die plate positioned axially in axial type extruder. In radial extruder the transport zone is short; the material is extruded radially through screen mounted around the horizontal axis of the screw.

Gravity fed extruder includes the cylinder and rotatory gear extruders, which differ mainly in the design of the tow counter rotating cylinder is hallow and perforated, whereas the other cylinder act as a pressure roller. Rotatory gear extruders, which differ mainly in the design of two counter rotating cylinders. In the rotator cylinder extruder one of two the counter rotating cylinder is hollow and perforated, where as other cylinder is act as pressure roller. Rotatory gear extruder has two counter rotating gears with the counter bored holes.

In ram extruder piston displaced and forced the material through die at the end. Ram extruder is preferentially used in the development phase because they can also be used in the determination of rheological properties of formulation.

Spheronizer also known as merumerizer consist of hallow cylinder with a horizontal rotating disk where extrude is broken up into smaller segment 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 pellets growth and is responsible for inter particulate friction.

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

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

Recently different type of fluidised bed rotatory processors have been developed more successfully for preparing compaction type pellets such as extrusion spheronization process in a one step process. This technique have solved many problems related to multiple step extrusion and spheronization process; it consume less time and lower labour costs and less space.

Procedure for extrusion and spheronization

On basic of term extrusion and spheronization process comprises four steps

- Granulation- preparation of wet mass
- Extrusion- shaping the wet mass into cylinder
- Spheronization- breaking up the extrude and rounding off the particle into round sphere.
- Drying- Drying of pellets.

Palletizations by solution and Suspension layering[10,11]

Layering process is probably the most well controlled and straight forward palletization techniques that's have been used over a year. Solution and suspension layering involve the deposition of successive layer of solution and substances, respectively, on the other started seeds that may be inert material or granules or crystals of the same drug. In principle the factor that control coating processes applying directly to solution or suspension layering and as a result require basically the same process equipment. Over the year the conventional coating pan, fluid bed centrifugal granulators or wurster coating have been used manufacture pellets by solution and suspension layering.

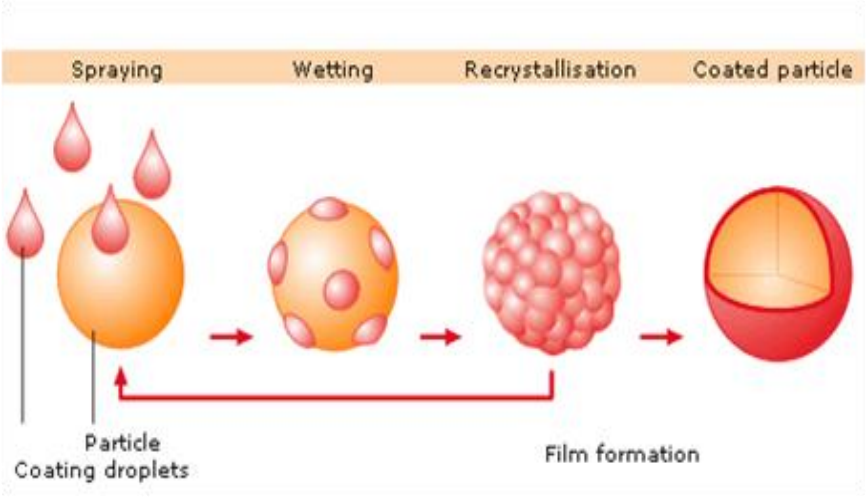
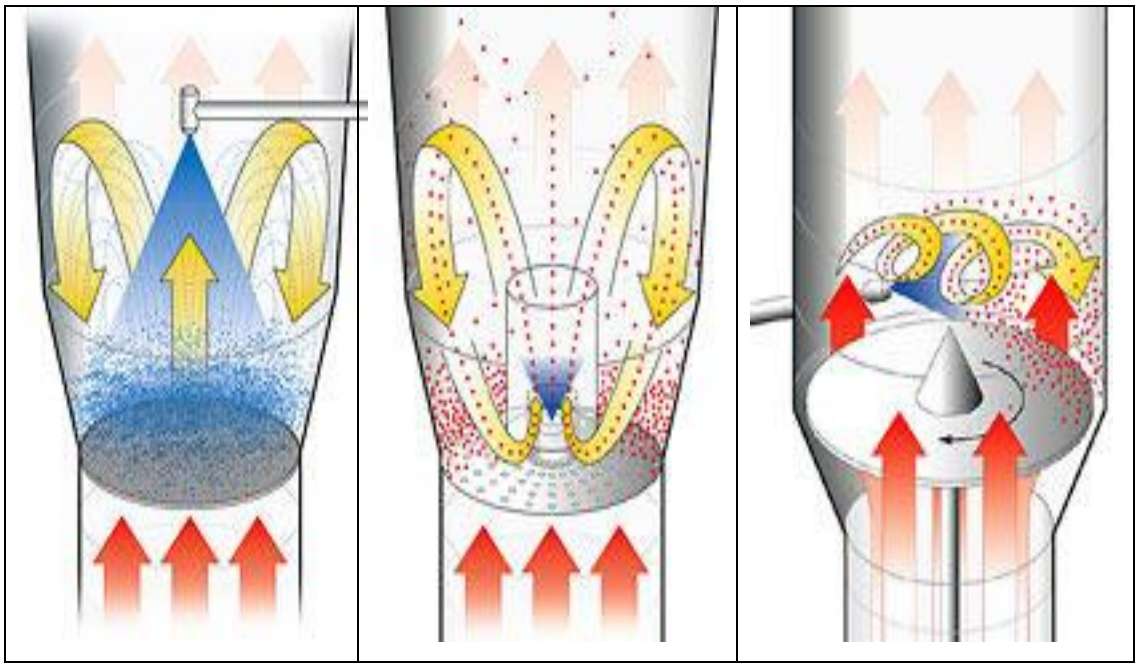


Figure1: Liquid layering



A.Top Spray **B. Bottom Spray** **C. Tangential Spray**

Figure2: Spraying techniques

A: Top Spray

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 upward 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 coating.

B. Bottom Spray

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 towards 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 particle continue travelling upward they dry and fall out side the the wruster tube back towards the base plate. Preferred for the application of modified release coating to a wide variety of multi particulate and also suitable for drug layering when drug dose is in the low to medium range.

C: Tangential spray coating

This process is particularly suitable for pellets 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 course 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 action achieve the desired coating thickness or granule size. It is suitable for the application of modified release film coating 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.

PROCESS

During solution and suspension layering, all the components of the formulation are dissolved suspended in the application medium and hence determine the solid content and viscosity of the liquid sprayed. As the solution or suspension spread on the pellets bed, the droplet impinge on starter seed 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 dissolve material to crystallize and form a solid bridge between core and initial layer of the drug substance as well as among the successive layer of drug substances. The process continues until the desire layer of the drug substance and target potency of the pellets is

achieved. The rate of particle growth is rather same due to particle population remain the same; the size of pellets is increase as a function of time and as a result total mass of pellets increase.

Hot Melt Extrusion[12]

This is newly modified variation of extrusion spheronization method. Here a drug substance and excipient are converted into molten or semi-molten state and subsequently shaped using appropriate equipment to provide solid spear or pellets. This is simple, efficient and continuous process which requires fewer processing stages. It doesn't require lengthy drying stage since it involve addition of water or other solvent, it disparity to granulation process.

Figure 1

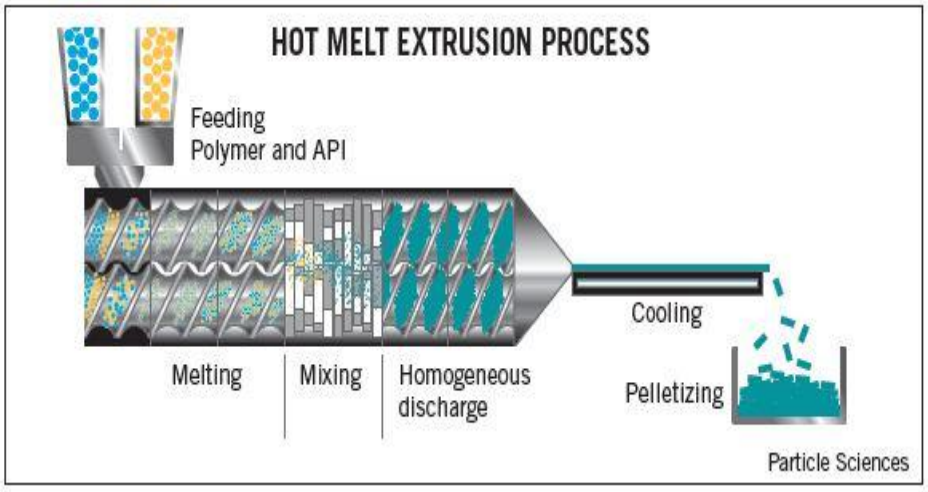


Figure 3: Hot melt extrusion process

CRYOPELLETIZATION[13]

In cryopelletization droplets of 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 dryer. The small size of droplets, and hence the large surface area facilitating the drying process. The most critical step in cryopelletization is droplet formulation which is influenced not only by formulation related variables, but also by equipment design and corresponding processing variables. The diameter and design of the shearing edge of the holes on the container plates are critical.

Freeze Pelletisation[14,15]

Freeze pelletization is a simple and novel technique for producing spherical matrix pellets contains active ingredients. In this technique a molten solid carrier along with the 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.

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 direction 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 re-melted at a temperature 5-10°C higher than the melting point of the carrier solids.

Two type of equipment 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 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 needle 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 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 carriers 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.

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 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.

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 GMSpellets and the release followed desorption kinetics. At higher loads theophylline existedin a crystalline state and the release followed dissolution-controlled constant release for all the waxes studied.

Evaluation of pellets[17,18]

Size of pellets

Size of pellets has a great importance because it has significant effect on release kinetics. Size determination studies are performed with the help of mechanical sieve shaker or Vernier caliper.

Surface morphology

Scanning Electron Microscopy has been used to study the surface morphology and cross section of pellets.

Pellets Shape

Sphericity is the most important characteristic is important characteristic and lots of method are used to determine it. The shape factor estimates the amount by which the projected image of particles deviate from a circle and it is calculated by means of 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 a 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 is and stereomicroscope is another method to determine shape of pellets one plane critical stability which an angle at which a plane has to be tilted before a particle begin to roll, is one of the important method.

Friability

The mechanical properties of pellets are important for processing. Pellets flake off during handling and coating process resulting in formulation of dust. In the case of subsequent coating it is desirable to have pellets with a low friability. Friability of pellets are determined by using Erweka type pellets friabilator or turbuls mixture for fixed period of time combined with a glass bed of certain diameter in order to generate abrasion. Friability can also be determined by fluidised bed with wurster insert by using stream of air.[17]

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