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PELLETS AND PELLETIZATION TECHNIQUES: A COMPREHENSIVE REVIEW

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ABSTRACT :

Pelletization is a process of agglomeration that converts fine powders or granules of bulk drugs and excipients into small, free flowing, spherical or semi-spherical units, known as pellets. Pellets are multiparticulate drug delivery system which suitable for promising and highly flexible system with various kinetics of drug release such as immediate release, sustained and controlled release which are easy to formulated. In order to eliminates the physicochemical interaction such as drug-excipient or drug-drug interactions multiparticulate dosage forms such as pellets can be implemented. Nowdays The process of pelletization as oral drug delivery system are gaining substantial attention. They form small spherical or semi-spherical free flowing solid units varying from 0.5 mm to 1.5 mm. Pellets are commonly used as multiparticulate systems as it has clinical as well as technical benefits as compared to single unit dosage forms. Pellet mainly for oral administration which can be further formulated into several other dosage forms such as tablets, capsules or can be administered as such. Oral administration has become the most versatile, convenient and common route of drug administration which ultimately focuses on patient compliance in present time. The present review focuses on process of pelletization, advantages, disadvantages, theory of pellet growth and formation, pelletization techniques, characterization of pellets, and also the recent approaches for pelletization techniques.

Keywords: - Pelletization, Pellets, Extrusion, Spheronization, Cryopelletization, fluidized bed technology, spraying and congealing , Controlled Drug Delivery, Theory of pellets growth and formation and characterization of pellets ,techniques of pelletization.

INTRODUCTION :

Pellets are spherical free-flowing granules with a narrow size distribution ,varying between 500 and 1500µm suitable for pharmaceutical applications. They are generally produced through a process of pelletization whereby a powder blend of an API and excipient particles is agglomerated into spherical granules. After being processed, pellets are typically filled into hard gelatin capsules or compressed into tablets. Then they can be formulated as immediate release dosage form or in sustain drug release over a long time or can be coated suitable to deliver a drug to a specific site of action in the gastrointestinal tract. During design and development of oral solid dosage forms, Pellets provide the development scientist with a high degree of flexibility. They can be divided into sufficient dose strengths without formulation or process changes, and also be blended to deliver incompatible bioactive agents simultaneously or particles with different release profiles at the same site or at different sites in gastrointestinal tract. Due to free-flowing characteristics Pellets provide development of formulation with high degree of flexibility. Therefore they are packed easily with no problems. The spherical shape and a low surface area to volume ratio of pellets suitable for uniform film coating. Pellets eliminate the dose dumping effect, which helps to achieved smoother plasma concentration profile and gradual absorption of drug than tablet, which further lowers the adverse effect of drugs. [1,2]

Advantages of pellets:

Technological advantages:

1. Pellets have excellent flowing properties, due to its elegance.
2. Extrusion Spheronization technique helps to achieved uniformity of dose with excellent accuracy.
3. Pellets allows safety by preventing dust formation which can caused health issues because of fine powders due to its dust explosives. The product appearance is improved.
4.The efficacy of product is improved due to the safety of the active ingredient.
5. It have less abrasion, decreased friability with uniform size. [1,13]

Therapeutical advantages:

1. Pellets prevent from dose dumping and cause lesser side effects when prepared in sustained release form.
2. They disperse freely in gastric intestinal fluids due to small in size, which gives a larger area for drug absorption and reduces peak plasma fluctuation.
3. Reduces accumulation of drugs which are irritant to gastric mucosa.
4. The incompatible drugs or recipients can be prepared as a single dosage form.
5. Used for masking the bitter taste of unpalatable drugs. [3,19]

DISADVANTAGES:

1. Pellets are usually filled in capsule which leads to increase the cost especially in the case where different subunits are involved.
2. Film coating of pellets can be destroyed due to compression of pellets into tablets.
3. Pellets size varies from formulation to formulation usually in the range of 0.05 mm and 2 mm
4. Excipients used are proportionally high.
5. Lack of efficiency and manufacturing reproducibility.
6. Huge amount of process variables.
7. Various formulation steps.
8. Advanced technology is essential.
9. Skilled person is required for manufacturing.
10. Multiple unit dosage forms is more difficult to manufacture and also expensive. [2,8]

Desirable Properties of Pellets:

1. For Uncoated pellets

a. Uniform spherical size

b. Narrow particle size distribution.

c. Good flow property.

d. Low friability.

e. Even surface .

f. Low dust formation .

g. Reproducible packing .

h. Ease of coating .

2. For Coated pellets

a. Maintain all above properties

b. Desirable drug release characteristics. [4,17]

Pharmaceutical applications of pellets :

1. Pellets in fast dissolution system: For immediate release like fast disintegration and fast dissolving pellets can be prepared for conventional oral drug delivery system.

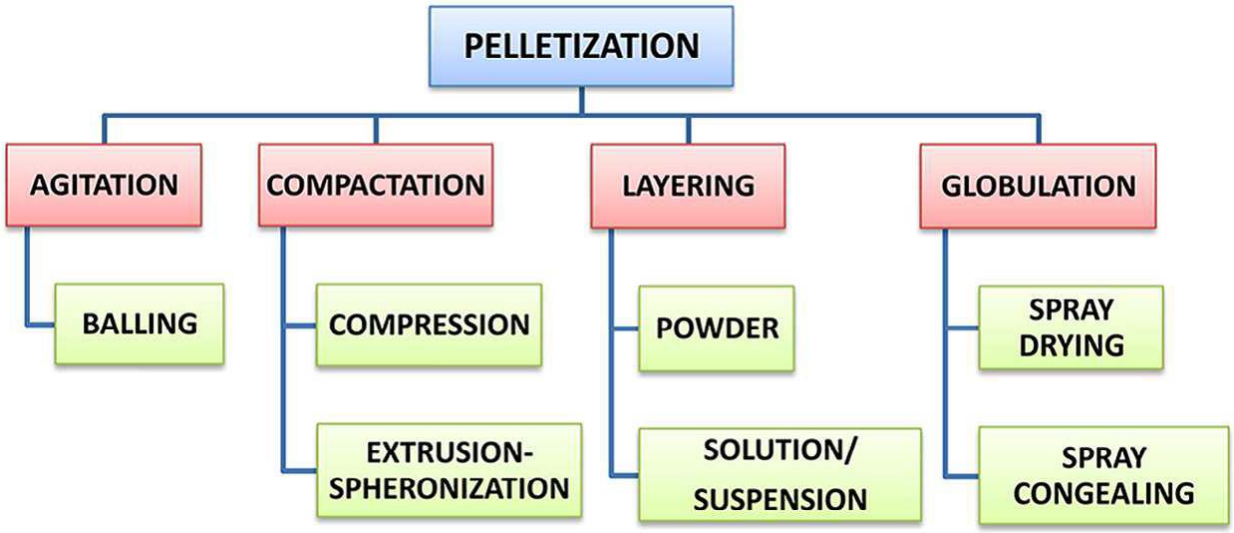
2.Pellet combination as control release drug delivery System: Different pellets of incompatible chemicals can be combined in the same dosage form.

3.Pellets for Inhalation: Non-irritating soft pellets are designed for inhalation with a maximum particle diameter of approximately 1 mm in size for treating respiratory disorders.

4.Pellets as Implants: Polymeric spheroidal particles can be used as implants for release of Active Pharmaceutical Ingredients over a longer period of time. Several methods of pelletization are used for pellet implant production, but widely used is an extrusion.

5. Pellets as Solid Self Emulsifying Drug Delivery System: Used for lower aqueous solubility drugs to improve the *in vivo* behavior of drug by achieving dose proportionality by reducing inter, intrasubject variability. [2,10,22]

PELLETIZATION TECHNIQUES :



A. AGITATION

Agitation involves the conversion of finely divided particles into spheroidal particles by the addition of required liquid by a continuous rolling or tumbling motion. The liquid can be added at the beginning of the process, or during the agitation process. Pans, discs, drums or mixers may be used to produce pellets by the balling process. It is the oldest and less efficient technique for production of pellets.

1) Balling :

It can be done either by adding the required volume of liquid into powder or by applying a high temperature. Spherical agglomeration can be divided into two categories, such as liquid-induced agglomerations and melt-induced agglomerations. Instruments like conventional horizontal drum pelletizers, inclined dish pelletizers or tumbling blenders, rotary fluid-bed granulators. This technique is popularly used in iron ore and fertilizer industries. The rate and extent of agglomeration formation depend on formulation variables such as particle size, the degree of liquid saturation, viscosity of liquid phase and solubility of powder [1,6].

B. COMPACTATION:

Agglomeration of drug particles or granules takes place in presence of pressure which gives out well-defined shape and size of pellet.

1) Compression :

It 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 tablets manufacturing. [7]

2) Extrusion-Spheronization

Produces pellets with high loading capacity of active ingredient without producing extensively larger particles and particles of uniform size distribution with good flow properties.

Steps involved in Extrusion-spheronization-

a) Dry Mixing

Dry mixing of ingredients is done to achieve homogenous powder dispersion using Twin shell blender, Planetary mixer, High speed mixer and Tumbler mixer.

b) Wet massing

It is done to produce a sufficient plastic mass for extrusion, by employing normal equipment and process as employed in wet granulation for compaction.

c) Extrusion

It produces rod shaped particles of uniform diameter from wet mass. The wet mass is forced through dies and shaped into small cylindrical particles with uniform diameter. Such shaping of wet mass into long rods, commonly termed 'extrudate'.

Types of extruder

1. Screw feed extruder
2. Gravity feed extruder
3. Piston feed extruder (Ram).

d) Spheronization

It is also known as 'Merumerizer' consists of a static cylinder and a rotating friction plate where the extrudate is broken up into smaller cylinders with a length equal to their diameter and these plastic cylinders are rounded due to frictional forces. Two geometric patterns are generally used. It includes a cross-hatched pattern with grooves running at right angle to one another, a radial pattern with grooves running radially from the center of the disc.

e) Drying:

A drying stage is required in order to achieve the desired moisture content. An increase in drying rate gives more porous pellets due to decrease pellet densification during drying process.

f) Screening

It is necessary to achieve the desired size distribution, and for this purpose sieves are used. [1,3,]

C. LAYERING :

Pellet formation by layering involves the deposition of successive layers of drug molecules from dry powder or granules, suspension, a solution of drug particles.

1) Powder Layering

In powder layering liquid saturation is low and irrespective of the solubility of the drug in the binding liquid, complete dissolution does not occur. Typically, a binder solution is first sprayed onto the nuclei, followed by the addition of powder. The most nuclei tumble in the rotating pan of disc, pick up powder particles, and form layers of small particles that adhere to each other and the nuclei by means of capillary forces developed in the liquid phase. As additional bonding, liquid is sprayed, layering of more powder on the nuclei continues until the desired pellet sizes are obtained. On drying, the binder and other dissolved substance crystallize out and the liquid bridges are partially replaced by solid bridges. On spraying with binder, fines may pick up moisture and enter a nucleate on phase.[1,3]

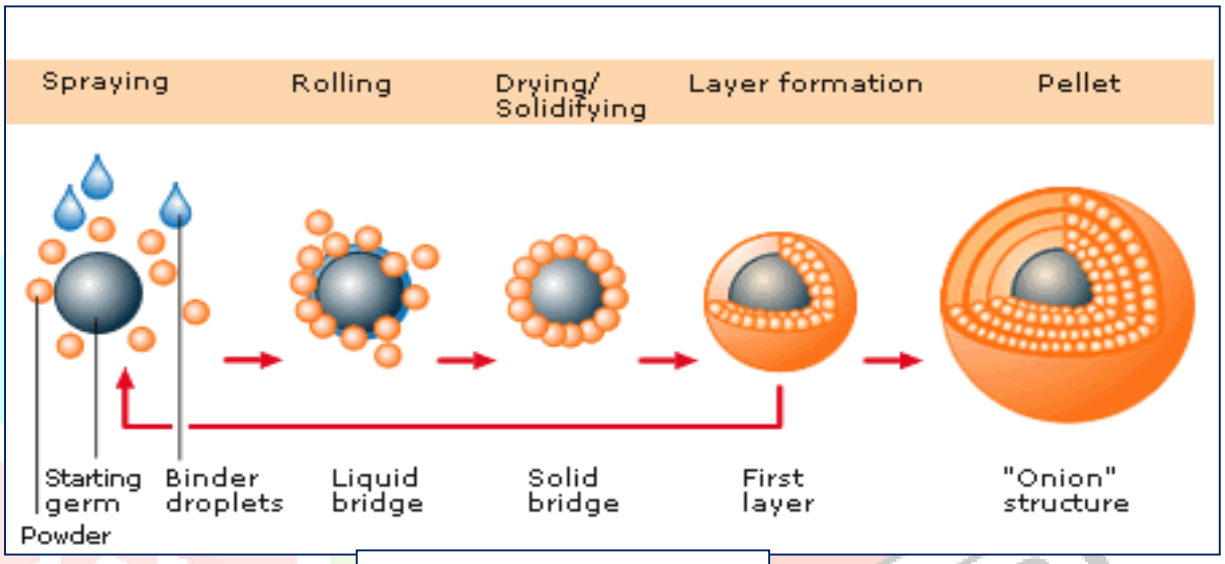


FIG.NO.1.POWDER LAYERING

2) Solution and Suspension Layering

Principle of the suspension and solution layering process: Solution and suspension layering involve the deposition of successive layers of solutions and suspensions of drug substances, respectively, on starter seeds that may be inert materials or crystals or granules of the same drug. In principle, the factors that control coating processes apply directly to solution or suspension layering. During solution or suspension layering, all the components of the formulation are dissolved or suspended in the application medium and hence determine the solids contents and the viscosity of the liquid sprayed. As the solution or suspension is sprayed onto the product bed, the droplets impinge on the starter seeds or cores and spread evenly on the surface, provided that the drying conditions and fluid dynamics are favorable. This is followed by the 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 are

achieved. The rate of particle growth is rather slow due to the incremental addition of the dissolved or suspended drug .In this process, though 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. Figure 2 shows the principal of solution or suspension layering. [3,7,13]

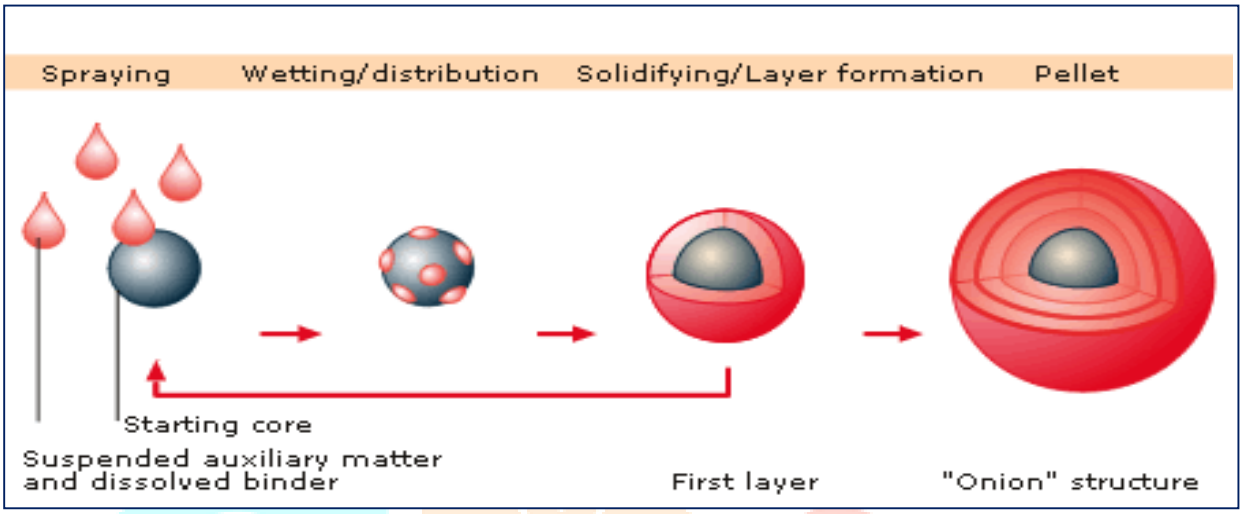


FIG.NO 2 Principle of Solution/suspension

D. Hot-Melt Extrusion technology (HME)

It is process of pumping raw materials with a rotating screw under elevated temperature through a die into a product of uniform shape. Rotating screw impose mixing and agitation result in the de-aggregation of suspended particles in the molten polymer resulting in the more uniform dispersion. [7,14]

E) GLOBULATION:

It is also known as droplet formation, it contains two process, spray drying and spray congealing. It works by atomization of hot melts, suspensions or solutions to form pellet particles Globulation or droplet formation includes spray drying and spray congealing.

1) Spray drying :

In this process the highly spherical and dry particles are generated, the drug molecules in solution or suspension form are sprayed, with or without excipients into the hot air stream. This process is generally used to improve the rate of dissolution and also increase the bioavailability of poorly soluble drugs.

2) **Spray congealing:**

It is a process in which the drug is permitted to melt, diffuse or dissolve in worm melts of gums, waxes, fatty acids, erc. and then it is sprayed into the air chamber where the temperature is below the melting point of formulation components to provide congealed spherical pellets under suitable storage conditions. [1,3,15]

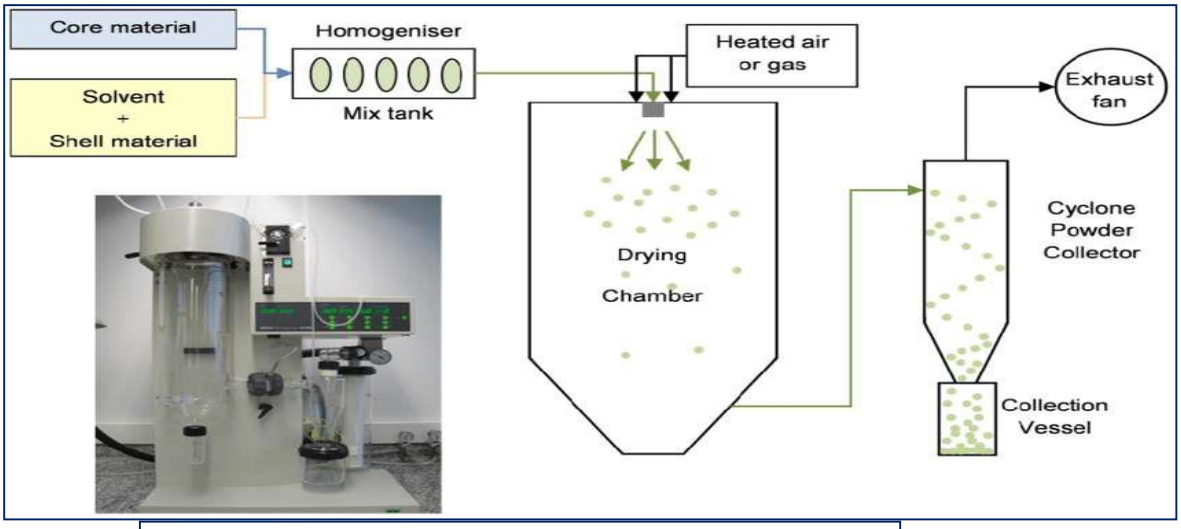


FIG NO.3.SPRAY DRYING AND CONGEALING

F. **Cryopelletization :**

Pellets here 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 freezing of the material being processed due to rapid heat transfer that occurs between the droplets and the liquid nitrogen for manufacturing a given quantity depends on the solid content and temperature of solution or suspension being processed. The pellets are dried in conventional freeze dryers to remove water or organic solvents. [3,17]

G.Freeze Pelletization:

In the process of freeze pelletization, a molten -solid carrier/matrix is introduced in the form of droplets into an inert column of liquid in which the molten solid is immiscible. The molten solid droplets move either upward or downward in the liquid column (depending on the droplet's density with respect to the liquid in the column) and solidify as spherical pellets. If the density of the molten -solid carrier/matrix is less than that of the liquid in the column, the droplets are introduced from the top of the column and the pellets solidify in the bottom. On the other hand, if the density of the molten solid carrier/matrix is more than that of the liquid in the column, the droplets are introduced from the bottom and the pellets solidify at the top. [6,18]

l) Fluid Bed Coating :

Fluid Bed Coating For Preparing Pellets Is Of The Following Three Types:

1) Top Spray Coating:

With top spray coating in the fluid bed (batch and continuous), particles are fluidized in the flow of heated air introduced into the product container through the base plate. The fluid bed is sprayed with the coating liquid through a nozzle from above against the air flow (counter-current). The particles dry as they continue to move upwards in the air flow. The coating liquid distributes uniformly owing to the small size of the droplets and

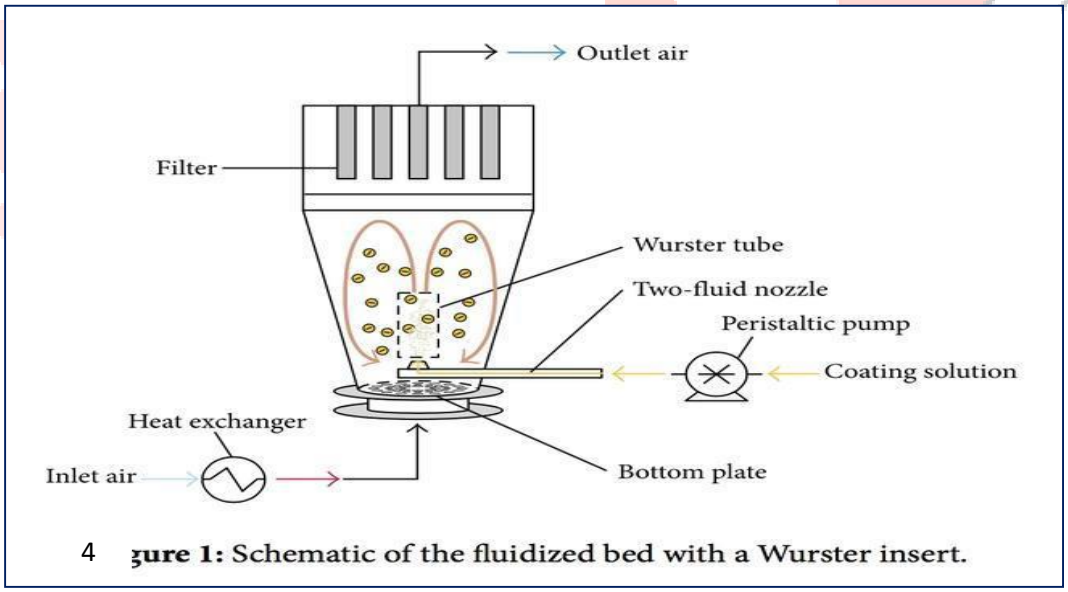
low viscosity of the spray medium. Coating in the continuous fluid bed is suitable for protective or colour coatings where the product throughput rates are high. In this method, the product is continuously fed into one side of the machine, and by means of air flow is transported forward via the sieve bottom. The dry coated particles are extracted continuously.

2) Bottom Spray Coating (Wurster Coating):

This process is used when a controlled release of active ingredients is required. In the wurster coating process, the surface is sealed completely by less use of the coating substance. The spray nozzle is fitted in the base plate resulting in a spray pattern concurrent with the air feed. By using a wurster cylinder and a base plate with different perforations, the particles to be coated are accelerated in the wurster tube and concurrently fed through the spray cone. As the particles move upwards, they dry and fall outside the wurster tube back towards the base plate. They are guided from the outside back to the inside of the tube, where they are again accelerated by the spray, thus producing a highly uniform film even on different sized particles.

3) Bottom Spray Coating (Continuous Fluid Bed):

This process is suitable for protective or colour coatings where the products throughput rates are high. The product is continuously fed into one side of the machine and by means of air flow is transported forward via the sieve bottom. Depending on the application, the system is sub-divided into pre -heating zones, spray zones, and drying zones where coating liquid is sprayed from below in the form of a bottom spray. The dry and coated particles are continuously extracted.



4 **gure 1:** Schematic of the fluidized bed with a Wurster insert.

4) Tangential spray Coating :

In the process of tangential spray coating, the product is set into a spiral motion by means of a rotating base plate which has air fed into the powder bed at its edge. The spray nozzle is arranged tangentially to the rotor disc and is sprayed simultaneously into the powder bed. This method is ideal for coatings with high solid content, and for applying thick film layers. [1,3,5,6]

Factors affecting pelletization techniques:

1. Moisture content :

Moisture in the wet mass brings cohesiveness to powder so that the wet mass can be extracted and spheronizer to give spherical shape. High moisture contents lead to agglomeration of pellets during the process of spheronization.

2. Rheological characteristics

The optimum rheological condition leads to good flow ability in order to extrudate the wet mass. The rheological variations make improper and non-uniform extrudate.

3. Solubility of excipients and drug in granulating fluid

Soluble drug get dissolve in a granulating liquid. Thus increasing the volume of liquid phase leads to over wetting of pellets. But increase in wetting liquid increases plasticity but includes sticky mass.

4. Composition of granulating fluid

Besides water, alcohol, water/alcohol mixture, ethyl ether, dilute acetic acid, isopropyl alcohol is used as a granulating liquid. Aqueous polymer dispersion containing HPMC, PVP, etc can also be used as granulating fluid.

5. Physical properties of starting material

Quality of pellets depend not only composition but also on different grades of the same product. The swelling property of material used in pelletization technique decides the release rate of drug in pellets.

6. Speed of Spheronizer

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

7. Extrusion screen

The quality of pellets is greatly influenced by the characteristics of orifice of the screen. And 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. [4,12,24]

THEORY OF PELLETS GROWTH AND FORMATION:

Before selection and optimization of any Pelletization/granulation process, it is important to understand the fundamental mechanisms of pellet formation and growth. Different theories have been postulated related to the mechanism of formation and growth of pellets. Some of these theories are derived from experimental results while others are derived by visual observations. Out of these hypothetical theories the most convincing classification of Pelletization process, involves three consecutive regions: nucleation, transition and ball growth. However, based on the experiments on the mechanism of pellet formation and growth, the following steps were proposed.

A. Nucleation phase :

Nucleation is a stage of Pelletization process that occurs whenever a powder is wetted with solvent system. The primitive particles are drawn together to form three phase air-water-liquid nuclei system which are held together by liquid bridges that are pendular in nature. The reduction of particle size will improve the bonding strength between them. Further the size, the rate and the extent of nuclear formation depends upon the size of the particles, the moisture content, the viscosity of the binding particles, the wettability of the substrate and the processing conditions, such as tumbling and drying rates.

B. Coalescence phase:

Coalescence is defined as the formation of large-sized particles by random collision of well-formed nuclei, this mechanism require slightly excess moisture on the surface of the nuclei although the number of nuclei is progressively reduced even though the total mass of the system remains unchanged during this operation.

C. Layering phase:

Layering is a slow growth mechanism and with the successive addition of fragments and fines on an already formed nuclei. In the layering step, the number of particles remains constant while the total mass of the system increases due to increasing particle size as a function of time. The fragments or fine particles can be formed by particle size reduction The fines and the fragments produced through size reduction are taken up by larger pellets.Production of fines and subsequent coalescence and layering continues until the number of collisions declines rapidly, thereby leading to a reduction in the rate of growth of the pellets. At this point the third phase, the ball growth region, is reached.

D. Abrasion transfer phase:

The main mechanism in the ball growth phase is the abrasion transfer which involves the transfer of materials from one granule formed to another without any preference in either direction. This phase does not result in any change in the total number or mass of the particles. However, the particles undergo a continuous change in their size as long as the conditions that lead to the transfer of material exist. [1,6]

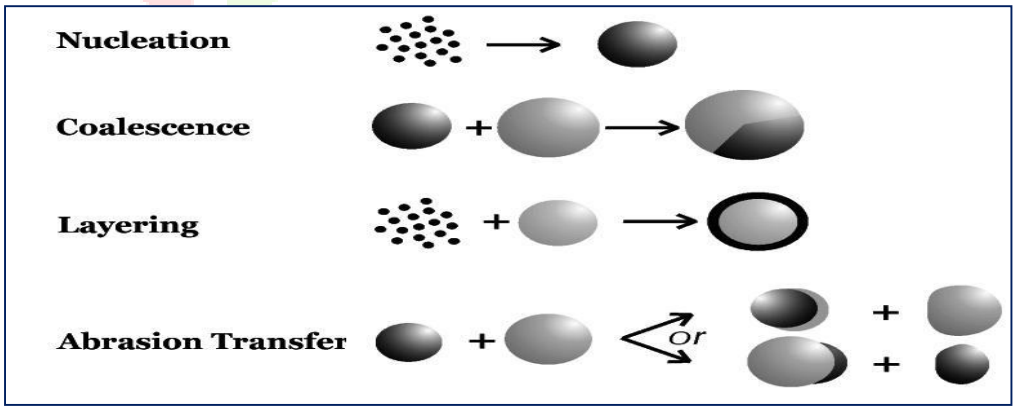


FIG.5.MECHANISM OF PELLETS GROWTH

Characterization and evaluation of pellets:

The prepared pellets must go through various parameters for characterization and evaluation of pellets.

Characterization of pellets as follows:

Particle size analysis:

The particle sizes of the formed pellets are to be measured using an optical microscope with ocular and stage micrometer where the particle size distribution can be calculated. The 'Wesmox model' with a resolution of 45x may be used. The particle size distribution study can also be done by 'Sieve Analysis' technique by using a set US standard sieve of different mesh size known as different sieve numbers such 14,16,18,22 and 44 with a pellet of the load of 10 gm. The sieve set is to be mechanically shaken for 10 min, total net weight of pellets retained on each sieve was determined and these values are used for calculating particle size distribution.

Micrometric properties

1. The angle of repose :

Angle of repose is used to know the pellet flow property by using a fixed funnel method. The radius (r) of the pellet pile formed and height of the pellet pile (h) is determined. The angle of repose for the pellet sample is calculated using the formula:

$$\theta = \tan^{-1}(h/r)$$

Where 'r' is the radius of the pellet pile formed and

'h' is the height of the pellet pile.

2. Carr's index :

It is a dimensionless parameter, which proves to be useful to the same degree as the angle of repose values for determining the flow property. Apparent bulk density was determined by pouring the bulk samples into a graduated cylinder. Tapped density can be determined by placing a graduated cylinder containing a known mass of powder on a mechanical tapper apparatus (Electro lab tap density tester).

Carr's index can be calculated by using the equation given below:

Carr's index=Tapped density-Bulk density/Tapped density

3.Hausner's ratio:

It measured by the ratio of tapped density to bulk density.

Hausner's ratio =Tapped density/Bulk density

4. Friability (F) :

Friability test for pellets takes place by using known mass pellets particle size ranging from 1000 to 1410 μm as (WO) placed in an apparatus called as "Roche friabilator" where the procedure involved is a simplest one by maintaining 25 rpm for a time period of 4 min. After completion of the required time period, the pellets are removed from the apparatus in a sterilized manner and further subjected to know the weight of the pellets as

final weight or weight after 100 rotations i.e,4 min(W) of time and the friability was calculated by using the equation mentioned below:

$$\text{Friability\%} = [1 - W/W0] \times 100$$

Where, *WO* is the initial weight and

W is the weight after100 rotations.

The friability test is performed on the formed pellets to ensure the ability of mechanical strength to withstand the property of strength where lower the friability value indicates good mechanical strength of the spheroids.

5. Pellet sphericity test:

The pellet size and spheroidal shape are determined by using an image analysis system. By using digital camera photomicrographs can be obtained where further analysis of the obtained pellet images is carried out by software (Digimizer, USA).

Therefore, characterization each individual pellet can be known by the aspect ratio (AR) and two-dimensional shape factor(eR).

The equation for pellet sphericity is as follows:

$$eR = 2\pi r/Pm\text{-}(b/l)\ 2$$

Where ‘r' is the radius, 'Pm' is the perimeter,

‘l' is the length and ‘b’ is the width of the pellet.

6. Compatibility studies :

It plays important role in selecting the appropriate excipients for a particular drug and a particular formulation because the drug maintains its continuous contact with one or more excipients which directly or indirectly may affect the stability of drug or a formulation. These compatibility studies can be carried out by using FT-IR Spectrophotometer and Differential Scanning Calorimetry.

7. FTIR studies :

FTIR stands for Fourier transform infrared spectroscopic, where the analysis is used for pure drug and pellet grains using KBr pellet process on FTIR spectrometer. The drug is mixed with KBr and spectra are taken. FTIR spectrum of pure drug is compared with FTIR spectra of drug formulations. The disappearance of peaks or shifting of peaks in any of the spectra can be studied by using the apparatus named FTIR 8400-S, Shimadzu, Japan model. [1,3,4,6,20]

Evaluation of pellets:

1. Percentage yield:

Percentage yield determination is carried out to know the preparation procedure chosen for pellet formation is effective or not, and also to know the importance of the procedure used regarding safety and efficacy with lesser effort and greater benefit. Hence the quantity or the amount of active pharmaceutical ingredients, polymers, binding agent, anti-frictional agents, starch paste and other process parameters are the factors which play a major role in deciding the yield of the pellets during pelletization process.

The formula for calculation of % yield of a pellet is written below:

% yield= weight of pellets/Weight of drug+weight of polymers×100

2. Loose surface crystal study (LSC) :

A total amount of 200 mg of pellets are suspended in a beaker containing 100ml of phosphate buffer (pH 7.4). The amount of drug present in the solution can be analyzed by spectrophotometrically at 265nm.

3. Determination of drug content :

Pellets drug content can be determined using UV/Visible spectrophotometer instrument were the prepared pellets are crushed into powder form. And the finely crushed sample of pellets equivalent to 100 mg of DPP is transferred to 100ml volumetric flask which is diluted with 100ml solvent which is particular for particular pellet particles and the absorbance value is noted at suitable wavelength, where initially before placing sample the background scan has to done and the drug content in pellet is determined using calibration curve.

4. Surface Morphology:

Scanning electron microscopy method is used to determine the surface morphology of formed pellets and also the cross-section pattern of pellets can be known. Some researcher analyzed surface roughness of pellet can be done by applying a non-contracting laser profile meter. And also by using an optical microscope the microstructure of spheroidal particles surface can be determined.

5. Specific Surface Area:

Specific surface area totally depends upon the size and the shape of the pellet granules and if the coated pellets are available then a desirable surface area can be achieved. The information regarding uncoated pellets plays a key role in increasing drug release by surface area. Thus specific surface area of a pellet is carried out by "Gas adsorption technique".

6. *In vitro* drug release studies:

In vitro dissolution studies are carried out either by using paddle type or basket type apparatus using IP or USP model. According to the IP model, type 1 is a paddle and type 2 is basket apparatus and according to the USP model, type 1 is basket and type 2 is paddle. 900ml of a solution which is suitable for the formulation is used as a dissolution medium. The paddles or basket is operated at a particular rpm based upon the drug, and the temperature has to be maintained at 37°c throughout the experiment. Dissolution samples should be withdrawn from the apparatus at regular intervals of a time period starting from minutes to hours up to 24h based on the type of drug delivery pattern and meanwhile replacement of equal volume of dissolution medium to maintain the volume throughout the experiment so that constant sink condition is achieved. Then further step is to dilute the withdrawn samples at a different interval of time with same dissolution media used and the amount of drug released was estimated by using “UV-Spectrophotometer” at suitable wavelength depending upon drug used . [1,6,9,16]

CONCLUSION :

The brief review on pellets and pelletization concludes pelletized dosage forms as one of the most efficient pathway of novel and multiparticulate drug delivery systems. In addition, hot-melt extrusion fluidized bed technology and spheronization, powder layering, solution layering, provides a wide scope to formulate pellets. Today, pelletization is challenging and growing technique to develop pelletized dosage forms for a wide range of drugs which are unstable or have compatibility problems with excipients and hence the market for these dosage forms is growing rapidly and gaining popularity with an impressive rate. This technology has remained much of an art for thousands of years due to its process, formulation and therapeutic advantages over single unit drug delivery systems.

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