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Review Article

PELLETS AND PELLETIZATION TECHNIQUES: A REVIEW

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ABSTRACT

Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free flowing, spherical or semi-spherical units, referred to as pellets. This review outlines manufacturing of spherical pellets. The manufacturing techniques include Drug layering, Extrusion-Spheronization, Cryopelletization, Compression, Balling, Hot-Melt Extrusion Technology, Freeze pelletization, Spray-drying & Spray-congealing. Factors affecting pelletization technique and advantages, disadvantages of pellets are discussed.

Keywords: Pelletization, Pellets, Extrusion-spheronization.

INTRODUCTION

Pellets are spherical or nearly spherical, free-flowing granules with a narrow size distribution, typically varying between 500 and 1500 µm for pharmaceutical applications. They are generally produced via a pelletization process whereby a powder blend consisting of an API and excipient particles is agglomerated into spherical granules. [2] After being processed, pellets are usually filled into hard gelatin capsules or compressed into tablets. Furthermore, they can be formulated as immediate release dosage form or in sustain drug release over a long duration time or can be coated also to deliver a drug to a specific site of action in the gastrointestinal tract. Pellets provide the development scientist with a high degree of flexibility during the design and development of oral dosage forms. They can be divided into desired 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 within gastrointestinal tract.

Pellets provide development of formulation with high degree of flexibility due to free-flowing characteristic. So they are packed easily without any difficulties. The spherical shape and a low surface area to volume ratio of pellets made uniform film coating. Pellets eliminate the dose dumping effect, which gives smoother plasma concentration profile and gradual absorption of drug than tablet, which further decrease the adverse effect of drugs.

Advantages

1. **Uniformity of dose-** Layering techniques and extrusion-speronization offers great accuracy with drug delivery the pellets
2. Spheres have excellent flow properties This becomes very useful in automated processes or in processes where exact dosing is required, e.g. tableting, moulding operations, capsule filling, and packaging.
3. Prevention of dust formation Resulting in an improvement of the process safety, as fine powders can cause dust explosions and the respiration of fines can cause health problems.
4. Controlled release application of pellets due to the ideal low surface area-to-volume ratio that provides an ideal shape for the application of film coatings.
5. They can be blended to deliver incompatible bioactive agents simultaneously and/or to provide different release profiles at the same or different sites in the gastrointestinal (GI) tract.

Therapeutic Advantages

6. Pellets can disperse freely throughout the GIT after administration and consequently the drug absorption is maximized.
7. The wide distribution of spherical particles in the gastrointestinal tract limits localized build-up of the drug, avoiding the irritant effect of some drugs on the gastric mucosa;
8. Reduce inter- and intra-patient variability.
9. Modified-release multiparticulate delivery systems are less susceptible to dose dumping than single-unit dosage forms.

Disadvantages

- Pellets filling involve capsule filling which can increase the costs
- Tableting of pellets destroy film coating on the pellets.
- The size of the pellets may vary formulation to formulation but usually is in range
- of 0.05 mm and 2 mm
- It is difficult to compress pellets into tablets as they are too rigid. Therefore, they are often delivered encapsulated in hard gelatin capsule shells.
- Pelletization demands highly sophisticated and specialized equipment, thereby increasing the cost of manufacturing.
- The control of manufacturing process is complicated with too many process variables as well as formulation variables.

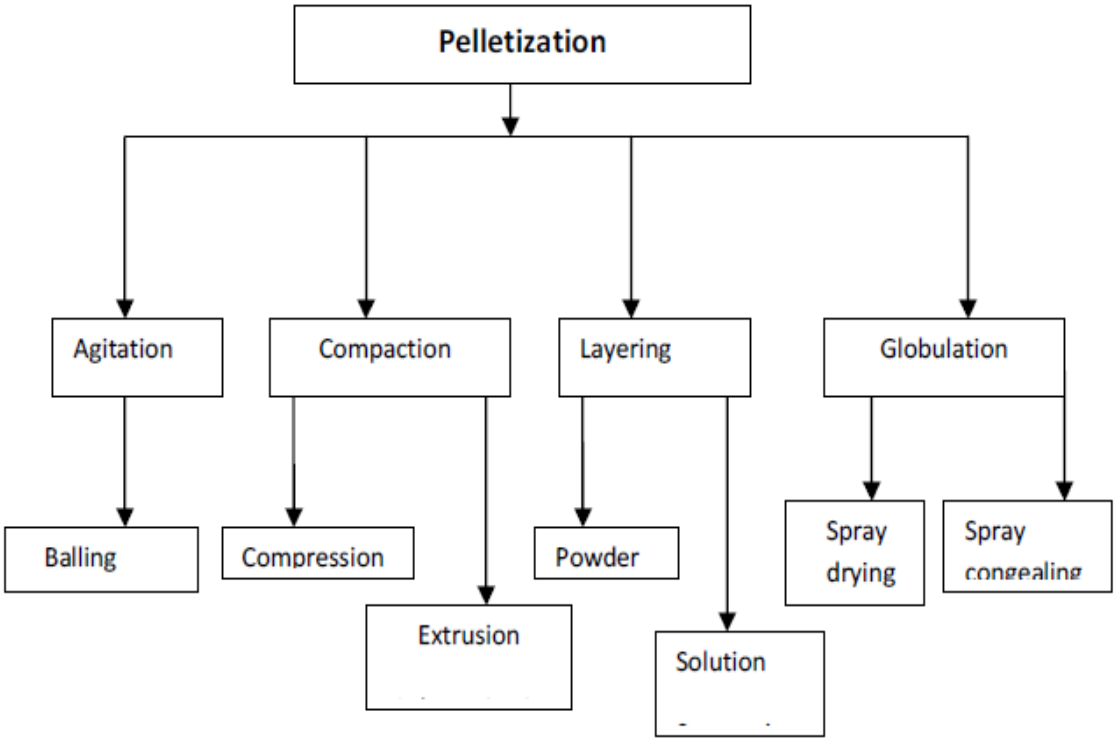
Desirable Properties of Pellets

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



Different techniques of Pelletization

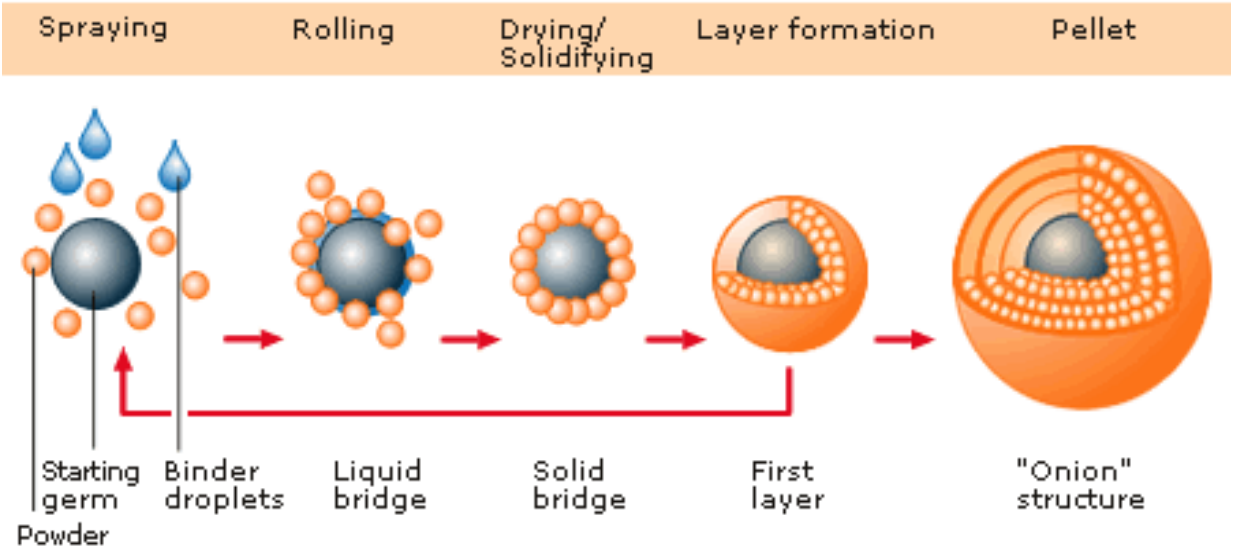
Pelletization techniques

1. Drug Layering

It includes 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. In solution/suspension layering, drug particles are dissolved or suspended in the binding liquid. In powder drug layering, a binder solution is first sprayed onto previously prepared inert seeds, followed by the addition of powder.

a)Powder Layering

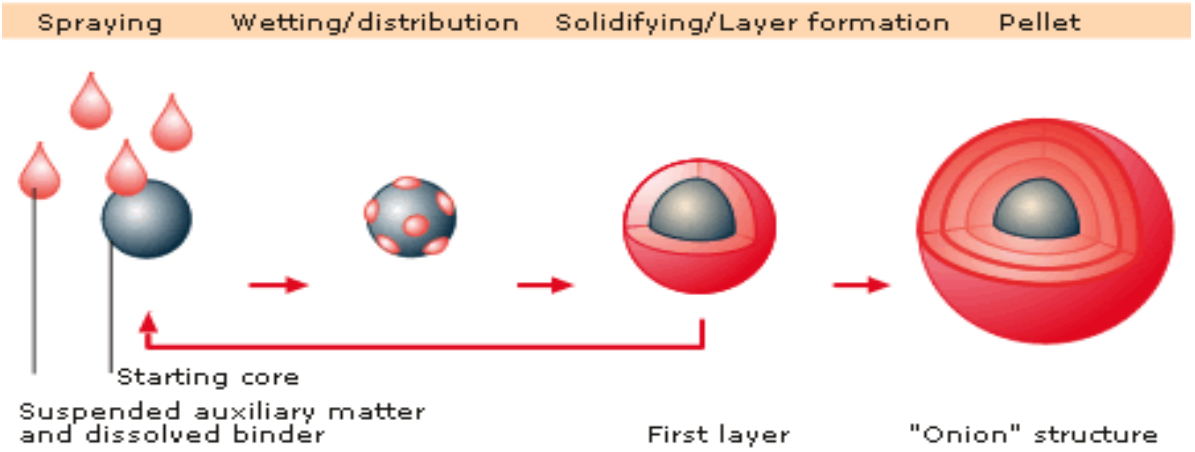
In powder layering liquid saturation is low and irrespective of the solubility of the drug in the binding liquid, complete dissolution does not occur. Typically, a binder solution is first sprayed onto the nuclei, followed by the addition of powder. The most nuclei tumble in the rotating pan of disc, 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.



Principle of Powder layering

b)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 3 shows the principal of solution or suspension layering.



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
Screw feed extruder
Gravity feed extruder
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.

3. 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.

4. 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.

5. Balling

It is pelletization process in which pellets are formed by a continuous rolling and thumbing

motion in pans, discs, drums or mixtures. The process consists of conversion of finely divided particles in to spherical particles upon the addition of appropriate amounts of liquid.

6. 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. Freeze pelletization

In this technique, a molten-solid carrier/matrix is introduced as droplets into an inert column of liquid in which the molten solid is immiscible. The molten solid moves in the liquid column as droplets and solidifies into spherical pellets. The molten solid droplets can move upward or downward in the liquid column depending on the droplet's density with respect to the liquid in the column. If the density of the molten-solid carrier/matrix is less than that of the liquid in the column, then droplets are introduced from top of the column and pellets solidify in the bottom portion of the column. Conversely, if the density of molten-solid carrier/matrix is less than that of the liquid in the column, then the droplets are introduced from the bottom of the column and pellets solidify at the top portion of column.

8. Spray-drying and Spray-congealing

1. Spray-Drying

During spray drying, a drug solution or suspension is sprayed, with or without excipients, into a hot-air stream generating dry and highly spherical particles. Though this technique is suitable for development of controlled release pellets, it is generally employed to improve the dissolution rates and hence improve the bioavailability of poorly soluble drugs. The spray dried powder particles are homogenous, approximately spherical and nearly uniform in size. The design and operation of spray drier can influence a great number of the characteristics of the final product, such as particle size and size distribution, bulk density, porosity, moisture content, flowability and friability.

2. Spray-congealing (Spray-chilling)

It is a technique similar to spray-drying. Spray congealing is a process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes, fattyacids or other melting solids. The dispersion is then sprayed into stream of air and other gases with a temperature below the melting point of formulation components. Under appropriate processing conditions, spherical congealed pellets are obtained.

Factors affecting pelletization technique[11]

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.

Evaluation parameters[10]

1. Particle size distribution

a) Particle size should be as narrow as possible. This will ensure minimum variation in coating, thickness, facilitate blending process if blending of different types is requires.
b) Sieve analysis using sieve shaker is most widely used method for measuring particle size distribution.
c) 100 gm of pellets are weighed using electronic weighing balance. Pellets are then transferred to set of
d) sieves having different mesh size for particle size analysis. Calculate the % retained on each sieve.

2. Surface Area

a) 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.
b) It can be calculated from particle-size distribution by measuring the mean diameter, gas adsorption, and air permeability.
c) Mean diameter- 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 pellets.
d) Air permeability method- It is widely used pharmaceutically for specific surface measurement, for controlling batch to batch variations. The principle for resistance to flow of a fluid such as air through a plug of compacted material is the surface area of material.
e) Gas adsorption method- In this method the volume of nitrogen that is absorbed by the substrate contained in an evacuated glass blub is measured at different pressures.

3. Porosity

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

4. Density

a) The density of pellets can be affected by changes in the formulation or process, which may affects other processes or factors, such as capsule filling, coating and mixing.
b) The bulk density of pellets can be measured by an automated tapper. True density indicates the extent of densification or compactness of substances.
c) Bulk Density= Weight of powder/ Bulk volume
d) Tapped density= Weight of powder/ Tapped volume

5. Hardness and Friability

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

6. Tensile Strength

The tensile strength of 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 pellets.

CONCLUSION

Pellets are the multi-unit dosage forms which offer improved safety and efficacy of the active ingredients with excellent flow properties which is then fabricated in single dosage form. Pelletization technique produces more spherical pellets and offers more advantages than granulation process. Today pelletization represents an efficient pathway for novel drug delivery in the scope for development of different modified-release solid oral dosage forms.

REFERENCES

1. Pathade Shriram Shankar, Phadtare Dipti Ganesh and Saudagar Ravindra Bhanudas, Pelletization: A most significant Technology in the Pharmaceuticals, World Journal of Pharmaceutical Research. 2014;3(6):1972-2003.
2. Gothi GD. Pelletization, Journal of Global Pharma Technology. 2010;2(1):45-57.
3. Mircea H and Cecilia A. Pelletization techniques used in pharmaceutical fields, Practica farmaceutica. 2011;4:206-211.
4. Ghebre-Sellassie. Pharmaceutical Pelletization Technology, Marcel Dekker, Inc., New York, 1989.
5. Punia Supriya, Bala Rajni and Rana AC. Pelletization Technique: A literature Review, International Research Journal of Pharmacy. 2012;3(3):43-47
6. Hiren P Patel, Patel JK, Ravi R Patel and Manish P Patel. Pellets: A General Overview, International Journal of pharma world Research. 2010.
7. Shyamala Bhaskaran and Lakshmi PK. Extrusion Spheronization –A Review, International Journal of PharmTech Research. 2010;4(2):2429-2433.
8. Jawahar N and Patel Hardik Anilbhai. Multi Unit Particulates Systems (MUPS): A Novel Pellets for Oral Dosage Forms. Journal of Pharmaceutical Sciences and Research. 2012; 4(9):1915-23.
9. Anshuli Sharma and Sandhya Chaurasia. Multiparticulate drug delivery system: Pelletization through Extrusion and Spheronization. 2013;4(2):6-9.
10. Afifa Bathool, Gowda D Vishwakanthe, Mohmmed S Khan and Vikas K Gupta. Pelletization as a key tool for oral drug delivery: A review, Journal of Pharmacy Research. 2011,4(11):3282-86.
11. Ramu S, Ramakrishna G, Balaji M, Kondala rao K, Haranadh reddy S and Pavan kumar D. Multiple Unit Drug Delivery System: Pelletization Techniques, American Journal of Advanced Drug Delivery. 2013;1(1):011-021.