



PELLETIZATION – A NEW HORIZON

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Abstract: Pellets are the multiparticulate drug delivery system which prove to be promising and highly flexible system with various kinetics of drug release such as immediate release, sustained and controlled release which are easy to formulate. In order to overcome the physicochemical interaction such as drug-excipient or drug-drug interactions multiparticulate dosage forms can be implemented. The technology of pelletization as oral drug delivery system are gaining substantial attention in the present time. Pelletization is the process where the aggregates of granules or fine powders mixture of drugs and excipients. They form small spherical or semi-spherical free flowing solid units ranging from 0.5 mm to 1.5 mm. Pellets are commonly used as multiparticulate systems as it has technical as well as clinical advantages over single unit dosage forms. The present review focuses on advantages, disadvantages, mechanism of pellet formation, different methods of pellet preparation, characterization of pellets, and also the recent approaches for pelletization techniques.

Key words: Pellets, multiparticulate, pelletization, Granules, Dosage forms, Techniques, Spherical.

Introduction.

History. ^(1,2,3)

Pelletization process were used to manufacture particles with disered size and shape by various industries. In early 1950s, the pharmaceutical industry developed sustained release dosage forms. Based on requirement of sustained release dosage forms new methods were developed such as spray dryer which has a wide application in industry. Meanwhile the new machine was developed by japan 'The Marumerizer' which could produce large quantities of pellets in short period of time. The pellets produced by this contains 90% active and physicochemical properties of drug where as other formulations are optimum.

Pellets. (1,2,3,4,5,6)

Pellets are the aggregates of granules or fine powders mixture of drugs and excipients, they are small spherical or semi-spherical free flowing solid units ranging from 0.5 mm to 1.5 mm, which are usually used for oral administration. There are many methods for preparing pellets. Today the widely used technique is drug layering and compaction technique. The pellets are usually compressed into tablets or filled into hard gelatine capsule they are usually formulated as immediate release or sustained release dosage forms, they can also be coated to target a particular site for its action. Pellets should meet certain requirements during manufacturing process such as:

1. Pellets should be spherical in shape and have smooth surface which is the optimum characteristic in film coating.
2. The optimum size of pellets is considered to range between 600 to 1000 μm .
3. The pellets should be loaded with maximum amount of active ingredient to maintain the final dosage form within reasonable size limits.

Advantages. (2,3,4,6,7)

1. The desired dose strength can be divided without any changes in process or formulation.
2. Product appearance is improved.
3. Pellets have good flowability when compared to powders due to its small size and shape.
4. Handling of pellets are easy if they are encapsulated.
5. Incompatible ingredients can be incorporated in single dosage form.
6. Pellets can be film coated in order to protect the active ingredients from getting degraded due to oxidation or moisture.
7. Patient acceptance is high when the pellets are filled in capsules compared to tablets due to its elegance.
8. Drug loading capacity is high without producing large pellets.
9. Decreased side effects and pellets are less inclined to dose dumping effects.
10. Gastrointestinal irritation are reduced due to the small pellet size compared to tablets.
11. It reduces inter and intra patient differences in gastric emptying rate and intestinal transit time.
12. Sustained, controlled, or targeted delivery of drug can be formulated by coating the pellets.
13. Useful in case of children and aged people like in the case of difficulty in swallowing and dysphagia.
14. Better distribution can be obtained in case of immediate release pellets due to large surface area.
15. In the development and design of oral dosage forms like tablets, capsule and suspension high degree of flexibility can be obtained.

Disadvantages. (2,3,4,6,7)

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.

Theory of pellet growth and formation. ^(1,2,5,8,9)

Several concepts have been hypothesized to correlate the growth of pellets and mechanism of formation of pellets. The most systematically studied and classified pelletization process, involves techniques such as rotating drum, pan or disc which is divided into three further steps: Nucleation, Transition and Ball growth. Whereas, based on the experiments on mechanism of pellet growth and formation the following steps were anticipated such as:

1. Nucleation
2. Coalescence
3. Layering
4. Abrasion transfer

Nucleation is common stage in all pelletization process usually it arises when the powder is wetted with binder solution. Here the primary particles are strained together to form three phases that is air-water-liquid nuclei these nuclei are attached to one another by the liquid bridges which are pendular in nature. Nucleation is followed by a transition stage, here the growth mechanism affects the transition stage due to coalescence and layering. The coalescence is defines as well formed nuclei due to the collision of large size particles, during this step the total mass remains uncharged and the number of nuclei reduces gradually. The layering step involves the layering of already formed nuclei by sequential addition of material. Followed by transfer of material from one pellet to another without any predilection in the direction is abrasion transfer. The growth mechanism is indirectly affected by the three size reduction mechanisms mostly layering and to some level coalescence. The size reduction of well-formed particles occur due to attrition, breakage and shatter.

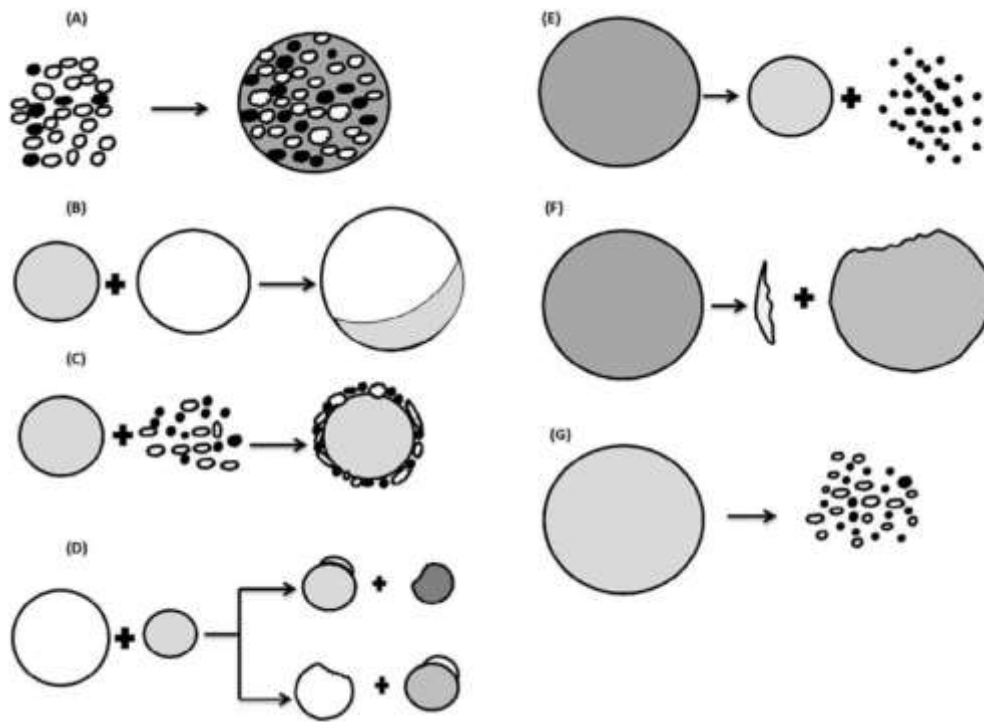
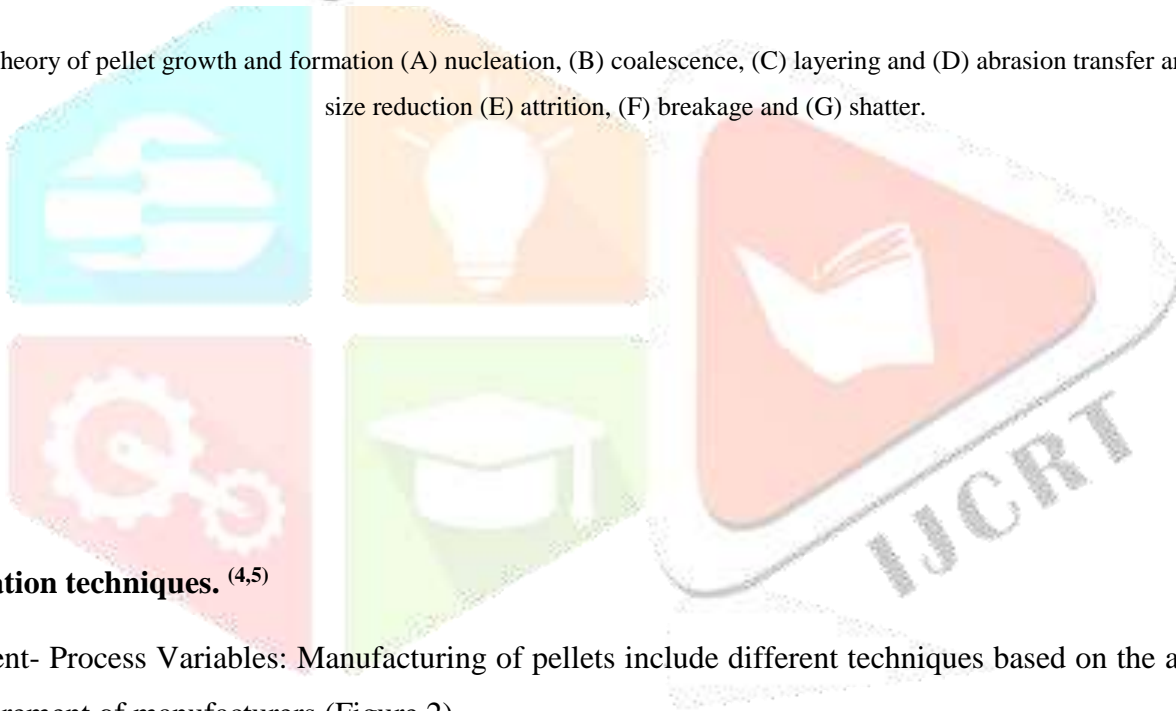


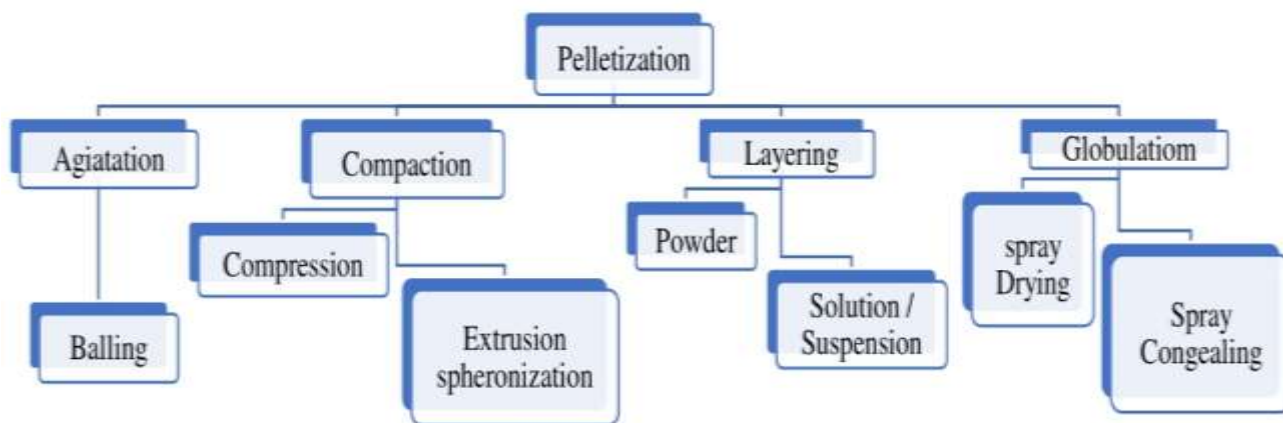
Fig. 1 – Theory of pellet growth and formation (A) nucleation, (B) coalescence, (C) layering and (D) abrasion transfer and mechanism of size reduction (E) attrition, (F) breakage and (G) shatter.



Pelletization techniques. ^(4,5)

Equipment- Process Variables: Manufacturing of pellets include different techniques based on the application and the requirement of manufacturers (Figure 2).

Fig. 2



Different Pelletization techniques.

a. Agitation: (8,9,10,12)i. Balling:

In this technique, liquid is added in requires amount prior or during agitation stage to finely divided particles, this mass under continuous rolling or tumbling motion results in spherical particles. Equipment used is pans, discs, drums, or mixers.

b. Compaction: (8,9,10,11,13,14)i. Compression:

The active ingredient and excipient mixtures are compacted in this process to obtain pellets under pressure of definite shape and size 15, 16. Such pellets are thinly dispersed and can be packed into the capsules.

ii. Extrusion - Spheronization:

It is a multi step process, the advantage of this method is to fabricate the spheres with high drug loading i.e.; up to 90%. This process involves the drymixing of the drug and excipients to achieve a homogeneous mixture, then followed by wet massing of the dry mixture, then it is granulated, extrusion of the wet mass is carried out where noodle like extrudates are obtained, then this mass is transferred into the spheronizer which produces the spherules, then these spherules are dried in dryer and at the end screening is done to obtain required particle size. This is also called as cold mass extrusion-spheronization.



Fig. 3 - Exruder Spheronizer techniques.

c. Layering: (5,11,12,15,16,17)

It is a well controlled pelletization technique where the drug is layered on to the starter materials such as coarse or nonpareil materials in powders. Where as the solution or suspension form the homogenous pellets are assisted with the aid of binder, which consist of an inner core and an outer shell region of different composition. To obtain uniform coating the nonpareil beads should have spherical shape, smooth surface and uniform particle size distribution.

The binder concentration is selected depending upon the drug as it influence physical and mechanical properties of pellets and also the drug release from the coated pellets. Gelatin, povidone, carboxymethyl cellulose, hydroxyl propyl methylcellulose, hydroxypropyl cellulose, sodium C MC and malto-dextrins are the most widely used binders.

Three types of layering are classified: direct pelletizing, layering of powder and solution and layering of suspension.

i. Direct pelletization:

The homogeneous pellets are formed in this process without any detectable core. In the high shear mixers and fluidized bed equipment, it is primarily done.

ii. Powder layering:

dry drug powder and excipients are sprayed with binding fluid in this process, resulting in the deposition of successive layers on preformed nuclei or nuclei. The equipment used is a tangential fluidized bed granulator / centrifugal / rotary spray and traditional coating bowl.

iii. Solution/Suspension layering:

The growth of pellets in this process involves the deposition on existing nuclei of successive layers of solution or suspension of product substance and binders. The molecules of the drug are dissolved or suspended with or without a binder in a solvent. The binding fluid droplets scatter uniformly across the nuclei's surface and are subjected to drying. The liquid evaporates during the drying process. And the dissolved substances crystallize and the particles move towards each other and towards the inert core due to capillary forces formed, which leads to solid bridges formation.

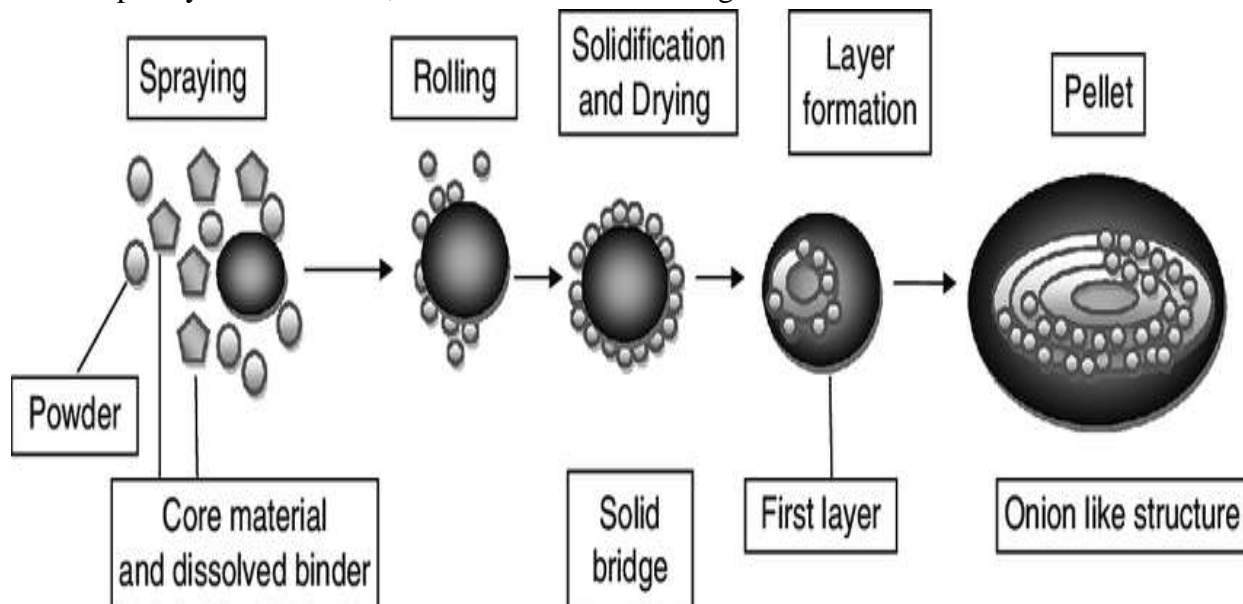


Fig. 4 - Layering techniques.

Sugar spheres consisting of saccharides and their derivatives (sugars, sucrose-starch mixtures, oligosaccharides, polysaccharides), micro-crystalline cellulose spheres, pure drug crystals, polymers such as plastic resins, inorganic substances (silica glass, hydroxy-apalite), organic substances (activated carbide) are the most frequently used materials in the production of coated pellets. Layering is carried out in Fluid bed systems. These are of three types.

1. Granulator, Top-spray method is favored when applying flavor masking, coating, and product granulation in conjunction with excipients. It is also suitable for hot melt coating application. The long expansion chamber allows the particles to decelerate for much longer periods as well as reduced agglomeration in a high velocity fluidized air stream. The nozzle was mounted in such a way without spray-drying to achieve uniform spray.
2. Wurster, Bottom spray method is used to apply modified-release coating to a wide variety of multiparticulates; it is also ideal for drug layering when the dosage of the drug is small to moderate. Bottom spray coater consists of (a) product container with bottom fitted perforated plate for particle fluidization (b) Wurster positioned at the bottom in such a way that floral particle circulation (c) spray nozzle is asserted.
3. Rotor, Tangential spray method is used to obtain modified-release film coating to a wide range of multiparticulate products. If the dosage is moderate to heavy, it is suitable for drug layering. It is also useful in the production of spheres by spheronizing process.

d. Globulation: (9,10,11)

Globulation or droplet formation includes spray drying and spray congealing.

- i. **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.
- ii. **Spray congealing:** It is a process in which the drug is permitted to melt, diffuse or dissolve in warm melts of gums, waxes, fatty acids, etc., 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.

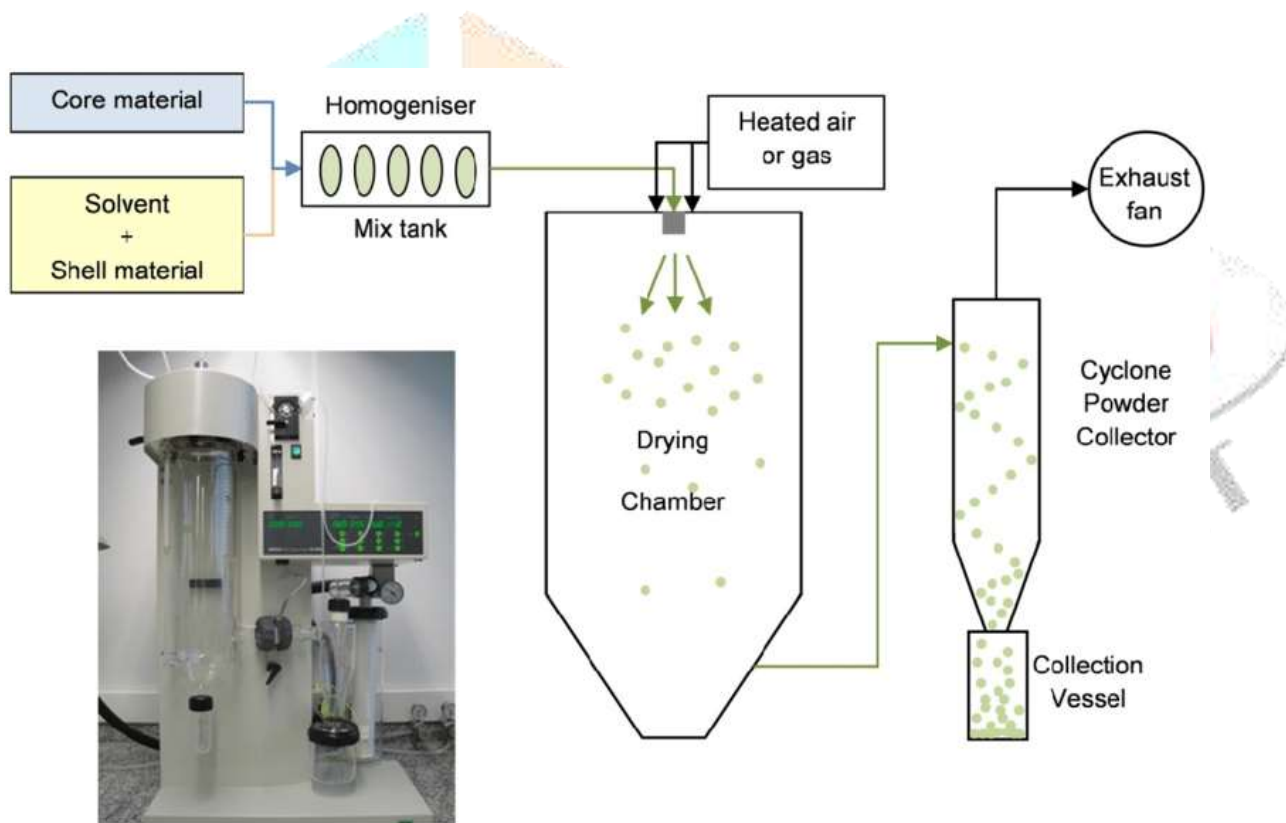


Fig. 5 - Spray drying / Congealing techniques.

Recent advances in Pelletization Techniques. (3,6,11,12,15,17)

1. **Hot-melt Extrusion and Spheronization:** It is a solvent-free technique that finds a great advantage during processing and storage of drugs that show signs of volatility due to residual water. No additional film coating is therefore required to achieve controlled release and therefore release is favored by;
 - (a) Diffusion process for formulations of water-insoluble polymers such as carnauba waxes or ethylcellulose.
 - (b) By diffusion and erosion with water-soluble polymers such as hydroxypropyl cellulose. This technique is used for the production of pellets, specific rate release dosage forms like tablets, capsules, transdermal implants etc.

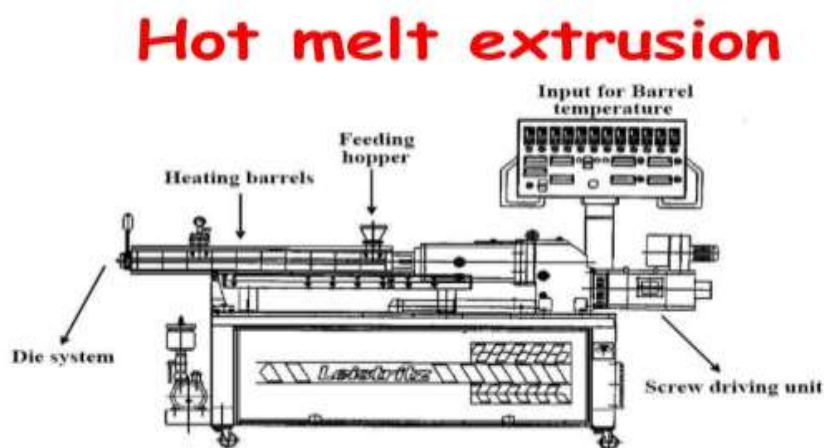
In the heating barrel and spheronizer, a hot melt extrusion row consists of a feed hopper, an extruder with 3 separate sections. Due to relatively low cost, reliability and robustness, extrusion is done in a rotating screw extruder ideally single screw extruder. This process includes in 4 steps;

- a) Melting or plasticizing of a solid material in which a thermal carrier usually contains low melting point wax or polymer e.g. vinyl polymers (polyvinylpyrrolidone, polyvinyl pyrrolidonevinyl acetate); copovidone, polyethylene oxide; polyethylene glycol; acrylates; cellulose derivatives include carb oxymethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose, acrylates.
- b) Forming of molten material by extruder into uniform cylindrical segments.
- c) High temperature spheronization of extrudes to deform by softening and help in the formation of uniform spheroids.
- d) Solidifying spheroids to get the desired shape spherules.

Factors influencing hot-melt extrusion and spheronization: nature of selectively thermoplastic extruders; composition of extruders such as drug and its melting point; physical and chemical properties of thermal carriers as they are transformed into molten state during the process; porosity of extruders that affect the release of drugs. In the case of thermolabile materials, plasticizer incorporation results in deterioration and increases polymer material durability by increasing tensile strength and glass transition temperature. Functional excipients like release modifiers, processing agents also play a key role in hot melt extrusion formulations.

Fig. 6 - Hot melt extrusion techniques.

2. Freeze Pelletization: It is a state - of - the-art and simplest technique for the manufacture of spherical pellets by adding droplets of immiscible molten solid carrier / matrix containing additives such as disintegrants,

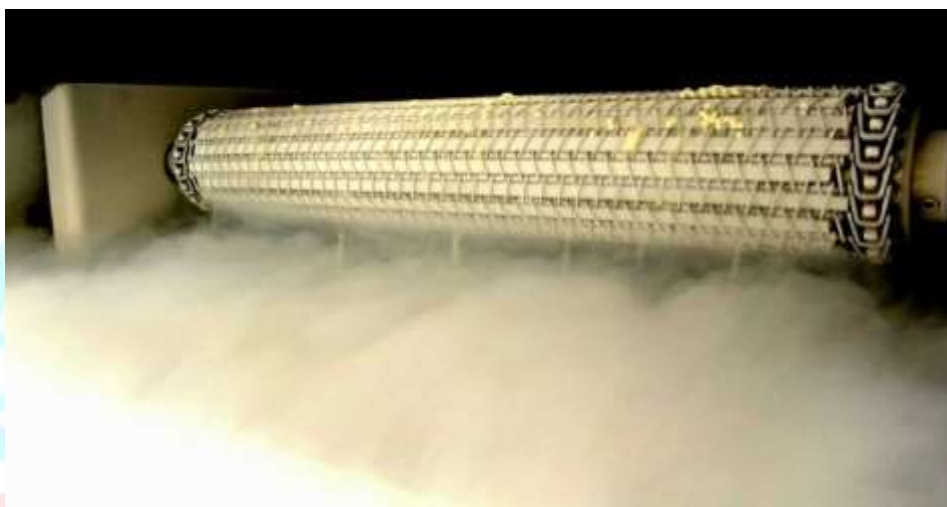


diluents, surfactants and drug-free release modifiers inserted into an inert liquid column. These droplets move in column to either the top or bottom of the column depending on their liquid density. Two devices are designed on the basis of the movement of molten-solid droplets. As the density of the matrix droplet is more than the liquid column, the former Apparatus I with an inlet at the top to introduce droplets and the droplets settle at the bottom of the column. Apparatus II is used when the size of the carrier droplet is greater than the column of fluid with an inlet at the bottom and the droplets at the top. The column is made of borosilicate

glass, 24 inches long. It is divided into two parts; initial portion with 25°C to 100°C temperature, a region where droplets are introduced.

The second is the cooling portion where the droplets solidify and form spherical pellets; maintaining temperatures from 0° C to -40° C using a cooling mixture such as acetonitrile-dry ice or salt-ice. At room temperature, the carrier used should be solid and molten at its melting point.

Molten solid matrices may be hydrophilic (polyethylene glycol; polyvinyl alcohol; low melting point sugars such as xylitol, dextrose, sorbitol, maltose; water-soluble derivatives of polyoxyethylene; polyethylene-propylene glycol copolymers; polyethylene oxide derivatives; PEG-PEO derivatives) or hydrophobic (glyceryl monostearate; glyceryl palmitostearate; glyceryl dibehenate; ethylene glycol palmixol palmium



derivatives).

Fig. 7 - Freeze Pelletization techniques.

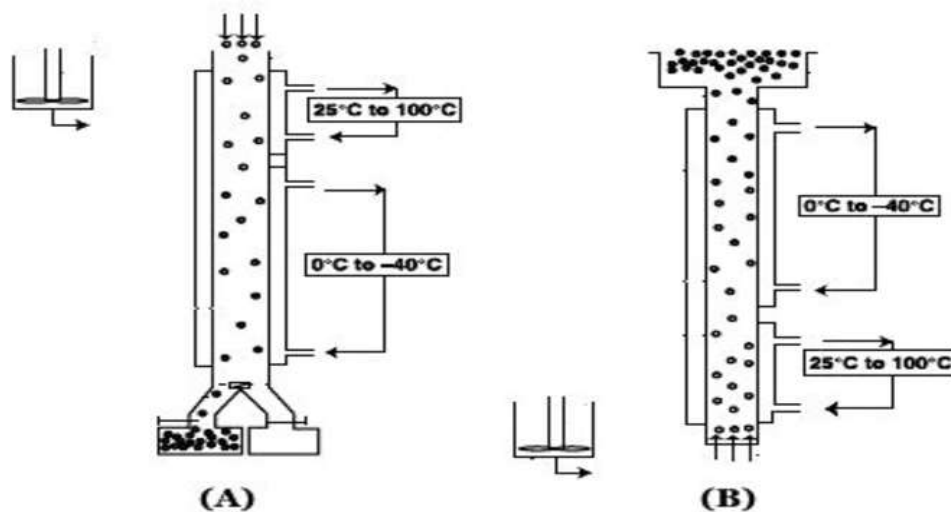
3. **Cryopelletization:** It is a technique by which freezing dried or lyophilized pellets are formed by using liquid nitrogen to solidify droplets of aqueous or organic solutions, suspensions or emulsions. The machinery has a perforated plate below which there is a liquid nitrogen tank with a conveyor belt of varying speed and a conveyor belt dipped into it. Because of its varying speed, pellets are frozen by the conveyor belt's residence time. The frozen pellets are transported and dried in a freeze dryer into a -60°C storage container. The factors influencing droplet size and shape are device design, process variables, droplet solid content, and viscosity. The distance between the perforated plate and the reservoir is arranged in such a way that, before it comes into contact with liquid nitrogen, the drops become spherical. Hydrophilic column is used for hydrophobic carriers, hydrophobic liquid column and for hydrophobic carriers. Hydrophobic fluid columns contain silicone oils, mineral oil, vegetable oils, aliphatic long-chain

hydrocarbons, and hydrophilic columns are molecular weight 200-600 liquid polyethylene glycols, propylene glycol, glycerin, ethyl alcohol, heat.

The main advantage of this technique is the development of small particle size array non-porous pellets that are feasible for further coatings such as delayed; colon focused and sustained release coatings. The diameter of the perforation in the perforated plate should be high in order to achieve smaller pellets. To avoid

agglomeration, the liquid nitrogen should be continuously shaken. The liquid's surface pressure can be decreased through the use of surfactants. Highly porous pellets are the main advantage of this technique.

Fig. 8 - Cryo-Pelletization techniques.



Characterization of Pellets. (1,7,8,13,15,18,19)

For certain performance controls, pellets are evaluated that indicate the suitability and durability of product during different operations such as filling, transport and handling.

The most common physical characteristics evaluated are:

- **Angle of repose / Flowability**

A funnel was kept vertically in stand at a specified height above a paper placed on horizontal surface. The bottom was closed and 10 gm of sample powder was filled in funnel. The funnel was opened to release the pellets on paper to form a smooth conical heap. The height of heap was measured using the scale. A border of heap was marked circularly and its diameter was measured at four points. The angle of repose was calculated using following formula.

$$\tan \theta = h / r$$

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

Where; h = height of the heap, r = radius of the heap

- **Bulk density (D_b)**

Bulk density is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of pellets was carefully poured in to graduated 100 mL measuring cylinder

through large funnel and volume was measured, which is called initial bulk volume. This is expressed in gm / mL and determined by the following formula;

$$\text{Bulk density } (D_b) = \frac{\text{powder mass (gm)}}{\text{initial volume (mL)}}$$

- **Tapped density (D_t)**

Accurately weighed quantity of pellets was carefully poured in to graduated 100 mL measuring cylinder through large funnel. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. This is expressed in gm / mL and determined by the following formula;

$$\text{Tapped density } (D_t) = \frac{\text{powder mass (gm)}}{\text{tapped volume (mL)}}$$

- **Carr's compressibility index (I)**

Carr's index is an indication of the compressibility of a powder. It is expressed in percentage and determined by the following formula;

$$\% \text{ Carr's consolidation index } (I) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

- **Hausner ratio**

A small index like percentage compressibility index has been defined by Hausner. Values less than <1.25 indicates good flow, whereas greater than 1.25 indicates poor flow. Added glidant normally improves flow of the material under study. Hausener's ratio can be calculated by;

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \times 100$$

- **Friability**

10 g pellets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting free fall of tablets (6 inches) within the chamber of the friabilator. It was rotated at a rate of 25 rpm. After 100 rotations (4 min.), the tablets were taken out from the friabilator and intact tablets were again weighed collectively.

$$\%F = \frac{W(\text{initial}) - W(\text{final})}{W(\text{initial})} \times 100$$

- **Porosity**

It influences rate of drug release from the pellets by affecting the capillary action of the dissolved drug; analysed qualitatively by scanning electron microscopy (SEM) and quantitatively by mercury porosimetry. The sample is introduced into the chamber, degassed, and then completely covered with mercury. Pressure

is applied and the volume of mercury that penetrates into the pores is recorded. Pore radius is given by Washburn equation:

$$R = \frac{2g[\cos q]}{P}$$

Where $g = 480 \text{ ergs/cm}^3$, $q = 140^\circ$, $r = \text{pore radius}$, $p = \text{mercury-intrusion pressure}$.

- **Moisture content**

Moisture content is determined by means of Karl Fisher titration.

- **Particle Size distribution**

The use of Vernier callipers to determine the size of pellets.

Sieving method: The pellets prepared were calculated by the process of sieving. The screening approach provides distribution of weight directly. Sieves had been set in a nest on top with the coarsest. A sample of the dried pellets (5 gm) was placed on top sieve and subjected to mechanical restlessness. The sieve collection was fixed (10 minutes) and shaken for a certain time span. The remaining pellets were weighed on each sieve. The pellets were also given the amount of screen mesh it went through, or was put on. It was expressed in terms of the two sieves Arithmetic mean.

$$\text{Mean particle size} = \frac{\sum X_i F_i}{\sum F_i}$$

Where, $X_i = \text{Weight size}$; $F_i = \text{Percent weight retained}$.

- **Wettability**

Pellet is put on clean glass slide. A $15\mu\text{l}$ drop of distilled water is carefully placed on the pellet, using micro-syringe. Throughout the static stage photographic impressions of the drop of water throughout contact with the pellet are registered.

- **Drug Content and Percent Production Yield**

The drug content of pellet formulation was determined in accurately weighed 100 mg pellets. The pellets were powdered in mortar, and the powder is dissolved in methanol using ultra sonication. After filtration, the UV absorbance of the suitably diluted filtrate through 0.45 μm filter (Millipore) was measured at 244 nm to determine the drug content. The content uniformity test was carried out three times for each formulation, and the results were expressed with the standard deviations.

To determine production yield, pellets were passed through 16/25 mesh sieves of Tylor's standard using a sieve shaker (Electromagnetic sieve shaker, EMS-8, Electrolab, Mumbai, India) at a frequency of 50 Hz with amplitude of 1 mm for 5 min. A fraction of pellets between 710 and 1,190 μm sizes were selected as the final product. The percent production yield was calculated by using following formula.

$$\text{Production yield of pellets(\%)} = \frac{\text{Practical weight of pellets}}{\text{Theoretical weight of pellets}} \times 100$$

- **Scanning Electron Microscopy (SEM)**

Scanning Electron Microscopy (SEM) is used to examine the surface morphology and cross section of the pellets. The sampling pellets were coated with thin layer of gold and these gold coated pellets were placed in SEM apparatus in front of camera and pellets were analyzed at 10 kv acceleration voltages using scanning electron microscope.

- **Disintegration Test**

Disintegration test was performed in water using disintegration tester (USP). The disintegration test was performed at 37 ± 1 o C in distilled water for pellets from each formulations using the disintegration unit. The pellets were considered completely disintegrated as no residue remains on the screen.

- **In- vitro Dissolution Study of Formulation**

In-vitro drug release was performed, Equivalent amount of dose of drug containing pellets of Irbesartan using DT – 6 USP 29 type II apparatus stirred at paddle speed of 50 rpm in 900 ml of 0.1 N HCl at 37 ± 0.5 oC, A 5 millilitre sample was withdrawn at predetermined time intervals and it was replaced with fresh dissolution media to maintain the sink condition. The withdrawn sample were filtered through 0.45 μ m membrane filter and analysed using UV spectrophotometer.

CONCLUSION.

This review

concludes that the pelletized dosage forms are one of the most successful and promising approaches for the delivery of new and multiparticulate drugs. It has many benefits over the dosage types of a single unit. Besides this, the recent progress offers a wide space for the processing of pellets. Currently, pelletization is a challenging and increasing technique which produces a wide range of unstable drugs with compatibility issues with excipients, hence these dosage forms are growing rapidly in remarkable rate.

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