International Journal of Pharmaceutical Development & Technology

www.ijpdt.com

e ISSN - 2248 - 910X

Print ISSN - 2248 - 9096

PELLETIZATION TECHNIQUE IN DRUG DELIVERY SYSTEM- A REVIEW

Veena MC, Senthil Kumar SK, Parthiban S

Department of Pharmaceutics Bharathi College of Pharmacy, Bharathi Nagara, Karnataka-571422, India.

ABSTRACT

In present times, the pelletization technologies are giving much attention as they represent an efficient pathway for manufacture of new drug delivery system .It has good advantage over the conventional dosage form. Pelletization technique help in the formation of spherical beads or pellets having a diameter 0.5 -1.5 mm which can be eventually coated for preparation of modified release dosage form. These pelletized dosage forms have gained popularity considerably from then because of their distinct advantages, such as ease of capsule filling because of better flow properties of the perfectly spherical pellets; enhancement of drug dissolution; ease of coating; sustained, controlled, or site-specific delivery of the drug from coated pellets; uniform packing; even distribution in the GI tract; and less GI irritation. The aim of this study is to provide detailed and different techniques of pelletization. Pelletized dosage forms can be prepared by a number of techniques, including drug layering on nonpareil sugar or microcrystalline cellulose beads, spray drying, spray congealing, roto granulation, hot-melt extrusion, and spheronization of low melting materials or extrusion-spheronization of a wet mass**.** The techniques namely extrusion-spheronization, hot melt extrusion, freeze pelletization, cryopelletization have been discussed along with formulation requirements for the process, parameters affecting pelletization. Evaluation of quality of the pellets is discussed with reference to the size distribution, shape, surface morphology, specific surface area, friability, tensile strength.

Keywords: Pelletization, Extrusion, Spheronization, Cryopelletization, Hot melt extrusion**.**

INTRODUCTION

Incorporating an existing medicine into a novel drug delivery system (NDDS) can significantly improve its performance in terms of efficacy, safety and improved patient compliance. In the form of a NDDS, an existing drug molecule can get new life, thereby increasing its market value and competitiveness.

Pelletization

Pellets can be prepared by a special technique called Pelletization. This technique is referred to an agglomeration process that convert fine powder or granules of bulk drug or excipient in to small , free flowing , spherical or semi spherical pellets .This technique is needed to produce pellets of uniform size with high drug loading capacity and also prevent segregation and dust [1].

In recent years, there has been a growing interest in the field of pelletization to produce spherical pellets which can be changed into several dosages forms like tablet and capsule or can be administered as such. Pelletization involves size enlargement process and if the final agglomerates are spherical in shape in the size range of 0.5-2.0 mm, they are called pellets. They are free-flowing, spherical or semi-spherical solid units. Pellets have numerous therapeutic as well as technical advantages such as enhanced drug absorption due to involvement of large GI surface in absorption process, less gastric irritation by limiting localized buildup and dose dumping good flowability due to uniform size and shape, high tensile strength, low friability, narrow particle size distribution, and uniform packing characteristics. The pelletized products can improve the safety and efficacy of the active agent [2]. The pellets are directly filled into capsule and can also be compressed into tablets. The compression of pellets into tablets is much more ideal than enclosing them in a hard gelatin capsule [3].

ADVANTAGES OF PELLETIZATION TECHNIQUE

1. When formulated as modified release dosage forms, pellets are less susceptible to dose dumping than reservoir type single unit formulations.

Corresponding Author :- **Veena MC** Email:- veenamc234@gmail.com

2. Pellets are recommended for patients with difficulty in swallowing and dysphagia like in case of children and aged people.
3. Pelletization reduces intra and inters subject variability of plasma profiles by reducing variations in gastric emptying rates and overall transit times.
4. Pelletization produces spheroids with high loading capacity of active ingredient without producing extensively large particles.
5. Pellets exhibit better roundness than the commercial nonpareil seeds and have excellent flow and packing properties.
6. Pellets composed of different drugs can be blended and formulated in single unit dosage form that facilitates delivery of two or more chemically compatible or incompatible drugs at the same or different site in GI tract.
7. Incompatible drugs processed separately and mixed later, or pellets with different release mechanisms can be mixed to give a new modified release profile.
8. Pellets reduce peak plasma fluctuations and minimize potential side effects without appreciably lowering the drug bioavailability.
9. Pellets disperse freely in the GI tract and hence greater absorption of the active drug occurs.
10. Particles less than 2-3 mm rapidly pass the pylorus regardless of the filling level of the stomach or the size and density of chyme. Also, GI irritations are limited spread as the particles spread in the intestine [1]**.**

PELLETIZATION TECHNIQUE

1. Powder Layering technique

Layering processes are probably the most well controlled and straight forward pelletization techniques. The layering process comprises the 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. They are classified into two categories: solution/suspension layering and powder layering.

In solution/suspension layering drug particles and other components are dissolved or suspended in the application medium. The droplets impinge on the started seed or cores and spread evenly as the solution or suspension is sprayed on the cores. Followed by drying phase allows dissolved material to crystallize and form solid bridges between the cores and initial layer of the drug substance and among the successive layers of drug substance or polymer. Continue this process until the desired layers of drug or polymer formed [4].

In powder layering the binding liquid helps to form successive layers of dry powder of drug and other components on starting cores. In this technique the drug particles are bound to the starter seeds and subsequently to the forming pellets with the help of liquid bridges originated from the sprayed binding liquid. These liquid bridges are eventually replaced by solid bridges derived either from a binder in the liquid medium or from any material. Successive layering of the drug and binder solution continues until the desired pellet size is reached [5]. The most commonly used equipments for layering are the standard or conventional coating pans and fluidized bed granulators (bottom spray, top spray and tangential spray) [2].

Conventional pan coaters have been used from the very beginning of the history of drug layering pelletisation. From the economic point of view, however, use of conventional pan coaters is not very reasonable due to the higher labour costs and time consumption, and lower yield. An important disadvantage of pan coaters is the shortage of process control.[12, 17] More recently modified forms of pan coaters have been developed, which resolves many of the drawbacks related to the old system [6].

Suspension / Solution layering technique

This technique involves the deposition of successive layer of solution and /or suspension of drug substances and binders on starter seeds which may be inert material or crystal of granules of the same drug. In this technique drug particles and others component are dissolved or suspended in the application medium.

The droplets impinge on the starter seeds or cores and spread evenly as the solution or suspension is sprayed on the cores. Followed by drying phase allows dissolved material to crystallize and form solid bridges between the cores and initial layer of the drug substances and among the successive layer of drug substances or polymer. Continue this process until the desired layer of drug or polymer formed. Consequently conventional coating press, fluidized bed centrifugal granulator of wurster coater has been used successfully to manufacture pellets.

The most common configuration for bottom spray coating is known as the Wurster system. In this study solution/ layering of neutral pellets has been conducted applying novel fluidized bed technology from .This technology claims to improve the product movement in defined direction in all the equipment by the Disk jet gas distribution plate. Furthermore, a 3 component spray nozzle is used in order to improve the film formation on the pellets due to constant and reproducible drop size distribution.

Accessibility of clogged nozzles without stopping and interrupting the process makes the equipment advantageous in respect to Wurster system. Hüettlin's three component nozzle is an air nozzle with an additional channel through which a second gas or component can be introduced to create a special microclimate around the nozzle which prevents excessive spray drying or clogging of the nozzle.

Such microclimates near nozzle apertures are very useful when a film former with a relatively high minimum film-forming temperature (MFT) issued. The MFT of

aqueous shellac suspensions, for example, lies between 35 and 55°C, depending on the plasticizer selected [7].

Extrusion and Spheronization

Extrusion spheronization was developed in the early 1960s as a pelletization technique. The extrusion-spheronization process is commonly used in the pharmaceutical industry to make uniformly sized spheroids. It is especially useful for making dense granules with high drug loading for controlled-release oral solid dosage forms with a minimum amount of excipients.

Advantages of spheronization.

- The flow characteristics of spheres make them suitable for transportation by most systems found in the pharmaceutical industry, including vacuum transfer.
- The packing of small sphere into small containers, such as hard gelatine capsules, or larger packages is much more convenient than other dry forms such as powders or granules. Eliminate quality problems with variable dosage due to packaging problems with powder.
- Spheres are a dense material and provide the lowest surface area to volume ratio and thus pharmaceutical compounds can be coated with a minimum of coating material. Important for effective release of some drugs.
- Coating can provide controlled, targeted release at different locations within the body. Important for effective release of some drugs.
- Spherical particles are easily mixed. Smooth spheres are an ideal base on which to apply a coating. Minimum coating time and coating material used.
- Spheres will reduce production of fines and dust during transportation, handling and packaging.
- Dependent upon adhesive forces and surface characteristics spheronization increases the hardness and reduces friability of granules. (Reynolds AD).

Extrusion spheronization is a multi-step compaction process comprising of following steps.

1) Dry mixing

Dry mixing of all ingredients is done to get homogeneous powder dispersion or mixer using different types of mixers like twin shell blender, high shear mixer, tumbler mixer and planetary mixer.

2) Wet massing

Wet massing of powder dispersion is done to produce a sufficient plastic mass for extrusion. This granulation is similar to a conventional wet granulation with the exception of the granulation endpoint. The granulation endpoint is determined by the behavior of the wetted mass during the extrusion operation.

The most commonly used granulator is planetary mixer or sigma blade mixer or high shear mixer and Hobart mixer. Typically, planetary mixer is used routinely for both blending and granulation operation. High shear mixer introduces a high amount of energy into the wet mass which is transformed into heat and induces evaporation of granulation fluid. This changes the extrusion behavior of the wet mass. By cooling the granulation bowl may avoid this problem.

3) Extrusion

This is the third step in the process. The extrusion operation can be considered to be a specialized wet granulation technique as well as an integral part of the overall spheronization process. Extrusion a method of applying pressure to a mass until it flows through an opening is a technique that determines two dimensions of an agglomeration of particles. Because the cross sectional geometry is defined by the orifice, extrudate length is usually the only dimensional variable. This operation is the major contributing factor in the final particle size of the pellets. The diameter of the extruder screen opening directly controls the diameter of the extrudate.

In this process the wetted mass is passed through the extruder to form rod shaped particles of uniform diameter. The extrudate must have enough plasticity to deform but not so much that the extrudate particles adheres to other particles when rolled during spheronization process. The granulation solvent serves as the binding agent to form the granules and as the lubricating during the extrusion operation**.**

4) Spheronization

The spheronization technology was first introduced by Nakahara in 1964. The formation of pellets during the spheronization operation depends on the formulation of extrudates. The extruded granulation must have the combined characteristics of cohesiveness, firmness and plasticity. This operation has been divided into three stages such as breaking of the cylindrical segments or extrudate, agglomeration of the broken segments and smoothing of the particles.

Breaking of the cylindrical segments occurs due to the interaction of the extrudate with the rotating plate, stationary wall and other extrudate particles. Agglomeration occurs when the small fragments produced during the breaking stage are picked up by the larger granules during smoothing. Spherical particles are created during smoothing stage by generating rotational motion of each granule about its axis in constantly changing planes [8].

Extrusion and Spheronizing Equipment

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

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

Gravity fed extruder includes the rotary cylinder and rotary gear extruders, which differ mainly in the design of the two counter rotating cylinders. In the rotary cylinder extruder one of the two counter rotating cylinders is hollow and perforated, whereas the other cylinder acts as a pressure roller. Rotary gear extruders have two hollow counter rotating gear cylinders with counter bored holes.

In ram extruders a piston displaces and forces the material through a die at the end. Ram extruders are preferentially used in the development phase because they can also be used to measure the rheological properties of formulations.

A spheronizer also known as merumerizer consists of a vertical hollow cylinder with a horizontal rotating disk (friction plate) where the extrudate is broken up into smaller segments 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 pellet growth and is provided in the form of interparticulate friction.

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

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

Recently, different types of fluidized bed rotary processors have been developed more successfully for preparing compaction-type pellets such as the extrusion spheronization process in a one-step process. This technique has solved many problems related to the multi-step extrusion and spheronization process; it consumes less time, requires lower labour costs and less space.

5) Drying

To get desired moisture content in pellets a drying stage is required. The pellets can be dried at room temperature or at elevated temperature in a tray drier/ oven or in a fluidized bed drier. Wan LSC and Lai WF [9] studied the effect of mode of drying upon the physical appearance and compaction characteristics of the extrusion–spheronization granules of a microcrystalline cellulose/propyl gallate/water paste. According to their study freeze-drying retained the shape and size of the granules, whereas oven-drying produced roughened granules due to the uneven shrinkage of the wet powders.

Compaction of one size fraction indicated that the granule strength differed noticeably, with the oven-dried samples producing tablets of lower voidage for a given applied compaction pressure. There was a reasonable correlation between tablet crushing strength and voidage. Major differences were observed in tablet dissolution, with the freeze-dried material exhibiting two-regime behaviour and an initial dissolution rate constant an order of magnitude greater than the oven-dried form.

6) Screening

Screening may be necessary to achieve the desired size distribution, and for this purpose sieves are used. In case of pellets prepared by extrusion spheronization, screening is essentially required after manufacturing, in order to avoid pellets having high size polydispersity index [10].

Spherical Agglomeration

Spherical agglomeration, or balling, is a pelletization process in which powders, on addition of an appropriate quantity of liquid or when subjected to high temperatures, are converted to spherical particles by a continuous rolling or tumbling action. Spherical agglomeration can be divided into two categories— Liquid-induced and Melt-induced agglomerations.

Liquid-induced agglomeration

During liquid-induced agglomeration, liquid is added to the powder before or during the agitation step. As powders come in contact with a liquid phase, they form agglomerates or nuclei, which initially are bound together by liquid bridges. These are subsequently replaced by solid bridges, which are derived from the hardening binder or any other dissolved material within the liquid phase. The nuclei formed collide with other adjacent nuclei and coalesce to form larger nuclei or pellets. At this point, coalescence is replaced by layering, whereby small particles adhere on much larger particles and increase the size of the latter until pelletization is completed.

Melt-induced agglomeration

Melt-induced agglomeration processes are similar to liquid-induced processes except that the binding material is a melt. Therefore, the pellets are formed with the help of congealed material without having to go through the formation of solvent-based liquid bridges. If the surface moisture is not optimum, some particles may undergo nucleation and coalescence at different rates and form different sizes of nuclei admixed with the larger pellets. As a result, spherical agglomeration tends to produce pellets with a wide particle size distribution.

5. Spray Drying and Spray Congealing

Spray Drying and Spray Congealing, also known as globulation process, involve atomization of hot melts, solutions, or suspensions to generate spherical particles or pellets. The droplet size in both processes is kept small to maximize the rate of evaporation or congealing, and consequently the particle size of the pellets produced is usually very small.

Spray Drying

The drug entities in solution or suspension are sprayed, with or without excipients, into a hot air stream to generate dry and highly spherical particles. As the atomized droplets come in contact with hot air, evaporation of the application medium is initiated. This drying process continues through a series of stages whereby the viscosity of the droplets constantly increases until finally almost the entire application medium is driven off and solid particles are formed. Generally, spray-dried pellets tend to be porous.

Spray Congealing

This process consists of suspending the particles in a molten coating material and pumping the resultant slurry into a spray dryer in which cold air is circulated. The slurry droplets congeal on contact with the air. The coating agents normally employed is low melting materials such as waxes. The congealing process require higher ratio of coating agents to active material than does the spray drying, because only the molten coating agent constitutes the liquid phase**.**

6. Melt Spheronization

Melt Spheronization is a process whereby a drug substance and excipients are converted into a molten or semi molten state and subsequently shaped using appropriate equipment to provide solid spheres or pellets. The drug substance is first blended with the appropriate pharmaceutical excipients, such as polymers and waxes, and extruded at a predetermined temperature. The extrusion temperature must be high enough to melt at least one or more of the formulation components. The extrudate is cut into uniform cylindrical segments with a cutter. The segments are spheronized in a jacketed Spheronizer to generate uniformly sized pellets [11].

Advantages

- Neither solvent nor water used in this process. Fewer processing steps needed thus time consuming drying steps eliminated. Uniform dispersion of fine particle occurs.
- There are no requirements on the compressibility of active ingredients and the entire procedure simple, continuous and efficient.
- Good stability at varying pH and moisture levels, do not require additional film coating since the drug release is diffusion controlled. Safe application in humans due to their non-swellable and water insoluble nature.

Disadvantages

- Requires high energy input. The melt technique is that the process cannot be applied to heat-sensitive materials owing to the elevated temperatures involved.
- Lower-melting-point binder risks situations where melting or softening of the binder occurs during handling and storage of the agglomerates.
- Higher-melting-point binders require high melting temperatures and can contribute to instability problems especially for heat-labile materials.

Applications

In pharmaceutical industry the melt extrusion has been used for various purposes, such as

- Improving the dissolution rate and bioavailability of the drug by forming a solid dispersion or solid solution.
- Controlling or modifying the release of the drug by preparing different release pellets and granules. Useful in masking the bitter taste of an active drug, enhancing dissolution rates for poorly water soluble drugs.

Cryopelletization

Cryopelletization is a process whereby droplets of a liquid formulation are converted into solid spherical particles or pellets by using liquid nitrogen as the fixing medium. The technology, which was initially developed for lyophilization of viscous bacterial suspensions, can be used to produce drug-loaded pellets in liquid nitrogen at -1600C. The procedure permits instantaneous and uniform freezing of the processed material owing to the rapid heat transfer that occurs between the droplets and liquid nitrogen. The amount of liquid nitrogen required for manufacturing a given quantity depends on the solids content and temperature of the solution or suspension being processed. The equipment consists of a container equipped with: Perforated Plates A Reservoir Conveyor belt with Transport baffles Storage Container The perforated plates generate droplets that fall and freeze instantaneously as they come in contact with the liquid nitrogen below. The frozen pellets are transported out of the nitrogen bath into a storage container at - 600C before drying [11].

FACTOR AFFECTING PELLETIZATION TECHNIQUE

1. Moisture Content

It is one of the critical parameter for pellet growth in pelletization technique .Moisture in the wet mass bring cohesiveness to the powder so that the wet mass can be extracted and spheronize to give spherical shape. High moisture contents lead to agglomeration of pellets during the process of spheronization which is one of the technique of pelletization due to excess of water in the surface of pellets and low moisture content lead to generation of fines with large variation in size distribution [12].

2. Rheological characteristics

The Rheological condition of the wet mass determines the flow ability in extruder optimum Rheological condition

leads to good flow ability in order to extrude the wet mass variation in rheology make improper and non-uniform extrusion [13].

3. Solubility of excipients and Drug in granulating fluid

A soluble drug get dissolve in a granulating liquid .Thusincreasing the volume of liquid phase lead to over wetting of system of agglomeration of pellet sand increase in wetting liquid increases plasticity but induces sticky mass [14].

4. Composition of Granulating Fluid

Besides water, alcohol, water/alcohol mixture, Ethyl Ether, Dilute Acetic Acid, Isopropyl alcohol is also used as a granulating liquid. According to researcher like Millili and Schwartz, a minimum of 5 % of granulation liquid have to be water in order to produce pellets be water in order to produce pellets containing Avicel pH (101) and theophylline [15]. Some researchers used water and dilute acetic acid in different powder to liquid ratio and concluded that mass fraction can be increased up to 100% by using dilute acetic acid for granulation step in place of demineralized water [8]. Aqueous polymer dispersion containing Eudragit, Hydroxy Propyl Methylcellulose (HPMC), Poly vinyl pyrrilodine (PVP) and Gelatin is used in the moistening liquid.

5. Physical Properties of Starting Material

Formulation variable such as type and content of starting material, type of filler and particle size of constituent have the effect on the pelletization process. Quality of pellets depends not only composition but also on different grades of the same product (Koo, O.M.Y.,2001). The swelling property of material used in pelletization technique decides the release rate of the drug in pellets.

6. Speed of the Spheronizer

The speed of the spheronizer affects the size, hardness,sphericity and density of pellets, high speed gives high sphericity, lower friability,smooth surface and higher crushing strength [9].

7. Drying technique and drying temperature

It is important to get proper size, shape and flow of pellets and it must be reproducible and consistent in all the batches. Variation in pellet's size, shape and flow will lead to difference in physicochemical properties of final dosage form like weight variation, improper filling etc, which will further affect the therapeutic efficiency of the delivery system. Wider particle size distribution may lead to variation in the dose of drug delivery. Variation in shape may lead to variation in flow and compressibility.

8. Extrusion Screen

The quality of the extrudate/ pellets is greatly influenced by the characteristics of the orifice of the screen. An 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, increasing the extrusion force, and then had a negative effect on granulometric distribution and on shape [16].

CHARACTERIZATION OF PELLETS

1. Particle size distribution

Particle size distribution should be as narrow as possible. That will ensure minimum variation in coating thickness; facilitate blending process if blending of different types of pellets is required. Sieve analysis using sieve shaker is the most widely used method for measuring particle size distribution. Microscopy is direct method for determining particle size distribution. Optical microscopy and scanning electron microscope are used to measure the diameter of pellets. Patappee.W. 2004 reported the use of vernier callipers to determine the size of pellets.

2. Surface area

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. It can be calculated from the particle-size distribution by measuring/using the mean diameter, since the surface area is equal to $\pi d2$. However, 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 the pellets. Therefore, two techniques, i.e. gas adsorption and air permeability, permit direct calculation of surface area [12].Air permeability methods are widely used pharmaceutically for specific surface measurement, especially to control batch to batch variations. The principal resistance to the flow of a fluid - such as air – through a plug of compacted material is the surface area of the material.

The gas adsorption method (commonly known as the BET method) was developed by Brunauer, Emmett and Teller (1937). In this method the volume of nitrogen that is adsorbed by the substrate contained in an evacuated glass bulb is measured at different pressures, and the results are plotted as P/V (p0-p) versus p/p0 to generate a linear plot where V is the volume of gas in cm3 adsorbed per gram of substrate at pressure p and p0 is the saturation vapour pressure of liquefied nitrogen at the temperature of the experiment. The slope and intercept of the plot yield the values b and Vm. The specific surface (sw) of the pellets is then obtained by using the following equation:

SW = 4.35 * Vm

3) Porosity

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

4) Density

The density of pellets can be affected by changes in the formulation and/or process, which may affects other processes or factors, such as capsule filling, coating, and mixing. The bulk density of the pellets can be measured by an automated tapper. True density indicates the extent of densification or compactness of substances.

5) Hardness and Friability

Hardness and friability determination of pellets is necessary because the pellets have to withstand during handling, shipping, storage and other processing such as coating. The instrument such as the Kaul pellet hardness tester provide relative harness values and friability of pellets are determined by using Erkewa type tablet friabilator or turbula mixer for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion. Friability can also be determined using fluidized bed with Wurster insert by using stream of air [12].

6) Tensile strength

The tensile strength of the 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 the pellets.

Today pelletization technology represents an efficient pathway for manufacture of drug delivery system. This review focused on frequently used pelletization techniques for producing pellets for oral drug delivery. Each technique has its own advantages and disadvantages. Layering processes have been used over the years for manufacturing of pellets. Most of the scientists have focused research on refining and optimizing existing pelletization techniques and also focused on the development of novel approaches and procedures of manufacturing pellets employing innovative formulation and processing equipment. These pelletization techniques have great impact on the development of different types novel drug delivery systems. A number of pelletized products are being designed to maximize the in vivo performance of medications already in the market and to meet all regulatory requirements

Figure 1. Principle of the powder layering process

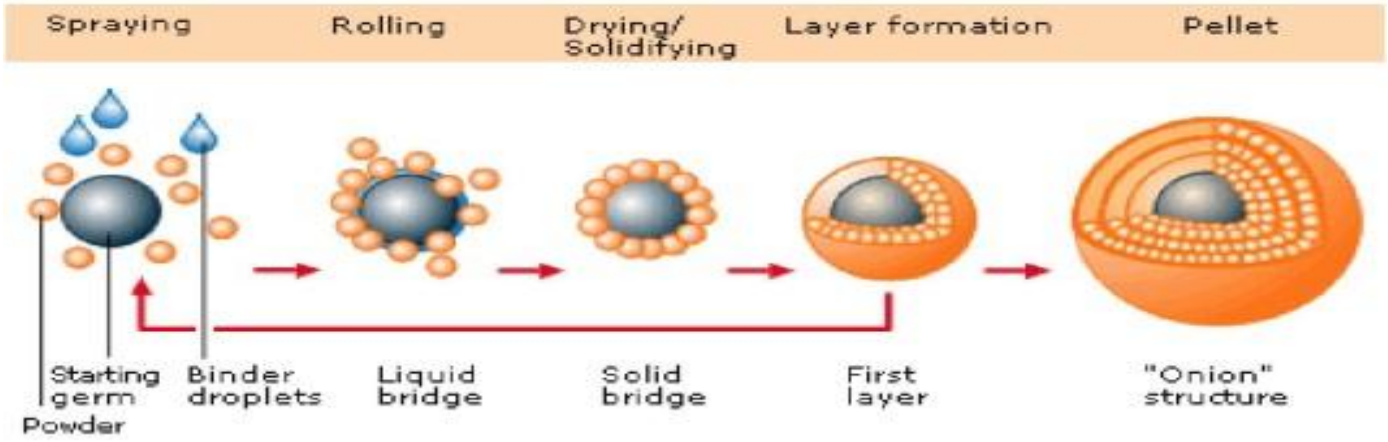


Figure 2. Principle of the suspension and solution layering process

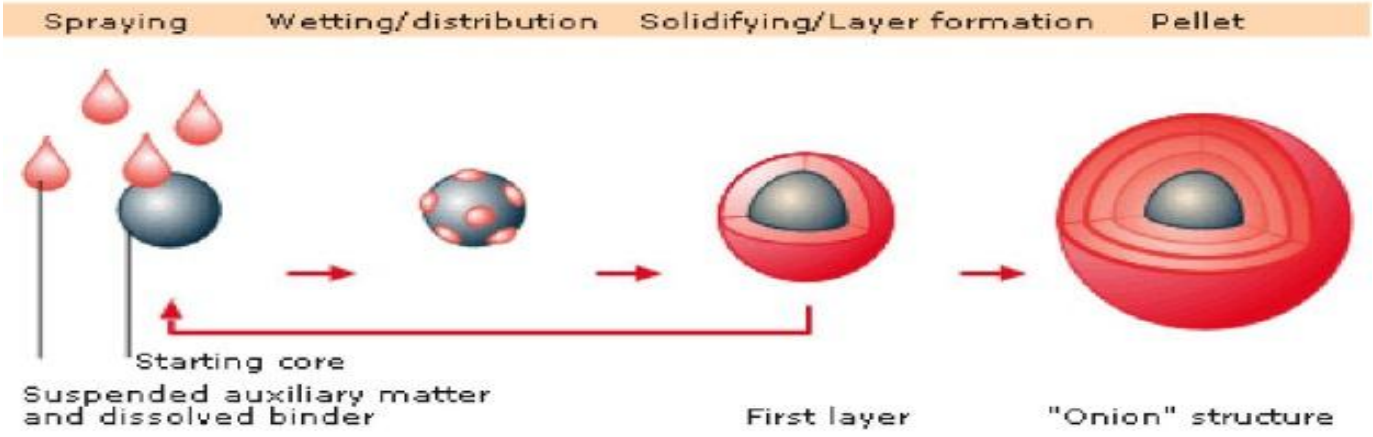


Figure 3. Drug Layering By Using Suspension

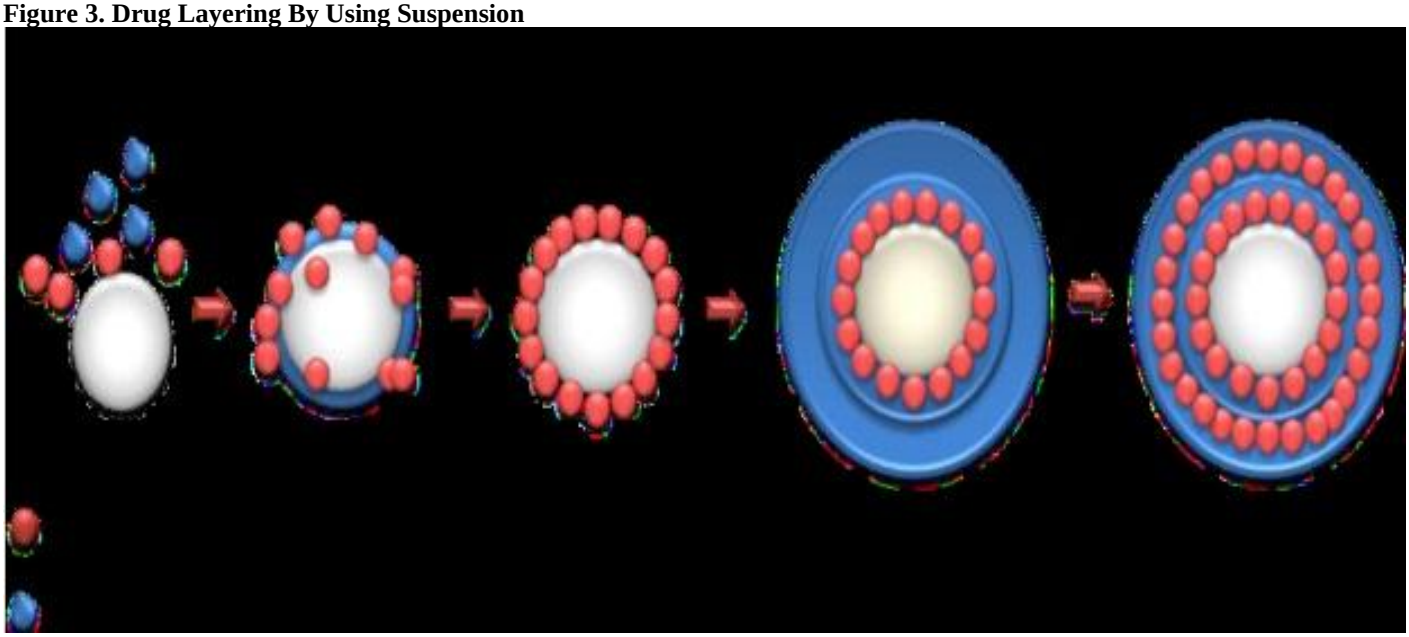


Figure 4. Schematic Representation of Different Pellet Formation Stages During Spheronisation

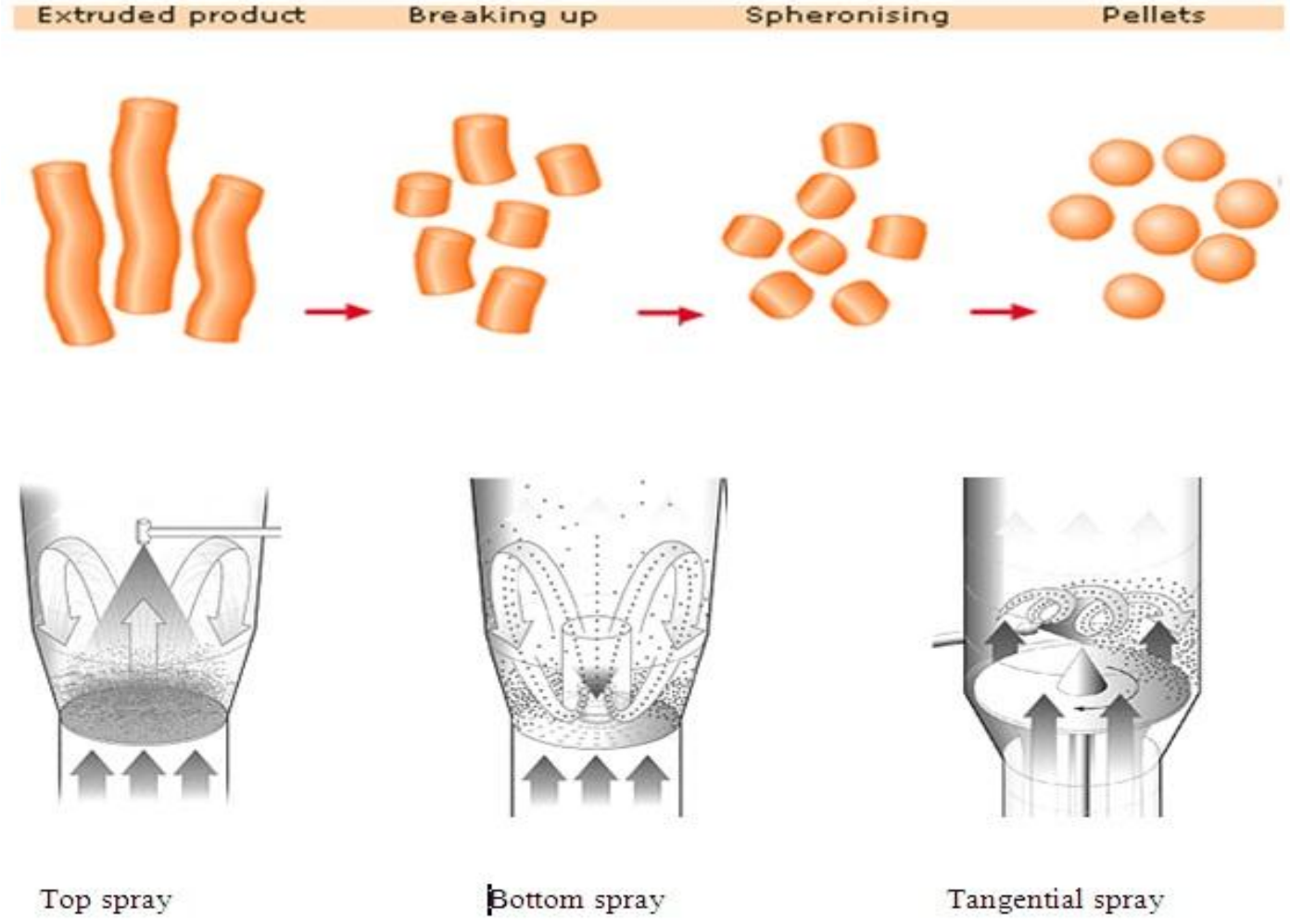


Figure 5. Spin flow of rotation plate in tangential spray coating

Figure 6. Dome Screw Feed Extruder

Figure 7. Radial Screw Feed Extruder

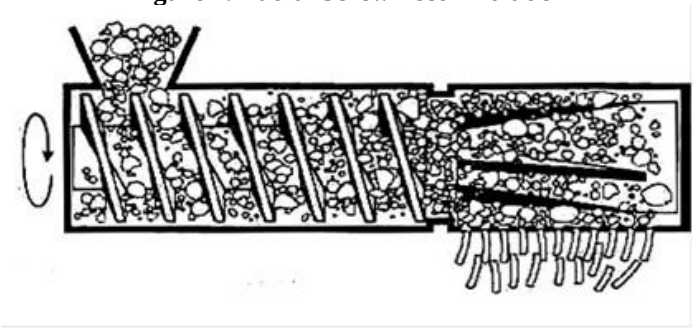


Figure 8. Cylinder Roll Type

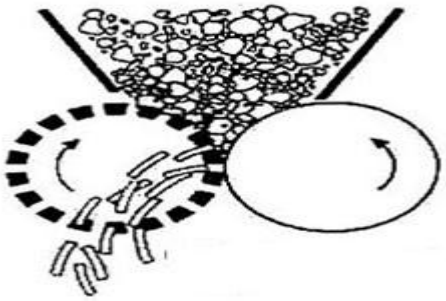


Figure 9. Axial Piston Extruder

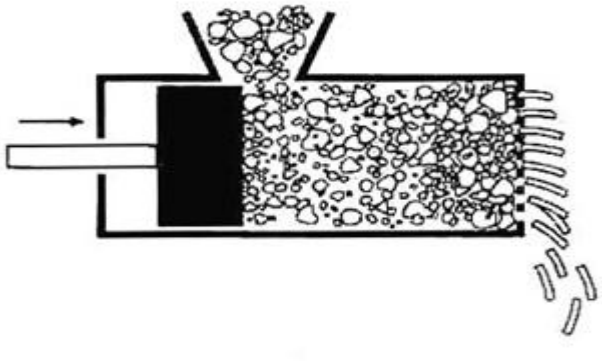


Figure 10. Radial Piston Extruder

Figure 11. Gear Roll Type

Figure 12. Radial Type

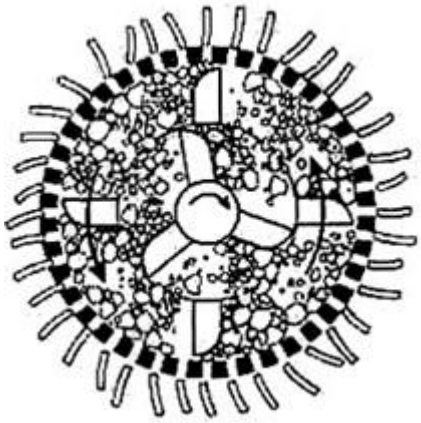
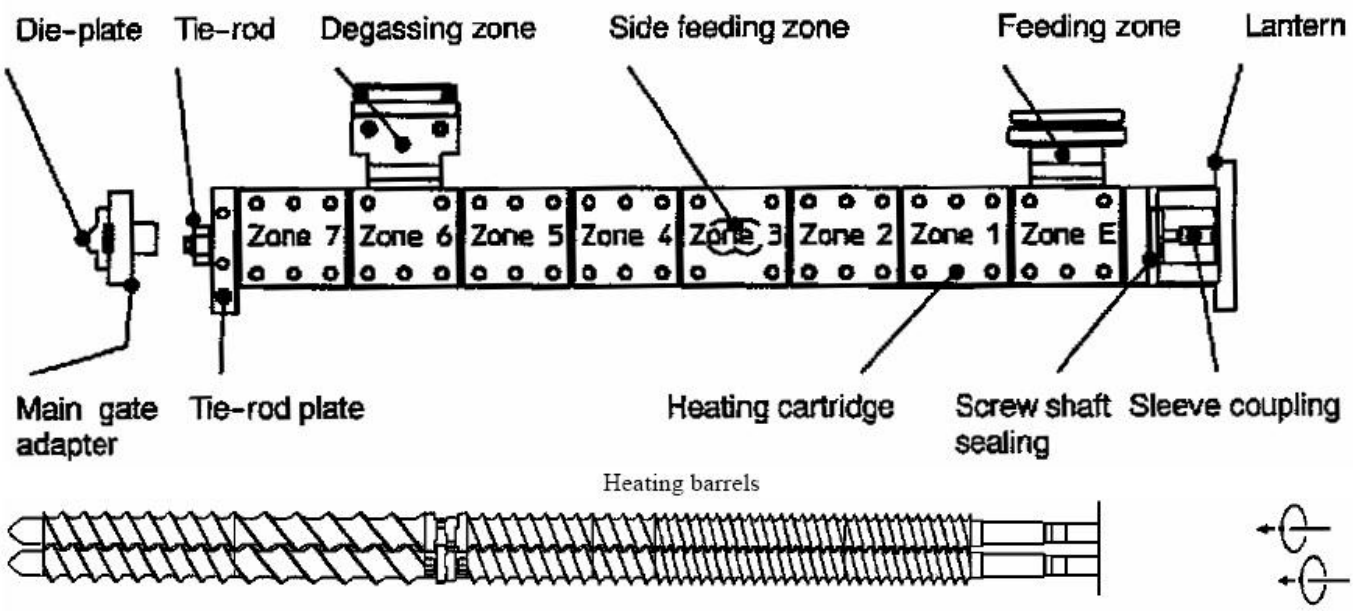


Figure 13. Heating barrels and co-rotating screws for hot-melt extruder



CONCLUSION

Today pelletization represents an efficient pathway for novel drug delivery in the scope for different oral immediate or controlled delivery systems. Because of its simple design, high efficiency of producing spherical pellets and fast processing, pelletization has found a special position in pharmaceutical industry and especially in case of production of multiparticulate oral controlled release dosage forms as compared to granulation. Pelletization technique produces more spherical pellets and offers more advantages than granulation process. In addition, hot-melt extrusion method has provided a new, wider platform to produce spherical pellets of drugs which are not stable or have compatibility problems in presence of solvents.

REFERENCES

1. Ghai D. Pelletization: An alternate to granulation. *Pharma times*, 43(1), 2011, 13-15.
2. Reynolds AD. A new technique for the production of spherical particles. *Manuf Chem Aerosol News*, 41, 1970, 40-6.
3. Celik M. Multiparticulate oral drug delivery, Marcel Dekker. New York, 1994, pp.181.
4. Zimm KR, Schwartz JB, Connor RE. Drug release from multiparticulate pellet system. *Pharma Dev Technol*, 1, 1996, 37-42.
5. Ganderton D. Sustained release for oral administration. *Manuf Chem*, 1985, 27-31.
6. Nastruzzi C, Cortesi R, Esposito E, Genovesi A, Spadoni A, Vecchio C, Menegatti E. Influence of formulation and process parameters on pellet production by powder layering technique. *AAPS Pharm Sci Tech*, 1, 2000, 9.
7. Kandukuri J M, Allenki V, Eaga CM, Keshetty V, Jannu KK. Pelletization Tecniques for Oral Drug Delivery. *Int. J. Pharm. Sci. & Drug Res*, 1(2), 2009, 63-70.
8. Steckel H, Mindermann-Nogly F. Production of chitosan pelletsby extrusion spheronization. *Eur. J. Pharm. Biopharm*, 57, 2004, 107-13.
9. Wan LSC, Lai WF. Factors affecting drug release from drug-coated granules prepared by fluidized-bed coating. Int J Pharm 1991; 72: 163-174.
10. Hicks DC, Freese HL. Extrusion and spheronizing equipment in pharmaceutical pelletization technology. Marcel Dekker Inc. 1989, pp.71.
11. Kumar V, Mishra SK, Lather A, Singh R. Multiple unit dosage form Pellet and Pelletization Techniques: An over view. *Int. J. Res. Ayurveda and Pharm*, 2(1), 2011, 121-125.
12. Fielden KE, Newton JM, Rowe RC. The influence of lactose particle size on spheronization of extrudate processed by a ram extruder. *Int J Pharm*, 81, 1992, 205-12.
13. Harrison PJ, Newton JM, Rowe RC. The application of capillary rheometry to the extrusion of wet powder masses. *Int. J. Pharm*, 35, 1987, 235-42.
14. Flament MP, Dupont G, Leterme P, Farah N, Gayot A. Development of 400µm pellets by extrusion-spheronization. Application with Gelucire 50/02 to produce a sprinkle form. *Drug Dev. Ind. Pharm*, 30, 2004, 43-51.
15. Millili GP, Schwartz JB. The strength of microcrystalline cellulose pellets: The effect of granulating with water/ethanol mixtures. *Drug Dev. Ind. Pharm*, 16, 1990, 1411-26.
16. Sawicki W and Lunio R. Compressibility of floating pellets with verapamil hydrochloride coated with dispersion Kollicoat SR 30 D. *Eur J Pharm Biopharm*, 60, 2005, 153-9.