IJPSR (2011), Vol. 2, Issue 6 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 08 March, 2011; received in revised form 20 April, 2011; accepted 16 May, 2011

PELLETIZATION TECHNOLOGY: A QUICK REVIEW

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Keywords:

Pelletization,
Extrusion,
Spheronization,
Scanning Electron Microscope,
Fluidized bed dryer

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ABSTRACT

Pelletization process first came into existence way back during the 1950s, when the first product was introduced to the market. 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. 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 present review outlines the recent findings on the manufacturing and evaluation of spherical pellets. 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.

INTRODUCTION: Since the time of immemorial centuries, oral drug administration has been one of the most convenient and widely accepted routes of delivery for most therapeutic agents. Traditionally, oral dosage forms are classified as single unit and multiple unit dosage forms. Multiparticulate dosage forms are receiving a immense attention as alternative drug delivery system for oral drug delivery even though single unit dosage forms have been widely used for decades. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules, out of which tablets being the most popular dosage form, accounting for 70% of all ethical pharmaceutical preparations produced [1, 2].

But soon it was sensed that some of the formulating and clinical problems (free flowing property, dose dumping, dysphagia, etc.) comes along with the single dose formulations. This soon led to the dividing of monolithic dosage forms into multiples. Multiple unit dosage forms (MUDFs), are formulated as granules, pellets, or mini tablets [3, 4]. The concept of this multiple unit dosage forms answers many formulating problems and is a common strategy to control the release of drug as showing the reproducible release profiles when compared to SUDFs. These MUDFs, can either be filled in to hard capsules or compacted in to bigger tablets or can be dispensed in a dose pouches or packlets.

The most increasingly interesting area in the development of MUDF'S is incorporation into tablets instead of hard gelatin capsules in order to make it more economical to the consumers and gaining more attention currently. The current review focuses on the pelletized form of multiple units, they are prepared by process called Pelletization which is referred to as a size enlargement process and the final product obtained is called pellets.

Thus, being a consumer-friendly alternative, over the single unit dosage forms many of the pharmaceutical companies are switching their product franchise to improve the technology. This technology option can also provide a good platform for patent non-infringing product development. This drug delivery platform shows business potential promise for future in pharmaceuticals, nutraceuticals [5, 6].

Pellets: Pellets are described to be produced systematically, as geometrically defined agglomerate obtained from diverse starting materials using different processing conditions. They are free-flowing, spherical or semi-spherical solid units with a size range of about 0.5 mm to 1.5 mm and that are intended mostly for oral administration [6, 7, 8].

Ideal properties of the pellets

- Spherical shape and smooth surface.
- The particle size of pellets should be in range of 600-1000μm.
- The quantity of the active ingredient in pellets should be maximum in order to maintain size of pellet

Advantages: In many cases the main reason for the use of pellets in the manufacture of products with controlled release properties. However there are reasons to believe that these multiple unit dosage forms in any case can offer a superior therapeutic effect even when modified release is not the primary objective [9, 10].

- Improved appearance of the product which is having fine pharmaceutical elegance.
- Pelletization offers flexibility into the dosage form design and development.
- Pellets improve the flow properties in formulation development.
- They flow freely and are easy to pack without significant difficulties (resulting in uniform and reproducible fill weight of capsules).
- Pellets are less susceptible to dose dumping.
- It reduces accumulation of drugs especially proven advantageous in the case of irritating drugs [11].
- It improves safety and efficacy of a drug.
- Pelletization is a convenient way to manage the separation of incompatible drugs.
- Pellets offer reduced variation in gastric emptying rate and intestinal transit time.
- Pellets disperse freely in G.I.T. and invariably maximize drug absorption and also reduce peak plasma fluctuation [12].
- Pelletization solves the problem of taste masking.
- Coating of pellets can be done with different drugs to enable a pellets release rate.
- The coating material may be colored with a dye material so that the beads of different coating thickness will be darker in color and distinguishable from those having fewer coats [12].
- In case of immediate Release Products larger surface area of pellets enables better distribution.
- Chemically incompatible products can be formed into pellets & delivered in a single dose by encapsulating them.
- In the chemical industries it is used to avoid powder dusting.
- The most important reason for the wide acceptance of multiple unit products is the rapid increase in popularity of oral pellets dosage forms, Pellets oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time.

Thus Pellets have attracted more attention due to their unit clinical and technical advantages.

Theory of pellet formation and growth: 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: nucleation, coalescence, layering and abrasion transfer [14].

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.

Nucleation is followed by a transition phase where the growth mechanisms affecting are coalescence and layering. 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. 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 (**fig. 1**).

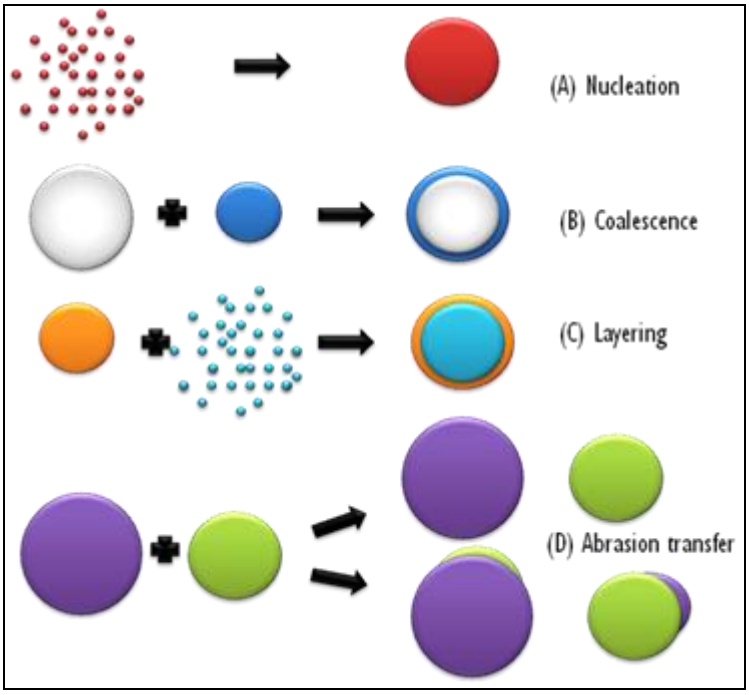

FIG. 1: PELLET GROWTH MECHANISM

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.

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.

Methods of preparing pellets: Compaction and Drug layering are the most widely used Pelletization techniques in the pharmaceutical industry. Of the compaction techniques used, extrusion and spheronization is the most popular method. There are other few Pelletization methods, such as Melt pelletization, Globulation, Balling and Compression are

also used in the development of pharmaceutical pellets although in a limited scale.

- **Drug layering:** 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. In solution/suspension layering, drug particles are dissolved or suspended in the binding liquid [15](**fig. 2, fig. 3**). In powder drug layering, a binder solution is first sprayed onto the previously prepared inert seeds, followed by the addition of powder. Conventional pan coaters have been used from the very beginning of the history of drug layering pelletization.

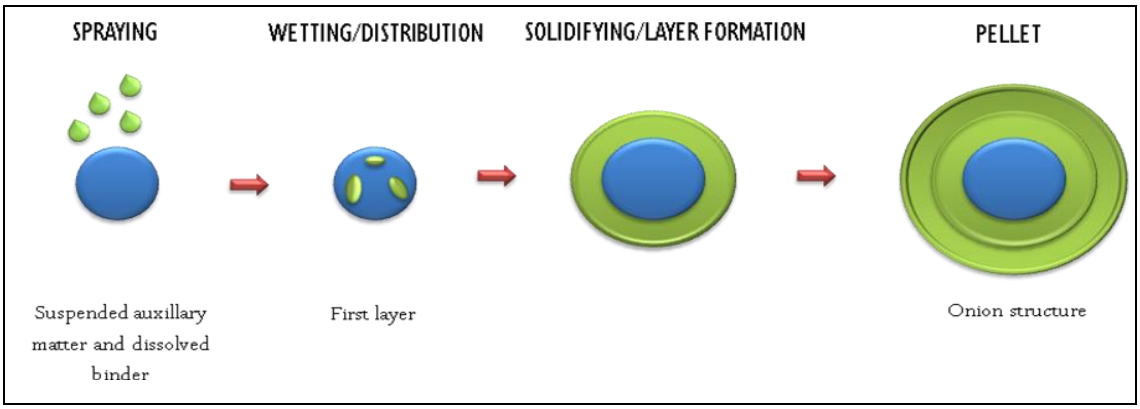

FIG. 2: DRUG LAYERING BY USING SOLUTION

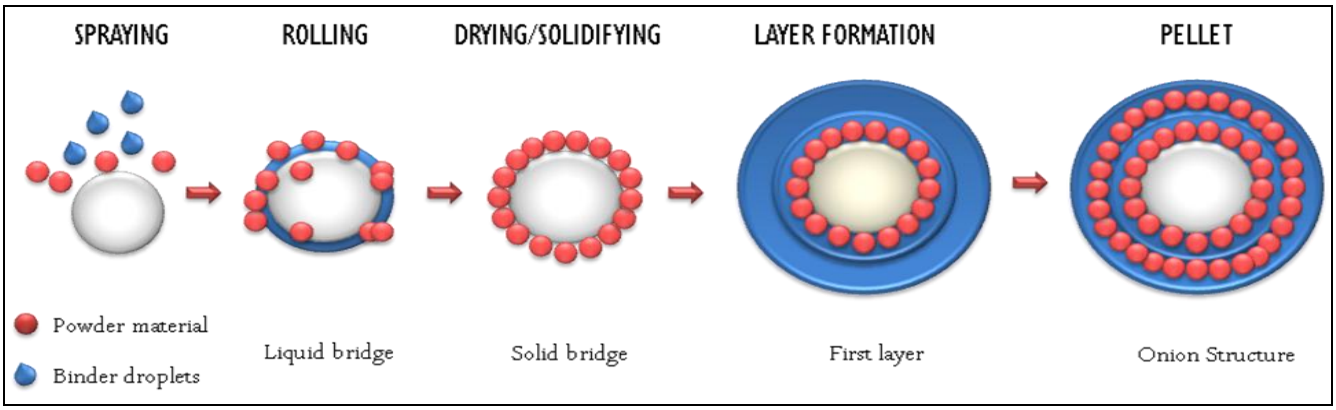

FIG. 03: DRUG LAYERING BY USING SUSPENSION

- **Direct pelletizing:** Sample material is blended and solvent or binder system is added to it. The material bed is then subjected to a centrifugal motion. The centrifugal forces act on the material in this process resulting in the formation agglomerates, which get rounded up into uniform sized dense pellets (fig 04). The size, density and shape of the pellets formed are influenced by the speed of rotation. The moist pellets formed are then dried up in the fluid bed. Organic solvents can also be used if required [16].

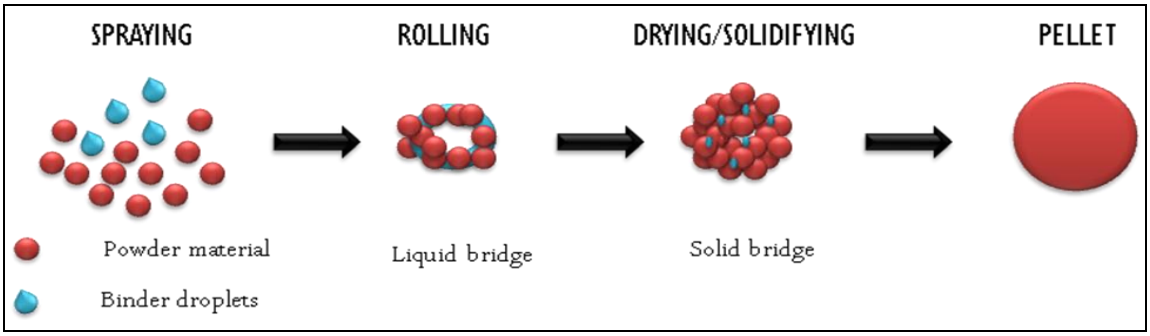

FIG. 4: DIRECT PELLETIZATION PROCESS FOR PREPARATION OF PELLETS

- **Pelletization by extrusion and spheronization:** Pharmaceutical pellets are typically manufactured via extrusion spheronization, a three-step process introduced in the late 1960s, that results in spherical granulates roughly 1 mm in diameter. Wet mass extrusion spheronization also called cold-mass extrusion spheronization has become the method of choice. When one is desirous of having dense spherical pellets of uniform size and shape. It involves the following steps;

(a) Dry Mixing: Dry mixing of ingredients is done to achieve homogeneous powder dispersion using twin shell blender, planetary mixer, high speed mixer and tumbler mixer [17, 18, 19, 20].

b) Wet Massing: Wet massing is done to produce a sufficient plastic mass for extrusion, by employing normal equipment and processes as employed in wet granulation for compaction. The most commonly used granulator is planetary mixer or Hobart mixer or sigma blade mixer and high shear mixer [17]. Evaporation of the fluid phase is a major problem with high shear mixers as they introduce a high amount of energy into the wet mass which is partly transformed into heat and induces evaporation of the granulation liquid thus changing the extrusion behavior of the wet mass. Cooling of the granulation bowl may avoid this problem.

c) Extrusion: This is the third step in the process, which produces rod shaped particles of uniform diameter from the wet mass. The wet mass is forced through dies and shaped into small cylindrical particles with uniform diameter. Such shaping of the wet mass into long rods, commonly termed 'extrudate.' The extrudate particles break at similar length under their own weight. Thus, the extrudate must have enough plasticity to deform but not so much that the extrudate particles adhere to other particles when rolled during spheronization process. Extruders are classified into three categories namely, Screw feed extruder (axial or end plate, dome and radial), the screw extruder consists of one or two (twin -screw) feeding the wet mass to an axial or radial extrusion screen [13, 14]. In the axial type, (**fig. 5**) the screen is placed at the end of the screw, while in radial type the screen is placed around the screw (**fig. 7**), discharging the extrudate perpendicularly to the axis of the screw.

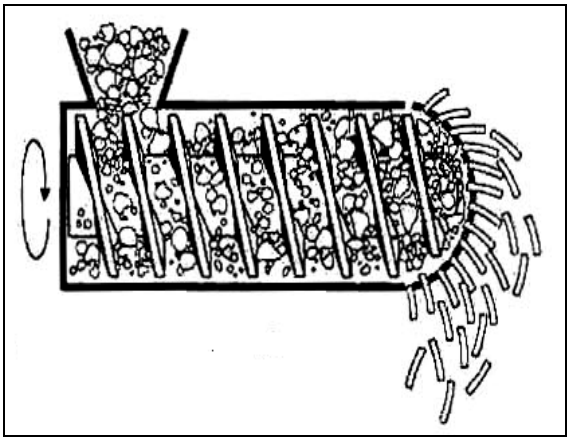

FIG. 5: AXIAL SCREW FEED EXTRUDER

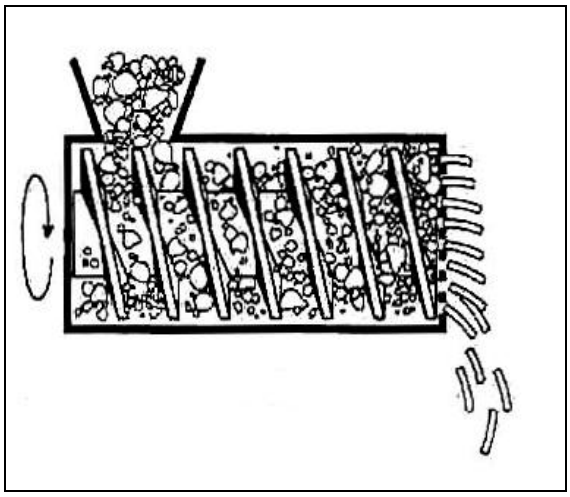

FIG. 6: DOME SCREW FEED EXTRUDER

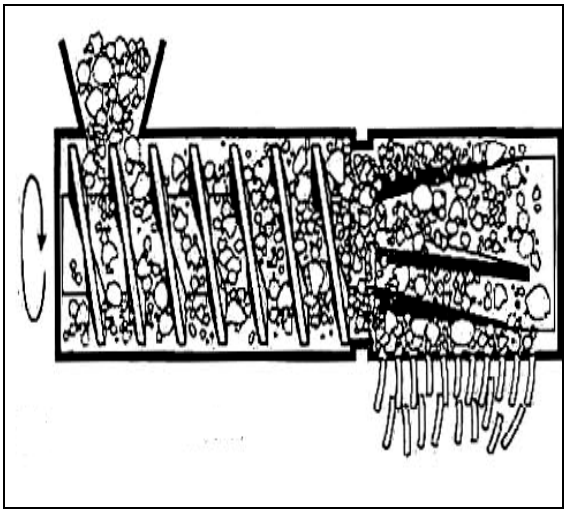

FIG. 07: RADIAL SCREW FEED EXTRUDER

Gravity feed extruder (cylinder roll or gear roll) and Gravity feed extruders include 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 is solid and acts as a pressure roller (**fig. 8; fig. 9; fig. 10**).

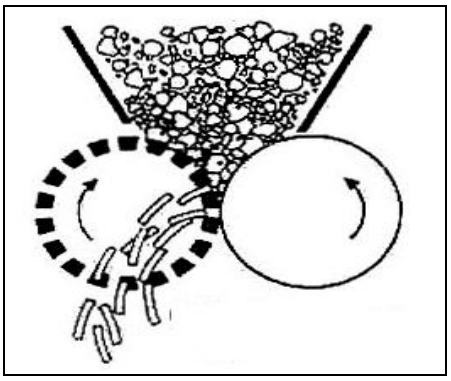

FIG. 08: CYLINDER ROLL TYPE

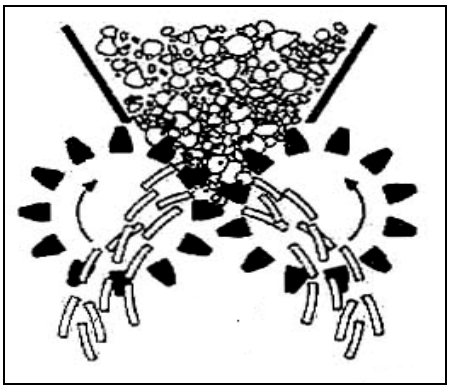

FIG. 09: GEAR ROLL TYPE

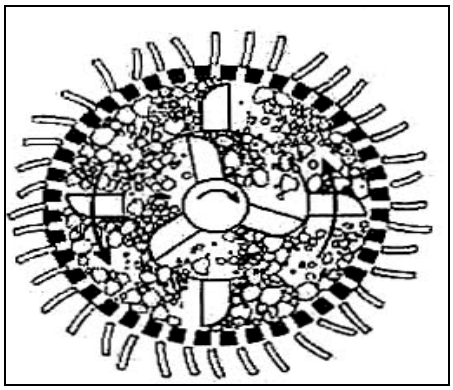

FIG. 10: RADIAL TYPE

In the rotary gear extruders there are two hollow counter rotating gear cylinders with counter board holes. Piston feed extruders (ram) which are probably the oldest type of extruders (**fig 11; fig 12**); 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 the formulations [17, 18].

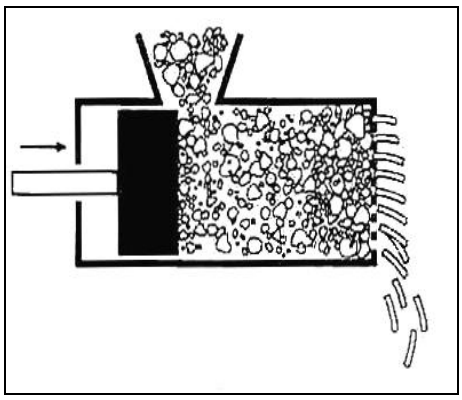

FIG. 11: AXIAL PISTON EXTRUDER

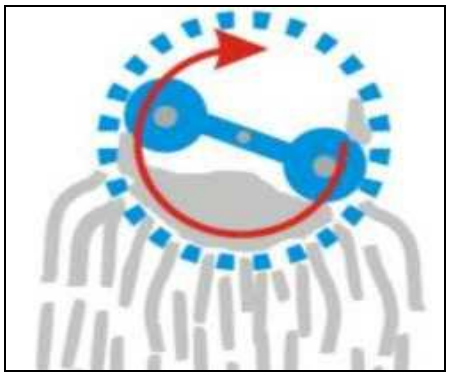

FIG. 12: RADIAL PISTON EXTRUDER

(d) Spheronization: The spheronization technology was first introduced by Nakahara in 1964. A spheronizer 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. During spheronization process different stages can be distinguished depending upon the shape. 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 [21, 22, 23, 24].

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. The rotational speed of the friction plate varies from 100- 2000 rpm. Spheronization process involves transition from rods to spheres that might occur in various stages which usually take 5 to 30 minutes provided mass should not be too dry wherein no more spheres are formed and the rods will transform as far as dumbbells only (**fig. 13**).

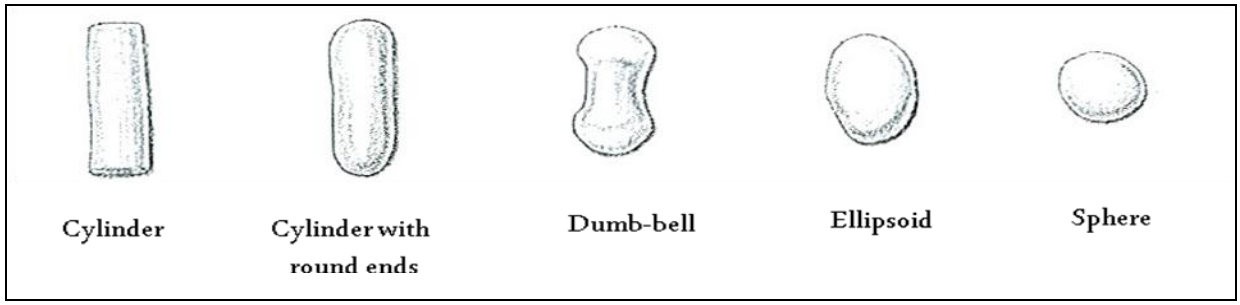

FIG. 13: SCHEMATIC REPRESENTATION OF DIFFERENT PELLET FORMATION STAGES DURING SPHERONISATION

(e) Drying: A drying stage is required in order to achieve the desired moisture content. Drying rate also important an increase drying rate gave more porous pellets due to decrease pellet densification during that drying process. The pellets can be dried at room temperature [25, 26] or at elevated temperature in a tray drier/ oven [27, 28, 29] or in a fluidized bed drier [30, 33, 34, 35]. Bataille *et al.*, 1993 [31] reported the use of microwave oven in the final phase of the production process of pellets to evaporate the slurry of the extruded mass during drying process. Huyghebaert *et al.*, 2005 [32] reported the use of freeze dryer in order to maintain viability of living bacterial spores. If solute migration occurs during drying of the wet mass, this may result in an increased initial rate of dissolution, stronger pellets with modified surfaces, which might reduce adhesion of any added film coats.

(f) 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 manufacture, in order to avoid pellets having high size polydispersity index [36].

Process parameters for the extrusion-spheronization techniques

a) Starting Material: The nature of the starting material influences the size, hardness and sphericity of the particle, as well as the release rate of the loaded drug. The material used in the formulation causes difference in pellet quality produced from different compositions. The use of similar products manufactured by different suppliers also showed changes in the characteristics of the pellet produced. Pellets prepared with three types of microcrystalline cellulose (MCC) from different manufacturers featured differences in size and roundness even though processed under the same conditions[37, 38, 39].

b) Extruders: According to Reynolds and Rowe an axial screw extruder produces a denser material than a radial screw extruder. The latter has a higher output but also produces but shows greater heat production during the processing. Pellet quality is dependent on the thickness of the screen and the diameter of the perforations [40, 41, 42]. A thinner screen produced a rough and loosely bound extrudate, whereas a thicker screen forms smooth and well-bound extrudate because of the higher densification of the wet mass. Similarly, the diameter of the perforations determines the size of pellets- a larger diameter in the perforations will produce pellets with a larger diameter under similar processing conditions [43, 44].

c). Extrusion Speed: The output from the extruder depends on the extrusion speed. The increasing speed causes at surface impairments, such as roughness and shark-skinning which leads to pellets with lower quality because the extrudate will break up unevenly during the initial stages of the spheronization process, resulting in a number of fines and a wide particle-size distribution [43, 44].

d) Extrusion Temperature: The extrusion cycle during the operation may lead to rise in the temperature which could cause the granulating liquid to evaporate from the granules which causes difference in the quality of the extrudate right in the beginning of the batch itself. Extrusion temperature control is especially taken into the consideration when processing a thermolabile drug formulation[44].

e) Spheronizer Specifications: Pellet quality is also dependent on spheronizer load which affects the particle-size distribution, bulk and tap density of the

final pellets. The increase in the spheronizer speed and a low spheronizer load will result in wider particle size distribution with less yield of pellets, whereas it increases with extended spheronization time at a higher spheronizer load. Barrau *et al*., reported that an increasing spheronizer load decreased the roundness and increased the hardness of pellets. Hellen *et al*., reported that the bulk and tap density increased and the size of the pellets decreased with an increasing spheronizer load [27, 34, 45].

Pelletization in fluid bed system: The multi-functional Precision coater and top spray coater systems can all be used to make pellets by layering the active material onto an inert core. Non-pareil starter pellets are sprayed with a solution or suspension of the active material, and dried simultaneously. Coating technology has many applications in the pharmaceutical industry for taste masking and drug release control. Fluid bed coating is particularly suitable for smaller particles and pellets. Making uniform spherical pellets in the Fluid Bed System is possible only in the Tangential Spray Attachment or Roto-Processor attachment.

The major advantage is that all the operations from mixing to bead formation to bead drying to bead coating all can be done in one machine. The top-spray attachment can be used for making granules and bottom spray attachment is used for coating. A fluidized bed is a bed of solid particles with a stream of air or gas passing upward through the particles at a rate great enough to set them in motion. As the air travels through the particle bed, it imparts unique properties to the bed simulating a liquid form. It is possible to propagate wave motion, which creates the potential for improved mixing.

In a bubbling fluidized bed, no temperature gradient exists within the mass of the fluidized particles. This isothermal property results from the intense particle activity in the system. Thus, the fluid bed can be used to dry the wet product, agglomerate particles, improve flow properties, instantize the product, or produce coated particles for pellets or taste masking. Modular systems designed to carry out multiple processes in which only a container change is necessary to change the type of unit operation being performed has been developed by all the manufacturers of fluid-bed processors [46].

Other pelletization methods: Other Pelletization methods such as globulation, cryopelletization, balling, and compression are also used, although a limited scale in the preparation of pharmaceutical pellets.

Globulation droplet formation consists of two related processes, spray drying and spray congealing:

a) **Spray drying:** It is the process in which drugs in the suspension or solution without excipients are sprayed in to a hot stream to produce dry and more spherical particles. This process is commonly used for improving the dissolution rates; hence bioavailability of poorly soluble drugs

b) **Spray congealing:** It is the process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes or fatty acids, and is sprayed into an air chamber where the temperature is kept below the melting point of the formulation components, to produce spherical congealed pellets. Both immediate and sustained released pellets can be prepared in this process depending on the physiochemical properties of the ingredients and other formulation variables

Cryopelletization: In aqueous-organic solution suspension or emulsion are dropped into liquid nitrogen to form frozen particles, these particles are than freeze-dried on lyophilized to remove water or organic solvents [47].

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 [48]. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablets manufacturing. Influence of formulation and compression parameters on the properties of tablets containing enteric coated pellets and on the integrity of the enteric polymer of the individual pellets often compression.

Balling: It is the Pelletization process in which pellets are formed by a continuous rolling and tumbling

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

Melt-Extrusion Technology: Wet mass extrusion is the most frequently used method current a part from extrusion spheronization technique for producing spherical pellets, many drugs exhibit stability problems since granulating fluid employed in this process is generally water. In addition to this, pellets exhibit a rapid drug release and require a film coating to provide if controlled release properties are to be maintained [49, 50].

A novel hot-melt extrusion and spheronization process has been recently reported to produce spherical pellets without the use of water or other solvents. This method eliminates instability problems during processing due to water and also proven advantageous as the pellets produced by melt extrusion do not require additional film coating since the drug release is diffusion controlled. Hot melt-extrusion is initially used in the plastic industry, slowly gaining popularity in the pharmaceutical industry for the production of pellets; immediate and sustained release tablets and transdermal drug delivery systems [51, 52, 53] and also the technique is being approved in the USA, and it is a fast, simple, continuous, solvent-free process with fewer processing steps.

Melt extrusion process consists of three basic steps: melting or plasticizing a solid material, shaping the molten material and solidification of the material into the desired shape. A hot melt extrusion line consists of a material feed hopper, extruder inside a heated barrel, having three different sections, and spheronizer. The feed hopper holds the material and continuously feeds it into the extruder, which has a heated barrel containing the rotating screw. The extrudate is then cut into uniform cylindrical segments, which are spheronized to generate uniform sized pellets. The temperature maintained in the spheronizer should be high enough to soften the extrudate partially and facilitate its deformation and eventual spheroid formation.

Freeze Pelletization: Freeze pelletization is a new and simple technique for producing spherical pellets for pharmaceutical use. 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 droplets' density with respect to the liquid in the column. If the density of the molten-solid carrier/matrix is more than that of the liquid in the column, then the droplets are introduced from the top of the column and pellets solidify in the bottom portion of the column .Conversely, if the density of the 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 the column**.**

Product characteristics of the Pellets:

a. Round pellets.
b. Good flow behavior.
c. Easy to dose.
d. Good dispensability.
e. Compact structure.
f. High bulk density and
g. Dense surface.

Pellet Coating Process: The coating process for pellets is carried out primarily in order to modify the release of the drug from the pelletized drug delivery systems. Following are the some of the Coating equipments used for this purpose

Most of the coating processes use one of three general types of equipments.

1. The standard Coating pan
2. The Perforated Coating pan
3. The Fluidized bed coater

Conventional Pan System

a) The standard coating pan: The standard coating pan system consists of a circular metal pan mounted somewhat angularly on a stand, the pan is rotated on

its horizontal axis by a motor, the hot air is directed into the pan and onto the bed surface, and is exhausted by means of ducts positioned through the front of the pan .Coating solutions are applied by spraying the material on the bed surface [51].

b) The perforated Coating Pan: Perforated pan coaters are efficient drying systems with high coating capacity, and can be completely automated for both sugar coating and film coating processes. There are four different type of coaters available Acela-Cota, Hi-Coater, Driacoater, Glatt coater. In all four of these perforated pan systems the coating solution is applied to the surface of the rotating bed of pellets through spraying nozzles that are positioned inside the drum [51].

c) The fluidized Bed Coater:

- The Fluid Bed Technology offers a very efficient coating technique with a major advantage of not only coating but granulation and pellet formation is also possible in the same machine. Fluid bed coating is currently a widely use technique because it allow among the other applications crystals or granules to be coated with a variety of available polymers to provide gastro resistance or controlled release system [52, 53].

- Fluid bed dryer technology is commonly employed in the film coating of pellets. The coating suspension is sprayed as a atomized droplets onto the fluidized pellets. A film coat is formed around the pellet with successive disposition of spray droplets accompanied by solvent evaporation due to the heat supplied by the fluidizing air. Fluid bed pen coater called Mini Wet develop recently, there are diversified methods of using fluidized bed technology however product formed from each method can offer markedly different finished product characteristics [54, 55].

Formulation:

1) Active Pharmaceutical Ingredient: This multiple unit dosage form technology has the potential for delivery of variety of APIs. The different drugs can be used to develop immediate release, sustained release pellets with diversified applications in different areas. Pellets can be formulated with the drugs that can be delivery even subcutaneously and intramuscularly depending on the size variations where the size range is maintained below 600 microns and are called as micropellets. Pellets technology is widely used to delivery GIT drugs at a specific site to release drug in a controlled manner.

2) Binder: They are also called as agglomerating inducers or bridging agents. These are adhesive materials that can be incorporated into pellet formulations to bind powders and maintain integrity on pellet formation and the addition of the binder may be as a solution than the dry form, which is considered to be more efficient than dry mixing followed by liquid addition. When applied as solution form, binders are dissolved or dispersed in organic or aqueous solvent; the latter is most preferred and commonly used system in pelletization. Choice of binders may differ from formulation to formulation and depends on the processing and physicochemical properties of the drug.

The mechanism of action of the binder involves formation of liquid bridge that holds the particles together; but as the liquid evaporates the precipitating and hardening of binder takes place leading to main bonding force and with a possibility of the soluble constituents to crystallize and contribute to the bonding mechanisms [56]. In drug layering process, the drug is layered onto the surface of the starter material along with the binders. Sequential layering of binder in the desired manner with the drug allows the formation and growth of pellets.

In the spray-drying process, the binder is intimately mixed as suspension or solution form with the drug to provide a fairly cohesive mixture which results in the pellets with appreciable strength after drying The binders are commonly used in the range of 2-10%w/w or v/v and should be optimized so that the pellets are durable and not friable and yet to maintain the other desirable properties of the pellets, such as releasing the drug at the intended rate.

3) Granulating fluid: Moisture content of the wet mass prepared is the most crucial parameter for pellet growth as it imparts the required plasticity and cohesiveness to the wet mass to extrude it and spheronize it to give a prefect spherical shape. An

optimum quantity of moisture content should be there to obtain a good quality pellet. The presence of excess moisture content leads to agglomeration of pellets during the preparation process due to the presence of excess solvent system on the surface of pellets while less quantity leads to generation of fines with large size distribution of pellets. In the case of soluble drug, it gets dissolved by the granulation liquid, thus, resulting in increase of the volume of the liquid phase which leads to over wetting of the system and agglomeration of pellets [57, 58].

Different types of granulating fluid are used for the pelletization process. Besides the use of aqueous forms as a granulation liquid, use of alcoholic or hydroalcoholic systems, ethyl ether, dilute acetic acid, isopropyl alcohol has also been reported. Millili and Schwartz, 1990 reported that a minimum of 5% of granulation liquid had to be water in order to produce pellets containing Avicel PH 101 and theophylline (90:10 w/w). Used water and dilute acetic acid in different powder to liquid ratios in order to increase the mass fraction of chitosan within the pellets and concluded that mass fraction can be increased to 100% by using dilute acetic acid for granulation step in place of demineralized water. Binders are usually not incorporated, as the addition of binders [Micro Crystalline Cellulose (MCC)] provides more cohesiveness. However, researchers have attempted to incorporate various binders in the moistening liquid.

4) Spheronizing Enhancer: Spheronization enhancers are formulation aids that improve the production of spherical pellets, mainly during spheronization and balling processes. They not only impart plasticity onto the formulation, but also impart binding properties that are essential for pellet strength and integrity.

5) Filler: These are the excipients used to form the bulk of the material, in the process of pelletization 70 to 80% of the excipients is formed by fillers. Generally microcrystalline cellulose is used for this purpose. Avicel PH 101 is considered to be the pelletization aiding excipient in this process. Glyceryl mono stearate, Starch RX1500, spray dried lactose.

6) Plasticizer: Plasticizers improve the flexibility of polymers by reducing the tensile strength and glass transition temperature of the material. Sometimes drugs and other excipients are employed as plasticizers. Reported that non-traditional plasticizers including methyl paraben and drugs such as ibuprofen, were able to lower the glass transition temperature of polymeric films prepared from aqueous latex dispersion of Eudragit RS30D. The plasticizer selection will depend upon its compatibility with the polymer and also solvent employed in the casting of strip. These excipients used in hot melt extrusion can affect the release behavior of the drug. The flow of polymer will be improved with the use of plasticizer that enhances the strength of the polymer. Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, Citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients.

7) Lubricant: In pelletization process, lubricants are rarely used as the high-speed rotary equipments are being used in the preparation of pellets. However, during compression and Extrusion-Spheronization, lubricants do play a crucial role in the successful manufacture of pellets. Their use reduces the friction between the die wall and material mix either during the compression process or in ejection phase. They also play a significant role in smooth discharge of the pellets from the Spheronizer [56].

8) Separating Agents: Separating agents are materials which are adsorbed on the surface and promote the separation of pellets into individual units during a pelletization process, which are incorporated initially in the formulation or externally during processing to prevent pellets attracting one another due to surface charge development during the process, binding the pellets together leads to the formation of aggregates due to subsequent addition of binding agents, and agglomeration of pellets due to the wetness of the surface of the pellets coupled with the local concentration of the binding agents. The amount of separating agent used differs with the type of formulation and the manufacturing process and they are used in dry form during spheronization to prevent adhesion of the spheres to the friction plate and the cylindrical wall of the Spheronizer [59].

9) Surfactant: In most pelletization processes, the initial pellet formation and subsequent growth into fully fledged smooth surfaced spherical pellets depends, to some extent, on the liquid bridges that hold the primary particles together, therefore, liquid (water in most cases) wetting the particles effectively is given more attention. Surfactants are added to the liquid to improve wettability by lowering the interfacial tension between the liquid and drug particles[60]. Surfactants help to weaken the liquid bridges and results in more friable pellets. In extreme cases, excess fines might be produced which brings in the focus to the addition of surfactants for pellet formulations. Care should be taken to avoid using surfactants unless it is absolutely essential for the production of pellets that possess specific properties.

10) pH adjusters: The pH adjusters are substances that are incorporated in pellet formulations which influence the microenvironment of drug molecules used for many reasons. Generally acid-labile drugs are protected from the pH conditions of the GIT by giving an enteric coating. Buffer systems may also be added to the core formulation to maintain the stability of core in a favorable range [59]. In addition, buffer systems may be included in pellet formulations to enhance the dissolution rate of drugs whose solubility's are influenced by changes in the pH this is particularly referred with pellets whose release rates are membrane-controlled as the solubility of the drug plays a major role in determining the rate of release. Therefore, specific buffer systems or dual buffer systems are incorporated in pellet formulations to adjust the solubility of drugs to fit a particular process.

11) Release modifiers: The main requirement of pelletization process is to manufacture spherical drug cores that will be subsequently coated in a separate unit operation. It is also possible to prepare pellet cores that inherently possess specific release profiles in a single step which can be achieved by the incorporation of release modifiers along with drug during the core formulation. Due to the diversity of chemical composition and physical properties of release modifiers, pellet formulations that provide a multitude of release profiles could be designed[61]. Generally, water soluble low molecular weight excipients, surfactants and disintegrants are incorporated in formulations to enhance the drug release kinetics, while water insoluble polymers, hydrophobic substances, inorganic salts, and hydrophilic polymers that swell and/or form gels are incorporated in pellets that retard release kinetics.

12) Flavoring agent: The choice for the flavors changes from individual to individual depending upon the age, ethnicity and liking which plays a significant role in the taste fondness. It was observed that the geriatric population like mint or citrus fruit flavors while younger generation like flavors like fruit punch, raspberry etc. The flavor selection for the particular formulation also depends upon the drug to be incorporated in the formulation. Mint flavor is generally added in products used for gastric related ailments like indigestion. The acceptance of the oral dosage formulation by an individual depends on the initial quality of the flavor which is observed in first few seconds after the administration of the product and shows the after effect which lasts for at least about 10 min.

Flavoring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors can be used alone or in the combination. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type. The amount of flavor needed to mask the taste depends on the type and strength of the flavor. Preferably up to 10%w/w flavors are added in the formulations. Cooling agents like monomethyl succinate, menthol can be added to improve the flavor strength and to enhance the mouth-feel effect of the product. Other cooling agents' likeWS3, WS23 and Utracoll II can also be used in conjunction with flavors (**Table 1**).

TABLE 01: RECOMMENDED FLAVOUR FOR THE PARTICULAR TASTE

Taste sensation	Recommended flavor
Salt	Butter scotch, Apple, Apricot, Vanilla, Peach
Bitter	Wild Cherry, Walnut, Chocolate, Mint, Passion fruit
Sweet	Berry, Vanilla.
Sour	Citrus Fruits, liquorice, Root beer, Raspberry

13) Sweetening agent: Sweeteners have become the significant part of the food products as well as pharmaceutical dosage forms intended to be disintegrated or dissolved in the oral cavity. The sweet taste in formulation is more preferred especially in case of pediatric population. Natural sweeteners as well as synthetic sweeteners are used to improve the palatability of the formulations. The traditional source of sweetener is sucrose (derived from cane or beet in the form of liquid or dry state), dextrose, fructose, glucose, liquid glucose and maltose.

The sweetness of fructose is dissolved rapidly in the saliva compared to sucrose and dextrose and also sweeter than sorbitol and mannitol for which it's used widely as a sweetener. Polyhydric alcohols such as sorbitol, mannitol, isomalt and maltitol can be used in combination as they additionally provide good mouth-feel and cooling sensation. Polyhydric alcohols are considered less carcinogenic and do not have bitter after taste which is a vital aspect in formulating oral preparations. The sweetness property of the polyols is less than half of that of sucrose except xylitol and maltitol which have similar sweetness as that of sucrose (scale of 0.8- 1.0). However the use of such natural sugars is restricted in the case of diabetic patients and diet conscious patients. Due to this reason, the synthetic sweeteners have gained more popularity both in food and pharmaceutical preparations. Saccharin, cyclamate and aspartame are the first generation of the synthetic sweeteners followed by acesulfame-K, sucralose, alitame and neotame that fall under the second generation artificial sweeteners.

Acesulfame-K and sucralose have more than 200 and 600 time sweetness. Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose. Rebiana which is a herbal sweetener, derived from plant *Stevia rebaudiana* (South American plant) has more than 200–300 time sweetness but these synthetic sweeteners carry a disadvantage of after taste effect which can be reduced by mixing or blending the natural and synthetic sweeteners. The flavor quality of these synthetic sweeteners is different than the natural sweeteners and is generally disliked by patients accustomed by the natural sweeteners. The amalgamation of sweeteners may lead to synergism and improvement in the taste of the formulations. Generally sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination.

14) Coloring agents: Coloring agents are generally used in order to improve the appearance and make it more patient compliance. Pigments such as Titanium dioxide or FD&C approved coloring agents are used either in the dry form or mixed with the granulating fluid during the formulation.

TABLE 2: SHOWING DIFFERENT POLYMERS USED IN THE PELLETIZATION PROCESS

Polymer used in pelletization	Formulation	Applications
Carbopol 974P,NF, Resin.	Beads containing Weakly basic drugs.	Slower release of the salts of weakly basic drugs.
Crosscarmellose sodium or sodium starch glycolate.	Super-disintegrants in avicel pellets.	Increase dissolution rate, increase the pellet micropore volume.
Eudragit RS PO and RL PO.	Polymer (with combination) based pellets.	Better characterization like elastic modulus of the pellets, surface characteristics, sphericity.
Eudragit RL 30D, RS 30D, NE 30D.	A multiple- unit floating drug delivery system.	Prolong the gastric residence time and to increase the overall bioavailability of the dosage form.
Gelucire.	Lipidic –matrix pellets.	Controlled drug release.
Methocel-E5 (HPMC) or AMB, Eudragit L 30D-55.	Enteric coated pellets.	Improved film formation and polymer coalescence.
Microcrystalline cellulose, Ac-Di- Sol.	Floating pellets with bacterial antagonist.	Improving floating property.
Microcrystalline cellulose and hydroxypropyl methyl cellulose.	Pellets with water insoluble drugs in self-emulsified form.	Controlling the drug release from the oral dosage forms.
Pectins or alginates.	Polysaccharide gel coated pellets.	Oral administration of theophylline in the coated pellets.

Evaluation of Pellets:

- **Size distribution:** The sizing of pellets is necessary because it has significant influence on the release kinetics. In most of the cases particle size determination is carried out by simple sieve analysis using sieve shaker. Wiwattaapatapee, 2004 reported the use of Vernier calipers to determine the size of pellets.

- **Sieving method:** The prepared pellets were estimated by sieving method. Sieving method directly gives weight distribution. Sieves were arranged in a nest with the coarsest at the top. A sample (5 gm) of the dried pellets was placed on the top sieve and subjected to mechanical agitation. The sieve set was fixed and shaken for a certain period of time (10 minutes). The pellets retained on each sieve were weighed [61, 62]. Frequently, the pellets were assigned the mesh number of the screen through which it passed or on which it was retained. It was expressed in terms of Arithmetic mean of the two sieves.

$$\text{Mean particle size} = \frac{\Sigma Xi\ Fi}{\Sigma\ Fi}$$

Where, $\Sigma Xi\ Fi$ = Weight size; $\Sigma\ Fi$ = Percent weight retained.

The size analysis of the pellets was done by carrying out the sieve analysis of the prepared batches. The cumulative particle size distribution was plotted, from which the 50% value (median) was obtained.

- **Pellets shape:** Sphericity of the pellets is the most important characteristics and various methods have been used to determine it. The pellets were mounted on a light microscope fitted to a Camera Lucida and the images of the pellets were drawn manually on a graph paper. The shape factor estimates the amount by which the projected image of particles deviate from a circle and it is calculated by means of the projected area of the pellets and its circumference. For acceptable quality of pellets the roundness index/shape factor should be between 1 and 1.2. For perfectly circular projected image, the shape factor should be 1 while a value of 0.6 describes a particle of good sphericity [63, 64, 65].

  Visual inspection of pellets by microscope and stereomicroscope are another method to determine shape of pellets. An angle at which a plane has to be tilted before a particle begins to roll is called to be One plane critical stability, is one of the important methods used for determining shape. The angle of repose is an indirect indication of the circularity of pellets and is calculated by the ratio of double the pile height and pile radius by fixed funnel method measured after a certain amount of pellets are allowed to flow through a specific orifice from a given height [66].

- **Surface morphology:** Scanning electron microscopy is used to examine the surface morphology and cross section of pellets [67]. The sampling pellets are mounted onto the aluminum stub, sputter-coated with a thin layer of Platinum using sputter coater (Polaron, UK) under Argon atmosphere, and then examined using SEM. The use of optical microscopy to examine the microstructure of pellet surface was first reported by Sood *et al.*, 2004. While the SEM pictures collected to observe the influence of different fillers and concluded that MCC and corn-starch gives best quality pellets with smooth surface was reported by Eurrkainea and Lindqvist, 1991. The analysis for surface roughness of pellets by applying a non-contracting laser profilometer was studied by Santosh *et al.*, 2004 [68, 69, 70].

- **Specific surface area:** Surface area of pellets is directly related with size and shape of the pellets. Knowledge of the surface area is desirable especially if film coating is considered. Knowledge about the surface area is important even in case of uncoated pellets, since drug release is influenced by the surface area. Specific surface area of pellets is determined by gas adsorption technique [71].

  - **Mathematical calculations:** A spherical pellet, which is smooth and dense, has minimum surface area per unit volume and can be characterized by its diameter. Since surface area is equal to πr^2.

True density measurements can also be used to determine the specific surface area.

- **Gas adsorption technique:** In this technique, the volume of nitrogen that is adsorbed by the substrate contained in an evacuated glass bulb is determined at various pressures, and the results are interpreted using a linear plot of the BET equation for the adsorption of nitrogen on a substrate.

- **Hardness and Friability:** The mechanical properties of pellets are important for processing. Pellets flake off during handling, shipping, storage coating process and other unit operations thereby resulting in formation of dust. Variations in the formulation and/or process of pellets, as well as variability in the raw materials, can potentially result in significant variations with hardness and/or friability of pellets [72]. Hardness of pellets can be determined using Kahl pellet-hardness tester but might not be accurate. Friability of pellets are determined by using Erkewa type tablet friabiliator or turbula mixer for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion and to generate friability index. Friability can also be determined using fluidized bed with Wurster insert by using stream of air [73].

Thus proven that the reproducibility in particle-size distribution, surface area, density, hardness, and friability tests, in addition with that of reproducibility of morphologic properties, will become the criteria by which a formulation and process for manufacturing pellets can be selected.

Mechanical tests:

- **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 [74].

- **Cushing strength:** The crushing strength (the load needed to break the pellets) and elastic modulus of 15 pellets (850–1000mm size fraction) were determined using a Material Testing Machine. The speed of the upper mobile platen fitted with a 1 kN load cell was set at 1 mm/min. Elastic modulus and force–displacement graphs were obtained by a computer system attached to the apparatus [75].

Density: Density of pellets (bulk and tapped) can be affected by change in the formulation or process which may affect other process or factors such as filling and packaging characteristic during capsule manufacture and tablet compression, and is determined simply by USP density apparatus.

The bulk density of pellets can be measured by using an automated tapper, while the true density of pellets can be determined by an air-comparison pycnometer or by solvent displacement method. Bulk density is indicates the packing properties of pellets or spherical seeds which provide higher bulk densities due to small intraparticle porosities [76, 77]. True density indicates the extent of densification or compactness of pellets.

Pellet surface roughness: The surface roughness measurements were carried out on the same samples of pellets as those used to measure the diameter. Samples were mounted on a non-reflective black plate, which was placed on an air-bearing table and the surface roughness measured with a laser profilometer. The light spot diameter of the sensor was 1 mm and the sensor aperture angle was 53^{O}. Measurements were performed in 3D at a frequencyof 100 points and a measuring depth of ±50_m. The area scan was carried out across the 2.00mm x-transverse, with a resolution of 1000 points/mm and the 0.20mm y transverse, with a resolution of 200 points/mm[78,79]. The roughness descriptors, *R*a (rugosity), *R*q (root mean square deviation of the asperity height distribution), and *R*tm (average peakto-valley ratio) were assessed. The results are the arithmetic mean and standard deviation of five replicates of the above procedure.

Porosity: The porosity of the pellets influences the release of drugs from the pellets by affecting the capillary action of the dissolved drug. The porosity of the pellets can be measured quantitatively by mercury porosimetry. The porosity of the pellets can also be determined qualitatively by SEM with image analysis

and quantitatively by using optical microscopy rarely [80]. Pore radius is given by Washburn equation;

$$R = 2 \gamma [\cos \theta] / P$$

Where; $\gamma = 480$ ergs/cm^3, $\theta = 140^o$, r = pore radius, p = mercury-intrusion pressure.

Thus, determination of the porosity of pellets by mercury porosimetry is a very well-established method showing reproducible results.

Disintegration time: Disintegration of pellets is one of the main characteristics for immediate release pellets. Huyghebaert *et al.*, 2005 reported disintegration test using the reciprocating cylinder method (USP Apparatus 3), while Thommes and Kleinbudde performed it in a tablet disintegration tester specially designed by inserting special transparent tubes of certain diameter and length with sieve of 710mm mesh size at the top and bottom of the tube [81].

***In vitro* dissolution studies:** *In vitro* dissolution studies are predominantly recognized as an important element both in drug development and quality assessment over the past four decades. These tests were performed for studying the release behavior of different formulations in different dissolution media and to establish a co-relation between in vitro release and in vivo absorption for the modified-release pellets. Release of drug from solid dosage form often constitute a determining step in the *in vivo* absorption process and used in conjunction with *in vivo*/*in vitro* correlation to establish quality control parameter. Release of the drug from pellet mainly depends on the composition, hardness and size of pellets and it is determined by using USP Apparatus I or by USP Apparatus II[82]. The drug release profiles from pellets also depends on the Polymer and binder used, aqueous solubility of the drug, physical state of the drug in the pellet, drug loaded into the pellet and the presence of additives such as surfactants. In case of wax based freeze dried pellets, the drug release decreased as the hydrophobicity of wax increases and the drug release increased as the aqueous drug solubility increased.

Applications: Pellets have varied applications in a number of industries and an innovative use of it's could achieve maximum profitability.

Taste masking: Pellets are ideal for products where perfect abatement of taste is required. Although various technique have been utilized to mask the bitter taste of a drug such as the addition of sweeteners and flavors, filling in capsules, coating with water insoluble polymers or pH dependent soluble polymers, complexing with ion-exchange resins, micro-encapsulation with various polymers, complexing with cyclodextrins and chemical modifications such as the use of insoluble prodrugs, few reports have described the masking of unpleasant taste without lowering of bioavailability especially for oral products. The pelletization technique solves difficult taste masking problem while maintaining a high degree of bioavailability due to their high surface area, especially for oral products.

Furthermore, because of the special design of the manufacturing process, dust fractions that representing an uncoated fragments which could cause taste problems are absent in pellets. Many products, such as antibiotics (clarithromycin, roxithromycin and cephelexin) and anti-inflammatory drugs with a bitter taste, can now be formulated in products with high patient compliance, thus increasing the sales potentially in the pharmaceutical markets for the product [83, 84].

1. **Immediate release:** Administering drugs in pellet form leads to an increased surface area as compared to traditional compressed tablets and capsules which would considerably reduce the disintegration time and have the potential for use in rapidly dispersible tablets.

2. **Sustained release:** The pellet form provides a smoother absorption profile from the gastrointestinal tract as the beads pass gradually through the stomach into the small intestine at a steady rate. Pellets are being increasingly used in the manufacture of sustained release dosage form of drugs. The advantages of the dosage form is well known

3. **Chemically Incompatible Products:** At times such ingredients are required to be delivered in a single dose. In the compressed tablet dosage form separate tablets would have to be administered,

but the pellets can be administered in a single capsule.

4. **Varying dosage without reformulation:** Pellets have excellent flow properties, due to this, they can be conveniently used for filling capsules and the manufacturer can vary the dosage by varying the capsule size without reformulating the product [85].

TAB 3: COMMERCIALY AVAILABLE MARKETED PELLET PRODUCTS

Product	Company
Bontril SR	Carnick laboratories, Inc.
Brexin L.A	Savage Laboratories, Bangalore.
Catazyme S	Organon pharmaceuticals, USA.
Compazine	Smith & French, MUMBAI.
Dilgard XL 180	Smith kline & French, MUMBAI.
Elixophyline	CIPLA Ltd, Ahmedabad.
Fastin	Berlex Laboratories, USA.
Hispril	Berlex Laboratories, USA.
Ibugesic S.R 300	CIPLA Ltd, Ahmedabad.
Indocrin S.R	Merk Sharp, MUMBAI.
Nicobid T.S	U.S Vitamin, USA.
Ornade	Smith kline.

TAB 04 CURRENT TRENDS IN PELLETIZATION

Date/Year	Current trend
30 JUL 2010	Peas starch-based film coatings for site-specific drug delivery to the colon. Peas starch: ethylcellulose-based film coatings are proposed for the pellets allowing for site-specific drug delivery to the colon of inflammatory bowel disease patients. They provide the long-term stable polymeric coating for the pellets which can remain unaltered even after one year of storage.
Oct 28, 2010	Bisphenol A (BPA) at low doses, early in life linked to prostate disease in rats. Bisphenol A (BPA) is a well-studied endocrine disruptor – a substance that can interact with hormones in the body. This chemical acts like estrogen. Which is implanted in the form of pellets mimicking the hormone levels

CONCLUSION: This brief review on the pelletization technology hereby concludes with a note that they are considered as a most promising drug delivery system today which is catching up with the pace of speed to have a high existence in the Pharma world. This system gain more popularity because of their easy portability improved patience compliance and ease of administration and flexibility in the fabrication as tablets or capsules or packed simply as a single dose packlets. They can be applied by both oral and buccal routes. This technology is growing in fast pace challenging most of the pharmaceuticals companies to develop pelletized dosage forms for wide range of active pharmaceuticals ingredients.

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