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REVIEW ON PELLETIZATION: TECHNIQUES, CHARACTERIZATION AND APPLICATIONS

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ABSTRACT

Multi-particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. Pellets are defined as spherical or semi- spherical, free flowing solid units with narrow size and diameter ranging from 0.5-1.5mm. the present review outlines the merits and demerits of pellets, need of pelletization, formation and growth mechanism of pellets and pelletization techniques. It also briefs about the factors that affect pelletization techniques, their characterization and applications.

KEYWORDS: Multiparticulates, pellets, techniques, characterization, applications.

INTRODUCTION

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage form is divided into number of subunits, consisting of thousands of spherical particles with diameter of 0.05-2.00mm.[1] Thus multi-particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet.[2] Multi-particulate drug delivery system include pellets, micropellets, granules, minitablets, etc.

Pellets are defined as spherical or semi-spherical, free flowing solid units with narrow size and diameter ranging from 0.5-1.5mm. Pelletization is a size enlargement or agglomeration process that converts fine powders or particulates of bulk drug and excipients into pellets.[3,4]

Merits of pellets

- Improved appearance of product.
- Pellets offer greater flexibility and have excellent flow and packaging properties without significant difficulties resulting in uniform and reproducible fill weight of capsules and tablets.
- Pellets composed of different drugs can be blended and formulated in a single dosage form. This facilitates the delivery of two or more drugs, chemically compatible or incompatible at the same or different sites of gastrointestinal tract. Also same drug with different release rates can be supplied in a single dosage form.
- High bulk density
- High drug loading capacity without producing extensively large particles.

Demerits of pellets

- Pellets are rigid and so cannot be pressed into tablets and have to be encapsulated into capsules.
- The production of pellets is quite an expensive process due to the requirement of highly specialized equipment and trained personnel.[5,10]

Micropellets are the pellets with dimensions less than 1.0 mm. They are gaining importance in market significance because of the many advantages they offer over powder or standard-sized pellets. Micropellets provide advantages like better flowability, virtually dust-free, better color distribution, smaller pellets (micros) offer increased surface area-to-volume ratio. They may be used for a wide range of applications, such as for compounding and master batches, packaging, micro injection molding, rotational molding and surface blasting.[11]

Need of pelletization

- They disperse freely in GIT due to their small size, providing larger surface area for drug absorption and also reduce peak plasma level fluctuations.
- To have less variation in transit time through the GIT than single-unit dosage forms like tablets prepared by granulation and compaction.
- For formulation of modified release preparation like enteric release, sustained release preparations
- They are less susceptible to dose dumping thus lowering the risk of side effects.[5,10]

Formation and growth mechanism of pellets

The mechanism of pellet formation and growth is necessary to review by a formulator in order to select and optimize any pelletization technique.

1. **Nucleation:** In nucleation the growth mechanism is a wet-agglomeration process in which powder particles are wetted with binder liquid. The particles are drawn together to form air-water solid-nuclei by liquid bridges and lead to formation of initial agglomerates.(fig 1:A)
2. **Coalescence:** The well formed nuclei collide with each other due to random movement and results in formation of large-sized particles. Due to this, the number of nuclei is reduced but the total mass of system remains constant. (fig 1:B)
3. **Layering:** The successive addition of fines or fragments on surface of already formed nuclei is called layering.(fig 1:C)
4. **Abrasion transfer:** Agitation of granule bed leads to attrition of material from granules. This abraded material adheres to other granules, increasing their size.(fig 1:D)
5. **Size reduction:** There are three size reduction mechanisms which have an indirect effect on the growth mechanism, particularly layering and to some extent coalescence. Well-formed particle may undergo reduction due to attrition (fig 1:E), breakage (fig 1:F) and shatter (fig 1:G).[12]

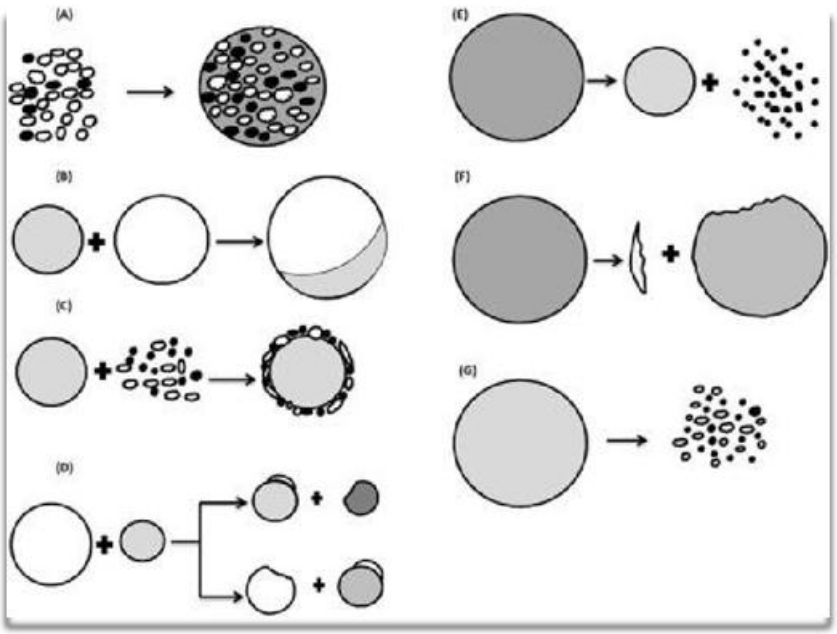

Fig. 1: Formation and growth mechanism of pellets.

Pelletization Techniques

Various techniques are available for pelletization:

Extrusion-spheronization

The extrusion-spheronization technique is the most popular method of producing pellets.

Principle: The extrusion operation densifies the material to saturation point while spheronization is only a shaping process which maintains hydro-textural state. The drying operation finalizes the textural characteristics of the product by densifying the medium through induces shrinkage.[13]

Advantages of extrusion-spheronization over other techniques are the ability to incorporate high levels of active ingredients without producing excessively large particles. It gives sphericals of uniform shape with good flow properties, high strength, low friability, reproducibility in packing and granules with smooth surface. It has gained worldwide attention because it is simple and fast processing technology.[14]

Extrusion spheronization is a multistep compaction process comprising of following steps:

1. **Dry mixing**

Dry mixing of all the ingredients is done to obtain homogenous powder dispersion. Mixing can be done using different types of mixers like twin shell blender, high shear mixer, tumbler mixer and planetary mixer.[15]

2. **Wet massing/granulation**

Wet massing of powder dispersion is done to produce sufficient plastic mass for extrusion. This process of granulation plays a very important role in extrusion-spheronization technique. Most commonly used granulators are sigma blade mixer or high shear mixer and Hobart mixer. Mostly, planetary mixer is used for both blending and granulation. High shear mixer introduces high amount of energy into wet mass which is transformed into heat and induces evaporation of granulation fluid. This changes the extrusion behaviour of wet mass. Cooling of the granulating bowl may avoid this problem.[16]

3. **Extrusion**

Principle: When pressure is applied to a wet mass it passes through the opening of a screen or die plate of the extruder and further shapes into small extrudate segments. These extrudate breaks at similar lengths under their own weight. Thus, the extrudates must have enough

plasticity to deform but not so much that the extrudates stick to each other when collected or rolled in the spheronizer.

Extruders for the extrusion process have been classified generally as screw, sieve and basket, roll and ram extruders.

Screw extruder utilizes screw to develop the necessary pressure and force the material to flow through uniform openings. Screw fed extruders have screws that rotates along the horizontal axis and transports the material horizontally, they may be axial or radial. In axial, the screen is placed at the end of the screw, perpendicular with the axis of the screw (fig 2:A). In radial, screen is placed around the screw. The material is extruded radially through screens mounted around the horizontal axis of the screw (fig 2:B).

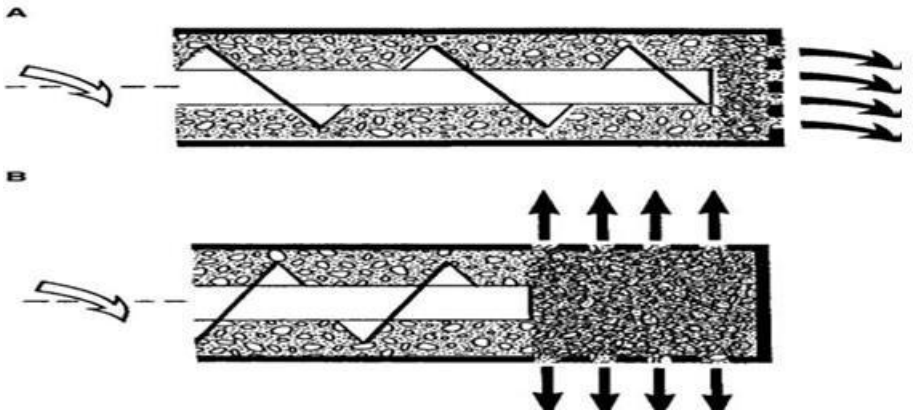

Fig. 2: Screw fed extruders.

In sieve extruder, the rotating or oscillating arm presses the wet mass material through sieve and the extrudate fall vertically from the sieve plate.

In basket extruder, the sieve or screen is part of vertical cylindrical wall and the extrudates are formed in horizontal plane.

Roller extruder operates by feeding material between a roller and a perforated plate or ring die.

In ram extruder, the piston inside the cylinder forces the material through orifice to the forward direction. This extruder is preferentially used in the development phase because they can also be used to measure rheological properties.

4. Spheronization

The function of the fourth step in the process is to round off the rods produced by extrusion into spherical particles. The process is carried out in a relatively simple apparatus. The apparatus consist of a bowl having fixed side walls, with a rapidly rotating bottom plate or friction plate.

Extrudates fall on the rotating plates are broken down into short segments by contact with friction plates, or other particle or wall. The rounding of the extrudate into spheres is dependent on frictional forces generated by particle-particle and particle-equipment collisions. The friction plate has a grooved surface to increase these forces. Two geometric patterns are generally used:

a. A cross-hatched pattern with grooves running at right angles to one another
b. A radial pattern with grooves running radially from the centre of the disc.[16,17]

Principle: Plastic cylinders are rounded due to frictional forces into cylinder with rounded, dumbbells and elliptical particles to eventually form perfect spheres.

The transition from rods to sphere during spheronization occurs in various stages. These are best described by examining the diagram in **Fig 3.**

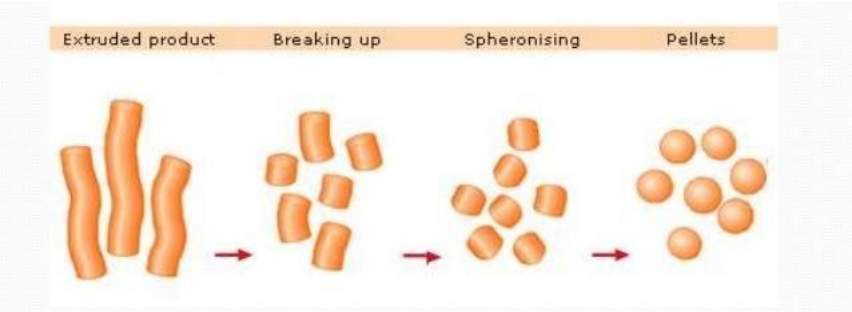

Fig. 3: Principle of Extrusion and speronization process.

5. Drying

A drying stage is required in order to achieve the desired moisture content. Drying is often the final step in the process. Drying of the pellets is achieved at room temperature or at elevated temperature in fluid bed drier or in an oven.[18]

6. Screening: (optional)

Screening may be necessary in order to achieve the desired narrow size distribution. Normal sieves can be used.[19]

Example: Ranitidine pellets were formulated with little or no MCC using extrusion-spheronization technique.[20]

Layering

Layering process is probably the most well-controlled and straight forward pelletization technique that has been used over years. In this technique the drug is layered onto the starter seed material (coarse material or nonpareil) with the aid of binder. The concentration of the binder is based on choice of drug because it influences physical as well as mechanical properties of pellets and drug release from coated pellets.[21,22] They are classified into three categories: solution layering, suspension layering and powder layering.

1. Solution/suspension layering

In solution and suspension layering, drug is dissolved or suspended in the binding liquid and is coated on non-pareil seeds or coarse material. Droplets of the binding liquid spreads on the surface of the nuclei. Dry air is simultaneously passed. During drying the liquid evaporates. The process is continued until the desired layer of drug or polymer is formed.

Principle: The growth of pellets involves deposition of successive layers of solution and or suspension of drug substance and binder on existing nuclei or coarse material. During drying, as the liquid evaporates the dissolved substance crystallizes out and capillary forces formed draw the particles towards each other and towards the nuclei forming solid bridges.[23]

Example: Esomeprazole delayed release pellets were prepared using suspension layering technique.[24]

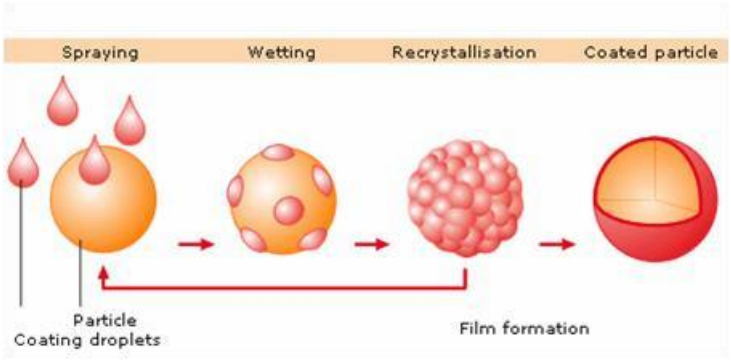

Fig. 4: Principle for solution/ suspension layering.

2. Powder layering

In powder layering, the dry powder of drug or excipients is deposited on the core with the help of binding liquid. Powder layering involves simultaneous application of the binding liquid and dry powder on a starter seed at controlled rate.

Principle: The binding liquids helps in forming successive layers of dry powder of drug and other components on starting core by forming liquid bridges which are eventually replaced by solid bridges.

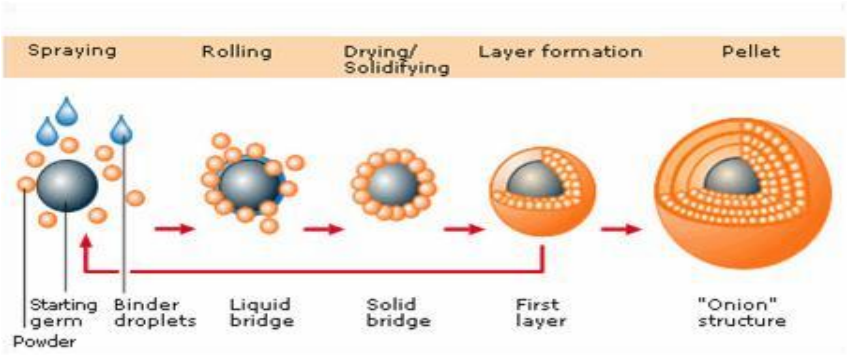

Fig. 5: Principle for powder layering.

Not all the equipments used for solution and suspension layering can be used for powder layering but reverse is true. The main equipment related requirement is the container should have solid walls with no perforation in order to avoid powder loss.

Example: Lansoprazole micropellets were prepared by powder layering technique.[25]

Most commonly used equipments for layering are the standard or conventional coating pans and fluidized bed processor.[26] Conventional pan coaters were used in the very beginning of history of drug layering pelletization process. But the use of conventional pan coaters is not economical as it involves high labor cost and time consumption.

Fluidized bed processor is an equipment that performs multiple functions like coating, drying, granulation and pelletization. In this equipment, uniform and continuous product coating can be achieved with efficent drying. With fluid bed coating, particles are fluidized and the coating medium is sprayed on and dried. Small droplets and a low viscosity of the coating medium ensures an even product coating. There are different types of fluidized bed processor: top spray coating, bottom spray coating (Wurster coating), and tangential spray coating(rotor pellet coating).

Top spray coating: The particles are fluidized in the air which enters the product container via a base plate. The binder solution is sprayed into the fluid bed from above against the air flow(counter current) by using nozzle. It is preferred when the taste masking coating is applied, additionally suitable for the application of hot melt coating.[27,28,29]

Bottom spray coating: This process is suitable for pellet suspension coating or film/sugar coating, particularly useful for a control release active ingredients. During the process the hot air flow through the bottom of the container. The pellets or granules are suspended in the upward moving air stream, where they receive coating from a spray nozzle located on the distributor plate at the bottom of the insert. Convection is created through the strong force from bottom toward top. As the particles continue travelling upwards, they dry and fall outside the Wurster tube back towards the base plate. This circulation of particles is repeated until the desired coat amount is deposited on the solid particles.[27,28]

Tangential spray coating (Rotor pellet coating): This process is particularly suitable for pellet powder coating, suspension coating or film/sugar coating. In this process the cores are placed on the turntables and hot air is blown upward between the turntables and the granulation area. The passage of air causes the cores to roll on the turntables. At the same time, the coating solution is sprayed on the rolling cores through the pump and spray gun. The process involves simultaneous coating and drying of the cores, layer after layer, until the repeated actions achieve the application of modified release film coating to a wide range of multiparticulate products, ideal for drug layering when the dose is medium to high and also useful as a spheronizeing process for producing spheres from powders.[27,28,30]

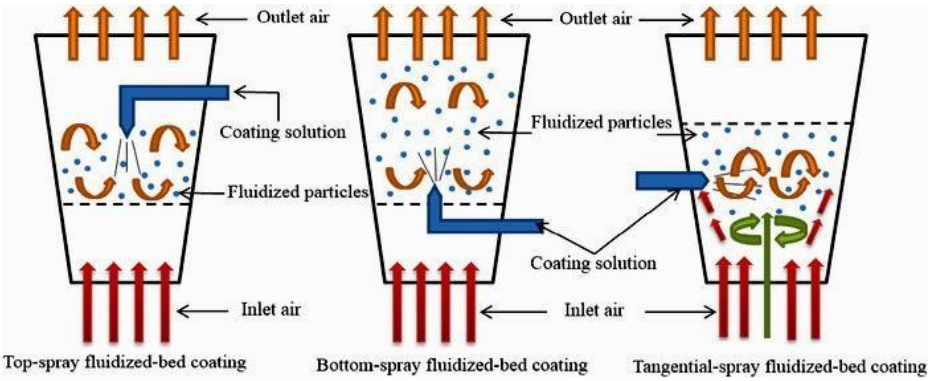

Fig. 6: Types of Fluid bed processor.

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 lyophilisation (process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through a liquid phase) of viscous bacterial suspensions, can be used to produce drug-loaded pellets by allowing droplets of liquid formulation to come in contact with liquid nitrogen at -160°C.

The equipment consist of perforated plates, a reservoir, conveyor belt with transport baffles storage container. The perforated plates generate droplets that fall and freeze as they come in contact with the liquid nitrogen below. The frozen pellets are then removed from nitrogen bath and transported to storage container at -60°C before drying. The most critical step is droplet formation, which is influenced not only by formulation related variables like viscosity, surface tension and solid content, but also by equipment design and corresponding processing variables. This technique can be used to produce drug loaded pellets for immediate as well as controlled release formulation.

Principle: The procedure permits instantaneous and uniform freezing of the processed material owing to the rapid heat transfer that occurs between the droplets and thus the large surface area facilitate the drying process. The amount of liquid nitrogen required for manufacturing a given quantity depends on the solid content and temperature of the solution or suspension being processed. The pellets are dried in conventional freeze dryers to remove water or organic solvents.[31,32]

Example: A cryopellet formulation of the diagnostic protein ecarin has been developed that is suitable for use to monitor blood coagulation via invitro thromboelastometry.[33]

Globulation/droplet formation

Globulation describes two related processes, spray drying and spray congealing. The droplet size in both processes is kept small to maximize the rate of evaporation or congealing and consequently the particle size of pellets formed is usually small.

1. **Spray drying:** In spray drying, drug entities in solution or suspension form is sprayed, with or without excipient, into hot air stream to generate dry and spherical particles. The drying process continues through a series of stages whereby viscosity of the droplets

constantly increase until almost all the application medium evaporates out. Though this technique is suitable for the development of controlled release pellets, it is generally employed to improve the dissolution rates and hence the bioavailability of poorly soluble drugs.[34,35]

Principle: During spray drying the atomized droplets are contacted by a hot gas stream and evaporation of the liquid is initiated, which involves simultaneous heat and mass transfer and depends on the temperature, humidity and transport properties of the air surrounding the droplet. As the liquid evaporates, surface saturation conditions are reached and formation of solid begins. These particles are initially held together by capillary forces developed by the liquid phase and are gradually replaced by solid bridges.[36]

Example: Spironolactone-loaded Gelucine microparticles were prepared using spray-drying technique.[37]

2 **Spray congealing:** It consist 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 coming in contact with cold air. The coating agents normally used are low melting agents 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. Both immediate and controlled release pellets can be prepared in this process depending on the physicochemical properties of ingredients and other formulation variables.[34,35]

Principle: During spray congealing, the atomized droplets are cooled below the melting point of the vehicle. The particles are held together by solid bonds formed from the congealed melts. Due to the absence of solvent evaporation during most spray congealing processes, the particles are generally nonporous and strong and remain intact upon agitation.[36]

Example: Aspirin spray-congealed micropellets.[38]

Freeze pelletization

Freeze pelletization technique is a novel technique for producing spherical matrix pellets containing active ingredients. In this technique, a molten-solid carrier/matrix is introduced as droplets into an inert column of liquid in which the molten solid is immiscible. The molten solid moves in the liquid column as droplets and solidifies into spherical pellets. The molten

solid droplets can move upward or downward in the liquid column depending on the droplet's density with respect to the liquid in the column. If the density of the molten-solid carrier/matrix is less than that of the liquid in the column, then droplets are introduced from top of the column and pellets solidify in the bottom portion of the column. Conversely, if the density of molten-solid carrier/matrix is less than that of the liquid in the column, then the droplets are introduced from the bottom of the column and pellets solidify at the top portion of column.[39,40]

Example: Novel sustained release matrix pellets of betahistine dihydrochloride were prepared using freeze pelletization technique.[41]

Hot-melt extrusion

Principle: Hot melt extrusion is a process of converting raw material into a product of uniform shape and density by forcing it through a die under controlled condition.

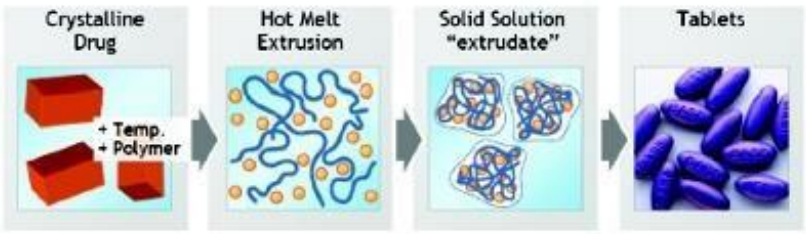

Fig. 7: Principle of hot melt extrusion.

Hot melt extrusion process consist of three basic steps: melting a solid material, shaping the molten material and solidification of the material into the desired shape. A hot melt extruder consist of a material feed hopper, extruder inside a heated barrel and spheronizer. The hopper feeds the material into the extruder which is a heated barrel containing the rotating screw. The extrudates are cut into uniform cylindrical segments, which are spheronised in a jacketed spheronizer to produce uniform sized pellets. The spheronization temperature should be high enough so that it partially softens the extrudate to facilitate its deformation and eventual spheronization.[42]

Example: Metoprolol tartrate sustained release pellets were prepared using hot-melt extrusion technique. [43]

Compression

Compression is a pelletization technique in which mixtures or blends of active ingredients and excipients are compacted under pressure to generate pellets of defined shape and size. The formulation and processing variables for production of pellets via compaction are similar to those that are employed in tablet manufacturing.[44] Infact, pellets produced by compression is nothing but small tablets that are approximately spheriodal in shape.

Principle: In this system, the particles are pretreated by blending or wet granulation and drying. Then, they are subjected to mechanical pressure where the spheroidal shaped pellets grows and bonding between spheroids accurs by mechanical interblocking.[36]

Balling

Balling describes a pelletization process in which finely divided particles are converted to spherical particles by addition of appropriate quantities of liquid and with continuous rolling and tumbling motion. The liquid may be added prior to or during the agitation stage.[44]

Principle: The liquid added to powder forms the agglomerates or nuclei which are bound together by liquid or melt bridges which are subsequently replaced by solid bridges and later forms the pellets by hardening the binder or melt.[45]

Example: Iron ore pellets prepared by balling technique.[46]

Factors affecting pelletization technique

1. **Moisture content:** Moisture in the wet mass brings 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.[47]
2. **Rheological characteristics**: The rheological condition of the wet mass determines the flow ability in extruder. The optimum rheological condition leads to good flow ability in order to extrude the wet mass. The rheological variation make improper and non-uniform extrusion.[48]
3. **Solubility of excipients and drug in granulating fluid:** A soluble drug gets dissolve in a granulating liquid. Thus increasing the volume of liquid phase lead to over wetting of system of agglomeration of pellets and increase in wetting liquid increases plasticity but induces sticky mass.[49]
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 containing Avicel pH (101) and theophylline.[50]

5. **Physical properties of starting material:** 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 on composition but also on different grades of the same material.[51]
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.[51]
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 which will further affect the therapeutic efficiency of the delivery system.
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.[52]

Characterization of pellets

Pellets are evaluated for certain quality measures, which reflect the suitability and endurance of material during various operations like filling, transportation and handling.

1. **Particle size distribution:** Particle size can be determined by sieve analysis by using sieve shaker which is simple and economical technique. Optical microscopy and scanning electron microscopy can be used for measuring the diameter of pellets. This characteristic feature of pellet helps in coating and drug release rate. Patappee.W. 2004 reported the use of vernier callipers to determine the size of pellets.[4,53,54]
2. **Surface area:** Surface area has an effect on drug release and results in batch to batch variability. To ensure the production of consistent shape pellets, surface area is analysed by particle size distribution, gas absorption (BET method-Brunauer, Emmett & Teller) and air permeability method.[53,54,55]
3. **Porosity:** The porosity of pellets influence the rate of release of drugs from the pellets by affecting the capillary action of the dissolved drug. Porosity 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.[53,54,56]

4. **Density:** The density of the pellets is affect by change in the formulation or process factors. Change in the density of pellets affects the other factors or process like capsule filling, coating and mixing. Bulk density can be measured by using an automated tapper or pycnometer. True density shows the extent of densification or compactness of substance.[4,53]
5. **Friability and hardness:** The friability and hardness determination is important as pellets need to withstand during handling, coating, packaging, shipping and storage. Roche friabilator, Erweka friabilator, Pharma test friabilator are different equipment used. The % friability of pellets should be less than 0.08%. Karl pellet hardness tester provides relative hardness values.[4,53]
6. **Tensile strength:** The tensile strength of the pellets is determined by using tensile apparatus with a 5 kg load cell. The pellets were strained continuously until failure occurs. Further load is recorded and the tensile strength is calculated applying the value for the failure load and the radius of the pellets.[4,54]

Application of pellets

1. **Intestinal protective drug absorption system**: Intestinal protective drug absorption system (IPDAS) is a multiparticulate tablet technology that has been developed to enhance the gastric tolerability of potentially irritant or ulcerogenic drugs such as the NSAIDs. It consist of high-density controlled release beads that are compressed into a tablet form.[1,57]
2. **Diffucaps**: In this multiparticulate system, drug profiles are created by layering an active drug onto a neutral core such as sugar spheres, crystals or granules followed by application of rate controlling, functional membrane.[1,58]
3. **Minitabs**: Eurand MINITABS are tiny (2mm X 2mm) tablets containing gel-forming excipients that control drug release rate. Additional membranes may be added to further control release rate. The small size of Eurand minitabs means that they can be filled into capsules as a final dosage form.[1,59]
4. **Pelletized tablets**: Pelletized tablets (Peltab®) system utilizes polymer-coated drug pellets or drug crystals, which are compressed into tablets. In order to provide a controlled release, a water insoluble polymer is used to coat discrete drug pellets is used to coat

discrete drug pellets or crystals, which then can resist the action of fluids in the GIT.[1]

5. **Flashtab**: Flashtab technology is a fast dissolving/disintegrating oral tablet formulation. It is a combination of taste masked multiparticulate active drug substances with specific excipients compressed into tablets.[1]
6. **Macrocap®:** Macrocap® consist of immediate release beads made by extrusion/ spheronization/ pelletization techniques or by layering powders or solutions on nonpareil seeds. Release modulating polymers are sprayed on the beads using various coating techniques.[1]
7. **Multiparticulate mucoadhesive formulations:** These are gastric juice-resistant device, consisting of at least one active substance in the form of a multiparticulate preparation with mucoadhesive properties and of a blowing agent which on contact with liquid produces gas.[60]

CONCLUSION

Pelletization lays the scope for different oral immediate or controlled delivery system. Due to its simple design, efficiency of producing spherical pellets and fast processing; it has found a special place in the pharmaceutical industry and moreover its use in production of multiparticulate oral controlled release dosage forms overtaking granulation. Today extrusion spheronization represents an efficient pathway for novel drug delivery system. Using these pelletization techniques we can formulate suitable dosage forms of drugs that will have more patient compliance, safety and efficacy.

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