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Review on: - Extrusion–Spheronization A Emerging Pelletization Technique

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ABSTRACT-
The extrusion-spheronization technique is covered in depth in this review article. The first section details the many procedures involved in making pellets, including granulation, extrusion, spheronization, and drying. The second section of this article discusses the factors that can affect the quality of pellets, such as formulation (moisture content, granulating liquid, excipients, and drugs), equipment (mixer, extruder, friction plate, and extrusion screen), and process (extrusion speed, extrusion temperature, spheronizer load, spheronization time, spheronization speed, and drying method). The methods for characterisation (particle size distribution, surface area, shape and sphericity, porosity, density, hardness and friability, flow characteristics, disintegration, and dissolution) of the pellets are explained in the last section.

I. INTRODUCTION

For pharmaceutical applications, pellets are spherical or nearly spherical, free-flowing granules with a restricted size distribution that typically range between 500 and 1500 m. They are often made via a pelletization technique, which involves agglomerating powder blends of API and excipient particles into sphere-shaped granules. Pellets are often squashed into tablets or put into firm gelatin capsules after processing. Additionally, they can be designed as dosage forms for instant release, for sustained drug release over an extended period of time, or coated to transport a medication to a particular site of action in the digestive system. Pellets give development scientists a great deal of versatility when designing and creating oral dosage forms.

They can be combined to deliver particles with distinct release profiles or incompatible bioactive chemicals simultaneously at the same site or at multiple sites throughout the gastrointestinal tract, without requiring changes to the formulation or manufacturing process. Due to their freeflowing nature, pellets enable highly flexible formulation creation. As a result, packing them is simple and hassle-free. Pellets' spherical form and low surface area to volume ratio made uniform film coating possible.

Pellets avoid the dosage dumping effect, which results in a smoother plasma concentration profile and more gradual drug absorption than tablets, further reducing the negative effects of medications. a lower plasma concentration profile and slower drug absorption than from a tablet, which further reduces side effects. Smoother plasma concentration profiles and more gradual drug absorption from tablets both help to reduce side effects.

Melt Agglomeration AND Hot Melt Extrusion – Spheronization

In order to solve the issues with the pellets made by layering and extrusion-spheronization, the processes of melt agglomeration and hot melt extrusion-spheronization have a significant advantage.

Melt agglomeration is a process in which the solid, small particles gradually alter their size and shape to form agglomerates with molten binding liquid that melts as a result of a rise in temperature caused by the heat of friction of the high shear mixer. The binder may be heated using hot air or by heating a jacket over its melting point before being added as a molten liquid, dry powder, or flakes. Dry agglomerates are created as the cooling solidifies the molten binder. The binders employed in melt agglomeration have melting points that range from 50°C to 80°C. Below this point, the binder softens and has an impact on the production and storage quality of the product. This method uses agitation, kneading, and layering to create agglomerates.

Hot melt extrusion is among the most widely used processing techniques in the diverse plastics, rubber, and food sectors. It is categorised as a

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semisolid viscous molten system that is controlled. As the drug release is diffusion controlled 6–10, it is frequently used in pharmaceutical manufacturing when creating modified release dosage forms (such as pellets, granules, tablets, transdermal implants, transmucosal drug delivery systems, etc.). In-situ salt creation, quick dispersing systems with foam-like structures, complex synthesis in the melt, and nanoparticles released from molecular dispersions are only a few potential applications for it. It is a quick, effective, solvent-free method that skips the lengthy drying stage and only needs a few processing steps. The continuous production of spherical shaped pellets with narrow range particle size distribution, the reduction of coating material loss during coating associated with wet mass extrusion process, and drugs that show signs of degradation during processing and storage due to residual water are all advantages of this technique. Incorporating poorly compatible materials into tablets made by cutting an extruded rod, uniformly dispersing fine particles, good stability at varying pH and moisture levels, masking the bitter taste of the active ingredient, and preparing and delivering poorly soluble drugs to solid dispersion and solid solution for improved dissolution rate and bioavailability.

A hot melt extrusion – spheronization

This comprises of a feed hopper, an extruder with three unique zones—the feed zone, the transition zone, the metering zone, and the spheronizer—in the heating barrel. Due to its comparatively low cost, reputation, and toughness, single screw extruders are preferred for extrusion in the heating barrel. Similar to wet granulation, but with a different binder is molten and won't liquefy with water or another substance. There are 4 steps in the process. (a) Feeding the solid material into the extruder and melting or plasticizing it, usually with wax or low melting point polymers (starting from high molecular weight to low molecular weight polymers), such as vinyl polymers (polyvinylpyrrolidone, polyvinylpyrrolidone-vinyl acetate), copovidone, polyethylene oxide, polyethylene glycol, acrylates, and cellulose derivatives (carboxy methyl cyclodextins, sodium alginate, guar gum, xanthan gum, cetyl palmitate, and cellulose bees wax. The preferred release mechanisms are (i) diffusion for formulations including water-insoluble polymers like ethylcellulose or carnauba waxes, and (ii) diffusion and erosion for formulations containing water-soluble polymers like hydroxypropylcellulose. (b) Mass transfer, flow through the die, and extruder-based shaping of molten material into uniform cylindrical segments. (c) Spheronization of extrudes at high temperatures to provide uniform spheroids and deform by softening. (d) Spheroids are solidified to take on the desired shape before leaving the die and undergoing further processing. The shape of the extruded goods is determined by the endplate die attached to the barrel's end.

The factors that influence hot-melt extrusion and spheronization:

(a) Process Parameters: Extruder die design, barrel temperature, feed rate, screw speed, motor load, melt pressure, and extruder operational parameters (b) Product Parameters: nature of selectively thermoplastic extrudates, composition of extrudates like drugs and their melting points, physical and chemical properties of thermal carriers like drug polymer miscibility, polymer stability and function of final dosage form since they are changed into a molten state during the process at low temperature, and extrudate porosity that affects drug release. By lowering the tensile strength and glass transition temperature in the case of thermolabile constituents, the introduction of plasticizer lowers degradation and increases flexibility of the polymer components.Functional excipients play a crucial part in formulations by hot melt extrusion, such as release modifiers, bulking agents, and processing agents14, 17. The need for high energy input, the handling and storage of binders with lower melting points, and the instability of heat-labile materials with higher melting point binders due to the high melting temperatures are a few drawbacks.

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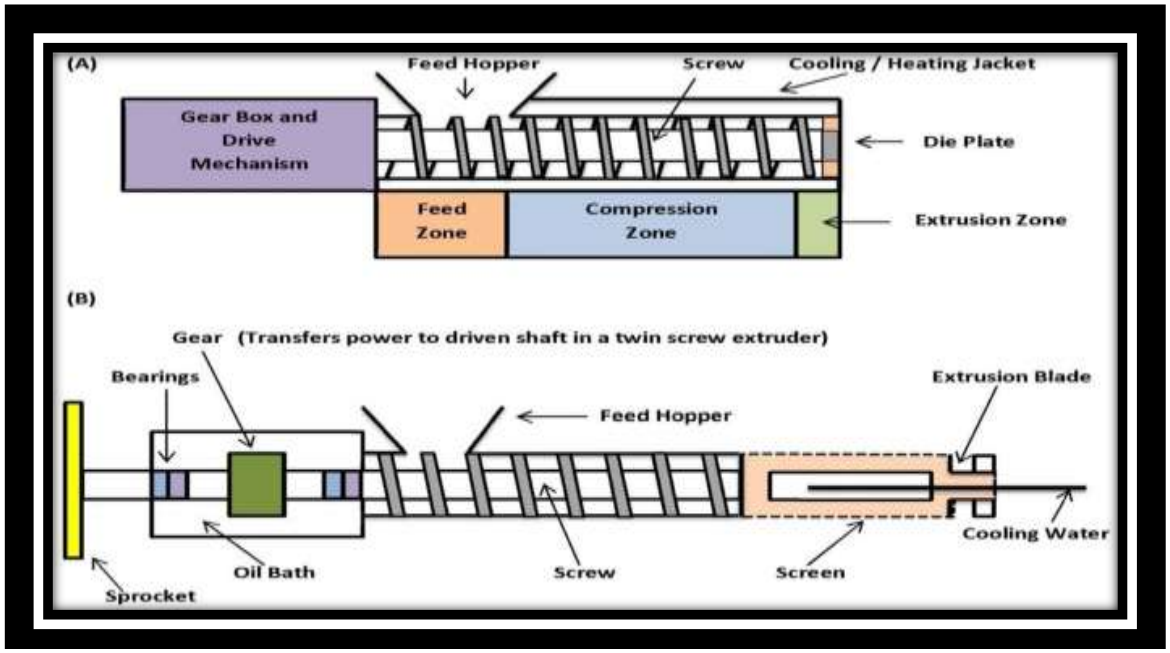

Fig-Hot Melt Extrusion Spheronization

Formation and growth mechanism of pellets

Understanding the fundamental mechanics of pellet creation and growth is crucial for choosing and optimising any pelletization technique. The processes that cause pellets to form and grow are nucleation, coalescence, stacking, abrasion transfer, and size reduction. Primary particles are pulled together during nucleation to create three-phase air-water-solid nuclei. collisions between properly structured nuclei to Coalescence is the process by which smaller particles get larger. Layering is a successful addition of material to already created nuclei. Abrasion transfer is the transfer of material from one particle to another without preference for either direction. Three size reduction strategies, specifically layering and to a lesser extent coalescence, have an indirect impact on the growth mechanism. Attrition, breaking, and shatterare three processes that can cause well-formed particles to shrink in size.

Pelletization techniques

Pellet formation and growth can happen in a variety of ways, depending on the tools and procedures chosen. The systematic formation of pellets during the various pelletization processes is described in the following phenomena.

1. Agitation

When liquid is added in the proper amounts during agitation, finely divided particles are transformed into spherical particles through a continuous rolling or tumbling motion.You can add the liquid either before or after the agitation stage. The balling process can make pellets using pans, discs, drums, or mixers.

2. Consolidation

In a compaction, medication granules or particles are mechanically pressed together with or without formulation aids to create pellets with clearly defined shapes and sizes. This process is a type of pressure agglomeration. When compressed, pretreatment particles that have undergone dry blending or wet granulation followed by drying rearrange to create a dense mass. The particles are pressed against one another and deform elasto- and plastically under greater pressures. A binding liquid is used to first agglomerate the dry powder mixture before extrusion-spheronization. High-density extrudates are then created by processing it in the extruder. On the spheronizer, these extrudates are ultimately transformed into pellets.

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3. Drug layering

Pelletization by layering includes depositing consecutive layers of drug entities over prefabricated nuclei, which can be crystals or granules of the same substance or inert starting material. The drug entities can be in solution, suspension, or dry powder form. In the process of stacking powder, a binder solution is sprayed onto the nuclei first, then the powder is added. A revolving pan or disc contains moist nuclei that roll around, gather up powder particles, and produce layers of tiny particles that cling to one another and the nuclei thanks to capillary forces created during the liquid phase. More powder is continuously layered over the nuclei while more binding liquid is sprayed, continuing until the appropriate pellet sizes are attained. The medication particles are dissolved or suspended in the tying liquid during solution/suspension layering. After the liquid has been spread out on the prepared nuclei, it is dried. Spreading is influenced by droplet dynamics, material wettability, and droplet wetting properties.

For the manufacture of enteric coated pellets, Kovacevic et al. examined powder, solution, and suspension layering. They found that suspension layering outperformed other methods in both the drug loading and enteric layering phases.

4. Globulation

Globulation is the process of atomizing liquid materials such as melt, solution, or suspension to produce spherical pellets or particles. When atomized droplets come into contact with a hot gas stream during spray drying, the liquid begins to evaporate. Heat and mass are simultaneously transferred during evaporation, anddepends on the air around the droplet's temperature, humidity, and transport characteristics. The atomized droplets are cooled below the vehicles' melting point during spray congealing. The need for substances to have clearly defined melting points or limited melting zones is essential to this procedure.

Pharmaceutical crystals are a method for improving the subpar physicochemical characteristics of medications. For the first time, Duarte et al. attempted spray congealing in the preparation of cocrystals [8]. preserves the hydrotextural condition. The drying process densifies the medium by induced shrinkage to complete the product's textural features.

Extrusion-spheronization has several benefits over other technologies, including the ability to incorporate higher levels of active ingredients without producing excessively larger particles, the ability to combine two or more active agents in any ratio within the same unit, the ability to modify the physical properties of the active ingredients and excipients, and the ability to produce particles with high bulk density, low hygroscopicity, high sphericity, dust-free, narrow particle size distribution, and smoot.

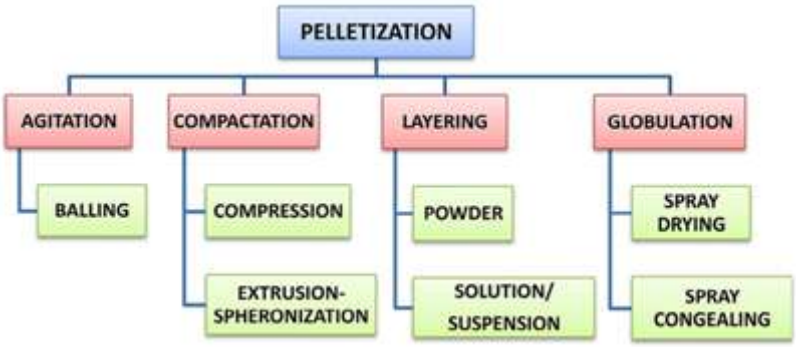

Fig.– Classification of pelletization techniques

Excipients used in pellet formulation-

Pellets are made up of a variety of formulation aids, including lubricants to reduce friction between individual particles or between the particles and surfaces of processing equipment (magnesium stearate),

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fillers/diluents to add bulk (dibasic calcium phosphate, lactose, microcrystalline cellulose, starch, and sucrose), binders to bind powders and maintain pellet integrity (hydroxypropylmethylcellulose, poly-vinylpyrrolidone), and a spheronization enhancer (microcrystalline cellulose) to aid in the production of spherical pellets, and a release modifier (ethylcellulose, shellac) to obtain modified release from the pellet formulation.

The most common procedure for making pellets is extrusion-spheronization.Four steps are required to complete this process, which was first described by Reynolds and Conine and Hadley. They are: (i) preparing the wet mass (granulation); (ii) shaping the wet mass into cylinders (extrusion); (iii) breaking up the extrudate and rounding the particles into spheres (spheronization); and (iv) drying the pellets.

Galland et al. claim that the wetting operation transforms the material into a state where porosity is correlated with water content. Spheronization is just a shaping procedure that preserves the hydro-textural condition of the material, whereas the extrusion operation densifies the material to the point of saturation. By densifying the medium through induced shrinkage, the drying process completes the textural properties of the result.Extrusion-spheronization has several benefits over other technologies, including the ability to incorporate higher levels of active ingredients without producing excessively larger particles, the ability to combine two or more active agents in any ratio within the same unit, the ability to modify the physical properties of the active ingredients and excipients, and the ability to produce particles with high bulk density, low hygroscopicity, high sphericity, dust-free, narrow particle size distribution, and smooth.

Table1–Differenttypesofextrudersusedinextrusion–spheronization.

Typeofextruder	Mechanism	Comment
Screwextruder	Utilizesascrewtodevelopthenecessarypressuretoforcethematerialtoflowthroughuniformopenings	a) Axial: Screen is placed at the end of the screw, perpendicularlywiththeaxisofthescrew.
Sieve extruderBasket extruderRollextruder	A rotating or oscillating arm presses the dampmaterialthroughasieve. Similartosieveextruders,exceptthatthesieveorscreenispartofaverticalcylindricalwall. Rollextrudersoperatebyfeedingmaterialbetweenarollerandaperforatedplateorringdie.	b) Radial:Screenisplacedaroundthescrew,dischargingtheextrudate perpendicularly to the axis of the screw.Extrudatefallsvertically fromthesieve plate
Ramextruder	Apistonridinginsideacylinderorchanneliusedto compress material and force itthrough an orificeontheforwardstroke.	Extrudateformedinthehorizontalplane Type1:Aringrotatesaroundoneormorerollersinstalledinsidethecylindricaldiechamber, eachofwhichrotatesonitsstationaryaxis. Type2:Therollerorrollersare mountedontheoutsideoftheringdieandmaterialisfedfromahopper,occasionallywithascrew,into the regionbetween the rollerand the die.

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	Type3:Rollersarepositioned aboveandrollalongthesurfac eofaflat,stationarydieplate. Extrusionforcesrecordedwit htheramextruderarealways greater, and force necessary to extrude the wet mass through theramextruderdecreasesast hequantity ofaddedwaterincreases.

Extrusion-

Extrusion is a process that produces extrudates by applying pressure to a mass of prepared plastic until it flows out through an aperture. Depending on the physical conditions, the extrudate length may change. features of the materials to be extruded, the extrusion process, and the handling of the extruded particles. The four basic classifications of extruders used for extrusion are the screw, sieve and basket, roll, and ram extruders. Table provides information for each type of extruder.

Spheronization

Spheronization is the slow transformation of cylindrically shaped extruded particles into spherical shapes. This shaping process is caused by plastic deformation. The three dimensions of agglomeration shape are determined as extrudates are first broken into nearly uniform lengths, and spheres with a nearly uniform diameter are generated. Depending on the shape of the particles, distinct stages of the spheronization process may be observed, progressing from a cylinder to a cylinder with rounded edges, dumbbells, and elliptical particles, and finally complete spheres (Fig. 7A). Another pellet-forming mechanism may exist, according to Baert and Remon (Fig. 7B). In this mechanism, the production of cylinders with rounded edges is followed by a twisting of the cylinder, which ultimately leads to the cylinder breaking into two separate sections. Each component has a flat and a round side. The edges of the flat side fold together like petals to form the cavity observed in certain pellets as a result of the rotational and frictional forces involved in the spheronization process.

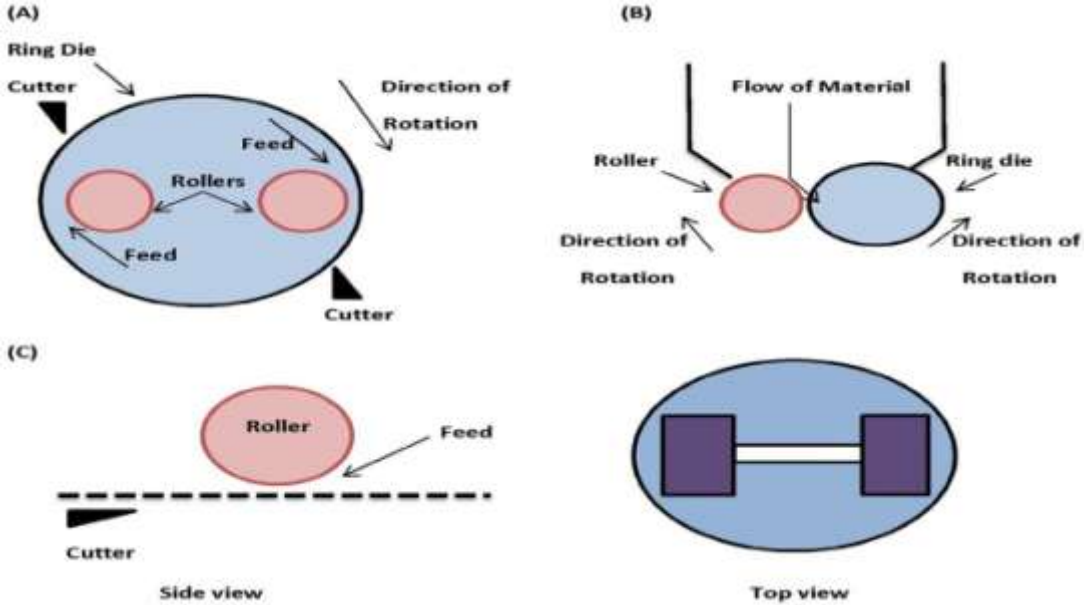

Fig.–Pelletmillwith(A)internalroller, (B)rollerexternaltodie,(C)rolleronflatdieplate

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Advantages

1.The stacking and extrusion processes provide highly precise medicine administration for pellets.
2. Spheres have better flow properties. This becomes very useful in automated processes or those needing precise dosage, like tableting, moulding operations, capsule filling, and packing.
3. The elimination of dust creation, which raises process safety because breathing in fine particles can cause health problems and dust explosions.
4. Due to their ideal low surface area to volume ratio, which produces the ideal form for applying film coatings, pellets can be applied with controlled release.
5. They can be coupled to deliver diverse release profiles at the same or different locations in the body, or to supply distinct bioactive chemicals at the same time.

The rapeutic Advantages

1. Pellets can freely distribute throughout the GIT after delivery, which maximises medication absorption. Reduce inter- and intra-patient variability.
2. The widespread distribution of spherical particles in the gastrointestinal tract prevents localised drug build-up, preventing the irritating action of some medications on the stomach mucosa.
3. Compared to single-unit dosage forms, modified-release multiparticulate delivery systems are less prone to dose dumping.

Disadvantages

- Filling capsules is a step in the pellets filling process that might raise prices.
- When pellets are tableted, the pellets' film coating is destroyed.
- The pellets' size may vary from formulation to formulation, however it typically ranges between 0.05 mm and 2 mm.Because they are overly hard, pellets are challenging to compress into tablets. As a result, they are frequently administered encapsulated within hard gelatin capsule shells.
- Pelletization necessitates the use of highly specialised and expensive equipment, raising the cost of production.
- With too many process and formulation variables, controlling the production process is difficult.

Desirable Properties of Pellets-

1. For Uncoated pellets

a. Uniform sphericalsize
b. Narrow particlesize distribution
c. Good flow property
d. Low friability
e. Even surface
f. Low dust formation
g. Reproducible packing
h. Ease of coating

2. For Coated pellets

a. Maintain all above properties
b. Desirable drug release characteristics

Evaluation parameters

1. Particle size distribution

a) It is best if the particle size is as small as feasible. This will guarantee little fluctuation in coating and thickness and make mixing processes easier if necessary.
b) The most used technique for determining particle size distribution is sieve analysis utilising a sieve shaker.
c) A 100 gramme batch of pellets is weighed using an electronic balance. The next step is to transport the pellets to a set of
d) sieves with varying mesh sizes for particle size examination. Determine the retention percentage for each sieve.

2. Surface Area

a) The size, shape, porosity, and surface roughness of pellets are the primary variables that determine their surface area. There are three ways to calculate a pellet's surface area.
b) By calculating the mean diameter, gas adsorption, and air permeability from the particle-size distribution.
c) Mean diameter - The surface area resulting from other morphologic properties, such as porosity, surface roughness, and pellet form, is not taken into account in this computation.
d) The air permeability method is frequently employed in the pharmaceutical industry for precise surface measurement and batch-to-batch variation management. The surface area of the material acts as a barrier to the movement of a fluid, such as air, through a plug of compressed material.

3. Porosity

a) The porosity of pellets affects the dissolved drug's capillary action, which in turn affects how quickly pharmaceuticals are released from pellets.

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b) Mercury porosimetry, optical microscopy, and scanning electron microscopy used in conjunction with an image can be used to quantify the porosity of pellets quantitatively and qualitatively.

4. Density

a) Modifications to the formulation or method may have an impact on the density of the pellets, which may have an impact on other procedures or elements including capsule filling, coating, and mixing.

b) An automatic tapper can gauge the bulk density of pellets. The degree of densification or compactness of a substance is indicated by its true density.

c) Bulk Density = Powder Weight/ Bulk Volume

d) Tapped density = Powder weight/Tapped volume

5. Hardness and Friability

a. The measurement of a pellet's hardness and friability is crucial since the pellets must endure handling, shipping, storage, and other procedures including coating.

b. Relative hardness values are provided by instruments like the Kaul Pellet Hardness Tester.

c. In order to create abrasion, glass beads of a specific diameter are used in conjunction with an Erkewa type tablet friabilator or a Turbula mixer for a set amount of time to determine the friability of pellets.

Tensile Strength

Using tensile apparatus with a 5 kg load cell, the tensile strength of pellets is assessed; the pellets are stressed to failure. The load is measured, and the radius of the pellets and the value for the failure load are used to compute the tensile strength.

II. CONCLUSION

Pellets are multi-unit dosage forms that have superior flow qualities and improve the safety and efficacy of the active components. They are then created into a single dose form. Compared to the granulation process, the pelletization approach yields more spherical pellets and has more benefits. Today, the development of various modified-release solid oral dosage forms includes pelletization as a viable method for the delivery of new drugs.

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