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REVOLUTIONIZING PRODUCTION: THE ASTONISHING POWER OF PELLETS AND PELLETIZING TECHNOLOGY AND THEIR APPLICATION

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ABSTRACT: In today's dynamic industrial landscape, the transformative potential of pellets and pelletizing technology stands as a beacon of innovation. Pellets, compacted forms of raw materials, have emerged as versatile solutions across diverse sectors, from agriculture to pharmaceuticals, offering enhanced efficiency and sustainability. The advent of advanced pelletizing technologies has further elevated their impact, enabling precise control over size, shape, and composition. This abstract explores the profound implications of pellets and pelletizing technology, delving into their role in optimizing processes, minimizing waste, and unlocking new avenues for resource utilization. Through a blend of engineering ingenuity and ecological consciousness, this paradigm shift underscores a promising future where pellets redefine the boundaries of production efficiency and environmental stewardship.

INTRODUCTION: Since immemorial centuries, oral drug administration has been one of the most convenient and widely accepted delivery routes for most therapeutic agents. Traditionally, oral dosage forms are classified as single unit and multiple unit dosage forms. Multi-particulate dosage forms are receiving 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].

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Soon, however, it was sensed that some of the formulating and clinical problems (free flowing property, dose dumping, dysphagia, *etc*.) came 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 form answers many formulating problems and is a common strategy to control the release of drugs, showing reproducible release profiles when compared to SUDFs. These MUDFs, can either be filled into hard capsules or compacted into bigger tablets or dispensed in a dose pouch or pack lets.

The most increasingly exciting area in the development of MUDF'S is incorporating tablets instead of hard gelatin capsules to make it more economical for consumers and gain more attention currently. This review focuses on the pelletized form of multiple units.

They are prepared by a process called Pelletization, referred to as a size enlargement process, and the final product obtained is called pellets. Thus, being a consumer-friendly alternative, many pharmaceutical companies are switching their product franchise to improve the technology over the single unit dosage forms. This technology option can also provide a good platform for patent-non-infringing product development. This drug delivery platform shows business potential promise for the future in pharmaceuticals and nutraceuticals [5-6].

METHODOLOGY: For the study to conduct this review data was taken from many databases which include (e.g., PubMed, Scopus, and Web of Science, such as peer-reviewed articles, systematic reviews, and meta-analyses published within a specific time frame (e.g., from 1989 to 2007) and search terms uses (e.g., "pellets," pelletizing technology ","method of pellets formation",). The methodology for studying the efficacy and impact of pellets and pelletizing technology encompasses a multidisciplinary approach, integrating aspects of materials science, engineering, and environmental analysis. Comprehensive literature reviews are conducted to understand the historical evolution, current trends, and potential developments in pellet production and application. Experimental studies form a critical component wherein various pelletizing techniques are evaluated for efficiency, scalability, and product quality. This involves laboratory- scale trials to optimize parameters such as temperature, pressure, and binder composition, followed by pilot-scale testing to assess feasibility and performance under realistic conditions.

Furthermore, computational modelling and simulation techniques elucidate the underlying physics and chemistry governing pellet formation and behaviour. Finite element analysis and computational fluid dynamics provide insights into the mechanical forces and thermal dynamics involved in the pelletizing process, aiding in the design and optimization of equipment and processes. Environmental impact assessments are also conducted to evaluate the sustainability of pellet production methods, considering factors such as energy consumption, emissions, and resource utilization.

Pellets: Pellets are 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 are intended chiefly for oral administration [6-8]. The ideal characteristics of the pellets are Spherical shape and smooth surface; the particle size of the pellets was 600-1000µm. The quantity of the active ingredient in pellets should be maximum to maintain pellet size. Pellets are not only manufactured for products with controlled release properties but also for reasons to believe that these multiple-unit dosage forms, in any case, can offer a superior therapeutic effect even where modified release is not the primary goal [9].

Technological Advantages of Pellets:

- Layering and extrusion-spheronization techniques offer great accurate formation of pellets, which play an important role in drug uniform drug delivery.
- Spheres have excellent flow properties, which makes them very useful in automated processes or processes where exact dosing is required, e.g. tabletting, moulding operation, capsule filling, and pouch packaging.
- Prevention of dust formation results in improved process safety, as fine powder can cause dust explosion and the respiration of fine can cause health problems.
- Controlled Release application of pellets due to the ideal low surface-to-volume ratio that provides an ideal shape for applying film coatings. So, the drug can be converted into a controlled release form by using coating techniques.
- They can be blended to deliver incompatible bioactive agents simultaneously and to provide different release profiles at the same or different sites in the gastrointestinal.

Therapeutic Advantage of Pellets:

- Pellet can disperse freely through the GIT after administration; consequently, the drug absorption is maximized.

- The broad distributions of spherical practical in the gastrointestinal tract limit localized build-up of the drug, avoiding the irritant effect of some drugs on the gastric mucosa.
- Reduce inter and intra-patient variability.
- Modified-release multi-particle delivery systems are less susceptible to dose dumping than single-unit Dosage forms [10].

Mechanism of Pellet Formation: Before selecting and optimizing any Palletization/granulation process, it is essential 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 from visual observations, which are trying to explain with suitable figures in this current review.

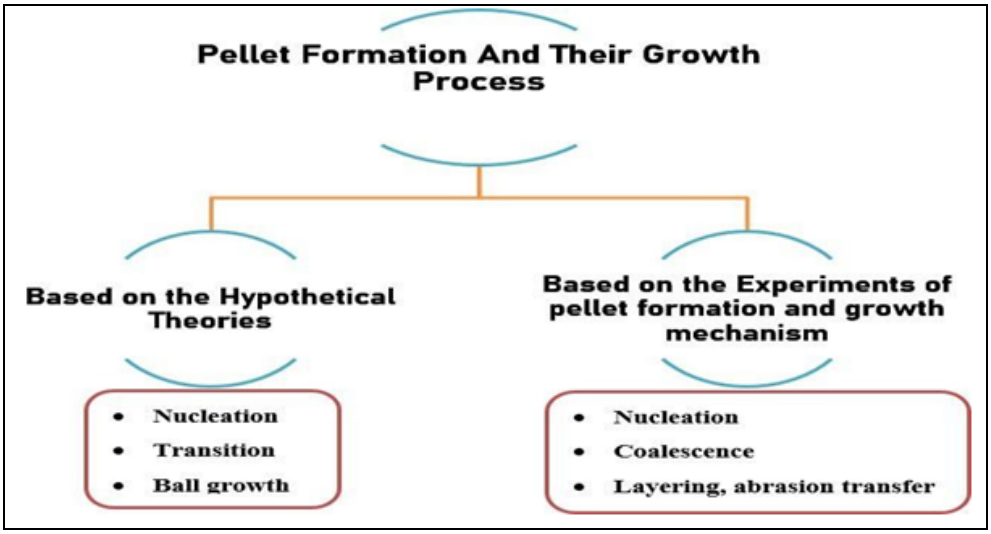

FIG. 1: PELLET FORMATION AND THEIR GROWTH PROCESS

Nucleation is a stage of the Pelletization process that occurs whenever a powder is wetted with a solvent system. The primitive particles are drawn together to form a 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, rate and extent of nuclear formation depend 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 particles by random collision of well-formed nuclei; this mechanism requires slightly excess moisture on the surface of the nuclei, although the number of nuclei is progressively reduced even though the system's total mass remains unchanged during this operation. Layering is a slow growth mechanism with the successive addition of fragments and fines on an already-formed nucleus. In the layering step, the number of particles remains constant while the system's total mass increases due to increasing particle size as a function of time. The fragments or fine particles can be formed by particle size reduction.

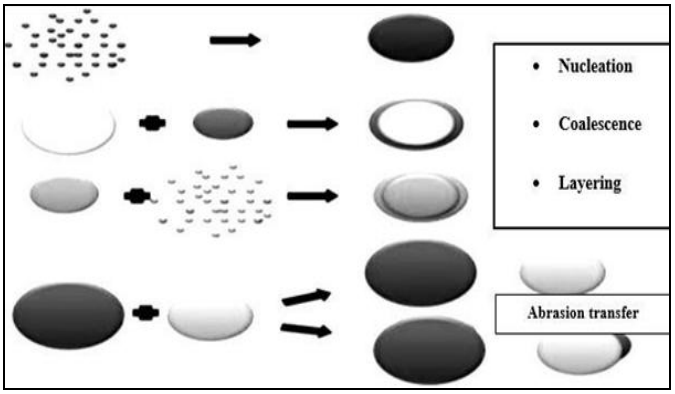

FIG. 2: PELLET GROWTH MECHANISM

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 reducing the rate of growth of the pellets. At this point, the ball growth region's third phase is reached. The primary mechanism in the ball growth phase is abrasion transfer, which involves transferring 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 continuously change in size as long as the conditions that lead to material transfer exist.

Methods of Preparation of Pellets: Compaction and drug layering are the pharmaceutical industry's most widely used pelletization techniques. Drug layering, direct palletization, Extrusion and spheronization are the most popular techniques for pelletization formation. Some other Pelletization methods are Melt palletization, Globulation, Balling and Compression, which are also used for pellet preparation. In that Compression is also used to develop pharmaceutical pellets, although on a limited scale.

Drug Layering: The layering process involves depositing 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 **Fig. 3-4.** In powder drug layering, a binder solution is first sprayed onto the previously prepared inert seeds, followed by powder addition. Conventional pan coaters have been used from the very beginning of the history of drug layering pelletization.

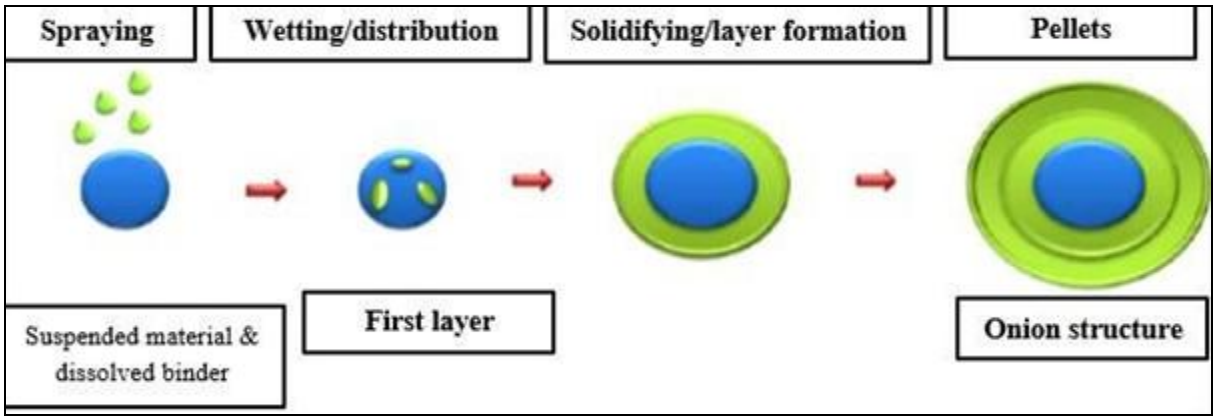

FIG. 3: DRUG LAYERING BY USING SOLUTION

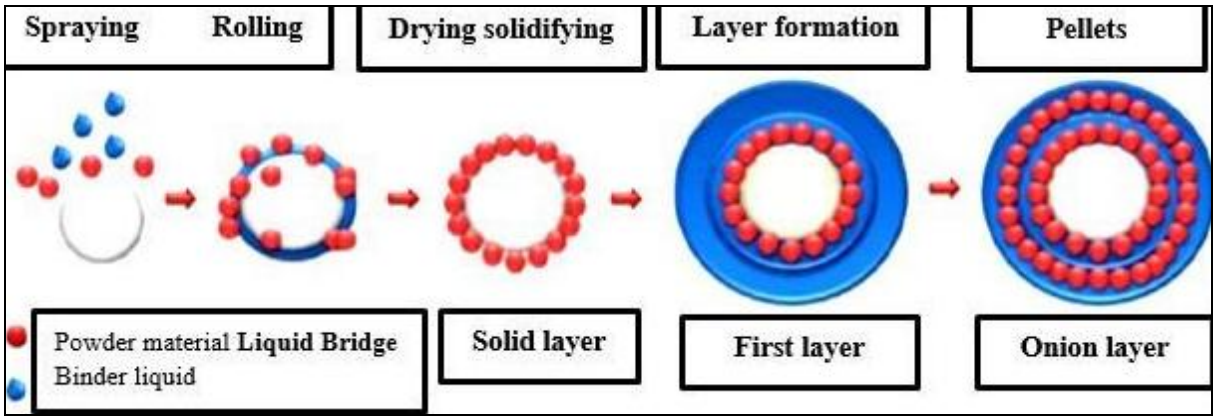

FIG. 4: DRUG LAYERING BY USING SUSPENSION

Direct Pelletizing: Sample drug material is blended and solvent or binder system is added. The material bed is then subjected to a centrifugal motion. The centrifugal forces act on the material in this process, forming agglomerates, which get rounded up into uniform-sized dense pellets **Fig. 5**. The size, density and shape of the pellets formed are influenced by the rotation speed. The moist pellets formed are then dried up in the fluid bed dryer. Organic solvents can also be used if required

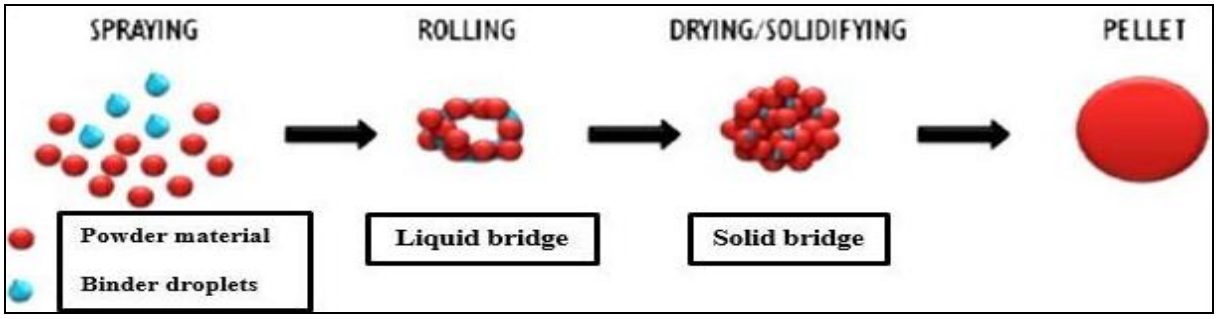

FIG. 5: DIRECT PALLETIZATION PROCESS FOR PREPARATION OF PELLETS

Pelletization by Extrusion and Spheronization: Pharmaceutical pellets are typically manufactured via extrusion spheronization, a three-step process introduced in the late 1960s, resulting in roughly 1 mm in diameter spherical granulates. Wet mass extrusion spheronization, also called cold-mass extrusion spheronization, has become the method of choice.

It involves the following steps:

Dry Mixing: Mixing ingredients to achieve homogeneous powder dispersion using a twin shell blender, planetary mixer, high-speed mixer and tumbler mixer [17-20].

Wet Massing: Wet massing is done to produce a sufficient plastic mass for extrusion by employing regular equipment and processes as employed in wet granulation for compaction. The most commonly used granulators are planetary mixer, 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 behaviour of the wet mass. Cooling of the granulation bowl may avoid this problem.

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 diameters. Such shaping of the wet mass into long rods, commonly termed 'extrudate.' The extrudate particles break at similar lengths under their 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. 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. 6**, the screen is placed at the end of the screw, while in radial type, the screen is placed around the screw **Fig. 6**, discharging the extrudate perpendicularly to the axis of the screw.

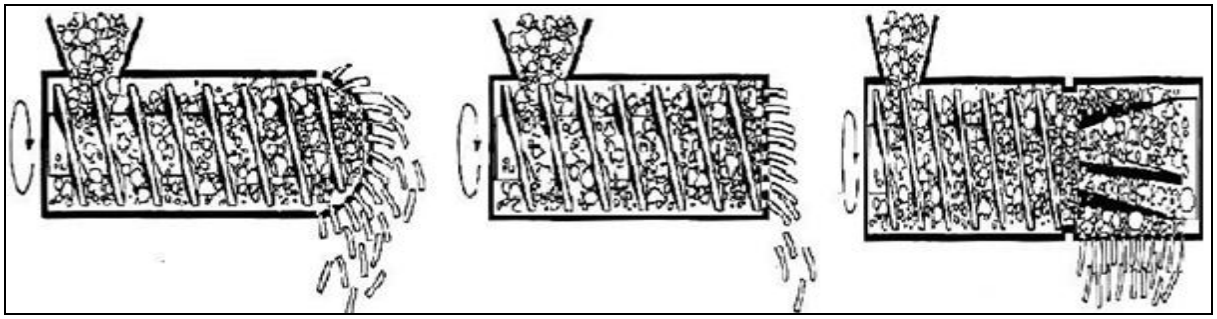

FIG. 6: AXIAL SCREW FEED EXTRUDER, DOME SCREW FEED EXTRUDER AND RADIAL SCREW FEED EXTRUDER

Gravity feed extruders (cylinder roll or gear roll) include rotary cylinder and rotary gear extruders, which differ mainly in the design of the two counter-rotating cylinders. One of the two counter-rotating cylinders in the rotary cylinder extruder is hollow and perforated, whereas the other cylinder is solid and acts as a pressure roller **Fig. 6**. The rotary gear extruders have two hollow counter-

rotating gear cylinders with counter board holes. Piston feed extruders are probably the oldest type of extruders a piston displaces and forces the material through a die at the end. Piston feed extruders are preferentially used in the development phase because they can also be used to measure the rheological properties of the formulations [17-18].

Spheronization: Firstly, Nakahara introduced this technology in 1964. The instrument known as spheronizer or 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 the process, different stages can be distinguished depending on the shape. The friction plate, a rotating disk with a characteristically grooved surface to increase the frictional forces, is the most critical component of the equipment. Two geometric patterns are generally used [21-24]. It includes a cross-hatched pattern with grooves running at right angle to one another and 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. The spheronization process involves a transition from rods to spheres that might occur in various stages, which usually take 5 to 30 minutes, provided the mass should not too dry, wherein no more spheres are formed, and the rods will transform as far as dumbbells only **Fig. 8.**

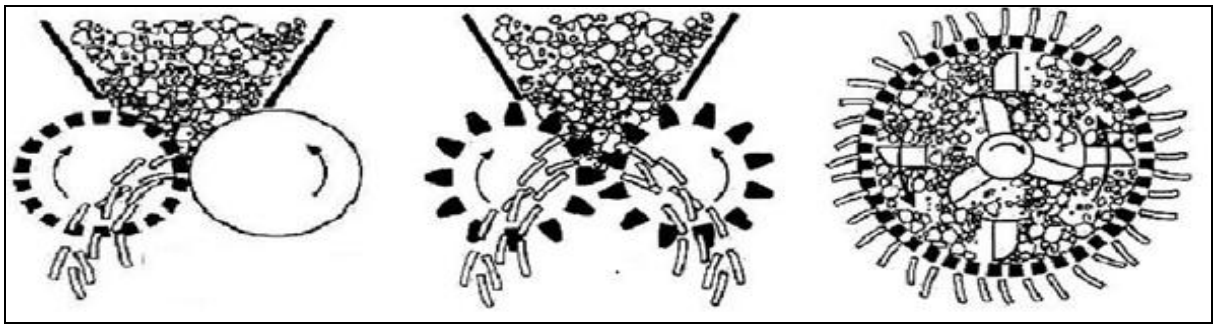

FIG. 7: CYLINDER ROLL TYPE, GEAR ROLL TYPE AND RADIAL TYPE

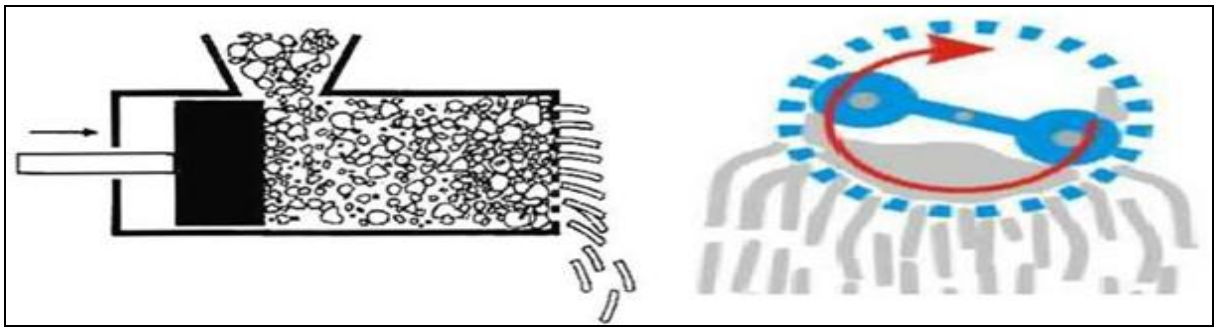

FIG. 8: AXIAL PISTON EXTRUDER AND RADIAL PISTON EXTRUDER

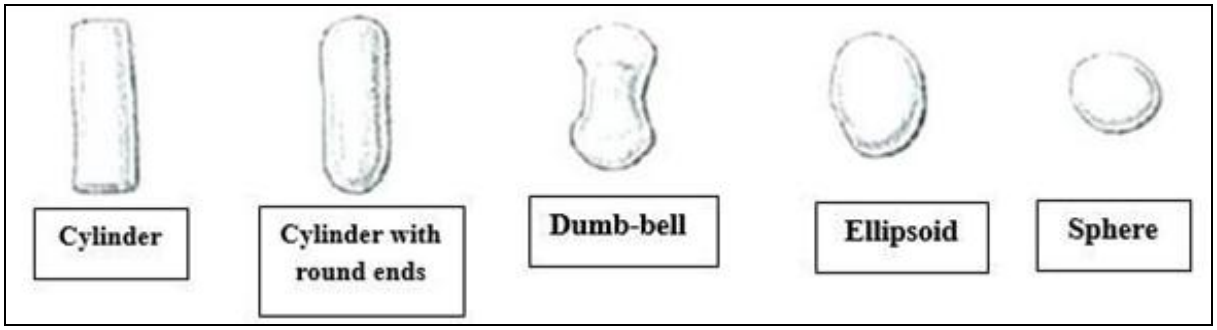

FIG. 9: SCHEMATIC REPRESENTATION OF DIFFERENT PELLET FORMATION STAGES DURING SPHERONISATION

Drying: A drying stage is required to achieve the desired moisture content. An increased drying rate gives more porous pellets due to decreased 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 [28-29] or in a fluidized bed drier. 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 the drying process. Reported the use of freeze dryer to maintain the viability of living bacterial spores. If solute migration occurs during the drying of the wet mass, this may result in an increased initial rate of dissolution and stronger pellets with modified surfaces, which might reduce the adhesion of any added film coats.

Screening: Screening may be necessary to achieve the desired size distribution, and for this purpose, sieves are used. In the case of pellets prepared by extrusion-spheronization, screening is essentially required after manufacture to avoid pellets having a high size polydispersity index.

Process Parameters for the Extrusion-Spheronization Techniques:

Starting Material: The starting material's nature influences the particle's size, hardness and sphericity, and release rate of the loaded drug. The material used in the formulation causes differences in pellet quality produced from different compositions.

The use of similar products manufactured by different suppliers also showed changes in the characteristics of the pellets produced. Pellets prepared with three types of microcrystalline cellulose (MCC) from different manufacturers featured differences in size and roundness even though they were processed under the same conditions [30-31].

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 more excellent heat production during the processing. Pellet quality depends on the screen's thickness and the diameter of the perforations. A thinner screen produced a rough and loosely bound extrudate, whereas a thicker screen formed a smooth and well-bound extrudate because of the higher densification of the wet mass. Similarly, the diameter of the perforations determines the size of the pellets- a larger diameter in the perforations will produce pellets with a larger diameter under similar processing conditions [1, 2, 22].

Extrusion Speed: The output from the extruder depends on the extrusion speed. The increasing speed causes 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 several fines and a wide particle-size distribution, so require to maintain optimum speed which depending upon type material used for pellet preparation. Method require validated before preparation of pellet regarding speed of extruder [5, 23, 27].

Extrusion Temperature: The extrusion cycle during the operation may lead to a rise in the temperature, which could cause the granulating liquid to evaporate from the granules causing the difference in the quality of the extrudate right at the beginning of the batch itself. Extrusion temperature control is especially considered when processing a thermolabile drug formulation [4, 5].

Spheronizer Specifications: Pellet quality is also dependent on spheronizer load, which affects the particle-size distribution and bulk and tap density of the final pellets. The increase in the spheronizer speed and a low spheronizer load will result in broader particle size distribution with less yield of pellets.

Whereas if increases with extended spheronization time at a higher spheronizer load, it will result in lower particle size distribution with a high yield of pellets, decreased roundness and increased hardness of pellets and also bulk and tap density increased, and the size of the pellets decreased with an increasing spheronizer load [27-28].

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 with the Tangential Spray Attachment or Roto-Processor attachment.

Globulation Droplet Formation Consists of two Related Processes

i. Spray Drying
ii. Spray Congealing

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

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 an aqueous-organic solution, suspension or emulsion is dropped into liquid nitrogen to form frozen particles; these particles are then freeze-dried and lyophilized to remove water or organic solvents [25-26].

Compression: This is a compaction technique used to prepare pellets. Pellets of definite sizes and shapes are prepared by compacting mixtures or blends of active ingredients and excipients under pressure. The formulation and process variables controlling the pellets' quality are similar to those used in tablet 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 [32].

Balling: The Pelletization process is known as balling, in which pellets are formed by a continuous rolling and tumbling motion in pans, discs, drums or mixtures.

The process consists of the conversion of finely divided particles into spherical particles upon the addition of appropriate amounts of liquid [27].

Melt-Extrusion Technology: Wet mass extrusion is the most frequently used method current apart from the extrusion spheronization technique for producing spherical pellets; many drugs exhibit stability problems since the granulating fluid employed in this process is generally water. In addition, pellets exhibit a rapid drug release and require a film coating if controlled release properties are to be maintained [11, 12].

A novel hot-melt extrusion and spheronization process has been recently reported to produce spherical pellets without water or other solvents. This method eliminates instability problems during processing due to water and has 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 was initially used in the plastic industry, but it is slowly gaining popularity in the pharmaceutical industry for producing pellets, immediate and sustained-release tablets, and transdermal drug delivery systems. The technique is also being approved in the USA, and it is a fast, simple, continuous, solvent-free process with fewer processing steps. The 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.

Novel Approaches in the Pelletization:

Freeze Pelletization: Freeze pelletization is a novel and easy technique for producing spherical pellets for pharmaceutical use. This technique introduces a molten-solid carrier/matrix as droplets into an inert liquid column 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 concerning 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 and pellets solidify in the bottom portion.

Conversely, if the density of the molten-solid carrier/matrix is less than that of the liquid in the column, the droplets are introduced from the bottom and pellets solidify at the top portion of the column**.**

Pellet Coating Process: The coating process for pellets is carried out primarily to modify the release of the drug from the pelletized drug delivery systems. Following are some of the Coating equipment used for this purpose. Most of the coating processes use one of three general types of pieces of equipment.

1. Standard Coating pan
2. Perforated Coating pan
3. Fluidized bed coater

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 using ducts positioned through the front of the pan. Coating solutions are applied by spraying the material on the bed surface.

Perforated Coating Pan: Perforated pan coaters are efficient drying systems with high coating capacity and can be entirely automated for both sugar coating and film coating processes. There are four different types of coaters available.

1. Acela-Cota
2. Hi-Coater
3. Driacoater
4. 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

Fluidized bed Coater: Fluid Bed Technology offers a very efficient coating technique with significant advantages in coating, granulation, and pellet formation, which are also possible in the same machine. Fluid bed coating is currently a widely used technique because it allows, among other applications, crystals or granules to be coated with various available polymers to provide gastro resistance or a controlled release system.

Components of Pellet's Formulation:

Active Pharmaceutical Ingredient: This multiple-unit dosage form technology has the potential to deliver various 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 drugs that can be delivered even subcutaneously and intramuscularly depending on the size variations where the size range is maintained below 600 microns and are called as micro pellets. Pellets technology is widely used to deliver GIT drugs at a specific site to release the drugs in a controlled manner [6, 9, 12].

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 to the dry form, which is considered more efficient than dry mixing followed by liquid addition. When applied as solution form, binders are dissolved or dispersed in an organic or aqueous solvent; the latter is the most preferred and commonly used system in pelletization. The 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 the formation of the liquid bridge that holds the particles together, but as the liquid evaporates, the precipitating and hardening of the binder take place, leading to the central bonding force and with a possibility of the soluble constituents to crystallize and contributing to the bonding mechanisms. In the drug layering process, the drug is layered onto the surface of the starter material and 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 reasonably 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 maintain the other

desirable properties, such as releasing the drug at the intended rate [14, 16].

Granulating Fluid: The 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 patronize it to give a perfect spherical shape. An optimum quantity of moisture content should be used to obtain a good-quality pellet. Excess moisture content leads to the agglomeration of pellets during the preparation process due to the presence of an excess solvent system on the surface of pellets, while a smaller quantity leads to the generation of fines with a large pellet distribution. In the case of soluble drugs, they get dissolved by the granulation liquid, thus increasing the volume of the liquid phase, which leads to over-wetting of the system and agglomeration of pellets. Different types of granulating fluid are used for the pelletization process. Besides the use of aqueous forms as a granulation liquid, the use of alcoholic or hydroalcoholic systems, ethyl ether, dilute acetic acid, and isopropyl alcohol have also been reported. Millili and Schwartz, 1990 reported that a minimum of 5% of granulation liquid had to be water 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 to increase the mass fraction of chitosan within the pellets and concluded that mass fraction could be increased to 100% by using dilute acetic acid for granulation step in place of demineralized water. Binders are usually not incorporated, as adding binders [Micro Crystalline Cellulose (MCC)] provides more cohesiveness. However, researchers have attempted to incorporate various binders in the moistening liquid.

Spheronizing Enhancer: Spheronization enhancers are formulation aids that improve the production of spherical pellets, mainly during spheronization and balling processes. They impart plasticity onto the formulation and binding properties essential for pellet strength and integrity.

Filler: These are the excipients used to form the bulk of the material; in the process of pelletization, 70 to 80% of the excipients are formed by fillers. Generally, microcrystalline cellulose is used for this purpose. Avicel PH 101 is the pelletization-aiding excipients in this process. Glyceryl mono stearate, Starch RX1500, spray dried lactose also used as filler agents in the pellet preparation [4, 6].

Plasticizer: Plasticizers improve the flexibility of polymers by reducing the material's tensile strength and glass transition temperature. Sometimes, drugs and other excipients are employed as plasticizers. Reported that non-traditional plasticizers, including methyl paraben and drugs such as ibuprofen, could 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 the solvent employed in casting the strip. These excipients used in hot melt extrusion can affect the drug's release behaviour. The polymer flow will be improved by using plasticizer that enhances the strength of the polymer.

Example: Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and di-butyl phthalate, and Citrate derivatives such as tri-butyl, tri-ethyl, acetyl citrate, tri-acetin and castor oil are some of the commonly used plasticizer excipients [9, 10].

Lubricant: In the palletization process, lubricants are rarely used as the high-speed rotary equipment is used to prepare pellets. However, during compression and Extrusion-Spheronization, lubricants play a crucial role in successfully manufacturing pellets. Their use reduces the friction between the die wall and material mix during the compression or ejection phase. They also play a significant role in the smooth discharge of the pellets from the Spheronizer [12, 14].

Separating Agents: Separating agents are materials that are adsorbed on the surface and promote the separation of pellets into individual units during a pelletization process, They are incorporated initially in the formulation or externally during processing to prevent pellets from 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 the adhesion of the spheres to the friction plate and the cylindrical wall of the spheronizer [14, 21].

Surfactant: In most palletization 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. Surfactants help to weaken the liquid bridges and result in more friable pellets. In extreme cases, excess fines might be produced, which brings the focus to adding surfactants for pellet formulations. Care should be taken to avoid using surfactants unless it is essential for producing pellets that possess specific properties [22, 23].

pH Adjusters: The pH adjusters are substances incorporated in pellet formulations that influence the microenvironment of drug molecules used for many reasons. Generally, acid-labile drugs are protected from the pH conditions of the GIT by an enteric coating. Buffer systems may also be added to the core formulation to maintain the stability of the core in a favourable range.

In addition, buffer systems may be included in pellet formulations to enhance the dissolution rate of drugs whose solubility is influenced by changes in the pH. This is mainly referred to pellets whose release rates are membrane-controlled, as the solubility of the drug plays a significant role in determining the release rate. Therefore, specific or dual buffer systems are incorporated in pellet formulations to adjust the solubility of drugs to fit a particular process [18, 22].

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 incorporating release modifiers along with the drug during the core formulation. Due to the diversity of chemical composition and physical properties of release modifiers, pellet formulations that provide many release profiles could be designed. Generally, water-soluble low molecular weight excipients, surfactants and disintegrates 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 [14, 18].

Flavoring agent: The choice of flavours changes from individual to individual depending on age, ethnicity, and liking, which play a significant role in taste fondness. The geriatric population was observed to like mint or citrus fruit flavours, while the younger generation likes flavours like fruit punch, raspberry, etc. The flavour selection for the particular formulation also depends upon the drug to be incorporated into the formulation. Mint flavour is generally added to 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 flavour, which is observed in the first few seconds after the administration of the product and shows the after-effect, which lasts for at least about 10 min. Flavouring agents can be selected from synthetic flavour oils, oleo resins, and extracts derived from various parts of the plants like leaves, fruits and flowers. Flavours can be used alone or in combination. Peppermint oil, cinnamon oil, spearmint oil, and nutmeg oil are flavour oils, while vanilla, cocoa, coffee, chocolate and citrus are fruity flavours. Apple, raspberry, cherry, and pineapple are examples of fruit essence types. The amount of flavour needed to mask the taste depends on the type and strength of the flavour. Preferably, up to 10%w/w flavours should be added to the formulations. Cooling agents like monomethyl succinate and menthol can be added to improve flavour strength and enhance the mouth-feel effect of the product. Other cooling agents' such as, WS3, WS23 and Utracoll II can also be used in conjunction with flavors **Table 1** [2, 14].

TABLE 1: RECOMMENDED FLAVOUR FOR THE PARTICULAR TASTE

Sr. no.	Taste sensation	Recommended flavor
1.	Salt	Butter scotch, Apple, Apricot, Vanilla, Peach
2.	Bitter	Wild Cherry, Walnut, Chocolate, Mint, Passion fruit
3.	Sweet	Berry, Vanilla.
4.	Sour	Citrus Fruits, liquorice, Root beer, Raspberry

Sweetening agent: Sweeteners have become a significant part of food products and pharmaceutical dosage forms intended to be disintegrated or dissolved in the oral cavity. The sweet taste in the formulation is preferred, especially in the case of the 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 is 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 combined as they provide good mouth-feel and cooling sensation. Polyhydric alcohols are considered less carcinogenic and do not have bitter aftertaste, which is vital in formulating oral preparations. The sweetness property of the polyols is less than half of that of sucrose except for 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; for this reason, synthetic sweeteners have gained more popularity in food and pharmaceutical preparations. Saccharin, cyclamate and aspartame are the first generation of synthetic sweeteners, followed by acesulfame-K, sucralose, alitame and neotame, which fall under the second generation of artificial sweeteners. Acesulfame- K and sucralose have more than 200 and 600 times sweetness. Neotame and alitame have more than 2000 and 8000-time sweetening power than sucrose. Rebiana, which is a herbal sweetener derived from the plant Stevia rebaudiana (A south American plant), has more than 200–300 times sweetness, but these synthetic sweeteners carry the disadvantage of a taste effect, which can be reduced by mixing or blending the natural and synthetic sweeteners. The flavour quality of these synthetic sweeteners differs from that of natural sweeteners and is generally disliked by patients accustomed to them. The amalgamation of sweeteners may lead to synergism and improvement in the taste of the formulations. Generally, sweeteners are used in concentrations of 3 to 6 %w/w, either alone or in combination [6, 8, 22].

Coloring agents: Colouring agents are generally used to improve the appearance and make it more patient friendly. Pigments such as Titanium dioxide or FD&C-approved colouring agents are used in the dry form or mixed with the granulating fluid during the formulation [23].

TABLE 2: POLYMERS USED IN THE PALLETIZATION PROCESS

Sr. no.	Polymer used inpelletization	Formulation	Applications
1.	Carbopol 974P,NF, Resin	Beads containing Weakly essentialdrugs.	Slower release of the saltsof weakly essential drugs
2.	Croscarmellose sodium or Sodium starch glycolate	Super-disintegrants in avicel pellets	Increase dissolution rateand increase the pellet micropore volume
3.	Eudragit RS POand RL PO	Polymer (with combination) basedpellets	Better characterizationlike elastic modulus of thepellets, surfacecharacteristics, sphericity
4.	Eudragit RL30D, RS 30D,NE 30D	A multiple-unit floating drug deliverysystem	Prolong the gastric residence time and increase the dosageform's overall bioavailability
5.	Gelucire	Lipidic –matrix pellets	Controlled drug release
6.	Methocel-E5 (HPMC) or AMB, EudragitL 30D-55	Enteric-coated pellets	Improved film formationand polymer coalescence
7.	Microcrystalline cellulose, Ac-Di- Sol.	Floating pellets with the bacterialantagonist	Improving floatingproperty

8.	Microcrystallinecellulose and hydroxypropyl methyl cellulose	Pellets with water-insoluble drugs inself-emulsified form.	Controlling the drugrelease from the oral dosage forms
9.	Pectins oralginates.	Polysaccharide gel-coated pellets.	Oral administration of theophylline in the coatedpellets

Evaluation Parameters of Pellets:

Size Distribution: The sizing of pellets is necessary because it significantly influences the release kinetics. In most cases, particle size determination is carried out by simple sieve analysis using a sieve shaker. Vernier callipers were used to determine the size of pellets in 2004 [22, 23].

Sieving Method: The prepared pellets were estimated using the sieving method. The 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. 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 the Arithmetic mean of the two sieves.

$$\text{Mean particle size} = \sum Xi\ Fi / \sum Fi$$

Where, $\sum Xi\ Fi$ = Weight size, $\sum Fi$ = 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 [12, 14, 24].

Pellets Shape: The sphericity of the pellets is the most important characteristic, 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 graph paper. The shape factor estimates the amount by which the projected image of particles deviate from a circle, and it is calculated using the projected area of the pellets and their circumference. For the acceptable-quality pellets, the roundness index/shape factor should be between 1 and 1.2. For a perfectly circular projected image, the shape factor should be 1, while a value of 0.6 describes a particle of good sphericity [6, 8, 12].

Visual Inspection of Pellets: Microscope and stereomicroscope are other methods to determine the shape of pellets. An angle at which a plane has to be tilted before a particle begins to roll is called one-plane critical stability, an essential method 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 the fixed funnel method measured after a certain amount of pellets are allowed to flow through a specific orifice from a given height [8].

Surface Morphology: Scanning electron microscopy examines the surface morphology and cross-section of pellets. The sampling pellets are mounted onto the aluminium stub, sputter-coated with a thin layer of Platinum using a sputter coater (Polaron, UK) under Argon atmosphere, and then examined using SEM. The use of optical microscopy to examine the microstructure of the pellet surface was first reported in 2004. While the SEM pictures collected to observe the influence of different fillers and concluded that MCC and corn-starch give the best quality pellets with smooth surfaces was reported by Eurrkainea and Lindqvist in the year 1991. The analysis for surface roughness of pellets by applying a non-contracting laser profilometer was studied in 2004 [20, 23].

Specific Surface Area: The surface area of pellets is directly related to the 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 essential even in uncoated pellets since drug release is influenced by the surface area. The specific surface area of pellets is determined by the gas adsorption technique [1, 5, 9].

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

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

Gas Adsorption Technique: In this technique, the volume of nitrogen 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 nitrogen adsorption on a substrate [19, 22].

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

Thus, it has been proven that the reproducibility in particle-size distribution, surface area, density, hardness, and friability tests, in addition to the 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 a 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 by applying the value for the failure load and the radius of the pellets [4, 8, 10].

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 [6, 7].

Density: The density of pellets (bulk and tapped) can be affected by changes in the formulation or process, which may affect other processes or factors, such as filling and packaging characteristics 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 indicates the packing properties of pellets or spherical seeds, which provide higher bulk densities due to small intra-particle porosities. True density indicates the extent of densification or compactness of pellets [8, 9, 10].

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 placed on an air-bearing table, and the surface roughness was measured with a laser profilometer. The light spot diameter of the sensor was 1 mm, and the sensor aperture angle was 53°. Measurements were performed in 3D at a frequency of 100 points and a measuring depth of ±50m. 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 200 points/mm resolution.

The roughness descriptors,

- *R*a (rugosity)
- *R*q (root mean square deviation of the asperity height distribution)
- *R*tm (average peakto-valley ratio)

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. The pore radius is given by the Washburn equation;

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

Where, $\gamma = 480$ ergs/cm3, $\theta = 140$o, r = pore radius, p = mercury-intrusion pressure.

Disintegration Time: Disintegration of pellets is one of the main characteristics for immediate release pellets. The disintegration test using the reciprocating cylinder method (USP Apparatus-3) in 2005, while other scientists performed it in a tablet disintegration tester specially designed by inserting special transparent tubes of a specific diameter and length with the sieve of 710mm mesh size at the top and bottom of the tube [9, 10].

***In-vitro* Dissolution Studies:** *In-vitro* dissolution studies have been predominantly recognized as an essential element in drug development and quality assessment over the past four decades. These tests were performed to study the release behaviour of different formulations in different dissolution media and to establish a correlation between *in-vitro* release and *in-vivo* absorption for the modified-release pellets. The release of the drug from a solid dosage often constitutes a determining step in the *in-vivo* absorption process and is used in conjunction with *in-vivo/in-vitro* correlation to establish quality control parameters. The release of the drug from the pellet mainly depends on the composition, hardness, and size of the pellets, and this determination is made using USP Apparatus-I or USP Apparatus.

The drug release profiles from pellets also depend on the Polymer and binder used, the aqueous solubility of the drug, the physical state of the drug in the pellet, the drug loaded into the pellet and the presence of additives such as surfactants. In the case of wax-based freeze-dried pellets, the drug release decreased as the hydrophobicity of wax increased and the drug release increased as the aqueous drug solubility increased [10, 12].

Applications of Pellets: Pellets have varied applications in several industries, and their innovative use could achieve maximum profitability. Taste masking: Pellets are ideal for products where perfect abatement of taste is required. Although various techniques have been utilized to mask the bitter taste of a drug, such as the addition of sweeteners and flavours, 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. Furthermore, because of the unique design of the manufacturing process, dust fractions that represent 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 sales in the pharmaceutical markets for the product.

Immediate Release: Administering drugs in pellet form leads to an increased surface area compared to traditional compressed tablets and capsules, which considerably reduces the disintegration time and has the potential for use in rapidly dispersible tablets.

Sustained Release: The pellet form provides a smoother absorption profile from the gastrointestinal tract as the beads steadily pass through the stomach into the small intestine. Pellets are being increasingly used to manufacture sustained-release dosage forms of drugs. The advantages of the dosage form are well known.

Chemically Incompatible Products: Chemical-incompatible drugs can be formulated in Pellets. One drug is in the core form, and the other is in the surrounding layer. Both drugs are separated by a polymer layer and can be given in a single dose form. Such ingredients must be delivered in a single dose. In the case of a compressed tablet dosage form, separate tablets must be administered.

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 tablets or capsules or packing simply as a single dose packet. They can be applied using both oral and buccal routes. This technology is growing quickly, challenging most pharmaceutical

companies to develop pelletized dosage forms for a wide range of active pharmaceutical ingredients.

Taste Masking: The pelletization technique solves complex taste masking problems while maintaining a high degree of bioavailability due to their high surface area, especially for oral products, without lowering the of bioavailability especially for oral products.

Some other Application:

- Improved appearance of the product, which has fine pharmaceutical elegance.
- Pelletization offers flexibility in 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 the accumulation of drugs, especially proven advantageous in the case of irritating drugs.
- It improves the safety and efficacy of a drug.
- Palletization 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., invariably maximising drug absorption and reducing peak plasma fluctuation [12].
- Palletization solves the problem of taste masking.
- Coating of pellets can be done with different drugs to enable a pellet release rate.
- In the case of immediate-release products, a 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 the popularity of oral pellet 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.

Commercially Available Marketed Pellet Products: Bontril SR, Brexin L.A, Catazyme S, Compazine, Dilgard XL 180, Elixophyline, Fastin, Hispril, Ibugesic S.R 300, Indocrin S.R, Nicobid T.S, Ornade.

CONCLUSION: This Review focused on various pelletization techniques, especially emphasizing extrusion Spheronization and solution/suspension layering. Some other novel techniques were also discussed. In recent times, growing interest in pelletization has been observed, owing to its advantage over conventional granulation methods. Each pelletization technique has its own advantages and limitations. Therefore, the techniques to be used must be chosen carefully, considering all the variables that may affect the product. It can be concluded that due to their good technological and biopharmaceutical advantages, pelletization has gained importance in modern pharmaceutical science, and pellets are expected to play a significant role in the design and fabrication of many novel drug delivery systems in the Future.

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