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A REVIEW ON PELLETS (MULTI PARTICULATE SYSTEM) AND ITS VARIOUS APPROACHES

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ABSTRACT

Pellets are tiny, spherical, free-flowing particles made by clumping together fine powder or granules. Pelletization techniques relate to several kinds of methods used to create pellets, (Extrusion spheronization, Hot melt extrusion, Solution or suspension layering, Powder layering, High shear pelletization, Freeze pelletization, Cryopelletization, Crystallo-co-agglomeration, Wet spherical agglomeration, Spherical crystallization etc..). Due to a number of benefits over the standard dosage form, including as dose homogeneity, dosage form flexibility, and the avoidance of dust production, pelletization has attracted a lot of interest in recent years. This review provides information on the benefits, drawbacks, ideal pellet features, medication selection criteria, and growth mechanism. It also provides a brief overview of pellet characterization, including particle size distribution, surface area, shape and sphericity, porosity, density, friability, flow property, and explanations of the disintegration and dissolution of the pellets using various applications of the techniques mentioned.

KEYWORD: Pellets, Extrusion spheronization, Pelletization technique, Multi-particulates.

INTRODUCTION

Pelletization can be defined as an agglomeration process for converting fine powders or granules of bulk drugs or excipients into small, free flowing, spherical or semi-spherical units, referred to as pellets. Pellets are oral dosage forms consisting of multiplicity of small, discrete units, each exhibiting their desired characteristics.[1,2]

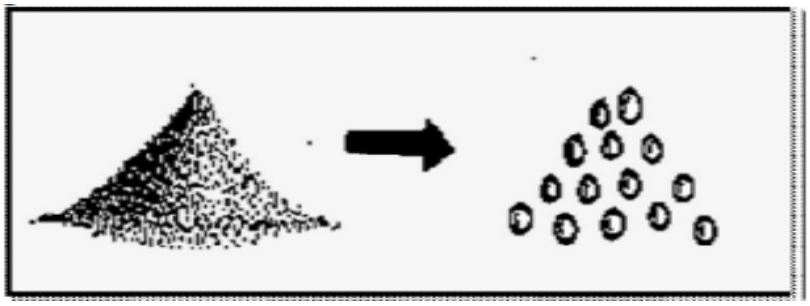


Fig. 1: pellets formation.

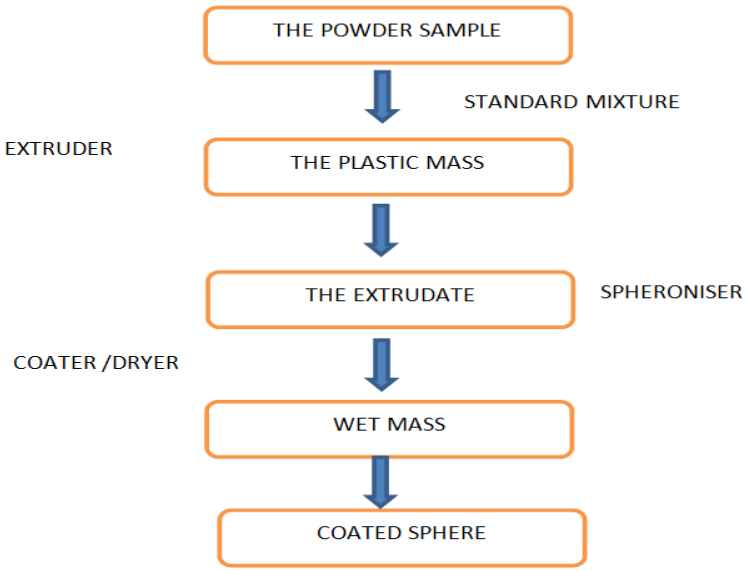
The demand for pellets that can be compressed into tablets or added to firm gelatin capsules is rising in the present. Pellets are the tiny, spherical, free-flowing particles created by the aggregation of fine powder or granules. Pellets, also referred to as micro-granules and having a range of diameters, can be produced using a variety of technologies. The use of pelletization methods to create a large number of spherical pellets that can be included in various dosage forms, such as capsules and/or tablets, or that can be administered directly via various routes, has recently attracted increasing interest. The final core material agglomerates produced by pelletization methods are spherical and range in size from 0.5 to 2.0mm. The use of pellets in dosage forms has several advantages over other dosage forms, including fast dissolution, which leads to rapid drug absorption, low gastric irritation due to fast dissolution, which reduces the time that drugs are retained in the body and dose dumping, good flow ability because pellets are uniform in size and shape, narrow particle size distribution, high tensile strength, a low surface to volume ratio, low friability, and uniform packing. Utilizing this technology, regulated drug delivery and sustained release formulations for oral administration can be created.[3,4]

Microcrystalline cellulose of various grades is the most essential components in the extrusion -spheronization process' as they possess good water uptake capacity, water holding capacity, cohesiveness and its plastic behaviour when it can be wetted. Some other hydrophilic gel-forming polymers like Hydroxypropyl methylcellulose (HPMC) can also incorporated. Some water-insoluble polymers like Eudragit RL and Eudragit RS used as an alternative excipient for the preparation of pellets.

Sometimes, granulation and pelletization terms are used synonymously. If a size-enlargement process produces agglomerates in size range of 0.1-2.0 mm and about 20-50% porosity, such process may be called granulation. Whereas, Pelletization is a size enlargement process of manufacturing agglomerates with a relatively narrow size range of 0.5-2 mm called pellets.

EXTRUSION- SPHERONIZATION

Process layout of extrusion spheronization



ES method was first reported by Reynolds (1970) and by Hadley and Conine (1970). Due to the simplicity and fast processing, ES technique of pelletization is most popular in the pharmaceutical industries. ES method produces pellets of uniform size with more drug loading capacity. Criteria for controlled and sustained release dosage form are fulfilled by this technique, and there is also a possibility to prepare sustained pellets without coating. For the production of pellets by ES four different steps are applying, different amounts of shear are used for granulation, planetary mixer, high-shear mixer and twin-screw extruder with two different screw assemblies. Extrusion is performed on a rotary ring die press. In ES method after the spheronization wet mass extrusion occurred which produce uniform size spherical particles, called as spheroids, beads or pellets, it is depending upon the material as well as equipment used. ES method is primarily used for the production of pellets for oral controlled drug delivery system. ES method require more labour than other method, but it is useful when it produce uniform spheres, uniform size, good flow properties, high strength, low friability and smooth surface. By the ES method any pharmaceutical products effectively utilize pellets as a drug delivery system.[5]

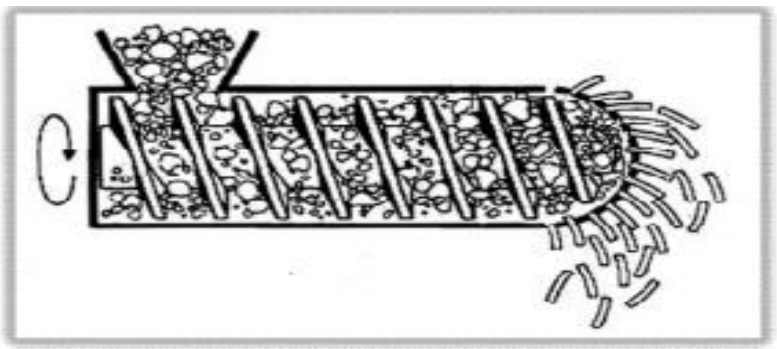


Fig. 2: Axil-screw feed extruder.

ADVANTAGE OF PELLETS

- Improved appearance of product.
- Improved flow properties and ease of packing resulting in uniform and reproducible fill weight of tablets and capsules.
- Improved safety and efficacy of active ingredient.
- Decreased handling hazards and easier transport.
- Pelletization can be used for taste masking of unpalatable drugs.
- It can also be used for separation of incompatible drugs and/or excipients. Such ingredients can be formed into pellets and delivered in a single dose after encapsulation.
- Pelletization offers a practical means of avoiding powder dust in the chemical sectors.
- There is no condensation or crystallization of solutions or suspensions.
- A reduction in hygroscopicity.
- High density in mass.
- Minimal friability and little scratching.
- Narrow size variation and uniform size.
- High drug loading capability without overly large particle production.
- They lessen drug build up, which irritates the GI mucosa.
- Due to their small size, pellets easily disperse in GIT fluids, increasing the surface area available for drug absorption and minimizing fluctuations in peak plasma levels.
- Pelletization can be used to mask the taste of unpalatable medications. Pellets offer reduced variations in gastric emptying rate and intestinal transit time, decreasing inter and intra subject variability.[6-10]

DISADVANTAGE OF PELLETS

- Pellets are rigid and so cannot be pressed into tablets. So they 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.
- The control of production process is difficult. (e.g. the amount of water added and time is critical for the quality of pellets as over-wetting can occur very easily).[11,12]

IDEAL PROPERTIES OF THE PELLETS

- Uniformity in shape, size and smooth surface, therefore it has good flow characteristic.
- The spectrum of pellets size should be in between 0.5 to 1.5 mm.
- Because of the low friability and great strength of pellets, there is less dust produced.
- To keep size, the maximum amount of API should be used in the pellets.[13]

COMMONLY USED EXCIPIENTS FOR PELLETS PREPARATION

Table1: Excipients used for pelletization process.

FILLER	MCC, Starch, sucrose, lactose, mannitol.
BINDER	MCC, Starch, MC, PVP, Gelatin, HPMC
LUBRICANT	Glycerin, PEG, Magnesium stearate, Calcium stearate
SEPARATING AGENT	Kaolin, Talc, silicon dioxide
DISINTEGRATE	Alginate, cross carmellose sodium
PH adjuster	Citrate, Phosphate, Meglumine
SURFECTANT	SLS, Polysorbate
SPHERONIZATION ENHANCER	MCC, Sod. CMC
GLIDANT	Talc, starch, Magnesium stearate
RELEASE MODIFIER	Ethyl cellulose, Shellac, Carnauba wax

MANUFACTURING PROCESS OF EXTRUSION SPHERONIZATION

The extrusion-spheronization technique involves four main steps

1. Granulation (Preparation of wet mass)
2. Extrusion (Shaping of wet mass into cylinder)
3. Spheronization (Breaking of the extrudates into spheres)
4. Drying of pellets.[14]

PELLETIZATION TECHNIQUES

1) Agitation
a. Balling

2) Compaction
a. Extrusion spheronization
b. Compression

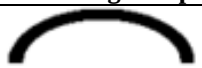
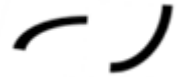
3) Layering
a. Solution/Suspension
b. Powder

4) Globulation
a. Spray congeling
b. Spray drying

Extrusion-spheronization, powder layering, and solution/suspension layering are the most widely used and extensively researched pelletization techniques. Pellet preparation can be done i0n a variety of ways. The following are a few of them.

Extrusion – Spheronisation

Table 2: Stages of pellet formation in spheronization process.

	Extrudate	It is the product of extrusion process subjected to spheronization
	Chopped cylinder	Extrudates are broken into smaller cylinder parts
	Round ended cylinder	Due to hatch plates, the end portion of cylinder become round shape
	Dumbbells	Subsequent form of cylinder due to spheronization
	Ellipsoids	Ellipsoidal shape product
	Pellets	Final stage product has round spherical shape

Early in the 1960s, the extrusion spheronization process was created as a pelletization method. A consistent smooth surface with a narrow size distribution is needed to guarantee uniform coating and free flowing properties when creating controlled or modified release. To accomplish this, spheronization by extrusion can be used. This method's primary goal is to create uniformly sized pellets or spheroids with high medication loading capacities. Extrusion spheronization is a multi-step process that produces uniform size spherical particles that can be referred to as spheroids, pellets, beads, or matrix pellets based on the material and method used for pre-consolidation. This technology has recently attracted interest due to its straight forward, quick working, and high efficiency. In order to be broken down into regular fragments that can be rounded into pellets with a narrow size distribution, effective extrudates must therefore have the desired characteristics.

Ingredients are **dry-mixed** to create uniform powder dispersions using a variety of mixers, including twin-shell blenders, high-shear mixers, tumbler mixers, and planetary mixers. Wet massing is the process of combining powders to create a mass that is suitably plastic. Planetary mixers are frequently employed in both blending and granulation processes.[15]

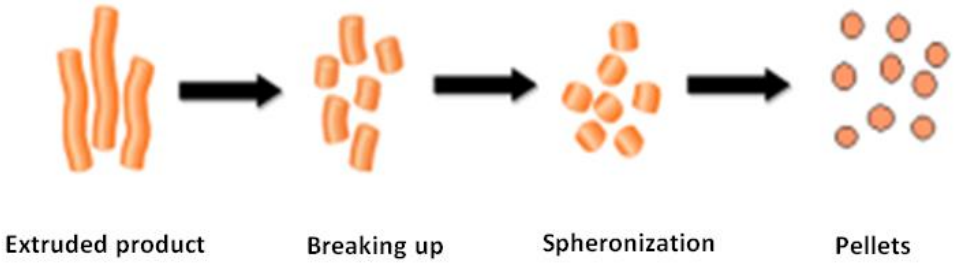


Fig. 3: Extrusion-spheronization mechanism.

Hot Melt Extrusion (HME)

In this method, the mixture is exposed to high temperature, and pressure and the drug is dispersed in the matrix at a molecular level by forming solid solution and extrudates. Extruded material can then further processed into pellets. Hot melt extrusion is commonly used in the delivery of poorly soluble drugs as it increases the dissolution, absorption, and therapeutic efficacy of the drugs by the mechanism of a solid solution.[16]

Balling

A method for pelletizing known as "balling," or "spherical agglomeration," entails continuously rolling or tossing powders into spherical pellets. Either a sufficient quantity of liquid can be added to the powder to achieve

this, or the powder can be heated to a high temperature. Spherical agglomerations can be divided into two categories: liquid-induced and melt-induced. A variety of equipment is used, such as rotating fluid-bed granulators, high-shear mixers, inclined dish pelletizers, horizontal drum pelletizers, and tumbling blenders.

Although the iron ore and fertiliser sectors make extensive use of this strategy, the pharmaceutical industry has yet to fully adopt it.

In liquid-induced agglomeration, liquid is introduced to the powder either before or during the agitation phase. When powders and liquid phases interact, they form agglomerates or nuclei. Similar to liquid-induced aggregation, melt-induced agglomeration uses a melt as the binding agent. The pace and extent of agglomeration formation are influenced by formulation variables such as powder particle size and solubility, liquid saturation, and liquid viscosity.[17]

Drug Layering

With the aid of binding liquids, dry powder drug and excipient layers are successively deposited on prepared nuclei like sugar spheres and MCC spheres. Powder layering calls for specialised tools like a spheronizer because it entails applying a binding agent and dry powders at the same time. In order to prevent powder loss in the product chute before the powder is picked up by the wet bulk of pellets being layered, the product container must have solid sides devoid of any perforations.[18]

Solution/suspension Layering

Fluid Bed Coater is used to spray drug or coating ingredients onto the cores or pellets. Solvents used for coating liquid can either be organic or aqueous and can take the shape of a solution or a dispersion. When layering with a solid dispersion, the coating must cure at its glass transition point after being finished. The Wurster method is frequently used for layering in a suspension or solution.[19]

Globulation

It is a process that forms the droplets and subsequently transforms into solid beads or pellets.

Two processes are related to globulation

Spray drying: It is a technique used to create desiccated, more spherical drug particles from a suspension or solution that does not contain any excipients. This method is frequently used to increase the bioavailability and dissolution rates of drugs with low water solubility.

Spraying Congealing: In this method, the drug is dissolved or dispersed in a hot melt of gums, waxes, or fatty acids and then sprayed into an air chamber with a temperature below the melting point of the formulation's constituents to create spherical congealed pellets.[20,21]

Compression of Uncoated Pellets

The compression behaviour of uncoated pellets has been explained by a number of different processes. The most prevalent mechanism entails five steps: repositioning, deformation (changing the shape of each pellet), densification (decreasing the porosity of the pellet), fragmentation (cracking the pellets into smaller pieces), and attrition of the smaller particles.

Pellets are compressed in four stages, starting with volume reduction through pellet rearrangement to cover inter-particle voids. Compression of pellets is four stage process which involve (1) volume reduction of the pellets by rearrangement of pellets to fill inter-particle voids (2) volume reduction of pellet bed by local surface deformation involving surface flattening of pellets (3) Bulk deformation of pellets (change in pellet dimensions) concurrent with densification of pellets, (4) The end of the and due to minimal inter- and intra-granular porosity, there has been a volume reduction.[22-23]

Compression of Coated Pellets

Pellets are given a coating to disguise their flavour and enhance their mechanical integrity, stability, and beauty. If the coat has particular qualities, coated granules can be compressed into tablet dosage shape. During compression, the coat must stay affixed to the pellets and intact. The coating polymer needs to be sufficiently flexible and deformable to be squeezed. Pellets that have been coated either experience plastic deformation or resist compression. While rigid pellets resist with compression, soft pellets are subject to plastic deformation. The elongation number is used to gauge plastic deformability and flexibility.[24,25]

Factors Affecting Pelletization Technique

Several factors can affect the quality and characteristics of pellets.

Moisture content

For spherical granules, a suitable level of moisture (10–15%) is needed. As a result of the dump mass's high moisture content, pellets may clump together during the spheronization procedure. Dump mass has a low moisture content, which can result in the creation of fine extrudates with a wide range in pellet size distribution.[26]

Rheological properties

The flowability in the extrusion machine is determined by the moist mass's rheological parameter. The best rheological conditions result in excellent extrudate flowability, which makes it possible to extrude wet mass. Rheological condition variations cause incorrect and uneven extrusion, which can result in uneven pallets.[27]

Composition of Granulating Fluid

As a substitute for water, granulating liquids include alcohol, water/alcohol mixtures, ethyl ether, diluted acetic acid, and isopropyl alcohol. To make high-quality

pellets, granulation liquid must contain no less than 5% water.[28]

Physical Properties of Starting Materials

The physical characteristics of all raw materials, including composition, filler kinds, particle size, etc., can have an impact on the pellets' quality. The swelling characteristics of all the raw materials used to make the pellets have an impact on how quickly the medication will be released from them.[29]

Characterizations of Pellets

The pellets are put through the following experiments to determine their nature.

Pellet size distribution

Due to numerous significant effects on the release kinetics of a drug from formulation, the pellet size is a crucial parameter. The average ferret diameter, average geometric diameter, average length, and average width of the pellets are all measured in order to ascertain the size of the pellets. To guarantee the least amount of variation between various coating thicknesses and to make the blending process easier, particle size distribution should be as narrow as possible.

The most effective technique for determining the particulate size distribution is the sieve analysis using a sieve shaker.

Optical microscopy and scanning electron microscopy (SEM) are additional techniques for directly finding the particle size distribution and measuring pellet diameter, respectively.[30,31]

Surface Area and Surface Roughness

First, the scientists Eriksson et al determined the surface area using the air permeametry technique. A laser profilometer with an aperture angle of 530, a laser beam size of 1 m, a measuring area of 200 x 200 mm, and resolutions of 1000 points/mm in the X-Direction and 500 points/mm in the Y-Direction is used to measure surface roughness.

100 pixels per second is the scanning rate for laser profilometry. The concluding finding is the five pellets' average surface roughness and standard deviation.[32,33]

Density

The distinctiveness of the particle size distribution of the pellets is assessed using the bulk density and tap density of the pellets. A variety of variables or processes, including capsule filling, coating, and mixing, as well as changing the method or formulation, can have an impact on the pellet density. The bulk density of the granules is measured using an automated tapper. The degree to which different materials are compact shows their true density, which can be assessed using the Solvent Displacement Method, the Air-Comparison Pycnometer Method, and the Helium Pycnometer Method.[34,35]

The following formula is used to calculate the bulk density.

$Bulk\ density$ = m/v

While "M" refers to the precise number of pellets put into a measuring cylinder and "V" refers to the capacity the pellets occupy without disturbing the cylinder.

The method below can be used to calculate tap density.

$Tap\ density$ = m/v_0

Whereas, 'M' is the exact quantities of pallets in measuring cylinder and V0 is the final volume after tapping.[36]

Tensile strength

Elasticity is the characteristic needed to give the pellet a stretched appearance. The pellets are stressed until they shatter, and it may very well be controlled by using an elastic mechanical assembly with a 5 kg load cell. Applying the reward for the disappointment weight and the range of the pellets, the heap is noted and the elasticity is established.[37]

Angle of Repose

An angle of repose measurement is used to identify the flow characteristics of powders, granules, and pellets. The angle of repose is determined by a fixed funnel technique. Until the highest part of the heap barely touches the funnel's pipe tip, pellets are poured into the funnel.

To calculate the angle of repose, use the following method.

$Tan\ \theta = h/r$

Whereas θ is the angle of repose

h is the height of the cone,

r is the radius of the cone base.[38]

SEM Analysis

The sample is coated with a thin layer of gold using a sputter coater, and pictures are then captured using a scanning electron microscope (SEM) that is run at an accelerated voltage of 1000 volts.[39]

Accelerated stability studies

A crucial step in the development of knowledge is stability testing. It shows that under certain conditions, the grade of formulation changes over time. According to ICH guidelines, various batches of the formulation are stored for a number of months at a variety of temperatures: 25°C with 60% relative humidity, 30°C with 65% RH, and 40°C with 75% RH. The appearance, percentage drug content, release profile, and other physicochemical aspects are constantly monitored for 3 months or as long as necessary to meet ICH guidelines during the accelerated stability studies.[40]

CONCLUSION

The possibility of different oral rapid or controlled delivery systems is made possible by pelletization. It has

a specific place in the pharmaceutical sector because to its straightforward design, effectiveness in manufacturing spherical pellets, and quick processing. It also replaces granulation in the creation of multiparticulate oral controlled release dosage forms. Extrusion spheronization and melt extrusion spheronization are effective drug delivery methods nowadays. These pelletization processes allow us to create pharmacological dose forms that are more patient-compliant, safe, and effective.

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