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PELLETIZATION: A MULTIPARTICULATE NOVEL DRUG DELIVERY SYSTEM

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Abstract:

Pellets possess major therapeutic and technical advantages which makes them as an exceptionally useful dosage form Multiparticulate system is a promising system for oral drug delivery. Palletization is a process in which fine powders or granules are converted into free-flowing semi-spherical units called as pellets. There are different palletisations techniques available to prepare drug loaded spherical particles. Extrusion Spheronization is one of them and utilized in formulation of pellets. Limitations which are related to bioavailability and site-specific drug delivery can be overcome by this technique. The other techniques for pelletization are namely hot melt extrusion, freeze pelletization, cryopelletization have been discussed along with formulation requirements for the process, parameters affecting pelletization.

Keywords: *Pellets, Multiple unit dosage form, Spheronization, Extrusion, Modified release, sustained released.*

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INTRODUCTION:

Multiparticulate dosage forms are gaining much favour over single unit dosage forms because of their potential benefits like predictable gastric emptying, no risk of dose dumping, flexible release patterns, and increased bioavailability with less inter and intra-subject variability. Multiparticulate dosage form is pharmaceutical formulations where the pharmaceutically active substance is in the form of number of small independent subunit like pellets, and minitablets etc. [1].

The concept of this multiple unit dosage forms answers many formulating problems and is a common strategy to control the release of drug as showing the reproducible release profiles when compared to Single Unit Dosage Form (SUDF)s. These Multiple Unit Dosage Form (MUDFs), can either be filled in to hard capsules or compacted in to bigger tablets or can be dispensed in a dose pouches or packets [2,].

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

The pellets or beads produced by the extrusion spheronization offer the following advantages over conventional drug delivery system. [4].

1. It produces spherical spheroids with high loading capacity of active ingredient without producing extensively large particles.
2. It produces particles of uniform size with narrow size distribution and good flow properties·
3. Successful coating is applied to spheroid because of its spherical shape and low surface area to volume ratio.
4. Facilitates delivery of two or more chemically compatible or incompatible drug at the same or different site in GI tract.ie targeted drug action.
5. Pellets are frequently used in controlled release delivery system as it facilitates free dispersion of spheroids in the GI tract and offer flexibility for further modification.
6. It improves the safety and efficiency of active ingredient.

Therapeutic Advantages of Multiple Units over Single Units:

a) When taken orally, multiple unit dosage forms.
b) Disperse freely in the gastro intestinal tract.
c) Maximize drug absorption, reduce peak plasma fluctuations, minimize local irritation of the mucosa by certain irritant drugs and minimize potential side effects without appreciably lowering drug bioavailability.
d) Offer reduced variation in gastric emptying rate and transit time which is less dependent on the state of nutrition.
e) Provides less risk of dose dumping.
f) Reduces localized concentration of irritative drugs.
g) Improves safety and efficacy of a drug. Reduce inter and intra patient variability

Theory of pellet formation and growth: Before selection and optimization of any Pelletization/granulation process, it is important to understand the fundamental mechanisms of pellet formation and growth. Different theories have been given related to the mechanism of formation and growth of pellets. Some of these theories are derived from experimental results while others are derived by visual observations. Out of these hypothetical theories the most convincing steps of Pelletization process, involves three consecutive regions: (1) nucleation, (2) transition and (3) ball growth. However, based on the experiments on the mechanism of pellet formation and growth, the following steps were given:

- Nucleation
- Coalescence
- Layering
- Abrasion Transfer

Nucleation is a stage of Pelletization process that occurs when a powder is wetted with solvent system. The primitive particles are drawn together to form three-phase air-water-liquid nuclei system which are held together by liquid bridges that are pendular in nature. The reduction in the particle size of the powder will improve the bonding strength between them. Further the size, the rate and the speed of nuclear formation depends upon the size of the particles, the moisture content, the viscosity of the binding particles, the wettability of the substrate and the processing conditions, such as tumbling and drying rates. Nucleation is followed by a transition phase where the growth mechanisms affecting are coalescence and layering.

Coalescence is defined as the formation of large-sized particles by random collision of well-formed nuclei, this mechanism requires slightly excess moisture on the surface of the nuclei although the number of nuclei is continuously reduced even though the total mass of the system remains unchanged during this operation.

Layering is a slow growth mechanism and with the successive addition of fragments and fines on an already previously formed nucleus. The addition of the this previously form nuclei is done to increase

the extent of pellet growth in the layering step, the number of particles remains constant while the total mass of the system increases because the particles agglomerate with each other and thus it can be said that increasing particle size as a function of time. The fragments or fine particles can be formed by particle size reduction (fig. 1). FIG. 1 shows the

PELLET GROWTH MECHANISM.

The main mechanism in the ball growth phase is the abrasion transfer which may involves the transfer of materials from one granule which is already 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 thus the number of particles remains same [7].

Pelletization is generally followed by capsule filling or tabletting which results in high cost and destruction of film coating of the pellets. [8]

Some of the methods used to prepare pellets are as follows:

1. Extrusion-spheronization technique or wet mass extrusion.
2. Hot melt extrusion process.
3. Layer building method.
4. Globulation or droplet formation.
5. Cryopelletization.
6. Balling.
7. Freeze Pelletization.
8. Compression.

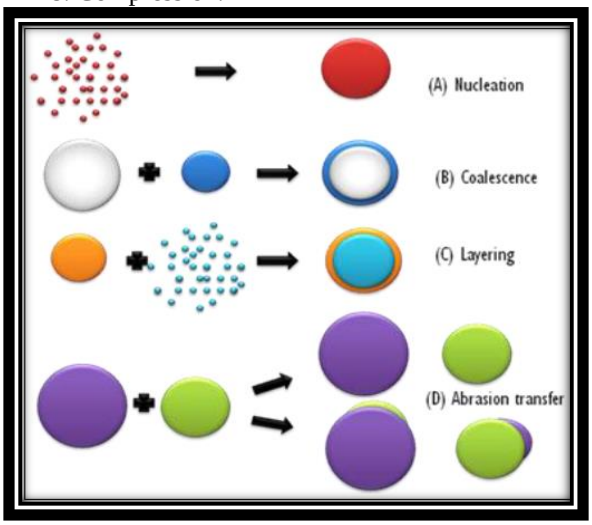

Fig 1: pellet growth mechanism [7]

1. **Pelletization by extrusion and spheronization**

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

a) Dry Mixing: Dry mixing of ingredients is done to achieve homogeneous powder dispersion using twin shell blender, planetary mixer, high speed mixer and tumbler mixer. [11]

b) Wet Massing: Wet massing is done in order to produce a sufficient plastic dump mass for extrusion, by employing normal equipment and processes as employed in wet granulation for compaction. The most commonly used granulator is planetary mixer or Hobart mixer or sigma blade mixer and high shear mixer. During mixing with high shear, the small amount of heat is generated in the mixing/granulation bowl which may lead to the evaporation of the solvent liquid from the mass thus changing the extrusion behaviour of the wet mass. Cooling of the granulation bowl may avoid this problem.

c) Extrusion: This is the third step in the process, which produces rod shaped particles of uniform diameter from the wet mass. The wet mass is forced through dies and shaped into small cylindrical particles with uniform diameter. Such type of shaping of the wet mass into long rods, commonly termed 'extrudate.' The extrudate particles break at similar length due to their own weight. [14] 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. In the axial type the screen is placed at the end of the screw, while in radial type the screen is placed around the screw

d) Spheronization: The spheronization technology was first introduced by Nakahara in 1964. A spheronizer also known as merumerizer consists of a static cylinder and a rotating friction plate where the extrudate is broken up into smaller cylinders with a length equal to their diameter and these plastic cylinders are rounded due to frictional forces. The friction plate, a rotating disk with a characteristically grooved surface to increase the frictional forces, is the most important component of the equipment. Two geometric patterns are generally used. [16,17]. It includes a cross-hatched pattern with grooves running at right angle to one another, a radial pattern with grooves running radially from the centre of the disc[18,19]. The rotational speed of the friction plate varies from 100- 2000 rpm. Spheronization process involves transition from rods to spheres that might occur in various stages which usually take 5 to 30 minutes provided mass should not be too dry wherein no

more spheres are formed and the rods will transform as far as dumbbells.[20,21]

e) Drying: A drying stage is required in order to achieve the desired moisture content. Drying rate also important an increase drying rate gave more porous pellets due to decrease pellet densification during that drying process. The pellets can be dried at room temperature or at elevated temperature in a tray drier/ oven [22]or in a fluidized bed drier[25].Bataller *al.*, 1993 reported the use of microwave oven in the final phase of the production process of pellets to evaporate the slurry of the extruded mass during drying process. Huyghebaert*et al.*, 2005 [26] reported the use of freeze dryer in order to maintain viability of living bacterial spores. If solute migration occurs during drying of the wet mass, this may result in an increased initial rate of dissolution, stronger pellets with modified surfaces, which might reduce adhesion of any added film coats.

f) Screening: Screening may be necessary to achieve the desired size distribution, and for this purpose sieves are used. In case of pellets prepared by extrusion-spheronization, screening is essentially required after manufacture, in order to avoid pellets having high size polydispersity index [29].

2. Hot Melt Extrusion-Spheronization

This process utilizes similar equipment with its conventional alternative. The mixing compartment is heated at a point that the carrier is melted. Additionally, the friction of the materials against the moving parts of the apparatus also provides significant amount of energy that melts the carrier [30]. Higher temperature my lead to the decomposition of the API prone [30]. Its most widely used method for wet material [31]. As a proof, Crowley *et al.* [32] have summarized almost 30 APIs treated with hot melt extrusion techniques. The process is also thoroughly described in WO2002035991 [33] entitled as "Spherical particles produced by a hot-melt extrusion spheronization process", emphasizing on the advantages of the process and especially the absence of solvents and enhanced control of drug release compared to products produced using aqueous techniques. In US20070264328 and US20107771632 [34]

Ghebre- Sellassie*et al.*, presented modifications of the requirements appropriate for the continuous application of the process. An example of hot melt extruded spheres is enclosed in US6706281 [35] release of a therapeutic agent. US6743442 [36] discloses oral extended release opioid dosage forms; comprising multiparticulates produced by melt extrusion techniques. [36]

A novel hot-melt extrusion and spheronization process has been recently reported to produce spherical pellets without the use of water or other solvents. This method reduces the instability problems during processing due to water. The advantage of the pellets produced by melt extrusion do not require additional film coating since the drug release is diffusion controlled. Hot melt-extrusion is initially used in the plastic industry, after this it gaining popularity in the pharmaceutical industry for the production of pellets; immediate and sustained release tablets and transdermal drug delivery systems [37, 38] and also the technique is being approved in the USA, and it is a fast, simple, continuous, solvent-free process with fewer processing steps. Melt extrusion process consists of three basic steps: melting or plasticizing a solid material followed by the shaping the molten material in the desired die and solidification of the material into the desired shape. A hot melt extrusion line consists of a material feed hopper and extruder inside a heated barrel, having three different sections and spheronizer. The feed hopper holds the material and continuously feeds it into the extruder, which has a heated barrel containing the rotating screw. The extrudate is then cut into uniform cylindrical long segment, which are then spheronized by using spheronizer to generate uniform sized pellets. The minimum temperature should be maintained in order to soften the extrudate [39].

Advantages:

1. Simple, continuous and efficient process.
2. It does not require the use of any solvent or water.
3. During processing, uniform dispersion of fine particles takes place.
4. Processing steps are short as do not require drying.
5. Improved stability of the product at varying pH and moisture levels.

Disadvantages:

1. High temperature needed for melting of high melting point binders contributes for instability problems for heat labile materials.
2. Low melting point binder risks situation where melting or softening of the binder occurs during handling and storage of agglomerates.
3. High energy input is required.
4. Elevated temperatures are involved. Hence it cannot be applied for heat-sensitive materials.

Applications:

1. Production of controlled release reservoir system and sustain-release pellets.
2. Useful in masking the bitter taste of an active drug and used in enhancing dissolution rates for poorly water-soluble drugs.

3. Improves dissolution and bioavailability of drug by forming solid dispersions or solid solutions.

3. Drug Layering:

The layering process comprises the deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of the same material or inert starter seeds. In solution/suspension layering, drug particles are dissolved or suspended in the binding liquid (fig.2). In case of powder drug layering, a binder solution is first sprayed onto the previously prepared inert seeds which is then, followed by the addition of powder drug. Conventional pan coaters have been used from the very beginning of the history of drug layering Pelletization.[40]

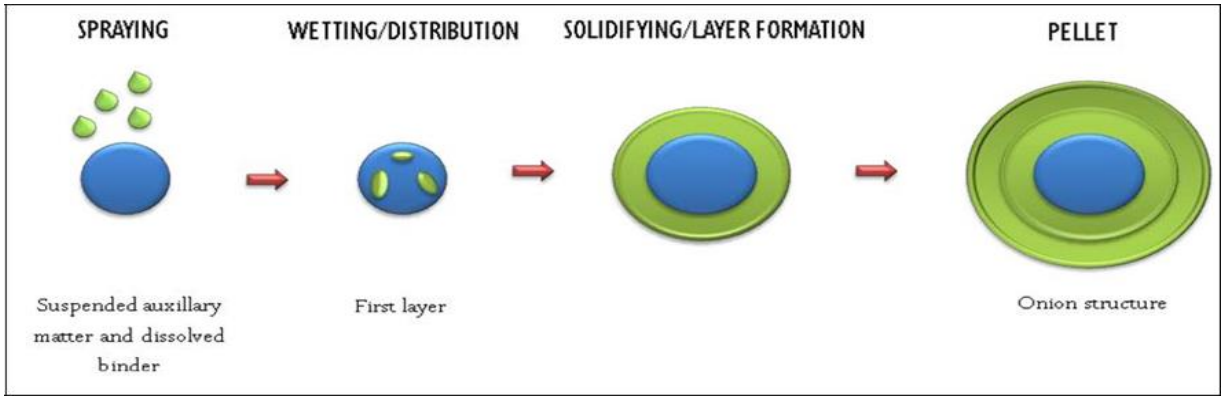

Fig 2: Pelletization by drug layering [40]

4. Globulation:

Globulation or droplet formation involves two related processes namely, spray drying and spray congealing.[41]

Spray drying:

In this method the drug particle is suspended in the solution or suspension then this mixture is sprayed by using nozzle in the stream of hot air. The circular motion of the air stream generates the dry spherical particles

Application: It is usually applied in development of controlled release systems, in the improvement of bioavailability of poorly soluble drugs.

Spray congealing:

In this process drug is melted and it is then this is dispersed with the melted waxes, gums. The final dispersion is then sprayed into the air chamber which having the temperature lower than the melting point of the dispersion waxes get congealed (solidified) and forms the layer on the drug particles and form the spherical pellets.

Application: It is employed in development of both immediate release and sustained release pellets

5. Cryopelletization:

In aqueous-organic solution suspension or emulsion are dropped into liquid nitrogen to form frozen particles, these particles are than freeze-dried on lyophilized to remove water or organic solvents [42]

6. Balling:

In this method, finely divided solid particles are mixed with sufficient amount of liquid to get wet mass and then pellets are formed by continuous rolling and tumbling of these wet masses. The equipment's like pans, discs, drums or mixers can be used. [43]

7. Freeze Pelletization:

In this method, solid particles in the molten state are introduced into the liquid medium in which molten solid is immiscible so that it forms droplets in the liquid medium. The droplets then convert into solid spherical pellets at room temperature. Since pellets are solid at room temperature, it does not require drying [44].

8. Compression:

This is simple as like a tablet compression method. The same principle can be used. This is simple pelletization method in which the mixture of active ingredients and excipients are compacted under pressure to generate pellets of defined shape and size [44].

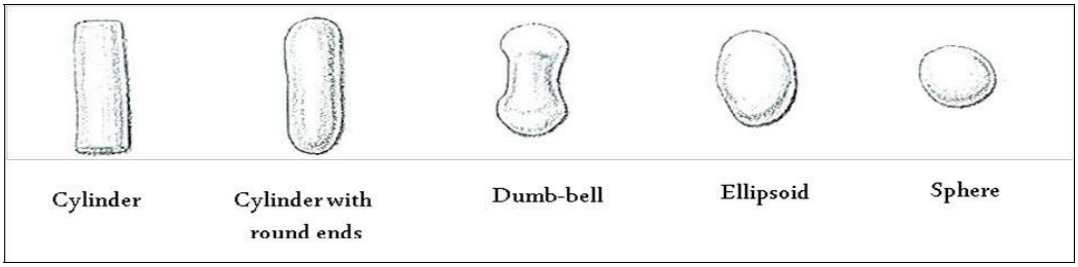

Fig 3: Schematic Representation of Different Stages of Pellet Formation during Pelletization

Mechanism of Drug Release from Pellets: The mechanism of drug release from pellets can occur in the following ways:

1. Erosion: Some coatings are designed to erode gradually with time, thereby releasing the drug contained within the particle.

2. Osmosis: In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.

3. Diffusion*:* On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Formulation of Pellets

The following ingredients are used during the formulation of pellets

1. Active pharmaceutical ingredients
2. Binder: starcap, starlac
3. Granulating fluid: Ethyl ether, dilute acetic acid
4. Filler: ARBOCEL, lactose
5. Plasticizers: sorbitol, HPC
6. Separating agent: Aerosil (silicon dioxide)
7. pH adjuster: buffer
8. Release modifier: polyacrylate.
9. Flavoring agent
10. Sweetening agent
11. Coloring agent

Product characteristics of the Pellets:

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

Coating of pellets

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

The following equipment's are used for the coating of the pellets:

- The standard coating pan.[46].
- The perforated coating pan.[47].
- The fluidized bed coater. [48].

Process parameters for extrusion spheronization method.

Material: The nature of the starting material influences the size, hardness and sphericity of the particle, as well as the release rate of the loaded drug. The use of similar products manufactured by different suppliers also showed changes in the characteristics of the pellet produced. For example, pellets prepared with three types of microcrystalline cellulose (MCC) may having same grade from different manufacturers featured differences in size and roundness even though processed under the same conditions [49,50].

a) Extruders: According to Reynolds and Rowe an axial screw extruder produces a denser material than a radial screw extruder. Pellet quality is dependent on the thickness of the screen and the diameter of the perforations [51 ,52]. A thin screen produced a rough and loosely bound extrudate, whereas a thicker screen forms smooth and well-bound extrudate because of the higher densification of the wet mass.

b) Extrusion Speed: The output from the extruder depends on the extrusion speed. If we increase the speed of the extruder then it may produce the rough and shark skinning pellets which may lead to production of poor quality of pellets [53,54].

c) Extrusion Temperature: During the extrusion process some amount of heat generated which may lead to the evaporation of granulating fluid from the mixture and thus

there will be no proper binding of the extrudate which may hamper the quality of the final pellets Extrusion temperature control is especially taken into the consideration when processing a thermolabile drug formulation [54] .

d) Spheronizer Specifications: Pellet quality is also dependent on spheronizer load which affects the particle-size distribution, bulk and tap density of the final pellets. Barrau *et al*., reported that an increasing spheronizer load decreased the roundness and increased the hardness of pellets. Hellen *et al*., reported that the bulk and tap density increased and the size of the pellets decreased with an increasing spheronizer load [55].

Evaluation of the pellets.

1. Size distribution:
   The sizing of pellets is necessary because it has significant influence on the release kinetics. Particle size distribution, means ferret diameter, geometric mean diameter, means particle width and length, it is the parameters by which size of pellets can be determined. In most of the cases particle size determination is carried out by simple sieve analysis using sieve shaker reported the use of Vernier callipers to determine the size of pellets [56].

2. Pellets Shape:
   Sphericity of the pellets is the most important characteristics and various methods have been used to determine it. The shape factor estimates the amount by which the projected image of particles deviates from a circle and it is calculated by means of the projected area of the pellets and its circumference [57]. For acceptable quality of pellets, the roundness index/shape factor should be between 1 and 1.2. For perfectly circular projected image, the shape factor should be 1 while a value of 0.6 describes a particle of good sphericity [57].
   Visual inspection of pellets by microscope and stereomicroscope is another method to determine shape of pellets [58]. One plane critical stability, which an angle at which a plane has to be tilted before a particle begins to roll, is one of the important methods used for determining shape [59].The angle of repose is an indirect indication of the circularity of pellets and is calculated by the ratio of double the pile height and pile radius by fixed funnel method measured after a certain number of pellets are allowed to fall from a given height through a specific orifice [59].

3. Surface Morphology
   Scanning electron microscopy is used to examine the surface morphology and cross section of pellets. Sood et al. in 2004 reported the use of optical microscopy to examine the microstructure of pellet surface [60]. Some researcher analysed surface roughness of pellets by applying a non-contracting laser profile meter [61].

4. Specific Surface Area
   Surface area of pellets is directly related with size and shape of the pellets. Knowledge of the surface area is desirable especially if film coating is considered. Knowledge about the surface area is important even in case of uncoated pellets, since drug release is influenced by the surface area. Specific surface area of pellets is determined by gas adsorption technique [63].

5. Friability
   The mechanical properties of pellets are important for processing. Pellets flake off during handling and coating process resulting in formation of dust. In the case of subsequent coating it is desirable to have pellets with low friability. Friability of pellets are determined by using Erkewa type tablet friabiliator [64] or turbula mixer for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion. Friability can also be determined using fluidized bed with Wurster insert by using stream of air [65].

Applications

1) Pellets as Controlled Release Drug Delivery Systems – Pellet Combination.
   - As an example, US6897205 describes a multi-particulate dosage form comprising at least two differently coated fractions of pellets [66].
   - The active ingredient is released within different areas of the gastrointestinal tract, as a function of the pH value of each region. US7781448 refers to a combination of immediate, extended and delayed release pellets for once daily administration of Tropsium [67].
   - US200 describes 16270805a dosage form comprising two pellet populations, one enteric coated and one capable of delaying the release in a pH independent manner [68].

2) Pellets as Solid Self Emulsifying Drug Delivery Systems (SSEDDS)
   SEDDs are typically mixtures of drug dispersions in oils with appropriate solubilizers which provide emulsions when introduced into aqueous environments. They are usually prepared as liquids, exhibiting disadvantages such as low stability compared to solids,

inconvenient storage and trans-port, restricted drug loading and the potential for irreversible precipitation of their constituents [69, 70, 71].

3) Pellets as Implants
Spherical polymeric particles have been used as implants, due to their ability to release APIs on a long-term basis. There are various microencapsulation methods for producing implants the majority of which is based on emulsion solvent removal techniques. Innovations in this field have been thoroughly presented by Obeidat [72].
4) Pellets in Fast Dissolving Systems
Pellets are also appropriate delivery systems for immediate release of active moieties. The plethora of materials and processes allows the preparation of fast disintegrating and dissolving pellets, which provide a potential use as orally dispersible systems. [73]
5) Immediate release:
Administering drugs in pellet form leads to an increased surface area as compared to traditional compressed tablets and capsules which would considerably reduce the disintegration time and have the potential for use in rapidly dispersible tablets. [73]
6) Sustained release:
The pellet form provides a smoother absorption profile from the gastrointestinal tract as the beads pass gradually through the stomach into the small intestine at a steady rate. Pellets are being increasingly used in the manufacture of sustained release dosage form of drugs. [74]
7) Chemically Incompatible Products:
At times such ingredients are required to be delivered in a single dose. In the compressed tablet dosage form separate tablets would have to be administered, but the pellets can be administered in a single capsule.[74]

8) 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. [75]

Table no 1: Marketed Product of pellets.

No.	PRODUCT	DRUG	COMPANY
1	Bontril SR	Phendimetrazine Tartrate	Carnick laboratories, Inc
2	Brexin L.A	Chlorpheniramine Pseudoephedrine	Savage Laboratories, Bangalore
3	Catazyme S	-	Organon pharmaceuticals, USA
4	Compazine	Prochlorperazine	Smith & French, Mumbai
5	Cymbalta	Duloxetine Hydrochloride	Eli Lilly and Company, USA
6	Dilgard XL 180	Diltiazem hydrochloride	Smith kline & French, Mumbai
7	Elixophyline	-	CIPLA Ltd, Ahamadabad
8	Fastin	Phentermine	Berlex Laboratories, USA
9	Hispril	Diphenylpyraline	Berlex Laboratories, USA
10	Ibugesic S.R 300	Ibuprofen	CIPLA Ltd, Ahamadabad
11	Inderal	Propranolol Hydrochloride	Astrazeneca US Ltd.
12	Indocrin S.R	-	Merk Sharp, Mumbai
13	Nexium	Esomeprazole	Astrazeneca US Ltd.
14	Nicobid T.S	Niacin	U.S Vitamin, USA
15	Omez	Omeprazole	Dr. Reddys lab, Hyderabad
16	Ornade	Chlorpheniramine & phenylpropanolamine	Smithkline & French
17	Prevacid	Lansoprazole	Takeda

18	Prilosec	Omeprazole	Astrazeneca US Ltd.
19	Sporanox	Itraconazole	Janssen

Recent advancement in Pelletization technology:

1) Hot melt extrusion extrusion spheronization
2) Cryopelletization
3) Microtablets: Nordmark Arzneimittek GmbH & Co. KG developed microtablets, a modern multiple unit dosage form with diameter and height 2 mm X 2 mm by compaction and compression. High speed rotary tabletting machine equipped with 10 - 19 multi-tip tabletting tools that produce 1- 2 million microtablets per hour. This design offers flexibility to compress active drug with poor compression properties in large concentrations and high mass uniformity. These compressed core microtablets can be matrix forms or functionally coated to get the desired release profiles. One or more microtablets formulations containing different active ingredients can be filled into capsules at varying dosage strengths. Microtablets are supplied as stick packs or filled into capsules. These formulations can be used in the therapies of pain relief, AIDS, oncology, hormones, paediatrics, etc. Various marketed formulations include Pancreatin Microtablets enteric coated with Kollicoat ®MAE 30 DP (Nordmark), Omeprazole (Ratiopharm), Sodium valproate (Desitin), Ferrous sulfate (Teofarma), Dimethyl-fumarate (Biogen)[76].

4) CEFORM™ is a pelletization technology for the production of microspheres from powders. These microspheres have a typical median particle size of 150-180µm expanding to 50-600µm when process parameters are appropriately adjusted. The process was introduced in the late 90's and could be characterized as a hybrid of extrusion, centrifugal granulation and congealing. The acronym refers to Centrifugally Extruded & Formed Microspheres/Micro-particles. A dry powder comprising the API and appropriate excipients is rapidly spinned inside a precisely engineered machine and is forced through small heated openings at specific and well controlled temperatures. The mixture is liquefied by a microburst of heat while passing through the openings, and a sphere is formed during cooling. Heat treatment of the material is practically instant, thus without affecting the stability of the API. It is claimed that with the appropriate selection of materials and process parameters the micro-spheres can improve some critical aspects of the API, such as its solubility or stability, in a similar way to other melt methods which incorporate drugs in solid dispersions. CEFORM™ technology has been used for taste masking, immediate and controlled drug release applications [77, 78, 79].

5) CPS™ (Complex Perfect Spheres) Pelletizing Technology
In the year 2000, this technology was invented by *Glatt GmbH in Binzen, Germany*; an advanced fluid bed rotor and a direct pelletization technology for the production of matrix type pellets and micropellets. The process equipment consists of a *modified fluid bed rotor system* with a conical shaped rotating disc and additional devices for direct movement of particles. This is a *batch process* suitable for drug layering by drug solution, suspension, emulsion etc. on starter cores as well as dry powder layering to achieve a particular drug layer quality. The layering liquid can be aqueous or organic with or without functional compounds. As an option, dry powder may be fed into the process. In powder layering, the endpoint of the pelletization can be measured with the help of torque at the CPS™ rotor. Densification of the particles is achieved by means of a characteristic rolling movement of particles and thereby the application of different forces particularly centrifugal forces on the arising pellet cores by the form and speed of the rotating disc [80,81].

CONCLUSION:

Today extrusion spheronization (wet mass extrusion) and melt extrusion spheronization represents an efficient pathway for novel drug delivery system. The potential of this technology is lies in the scope for different oral controlled delivery systems including oral and topical delivery systems. Because of its simple design, high efficiency of producing spheres and fast processing, extrusion spheronization has found a special position in pharmaceutical industry and especially in case of production of Multiparticulate oral controlled release dosage forms. Pellet formation by this technique produces more spherical pellets and offers more advantages than other pelletization process. In addition, hot melt extrusion method has provided a new platform to produce spherical particles of drugs which are not stable or having compatibility problem in presence of solvents,This brief review on the pelletization technology hereby concludes with a note that they are considered as a most promising

drug delivery system today which is catching up with the pace of speed to have a high existence in the Pharma world. This system gains more popularity because of their easy portability improved patience compliance and ease of administration and flexibility in the fabrication as tablets or capsules or packed simply as a single dose packet. They can be applied by both oral and buccal routes. This technology is growing in fast pace challenging most of the pharmaceuticals companies to develop pelletized dosage forms for wide range of active pharmaceuticals ingredients.

Today pelletization represents an efficient pathway for novel drug delivery in the scope for different oral immediate or controlled delivery systems. Because of its simple design, high efficiency of producing spherical pellets and fast processing, pelletization has found a special position in pharmaceutical industry and especially in case of production of multiparticulates oral controlled release dosage forms as compared to granulation. Pelletization technique produces more spherical pellets and offers more advantages than granulation process. In addition, hot-melt extrusion method has provided a new, wider platform to produce spherical pellets of drugs which are not stable or have compatibility problems in presence of solvents.

This brief review focus on different techniques for manufacturing of spherical pellets. It concludes with a note that pellets are the promising drug delivery system with high-existence in a pharma world. Pellets are the multi-unit systems offering improved safety and efficacy of the active ingredients, ex-cellent flow properties to be fabricated as single dosage systems.

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