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MULTIPARTICULATE DRUG DELIVERY SYSTEMS – A BRIEF REVIEW ON PHARMACEUTICAL PELLETS AND PELLETIZATION TECHNIQUES.

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ABSTRACT:

The present time is considered as an period of advancements in drug delivery systems.various new approaches are discussed ranging from uniparticulate to multi particulate system, macro to micro and nano particulate systems. Pelletization is one of the new drug delivery technique that gives an effective way to deliver the drug in modified pattern .Pelletization is novel drug delivery system which converts fine powder particles into pellets.Pellet for pharmaceutical use are defined as tiny, discrete, free flowing spherical units which Prepared from fine powders by a various of size agglomeration processes.However, some applications requires the use of smaller pellets, example such as Pellets used in oral dispersible tablets have smaller particle sizes (<0.3 mm) in order to minimize gritty mouth feel. Pelletization has attained much further interest in recent time due to colourful advantages with respect to conventional dosage form, such as dose uniformity, flexibility in dosage form, prevention of dust formation. This review gives information about advantages,disadvantages,desirable characterization of pellets.currently the Pelletization is receveing important attention Because it represents an efficient pathway to produce a new drug delivery system. the manufacturing techniques consists Drug layering, Extrusion-Spheronization, Cryopelletization, Compression, Balling, Hot-Melt Extrusion Technology, Freeze pelletization, Spray-drying etc.

KEYWORDS: multiparticulate drug delivery systems, pellets, Pelletization techniques, extrusion – speronizer ,Drug layering.

INTRODUCTION :

The multiparticulate dosage Form has caught the attention of formulation Scientists due to their tremendous potential as a Multidimensional drug delivery system. The risk of Dose dumping, intra- and inter-subject variability in Gastric emptying times can be reduced if the drug is Formulated into multiparticulate systems instead of Reservoir/monolithic tablets [1].

Pellets :

Pellet for pharmaceutical use are defined as small, separate, free flowing globular units Prepared from fine powders by a variety of size agglomeration processes. Their size Distributions are generally fairly narrow with mean particle sizes ranging from about 0.5To 1.5mm. However, some applications bears the use of smaller pellets, for example, Pellets which are used for preparing oral dispersible tablets are of smaller particle sizes (<0.3 mm) in order to minimize gritty mouth feel[2].The important parameter in pellet is size and shape of The pellet which is influenced by various parameters Like binder types,quantity of binder, screen hole Diameter, speed of extruder, spheronization time, Spheronization speed, spheronization load. To obtained Desired the shape of pellets, size and yield, one of the step has been added in the process after extrusion Step[3].

History of pellets

In the 1950's, pellets came into acutuality in the field of "Pharmaceutical Industry" with an impact of sustain release dosage Form. In terms of manufacturing, processing methods and equipment Used were faster, less costly and more efficient. It can also be used for Sustained release of active constituents [4].

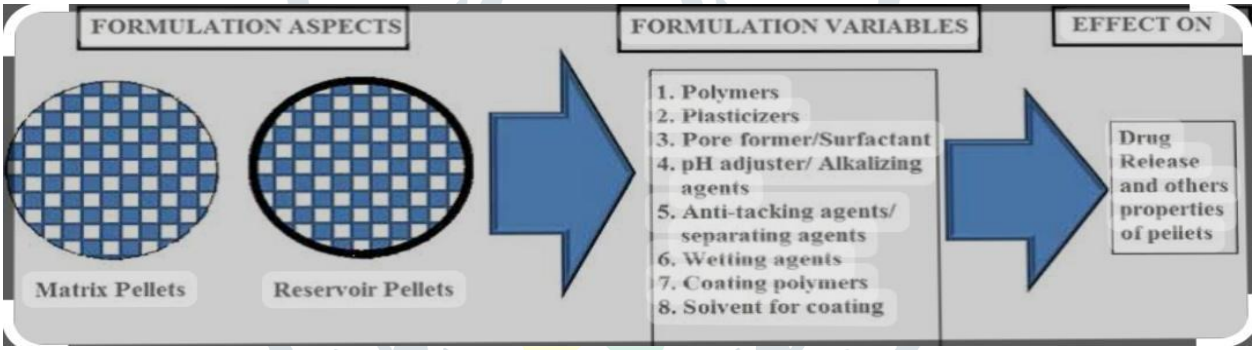

FIG 1 : FORMULATION ASPECTS OF PELLETS

Advantages :

Pellet formulations have attracted the attention of researchers because they provide several advantages over conventional solid dosage forms. The large surface area of the pellets is considered the main advantage of this formulation.After Administration, the pellets will be distributed in the gastrointestinal tract (GIT), with possible risk of gastric irritation [5]. The ultimate dosage forms for pellets can be capsule or may be compressed into disintegrating tablets. Interest in this area is constantly growing as it offers some important pharmacological as well as technological advantages [6].

Pellets offer a significant number of benefit over Conventional unit-dose systems.

Technological Benefits:

1.Dose uniformity, the Layering techniques and extrusion spheronization technique offers great precision with Uniform drug delivery to the pellets.

2. Spheres have excellent flow properties. This becomes Very useful in automated processes or in processes where precise dosing is required, e.g. tableting, Compression Operations, capsule filling, and packaging.

3. Prevention of dust formation,leading to improved process safety, as fine powders can Cause dust explosions and the inhalation of fines can Cause health problems.

4. Controlled release pellet application due to the ideal Low surface area-to-volume ratio that provides an ideal Shape for film coating application .

5. They can be mixed to deliver incompatible bioactive Agents simultaneously and/or to provide different release Profiles at the same or different sites in the Gastrointestinal (GI) tract.

Therapeutic Benefits:

6. Pellets can disperse freely throughout the GIT after Administration and consequently the d

Absorption of drug is Maximized.

7. The wide distribution of spherical particles in the Gastrointestinal tract limits localized build-up of the Drug and prevent the irritating effect of some drugs on the Gastric mucosa;

8. Reduce inter- and intra-patient variability.

9. Modified-release multiparticulate delivery systems are Less susceptible to dose dumping than single-unit dosage Forms [7].

Disadvantages of pellets:

1.Dosing by volume rather than Number and dividing into individual dose as needed.

2.It Involves capsule filling which can Increase the costs or tabletting which Destroy the film coatings on the pellets.

3.The size of pellets varies according to receipe but is Usually between 1 to 2mm[8].

Desirable Properties of pellets:

1.For Uncoated pellets

a.Uniform spherical size

b.Narrow particle size distribution

c.Good flow property

d.Low friability

e. flat surface

f.Low dust generation

g.Reproducible packing

h.Ease of coating

2.For Coated pellets

a.Maintain all above properties

b.Desirable properties of drug release [9].

The recent new pellets trends are;

They help in preparation of modified Release multiple dosage form with different Release patterns such as immediate and Sustained release pattern.

1. They help in taste masking of the medicine Which are bitter in taste.
2. They're available as a pellets to dissolve In mouth.
3. Polymer based pellets for control release Pattern of drug.As
4. fast dissolving tablets containing micro pellets.
5. As a self-emulsifying pellets.
6. Gastro retentive floating pellets etc.

This trend of pellets has increased patient Acceptance. This nov trends helps in providing the Information about the releasing pattern of the drug And its bioavailability of the drug to the systemic Circulation of the and how it as increased the Patient acceptance of ph sensitive drugs releasing Pattern pf drugs, taste mask of the drugs, selfemulsifing pellets, and polymer based Controlled drug release increases pellets that dissolve in mouth[10].

Theory of pellet formation:

To understand the basic mechanisms of granule formation and growth it is very necessary. Different theories are postulated associated with the mechanism of formation and growth of pellets. As the typical granulation, the foremost fully studied, most classified Pellatization method, which involves a rotating drum, a pan or a disc, has been divided into 3 consecutive areas: nucleation, transition and ball growth. However, supported the experiments on the mechanism of pellet formation and growth, the subsequent steps were proposed: nucleation, coalescence, layering and abrasion transfer [11].

Pelletization :

Generally, the particle sizes of the pellets are within 0.5 and 1.5mm which based on the pelletization technique12. Pelletization is a term used to define agglomeration of drug substances in either powder or granule form Resulting in the form of semi spherical and spherical agglomerates having good flow properties .The particle Sizes of the resulting pellets are between 0.05mm and 2mm . Extrusion-spheronization is the most commonly Used method for pellet production [13].

Application of pellets :

1.Controlled release pellets for encapsulations.

2. Sustained release pellets / Delayed release enteric coated pellets.

3. Floating multiparticulate system for sustained release oral drug delivery.

4. Preparation, Evaluation and Optimization of Multiparticulate System for Colon Targated drug delivery system using natural polysaccharides.

5. Multi-unit erosion matrix pellets.

6. Pellets for special tableting applications.

7. Immediate release pellets for sachets.

8. Multiparticulate Colon Targeted Drug Delivery System by Combine Approach of pH and bacteria.

9. Taste masking: The pelletization technique solves difficult taste masking problem while maintaining a high degree of bioavailability due to their high surface area, especially for oral products.Many products, such as antibiotics(clarithromycin, roxithromycin and cephelexin) and antiinflammatory drugs with a bitter taste, can now be formulated in products with high patient compliance.

10. Chemically Incompatible Product: In the compressed tablet dosage form separate tablets would have to be administered, but the pellets can be administered in a single capsule.

11. 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 [14].

Need / purpose of pelletization techniques :

- Improve flow, dispersion, solubility, stability and contraction.

-Have less variation in the GIT Transit time than unit dosage forms like tablets prepared by granulation and compression.

-produce pellets of invariant size with high drug capacity.

- To prevent segregation and dust [14].

Pelletization techniques :

Different techniques have been used for Pelletization .

●Pelletization by:

- ●Extrusion spheronization
- ●Drug layering
- ●Dry powder layering
- ●Solution and suspension layering
- ●Direct compression
- ●Cryopelletization
- ●Hot melt extrusion
- ●Balling
- ●Freeze pelletization [15].

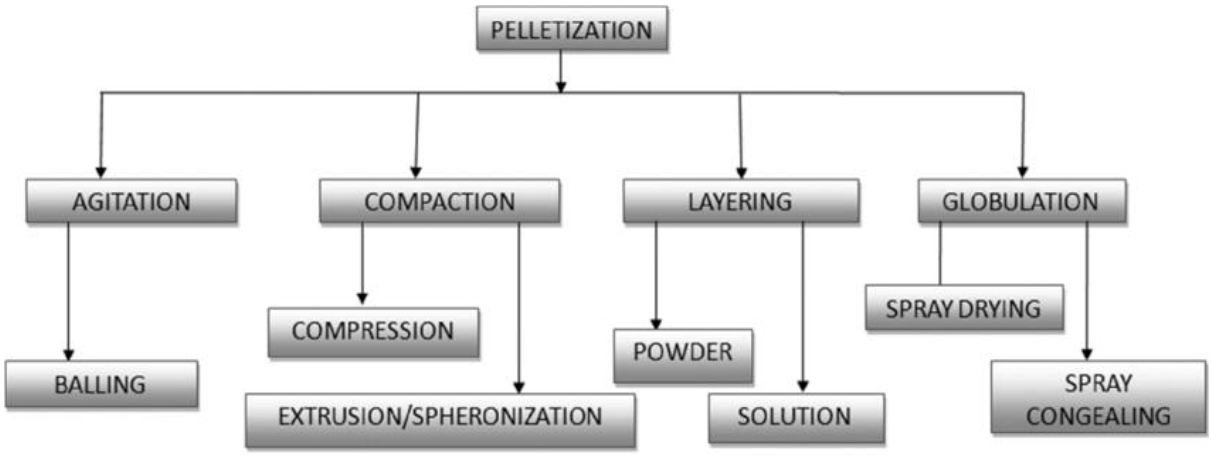

FIG 2 : PELLETIZATION TECHNIQUES

Extrusion speronization:

Extrusion, Spheronization was first discovered by Reynolds, Connie and Hadley in 1970. It is the most convenient and effective method used in the pharmaceutical industry to obtain pellets of uniform sized . It is a multistep process that involves following four steps as follows

• Granulation (Preparation of moist mass)

• Extrusion (Shaping of wet material into cylinder)

• Spheronization (Breaking of the extrudates into spheres)

• pellets drying.

• Granulation Preparations of the wet mass of the material, most commonly used granulators. are planetary mixer and sigma blade mixer.

• Extrusion Wet mass prepared was converted into cylinder force is applied to a mass until it flows out through an orifice to produce the extrudates. Different size and type of extrudates can be used depending on the load they can withstand and quality of extrudates.

• Spheronization The obtained extrudates must be chopped into pieces and transfer to spheronizer. During spheronization, the obtained cylindrical extrudates are shaped into spherical pellets of uniform length, the shaping process is consequence of plastic deformation formed fragment are damaged into uniform lengths.

Drying the Final step is the drying of pellets in dryer or fluidized bed drier to adjust the size, density of the pellets[16].

PROCESS VARIABLES FOR THE EXTRUSION SPHERONIZATION

• Starting material

The starting material which is available in nature affects the hardness, particle size, and shape of the particle , resulting in a difference in the release rate of the loaded drug. The materials used in the composition Of pellets, there is a difference in the quality of pellets of the different compositions. The pellets that are produced using

MCC (microcrystalline cellulose) of three different types, there is a difference in the shape and size even though they are produced under the same conditions by different manufacturers.

• Rheological characteristics

The wet mass of the rheological state determines the flowability of the extruder. The presence of optimum rheological conditions leads to good flowability of the wet mass from the extrudate. The changes in the rheological state cause the extrusion to be uneven and inappropriate, leading to the formation of non-uniform pellets

• Moisture content

Moisture content is one of the most critical parameters in the production of pellets from spheronization. The presence of moisture in the wet mass gives cohesion to the powder this wet mass can be extracted and the spheronizer produces a spherical shape. For the preparation of the pellets, the moisture content should be 10-15%[17].

INFLUENCE OF PROCESS VARIABLES:

Operational variables can affect several important pellet Properties, that can make a pellet suitable or unsuitable for use. The process variables considered were Granulation Liquid, extruder speed, spheronization time,Spheronization speed, spheronization load.

Amount of Granulation Liquid:

The plasticity of the wetted matter is closely related to its moisture content. Lower humidity Levels can increase friction in the extruder, causing Forced flow during extrusion because wetted mass is not Sufficiently lubricated on the mold surface. The severity Of shark skinning increases with decreasing humidity Levels. Plasticity of the pellets may be reduced and the Pellets would not be fully rounded .

Extrusion speed:

The extrusion performance and the the final Pellets quality depend on the extruder speed. Higher Extrusion speeds result in an increased compression Force on the wetted mass in the extruder. This results in Increased damage to the extrudate surface .

Spheronizer speed:

Several researchers have reported the effect of Spheronizer speed on the pellets size. An increase In the spheronization speed provides more spherical pellets And lead to increase in bulk densities due to improved Packing properties.

Spheronization time:

According to some studies, a longer spheronization time Was responsible for increased pellets size, increased pellets Sphericity, increased density and a Narrow particle size distribution. In contrast, some Researcher, report no change in the shape and density of The beads with increasing spheronization time.

Speronizer load :

At high loading of speronizer, interactions of particle to plate are low. The particle to particle interactions are dominant and Opportunities for agglomeration are greater. The Resultant pellets are subsequently larger in size[18].

- **Drug Layering**:

Layering

In this process, drug is layered on the Seed materials (generally, a coarse material or Nonpareil) in powder, solution or suspension Form and results in heterogeneous pellets, that consist of an inner core region and an Outer shell region of a different composition. This process is classified into three categories Namely direct pelletization, solution or Suspension layering and powder layering[19]. It includes deposition of successive layers of drug entities from solution, suspension or dry Powder onto core 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.The droplets are immediately sprayed onto starter seeds and spread evenly over The surface, provided the drying conditions and fluid dynamics are favourable. This is Followed by a drying phase that renders dissolved materials to precipitate and form solid Bridges that would hold the formulation components together as successive layers on the Starter seeds. The process continues until the desired quantity of drug substance is layered And the target effectiveness of the pellets is achieved. In this, the particle population remains Same, but size and total mass of system increases with time .

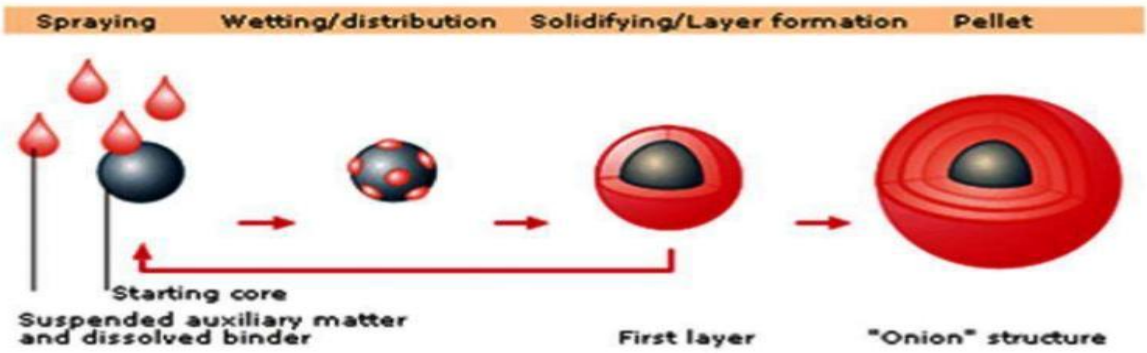

FIG 3: SOLUTION/ SUSPENSION LAYERING

In powder drug layering, a binder solution is first sprayed onto previously prepared inert Seeds, then powder is added. In this, the successive layers of powder and Excipents are added to the starting seeds using binding liquid. The small particles and Nuclei adhere to each other by capillary forces developed in liquid medium. The Process continues until the desired pellet size is obtained.The main problem is formation of Fines due to friction between particles and the particles wall at the end of process which can be Avoided by spraying the application medium at the end of process.

If the powder Addition rate is high, dust formation may occur and if the liquid addition rate is high, excessive Wetting of the pellets may occure and product quality and yield cannot be maximized .

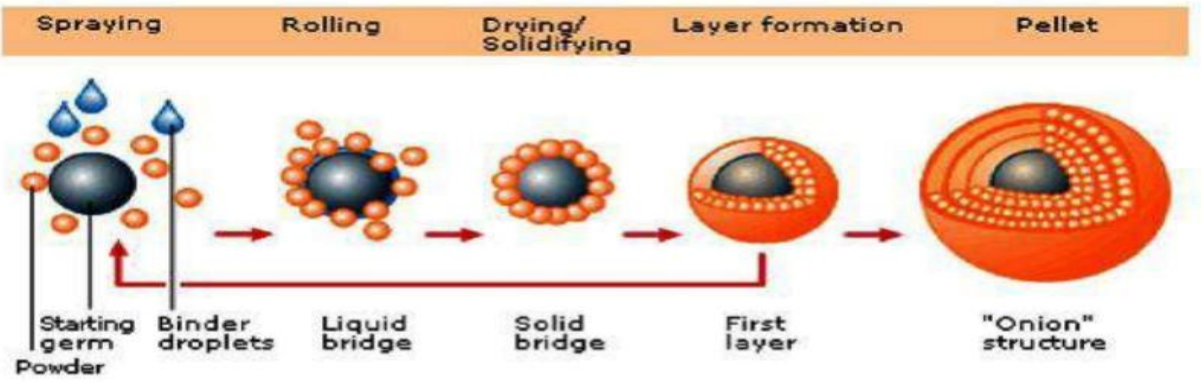

FIG 4:POWDER LAYERING

The most commonly used layering equipment are coating pans (standard or Conventional) and Fluidized bed granulators-bottom spray (wurster coating and continous Fluid bed), top spray and Tangential spray (rotor pellet coating) [20].

- **Compression:**

The pelletization process in which Mixtures or mixtures of active ingredients and Excipients are compressed under pressure to Obtain pellets of definite shape and size.These pellets have narrow size distribution and Can be filled into capsules[21]. The pellets are small Enough to be filled into capsules. The formulation and processing variables that govern the pellets Production during compression are similar to those that are commnly used in Tablet production. In fact, pellets made by compression are nothing more than small tablets That are approximately spheroidal in shape[22].

- **Cryopelletization**:

The form depends up on the distance the droplet travel before contacting liquid nitrogen.The process involve sudden and uniform freezing Of the processed material due to the rapid heat transfer That occur between the droplets and liquid nitrogen.The amount of liquid nitrogen required for production A given amount depends on the solid content and Temperature of processed solution or suspension[23].

This is the process in which droplets of liquid formulations are Converted into solid spherical particles or pellets by using liquid Nitrogen as fixing medium. The technology which was initially Developed for lyophilization of viscous bacterial suspension can be Used to produce drug-loaded pellets in liquid nitrogen at 160ºC[24].

- **Hot melt extrusion (HME):**

HME is a robust and new technique used in pharmaceutical industries to manufacture various drug delivery Systems. It is a widely used process in plastic, rubber And food industries. This technique is applicable for the production of various dosage forms like granules, Pellets, tablets, implants etc. The Melt extrusion process using polymers with high glass transition temperature (such as Polyvinyl Pyrrolidone) was firstly applied by BASF SE to pharmaceuticals. The technology was later Commercialized and several drugs were subsequently marked by Solids, the drug delivery business unit Abott GmbH and Co KG.53 This method involves compaction and conversion of blend of powder into uniform Shape product. Polymers were melted and forced these Polymers and active ingredients along with other additives were forced Through an hole or die that was

placed under controlled Temperature, pressure, screw speed etc, to obtain products Of different shapes and sizes.

Whole process Can be classified into following steps:

1. Filling of the extruder through a hopper
2. Mixing, grinding and kneading
3. Flow through the die, and
4. Extrusion from the die and further downstream Processing[25].

- **Balling:**

It is pelletization process in which pellets are formed by a Continuous rolling and thumb movement in pans, discs, Drums or mixtures. The process consists converting Finely dispersed particles in to spherical particles after the Adding of suitable amounts of liquid[26].

- **Freeze pelletization:**

Freeze pelletization is a new and Simple technique for producing spherical pellets for Pharmaceutical use. In this technique, a molten-solid Support/matrix is introduced as droplets into an inert liquid column in which the molten solid is Immiscible. The molten solid moves in the liquid Column a droplets and solidifies into spherical pellets. The droplets of molten-solid can move up or Down in the liquid column depending on the density of droplets relative to the liquid in the Column. If the density of the molten-solid Carrier/matrix is greater than Density of the liquid in the Column, then the droplets are fed from the top Of the column and pellets solidify at the bottom of the column . the density of the Molten-solid carrier/matrix is smaller than the Liquid in the column, then the droplets are introduced From the bottom of the column and pellets solidify at The top portion of the column[27].

TABLE 1 : MARKETED PRODUCTS

S no.	Pellets.	Manufacturer
1.	Budesonide EC Pellets 1.25% w/w Cinitapride SR Pellets 5% w/w. Levocetirizine Di HCL IR Pellets Metoprolol Succinate SR Pellets 65% w/w	Pelcoat formation
2.	ACECLOFENAC AMBROXOL HYDROCHLORIDE. DABIGATRAN DOMPERIDONE	Sainor laboratories
3.	Omeprazole pellets Esomeprazole pellets Lansoprazole pellets. Domperidone pellets	Spansules

	Rabeprazole pellets	
4.	Omeprazole Pellets Esomeprazole Magnesium Pellets Lansoprazole Pellets. Rabeprazole Pellets Pantoprazole Pellets	Metrochem API Pvt Ltd

CONCLUSION :

This review gives brief information about pellets are the multiunit dosage form which improved safety and efficacy of active ingredients excellent flow property which is fabricated in single dosage form.Pellet formulations have attracted researchers' attention,since they provide several advantages over conventional solid dosage forms.now a days Pelletization techniques has gained much interest in pharmaceutical industries due to simple design, more efficient pathway and faster processing. Today Pelletization represent efficient pathway for novel drug delivery in the scope for different oral immediate or controlled delivery.

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CONFLICT OF INTEREST :

The authors declare no conflict of interest.

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