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A REVIEW ON PELLETS AND PELLETIZATIONTECHNIQUES

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ABSTRACT

Oral Multiarticulate system (OMS) has more therapeutic applications when compared to unit solid dosage forms. Multiarticulate are discrete units which constitute multiple unit systems. The drug can be enhanced for prolonged period of time by manufacturing OMS into extruded spherical particles. Alot of research studies are being done on multiarticulate system as drug delivery systems. With the advancement of technology, various techniques have been developed for the preparation of pelletsas it seems to be good way for administration of many drugs. The more focus is on operational Procedures, preparative areas and physical properties of particles which have greater effect on the efficacy of the developed system. The present review mainly discusses advancements in the manufacturing techniques for pellets pertaining to their oral delivery. In addition, conversion of pellets into suitable dosage from for oral delivery and evaluation thereof has also beendiscussed here.

KEYWORDS: Multiarticulate system, pelletization, extrusion spheronization.

INTRODUCTION

Pellets is a medicated compound containing APIs with excipients, having spherical or nearly spherical shape, which are able to flow freely and size varying between 500and 1500 micrometer. These are used in oral drug delivery systems and are designedto offer several advantages over conventional tablets or capsules. They are generally produced via a pelletization process, pellets are usually filled into hard gelatin capsules or compressed into tablets and a technique used for the preparation of pellets also known as pelletization whereas a mixture of API and excipients are combinedto form spherical shaped granules by the process of agglomeration. Pellets are currently a very popular dosage form for oral

application.[19,20,21,22]

Ideal Properties of The Pellets

1. Spherical shape and smooth surface.
2. The particle size of pellets should be in range of 600-1500µm.
3. The quantity of the APIs in pellets should be maximum to maintain size of pellets.

ADVANTAGES

1. It offers flexibility to the dosage form and design development.
2. It improves the flow properties in formulation development.
3. Pellets are less susceptible to dose dumping.
4. It reduces accumulation of drugs especially in case of irritating drugs.
5. It improves safety and efficacy of a drug.
6. This process helps in the separation of incompatible drugs.
7. Pellets disperse freely in G.I.T. and increase drug absorption and also reduce peakplasma fluctuation
8. Pelletization solves the problem of taste masking.
9. Pellets enables better distribution in case of immediate release products at largersurface area.
10. Chemically incompatible products can be delivered in a single dose byencapsulating drugs into pellets.
11. In the chemical industries it is useful to reduce powder dusting.[1,2,3,4]

DISADVANTAGE

1. Compressing pellets into tablets is problematic as the film coat of pellet isdestroyed.
2. Filling of pellets in a capsule is expensive.
3. Production process is very difficult to control.
4. Required highly specialized equipment and qualified or trained person.
5. The size of the pellets may vary formulation to formulation but usually is in rangeso have to follow procedure again and again for different formulation.
6. It is difficult to compress pellets into tablets as they are too rigid and may chancesof loss of APIs.
7. Pelletization techniques demands highly specialized equipment as it increasing thecost of manufacturing.
8. If there may cause any problem to machine or equipment may cost very high in

recovery.[23,24,25]

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. Low surface.
f. Low dust formation.
g. Ease of coating.

2. ***For Coated pellets***

a. Uniform spherical size.
b. Narrow particle size distribution.
c. Good flow property.
d. Low friability.
e. Low surface.
f. Low dust formation.
g. Ease of coating.
h. Desirable drug release characteristics.

Factors affecting pelletization technique

1. **Moisture content:** High moisture contents lead to agglomeration of pellets during the process of spheronization.
2. **Rheological characteristics:** The rheological property leads to good flow ability.
3. **Solubility:** Increasing the liquid phase leads to over wetting of pellets and if increase in wetting liquid increases plasticity but includes sticky mass.
4. **Composition of granulating fluid:** Besides water, alcohol, ethyl ether, dilute acetic acid, isopropyl alcohol is used as a granulating liquid. Where HPMC, PVP, etc. can also be usedas granulating fluid.
5. **Physical properties of starting material:** Quality of pellets depend not only composition but also on different grades of the same product.
6. **Speed of Spheronizer:** It affects the size, hardness, sphericity and density of pellets. The high speed gives high sphericity, lower friability, smooth surface and higher crushing

strength.

7. **Extrusion screen:** The quality of pellets is changes by the property of orifice ofthe screen, if increase in orifice size resulted in increased pellet size.[5]

Evaluation parameters

1. **Particle size distribution:** Particle size should be as narrow as possible.
2. **Sieve analysis:** using sieve shaker is most widely used method for measuring particlesize distribution.

PROCEDURE

i. 100 gm of pellets are weighed using weighing balance.
ii. Pellets are then transferred to set of sieves having different mesh size for particlesize analysis.
iii. Calculate the % retained on each sieve.

3. **Surface Area:** The characteristics of pellets, are mainly size, shape, porosity and surface roughness.

Method Used

- **Air permeability method**- It is widely used in pharmaceutics for specific surface measurement. The principle for resistance to flow of a fluid such as air through a plug of compacted material is the surface area of material.
- **Gas adsorption method-** In this method the volume of nitrogen that is absorbed by the substrate contained in an evacuated glass blub is measured at different pressures.
- **Porosity:** The porosity of pellets influences the rate of release of drugs by affectingthe capillary action of the dissolved drug. The porosity of pellets can be measured by scanning electron microscopy (SEM), mercury porosimetry and optical microscopy.
- **Density:** The density of pellets can be affected by changes in the formulation or process.

Calculation

Bulk Density= Weight of powder/ Bulk volume Tappeddensity= Weight of powder/ Tapped volume

Where, the bulk density of pellets can be measured by an automated tapper and True density indicates the extent of densification or compactness of substances.

- **Hardness and Friability:** Hardness and friability determination of pellets is necessary

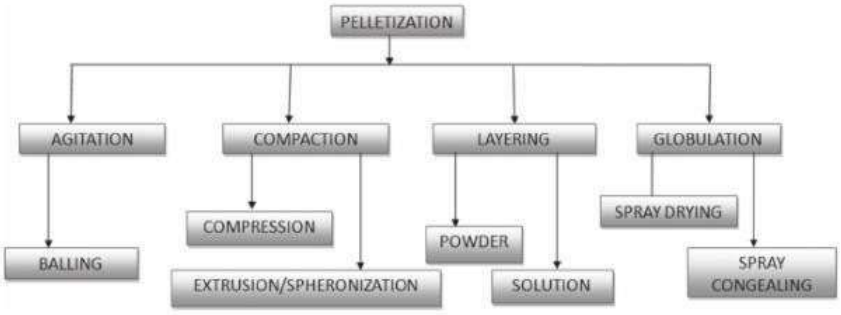
because the pellets have to stable and rigid during handling, shipping and storage.

The instrument used such as Kaul pellet hardness tester provide relative hardness values and Erkewa type tablet friabilator or Turbula mixer for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion and Roche friabilator etc.

- **Tensile Strength:** The tensile strength of pellets is determined by using tensile apparatus with a 5 kg load cell, the pellets are strained until failure occurs. The load isrecorded and the tensile strength is calculated applying the value for the failure load and the radius of pellets.

Different Types of Pelletization Techniques

- Direct Pelletization technique.
- Extrusion – Spheronization technique.
- Hot melt direct Pelletization technique.
- Layering technique.
- Compression technique.
- Spray drying technique.



1. Direct Pelletization Technique

In this technique pellets are directly manufactured by powder with the help of binder and solvent. This process is fast and require a less amount of auxiliary materials. by this process compact and round shaped pellets are formed and the diameter of pellets are between 0.2 -1.2 mm.

Principle

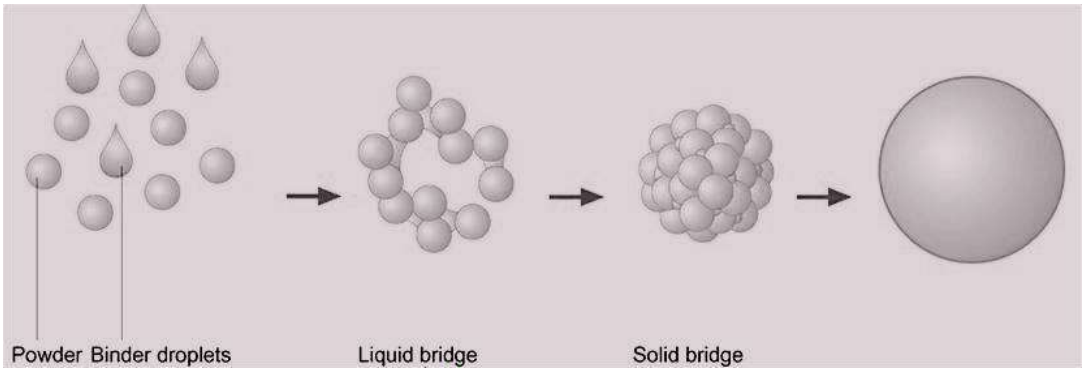
Powder is mixed and moistened with a solvent or binder the obtained powder bed is subjected to centrifugation shown as figure 1&2. the Impact and acceleration forces lead to the formation of agglomerates, which become rounder into uniform and densepellets. The rotation speed

directly influences the density and size of pellets. then theparticles dried in the fluid bed.

Figure 1: Direct Pelletization.

PROCEDURE

- Select the desired API.
- Choose appropriate binders, fillers, lubricants for the formulation.
- Then weigh accurately API and excipients.
- After weighing the material mix the material with (v-blender) for uniform mixing.
- Then add the liquid binder (for Eg: -distilled water or ethanol) for making powdermixture.
- After making the powder mixture moisted mixture transfer into the Pelletization equipment(eg: -granulator).
- Drying (if necessary) if material needed to be dry then dry the material.



1. Extrusion – Spheronization technique.Principle

The technique is used for pellets with high loading capacity of API without producing extensive large particle. Drug mixing of ingredient to active homogeneous powdered dispersion by planetary mixture then add required amount of binder and wet mass is done to produce a sufficient plastic mass. Extrusion produces rod shaped particle of uniform diameter of wet mass. Wet mass is formed threw dies and shaped into small cylindrical particle when spheronization consisting of stating cylinder and rotating friction plates. When extruded

product broken into spherical particle with the help of frictional force so this technique is also known as extrusion and spheronization. As shown in fig. 3.

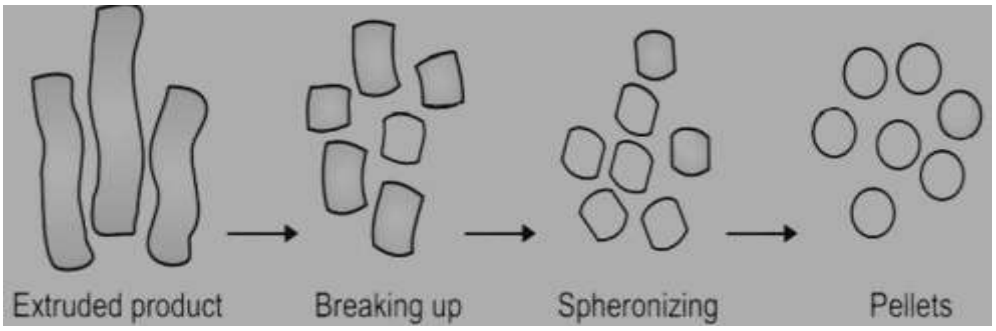


Figure 3: Spheronization.

PROCEDURE

Starting Material

The nature of the starting material influences the size, hardness and sphericity of theparticle, as well as the release rate of the loaded drug. The material used in theformulation causes difference in pellet quality produced from different compositions. The use of similar products manufactured by different suppliers also showed changesin the characteristics of the pellet produced. Pellets prepared with three types of microcrystalline cellulose (MCC) from different manufacturers features differences insize and roundness even though processed under the same condition.[12,13,14]

b) Extruders

According to Reynolds and Rowe an axial screw extruder produces a denser materialthan a radial screw extruder. The latter has a higher output but also produces butshows greater heat production during the processing. Pellet quality is dependent onthe thickness of the screen and the diameter of the perforations. A thinner screenproduced a rough and loosely bound extrudate, whereas a thicker screen form smooth and well-bound extrudate because of the higher densification of the wet mass. Similarly, the diameter of the perforations determines the size of pellets- a largerdiameter in the perforations will produce pellets with a larger diameter under similarprocessing conditions.[7,8,9,10]

c) Extrusion Speed

The output from the extruder depends on the extrusion speed. The increasing speedcauses at surface impairments, such as roughness and shark-skinning which leads topellets with lower quality because the extrudate will break up unevenly during the initial stages of the

spheronization process, resulting in a number of fines and a wideparticle-size distribution.[9,10]

d) Extrusion Temperature

The extrusion cycle during the operation may lead to rise in the temperature which could cause the granulating liquid to evaporate from the granules which causes difference in the quality of the extrudate right in the beginning of the batch itself. Extrusion temperature control is especially taken into the consideration when processing a thermolabile drug formulation.[10]

e) Spheronizer Specifications

Pellet quality is also dependent on Spheronizer load which affects the particle-size distribution, bulk and tap density of final pellets. The increase in the Spheronizer speed and a low Spheronizer load will result in wider particle size distribution with less yield of pellets, whereas it increases with extended spheronization time at a higher spheronization load. 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.[15,16]

2. Hot melt Pelletization technique

Principle: - it is a process by which or involve using heat and shear to make pellets from molten material (liquid material or substance). This process can be used for the making of pellets for a variety of material, including: starch, adhesives and drugs.

PROCEDURE

The pellets were produced with the tangential spray technique in a rotor granulator (Glatt GPCG3, Glatt GmbH, Dresden, Germany) equipped with a powder feeder (PF). Powder mixtures of CW and HPMC K100M were prepared at various ratios using a laboratory blender (Erweka AR 402, Erweka GmbH, Germany). About 500 g of the powder mixture were inserted into the product chamber and a specific quantity of the same mixture was added via the PF, B while spraying the melted material through a 1.2mm binary nozzle. The inlet air temperature was set at 60 C, resulting to product temperature between 52 and 55 C.

The atomizing air was preheated at 85 C and its pressure was set at 3 bar. Gelucire 50–13 was selected as the binding material (BM) and it was melted at 80 C, using a heater circulator and a jacketed glass vessel. This system allowed for the continuous monitoring and control of the

spraying rate. The addition of the melted material was performed through a tube heated at 100 Preventing its solidification prior to spraying. After the completion of spraying and powder feeding, additional spheronization was carried out, while the product chamber was gradually cooled to room temperature. In all experiments the total duration of the manufacturing process did not exceed 30min.

Estimation The Product Yield

After the completion of the process the product was passed through a 2.0 mm sieve and all agglomerates were removed. Theremaining product was weighted and the percentage yield of the process was calculated, with reference to the amount of the raw materials used for each experiment.

3. Layering Technique

It includes 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. Drug particles are dissolved or suspended in the binding liquid. Fig.4. A binder solution is first sprayed onto previously prepared inert seeds followed by the addition of powder.[27,28,29]

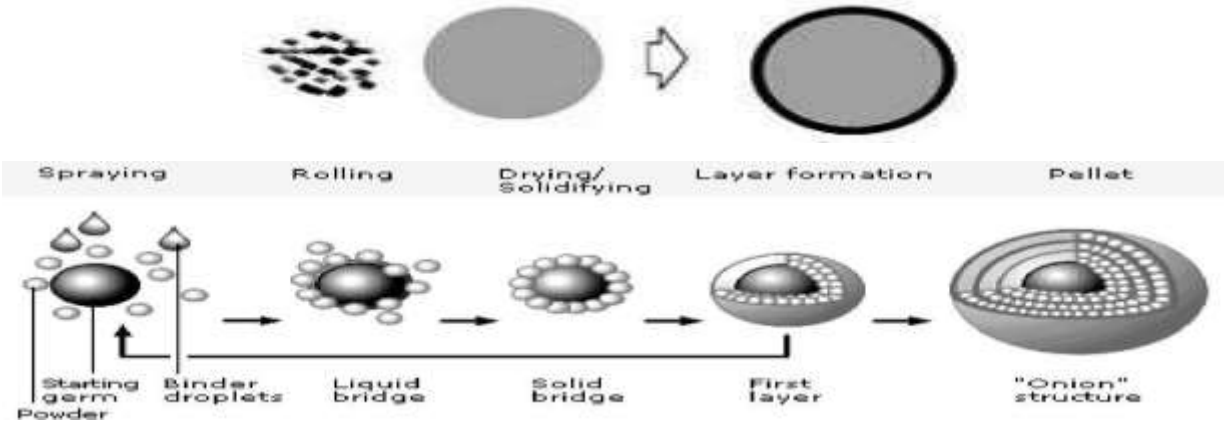


Figure 4: Layering Technique.

PROCEDURE

This process is classified into two types: -

a) Powder layering.

b) Solution or suspension layering

- **Powder layering:** - This technique involves the deposition of successive layers of powdered drug and excipients or both on performed cores or nucleus with the aid of a binding liquid. the binding solution and the finely milled powder are added simultaneously

in a controlled manner to maintain equilibrium. In the initial steps the drug particles are bound to the starter seeds to form the pellets using a liquid bridge from a spray binding liquid. the liquid bridges are replaced by solid bridges during solidification. This treatment leads to the formulation of successive layers of a drug and the binder solution until the desired pellet size is reached.

Therefore, now a day, a tangential spray granulator and a centrifugal bed granulator are used.

- **Solution and suspension layering:-** This technique involves the deposition of successive layers of solution and /or suspension of drug substances and binders or starter seeds, which may be inert materials or granule crystals of the same drug. In this technique, drug particles and other components are dissolved or suspended in the binding liquid. the droplets impinge on the starter seeds or cores andspread evenly when the solution or suspension is sprayed onto the nuclei. During drying, solid bridges are formed between the nuclei and the initial layer of drug substances and the between the successive layers of drug substances or polymer layer is formed.

4. Compression technique

Pellets here can be produced by allowing droplets of liquid formulation such as solution, suspension or emulsion to come in contact with liquid nitrogen at -160C in

- Apply Pressure: The machine compresses the powder into pellets at apredetermined force. Monitor parameters like pressure and duration.
- Ensure Uniformity: Check for consistency in pellet size and density.

5. Spray drying technique

In this process the highly spherical and dry particles are generated, the drug molecules in solution or suspension form are sprayed, with or without excipients into the hot air stream. This process is generally used to improve the rate of dissolution and also increase the bio-availability of poorly soluble drugs.[30,31]

PROCEDURE

Spray drying can be effectively utilized for pellet formation by converting liquid feedsinto solid granules or pellets. Here's a detailed look at the process.

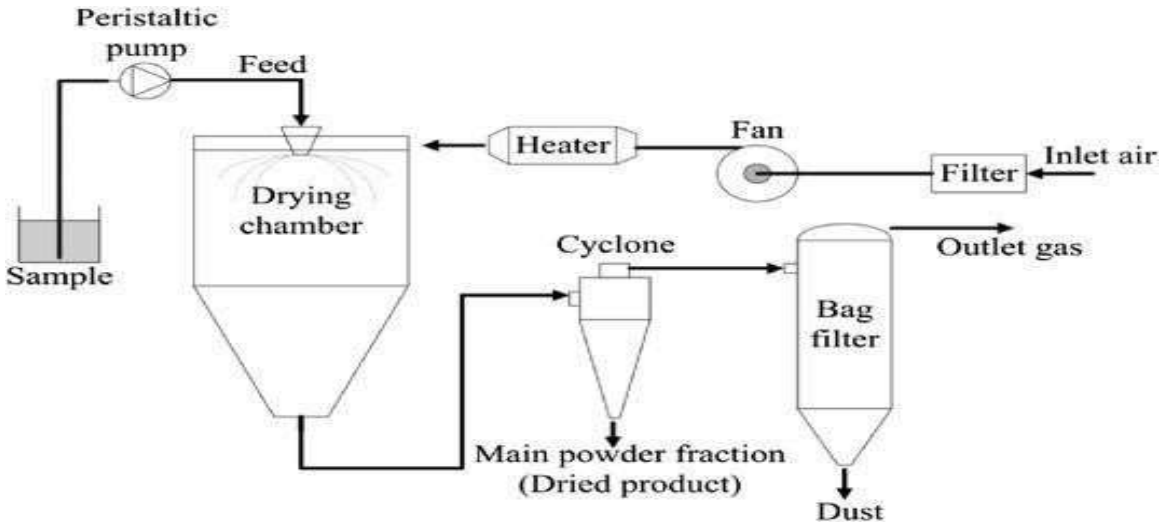


Figure 5: Spray Dryer.

Process Steps

1. **Feed Preparation**

- Create a liquid feed solution or suspension containing the material to be pelletized, such as polymers, nutrients, or active compounds. This often includes binders or additives to enhancepellet properties.

2. ***Atomization***

- The liquid feed is atomized into fine droplets using a spray nozzle. This is critical for ensuring uniformity in the size and shape of the resulting pellets.

3. ***Drying***

- The atomized droplets are introduced into a hot air chamber. As they travel through this chamber, moisture evaporates rapidly, leading to solidification. The drying temperature andair flow rate are crucial parameters that influence the final pellet characteristics.

4. ***Particle Formation***

- During drying, the droplets shrink and agglomerate to form solid particles. The drying conditions can be adjusted to control the size and density of the pellets.

5. ***Collection***

- The dried pellets are collected at the bottom of the spray dryer, typically using a cyclone separator or a bag filter to remove any remaining fine particles from the air stream.[32,33]

CONCLUSION

This review focused on the brief review on pellets, pelletization, factor affecting, equipment's, and evaluation parameter of pelletization techniques. Extrusion spheronization is a widely used method for producing spherical pellets, an aqueous system which requires drying which is a time-consuming process. In the past few decades pelletization technology has gained an increased interest within the pharmaceutical industry because of its simple design, high efficiency of producing spherical pellets & fast processing. In this review attempt has been done to outline general techniques of pelletization & to assess its importance in the development of a multiarticulate drug delivery system. In this review attempt has been done to outline various factors affecting the pelletization process. In this review we briefly discussed about the pelletization techniques for the standardization of the pharmaceutical industries.

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