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Pelletization in Pharmaceuticals: Comprehensive Insights for Optimal Design and Versatility

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Abstract: Pellets can be defined as small, free flowing ,spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and intended usually for oral Administration, manufactured by the agglomerates of fine powders or granules of bulk drugs and Excipients using appropriate processing equipment. Different types of techniques used to produce pellets are referred to as pelletization techniques. In relation to pharmaceuticals, pellets offer high degree of flexibility in design and development of oral dosage form. They offer desired dose strength, can be blended to deliver incompatible bioactive agents and can be blended to provide different release profiles. The most commonly use pelletization processes are Solution or suspension layering, Powder layering, Hot melt extrusion, High shear pelletization, Extrusion spheronization ,Freeze pelletization, Cryopelletization, Crystallo-co-agglomeration, Wet spherical agglomeration, Spherical crystallization etc. In present review we will be explaining widely used pelletization techniques especially are layering techniques includes powder layering and suspension or solution layering in detail with principle, methods and applications in pharmaceutical industries.

Keywords: Pellets, pelletization techniques, drug layering techniques, pellets coating Equipments, fluidize bed coater, etc.

INTRODUCTION : [1,2]

Pellets are small free flowing, spherical particulate, manufactured by the agglomeration of fine powder or granules. Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used today. Manufacturing of pellets using layering process such as solution layering, suspension layering or powder layering and extrusion-spheronization process have been used over the years. These processes have major limitation such as use of granulating liquid which causes stability problems during processing and storage.

Pellets offer a great flexibility in pharmaceutical solid dosage form design and development. They flow freely and pack easily without significant difficulties, resulting in uniform and reproducible fill weight of capsules and tablets. Successful film coating can be applied onto pellets due to their ideal spherical shape and a low surface area-to-volume ratio. The most important reason for the wide acceptance of multiple-unit products is the rapid increase in popularity of oral controlled-release dosage forms. Controlled-release oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time. With pellets, the above mentioned goals can be obtained through the application of coating materials (mainly different polymers), providing the desired function or through the formulation of matrix pellets to provide the desired release pattern.

Objectives:

The main objectives of given work are as follows;

a. to improve aesthetic appearance of products.
b. to achieve control release rate of drugs when coated with polymers.
c. to improve flow properties and flexibility in formulation development and manufacturing.
d. to reduces intra and inters subject variability of plasma profiles by reducing variations in gastric emptying rates and overall transit times.

Advantages :[2-6]

1) Improved appearance of the product and the core is pharmaceutically elegant.
2) It reduces localized concentration of irritative drugs.
3) It improves safety and efficacy of a drug.
4) Pellets ensure improved flow properties in formulation development
5) When formulated as modified release dosage forms, pellets are less susceptible to dose dumping than reservoir type single unit formulations.
6) Pellets are recommended for patients with difficulty in swallowing and dysphasia like in case of children and aged people.
7) Pelletization reduces intra and inters subject variability of plasma profiles by reducing variations in gastric emptying rates and overall transit times.
8) Pelletization produces spheroids with high loading capacity of active ingredient without producing extensively large particles.
9) Pellets exhibit better roundness than the commercial non-pareil seeds and have excellent flow and packing properties.
10) Pellets composed of different drugs can be blended and formulated in single unit dosage form that facilitates delivery of two or more chemically compatible or incompatible drugs at the same or different site in GI tract.

11) Incompatible drugs processed separately and mixed later, or pellets with different release mechanisms can be mixed to give a new modified release profile.
12) Pellets reduce peak plasma fluctuations and minimize potential side effects without appreciably lowering the drug bioavailability.
13) Pellets disperse freely in the GI tract and hence greater absorption of the active drug occurs.

Disadvantages :

1) The manufacturing of multiple unit dosage forms is more complicated and more expensive.
2) The filling into gelatin capsules is difficult to accomplish, especially in the case where different subunits are involved

PELLETIZATION TECHNIQUES :[7,8]

The term pellet has been used by a number of industries to describe a variety of agglomerates produced from diverse raw materials, using different pieces of manufacturing equipment. In the pharmaceutical industry, pellets can be defined as small, free flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment. The term also has been used to describe small rods with aspect ratios of close to unity. Pellets offer a high degree of flexibility in the design and development of oral dosage forms. They can be divided into desired dose strengths without formulation or process changes and also can be blended to deliver incompatible bioactive agents simultaneously and to provide different release profiles at the same or different sites in the GT tract.

Followings are the different types of pelletization techniques ; (9, 10,11,12)

1. Layering Techniques :

I. Powder Layering Technique
II. Suspension / Solution Layering Technique

2. Extrusion And Spheronization :

3. Spherical Agglomeration :

I. Liquid-Induced Agglomeration
II. Melt-Induced Agglomeration

4. Globulation :

I. Spray Drying
II. Spray Congealing

5. Cryopelletization :

6. Hot Melt Extrusion :

7. Freeze Pelletization :

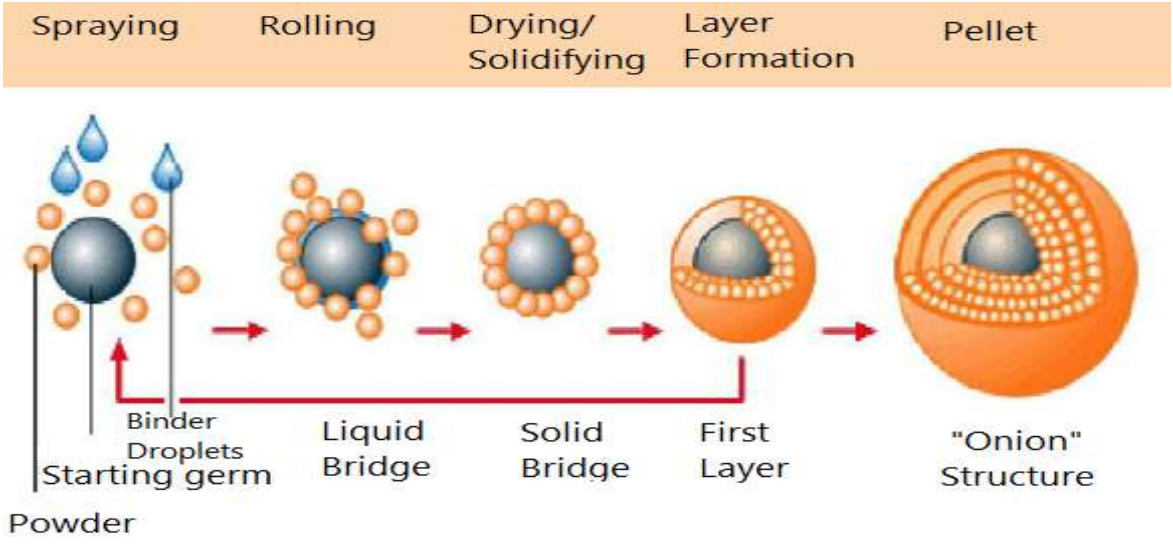
➢ **Drug Layering Techniques** :[13,14,15]

Layering processes are probably the most well controlled and straight forward pelletization techniques. 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. They are classified into two categories: solution/suspension layering and powder layering.

1. **Powder layering**
2. **Solution/suspension layering**

1. Powder Layering Technique :

In powder layering the binding liquid helps to form successive layers of dry powder of drug and other components on starting cores. In this technique the drug particles are bound to the starter seeds and subsequently to the forming pellets with the help of liquid bridges originated from the sprayed binding liquid. These liquid bridges are eventually replaced by solid bridges derived either from a binder in the liquid medium or from any material. Successive layering of the drug and binder solution continues until the desired pellet size is reached.



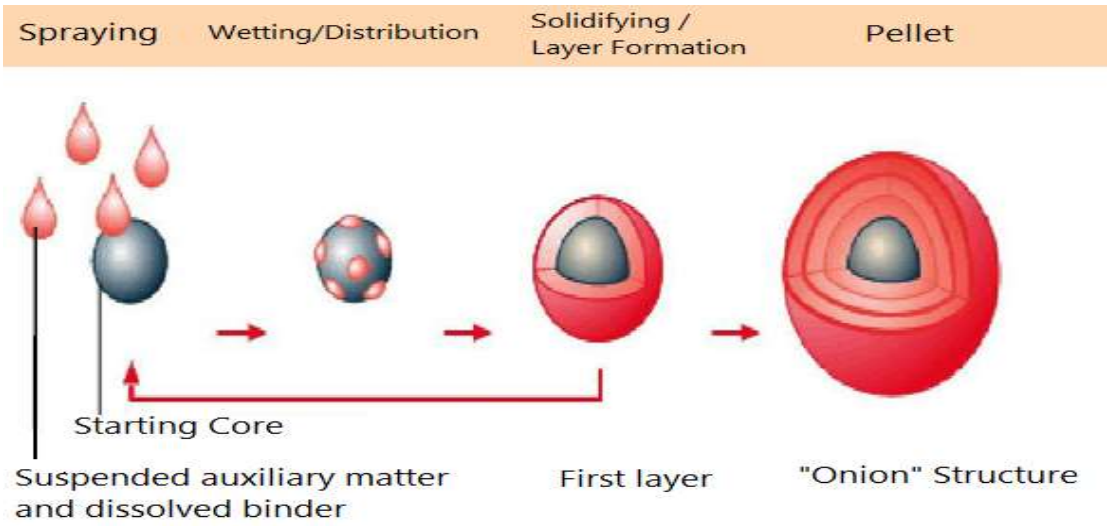
Powder Layering Technique

Converting powders to pellets can be achieved by a variety of techniques. Layering a suspension or solution of drug onto a seed material can result in pellets that are uniform in size distribution and generally possess very good surface morphology. These subsequently be coated for some type of controlled release for 24 h. This method involves the disposition of successive layers of solutions and/or suspensions of drug substances and binder on starter seeds, which may be inert materials or granules of the same drug. In principle, the factors that control coating processes apply to solution or suspension layering and as a result, require basically the same processing equipments. In the initial stages, the drug particles are bound to the starter seeds and subsequently to the forming pellets with the help of liquid bridges originated from the sprayed liquid. These liquid bridges are eventually replaced by solid bridges

derived either from a binder in the application medium or from any other material, including the drug substances, that is soluble in the liquid. Successive layering of the drug and binder solution continues until the desired pellet size is reached. Throughout the process, it is extremely important to deliver the powder accurately at a predetermined rate and in a manner that maintains equilibrium between the binder liquid application rate and the powder delivery rate. If the powder delivery rate is not maintained at predetermined equilibrium levels, over wetting or dust generation may occur and neither the quality nor the yield of the product can be maximized. Towards the end of the layering process, it is likely that fines may be generated owing to potential inter particle and wall-to-particle friction and appears in the final product thereby lowering the yield. The problem can be overcome if the application medium is sprayed on the cascading pellets at the end of the layering process to increase the moisture level at the pellet surface and facilate layering of the fines onto the pellets. The equipments like tangentianal spray equipment, centrifugal fluid bed granulator, rotary granulator are used for this purpose.[16]

2. Solution / Suspension Layering Technique :

In solution/suspension layering drug particles and other components are dissolved or suspended in the application medium. The droplets impinge on the started seed or cores and spread evenly as the solution or suspension is sprayed on the cores. Followed by drying phase allows dissolved material to crystallize and form solid bridges between the cores and initial layer of the drug substance and among the successive layers of drug substance or polymer. Continue this process until the desired layers of drug or polymer formed.



Solution or suspension layering technique

This method involves the deposition of successive layers of solution and/or suspensions of drug substances and binders on starter seeds, which may be inert materials or crystals/granules of the same drug. The factors that control coating processes apply to solution or suspension layering and require basically the same processing equipment. Consequently, conventional coating pan, fluid bed granulator and wruster coaters have been used successfully to manufacture pellets. The wruster coating process

which was invented about 30 years ago, had evolved through elaborate design modifications and refinement into ideal equipment for the manufacture of pellets by solution/suspension layering. The high drying efficiency inherent in fluid bed equipment, coupled with the innovative and efficient design features of the Wruster process, has allowed the machines to hold center stage in pharmaceutical processing technology. The disadvantage of the Wruster process is the inaccessibility of the nozzle. If the nozzles are clogged at any time during the layering process, the operation has to be interrupted and the spray guns must be removed for cleaning. The problem can be alleviated by screening the formulation or by using a spray gun with a bigger nozzle. Another aspect of the process that is challenging when multiple nozzles are used is the potential overlap of adjacent spray zones. Although the position of the nozzle is fixed, the spray zone overlap can be minimized using the air cap at the end of the spray gun. During processing, all the components of the formulations are first dissolved or suspended in an appropriate quantity of application medium to provide a formulation with the desired viscosity and is then sprayed onto the product bed. The sprayed droplets immediately impinge on the started seeds and spread evenly on the surface, provided the drying conditions and fluid dynamics are favorable. This is followed by a drying phase that renders dissolved materials to precipitate and form solid bridges that would hold the formulation components tighter as successive layers on the started seeds. The process continues until the desired quantity of drug substance and thus target potency of the pellets is achieved. Ideally, no new nuclei are formed, and the particle population remains the same. However, the sizes of the pellets increase as a function of time, and as a result, the total mass of the system also increases. Optimization of process variables is difficult for the successful development of a palletized product.[17]

Pellets Coating Equipments : [18,19,20]

Most of the coating processes use one of the three general types of equipments, viz;

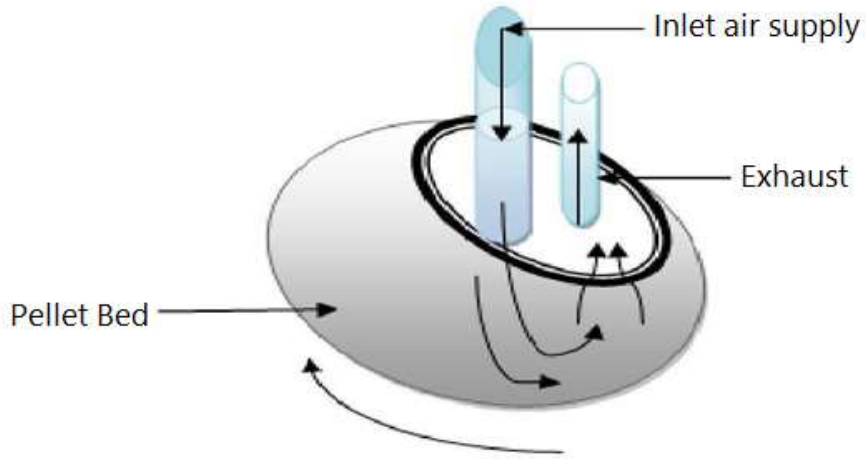
i. The conventional standard coating pan

ii. The perforated coating pan

iii. The fluidized bed coater

I. Conventional coating system:

The standard coating system consists of a round metal container installed at a small angle to the pedestal. The shell rotates around a horizontal axis using the engine, and hot air is supplied to the surface of the pellet and bed and dried through channels in the front of the channel tray. The coating solution is applied to the surface of the coating by spraying the components.[18]



Conventional coating pan

II. The perforated coating pan:

Neocota is an automated system for coating tablets and pellets. Neocota is a fully modern automatic coating system with a capacity from 500 to 1 kg. This model performs the following powerful tasks: tablet / pellet film layer; Refining film / granules from inorganic organic solvents; and enteric pellets. The main unit of the system is as follows. Loop vessels have perforations in the cylinder section. It is driven by a fire engine and variable speed drive. The supply of hot air from dry air and exhaust gases is controlled so that the coating system is facilitated by stainless steel plantations located on both sides of the perforated coating pan. Cylindrical enclosure with matching door and window. This single element tray is a stainless steel case that houses gearboxes, AC drives, power panels, hot air systems, exhaust systems and air devices. Pumps, automatic guns and flexible hoses.[18]

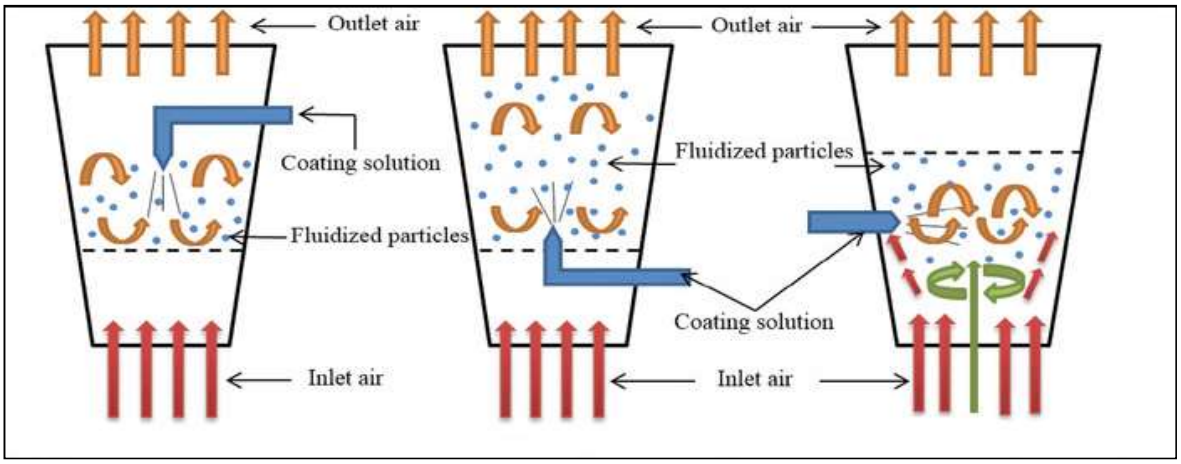
III. The fluidized bed coater: [19,20]

Fluidized bed processor is equipment that can perform multiple functions like coating, drying, granulation and pelletizing. It has highly efficient drying system and uniform, continuous product coating achieved. Ideal for a wide range of process applications includes coating, heating, drying, agglomeration and granulation.Protects product against moisture, light, air. Ideal for control release film coating, pellet granulation and hot melt coating. Applied to Specific manipulation of the particle surface characteristics. With fluid bed coating, particles are fluidized and the coating fluid sprayed on and dried. Small droplets and a low viscosity of the spray medium ensure an even product coating. Different types of fluidized bed processors include top spray coating, bottoms spray coating (Wurster coating) and tangential spray coating (Rotor pellet coating).

- **Top spray coating:-** This process is used to spray binder solution for powder granulation. Particles are fluidized in the flow of heated air, which is introduced into the product container via a base

plate. The binder solution is sprayed into the fluid bed from above against the air flow (counter current) by using nozzle. Air volume is adjusted to have the center of the particle stream very close to the nozzle. Drying takes place as the particles to move upwards in the air flow. It is preferred when a taste masking coating is applied, additionally suitable for the application of hot melt coating. Continuous spray coater is particularly suitable for protective coatings/ color coatings.

- **Bottom spray coating:-** The process is suitable for pellet suspension coating or film/sugar coating, particularly useful for a control release active ingredients. In this process, a complete sealing of the surface can be achieved with a low usage of coating substance. When the hot air flows through the bottom screen of container and coating column, it will generate the siphonage principle. Convection is created through the strong force from bottom toward top. The granules will then fall down and will be sucked into the coating column again, while the bottom spray gun will spray towards top to achieve coating purpose. As the particles continue traveling upwards, they dry and fall outside the Wurster tube back towards the base plate. Preferred for the application of modified release coatings to a wide variety of multi particulates and also suitable for drug layering when the drug dose is in the low to medium range.
- **Tangential spray coating (Rotor pellet coating) :-**This process is particularly suitable for pellet powder coating, suspension coating or film/sugar coating. In this process the cores are placed on the turntables and hot air is blown upward between the turntables and the granulation area. The passage of air causes the cores to roll on the turntables. At the same time, the coating solution is sprayed on the rolling cores through the pump and spray gun. The process involves simultaneous coating and drying of the cores, layer after layer, until the repeated actions achieve the desired coating thickness or granule size. It is suitable for the application of modified release film coatings to a wide range of multi particulate products, ideal for drug layering when the dose is medium to high and also useful as a spheronizing process for producing spheres from powders.



Top spray Bottom spray Tangential spray

Other Pelletization Techniques: [21,22,23]

- **Cryopelletization:**

In cryopelletization the pellets can be produced by allowing droplets of liquid formulation such as solution, suspension or emulsion to come in contact with liquid nitrogen at -160°C in which liquid nitrogen used as solidifying medium. The procedure permits instantaneous and even freezing of the material being processed due to the rapid heat transfer that occurs between the droplets and the liquid nitrogen. The required amount of liquid nitrogen for manufacturing a given quantity depends on the solids content and temperature of the solution or suspension being processed. The pellets are dried in conventional freeze dryers to remove water or organic solvents.

- **Freeze Pelletization:**

Freeze pelletization is a simple and novel technique for producing spherical matrix pellets containing active ingredients. In this technique a molten solid carrier along with a dispersed active ingredient is introduced as droplets into an inert and immiscible column of liquid. The technique involves less process variables and also offers several advantages over other pelletization methods, In terms of quality of pellets and process cost. The pellets produced by this technique are spherical in shape with narrow size distribution. Since the pellets are solid at room temperature, they do not require drying.

- **Extrusion and Spheronization :**

Extrusion spheronization was developed in the early 1960s as a pelletization technique. The extrusion-spheronization process is commonly used in the pharmaceutical industry to make uniformly sized spheroids. It is especially useful for making dense granules with high drug loading for controlled release oral solid dosage forms with a minimum amount of excipients.

- **Hot Melt Extrusion :**

Industrial application of the extrusion process dates back to 1930's. Wet mass extrusion is the most frequently used method for producing spherical pellets. Hot-melt extrusion is one of the most widely applied processing technologies in the plastic, rubber and food industry. Currently, more than half of all plastic products, including plastic bags, sheets and pipes are manufactured by this process. Recently melt extrusion has found its place in the array of the pharmaceutical manufacturing operations. This process is currently applied in the pharmaceutical for the manufacture of variety of dosage forms and formulation to modify drug release such as immediate and sustained release pellets, granules and tablets, transdermal passage of the drug and enhancing dissolution rates for poor water soluble drugs.

- **Globulation :**

Globuation technique mainly has two different types, viz **;**

- **Spray drying:**

This is the process in which the active ingredient in a suspension or solution is sprayed without the aid of heat flux to obtain dry particles and spheres. This method is commonly used to increase the dissolution rate and increase the bioavailability of less soluble drugs.

- **Spray congealing:**

This is the process of making a ball-sealed tablet by melting, dissolving or dissolving the active component of a molten resin, wax or fatty acid in an air chamber that is stored below the melting point of a component of the composition. In this process, direct and controlled release pellets can be produced in accordance with the physicochemical properties of the material and other formulation parameters

FACTORS AFFECTING PELLETIZATION TECHNIQUE : [24,25]

i. **Moisture content:** Moisture sticks to the powder, removes the wet mass and ferments to give a rounded shape. Higher moisture content leads to aggregation of the granules during sphering.

ii. **Rheological characteristics**: The rheological state of the wet mass determines the fluidity of the extruder. Optimal rheology conditions lead to excellent flowability, which depletes wet mass. Rudimentary aberrations lead to irregular and irregular extrusion.

iii. **Solubility of excipients and drug in granulating fluid:** The dissolved active ingredient is dissolved in the granulating liquid. Increasing the volume of liquid will cause the pelletization system of the pellets to overlap; an increase in the wetting liquid will increase the plasticity, but will lead to the formation of a sticky mass.

iv. **Composition of granulating fluid**: Besides water, alcohol, water/alcohol mixture, ethyl ether, dilute acetic acid, isopropyl alcohol is also used as a granulating liquid. According to researcher like Millili and Schwartz, a minimum of 5% of granulation liquid have to be water in order to produce pellets containing Avicel pH (101) and theophylline.

v. **Physical Properties of starting material:** The nature and content of the raw materials, the filler properties of the materials and the particle size affect the pelletization process. The quality of the tablets depends not only on the ingredients, but also on different types of the same substances**.**

vi. **Speed of the spheronizer**: The speed of the spheronizer affects the size, stiffness, roundness and density of the granule. High speed has high roundness, low friction, smooth surface and high-pressure resistance**.**

vii. **Drying technique and drying temperature**: It is important to obtain the correct size, shape and fluidity of the pellets and to be reproducible and consistent in all batches. Differences in pellets size, form and flow cause differences in the physicochemical properties of the final dosage form and affect the therapeutic efficacy of the delivery system**.**

viii. **Extrusion screen:** The quality of the filter hole has a great influence on the quality of the extrudate ball. As the whole increases, the average granule size increases. Increasing the depth of the holes decreases in the presence of water on the extrudate surface, increases the extrusion strength and affects the particle size and shape distribution.

EVALUATION OF PELLETS:

1. Particle Size Distribution. [26]

In order to determine the particle size distributions of the prepared pellets containing lansoprazole, standard sieve method was used. Mechanical sifter with sieves between apertures 355-2000 μm were used by using all the amount of pellets prepared. The fraction collected on each of the sieves was calculated by the percentage value.

2. Surface Area.[27]

The surface area of pellets is obviously controlled by particle size, shape, porosity and, surface roughness and it is a very important parameter which can affect the release rate of pellets . There are three methods of measuring surface area of pellets.

Mathematical calculation: The surface area of the pellet can be calculated from the measurement of its diameter since the surface area is equal to πd2.

Gas adsorption: The volume of nitrogen that is adsorbed by the substrate contained in an evacuated glass bulb is determined at various pressures,and the results are plotted as P/V (Po-P) versus P/Po to generate a linear plot of the BET equation for adsorption of nitrogen on a substrate.

Air permeability: Because of the simple instrumentation and the speed with which determinations can be made,permeability methods are widely used pharmaceutically for specific surface determinations.

3. Shape and Sphericity. [28-32]

One of the most important characteristics of a pellet is its roundness. Several methods exist to determine the roundness: visual inspection of the pellets and classification into a group, one-plane-critical-stability (OPCS), being the angle to which a plane has to be tilted before a particle begins to roll; the ratio of the largest and the smallest diameter of a pellet; shape factors calculated by means of the projected area of the pellet and its perimeter measured with computer-aided image analysis.

4. Porosity.[33,34]

The porosity of pellets can affect the capillarity action of the dissolved drug and,consequently,influence the rate of release of drugs from the pellets.It also affects the film deposition and formation during coating. The pores can be analyzed, qualitatively, by scanning electron microscopy and, quantitatively, by mercury porosimetry.

5. Hardness and Friability. [35]

The hardness of the pellets can be correlated with the friability according to Reynolds (1970). It is necessary to attain acceptable hardness and friability of pellets that can withstand handling, shipping, storage and other processing such as a coating that pellets may be subjected to.Variation in the formulation and/or process of pellets, as well as variability in the raw materials, can potentially result in significant variations in the hardness and/or friability of pellets.Hardness and friability determination of pellets are recommended, just as they are for tablets.The determination of hardness is performed by measuring the force required to break a pellet of well-known diameter as the strength increases with

increasing diameter. The instrument such as the Khalpellethardness tester provides relative hardness values, and a friabilator may be employed for generating the friability index .

6.Flow Properties.[36-37]

Proper characterization is an important aspect of any dosage form design; flow property is one of them. The flow properties of pellets are determined to ensure a homogeneous filling of the pellets in the capsules.

7. Disintegration.[38-39]

Disintegration determines whether pellets disintegrate within a prescribed time when placed in a liquid medium under the prescribed experimental conditions. Disintegration is defined as that state in which no residue of the unit under test remains on the screen of the apparatus or,if a residue remains,it consists of fragments of disintegrated parts such as insoluble coating.If discs have been used with capsules,any residue remaining on the lower surfaces of the discs consists only of fragments of shells. The apparatus consists of a basket-rack assembly, a 1-litre beaker, a thermostatic arrangement for heating the fluid and a mechanical device for raising and lowering the basket in the immersion fluid at a constant frequency rate .One can easily find the detail procedure for performing the test and other details in official books (Pharmacopoeia).

8.Gastric Acid Resistant Test .[40]

Acid resistance test is a significant index of drug dissolution performance of enteric coated formulations. Model fraction of coated pellets was subjected for acid resistance test in USP dissolution test apparatus – II (SR-8, Hanson Research, and Chatsworth, USA). Weighed amount of pellets were placed in the vessel and test was carried out in 0.1N HCl for 1hr at 75 rpm. Lansoprazole released at 1hr in 0.1 N HCl was estimated as per method specified in USP. Minimal amount of drug release in this test is indicative of gastric acid resistance.

9.Scanning Electron Microscopy. [41,42]

Photo micro graphs were taken with a scanning electron microscope for visualization of spherocity of the pellets. Pellets were coated with platinum by means of a sputter coater to assure conductivity.

CONCLUSION:

Layering pelletization is very promising technique for the production of pellets and through which one can achieve attractive dosage form which assist to improve bioavailability of drug and reduction in dose. Layering or coating can be done by using different polymers in equipments like fluidized bed coater. This helps to retain pellets at gastic pH , prolong the release of drug and prolong effective blood levels to maintain fluctuation of peak plasma concentration. pelletization technique produces more spherical pellets and offers more advantages than granulation process. Thus pelletization represents an efficient pathway for novel drug delivery.

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