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A REVIEW ON PELLETIZATION TECHNOLOGY

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Abstract:

The pelletization process was first introduced in 1948, when the first product was released. This preformed dosage form is becoming more and more popular due to its very beneficial use, such as the simplicity of filling capsules due to its better flowability than that of ideal round pellets, increase drug clearance, analysis, ease of use; Permanent, controlled or site-specific drug delivery from layered pellets; Smooth packaging; Uniform distribution in the digestive tract; Irritation of the gastrointestinal tract is weak. Pellet compositions include a variety of methods, including drug stratification, spray drying, spraying, granulating, hot melt extrusion and low spheroidizing extruded spherical materials from unmodified sugar (starch or lactose) or microcrystalline cellulose balls Wet weight. This review provides current results for production and evaluation and implementation of spherical pellets. Extrusion spheronization, hot melt extrusion, freeze drying and protection from cold are discussed together with the requirements of the process formula. The quality assessment of the granules is described by the size, shape, surface morphology, specific surface, vulnerability, tensile strength and mechanical tests.

Keywords: *Pellets, Pelletization techniques, Coating Pan, Top Spay, Bottom Spray*

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INTRODUCTION:

Pellets can be defined as typically small, flowing, round or hemispherical solid particles with a size of approximately 0.5 to 1.5 mm and are usually oral powders consisting of finely dispersed coagulants or pharmaceutical materials and excipients.

Pelletization is one of the most effective methods in drug delivery systems with multiple drugs. The importance of pellets, such as formulations filled with hard gelatin capsules or compressed into disintegrating tablets, continues to increase, since the properties of many particles provide more pharmacological and technical advantages compared with conventional standard dosage forms. Traditionally, the term pellets has been used to describe a number of systematically generated aggregates that are geometrically obtained from different raw materials using different processing conditions. Produced primarily for pharmaceutical pellets and controlled-release dosage forms for oral administration Medications with gastrointestinal release or delayed or water-soluble properties of a specific drug delivery site. For this, coated pellets are introduced in the form of hard gelatin capsules or rolled pellets for the quick release of the contents of pellets in the stomach. As the drug delivery systems become more complex, the role of the pellets in the development and development of the drug increases. The composition of the dosage form with two doses, such as a tablet with a coating filled with a capsule or tablet, provides plasticity for the intended release profile. The safety and effectiveness of the composition is higher than that of other formulations. Pellets provide a high degree of flexibility in the design and development of oral dosage forms. They can be divided into the desired capacity without changing the composition or method and can be mixed and not mixed to provide particles with different release profiles in the same place or in different places in the biologically active agent or the digestive tract. In addition, pellets have many therapeutic advantages over conventional unit units, such as tablets and powder capsules. In the mouth, the pellets are usually freely dispersed in the digestive tract, and then maximize drug absorption, minimizing local irritation of the mucous membranes caused by various stimulant drugs, and reduce liver and interference due to fewer drugs available in the pellets.

Technological advantages :(1,2,3,4)

Uniformity of dosage: the coating technology and the technology of extrusion of pellets ensure the accuracy of drug delivery to the pellets,

The pellet have excellent fluidity.

- Avoid dust that increases process safety, because fine powder can cause dust explosion and health problems.
- The controlled release of pellets is based on an ideal surface-to-volume ratio, which provides an ideal shape for film coating.
- You can mix them to provide inappropriate physiologically active substances or to provide different parts of the digestive tract (GI).

Therapeutic advantages:

- Since pellets are limited to the gastrointestinal tract, they can be freely released during the gastrointestinal tract and the absorption of drugs.
- The distribution of spherical particles emerging from the digestive tract limits the local increase of the drug locally and avoids the stimulating effect of certain drugs on the gastric mucosa.
- Modified release systems from a plurality of particles are more susceptible to delivery ability than standard dosage forms.Because of this tremendous advantage,pelletization has become the subject of general engineering and new production approaches.

Disadvantages of Pellets:

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.

Ideal Characteristics of Pellets:

- Core or uncoated pellets are of uniform spherical shape and smooth surface with improved flow.
- High physical strength and integrity, good hardness and low friability for ease and superior.

DIFFERENT POLYMERS USED IN THE PELLETIZATION PROCESS (1)

Polymer used in pelletization	Formulation	Applications
Carbopol 974P,NF, Resin	Beads containing Weakly basic drugs	Slower release of the salts of weakly basic drugs
Crosscarmellose sodium or sodium starch glycolate.	Super-disintegrants in avicel pellets	Increase dissolution rate, increase the pellet micropore volume
Eudragit RS PO and RL PO	Polymer (with combination) based pellets.	Better characterization like elastic modulus of the pellets, surface characteristics, sphericity.
Eudragit RL 30D, RS 30D, NE 30D.	A multiple- unit floating drug delivery system	Prolong the gastric residence time and to increase the overall bioavailability of the dosage form
Gelucire.	Lipidic –matrix pellets	Controlled drug release
Methocel-E5 (HPMC) or AMB, Eudragit L 30D-55.	Enteric coated pellets	Improved film formation and polymer coalescence.
Microcrystalline cellulose, Ac-Di-Sol.	Floating pellets with bacterial antagonist.	Improving floating property.
Microcrystalline cellulose and hydroxypropyl methyl cellulose.	Pellets with water insoluble drugs in self-emulsified form	Controlling the drug release from the oral dosage forms.
Pectins or alginates	Polysaccharide gel coated pellets.	Oral administration of theophylline in the coated pellets

PELLETIZATION:

Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free flowing, spherical or semi-spherical units, referred to as pellets.

Pelletization Techniques/Principle of Pellets coating (5, 6,7):

The most widely used and studied assembly methods include spherization, powder coating and extrusion of a solution / suspension layer. There are other ways to make pellets. Some of them are,

1)Powder layering

2) Solution/Suspension layering

- **Powder layering (5)**

Powder coating includes storing a layer of pharmaceutical powder and a sequential filler on the core or core, formed using a binder liquid. As a rule, the process is carried out in a conventional pan to cover it. The main requirement of this method is that the product container must have a solid wall without perforations so that the dust under the duct is not lost before the powder is separated from the mass of the wet mass the dust is removed from the wet mass of the precipitated pellets.

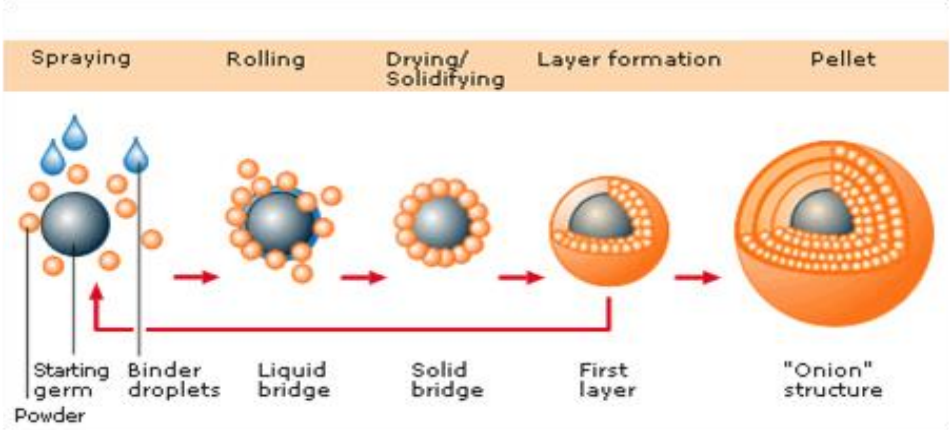

Figure 1: Principle for Powder layering technique(7)

- **Solution / suspension layering:(6)**

The solution / suspension layer consists of applying a continuous layer of a solution or suspension of a non-combustible binder and an inert material or a crystalline / granular drug of the same drug. In fact, coating methods are typically applied to methods of applying a solution or suspension. Consequently, in the production of pellets in accordance with this method, a conventional vessel for applying the coating Siedeschichten, the centrifugal granulator and the coating Wurster are consistently used. The efficiency of the process and the quality of the pellets produced are partly related to the type of equipment used.

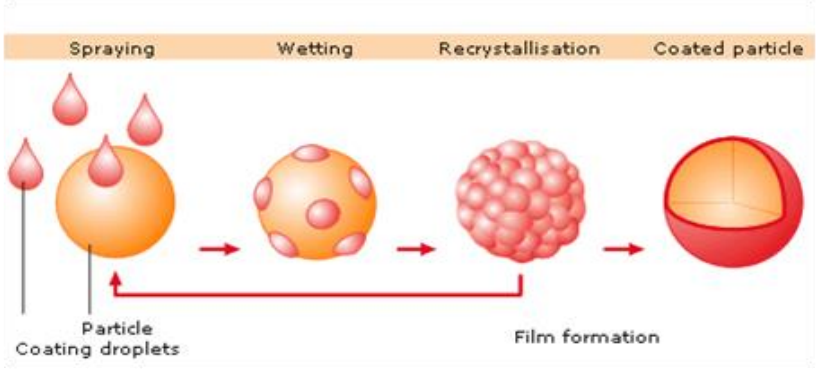

Figure 2: Principle for Suspension layering technique(7)

Coating Equipments/Pellets Coating Process (7,8,9,10)

Most of the coating processes use one of the three general types of equipment's.(7)

i. **The 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.

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.

III. The fluidized bed coater: (7)

Liquid coating technology provides a highly efficient coating process.

Advantages

1. The most important advantage of fluidized bed systems is the GMP standard, called the closed system.
2. The second advantage of a fluidized bed system is that it is possible to granulate and granulate not only the coating in the same machine.

A fluidized bed coating is a process that flows into a fluidized bed, providing a coating that covers the desired object to protect or change the behavior of the coating. The particle layer is a fluidized bed that binds the solid layers in the bed. In this case, the solution / suspension of the coating material is sprayed to place a layer on the surface of the liquid phase of the solid. Fluidized gas is also used to dry the solution deposited on the surface layer of the particles. There are significant differences in technology using fluidized bed technology.

For Examples: Fluids can be applied to fluidized particles in various ways, including tip, bottom, and tangential injection. For this product, each method may have characteristics different from the final product. The fluidized film layer can be divided into three groups.

- ✓ **Top spray**
- ✓ **Bottom-spray equipment**
- ✓ **Rotor, tangential spray**

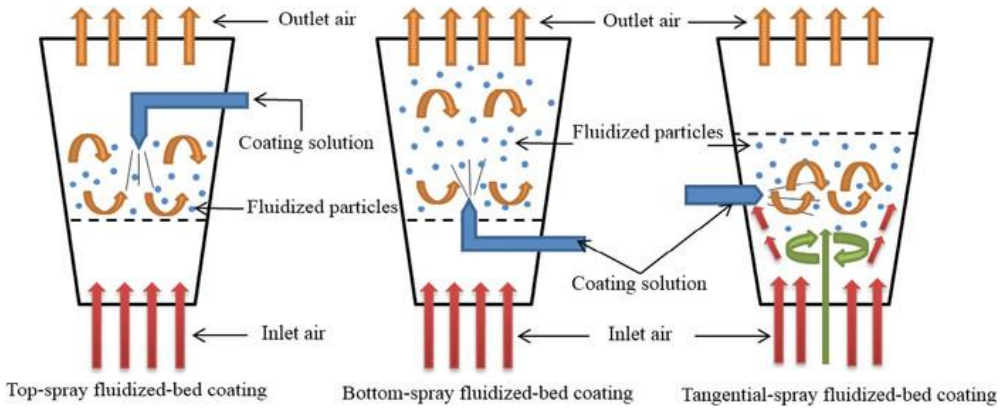

Figure 3: Types of fluid bed coater (7)

- ➢ **Granulator, Top spray:**

The top spray method is preferred when masking is applied and the granulation of the drug is combined with the excipient. It is also suitable for thermal layer. The expansion space of an algebraic particle slows down

particles in a jet fluid at high speed over a long period of time and minimizes aggregation. The nozzles are set to spray evenly before reaching the sprayer.

- **Bottom spray coating: (Wurster process, Make-GLATT) (9)**
  The Wurster machine uses a cylindrical container with a perforated plate. Inside the container is a second cylinder (compartment on the roof), raised slightly above the perforated plate at the bottom of the plate center. There is a spray nozzle on this barrier where the coating solution is released. The perforated plate has a large hole in the area below the dividing wall and a small hole in the other plate, with the exception of rings with large peripheral devices. This design allows pneumatic delivery of the main particles through the roof and lower barriers. The material passing through the barrier chamber receives a layer of coating material, which dries and returns to a semi-bubbling state in the expansion chamber. This material circulates quickly, absorbing the coating layer, dries in the expansion chamber, returns to the semi-liquid material, circulates quickly and gets a coating with each pass through the roof barrier. A ring with a large hole around the perforated plate prevents material from accumulating on the wall of the container. It is used to coat small particles, tablets and tablets.

- **Rotor, tangential spray:**
  This method is useful for applying modified release films on various multiparticulates. It is ideal to give medication when the dosage is moderate or higher. It is also useful as a ball production process.

  - **Pelletization by Extrusion and Spheronization: (11,12,13)**

The process involves first removing the extrudate from the powder, and then transforming the extrudate into balls using a spheater. Powder ingredients can be any kind of powder (medicinal powder, ayurveda powder, food powder, detergent powder, core powder, etc.). You can make a 0.5 mm ball.

Other pelletization methods:

Other pelletization methods, such as globalization, cold cryopreservation, compression and compression, are used only for the production of pharmaceutical pellets.

- **Globulation or droplet formation** consists of two related processes, spray drying and spray congealing.

  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.
- **Cryopelletization:**
  This is the process by which a liquid composition is converted into solid ball particles or balls in the presence of liquid nitrogen as a binder medium. The shape depends on the distance traveled before contact with liquid nitrogen.
- **Compression:**
  This is a kind of compression process for the production of pellets. A mixture of sealant or drug and adjuvant under pressure gives pellets of a certain size and shape. The compositional variables and processes controlling the quality of the pellets produced are similar to those used to make tablets.
- **Balling:**
  This is a pellet production process in which pellets are formed by continuous rolling and rolling into a fan, disc, drum or mixture. This method consists in converting particles, which are divided into spherical particles, by adding an appropriate amount of liquid.

Factors affecting Pelletization technique (14,15,16)

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. **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 (17,18,19)

Size distribution: The size of the pellets is necessary, since they have a significant effect on the kinetics of emission. In most cases, the particle size is determined by sieving with a filter shaker.

Sieving method: The obtained granules are approximated by a screening method. Screening method provides direct weight distribution. Chairs are located in nests with jagged edges. A sample (5 g) of dry sediment is placed on the upper sieve and mechanically mixed. The filter was repaired and shaken for 10 minutes. Weigh the pellets stored in each filter. As a rule, pellets receive a network number on screens that are transmitted or stored. This is expressed as the arithmetic average of the two screens.

Pellets shape: Round Pellets are the most important feature, and other definitions are used. Images of pellets and pellets mounted on optical microscopes mounted on Lucida cameras are hand-drawn on graph paper. The shape factor determines the value at which the image of the projected particle deviates from the circle, and is calculated around the projected area of the Pellets and its perimeter. For an acceptable pellets quality, the exponent / curvature coefficient should be between 1 and 1.2. For ideally rounded projected images, the form factor should be 1, and a value of 0.6 represents a good circle. Visual inspection of the pellets through a microscope and a stereoscopic microscope is an additional way to determine the shape of the pellets. The angle at which the plane must be inclined before the particle roll is called the field of critical stability. This is one of the most important ways to determine shape. The natural opening angle is an indirect measure of the circumference of the pellets and is a fixed funnel method, measured after measuring the flow of pellets through a specific opening of a certain height, and is calculated as the ratio between the height of the dipole and the radius of the pole.

Specific surface area: The area of the granules depends on the size and shape of the pellets. In particular, you need to know your surface when measuring film layers. Knowledge of surfaces important to open pellets, as the surface affects the

release of the active ingredient. The specific surface of the granules is determined by gas adsorption.

Hardness and Friability: The mechanical properties of the pellets are important for processing. During operation, transportation, storage and other operations, the pellets are removed and dust is generated. Changes in the composition of the pellets and / or processing of the pellets and the variability of the raw materials can significantly change the hardness and / or vulnerability of the pellets. The hardness of the pellets can be determined using the Kahl pellet hardness test, but may not be accurate. Pellet hardness is determined by combining a fragile Erkewa tablet or turbine mixer with a glass bead of a specific diameter for a certain period of time to cause wear and create a friction coefficient. Density can also be determined using a fluidized bed with Wurster inserts using an air stream.Thus, in addition to the reproducibility of morphological characteristics; it was found that the reproducibility of the distribution of particle size, surface density, density, stiffness and fragility is the basis for compositions and methods for producing granules.

Mechanical tests of Pellets (20,21,22,23):
Tensile Strength: The tensile strength of the pellets is determined using a traction device with 5 kg of liquid tool, and the granules are stretched to damage. Record the load and calculate the tensile strength of the damage load and the ball radius.

Cushing strength: A material strength tester was used to measure the compressive strength (the load required to destroy the granules) and the elastic modulus of 15 granules (fraction 850-1000 mm). 1 mm / min. The elastic modulus graph and force transfer are obtained by the computer system associated with the device.

Density: The density of the pellets (volume and cutting) can be affected by changes in the composition or process that may affect other processes or other factors, such as filling and packing characteristics in other processes and tablet presses with USP density controllers. The bulk density of the pellets can be measured using an automatic detonating device, but the actual density of the pellets can be measured using an air comparison pycnometer or a solvent transfer method.Density indicates the packaging characteristics of round pellets or seeds, which provide higher bulk density due to small internal particles.

Porosity: The porosity of the pellets affects the release of the drug from the pellets and affects the capillary action of the dissolved drug. The porosity of the pellets can be measured by mercury porosimetry. The porosity of the pellets can be qualitatively determined using image analysis using SEM and is rarely measured using 80 optical microscopes. The pore radius is determined by the Washburn equation. R = 2? [Cos?] / P, where? = 480 erg / cm3 ,? = 140o, r = pore radius, p = mercury penetration pressure. Therefore, the determination of the porosity of the pellets by mercury porosimetry is a highly recognized method and gives reproducible results.

Disintegration time: pellets are one of the key features of direct release pelletes. Huyghebaert et al. (2005) reported a coagulation test (USP Apparatus 3), in which Tomms and Kleinbud conducted a special tester for crushing tablets by inserting a special transparent tube of a certain diameter and length into a 710 mm filter above and below the pipe.

***In vitro* dissolution studies:** In vitro dissolution testing has been recognized as an important factor in drug development and quality assessment over the past 40 years. These tests were performed to test the behavior of various compositional separations in different elution media and to establish relationships between modified in vitro and in vivo modified granules. Drug release from solid dosage forms is often an important step in the in vivo absorption process and is used with in vivo / in vitro correlations to establish quality control parameters. The release of pellets depends mainly on the composition, hardness and size of the pellets and is determined by device I USP or device II USP. The drug release profile in the tablets also depends on the polymer and binder used, the solubility of the drug, the physical condition of the drug in the tablet, the drug loaded in the tablet, and the presence of the additive as a surfactant.In the case of fixed wax pellets, the drug release is reduced, and the solubility of the drug is increased to increase the hydrophobicity of the wax and the release of the drug.

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