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"Advancements in Extrusion/ Spheronization as a Granulation Technique:A Comprehensive Research"

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Abstract -: ***This article discusses the extrusion spheronization technique, covering granulation, extrusion, spheronization, and drying steps. It discusses factors influencing pellet quality, including formulation, equipment, and process. The article also details available characterization methods for pellets, including particle size distribution, surface area, shape, and specificity.***

Keywords: Different pellet formation techniques, Extrusion-Spheronization, Pellets.

I. INTRODUCTION

Extrusion and spheronization are processes used in the pharmaceutical industry to create desired shapes in pharmaceutical materials. Extrusion is a multiple-step process that creates uniformly sized spherical particles, while spheronization is a rapid and flexible method that creates small spheres or spheroids of varying diameters. Pellets are small, free-flowing units made up of bulk drugs and excipients, used for controlled drug delivery. Both processes offer advantages over other methods. Spheronization is a granulating technique used in pharmaceuticals to produce particles with essential properties. Advances in extrusion/spheronization equipment engineering have made it easier for scientists worldwide to use this method. Pellets offer flexibility in development, allowing for the incorporation of chemically incompatible ingredients into single capsules. They have a low surface area-to-volume ratio and are typically filled into hard gelatin capsules or tablets.

- OBJECTIVES

Extrusion spheronization techniques aim to produce pellets with uniform particle size, spherical shape, uniform density, smooth surface, enhanced drug release, improved flow properties, and customized formulations. These objectives ensure dosage uniformity, reproducibility, and improved patient acceptance in pharmaceutical formulations. The technique also enhances flowability, facilitating handling during manufacturing processes. By achieving these objectives, extrusion spheronization contributes to the development of high-quality pharmaceutical products with improved performance

II. MATERIALS AND METHODS

Extrusion spheronization is a process in pharmaceutical manufacturing to create spherical pellets for controlled -release formulations. It involves the use of Active Pharmaceutical Ingredient (API), excipients like binders, fillers, lubricants, disintegrants, plasticizers, and water or solvent. The API is the primary drug substance, while excipients help bind particles, fillers increase the formulation volume, lubricants prevent adhesion, disintegrants promote drug release, plasticizers improve flexibility, and water or solvent forms the wet mass.

Equipment:

- Extruder: A machine used to force the damp mass through a die to form cylindrical extrudates.

- Spheronizer: A specialized apparatus that rounds the extrudates into spherical pellets through mechanical agitation and friction.

- Drying equipment: Ovens or fluidized bed dryers are typically used to remove moisture from the wet pellets.
- Sieves: Used to ensure uniform particle size distribution of the final pellets

Fig.1 Spheronizer

III. EQUIPMENT DESCRIPTION AND PROCESS PARAMETERS

1. Dry mixing: is a crucial step in powder production, ensuring uniform distribution before wet granulation. This process is typically done in the same mixer used for granulation. However, if a continuous granulator is used, a separate mixer is required for dry mix.

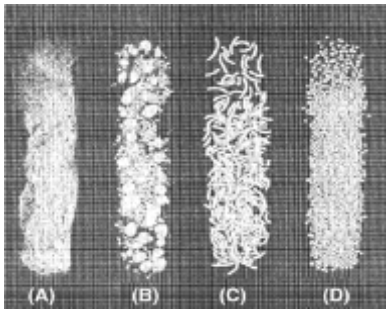
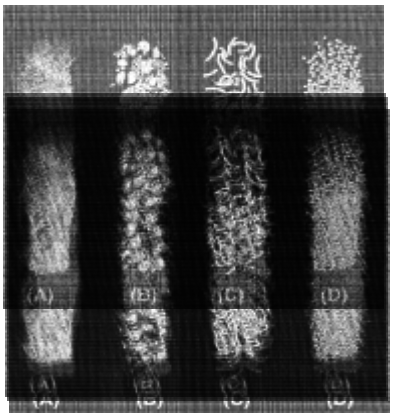


Figure 2: Product produced by the first four extrusion/spheronization process steps.

(A) Powder from dry mixing; (B) granules from granulation;
(C) extrudate from extrusion;and (D) spheres from spheronization.

2. Granulation: The granulation process produces spherical particles due to uneven distribution of materials with varying properties, leading to overwetting and dissolved components. The uniformity of sphere size and shape depends on the uniform distribution and composition of the granulating fluid. The second step is granulation, during which a wet mass having the requisite plasti-city or deformation characteristics is prepared. With a few exceptions, this step is similar to conventional granulation techniques used to produce product for com-pression. It is typically carried out in a batch type mixer/granulator; however, any equipment capable ofproducing a wet mass, including the continuous type, canbe used. Batchtype processors include planetary mixers, vertical or horizontal high shear mixers, and sigma blade mixers. Examples of continuous mixers include the Nica M6 instant mixer (26) and high shear twin screw mixer/extruders



3. Extrusion

The third step is the extrusion step which forms the wet mass into rod-shaped par- ticles. The wet mass is forced through dies and shaped into small cylindrical particles having a uniform diameter. The extrudate particles break at similar lengths under their own weight.

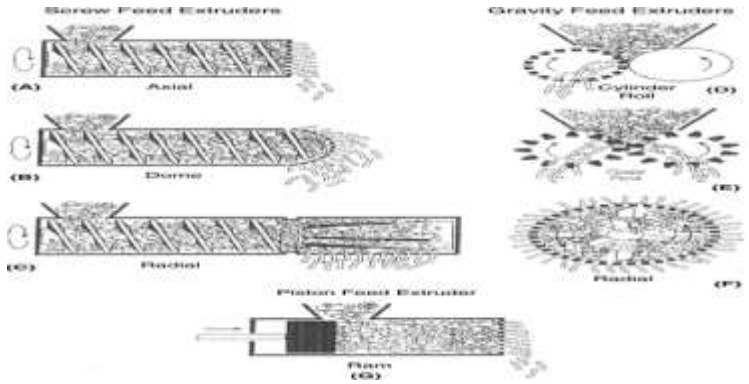


Figure 4: Schematic diagrams of extruder types used in extrusion/spheronization

4. Spheronization

The spheronization step is the fourth step in the extrusion/spheronization process, which involves a bowl with fixed sidewalls and a rotating bottom plate. The extrudate is rounded into spheres using frictional forces generated by particle-to-particle and particle-to-equipment interactions. Two geometric patterns are produced: a cross-hatched pattern and a radial pattern. The rate of spheronization varies, but both plates yield acceptable products. The extrudate is drawn to the walls of the extruder due to centrifugal forces. Under ideal conditions, the extrudate breaks into smaller, more uniform pieces, with each piece approximately equal to the diameter. This formation, known as a rope-like formation, is a critical indicator of the quality of the granulation or extrudate. If the disk rotates without movement, it indicates an over wet condition.

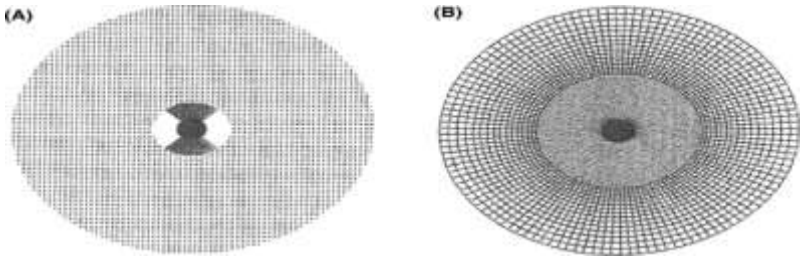


Figure 5: Spheronizer disks having two geometric patterns: (A) a cross-hatched pattern with the groves running at right angle to one another and (B) a radial pattern with the groves running radially from the center.

The extrusion process is a continuous process, while spheronization is a batch process. Two systems have been developed for commercial operations: a semicontinuous shuttle system and a cascade system. The shuttle system is used for uniform particles, like controlled release coating applications, while the cascade system is used for smaller size and shape uniformity. Both systems are designed to efficiently feed material to spheronizers.

The spheronizing system uses modified spheronizers to create a fixed volume spheronization zone. The product is fed from either the extruder or previous spheronizer, and as the charge volume grows, some product is discharged. The residence time depends on the feed rate, and the number of spheronizers depends on the desired outcome. Commercial manufacturing of pellets using the extrusion/spheronization process can be achieved by discharging the pellets in a continuous fluid bed unit.

Spheronization involves variables such as spheronizer size, charge, disk speed, and residence time. These factors can significantly influence the physical characteristics of the resulting product. Studies have shown that higher disk speed and longer residence time increase coarse fraction and mean diameter, while decreasing fine fraction.

5. Drying:

Drying techniques vary based on water removal rate, with tray drying being the slowest. Fluidized bed dryers have a more rapid drying rate due to higher air volumes and inlet temperatures. Column fluid beds are batch dryers, while deck type dryers offer continuous

processes. The drying process must be chosen based on desired particle properties, such as spheronization resistance and integrity. Tray drying in static beds can cause drug migration and recrystallization, impacting dissolution rates and film coating applications.

IV. GENERAL PROCESS DESCRIPTION

Extrusion/spheronization is a process requiring at least five units of operation with an optional sixth screening step. First, the materials are dry mixed (i) to achieve a homogeneous powder dispersion and then wet granulated (ii) to produce a suffi- ciently plastic wet mass. The wet mass is extruded (iii) to form rod-shaped particles of uniform diameter that are charged into a spheronizer and rounded off (iv) into spherical particles. The spherical particles are then dried (v) to achieve the desired moisture content and optionally screened (vi) to achieve a targeted size distribution. The process flow diagram,

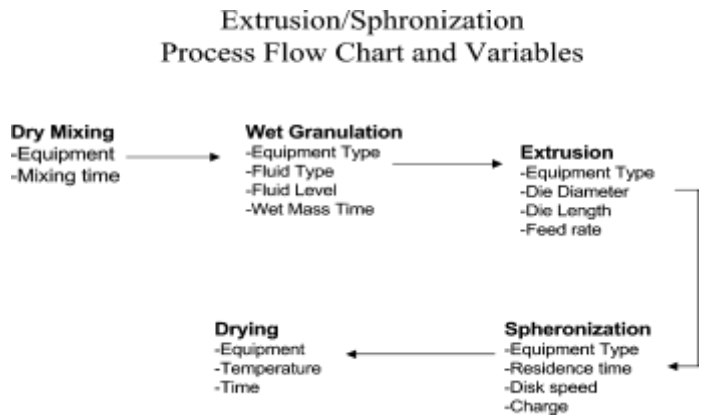
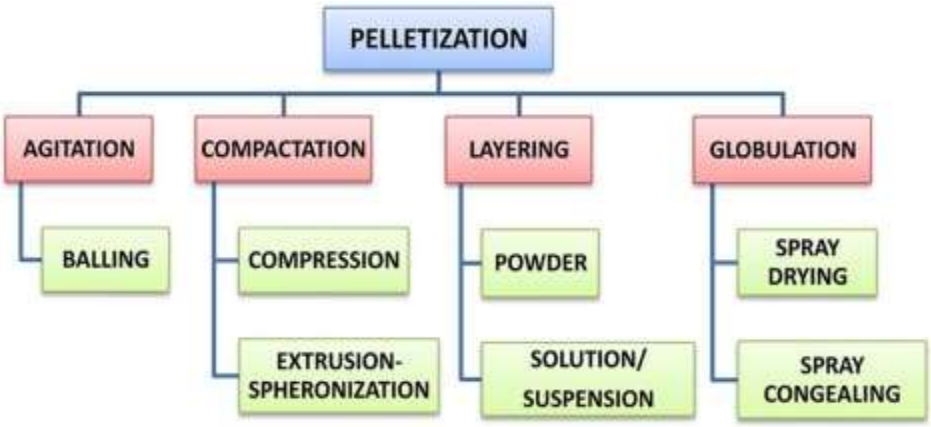


Figure 6: Process flow chart of the extrusion/spheronization process showing the process variables for each individual step

1)PELLETIZATION TECHNIQUES



V. RESULTS & DISCUSSION

In extrusion spheronization techniques, various readings and measurements are taken throughout the process to monitor and control key parameters. Some of the readings commonly taken include:

1. Extrusion Parameters: This includes readings such as screw speed, barrel temperature, and extrusion pressure, which are critical for controlling the extrusion process and ensuring the proper formation of the extrudate.

2. Spheronization Parameters: Readings such as spheronization speed, spheronization time, and spheronization load are monitored to control the tumbling action in the spheronizer and achieve the desired pellet size and shape.

3. Moisture Content: Moisture content readings are taken before and after drying to ensure that the pellets have the appropriate moisture content for stability and storage.

4. Particle Size Distribution: Particle size analysis is conducted to measure the size distribution of the pellets and ensure uniformity and consistency in size.

5. Density Measurements: Readings such as bulk density, tapped density, or true density may be taken to assess the density of the pellets, which can impact factors such as flow properties and dosage uniformity.

6. Drug Content: Samples of the pellets may be analyzed to ensure uniform distribution of the active pharmaceutical ingredient throughout the formulation.

These readings are essential for process optimization, quality control, and ensuring that the pellets produced meet the desired specifications for pharmaceutical applications.

Table 1 : Results for evaluation parameters of tablet

Parameters	Pre marketed	Post marketed
Hardness	4.2	4.1
Friability	0.48	3.38
Disintegration	0.45	1.0
Weight variation	0.8	0.4
Dissolution	106 (6 min)	98.19 (6 min)

Table 2 : Reading for extrusion -spheronization process

Parameter	Reading	Measurement Unit	Purpose
Extruder Screw Speed	50 rpm	Revolutions per minute (rpm)	Controls the rate of extrusion of the wet mass through the extruder.
Barrel Temperature	60°C	Degrees Celsius (°C)	Maintains the temperature of the wet mass to ensure proper extrusion.
Extrusion Pressure	100 bar	Bars (bar)	Indicates the pressure applied during extrusion, affecting the density of the extrudate.
Spheronization Speed	300 rpm	Revolutions per minute (rpm)	Controls the speed of the spheronizer, influencing the size and shape of the pellets.
Spheronization Time	5 minutes	Minutes (min)	Specifies the duration of the spheronization process.
Moisture Content	3% before drying, 2% after drying	Percentage (%)	Determines the moisture content of the pellets before and after drying.
Particle Size Distribution	Mean diameter: 1.5 mm	Millimeters (mm)	Analyzes the size distribution of the pellets to ensure uniformity.

In a discussion of the extrusion spheronization process, several key points are typically addressed:

1. Process Overview: An introduction to the extrusion spheronization technique, explaining its purpose and basic principles.

2. Equipment: Description of the equipment involved, including the extruder and spheronizer, and their functions in the process.

3. Formulation: Discussion of the formulation ingredients, including the active pharmaceutical ingredient, excipients, and binders, and their roles in pellet formation.

4. Process Steps: Detailed explanation of the steps involved in extrusion spheronization, from wet mass preparation to extrusion, spheronization, and drying (if necessary).

5. Parameters and Controls: Explanation of the critical process parameters such as screw speed, barrel temperature, spheronization speed, and time, and how they are monitored and controlled to achieve the desired pellet characteristics.

6. Quality Considerations: Discussion of quality control measures, including tests and readings taken during the process to ensure the quality, uniformity, and consistency of the pellets.

7. Applications: Overview of the pharmaceutical applications of extrusion spheronization, such as controlled-release dosage forms, improved flow properties, and uniformity of drug formulation

CONCLUSION

Extrusion/spheronization is a versatile process that produces unique physical properties in granules or spheres. It has potential applications in immediate and controlled release, but requires careful understanding of desired properties and formulation variables. Statistical experimental design is recommended for formulation and process development. New technologies like hot melt extrusion and spheronization are gaining Interest in pharmaceutical drug delivery for improved taste masking, Solubility, and bioavailability.

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