



Enhancement Of Solubility Of Class IV Drugs By Using Spheronization Technique (Furosemide)

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ABSTRACT: -Extrusion/spheronization is a multistep process that results in uniform particles. Many techniques are now widely used in the pharmaceutical industry, Extrusion and spheronization are one of them. It is often used as a way to create different products for immediate release and controlled release. Its main advantage over other methods of producing drug-loaded spheres or pellets is the ability to incorporate high levels of active drugs without producing large particles. Spheronization techniques used to produce pharmaceutical pellets. The pellets with specific characteristics were obtained with each production technique. The class IV drug of BCS classification exhibits many characteristics which may affect oral and per oral delivery, such as low aqueous solubility, poor permeability, low absorption leads to low and variable bioavailability. Preparation of pelletised dosage form done by number of techniques including drug layering on nonpareil sugar or MCC (micro cellulose) beads, spray drying, spray congealing, roto granulation, hot melt extrusion and spheronization low melt materials or extrusion spheronization of a wet mass. In this review we studied about various stages of spheronization.

KEYWORDS: - Spheronization, Controlled Release, MCC,

INTRODUCTION: -The concept of multiparticulate dosage forms was introduced in the 1950s, and with the increasing use of controlled-release (CR) oral formulations, there has been interest in their preparation in recent years. *1

Extrusion spheronization appears to be the best method for the approval of many potent drugs with high bacterial toxicity. It also has excellent medical utility due to its advantages of high loading capacity of active ingredients, narrow particle size distribution, and cost-effectiveness. *²

Oral multiparticulate drug systems (e.g. tablets, granules) provide biopharmaceutical quality in terms of more uniform and predictable drug distribution in the intestinal tract compared to unit dosage form. Extrusion spheronization is one of the most widely used techniques in the production of beads and pellets to promote and control the release of drugs or to alter their distribution. *³

The history of granulated dosage dates back to the 1950s when the first products were introduced to the market. Since then, dosage forms have evolved due to the better properties of the pellets, the ease of filling the capsules, the improvement of the simple procedure combination of the composition; even distribution in the digestive tract. *⁴

Hot melt extrusion (HME) is a process widely used in the plastics industry for the production of tubes, pipes, wires, and films. For pharmaceutical systems, this method has been used to prepare granules, tablets, and delivery systems. HME does not use water or solvents and requires only a few steps, making the process simple, efficient, and continuous. The intense mixing and stress during processing cause suspended chemicals to disperse in the polymer melt, allowing fine particles to be dispersed more efficiently. *⁵

Biopharmaceutical classification system (BCS) class IV drugs (low-solubility low-permeability) are generally poor drug candidates, yet, ~5% of oral drugs on the market belong to this class. Furosemide was found to be a low-solubility compound. Log D of furosemide at the three pH values 6.5, 7.0, and 7.5. *Furosemide, being a potent loop diuretic used in the treatment of congestive heart failure and edema. Due to its low solubility and permeability, FSM is known for exhibiting poor oral bioavailability. *⁶

MATERIALS AND METHODS:

Spheronization involves various stages, mentioned as follows- The first section covers the different steps in the pellet process, such as granulation, extrusion, spheronization, and drying. The second section shows the disadvantages that affect the quality of pellets, including the formula (moisture content, granulation fluid, excipients, drugs), equipment (mixer, extruder, brush plate, extrusion screen), and process (extrusion speed, extrusion screen), rounding machine load, rounding time, rounding speed, and drying method) are discussed. The last section describes the methods that can be used in characterization (particle size distribution, surface area, shape and surface, porosity, density, hardness and friability, flow energy, fragmentation, and dissolution). *⁷



Fig. 01 Spheronizer

The particles are then obtained through the extrusion/spheronization process and their physical strength is measured by measuring particle size, density, porosity, total strength, residual water after drying and photography.^{*7} The results were first analyzed by variance analysis to determine the main related factors. Screw speed, number of die holes, friction plate speed and spheronizer temperature affects on the pellet properties of shape, size, size distribution, tensile strength and drug release. The pellet properties are affected by the process parameters and the active pharmaceutical ingredient used.^{*8}

BCS CLASSIFICATION:-

Based on the BCS, drugs are classified into four categories according to their solubility and permeability properties as follows; high solubility–high permeability (class I); low solubility–high permeability (class II); high solubility–low permeability (class III); and low solubility–low permeability (class IV).

Class	Permeability	Solubility	Examples
I	High	High	Metoprolol
II	High	Low	Neteglinide
III	Low	High	Cimetidine
IV	Low	Low	Hydrochlorothiazide

BCS class IV drugs (*e.g.*, amphotericin B, furosemide, acetazolamide, ritonavir, paclitaxel) exhibit many characteristics that are problematic for effective oral and per oral delivery. Some of the problems associated include low aqueous solubility, poor permeability, erratic and poor absorption, inter and intra subject variability and significant positive food effect which leads to low and variable bioavailability.^{*9}

Furosemide (FSM) is a biopharmaceutical classification system (BCS) class IV drug, being a potent loop diuretic used in the treatment of congestive heart failure and edema. Due to its low solubility and permeability, FSM is known for exhibiting poor oral bioavailability.^{*10}

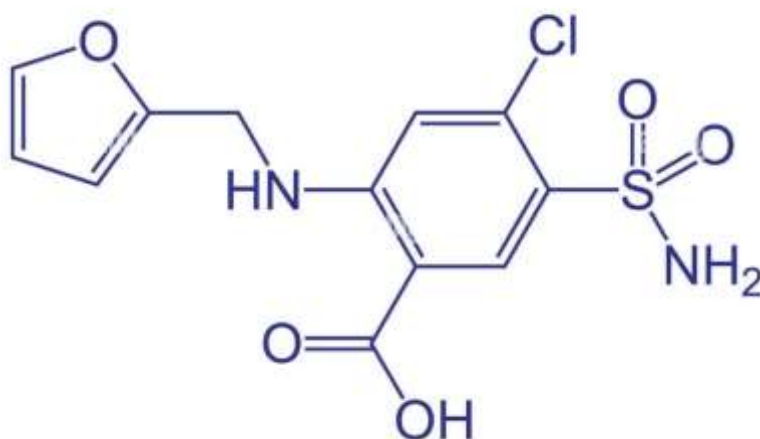


Fig. 02. Structure of furosemide

Solubility:-

The solubility is defined as a maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature.

Definition	Parts of solvent required for one part of solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
slightly	100-1000
Very slightly soluble	1000-10,000
Insoluble	>10,000

FACTORS AFFECTING THE SOLUBILITY:-

- 1.Nature of solute and solvent.
- 2.Particle size
- 3.molecular Size.
- 4.Temperature.
- 5.Pressure*^{11,18}

METHODS FOR SOLUBILITY ENHANCEMENT;-

A. Solid Dispersion

In this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug. Solid dispersion techniques can yield eutectic (non molecular level mixing) or solid solution (molecular level mixing) product.

B. Co solvency

The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as cosolvents. CoSolvents can increase the solubility of poorly soluble compounds several thousand times compared to the aqueous solubility of the drug alone

C. Super critical fluid method:[SCF]

It is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research

D. Particle size reduction method

The bioavailability intrinsically related to drug particle size. By reducing particle size, increased surface area improves the dissolution properties. Particle size reduction, it is done by milling techniques using jet mill, rotor stator colloid mills etc. Not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

E. Microemulsions

Microemulsions have been employed to increase the solubility of many drugs that are practically insoluble in water, along with incorporation of proteins for oral, parenteral, as well as percutaneous / transdermal use*^{12,17}

Spheronization process:-

Hot-melt extrusion (HME) is a widely applied processing technique used in the plastics industry to produce tubes, pipes, wires and films. For pharmaceutical systems, this method has been used to prepare granules, sustained-release tablets and transdermal drug delivery systems (Aitken-Nichol et al., 1996, Repka et al., 1999, McGinity et al., 2000). HME does not require the use of water or solvents and few processing steps are needed, making the process simple, efficient and continuous. The intense mixing and agitation during processing cause suspended drug particles to deaggregate in the polymer melt, resulting in a more uniform dispersion of fine particles.*^{13,15}

Pelletized dosage forms can be prepared by a number of techniques, including drug layering on nonpareil sugar or microcrystalline cellulose beads, spray drying, spray congealing, rotogranulation, hot-melt extrusion, and spheronization of low melting materials or extrusion-spheronization of a wet mass.*^{14,16}

This process is primarily used as a method to produce multi-particulates for controlled release application. It is a multiple step process involving at least 5 steps capable of making uniform sized spherical particles.

1. Dry mixing of materials to achieve homogeneous dispersion.
2. Wet granulation of the resulted mixture to form wet mass.
3. Extrusion of wet mass to form rod shaped particles.
4. Rounding off (in spheronizer)
5. Drying These dried rounded particles can be optionally screened to achieve a targeted mean size distribution. describes schematically the steps involved in the extrusion spheronization process*^{19,20}.

Conclusion:-

In this review, we studied about the different methods and process used during spheronization. solubility of Furosemide, class IV drug according to BCS classification, having low solubility and low permeability, can be enhanced by spheronization technique. It is a novel technique to improve solubility of low soluble drugs by formulation of spherical pellets.

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