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Extrusion Spheronization –A Review

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Abstract: Compared to single-unit dosage forms, oral multiparticulate drug-delivery systems (e.g. pellets, granules) offer biopharmaceutical advantages in terms of a more even and predictable distribution and transportation in the gastro-intestinal tract. There are different pelletization and granulation techniques available to prepare drug loaded spherical particles or granules. Extrusion Spheronization is one of them and utilized in formulation of beads and pellets. Limitations related to bioavailability and site specific drug delivery can be over come by this technique. Extrusion spheronization is widely applied method for the production of multiparticulates, like pellets and beads, for the oral controlled drug delivery system. Today this technology has gained attention because of its simple and fast processing. Extrusion spheronization is widely utilized in formulation of sustained release, controlled release delivery system. This article discusses about the extrusion spheronization process and its application in pharmaceutical industry as well as focuses on modified process called as melt extrusion process utilized for formulation of sustained release tablets, transdermal delivery system and transmucosal delivery system in pharmaceutical industry.
Key words: Extrusion Spheronization.

Introduction

Controlled and sustained release of drug application within the pharmaceutical industry require consistent smooth surface with a narrow size distribution, to ensure uniform coating and accurate free flow of granules for filling operations (like capsule filling), and this can be achieved by extrusion spheronization technique. It is also possible to prepare a sustained release pellets without coating of the pellets by extrusion spheronization process.

The main objective of the extrusion spheronization is to produce pellets/spheroids of uniform size with high drug loading capacity. Extrusion spheronization is a multiple process of wet mass extrusion followed by spheronization to produce uniform size spherical particles, called as spheroids, pellets, beads or matrix pellets depending upon the material as well as process used for extrusion spheronization[1]. Extrusion Spheronization has been used in agrochemicals, detergent additives, sweeteners, food and now it is used in pharmaceuticals. Extrusion spheronization is primarily used for the production of multiparticulates for oral controlled drug delivery system.

It is more labour intensive than other granulation method, but it is useful when uniform spherical shape, uniform size, good flow properties, reproducibility in packing, high strength, low friability and smooth surface of granules is desired. Extrusion spheronization process has gained world wide attention because it is a simple and fast processing technology[2]. Any pharmaceutical products utilize pellets or beads as a drug delivery system can be effectively produced by the extrusion spheronization process. Wet mass extrusion and spheronization is established method for the production of spherical pellets, and are coated effectively to achieve controlled release product[3].

The pellets or beads produced by the extrusion spheronization offer the following advantages over conventional drug delivery system.

- It Produces spheroids with high loading capacity of active ingredient without producing extensively large particles.

- It produces particles of uniform size with narrow size distribution and good flow properties.
- Successful coating is applied to spheroid because of its spherical shape and low surface area to volume ratio.
- 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 drug at the same or different site in GI tract.
- Pellets are frequently used in controlled release delivery system as it facilitates free dispersion of spheroids in the GI tract and offer flexibility for further modification.
- It improves the safety and efficiency of active ingredient.
- It helps to increase bioavailability of drugs by controlling or modifying the release rate of drugs.

Process of extrusion and spheronization

Extrusion spheronization follows mainly five steps that is mixing or blending, extrusion, spheronization, coating and finally drying, which can be explained/described as

- Dry mixing of ingredient to achieve homogenous powder dispersion.
- Wet massing to produce a sufficient plastic mass.
- Extrusion to form rod shaped particles of uniform diameter.
- Spheronization to round off these rod shaped particles into spherical particles with narrow size distribution.
- Drying to achieve desired final moisture content.
- And screening to obtain desired size of spheres/pellets[4].

Extrusion/spheronization begins with extrusion process in which the wet metered mass is placed into the extruder where it is continuously formed into cylindrical rods of uniform size and shape. Amount of granulating fluid and uniform dispersion of fluid plays an important role in preparation of wet mass as optimum plasticity and cohesiveness directly affect the final production of pellets. Once the extrudates are prepared, they are then taken to spheroniser where it is spheronized or rotated at higher speed by friction plate that breaks the rod shaped particles into smaller particles and rounded them to form spheres. The size of the spheroids is mainly depending upon the diameter of circular die that modifies the diameter of cylindrical rods produced in extrusion stage.

Based upon the type of feed mechanism used to transfer the mass towards the die, extruders are divided in three class i.e. 1) Screw feed extruder [axial or end plate, dome or radial].2) Gravity feed extruder [cylindrical roll, gear roll, radial] .3) Piston feed extrude [ram] (generally utilized for experimental development[5, 6, 7].

The quality of pellets is highly influenced by the process parameters associated mainly with the extrusion stage and is widely studied by various research scientists. When comparison studies of spheroids produced from ram extruder and cylindrical extruder with fillers of different particle size were evaluated, it was concluded that the different extruder influences the final spheroidal size. The studies showed that differences in uniformity of spheroids are associated with the rate of shear and the shear stress applied by extruder[8]. Parameters such as morphology, size distribution, porosity, sphericity etc influences the release profile and stability of pellets while the formulation parameters such as presence and absence of soluble or insoluble fillers, surface active agents, pH adjusters**,** drug load, ratio of filler and drug influences release profile[9,10,11,12,13].

Examples: Pellets comprising of ibuprofen, eudragit S (pH sensitive polymer), citric acid (pH adjusting agent) and microcrystalline cellulose for pH sensitive colon targeting drug delivery by extrusion and spheronization technique was prepared and evaluated for its controlled release profile. It is reported that pH sensitive matrix pellets prepared by eudragit S was failed to delay the drug release but combination of citric acid and enteric coated pellets found to delay the release for 15 mins[14].

Influence of liquid binder on liquid mobility and preparation of spherical granules which were prepared by extrusion and spheronization was evaluated for formulation comprising of microcrystalline cellulose: barium sulphate using two different solvent water combination, i.e. 25% solution of glycerol in water and concentration of two non ionic surfactant like sodium laryl sulphate and pluronic F68. Studies showed that increase in glycerol solution increases the extrusion force while the surfactant solution reduces the extrusion force. The low level of liquid results in an elongated pellet while higher level of liquid produces pellet agglomerates with larger particle size and high porosity. It is concluded that the change in liquid movement is influenced by the rate of extrusion and the level of liquid that in tern influences the quality of pellets[15].

J J Sousa et al have demonstrated that the solubility of the material used (both drug and fillers) plays an important role in the quantity required to form the satisfactory pellets and its physical characteristics. Pellets of different drugs like propranolol HCl, Paraetamol, Ephedrine HCl, Ibuprofen and Sodium Salicylate using fillers of different solubility like mannitol and glucose being more soluble while

calcium phosphate and barium sulphate as insoluble fillers were prepared. Quantitative relationship were identified as (a) the extrusion force required to form extrudates are directly related to rheological properties of wet mass.(b) the size and reproducibility of pellets were found to be related with the solubility of the drug/filler ; the drug with high solubility were the least reproducible and provided lowest quantity of pellets.(c). There is an increase in pellet density as the drug solubility increases, indicating that drug solubility influences the pellet structure. (d) It is also demonstrated that the apparent density of pellets followed the density of the corresponding filler density. The values were closer for powder with low density than higher ones. (e) The porosity of the pellets is not dependent upon the water required during processing stage but the relation ship was established between the quantity of the drug and the inverse fraction of the filler solubility. (f) Increase in a drug level signifies a decrease in a mechanical strength of the pellets[16].

Hydrophilic polymers like HPMC, HPC, and PVP were taken in one part and MCC in 19 parts and then combined by spray drying, and this combination in 20% is mixed with lactose and water to prepare the pellets by extrusion spheronization. It was suggested that hydrophilic polymers, like HPMC and PVP produce highly spherical pellets by disintegration of MCC in small component (crystallites) that improves the dispersion of MCC throughout the lactose[17].

Verapamil hydrochloride floating pellets were prepared by spheronization process using avicel PH 102 , mannitol and kollidon CL. Evaluation studies carried out for its release and floating properties considering the effect of compression force suggest that verapamil hydrochloride compressed tablet shows slower release than the non compressed pellets[18]. Dissolution performance of Eudragit L 100 55 and Eudragit S 100 based multi unit controlled release system formulated by extrusion spheronization using poorly soluble drug thiazide leukotrine antagonist when evaluated.

Drug release occurred simultaneously from the pellet and followed zero order kinetics by the polymer controlled surface erosion mechanism to achieve sustained release profile[19].

Hot Melt Extrusion [HME]

Researchers have investigated a new modified method for preparing matrix pellets for controlled release drug delivery system to overcome the disadvantages associated with wet mass extrusion and spheronization process which is called as a Hot Melt Extrusion (HME) method where a thermal agent softens or gets melted during the process to obtain matrix pellets[3].

HME has been widely used technique in plastic industries and now it is used in pharmaceutical industries for formulation of sustained release, controlled release and transdermal as well as transmucosal drug delivery system [20, 21, 22]. HME consists of thermal agent or polymer, an active ingredient, release modifying agents, bulking agents and processing agents[23].

The HME offers following advantage over a wet mass extrusion and spheronization method, and are as follows,

- It is a simple, efficient, continuous process that requires fewer processing stages.
- HME is continuous process as it does not require a lengthy drying stage since it does not involve addition of water or other solvent.
- The absence of water may prevent drug degradation as many drugs are unstable in presence of water.
- It produces a spherical shape pellets with narrow range particle size distribution.
- Reduce the loss of coating material during the coating process associated with wet mass extrusion process.
- It is a convenient technology for preparation of solid dispersion and solid solution for delivery of poorly soluble drug as it offers a advantage of solvent free formulation of solid dispersion.
- It helps to mask the bitter taste of the active ingredient.
- Poorly compatible materials can be incorporated into tablets produced by cutting an extruded rod.

HME requires

- Pharmaceutical grade polymer which is functional at low temperature and its selection depends on drug polymer miscibility, polymer stability, and function of final dosage form.
- Thermal stability of drug as well as excipients[24].

Hot melt extrusion is classified as the molten system under control and semisolid viscous system, in former case heat is applied to material in order to control its viscosity and enable it to flow through the die, while the later case is a multiphase concentrated dispersion where high solid content portion is mixed with liquid phase[25].

Hot melt extrusion equipment consist of an extruder, auxiliary equipment for down stream processing and monitoring tool for performance and product quality evaluation[26]. HME process is divided in four sections that are

1) Feeding of extruder
2) Conveying of mass[mixing and reduction of particle size].
3) Flow through the die
4) Exit from the die and down stream processing[27].

In hot melt extrusion process, extrusion channel is conventionally divided into three sections that is feed zone, transition zone, and metering zone. The monitor and controlling parameter in HME are barrel temperature, feed rate, screw speed, motor load and melt pressure. Extruder consist of two rotating screw inside a stationary cylindrical barrel. And an endplate die connected to the end of barrel determines the shape of extruded products[28].

Examples: In 1994 fallonier and coworker have investigated hot melt extrusion technpology to produce sustained release pellets of diltiazem HCl, using polymers such as ethyl cellulose, cellulose acetate butyrate, poly ethylene co vinyl acetate. The resulting pellets exhibited smooth surface, low porosity and showed slow drug release[29]. Repka and coworker have fabricated a transdermal patch using Killion melt extruder for HPMC films employing PEG 8000, 2% triethyl citrate, 2% acetyl tributyl citrate, 2% PEG 400 using 1% hydrocortisone and 1% chlorpheniramine meleate as a model drug[21]. Perissutti and co worker have utilized a ram extruderto prepare a fast release dosage form with uniform shape and density, containing carbamazepine as poorly soluble model drug and PEG 4000 as a hydrophilic carrier and low melting binder. The evaluation studies revealed that the extruded mixture of equal composition exhibited more rapid release than simple physical mixture[30]. Controlled release theophylline pellets were prepared by hot melt extrusion method using eudragit preparation 4135 F, microcrystalline cellulose and poly ethylene glycol 8000 powder. The evaluation studies showed that pellet follows diffusion controlled drug release which is influenced by polymer swelling and pH dependent dissolusion[31]. Sustained release matrix tablets of chlorpheniramine maleate were prepared by hot melt extrusion method using polyethylene oxide as drug carrier, the evaluation studies revealed that drug release was controlled by erosion of matrix and the diffusion of drug took place through swollen gel layer at surface of the tablet[32].

Conclusion:

Today extrusion spheronization (wet mass extrusion) and melt extrusion spheronization represents an efficient pathway for novel drug delivery system. The potential of this technology is lies in the scope for different oral controlled delivery systems including oral and topical delivery systems. Because of its simple design, high efficiency of producing spheres and fast processing, extrusion spheronization has found a special position in pharmaceutical industry and especially in case of production of multiparticulate oral controlled release dosage forms. Pellet formation by this technique produces more spherical pellets and offers more advantages than other pelletization process. In addition, hot melt extrusion method has provided a new platform to produce spherical particles of drugs which are not stable or having compatibility problem in presence of solvents.

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