REVIEW

Pelletization by Extrusion-Spheronization: A detailed review

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Pelletization by Extrusion-Spheronization- A detailed review

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Abstract

Oral multiparticulate drug systems (e.g. pellets, granules) in comparison to single unit dosage forms offer biopharmaceutical advantages in terms of more even and predictable drug distribution in the enteric system. Extrusion spheronization is one of the most commonly used techniques in the formulation of such multiparticulate beads and pellets providing sustained and controlled release or modified release drug delivery. This review outlines the various steps involved in the extrusion spheronization process, the excipients used in such formulations along with some modifications and various processing variables affecting the quality of pellets formed. In addition, an overview of the methods available for the quality check of the pellets is reviewed.

Keywords: Extrusion, spheronization, multiparticulate, pellet

1. Introduction

Drugs designed in the form of uniform spherical sized pellets offer various advantages in the pharmaceutical industry. Applications are found not only in the pharmaceutical industry but also in the agricultural sectors and in the polymer and biotechnology industry. By formulating drugs into pellet form, it becomes possible for developing a controlled release drug delivery**,** actualizing a predictable and reproducible drug over an extended period of time, thus allowing reduced dosing frequency providing constant drug levels in the blood yielding increased patient compliance and decreased adverse drug events.[1, 2]

Pellets in addition to providing therapeutic advantages such as reduced gastric irritation and a lowered risk of side effects due to dose dumping, also offer technological advantages such as better flow properties, less friable dosage form, narrow particle size distribution, ease of coating and uniform packing.[3]

The manufacturing of pellets using layering processes such as solution layering, suspension layering or powder layering have been utilized over the years. These processes have limitations such as non-uniformity in the size of pellets and reduced drug loading. Pellets of uniform particle size between 500-1500 µm with smooth surface morphology, narrow size distribution, good flowability, high strength and low friability are desirable for providing sustained and controlled release effects in the formulations. This can be achieved by the extrusion spheronization technique. To produce fine spherical granules of 500 µm or smaller in the spheronization process, a pore size screen of 0.4 mm or smaller has to be used. Due to increased resistance caused by the narrow pore sized screen, the extrusion pressure is increased. Hence, the use of lubricants such as macrogol, polyethylene glycol, poloxamer, and silicone oil was attempted.[4, 5]

The main objective of extrusion spheronization is to provide pellets of uniform size with high drug loading capacity. It is a composite process of wet mass extrusion followed by spheronization to produce uniform sized spherical particles called spheroids/pellets/beads/matrix depending upon the process of spheronization.[6]

The pellets produced by extrusion spheronization provide the following edge over conventional solid dosage forms:

- Small spheroids with a high loading capacity of active ingredients can be produced.
- Production of pellets of uniform size, smooth surface and narrow size distribution with good flow property.
- Due to their spherical shape and low surface area to volume ratio sucessive coatings can be applied to the spheroids.
- The process can be used in preparing pellets for taste masking purposes of bitter APIs(Active Pharmaceutical Ingredients) by using taste masking polymers that create solid dispersions to prevent bitter drugs from coming in contact with the patient's taste buds.[7, 8, 9, 10]

- Enhancement of drug dissolution.
- Dosage forms with different doses can be produced from the same batch by adjusting the fill weight of the pellets.[11]
- It increases the hardness and reduces the friability of the pellet produced, hence minimizing the damage and loss during transportation.
- Various chemically compatible or incompatible drugs can be blended and formulated into a single unit dosage form for delivery at different sites in the gastrointestinal tract (G.I tract).
- Bioavailability of the drug is increased by providing sustained release.
- Dose dumping due to drug overload can be minimized and hence the safety and efficacy of the drug can be improved.
- Packaging these spheres into small containers such as hard gelatin capsules or compressing it into tablets is much more convenient than other dry forms such as powders or granules.

2. Extrusion spheronization process

The extrusion spheronization process was first reported by Reynold (1970) and Conine and Hadley (1970).[12, 13]

1. Dry mixing and Granulation.
2. Extrusion
3. Spheronization
4. Drying
5. Screening

2.1. Dry mixing and Granulation

The process involves mixing all the required ingredients in different types of mixers such as a twin shell blender, high shear mixer, tumbler mixer, and a planetary mixer to get homogenous powder dispersion.[13,14, 15, 16] The dry powder is then made into fine granules by mixing with a suitable granulation liquid. Different types of granulators are used for mixing the powder blend with the granulation liquid.The most commonly used granulator is a planetary mixer. [14, 17, 18, 19]

During this step, the evaporation of the fluid phase should be restricted to a minimum. This could especially be a problem with the high shear mixture which produces large amount of heat. This rise in temperature will cause evaporation of the granulating fluid[20] and influence the extrusion behavior of the wet mass. Cooling of the granulation bowl might avoid this problem. During the granulation step, there exists a homogenous distribution of the liquid phase throughout the granulated mass.

2.2. Extrusion

It is the second step in the process of spheronization following granulation. This process involves shaping the wet mass into long cylindrical rods of uniform diameter by forcing it through the dies of the extruder. This process is not only used in the pharmaceutical industry but also in food, ceramics and polymer industries.

4 main classes of extruders are used:

a. Screw feed extruder (axial or end plate, dome and radial extruder).
b. Sieve and basket.
c. Gravity feed extruder (cylinder roll or gear roll extruder).
d. Piston feed extruder (ram extruder).

The screw extruder consists of one or two (twin -screw) feeding the plastic mass to an axial (fig. 1) or radial extrusion screen (fig.2).[21, 22] In the axial type, the screen is placed at the end of the screw, while in the radial type the screen is placed around the screw, discharging the extrudate perpendicularly to the axis of the screw.[23]

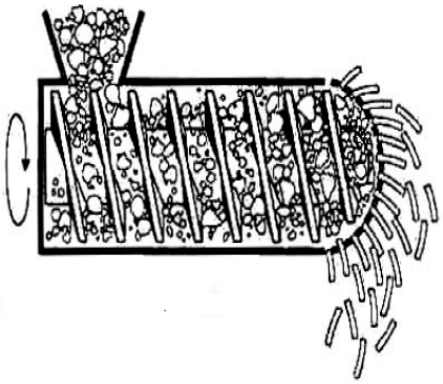

Fig. 1: Axial Screw feed extruder

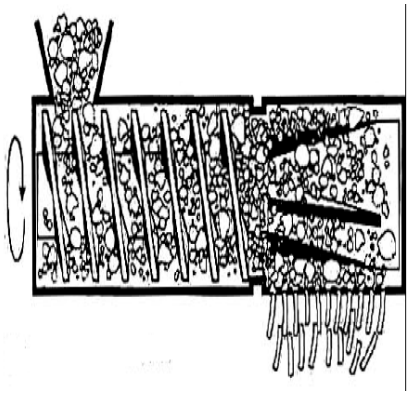

Fig. 2: Radial Screw feed extruder

In sieve (fig. 3) and basket (fig.4) extruders, the granulate is fed by a screw or by gravity into the extrusion chamber, where a rotating or oscillating device pushes the plastic mass through the screen. The difference between the sieve and basket extruder is similar to that between the radial and axial screw extruders.[23]

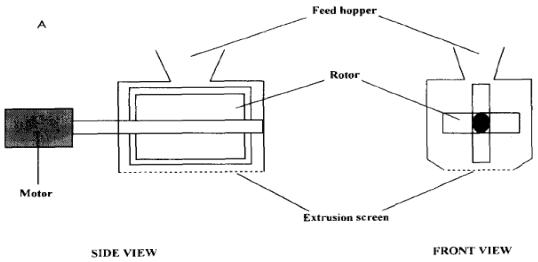

Fig. 3: Sieve extruder.

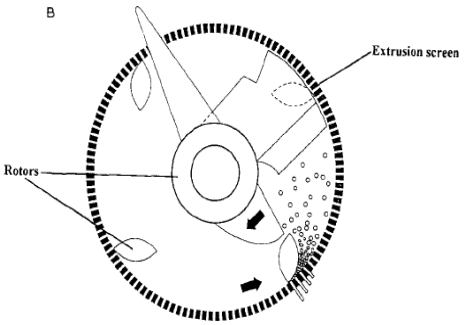

Fig. 4: Basket extruder.

Gravity feed extruders include rotary cylinder (fig. 5) and rotary gear (fig. 6) extruders, which differ mainly in the design of the two counter rotating cylinders. In the rotary cylinder extruder, one of the two counter rotating cylinders is hollow and perforated, whereas the other cylinder is solid and acts as a pressure roller. In the rotary gear extruders there are two hollow counter rotating gear cylinders with counter board holes. [23]

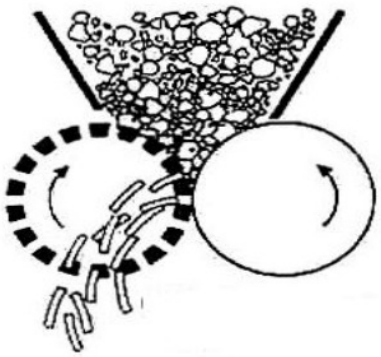

Fig. 5: Cylinder roll type

Fig. 6: Gear roll type

In ram extruders (fig. 7) which are probably the oldest type of extruders, a piston displaces and forces the material through a die at the end. Ram extruders are preferentially used in the development phase, because they can also be used to measure the rheological properties of the formulations.[14, 15]

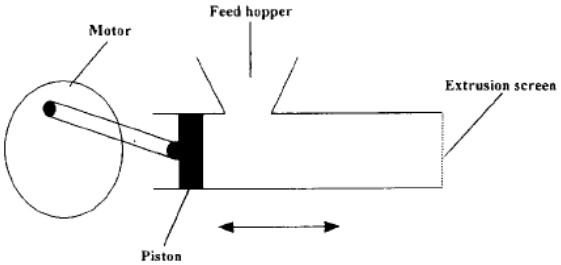

Fig. 7: Ram extruder

The extruded masses must have enough plasticity to deform, at the same time it must not adhere to other particles when rolled during spheronization process. This process mainly determines the final particle size of the pellets. The diameter of the extruder screen opening directly controls the diameter of the extrudate.[24, 25]

2.3 Spheronization

Spheronization, also known as Marumerization, is the third step in the extrusion spheronization process. It was first introduced by Nakahara in 1964. It involves dumping the extruded cylinders onto the spinning plate of the spheronizer, called the friction plate, in which the extrudate is broken up into smaller cylinders with an equal length to their diameter.[13] These plastic cylinders are rounded due to frictional forces[14]. Different stages can be distinguished depending upon the particle shape, i.e. it starts from a cylinder over a cylinder with rounded edges, dumb bells and elliptical particles to eventually perfect spheres (fig. 8a). This process may be divided into 3 steps such as breaking of the cylindrical segments or extrudate, agglomeration of the broken segments and smoothing of the particles.[24, 25, 26, 27]

Breaking of the cylindrical extrudate occurs due to the interaction of the extrudate with the rotating grooved or smooth plate, stationary wall and other extrudate particles. Agglomeration occurs when the small fragments produced during the breaking stage are picked up by the larger granules during smoothing. Spherical particles are created during the smoothing stage by generating rotational motion of each granule about its axis in constantly changing planes.

Baert and Remon (1993) suggested another mechanism in which a twisting of the cylinder occurs after the formation of cylinders with rounded edges, finally resulting in the breaking of the cylinder into two distinct parts. Both parts have a round and a flat side. The edges of the flat side fold together like a flower**,** forming the cavity due to the rotational and the frictional forces involved in spheronization process (fig. 8b).[28]

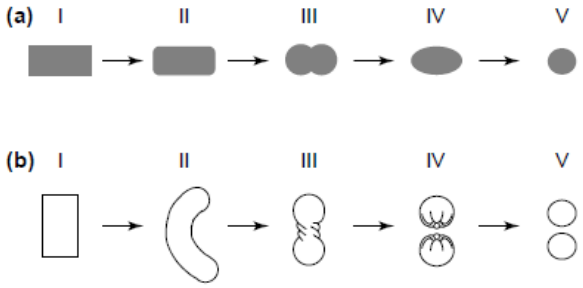

Fig. 8:Pellet-forming mechanism according to: (a) Rowe – I) Cylinder; II) Cylinder with rounded edges; III) Dumb-bell; IV) Ellipse; V) Sphere. (b) Baert – I) Cylinder; II) Rope; III) Dumb-bell; IV) Sphere with a cavity outside; V) Sphere.[28]

The most important component of the spheronizer is the friction plate, a rotating disk having a characteristically grooved surface in order to increase the frictional force. This grooved surface has two types of geometry, a cross-hatch geometry in which the grooves form right angles and a radial geometry in which a radial pattern is used. The duration of spheronization is usually 2-10 min[29] and a rotational speed between 200-400 rpm of the friction plate is optimum to obtain a highly spherical pellet.[30]

2.4. Drying

To achieve the desired moisture content in the final pellet, drying is done. The pellets can be dried at room temperature[31, 32] or at elevated temperature in a tray drier or fluidized bed drier.[33, 34, 35, 36] Bataille et al., (1993) reported the use of a microwave oven in the final phase of the production process of pellets to evaporate the slurry of the extruded mass during drying process.[37] Huyghebaert et al., (2005) reported the use of a freeze dryer in order to maintain the viability of living bacterial spores for the development of an oral vaccine.[38]

2.5 Screening

Screening of the pellet may be done to achieve the desired size distribution, and for this purpose sieves are used. In the case of pellets being prepared by extrusion-spheronization, screening is essentially required after manufacture, in order to avoid pellets with a high size polydispersity index.[36,39]

The overall process of extrusion spheronization is depicted in fig. 9.

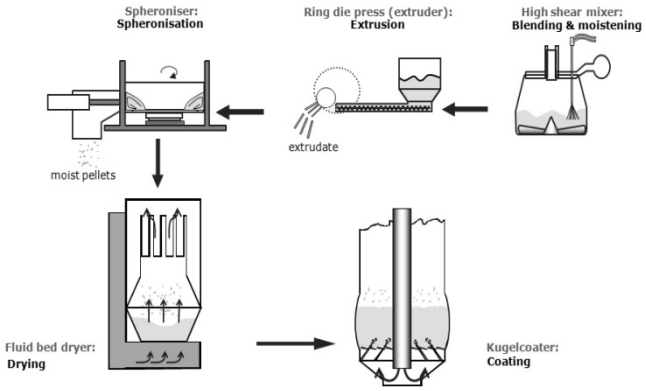

Fig. 9: Extrusion-spheronization process.

Hot-Melt Extrusion

The extrusion spheronization technique usually requires a film coating to control drug release resulting in complex processing steps. To avoid this difficulty, a novel hot-melt extrusion (HME) technique was developed to prepare granules, sustained release tablets and transdermal as well as transmucosal drug delivery systems.[40, 41, 42] This process does not require the use of water or solvents and few processing steps are needed, making the process simple, efficient and continuous. Furthermore, by HME it is possible to improve the bioavailability of ‘‘difficult’’ actives by the formation of solid dispersions and solid solutions.[43, 44, 45]

3. Pelletization aids to extrusion spheronization.

3.1 Microcrystalline cellulose (MCC)

MCC is considered the golden standard as extrusion spheronization aid because of its unique characteristics of plasticity and cohesiveness of their wet masses. Furthermore, it is capable of absorbing and retaining a large quantity of water due to its large surface area and high internal porosity[46], which facilitates extrusion and spheronization. MCC based pellets produced via extrusion spheronization have a good sphericity, low friability, high density and smooth surface properties.

MCC has been described as a “molecular sponge”.[47, 48] The MCC particles retain water in a manner similar to sponge. During the process of extrusion, these sponges are compressed and water that is squeezed from the internal structures acts as a lubricant. After extrusion, the sponge volume expands and they appear dry and brittle, which facilitates the breaking of the extrudates during the initial phase of spheronization. During the spheronization phase, the sponges are densified due to collision between particles, the spheronizer plate as well as the wall, and water facilitates the spheronization of pellets.

Although MCC is an ideal spheronization aid, it is associated with several limitations such as a prolonged drug release profile in the case of low solubility drugs due to the lack of disintegration of MCC-based pellets[49], drug decomposition in presence of MCC[50] and drug adsorption

onto the surface of MCC fibres.[51] Due to these limitations, various technological alternatives have been proposed and evaluated. To remark, wetting the mass with water–alcohol mixtures instead of water alone reduces the mechanical strength of the pellets[52] or the addition to the pellets of different excipients as disintegrants[53], surface active agents[54] or water-soluble fillers[55, 56] are the notable ones. Another alternative that has been used is complete or partial replacement of microcrystalline cellulose by other diluents **ii**r excipients.

Incorporation of superdisintegrants (croscarmellose sodium or sodium starch glycolate) into MCC pellets prepared by extrusion spheronization does not lead to their disintegration in drug dissolution medium, however, they afford a slight increase in the drug dissolution rate.[57] Similarly in another study by Michelle and Patrick (1998), the use of hydrophilic polymers with MCC, using spray drying produced pellets in a higher yield and better sphericity.

The less adhesive polymers hydroxypropyl cellulose and polyvinyl pyrrolidone appear best in regard to achieving a good yield with the proper rounding of pellets over an adequate range of water content.[58] Beads of acceptable physical characteristics can be produced using extrusion and spheronization with Carbopol® 974P, NF, resin as a release rate-controlling polymer. Drug dissolution from the beads can be slowed down by increasing the Carbopol content. High Carbopol and water content, a low calcium chloride level, low spheronization speed and a long spheronization time period produced the highest quality bead possessing **the**longest drug release duration.[59]

3.1. Alternative excipients for microcrystalline cellulose

The excipients intended to be used for the production of pellets via extrusion spheronization require the following properties:

- Water insolubility
- Large water absorption and retention capacity
- Binding properties
- Sufficiently large surface area for interaction with water and other ingredients in the powder mixture
- Ability to enhance drug release. **iii.**

3.1.1. Biopolymers

i. Powdered cellulose

Lisardo Alvarez et al., (2003) evaluated the use of powdered cellulose as the sole excipient in the preparation of furosemide pellets by extrusion spheronization.[60] Pellets formulated with PC and 25 or 50% furosemide showed smaller mean size, a broader particle size distribution, similar sphericity, greater surface roughness and higher friability than equivalent pellets formulated with MCC but showed rapid release, hence pellets of highly cohesive poorly water soluble drugs can be formulated using this excipient. Also, the pellets formulated with powdered cellulose were difficult to prepare since it required more water for extrusion, but its water holding capacity was lower. Due to water movement during extrusion, the material inside the extruder was compressed resulting in a dry mass which blocked the extruder.[61, 62] Hence, the powdered cellulose cannot be considered a suitable alternative to MCC compared to other pelletization aids.

ii. Starch and starch derivates

O'Connor et al., (1984) reported the unsuccessful production of pellets via extrusion spheronization using starch (native and pregelatinized) as the main excipient in the formulation. Otsuka et al. used a mixture of starch (27%, w/w) and lactose (63%, w/w) to produce pellets with 10% w/w of theophylline as a model drug.[63] Junnila et al. used up to 30% (w/w) native starch, combined with MCC and 2.5% (w/w) of anhydrous theophylline. However, no model was accepted because of poor pellet sphericity.[63]

Recently, Dukic et al., (2007) suggested the use of a modified starch (high amylose, crystalline and resistant starch) as an alternative excipient to MCC using anhydrous theophylline (25%, w/w) as a model drug. This resulted in high pellet yield (>90%), acceptable sphericity (AR<1.2), low friability (<0.01%), fast disintegration (<10 min) and complete drug release in less than 20 min in all formulations.[64]

In another study by the same authors, the immediate release of poorly water soluble drugs (up to 50% hydrochlorthiazide and 2.5% piroxicam) was achieved (more than 80% release after 30 min) due to pellet disintegration within 15 min.[65] In another study by Prieto et al. the use of starch (corn starch or wheat starch) + 20% white dextrin gave high quality pellets with good size and shape distribution.[66]

Despite promising results for specific starch grades, starch derivatives do not meet all the properties required for an ideal extrusion spheronization aid: an additional binder had to be incorporated in the formulation in order to obtain the proper wet mass consistency, and these formulations will be less robust than MCC formulations due to a narrow range of optimal water content.

iii. K- Carrageenan

Bornhoft et al., (2005) used carrageenan as a pelletization aid for extrusion spheronization. [67] Three commercial subtypes of different carrageenans namely ι-, κ-, and λ-carrageenan were investigated for their pelletization behavior, and κ-carragennan was found to be a very promising substitute for MCC in extrusion spheronization. K-carrageenan required higher water content for the formation of the pellets, but the formulation was robust as the optimal range of water content was much broader. Further studies on κ- carrageenan were carried out to examine the effect of other ingredients on the pellet properties. Four different drugs (acetaminophen, theophylline, mesalamine and hydrochlorthiazide) and four different fillers (lactose, mannitol, maize starch and dicalciumphosphate dihydrate)

were varied systematically with fixed ratio of κ-carrageenan (20%) in 36 formulations.[67, 68] Pellets with good shape and size characteristics were obtained in all formulations.

K-carrageenan pellets were characterized by a low tensile strength, fast disintegration and fast drug release and the drug release is independent of the solubility of the drug in contrast to MCC pellets. Hence, κ-carrageenan could be used as a suitable pelletization aid. However, the major disadvantage of pellets formulated with κ-carrageenan is their lower mechanical stability and the possibility of ionic interactions.

iv. Pectinic acid

ii.

Tho et al. evaluated different pectin derivatives for aid to extrusion spheronization. Three different drugs (Riboflavin with low water solubility, and paracetamol and theophylline with high water solubility) with concentration varying from 1 to 80% wt were used as model drugs. The low soluble pectin derivative, PA (degree of methoxylation<10%) was found to be well suited as an extrusion aiding excipient in pellet preparation. This has a high drug loading capacity and produces disintegrating pellets that are suitable for the fast delivery of drugs with low water solubility. In a similar study, the low methoxylated (4%) pectin derivative was successfully pelletized in combination with lactose and 1% riboflavin as a model drug using water for pelletization. All pectinic acid pellets were mechanically stable and partly disintegrated during dissolution experiments. However, with pectinic acid, the process is more sensitive to the type and amount of drug and is not a universally accepted pelletization aid, such as the conventionally used MCC.[69, 70]

v. Chitosan

Chitosan alone[71, 72, 73] as well as in mixtures with MCC[74, 75, 76, 77, 78] has been used for the production of pellets via **iii.** extrusion spheronization. Jess and Steckel investigated the influence of the degree of deacetylation of chitosan on the properties of pure chitosan pellets. Chitosan with a high degree of deacetylation (99.9%) and wetted with 0.2 N acetic acid provided the best wetted mass plasticity in order to obtain pellets with adequate size, sphericity, friability, mechanical strength and surface properties.[72] Agrawal et al., (2004)[71] prepared MCC free pellets using up to 15% (w/w) chitosan and up to 10% (w/w) hydroxypropylmethylcellulose (HPMC) as an additional binder.

Chitosan as a pelletization aid is not ideal since it requires the addition of either a granulation liquid with a specific pH (e.g. HPMC, sodium acetate) or binder (HPMC). Also, ionic interactions with drugs are possible due to the ionic nature of the chitosan.

3.1.2. Semi synthetic polymers

i. Hydroxypropyl methyl cellulose and hydroxyethyl cellulose

Chatlapall and Rohera (1998) evaluated the physical characteristics of HPMC and HEC for their use as pelletization aids. Since HPMC and HEC are water soluble, it was not possible to use water as granulation liquid and it further resulted in the formation of tacky masses. However, the pellets were prepared using isopropyl alcohol (IPA) as a non-dissolving granulating fluid. It was necessary to include the binder due to the low mechanical strength of the dried pellets in the formulation. With HPMC and HEC, pellets absorbed water producing a viscous gel matrix and dissolved or eroded slowly, unlike MCC pellets which stayed intact without dissolution or erosion.[79] Hence, these excipients find application in pellet formulation of water sensitive drugs and in those formulations where organic liquid must be used as wet massing liquid in place of water.

ii. Cross-linked polyvinylpyrrolidone (Crospovidone)

Crospovidone has proven to offer substantial advantages as a pelletization aid because of its ability to turn low-soluble active ingredients into fast-dissolving stable pellets. Verheyen et al., (2008) prepared pellets by extrusion spheronization from crospovidone with different amounts of paracetamol, hydrochlorothiazide, and spironolactone as model drugs. Only crospovidone types exhibiting small particle sizes were suitable as pelletization aid and it was possible to incorporate up to 60% (w/w) active pharmaceutical ingredients (API) into pellets with crospovidone. The pellets containing binary mixtures of the low-soluble APIs and crospovidone resulted in fast release in contrast to the pellets with MCC as a pelletization aid, which exhibited a slow release.[80] Compared to microcrystalline cellulose (MCC), that yields non-disintegrating pellets, Polyplasdone crospovidone offers enhanced drug release characteristics by combining pellet disintegration with the solubility enhancing characteristics of crospovidone. This property is highly desirable with poorly soluble drugs or to form "melt-in-mouth" pellets.[81]

iii. Polyethylene oxide

Howard et al. (2006) presented a means to produce extruded–spheronized beads, devoid of microcrystalline cellulose (MCC) and with a high drug load (>80%, w/w). Immediate release bead product with a high yield (>60% of 1mm diameter beads) and low friability (mass loss<4.0%) that were spherical to the naked eye (roundness score<1.20) were obtained. Polyethylene oxide, a highly water soluble polymer, provided sufficient plasticity to the wetted mass and a low molecular weight methoxypolyethylene glycol (MPEG) acting as a plasticizer was needed to improve the self-lubricating properties of the wetted mass.[82]

4. Process variables and parameters influencing pellet quality

4.1. Water content

Moisture is necessary to give plasticity to the powder mass for extrusion and spheronization into the pellets of an acceptable quality. At low moisture content, excessive pressure is required to remove the air voids during extrusion. The brittle mass thus formed does not have enough plasticity

to form spheres and thus breaks on spheronization generating a large amount of fines. Optimal water content fills the voids and increases the tensile strength of the granule to an ideal form for extruding. On the other hand, at higher moisture content, pellets agglomerate during Spheronization due to the excess water at the surface of the pellets.[83] The moisture content also influences the release pattern of the entrapped drugs.[84]

4.2. Granulation liquid

Water is mostly used as the granulating liquid. Ethanol when used along with water produces pellets with excellent compressibility and increased friability, hardness and dissolution rate.[54] Glycerol solution produces more porous pellets than water.[85] Formulations containing viscous granulating liquids with hydrophilic polymer yields long, dumbbell-shaped pellets while those containing watery granulation liquids with calcium chloride yield short, spherical pellets due to the influence on the swelling capacity of sodium alginate.[86]

4.3. Plasticizer

Lower plasticizer content in the granulating polymer produces pellets with increased tensile strength and brittle fracture under compression whereas higher plasticizer content produces pellets with a ductile property due to the transition of the polymer from a glassy to a rubbery state.[87]

4.4. Surfactant

Surfactant with a high HLB value reduces the surface defects of the extrudate due to reduced friction at the die wall of the extrusion screen and produces spherical pellets.[88] It may facilitate the permeability of the drug through the gastro-intestinal wall.[89] At optimum concentration, it ensures rapid in vitro-drug release within 30 min.[90] It can also facilitate the formulation of hydrophobic drugs as pellets.[91]

4.5. Drug solubility

Increase in drug solubility increases the volume of the granulating liquid, leading to an over wetting of the system.[21]

4.6. Type of extruder

Pellets obtained from various extruders differ in optimal moisture content, particle size distribution and sphericity. This may be attributed to the difference in the amount of granulation liquid required, in the length to radius ratio of the extrusion screen used or in the shear rate.[92, 93, 94, 95]

4.7. Extrusion force

At lower force, the extrudate agglomerates while at higher force, it becomes dry and fails to form spherical pellets.[96] So the extrusion force has to be optimized based on the characteristics of the active constituents.

4.8. Extrusion speed

Higher extrusion speed produces extrudate with a rough surface and wide particle size distribution.[18]

4.9. Extrusion screen

Change in the thickness of the extrusion screen and/or diameter of its perforations influences the pellet quality. Perforation diameter determines the pellet size.[18, 93]

4.10. Extrusion temperature

A rise in temperature during the extrusion cycle decreases the moisture content of the extrudate at the end of a batch compared to that in the beginning of a batch.[97]

4.11. Spheronization speed

Higher spheronizer speed produces more spherical pellets than low spheronizer speeds.[98] The spheronizer speed also affects the particle size, porosity and friability of the pellets.[99, 100, 101]

4.12. Spheronization time

Extended spheronization time produces pellets with higher sphericity, narrower particle size distribution and increased diameter.[65, 100, 101]

4.13. Spheroniser load

An increase in spheroniser load decreases the pellet size and increases hardness.[102, 103]

4.14. Drying method

Microwave dried pellets are more porous, softer and rougher than oven dried pellets.[39] Freeze dried pellets are larger, weaker and more porous and have faster drug release than pellets dried with the other processes like hot air drying and microwave drying.[104]

5. Evaluation of pellets

a. Particle size analysis

Mostly, pellets are analyzed for particle size by a simple sieve analysis.[65,84, 85, 96, 99]

b. Specific area

Pellet specific surface area is determined by a gas adsorption technique with Krypton.[84, 105]

c. Shape

Sphericity or roughness of pellets is determined by an image analysis system.[84, 95, 106]

d. Microstructure and surface

Pellet microstructure and surface morphology are assessed by scanning electron microscopy.[84]

e. Pellet strength

Pellets are evaluated for crushing force using a tablet strength tester and friability by using a friabilator. [65, 84, 99]

f. Density and porosity

The bulk and tap densities of pellets evaluate the homogeneity of the particle size distribution.[107] The true density evaluates the porosity of the pellets and can be determined by an air compression pycnometer or helium pycnometer.[84, 85, 106, 107]

g. Water content

Residual water content in the pellets after drying is evaluated by thermogravimetric analysis or moisture balance.[84, 104]

h. Dissolution testing

Drug release is assessed by a USP rotating paddle apparatus 2.[84, 106]

i. Flow property

Flow property is assessed by using the inverted funnel method or compressibility index.[107, 108]

6. Therapeutic Applications

Pellets formulated by the extrusion-spheronization process provide controlled drug release, targeted drug delivery and reduced side effects associated with conventional oral dosage forms. Some notable examples are as follows:

Diclofenac sodium, having a short biological half-life, may be formulated as sustained release mini-matrices to provide zero order drug release for the long term management of rheumatic disorders.[109]

Matrix based controlled release formulation of azithromycin may reduce the adverse effects associated with the conventional immediate release formulation.[110]

Pellet formulation of the non-steroidal anti-inflammatory drugs like indomethacin, ibuprofen, piroxicam etc. may reduce the gastrointestinal disturbances associated with conventional oral dosage forms.[111, 112, 113]

Triamcinolone acetonide or 5-amino salicylic acid coated pellets may provide colon targeting and reduce the side effects associated with the conventional oral dosage forms used in the long term treatment of ulcerative colitis and Crohn's disease.[114, 115]

More recently, mucoadhesive biopolymer chitosan based pellets of 5-amino salicylic acid are prepared for topical delivery to colonic mucosa to achieve effective concentration at the site of inflammation.[116]

Zhang et al., (2012) developed self-microemulsifying drug delivery systems (SMEDDS) in sustained release pellets of puerarin to enhance the oral bioavailability of puerarin.[117]

Similarly, formulation of solid self-nanoemulsifying drug delivery systems (S-SNEDDS) of carvedilol having capability of bypassing hepatic portal route and promoting the lymphatic transport of lipophilic drugs, was made possible, thus reducing metabolism by cytochrome-P450 family of enzymes present in the gut enterocytes and liver hepatocytes and/ or inhibiting P-glycoprotein (P-gp) efflux.[118]

Table I: Commercially available marketed pellet products.[23]

Product	***Company***
Bontril SR	*Carnick laboratories, Inc.*
Brexin L.A	*Savage Laboratories, Bangalore.*
Catazyme S	*Organon pharmaceuticals, USA.*
Compazine	*Smith & French, MUMBAI*
Dilgard XL 180	*Smith kline & French, MUMBAI*
Elixophyline	*CIPLA Ltd, Ahmedabad.*
Fastin	*Berlex Laboratories, USA.*
Hispril	*Berlex Laboratories, USA.*
Ibugesic S.R. 300	*CIPLA Ltd, Ahmedabad.*
Indocrin S.R.	*Merk Sharp, MUMBAI.*
Nicobid T.S.	*U.S.Vitamin, USA.*
Ornade	*Smith kline.*

7. Some of the negative results of extrusion-spheronization process

7.1 Physical factors:

7.1.1 Temperature

Oosaka et al reported that the application of a temperature sensor in the extrusion process yielded spherical granules of low sphericity. However, this is a more important parameter to be considered when the drug content is especially high, and use of fine granules is not practically possible to coat them. This ultimately causes increases in particle size and leads to a time consuming and costly process of pelletization.[119]

7.1.2 Sphericity

Kanbe et al observed that the low substituted hydroxypropyl cellulose offered highest sphericity as compared with croscaramellose sodium and croscaramellose calcium. The spheroids obtained through the later excipients exhibited a poor sphericity. [120]

7.2.Role of Excipients and drugs in the formulation of Pellets:

It was observed during the formulation of diphenhydramine HCl pellets that the low substituted hydroxyl propylcellulose offered the highest sphericity while the cross caramellose sodium and cross caramellose calcium offered unsatisfactory sphericity. It was also observed in the study that the production of 500 µm or smaller fine spherical was not succeeded with microcrystalline cellulose.

The formulations prepared with microcrystalline cellulose and corn starch as excipients resulted in best quality pellets with smooth surfaces. Whilst the pellets prepared using excipients such as glucose, lactose and calcium hydrogen phosphate produced pellets with much rougher surfaces.[121]

Additionally, the incorporation of lactose at a concentration of 15% w/w with higher moisture content (> 25% w/w) lead to the agglomeration of pellets. The water soluble excipients (lactose) caused channels (or) cracks to form on the pellets surface.[122, 123]

In another study, Panchagnula et al reported the unsuitability of the hydrophilic swellable polymer (HPMC) for water soluble drugs. A synergistic effect of the swelling property of HPMC and disintegrating property of MCC (microcrystalline cellulose) resulted in a faster drug release of 70% azithromycin within 1 hour. These combinations of excipients failed to provide a controlled release of azithromycin. However, in the same investigation the effect of waxy materials GMS (glyceryl monostearate and carnauba wax) on the release rate of drugs was investigated. It is known from the literature that the waxy materials serve as potential release retardants in the controlled release systems. [124, 125]

But, as compared with carnauba wax, glyceryl monostearate resulted in a better yield, crushing strength and density of pellets. This indicates that the unsuitability of spheronizing property of carnauba wax resulted in poor pellet shape as a result of hydrophobicity and poor molding capacity[126]

O' Connor et al reported the unsuccessful production of pellets using starch (native and pregelatinised) due to poor sphericity.[63]The release of caffeine from pellets was not sustained when prepared in combination with chitosan and HPMC lacking MCC.[127]

An increase in the amount of citric acid revealed a negative effect in the roundness of the pellets [128]

Indomethacin

Pellets prepared using sodium lauryl sulphate (SLS) offered the highest bioavailability as compared to commercial product due to a better drug penetration effect .[111] In another study, Quinn *et al.* reported the inability of using poly vinyl pyrrolidine in isopropyl alcohol as liquid adhesive. The pellets had an irregular spiky appearance and required coating.

Furosemide

Powdered cellulose is an alternative to microcrystalline cellulose, however the size and size distribution of pellets are less appropriate than those pellets prepared using MCC. Compared to MCC pellets, powdered cellulose showed a higher porosity, surface roughness and friability. The release of furosemide was very rapid.

Indomethacin

Indocid–R, a commercial product found to possess disappointing *in vivo* performance in humans. However, a competitor product developed for Indocid-R by extrusion spheronization without any coating offered a high yield, adequate sphericity with better in vitro dissolution.[129]

Diltiazem

A matrix based multiunit pellet system for the controlled delivery of diltiazem was observed to be laborious due to its high aqueous solubility of the drug and larger surface area of the pellet. The outcome of the work ended with a high burst effect which may lead to a toxic level of the drug.

8. Conclusion

This comprehensive review hereby concludes with a note that pellet production via extrusion spheronization can be an effective, efficient and easy method which can keep pace expediently and retain a high longevity in the field of pharmaceutics. Also, the article gives a detailed insight on the meritorious usage of this method over single unit dosage forms. Improved patient compliance, flexibility in fabrication and ease of portability and administration has made this method more popular compared to other oral sustained and controlled release formulations.

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