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Review Article

AN OUTLINE OF VARIABLES IN PELLETIZATION BY EXTRUSION AND SPHERONIZATION

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ABSTRACT

Pelletization is an agglomeration process which converts fine granules or powders of bulk drugs into small, free-flowing, spherical units, known as pellets. The pelletization can be achieved either through agitation, compaction (extrusion-spheronization), drug layering and globulation. Among the various pelletization techniques extrusion–spheronization process is preferred over other methods for the preparation of pellets as it allows the incorporation of the higher amount of drug, modified physical characteristics of the drug (density, sphericity, narrow size distribution, smoother surface) and multiple drugs can be easily combined in the same unit. This current review summarizes the findings or investigations by the researchers on various variables, including process parameters, equipment parameters and formulation parameters influencing the quality of pellets. The article also focuses on process optimization and additives used in pellets formulation. To prepare the current review search criterion used was the parameters affecting final pellet characterization in the extrusion spheronization process. The sources were peer-reviewed relevant scientific articles of recognized journals. Keywords used as filters were extrusion, spheronization, formulation parameters, process parameters, equipment parameters, moisture content, granulating liquid, drying rate, extrusion temperature, spheronizer load, pelletization. Literature survey has been done in a range of years (1992-2019) regarding the various variables of the extrusion spheronization process, which affects and has foremost impact on the final quality of pellets so as to make the review updated and comprehensive.

Keywords: Pelletization, Extrusion, Spheronization, Pellets, Process parameter and Formulation parameter

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INTRODUCTION

Pelletization is a size-enlargement process that converts small fine particles of bulk drugs and excipients into small, free-flowing, spherical units known as pellets. The pellet size range typically lies in the range of 500 to 1500 µm. Pellets as multiparticulate dosage forms are preferable over single unit dosage forms because of their potential benefits like predictable gastric emptying, uniformity of dose, prevention of dust formation, no risk of dose dumping, flexible release patterns, less inter and intra-subject variability [1]. Pellets are commonlyfilled into hard ge latin capsules but can also be compressed to tablets. The pellet preparations can be coated with different polymers in order to obtain a sustained-release effect [2]. The thickness and composition of the polymer affects the release pattern. The most straight forward strategy for formulating pellets is by the extrusion spheronization method. This method was first introduced by Reynolds (1970) and by Conine and Hadley (1970), which includes four stages [3]:

- Formation of the wet mass (granulation)
- Forming the wet mass into extrudates (extrusion)
- Separating the extrudate and adjusting of the particles into spherical form with the help of friction plate (spheronisation)
- Drying of the pellets

Growth mechanism of pellet

The pellet growth mechanism consists of four steps as mentioned below:

- Nucleation
- Coalescence
- Layering
- Abrasion transfer and size reduction

In nucleation, step particles are drawn together to form three-phase (air-water–solid) nuclei as shown in fig 1. The collision of well-formed nuclei to form larger size particles is called as coalescence. The continuous addition of material on already formed nuclei is termed as layering. Transfer of material from one particle to another without any linking in either direction is abrasion transfer. During pelletization, the three factors responsible for size reduction is either due to attrition, breakage and shatter [4].

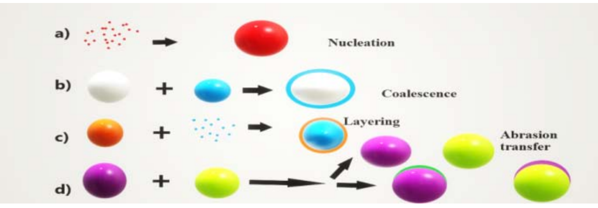

Fig. 1: Growth mechanism of pellet (A) Nucleation, (B) Coalescence, (C) Layering and (D) Abrasion transfer [1]

To prepare the current review search criterion used was the parameters affecting final pellet characterization in extrusion spheronization process. The sources were peer-reviewed relevant scientific articles of recognized journals. Keywords used as filter were extrusion, spheronization, formulation parameters, process parameters, equipment parameters, moisture content, granulating liquid, drying rate, extrusion temperature, spheronizer load, pelletization. Literature survey has been done in a range of years (1992-2019) regarding the various variables of the extrusion spheronization process, which affects and has a foremost impact on the final quality of pellets so as to make the review updated and comprehensive.

Additives used in pellet formulation

A wide range of materials has been investigated as additives to improve ease of processing, physical properties of the final pellets or for modifying the drug release profile (sustained release or immediate release) as indicated in table 1.

Table 1: Additives used in pellet formulation

Formulation aid	Examples	References
Filler to add a bulk	Calcium sulfate, Dibasic calcium phosphate, Lactose, Mannitol, Microcrystalline cellulose (MCC), Starch, Sucrose	[4, 5]
Binder to maintain the pellet integrity	Gelatin, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose, Methylcellulose, Starch, Sucrose, Polyvinylpyrrolidone	[4, 5]
Lubricant to reduce the coefficient of friction	Calcium stearate, Glycerin, Hydrogenated vegetable oil, Magnesium stearate, Mineral oil, Polyethylene glycol, Propylene glycol	[4]
Separating agent to promote the partition of pellets into particular units during a pelletization process	Kaolin, Talc, Silicon dioxide	[4]
Disintegrant to enhance the disruption of pellets	Alginates, Croscarmellose sodium, Crospovidone, Sodium starch glycolate, Pregelatinized starch	[2, 4, 5]
pH adjuster to maintain pH	Citrates, Phosphates	[4]
Surfactant to improve wettability	Polysorbates, Sodium lauryl sulphate	[5]
Spheronization enhancer to improve the production of spherical pellets	Microcrystalline cellulose, sodium carboxymethyl cellulose, Lactose	[5, 6]
Glidant to facilitate flow	Colloidal silicon dioxide, Magnesium stearate, Starch, Talc	[4, 7]
Release modifier to get the modified release from the pellet formulation	Ethylcellulose, Carnauba wax, Shellac, Eudragit	[2, 5, 6]

Parameters affecting final pellet characterization

In the extrusion–spheronization method, the various parameters which affect final pellet quality are, process parameters, equipment parameters and formulation parameters. Extrusion speed, extrusion temperature, spheronization load, spheronization time, spheronization speed and drying method are the process parameters which mainly influences the hardness and sphericity of the pellets. In the case of equipment parameters such as extrusion screen, extruder, mixer and friction plate affects pellet size distribution and strength characteristic of pellets [2, 3, 7]. The formulation parameters such as nature of drug and excipients, moisture content and granulating liquid significantly affects the surface morphology and mechanical properties of pellets. The various parameters which are reported by the researchers affecting final pellet quality are mentioned below:

Process parameter

Extrusion speed and temperature

The total amount of the extrudate produced is mainly influence by extrusion speed. The amount produced should be as high as possible for economic reasons, but an increase in extrusion speed affect the size and surface properties of the final pellet [3]. Extrusion speed is not always consistent due to various extruder designs and different formulation used. Mesiha and Valltes, screened various lubricants for their impact on lessening pellet surface imperfections at different extrusion speed. The study reveals that sodium lauryl sulphate at levels as low as 0.125%, enhances extrudability and significantly decreases surface deformities [8]. The control of temperature during the extrusion and spheronization is important when formulation containing thermolabile drug and to optimize the moisture content [3]. In order to gain an idea about the temperature increase during extrusion, some researchers built in a temperature probe. However, some researchers also used a screw extruder with a cooling jacket around the barrel in order to keep the temperature of a given formulation between predetermined limits so as to not affect the pellets formulations. Fielden *et al.*, reported the association of water and microcrystalline cellulose through thermal examinations. The study outcomes showed that the majority of the water held inside a framework utilized for the readiness of circular granules by extrusion and spheronization is available as free water. The results indicated that approximately 0.856 mol of water per 100 g of MCC appears to be absorbed as structured water and described MCC as a molecular sponge [9].

Drying method

During extrusion spheronization, various drying techniques influences final pellet characteristics. Homogeneity of the mixing, state of the drug (amorphous or crystalline), dissolution rate and the residence time can be affected by variations in the drying method [10, 11]. Drying temperature and drying method both are important factors that affect the shape and porosity of pellets [12]. Drying affects the structural as well as mechanical properties of pellets in the term of shape, density/porosity (open and closed), surface area, surface tensile strength, and deformability. Dyer *et al.*, studied the effect of fluid-bed drying and tray drying for drying of pellets. The pellets dried by fluidized-bed technique achieve the desired moisture content much more quickly due to the rapid evaporation of water and due to the turbulent motion of the fluidized particles. Water removal from tray-dried material is slow due to the static nature of the bed compared to fluid-bed drying [13]. Berggren *et al.*, has reported the impact of drying rate on the quality of pellets. The result reveals that an expanded drying rate did not influence the shape and surface of the dried pellets. The drying conditions affected pellet porosity and produced permeable pellets [14]. Bashaiwoldu *et al.*, investigated different drying techniques including freeze-drying, desiccation, hot air oven drying, fluid-bed drying to dry the pellets. The pellets dried by freeze-drying contained more porous, higher surface area and smoother than pellets dried by the other methods. Desiccation method provided dried pellets with the highest proportion of closed pores. Pellets dried by the oven, desiccated with silica-gel, fluid-bed drier to the freeze-dried pellets deformability increased by these orders [15]. Murray *et al.*, investigated the effect of oven and freeze-drying on pellets quality. The yield point is significantly lower for the freeze -dried pellets. Freeze-drying retained the shape and size of the pellets, whereas oven drying produced roughened pellets due to the uneven shrinkage of the wet powders [16].

Spheronization load, time and speed

As reported by Newton *et al.*, a low load appeared to give poor molecule interaction while a high load produced poor plate and molecule interaction [17]. The study suggested that a low load of 50 and 100 g produce pellets of the best length and have the most minimal thickness and least circular structure. However, a higher load of 750 and 1000 g, in the long run, produces round granules but the procedure takes additional time. The yield of pellets of a specific range decreased with increased spheronization speed at a lower spheronizer load and increased with extended spheronization time at higher spheronizer load [18]. Spheronization time significantly affects the quality of the sphere during extrusion spheronization. Narrower particle size distribution, high sphericity, change in bulk and tapped densities and change in the yield of a certain size range were observed with extended spheronization time [19]. The effect of the spheronization time on the high spheronizer speed is nearly less. A more extended spheronization time with the lower spheronizer speed provides a suitable environment, resulting in an improved total yield of pellets. A more spheronization time at low spheronizer speed allows moist extrudate particles to aggregate with fine particles and decreases the loss of fine particles from the spheronizer [20]. Hardness, roundness, porosity, bulk densities, tapped densities, friability, flow rate and surface structure of the pellets were also influenced by a change in the spheronization speed [21]. Wan *et al.*, reported that at the fusion of speeds ranging from 1000 to 2000 rpm and residence times between 5 and 15 min produced pellets in the size range of 0.7–1.0 mm [22]. Ronowicz *et al.*, observed that spheronization speed and spheronization time are the key factors influencing pellet quality. The most spherical pellets are achieved by employing high spheronizer speed and longer time of spheronization. The high spheronizer speed leads to a fracture of the extrudates into smaller particles. On the other side, at lower spheronizer speed, a less harsh environment exists in the spheronizer and extrudate particles piece to a lesser degree [23]. Spheronization speed and residence time are important for producing good quality of pellets. The high spheronization speed with high residence time increases sphericity, decreases fine generation and enhances the densification of pellets.

Equipment parameters

Extrusion screen

Extrusion screen is mainly characterized by two-parameter the thickness and diameter of perforations. Changing one of this parameter influences the extrudate and hence affects the quality of pellet. Additionally, pressure on the extrusion screen is the most important factor which depends upon the amount of water used for granulation. The reduction in screen pressure decreases the chances of extrudate breaking through screen as well as effect pellet size distribution and yield value [12]. The die opening in the extrusion screen or die plates have several basic designs and vary with application. The upper limit of hole size depends upon the flow rate of the formulation or extrusion rate. If a denser product is required, a thicker plate or screen is needed to withstand the greater extrusion pressure. For thin screens or die plates, the hole is typically straight with a taper at the entrance or slight neck. Vervaet *et al.*, showed the effect of an extruder equipped with a screen of a length-to-radius ratio (L/R ratio) of 2 and 4 screen on final pellet quality. The study results indicated that the screen with the L/R ratio of 2 screen formed rough and loosely bound extrudates, while the screen with an L/R ratio of 4 screen produced smooth and well-bound extrudates. The proposed mechanism explained was as the extrusion screen thickness increases densification of wet mass occurs [24]. Sonaglio *et al.*, has observed strong interaction between water content and extrusion screen size, which significantly affects pellet size distribution and sphericity [25].

Extruder

Numerous researchers have reported the influence of the type of extruders such as a screw (axial, radial), sieve, basket, roll, and ram extruder on the quality of pellets [1]. Different type of extruders results in pellets exhibiting different characteristics. Single screw extruder has lower throughput compared with the flat die press. Axial screw extruder produces more dense material compared to the radial screw extruder. Pellets prepared with laboratory roller screen (LRS) extruder are smaller in size with a more extensive size circulation compared to ram extruder. The LRS extruder needs a more cohesive paste for the preparation of pellets compared to ram extruder. In lab roller extruder, the apparent shear rate based on the blade-screen clearance provides a quantitative criterion for scale-up [26]. Sonaglio *et al.*, formulated the paracetamol pellets utilizing axial and radial screw extruders. The study reported that the temperature deviation and the extrusion time are considerably higher on the axial system. However, the axial system generates less heat in comparison to the radial system during the preparation of pellets [27]. Zhang *et al.*, compared ram and screen extruder for the preparation of pellets. Pellets prepared with screen extruder are smaller in size with wider size distribution compared to ram extruder. The study outcome suggested that ram extruder produced non-deformable pellets in comparison to screen extruder [28].

Mixer

In the extrusion-spheronization formulation of plastic mass is the primary step. Different types of granulators are used for mixing of the powder blend with the granulating liquid. The most commonly used granulators are either planetary mixer, high shear or sigma blade mixer. Lee *et al.*, developed pellets of pure MCC using a twin-screw extruder (TSE) and a high shear mixer (HSM) technique with water as a liquid binder under different process conditions. The results reveals that pellets developed by the HSM technique are spherical in shape and are made up of smaller granules through the coalescence process. On the other hand, pellets develop by TSE have irregular shapes with tiny pores spread uniformly throughout the pellets. The pellets developed by HSM technique are affected by process conditions and are stronger at higher impeller speed. However, pellets prepared by TSE are consistent in strength and relatively independent of process conditions [29]. Bryan *et al.*, reported a comparison between the planetary mixer and screw-based mixer process for extrusion spheronization. The study outcomes suggested that pellets prepared using screw-mixed material showed higher yield, strength and produced smaller pellets with a narrower size distribution when spheronized under specific conditions [30].

Friction plate

The friction plate is the important component of spheronization, which consists of a grooved surface and increases the frictional force during spheronization. Friction plate design and diameter are the important parameter which affects the quality of pellets [12]. The two type of geometry grooves exit are crosshatch and radial geometry. Michie *et al.*, have investigated the effect of three distinctive spheronizer contact plate designs including crosshatch, radial, striated edge design on the physical properties of pellets. The results suggested that change in plate design significantly affected yield values whereas marginal affect was observed on pellet shape and dissolution properties [31]. In the recent past Zhang *et al.*, investigated the plate surface protuberance size and shape on the yield value of pellets. The investigation includes four cross-hatched pattern plates large studs, pyramidal, saw-toothed and small studs. A decrease in yield value was evident in order (large studs, pyramidal, saw-toothed and small studs) [32].

Formulation parameters

Drug and excipients

Extrusion and spheronization method widely used for the preparation of pellets of various materials; natural extract, bacterial culture, drugs, etc. with immediate release, and modified release pattern [1]. Presence and absence of drug is important, which influences mean diameter of pellets. Formulations containing a lower proportion of drugs and water-insoluble drugs are easy to spheronize [33-35]. Various researchers have reported the formulation of pellets for different purposes using various excipients to overcome the issues of solubility, stability and drug release properties etc. Immediate-release pellets of poorly soluble drug (hydrochlorothiazide and piroxicam) using modified starch (high - amylose, crystalline, and resistant starch) as the main ingredient [36]. Solid dispersion of furosemide pellets for oral administration to improve the solubility [37]. Delayed-release pellets of omeprazole magnesium, which is unstable in stomach pH, hence formulated as delayed-release dosage form to allow absorption in intestinal pH [38]. Deshkar *et al.*, designed curcumin solid dispersion pellets for improving the solubility of poorly soluble curcumin and observed a significant enhancement in dissolution compared to pure curcumin pellets [39]. Fielden *et al.*, reported that particle size of lactose powder (fine and coarse) has an effect on the extrusion characteristics of the wet mass and on the size and the roundness of the resulting pellets when prepared using cylinder extruder and a ram extruder [40]. Fielden *et al.*, also observed that pellets containing a mixture of MCC and lactose and prepared with the coarser lactose agglomerated at lower water content. The agglomeration occurs due to the lower capillarity inside the pellets compared to the pellets prepared with the fine lactose. Additionally due to the moisture at the surface, these pellets tend to stick together and formed large agglomerate [41]. Luukkonen *et al.*, studied the influence of MCC type and water content on the rheological properties of the wet powder masses using two different MCC grades (Avicel and Emcocel) and si-licified MCC (SMCC). The study results reveals that SMCC grade proved to be more elastic than the simple MCC grades at different moisture content levels [42]. However, Dukic *et al.*, reported that MCC is not universally applicable due to a number of drawbacks: prolonged drug release of poorly soluble drugs, drug adsorption, chemical incompatibility with specific drugs. Powdered cellulose, starch, chitosan, kappa carrageenan, pectinic acid, HPMC, polyethylene oxide, PVP can also use as diluents [43, 44]. Levis *et al.*, studied the effect of ultra-fine microcrystalline cellulose without sodium lauryl sulphate (grade X) and with variable percentage of sodium lauryl sulphate (SLS; grade Y) on dissolution behavior. Among these two grades, grade Y was found to be effective at delaying drug dissolution, mainly due to decrease in the porosity of the prepared pellets [45]. Mallipeddi *et al.*, studied the effect of ethylcellulose particle size (fine and coarse) on the preparation of pellets. The fine particle grade of ethylcellulose produces more rugged pellets but with lower yield compared to coarser grade ethyl cellulose [46].

Moisture content

Water is the most important variable as extrusion process variables. Moisture content has a significant impact on spheres quality [47]. Less moisture content in pellets causes the generation of fines with large variation in pellet size distribution. On the other side higher moisture content results into over wetted mass and agglomeration between the individual pellets during spheronization due to the excess of water at the surface of the pellets [3]. The rheological characteristics of the wet mass are important for achieving good properties for the extrusion process. Sonaglio *et al.*, demonstrated the significant impact of water content on sphere density. The study reveals that for a given amount of water, the increase in moisture content is translated into an increase in sphere density from a value of 1.41 to 1.48 [25]. Lustig-Gustafsson *et al.*, has showed that the amount of solvent (water) require for forming pellets was dependent on the type of drug, its solubility and particle size. The study results reveals that optimum moisture content can be calculated from the linear relationship between water level and the natural logarithm of the drug solubility [48]. Tomer G. has observed a significant correlation between extrusion force and moisture content. The study results demonstrated that using higher extrusion force in wettest formulation leads to less water movement in the die, which is found to be suitable for pellet preparation [49]. Sinha *et al.*, reported that during extrusion spheronization, increasing water content increases the pellet size and produces less friable pellets [12]. Recently Stefan *et al.*, investigated the effect of moisture content on the densification of pellets and reported that water does not affect compression up to 5 kN value. In contrast, above 5 kN water decreases the energy needed for the densification of polysaccharide substances [50].

Granulating liquid

Pellets preparation by extrusion and spheronization is impossible without the presence of suitable granulating liquid. In most cases, water is used as the granulating liquid. Apart from water, ethanol, water/ethanol mixture, dilute acetic acid, isopropyl alcohol can also be used as a granulating liquid. Dreu *et al.*, investigated the use of water, ethanol and ethanol/water mixtures as granulation liquids for the preparation of pellets. The prepared pellets have significantly different mechanical and structural properties from those prepared using water alone. The tensile strength and disintegration time of pellets produced with 4.9 mol % ethanol/water mixture are equal to those of pellets produced with water alone. However, pellets prepared with ethanol/water mixtures showed lower friability and porosity compared to pellets prepared with water alone [51]. Mascia *et al.*, investigated the use of dimethyl sulfoxide (DMSO), water, ethanol as a granulating liquid in the preparation of pellets. The investigation includes the study of physicochemical properties required for solvents to be suitable for the extrusion of MCC. The study results indicated that MCC was found to form a mechanically stable structure when wetted with water or DMSO but not with ethanol [52]. Hamedelniel *et al.*, studied and reported that the presence of ethanol in the wetting liquid led to a decrease in the liberation of the active agent in the first phase of the dissolution process with a reduction in the hardness of the pellets. The investigation also reveals that the plasticity of the mass can be varied by the type of the granulating liquid [53]. Recently, Gaith *et al.*, studied the effect of aqueous and organic granulating fluid on the physical properties of the pellets. The pellets prepared with water as the granulation fluid demonstrated higher swelling and are denser than those prepared with isopropyl alcohol/water mixture [54].

CONCLUSION

In the current review, an attempt has been made to outline the various variables of the extrusion spheronization process, which affect the final quality of pellets. In extrusion–spheronization method process parameters, equipment parameters and formulation parameters should be critically investigated as they have the foremost impact on the final pellet characteristics. In the case of process parameters including drying rate, extrusion–spheronization speed and time, which influences the hardness, porosity, surface morphology and sphericity of the pellets. On the other side, equipment parameters affects yields, size distribution and strength characteristic of pellets. The formulation parameters such as moisture content and granulating liquid significantly affect the surface morphology, density, structural and mechanical properties of pellets. However, the extrusion–spheronization process is gaining much interest and a very promising technique for the manufacturing of pellets. Still, the major limitation of this process is that it is a multiple-step process. In the future, there is a possibility for improvement in the process or equipment system so as to overcome the limitation of the multi-step batch process.

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CONFLICTS OF INTERESTS

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