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Review

# Extrusion–spheronization a promising pelletization technique: In-depth review

*Sagar Muley* *, *Tanaji Nandgude*, *Sushilkumar Poddar*

*Department of Pharmaceutics, D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune, Maharashtra 411018, India*

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ABSTRACT

This review article deals with various aspects of the extrusion–spheronization technique. The first part includes different steps in the production process of pellets such as granulation, extrusion, spheronization, and drying. In the second part, the parameters which can influence the quality of pellets including formulation (moisture content, granulating liquid, excipients, and drugs), equipment (mixer, extruder, friction plate, and extrusion screen) and process (extrusion speed, extrusion temperature, spheronizer load, spheronization time, spheronization speed, and drying method) are discussed. In the final part, methods available for characterization (particle size distribution, surface area, shape and sphericity, porosity, density, hardness and friability, flow properties, disintegration, and dissolution) of the pellets are explained.



## 1. Introduction

Multiparticulate dosage forms are gaining much favor over single-unit dosage forms because of their potential benefits like predictable gastric emptying, no risk of dose dumping, flexible release patterns, and increased bioavailability with less inter and intra-subject variability [1]. Pellets are one of the most popular multi-particulate dosage forms. Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units, referred to as pellets. Pellets range in size, typically, between 0.5 mm and 1.5 mm [2]. Pellets as a drug delivery system offer not only therapeutic advantages, such as less irritation of the gastro-intestinal tract and a lowered risk of side effects due to dose dumping, but also technological advantages, for example, better flow properties, less friable dosage form, narrow particle size distribution, ease of coating and uniform packing. The reproducibility of the drug blood levels is an additional advantage to the use of a pellet formulation. Pellets are commonly filled into hard gelatin capsules but can also be compressed to tablets. The commercially available pellet formulations are mainly coated with a polymer film in order to obtain a controlled release effect. The thickness and composition of the film influence the release pattern; so by mixing different types of coated pellets, the desired release profile can be obtained [3].

* *Corresponding author.* Department of Pharmaceutics, D Y Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune, Maharashtra 411018, India. Fax: +912441282957.
*E-mail address:* sagarmuley007@gmail.com (S. Muley).

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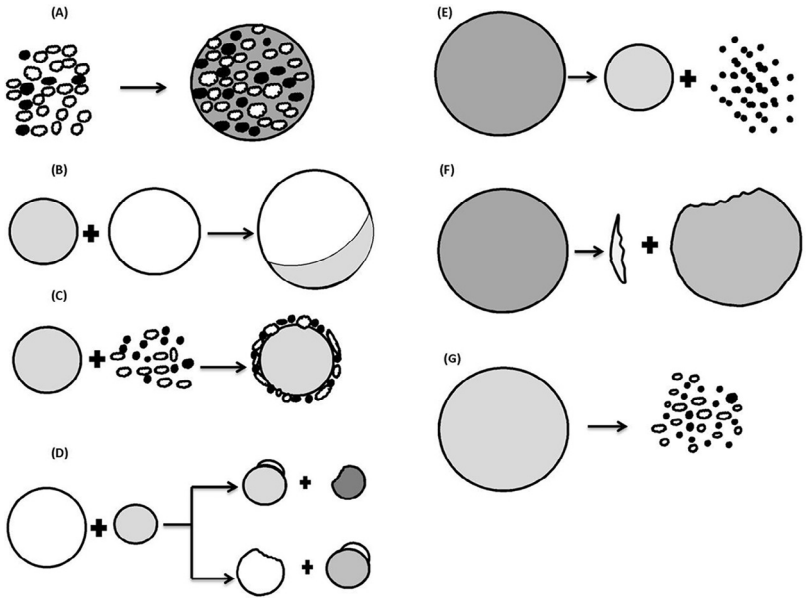



**Fig. 1 – Formation and growth mechanism of pellet (A) nucleation, (B) coalescence, (C) layering and (D) abrasion transfer and mechanism of size reduction (E) attrition, (F) breakage and (G) shatter.**

### 1.1. *Formation and growth mechanism of pellets [4]*

In order to select and optimize any pelletization process, it is essential to understand the fundamental mechanisms of pellet formation and growth. Nucleation, coalescence, layering, abrasion transfer and size reduction are the events that lead to the formation and growth of pellets. In nucleation, primary particles are drawn together to form three-phase air–water–solid nuclei (Fig. 1A). The collision of well-formed nuclei to form larger size particles is known as coalescence (Fig. 1B). Successive addition of material on already formed nuclei is layering (Fig. 1C). Transfer of material from one particle to another without any preference in either direction is abrasion transfer (Fig. 1D). There are three size reduction mechanisms which have an indirect effect on the growth mechanism, particularly layering and to some extent coalescence. Well-formed particles may undergo size reduction due to attrition (Fig. 1E), breakage (Fig. 1F) and shatter (Fig. 1G).

### 1.2. *Pelletization techniques*

Depending on the type of equipment and processes selected, pellet formation and growth may occur in a number of ways (Fig. 2). Here are phenomena that describe the systematic formation of pellets during the various pelletization processes.

#### 1.2.1. *Agitation*

In agitation, finely divided particles are converted to spherical particles, upon the addition of appropriate quantities of liquid, by a continuous rolling or tumbling motion. The liquid may be added prior to or during the agitation stage. Pans, discs, drums, or mixers may be used to produce pellets by the balling process [5].

#### 1.2.2. *Compaction [4,6]*

A compaction is a form of pressure agglomeration in which drug particles or granules are forced together with or without formulation aids by a mechanical force to generate pellets of well-defined shape and sizes. In compression, particles that are pretreated through dry blending or wet granulation followed by drying rearrange themselves to form a closely packed mass. At higher pressure, the particles are forced against each other and undergo elastic and plastic deformation. In extrusion–spheronization, first the dry powder mix is agglomerated with the help of a binding liquid. Then it is processed in the extruder to produce high-density extrudates. These extrudates are finally converted to pellets on spheronizer.

#### 1.2.3. *Drug layering*

Pelletization by layering involves the deposition of successive layers of drug entities from solution, suspension, or dry powder on preformed nuclei, which may be crystals or granules of the same material or inert starter material. In powder layering, a binder solution is first sprayed onto the nuclei, followed by the addition of powder. The moist nuclei tumble in the rotating pan or disc, pick up powder particles and form layers of small particles that adhere to each other and the nuclei by means of capillary forces developed in the liquid phase. As additional binding liquid is sprayed, layering of more powder on the nuclei continues until the desired pellet sizes are obtained. In solution/suspension layering, the drug particles are dissolved or suspended in the binding liquid. The liquid is then sprayed on preformed nuclei and spread out on nuclei followed by drying. Spreading depends on the droplet wetting characteristics, the wettability of the material, and droplet dynamics [4].

Kovacevic et al. have compared powder, solution and suspension layering for the preparation of enteric coated pellets and reported that suspension layering proved to be superior to other techniques both in drug loading and enteric layering phase [7].

#### 1.2.4. *Globulation*

Globulation is a process where liquid materials like melt, solution, or suspension are atomized to generate spherical

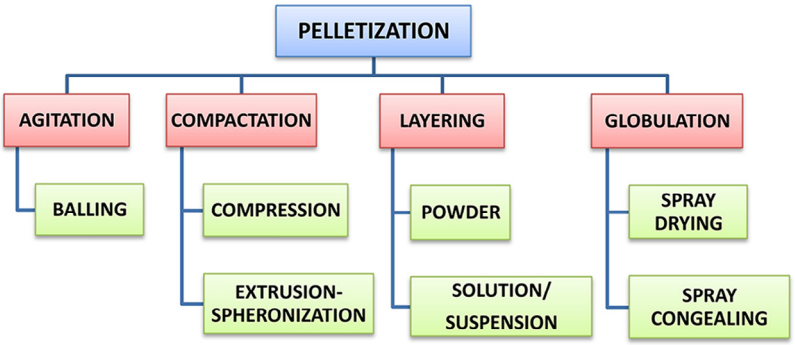



**Fig. 2 – Classification of pelletization techniques.**

particles or pellets. During spray drying, the atomized droplets are contacted by a hot gas stream and evaporation of the liquid is initiated. Evaporation involves simultaneous heat and mass transfer and depends on the temperature, humidity, and transport properties of the air surrounding the droplet. During spray congealing, the atomized droplets are cooled to below the melting point of the vehicles. A critical requirement in this process is that substances should have well-defined melting points or small melting zones [4,5].

Pharmaceutical cocrystals are used as a strategy to overcome poor physicochemical properties of drugs. Duarte et al. have tried spray congealing for the first time in the preparation of cocrystals [8].

### 1.3. *Excipients used in pellet formulation*

Pellets consist of various formulation aids such as filler/diluent – to add bulk (dibasic calcium phosphate, lactose, microcrystalline cellulose, starch, sucrose), binders – to bind powders and maintain pellet integrity (hydroxypropylmethylcellulose, polyvinylpyrrolidone), lubricant – to reduce the coefficient of friction between individual particles or between the particles and the surfaces of the processing equipment (magnesium stearate), separating agent – to promote the separation of pellets into distinct units during a pelletization process (talc), disintegrant – to promote the disruption of pellets (croscarmellose sodium, sodium starch glycolate), spheronization enhancer – to facilitate the production of spherical pellets (microcrystalline cellulose), and release modifier – to get the modified release from the pellet formulation (ethylcellulose, shellac) [9].

### 1.4. *Extrusion–spheronization*

The extrusion–spheronization technique is the most popular method of producing pellets .This process was first reported by Reynolds and by Conine and Hadley and involves four steps: (i) preparation of the wet mass (granulation); (ii) shaping the wet mass into cylinders (extrusion); (iii) breaking up the extrudate and rounding of the particles into spheres (spheronization); (iv) and drying of the pellets [3].

According to Galland et al., wetting operation brings the material to a state in which porosity is linked to water content. The extrusion operation densifies the material to saturation point while spheronization is only a shaping process which maintains hydro-textural state. The drying operation finalizes the textural characteristics of the product by densifying the medium through induced shrinkage [10].

Advantages of extrusion–spheronization over other techniques includes: ability to incorporate higher levels of active components without producing excessively larger particles; two or more active agents can be easily combined in any ratio in the same unit; physical characteristics of the active ingredients and excipients can be modified; and particles having high bulk density, low hygroscopicity, high sphericity, dust free, narrow particle size distribution and smoother surface can be produced [11].

## 2. Steps and equipment used in extrusion–spheronization

### 2.1. *Granulation*

Granulation involves preparation of the plastic mass of the material. Different types of granulators are used to perform the mixing of the powder blend and the granulation liquid. The most commonly used granulators are a planetary mixer, high-shear or sigma blade mixer [3].

Gao et al. have proposed a protocol that could be a valuable asset in a formulation development project to assess the physical properties of wet masses and to predict formation and pellet quality. So, the tedious and expensive pre-production (preformulation and optimization) work could be considerably reduced [12]. The wet granulation process plays an important role in extrusion–spheronization. With the introduction of a twin screw extruder (TSE), it allows the possibility of wet granulation to run continuously in contrast to a conventional batch process using a high shear mixer (HSM). Lee et al. have investigated this process and compared it with HSM granulation process with regard to the granule properties [13].

### 2.2. *Extrusion*

Prepared plastic mass undergoes extrusion in which pressure is applied to a mass until it flows out through an orifice to produce the extrudates. The extrudate length may vary, depending on the physical characteristics of the materials to be extruded, method of extrusion, and how particles are

**Table 1 – Different types of extruders used in extrusion–spheronization.**

| Type of extruder | Mechanism | Comment |
|---|---|---|
| Screw extruder | Utilizes a screw to develop the necessary pressure to force the material to flow through uniform openings | a) Axial: Screen is placed at the end of the screw, perpendicularly with the axis of the screw (Fig. 3A).<br>b) Radial: Screen is placed around the screw, discharging the extrudate perpendicularly to the axis of the screw (Fig. 3B). |
| Sieve extruder | A rotating or oscillating arm presses the damp material through a sieve. | Extrudate falls vertically from the sieve plate (Fig. 4A) |
| Basket extruder | Similar to sieve extruders, except that the sieve or screen is part of a vertical cylindrical wall. | Extrudate formed in the horizontal plane (Fig. 4B) |
| Roll extruder | Roll extruders operate by feeding material between a roller and a perforated plate or ring die. | Type 1: A ring rotates around one or more rollers installed inside the cylindrical die chamber, each of which rotates on its stationary axis (Fig. 5A).<br>Type 2: The roller or rollers are mounted on the outside of the ring die and material is fed from a hopper, occasionally with a screw, into the region between the roller and the die (Fig. 5B).<br>Type 3: Rollers are positioned above and roll along the surface of a flat, stationary die plate (Fig. 5C). |
| Ram extruder | A piston riding inside a cylinder or channel is used to compress material and force it through an orifice on the forward stroke (Fig. 6). | Extrusion forces recorded with the ram extruder are always greater, and force necessary to extrude the wet mass through the ram extruder decreases as the quantity of added water increases. |

manipulated after extrusion. Extrusion is performed using four main classes of extruders: screw, sieve and basket, roll, and ram extruders [14]. Details for all types of the extruder are given in Table 1.

### 2.3. *Spheronization*

In spheronization, the extruded, cylindrically shaped particles are broken into uniform lengths and are gradually transformed into spherical shapes; this shaping process is due to plastic deformation. As extrudates are first broken into nearly uniform lengths, all three dimensions of agglomerate shape are determined, and spheres with a nearly uniform diameter are produced [14]. In the spheronization process, different stages can be distinguished depending on the shape of the particles, i.e., starting from a cylinder over a cylinder with rounded edges, dumbbells, and elliptical particles to eventually perfect spheres (Fig. 7A). Baert and Remon suggested that another

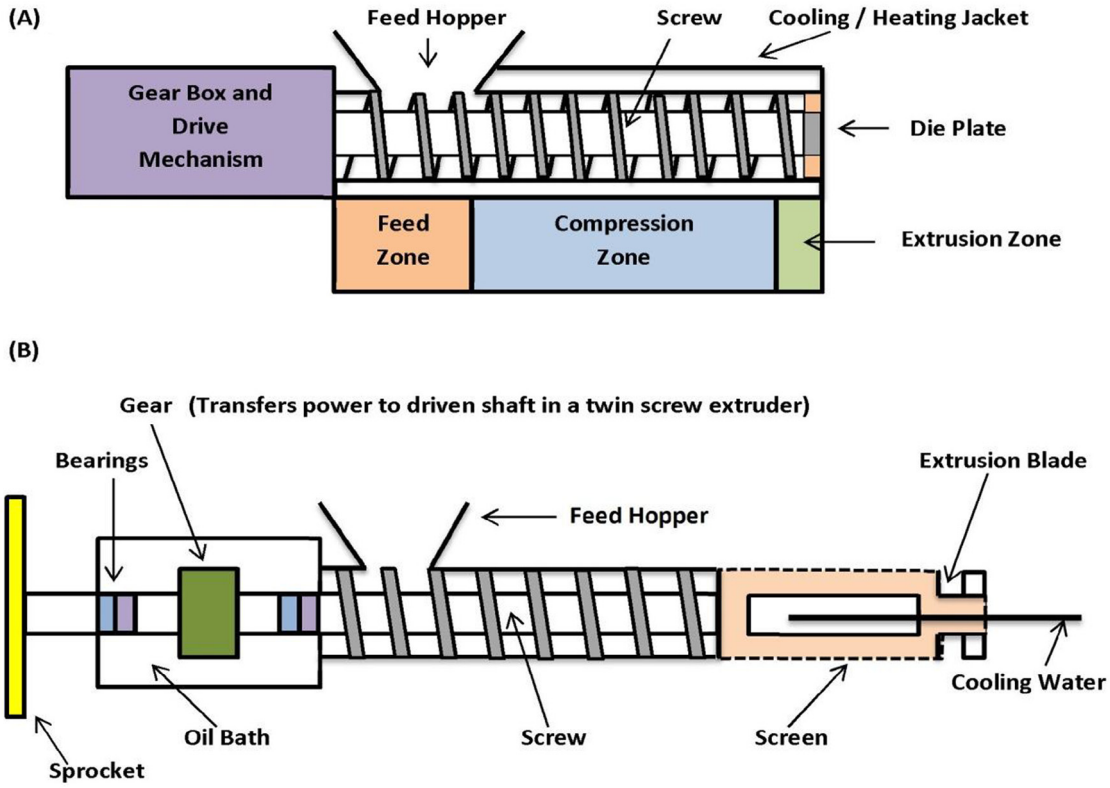



**Fig. 3 – Schematic of Screw extruder; (A) axial type, (B) radial type.**

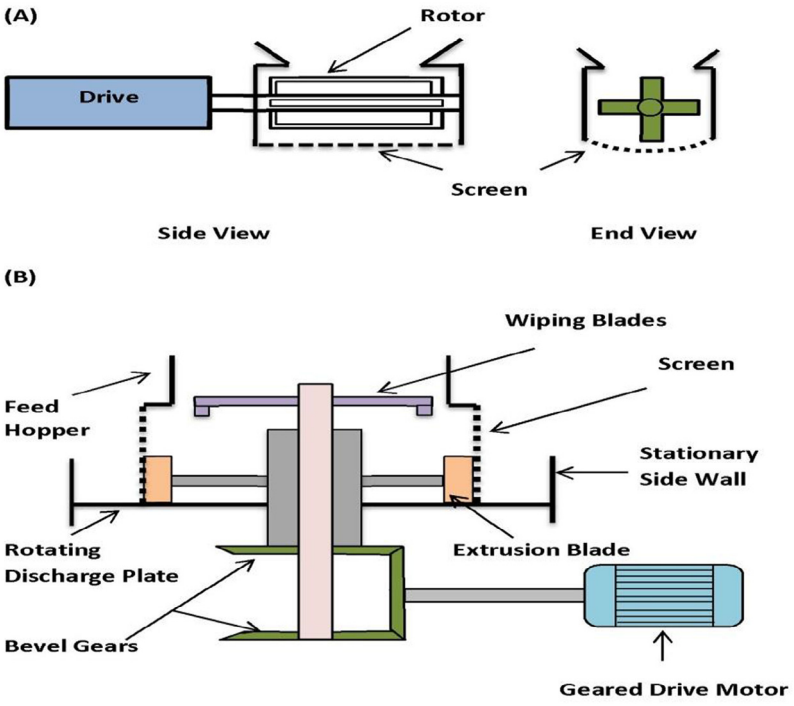



**Fig. 4 – Schematic of (A) sieve extruder, (B) basket (gravity feed) extruder.**

pellet-forming mechanism might exist (Fig. 7B). In this mechanism, 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. Due to the rotational and the frictional forces involved in the spheronization process, the edges of the flat side fold together like a flower forming the cavity observed in certain pellets.

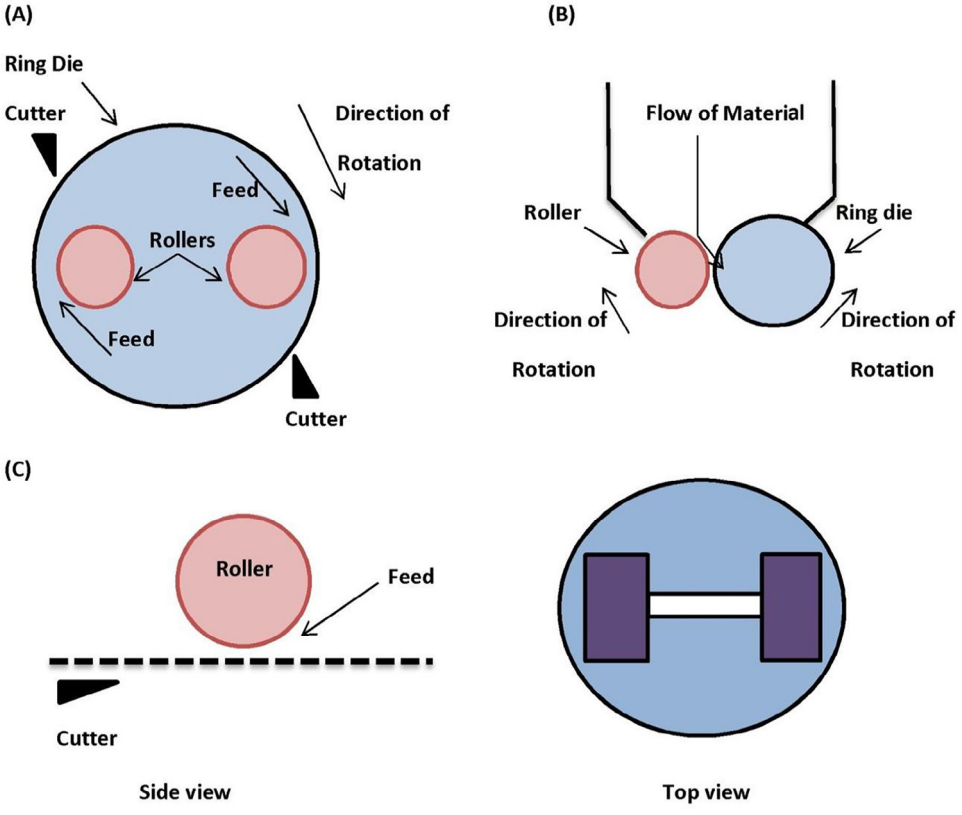



**Fig. 5 – Pellet mill with (A) internal roller, (B) roller external to die, (C) roller on flat die plate**

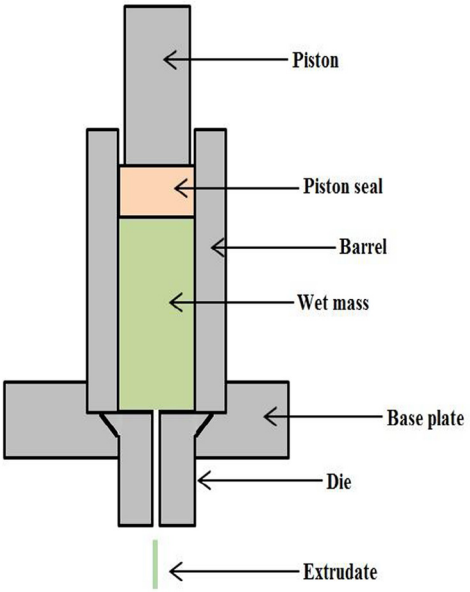



**Fig. 6 – Ram extruder.**

A spheronizer is a device consisting of a vertical hallow cylinder with a horizontal rotating disk (friction plate) located inside (Fig. 8). Extrudates are charged onto the rotating plate and broken into short segments by contact with friction plate, collisions between particles and collisions with the wall. Mechanical energy introduced by the spinning friction plate is transmitted into kinetic energy in the form of mechanically fluidized bed. Further processing will cause the extrudate to deform gradually into a spherical shape [14]. The friction plate has a grooved surface to increase the frictional forces. Two types of the geometry of the grooves exist, cross-hatch geometry where the grooves form right angles and radial geometry where a radial pattern is used.

Fig. 8 shows the fundamental components of the spheronizer. The most important component is the friction plate (Fig. 9) which can have a variety of surface textures designed for specific purpose. The cross-hatch pattern is most common where the grooves intersect each other at $90^0$ angles [14].

Lau et al. reported that in spheronization process, breakage of the extrudate occupies the first 10% of the process duration: rounding off is the rate-determining step. The evolution of pellet shape is classified into five stages, the duration of which is found to scale with spheronization [15]. Vonk et al., when they studied the high shear pelletization, found that pelletization starts with the formation of large primary nuclei. Small secondary nuclei are formed due to the break-up of the primary nuclei. Due to densification, the secondary nuclei became stronger and growth proceeded exponentially by coalescence. During the kneading stage, net growth is diminished until a steady state is observed. The mean pellet size did not change during the final stage of the kneading phase which resulted in a well-defined product [16].

### 2.4. *Drying*

The fourth and final step of the process is the drying of the pellets. The pellets can be dried at room temperature or at elevated temperature in a fluidized bed or in an oven [3].

## 3. Parameters influencing final pellet quality

### 3.1. *Formulation parameters*

#### 3.1.1. *Moisture content*

Water content has a significant influence on the quality of the spheres and is the most important variable for the extrusion process variables [17]. If the moisture content is less than the lower limit, a lot of dust will be formed during spheronization resulting in a large yield of fines. Exceeding the range of the moisture content leads to an over wetted mass and agglomeration of the individual pellets during spheronization due to the excess

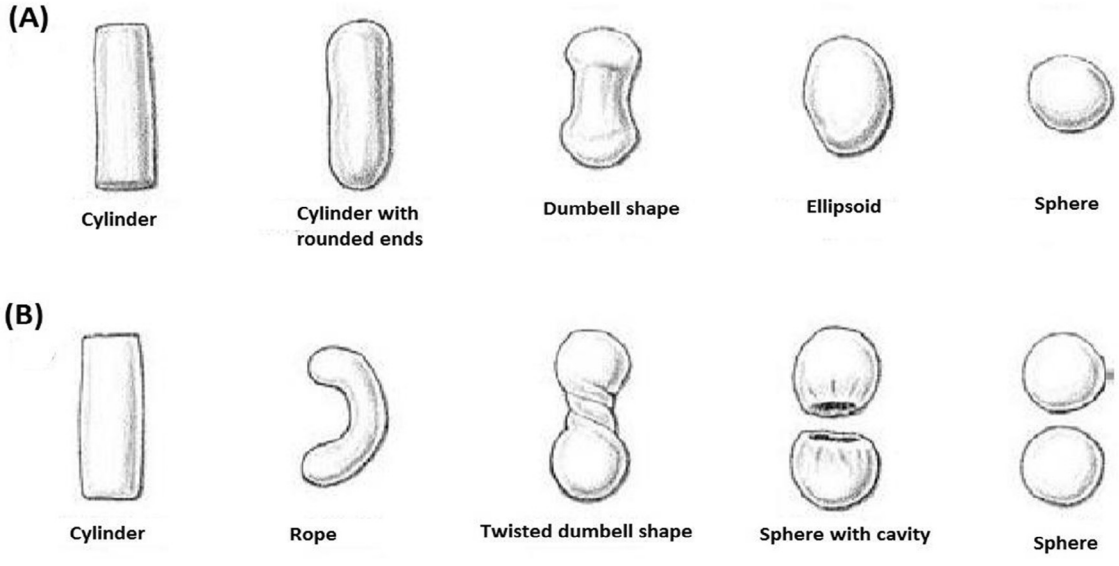



**Fig. 7 – Pellet-forming mechanism according to (A) Rowe and (B) Baert.**

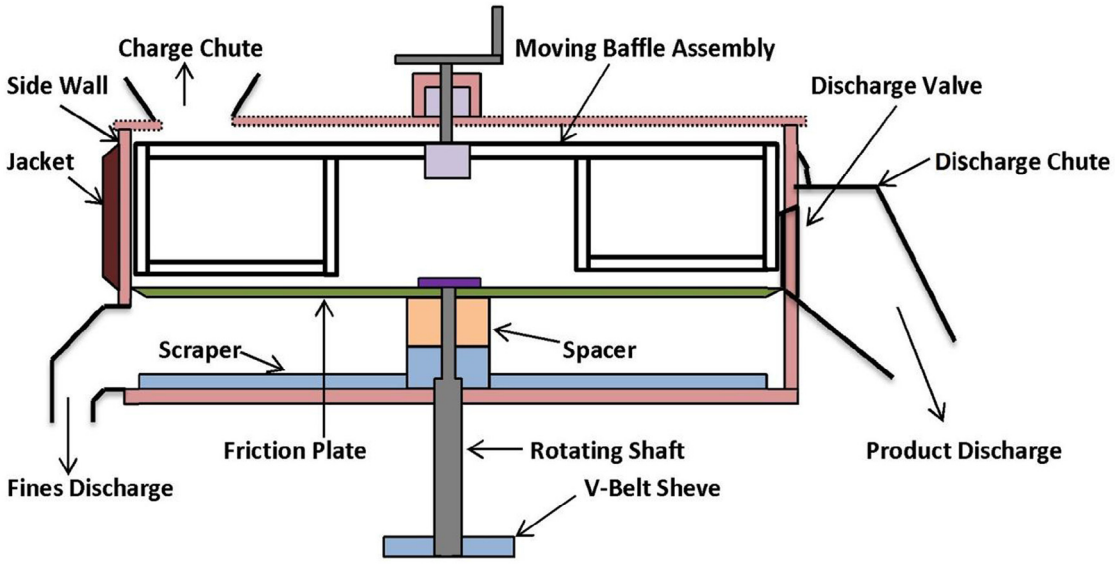
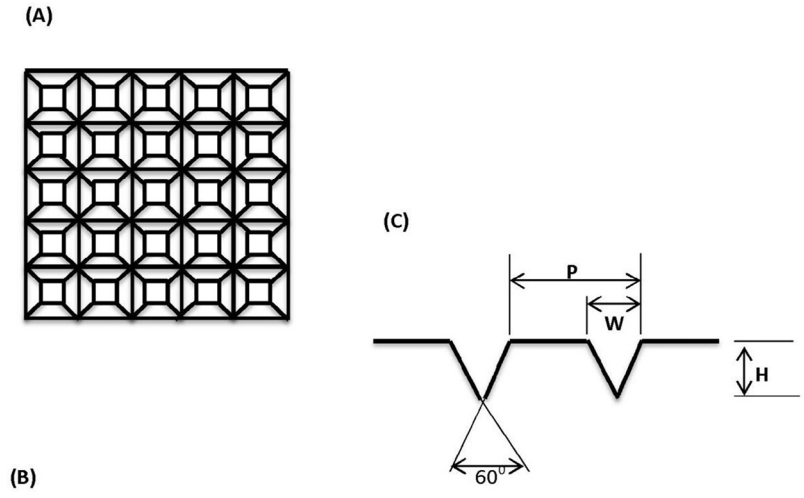



**Fig. 8 – Schematic of spheronizer.**

of water at the surface of the pellets [3]. Water content has the influence on sphere density [18], surface morphology of pellets, and torque of extrusion [19]. According to Lustig-Gustafsson et al. amount of solvent (water) requires for forming pellets was dependent on the model drug and its particle size [20]. Galland et al. stated that it is possible to locate a wetting optimum using hydro-textural diagram [21]. Tomer et al. mentioned that extrusion–spheronization technique is tolerant to some extent of water movement during the extrusion process but excessive water movement is not appropriate [22]. Rantanen et al. were able to get different moisture profiles of the granules and different drying end points during different unit operations performed in a fluidized bed granulator by using near-infrared reflectance spectroscopic method [23].

### 3.1.2. *Granulating liquid*

In most cases, water is used as the granulating liquid although the use of alcohol or water/alcohol mixtures has also been reported [3]. Dreu et al. reported that use of ethanol or ethanol/water mixtures as granulation liquids in the




| P | W | H |
|---|---|---|
| 2 | 1 | 1 |
| 3 | 1.8 | 1.2 |
| 5 | 3 | 2 |

**Fig. 9 – Typical grid pattern of friction plate: (A) detail of grid pattern (cross-hatch design); (B) typical dimensions of plate design (mm); (C) cut away view of the plate.**

extrusion–spheronization process results in the formation of pellets with significantly different mechanical and structural properties from those prepared using water alone. Granulation liquid influences the mechanical and structural properties of the pellets through the contraction driving and contraction counteracting forces during drying [24]. According to Hamedelniel et al. 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 but also caused a reduction in the breaking hardness of the pellets [25]. When Mascia et al. used the dimethyl sulfoxide (DMSO) as the granulating liquid, they got important information regarding the physicochemical properties necessary for solvents to be suitable for the extrusion of microcrystalline cellulose [26].

### 3.1.3. *Excipients*

There is not only the obvious difference in pellet quality starting from different compositions but also a difference when different types of the same product are used [3]. Fielden et al. reported that the particle size of lactose powder (fine and coarse) has a profound influence on the extrusion characteristics of the wet mass and on the size and the roundness of the resulting pellets when prepared using ram extruder and a cylinder extruder [27]. Tho et al. in their work on pectin mentioned that independent of the pectin grade, the two most important factors favoring formation of small spherical pellets were a small molecular size and a strong hydrogen bond forming ability of the additive molecules [28]. But Chohan et al. observed that particle size of the microcrystalline cellulose is not important, the greatest extrudate distortions occur for systems having relatively low shear viscosities at low flow rates. There appears to be an optimal elasticity for the formation of satisfactory spheres in the spheronization stage, i.e., they must neither be too elastic nor have low elasticity [29]. Levis et al. have done comparison between, (i) ultra-fine microcrystalline cellulose (MCC), without sodium lauryl sulphate (grade X), (ii) with variable percentage of sodium lauryl sulphate (SLS; grade Y), both prepared by an ultrasonic homogenization process from Avicel PH-101 and (iii) Avicel PH-101 (grade C). Both new grades (X and Y) proved superior to grade C in an aqueous extrusion–spheronization application for the preparation of indomethacin pellets, producing smoother pellets in greater yield. Grade Y was particularly effective at delaying drug dissolution, due mainly to decreased porosity in the pellets formed and retardation of their break-up [30]. Luukkonen et al. have studied the influence of microcrystalline cellulose (MCC) type and water content on the rheological properties of the wet powder masses using two different MCC grades (Avicel and Emcocel) and silicified microcrystalline cellulose (SMCC, Prosolv) and found that elastic properties of wet masses increase with increasing water content and decrease with increasing shear stresses. SMCC grade proved to be more elastic than the simple MCC grades at each moisture content. Thus, the rheological properties of MCC and SMCC wet masses were different and changed with water content. Consequently, it was not possible to achieve similar rheological properties between different grades of cellulose by altering the water content of the wet mass [31].

MCC is the most important excipient in the pellets prepared by extrusion–spheronization. Facts and findings of researchers about MCC and other excipients are presented here. Fielden et al. suggested that water is an appropriate fluid to use with MCC, but with binary mixtures of lactose and MCC a 50:50% mixture of ethanol and water proved acceptable. They also observed differences in the movement of fluid in the two grades of lactose which differed in particle size and between lactose and MCC. They also mentioned that MCC introduces absorptive and adsorptive influences into the binary mixtures with lactose which are absent or minimal in the lactose systems. Binary mixtures can be used to produce spherical granules by extrusion/spheronization [32]. Krueger et al. studied the spheronization mechanism of pellets prepared by MCC II – a polymorph of commonly used MCC I. They observed MCC II behaves in a different manner than MCC I in spheronization [33]. Mallipeddi et al. suggested that fine particle ethyl cellulose (FPEC) is a good diluent for extrusion–spheronization [34].

However, microcrystalline cellulose is not universally applicable due to a number of limitations: prolonged drug release of poorly soluble drugs, chemical incompatibility with specific drugs, and drug adsorption onto MCC fibers. Hence, several products have been evaluated to explore their application as extrusion–spheronization aid, aiming to avoid the disadvantages of MCC and to provide a broad application platform for extrusion–spheronization: powdered cellulose, starch, chitosan, kappa-carrageenan, pectinic acid, hydroxypropyl methylcellulose, hydroxyethyl cellulose, polyethylene oxide, crosslinked polyvinylpyrrolidone, glycerol monostearate [35], natural excipients, such as saccharides, oligosaccharides, alginate or synthetic polymers, mainly polyacrylates and polyvinylpyrrolidone [35].

Lower tensile strength, fast disintegration and release [36], pellets of a sufficient quality independent of the incorporated fillers and drugs [37], improved bioavailability of the poorly soluble HIV-protease inhibitor darunavir [38], more robust formulation as the optimal range of water content is much broader [39], such distinguished behaviors were observed for kappa-carrageenan pellets when they were compared with MCC pellets. When Thommes et al. studied the effect of drying on extruded pellets based on kappa-carrageenan, they found that ionic interaction between calcium ions of dicalcium phosphate and sulfate ester groups of kappa-carrageenan affected the pellet properties like drug release [40].

Modified starch [41], low soluble pectin-derivative pectinic acid [42], calcium stearate as pelletization excipient for slow release formulations [43], lipids like hard fat, glycerol distearate and glycerol trimyristate alternatives to commonly used binders [44], xanthan gum [45], chitosan, sodium alginate [46], these are the examples of other excipients studied by researchers to fulfill the special requirements in pelletization.

### 3.1.4. *Drugs*

Extrusion/spheronization technique can be used for the preparation of pellets of various materials; natural extract, bacterial culture, drugs, etc., and one can also prepare different types of pellets (immediate release, modified release). To achieve this versatility, there is a requirement of changes in the formulations, process, and excipients. Here are some examples indicating various attempts of researchers to achieve versatility in pellet formulations; self-emulsifying pellets of good quality to deliver milk thistle extract (silymarin) [47], pellets containing furosemide solid dispersion (SD) for oral administration [48], pellets

with a high loading (≥90wt%) of 5-aminosalicylic acid (5-ASA) [49]. Taste-masking of quinine sulphate [50] and metformin hydrochloride [51], immediate-release pellets containing poorly soluble drugs (hydrochlorothiazide and piroxicam) using modified starch (high-amylose, crystalline and resistant starch) as the main excipient [52]. An oral modified-release formulation for the purposes of site-specific targeting of ranitidine was prepared [53]. Naringin, which is widely present in foods of plant origin and traditional Chinese medicines, has been reported to possess various biological and pharmacological properties, short half-life (t1/ 2) restricts its use as an oral dosage form hence sustained release (SR) pellets of naringin were prepared to solve this problem [54]. For use in dehydration unit spherical pellets of canola meal were prepared [55]. Pellets of omeprazole with osmotic pressure-activated rupturable membrane were developed for pulsatile drug delivery [56]. Bioadhesive hexylaminolevulinate pellets were formulated intended for photodynamic therapy in the treatment of cervical cancer [57]. Enteric-coated spheres were formulated containing probiotic bacteria (Lactobacillus casei). Oral delivery of live bacterial cells (LBC) requires live cells to survive, first, manufacturing processes and second, GI microbicidal defenses including gastric acid. Live L. casei directly incorporated in the granulation liquid, followed by granulation, extrusion, spheronization, drying and spray coating to produce dried live probiotic spheres [58].

## 3.2. *Equipment parameters*

### 3.2.1. *Mixer*

Bryan et al. reported that mixer type (rather than shear strain rate) has the strongest influence on paste properties when there is comparison between the planetary mixer and screw-based mixer. Pellets formulated using screw-mixed material show higher yield, strength and forms smaller pellets with a narrower size distribution when spheronized under identical conditions [59].

### 3.2.2. *Extruder*

Many researchers have done work on different types of extruder. They found that extrusion forces recorded with the ram extruder are always greater than those with gravity feed extruder, and force necessary to extrude the wet mass through the ram extruder decreases as the quantity of added water increases [20]; for the ram extruder, a decrease in water content with increasing ram displacement and redistribution of liquid during extrusion is an important factor, affecting the quality of the spheres [60]. Optimal moisture content is higher using the twin-screw extruder compared to the ring die press which is explained by the crystallite-gel model [61]. Pellets obtained from screen extruder are in general smaller, with a wider size distribution, than those from ram extruder [62]. For roll extruder, the key operating parameters which controlled the extrudate mass flow rate, force on the screen and roller torque are (i) the size of the gap between the top of the roller blade and the screen and (ii) the roller rotational speed [63]. Axial screw extruder produces a more dense material compared to a radial screw extrude [3]. Sonaglio et al. have prepared the pellets of paracetamol using axial and radial screw extruder and found that the temperature variation and the extrusion time are considerably higher on the axial system. The influence of particle size of paracetamol over the temperature is more significant than its concentration; fine particle size generates less heat, at the minimal concentration of paracetamol for the axial system and at the maximal for the radial system. Extrusion time is smaller with the fine powder for both systems and interactions between the concentration and particle size of paracetamol are significant for both extrusion systems when the axial and radial extrusion systems are applied as process variables [64].

### 3.2.3. *Friction plate*

The friction plate is a very important component of spheronizer which has a grooved surface to increase the frictional forces. Two types of the geometry of the grooves exist, cross-hatch and radial geometry. Zhang et al. studied the four cross-hatched pattern plates (large studs, pyramidal, saw-toothed and small studs) of different dimensions and/or shape of the surface protuberances. A systematic effect of protuberance geometry on the product yield (a measure of losses due to fines) is evident, with yields decreasing in the order (large studs), (pyramidal), (saw-toothed), and (small studs) [65]. Michie et al. have studied three different spheronizer friction plate patterns (i.e. cross-hatch, radial, striated edge pattern) and found that the pattern of the friction plate used in the spheronization of extrudates affects the properties of the pellets [66].

### 3.2.4. *Extrusion screen*

The die openings in the screen or die plate may be of several basic designs. The shape of opening varies with the application. If a denser product is needed, a thicker plate or screen is required to withstand the greater extrusion pressure used. Fig. 10 shows some of the common die configurations. For thin screens or die plates, the hole is typically straight with a slight neck or taper at the entrance due to punching method; hole sizes from 0.5–1.5 mm are typical. Holes in die plates greater than about 1.5 mm thick are usually drilled. The upper limit of hole size is determined by flow properties of the particular formulation, extrusion rate and the ability of the extruder screws to compress and transport the material so that a consistent extrudate is obtained [14].

Vervaet et al. have studied the effect of an extruder equipped with a screen of a length-to-radius ratio (L/R ratio) of 2 and 4 on final pellet quality. They observed that screen with the lowest L/R ratio formed a rough and loosely bound extrudates, while the screen with an L/R ratio of 4 formed a smooth and well-bound extrudates. This observation can be explained by the higher densification of the wet mass in the screen with the greatest thickness [67]. Sonaglio et al. on applying the factorial design have observed the strong interaction between water content and extruder screen size for the particle size distri-

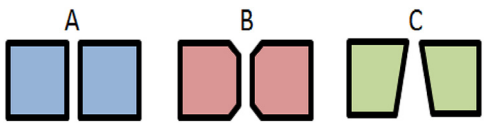



**Fig. 10 – Alternative die designs: (A) cylindrical; (B) tapered inlet and/or outlet; (C) conical.**

bution response and also found that extruder screen size has a significant effect on the bulk density of pellets [18].

### 3.3. *Process parameters*

Thiry et al. suggested that while using extrusion–spheronization, similar to formulation parameters, process parameters should also be investigated since they have a major impact on the final product characteristics. Homogeneity of the mixing, the state of the drug (crystalline or amorphous), the dissolution rate, and the residence time can be influenced by variations in the process parameters. In particular, they have reviewed the impact of temperature, screw design, screw speed and feeding on the final product [68].

#### 3.3.1. *Extrusion speed*

The total output of the extrudate is mainly governed by the extrusion speed. The output should be as high as possible for economic reasons but an increase in extrusion speed influenced the final pellet quality [3]. Mesiha and Valltés evaluated fourteen different substances for their usefulness in reducing surface defects, heat due to friction and energy consumption in an instrumented extruder. The materials include several common lubricants and glidants, surface active agents, humectants, polyethylene glycol and a binder in a simple binary system with high drug loading. High HLB surfactants, particularly SLS, performed best at levels as low as 0.125%, keeping heat and amperage draw to a minimum and greatly reducing surface defects. This was correlated with reduced power consumption during extrusion as the friction at the die wall of the extrusion screen was lowered [69].

#### 3.3.2. *Extrusion temperature*

Fielden et al. have studied the interaction of water and microcrystalline cellulose through thermal studies. The results indicate that most of the water held within a system used for the preparation of spherical granules by extrusion/spheronization is present as free water which may be readily lost by evaporation during the extrusion process and ultimately affect the final quality of pellets [70].

#### 3.3.3. *Spheronizer load*

The yield of pellets of a specific range decreased with increased spheronization speed at a low spheronizer load and increased with extended spheronization time at higher spheronizer load [71]. Mean diameter increased with increasing spheronizer load [3]. According to Newton et al., low load appeared to give poor particle/particle interaction while a high load produced poor plate/particle interaction [72].

#### 3.3.4. *Spheronization time*

Spheronization time has a significant influence on the quality of the spheres [17]. A wide variety of effects was witnessed when assessing the importance of this parameter on formulations containing mixtures of microcrystalline cellulose: increased diameter [3], narrower particle size distribution, higher sphericity, change in the bulk and tapped densities [73] and change in the yield of a certain size range [71,73] were observed with extended spheronization time.

#### 3.3.5. *Spheronization speed*

Spheronizer speed has a significant influence on the quality of the spheres [17]. Very low speed produced no significant shape changes in the extrudate and very high speed resulted in a size reduction of the particles [72,74]. The hardness, roundness, porosity, bulk and tapped densities friability flow rate and surface structure [18,73] of the pellets were also influenced by a change in the spheronization speed. Ronowicz et al. have recognized that spheronization speed, spheronization time, number of holes of extrusion screen and water content of extrudate are the key factors influencing pellet aspect ratio. The most spherical pellets are achieved by using a large number of holes during extrusion, high spheronizer speed and longer time of spheronization [75]. Wan et al. observed that at the combination of speeds ranging from 1000 to 2000 rpm and residence times between 5 and 15 min spheroids with a modal fraction in a size range of 0.7–1.0 mm may be produced [76]. Newton et al. from their study suggested that to predict the spheronization performance, it is necessary to use a good quality extrudate and operate the spheronizer at rotational speeds which give the same linear peripheral velocity of the plate [77].

#### 3.3.6. *Drying method*

The drying technique has great influence on the pellet quality. Bashaiwoldu et al. have done the comparison between freeze-drying, fluid-bed drying, hot air oven drying and desiccation with silica-gel to less than 5% (w/w) water content. They found that freeze-drying is more porous, with most of the pores open to the atmosphere and having a higher surface area than pellets dried by the other methods. Pellets dried by desiccation contained the highest proportion of closed pores. The drying techniques, which produced porous, deformable and weak pellets, produced stronger tablets [78]. Murray et al. observed that when oven and freeze-drying is compared the granule yield point (GYP) is significantly lower for the freeze-dried granular material. Granules with a lower GYP produced tablets of increased strength. Dissolution profiles are similar for both the oven and freeze-dried samples [79]. Song et al. have reported that freeze-drying retained the shape and size of the granules, whereas oven-drying produced roughened granules due to the uneven shrinkage of the wet powders [80]. According to Berggren et al., the difference in drying behavior of pellets can be explained by a liquid related change in both contractions driving force and contraction counteracting force or by a different contraction mechanism. The difference in final pellet porosity between the two types was caused by a difference in densification during drying rather than a different degree of densification during the pelletization procedure [81]. Berggren et al. has done their work on the effect of drying rate on pellets quality. In their study, they found that drying of the pellets occurred at a falling rate and the reduction in liquid content with time obeyed a first order type of relationship. An increased drying rate did not affect the shape and surface texture of the dried pellets and did not cause them to fracture, drying conditions did affect pellet porosity, with an increased drying rate resulting in more porous pellets, the drying rate also affected the deformability of the pellets (as assessed from Kawakita 1/b values) and their ability to form tablets, marked changes in tablet tensile strength with variations in drying rate may be obtained [82].

## 4. Evaluation of pellets

### 4.1. *Particle size distribution*

Pellets are invariably coated, may it be for enteric release, taste masking, stability, or controlled release. In order to achieve any of these desired end point product performances, it is necessary to determine the amount of coating required to produce the desired film thickness and/or coverage. Since particle size directly affects the surface area and consequently, the amount of coating necessary for the desired coverage, it is advantageous to use the largest possible particle size for the substrate that may provide the desired end product performance. It is essential that particle size distribution should be as narrow as possible [83]. Evaluation of particle size distribution is done by using sieving and microscopy.

#### 4.1.1. *Sieving*

Sieving is the most widely used method for measuring particle size distribution of pellets, because it is inexpensive, simple, and rapid, with little variation among operators. The procedure involves the mechanical shaking of a sample through a series of successively smaller sieves, and the weighing of the portion of the sample retained on each sieve [83].

#### 4.1.2. *Microscopy*

Microscopy provides a direct method for determining particle size distribution of pellets. In the case of optical microscopy, the diameter of pellets can be measured either by using a calibrated micrometer or with the help of eyepieces with grids of circles and squares. In either case, the magnification is determined by the use of a calibrated stage micrometer since the magnification is not equal to the product of the nominal magnification of the objective and the eyepiece. In scanning electron microscopy (SEM), pictures are taken to examine the microstructure of the pellet surface. It can be employed to keep a permanent record by means of the photograph and, in most cases, a microbar, used for reference, can be imprinted on these photographs. The pellets first need to be sputter coated with gold or gold-palladium to improve conductivity. Generally, a 70 $A^0$ thick film of conductive material is applied with an average grain size of 20–30 $A^0$. The coating time ranges between 1 and 4 minutes [83]. Bashaiwoldu et al. have used the laser profilometry technique in conjunction with SEM to determine permanent structural changes induced by compaction of pellets [84].

### 4.2. *Surface area*

The surface area of pellets is obviously controlled by particle size, shape, porosity and, surface roughness and it is a very important parameter which can affect the release rate of pellets [83]. There are three methods of measuring surface area of pellets.

#### 4.2.1. *Mathematical calculation*

The surface area of the pellet can be calculated from the measurement of its diameter since the surface area is equal to $\pi d^2$. True density measurements can also be used to determine the specific surface area using following formula;

$$SA = \frac{6}{\rho dvs}$$

Where;

SA = specific surface area
dvs = mean volume surface diameter
ρ = true density

#### 4.2.2. *Gas adsorption*

The volume of nitrogen that is adsorbed by the substrate contained in an evacuated glass bulb is determined at various pressures, and the results are plotted as P/V (Po-P) versus P/Po to generate a linear plot of the BET equation for adsorption of nitrogen on a substrate. This procedure is developed by Brunaure, Emmett, and Teller and is commonly known as BET method. V is the volume of gas in $cm^3$ adsorbed per gram of substrate at pressure P; Po is the saturation vapor pressure of liquefied nitrogen at the temperature of the experiment. The slope and intercept of the above plot yield the values b and Vm. The specific surface (Sw) of the particles is then obtained by application of the equation.

$$Sw = 4.35 \times Vm$$

#### 4.2.3. *Air permeability*

Because of the simple instrumentation and the speed with which determinations can be made, permeability methods are widely used pharmaceutically for specific surface determinations, especially when the aim is to control batch-to-batch variation. A commercially available, instrument is the Fisher sub-sieve sizer. The resistance to the flow of air through a plug of compacted material is the surface area of the material. Since the flow rate through the plug or bed is also affected by the degree of compression of the material, the applicability of air-permeability methods for pellets is questionable.

### 4.3. *Shape and sphericity*

One of the most important characteristics of a pellet is its roundness. Several methods exist to determine the roundness: visual inspection of the pellets and classification into a group, one-plane-critical-stability (OPCS), being the angle to which a plane has to be tilted before a particle begins to roll; the ratio of the largest and the smallest diameter of a pellet; shape factors calculated by means of the projected area of the pellet and its perimeter measured with computer-aided image analysis [3]. Eriksson et al. have studied some methods for the assessment of the sphericity of pellets including, analysis of the two-dimensional images in the form of an elongation ratio (direct microscopic measurement), aspect ratio (image analysis), OPCS and a shape factor ρR plus 3-dimensional characterization by the Heywood shape coefficient and a permeameter shape factor. The results indicate that OPCS and the shape factor, ρR, were more distinguishing in terms of detecting batch differences and inter-batch differences. The two-dimensional image methods ranked the batches in equivalent

order of ranking. The Heywood shape coefficient gave the same ranking but the permeameter shape factor gave a significantly different ranking which could be associated with the surface texture of the spheres [85]. Podczeck et al. have developed a three-dimensional shape factor ($e_c3$) for the characterization of the quality of pellets based on image analysis. A comparison with the Heywood shape factors demonstrates the ability of $e_c3$ to differentiate various batches of pellets based on a defined mathematics, whereas the Heywood shape factors require certain assumptions about the particle outline to be applicable [86]. Podczeck et al. have done an evaluation of a standardized procedure to assess the shape of pellets using image analysis. They have investigated the influence of threshold definition, a number of pellets counted, image magnification and lightning technique on the assessment of pellet shape using three batches of pellets and an image analysis system. They have measured the pellet parameters which include aspect ratio, circularity, projection sphericity, eR and feret diameter. After all the evaluation they have given some suggestions: (i) one pixel should not cover more than 30 μm for pellets of an average particle size of 1.2 mm; (ii) an upper value for the aspect ratio of 1.1 and a lower value of 0.6 for eR are recommended; (iii) the circularity should not be used as the shape factor to characterize spheres, because errors in image recognition can affect strongly the applicability of this shape factor; and (iv) the projection sphericity has only a limited sensitivity to variations in particle shape [87]. Bryan et al. have developed a new quantitative parameter, named 'dumb-bellity', to monitor the formation and disappearance of 'dumb-bell' shaped pellets in the early stages of the rounding process [88]. Rowe et al. have used Monte-Carlo technique to investigate the influence of pellet size, dispersity, shape and aggregation on the filling of hard shell capsules. Results show that filling is a function of pellet shape and that above an aspect ratio value of 1.2 filling reproducibility is reduced [89].

### 4.4. *Porosity*

The porosity of pellets can affect the capillarity action of the dissolved drug and, consequently, influence the rate of release of drugs from the pellets. It also affects the film deposition and formation during coating. The pores can be analyzed, qualitatively, by scanning electron microscopy and, quantitatively, by mercury porosimetry [83]. Relationship between mercury intrusion pressure and pore radius is described by Washburn equation as follows;

$$r = \frac{2\gamma|\cos\theta|}{p}$$

Where;

$\Upsilon = 480$ ergs/cm$^2$
$\Theta = 140^0$
r = pore radius
p = mercury- intrusion pressure

Here are some factors to be considered while using the mercury porosimetry for the determination of the pore-size distribution:

(1) Vacuum to be applied for evacuation of the samples
(2) Rate of pressure buildup
(3) Purity of mercury
(4) Difficulties in contact-angle measurements
(5) Effect of species adsorbed on the solid surface
(6) Damage of weak particles by high pressure
(7) Repeatability of the data for the same system
(8) Overlap of pore-size distributions, as obtained by nitrogen adsorption and mercury porosimetry
(9) Mercury retraction

Tunón et al. mentioned that porosity of pellets is a potential factor that the formulator can use to optimize drug release and one that can affect the robustness of a formulation during manufacture [90]. Westermarck et al. have used mercury porosimetry and nitrogen adsorption methods in pore structure and pore surface area characterization of microcrystalline cellulose powder, granules, and tablets. Mercury porosimetry gives information on the behavior of powder and granule particles in granulation or compression and nitrogen adsorption brings out the changes in the intra-particular structure of particles. The results obtained using these methods together can be used in the characterization of the behavior of materials in granulation and tableting [91].

### 4.5. *Density*

Density of pellets can be affected by change in the formulation and/or process, and consequently may affect other processes or factors, such as the following:

(1) Most pellets are filled into hard gelatin capsules volumetrically, using automated capsule-filling machines. Obviously, if the density of pellets varies significantly from batch to batch, the potency of the finished capsule will also vary.
(2) Any significant variation in the density of pellets will affect the batch size determinations in the coating equipment.
(3) If the mixing of different types of pellets or different batches of pellets is necessary prior to filling them into capsules or prior to tableting, it is advisable and may be necessary not only to have similar densities but also reproducible density from batch to batch.
(4) Gastrointestinal transit did appear to be prolonged with an increase in density, heavier the density longer the gastric emptying and prolonged small intestinal residence time.

The bulk and tap densities of pellets are determined to gain an idea of the homogeneity of the particle size distribution [3]. The bulk density of pellets can be measured by using an automated tapper, while the true density of pellets can be determined by an air-comparison pycnometer or by solvent-displacement method. Bulk density is indicative of the packing properties of particles and, as such, is greatly influenced by the diameter of spherical pellets. By contrast, true density indicates the extent of densification or compactness of substances and, therefore, is influenced by the diameter of spherical pellets to a lesser extent [83].

### 4.6. *Hardness and friability*

The hardness of the pellets can be correlated with the friability according to Reynolds (1970). It is necessary to attain acceptable hardness and friability of pellets that can withstand handling, shipping, storage and other processing such as a coating that pellets may be subjected to. Variation in the formulation and/or process of pellets, as well as variability in the raw materials, can potentially result in significant variations in the hardness and/or friability of pellets. Hardness and friability determination of pellets are recommended, just as they are for tablets [83]. The determination of hardness is performed by measuring the force required to break a pellet of well-known diameter as the strength increases with increasing diameter [3]. The instrument such as the Khal pellet-hardness tester provides relative hardness values, and a friabilator may be employed for generating the friability index [83]. Friability is determined by rotating the pellets in a friabilator or by shaking the pellets in a Turbula mixer for a fixed period of time. Both techniques make use of glass beads to increase the mechanical stress on the pellets [3].

Podczeck et al. have determined the mechanical properties of pellets and film coated pellets using dynamic mechanical analysis (DMA). Elastic and viscoelastic properties of pellets and film coatings applied to pellets were studied [92]. Bashaiwoldu et al. have used dynamic mechanical analysis (DMA) to determine the mechanical properties of pellets. The application allowed the determination of (i) an accurate Young's modulus of elasticity, (ii) the presence of a reversible elastic deformation even after the yield point in terms of storage modulus and (iii) a change in the values of the phase angle, which illustrate the increase in viscoelasticity of the pellets formed with ethanol, glyceryl monostearate (GMS) or glycerol. Decrease in viscoelasticity was observed with the incorporation of lactose into the MCC pellets [93].

### 4.7. *Flow properties*

Proper characterization is an important aspect of any dosage form design; flow property is one of them. The flow properties of pellets are determined to ensure a homogeneous filling of the pellets in the capsules [3,73].

### 4.8. *Disintegration*

Disintegration determines whether pellets disintegrate within a prescribed time when placed in a liquid medium under the prescribed experimental conditions. Disintegration is defined as that state in which no residue of the unit under test remains on the screen of the apparatus or, if a residue remains, it consists of fragments of disintegrated parts such as insoluble coating. If discs have been used with capsules, any residue remaining on the lower surfaces of the discs consists only of fragments of shells. The apparatus consists of a basket-rack assembly, a 1-litre beaker, a thermostatic arrangement for heating the fluid and a mechanical device for raising and lowering the basket in the immersion fluid at a constant frequency rate [94]. One can easily find the detail procedure for performing the test and other details in official books (Pharmacopoeia).

Lundqvist et al. have reported that disintegration time increases with the use of high density disintegrating agent [95].

### 4.9. *Dissolution*

This test is designed to determine compliance with the dissolution requirements for solid dosage forms administered orally. This test is used to measure the drug release at given time under certain conditions from the given formulation [94]. One can easily find the detail procedure for performing the test and other details in official books (Pharmacopoeia).

Several authors correlated parameters such as hardness, composition and drug loading with the release profiles of a drug [3]. Others have studied the influence of film coating, drug and filler solubility [96], physical structure changes of the matrix [97], pellet shape and surface properties [98] on the release profiles of a drug.

## 5. Conclusion

Though the extrusion–spheronization is a very promising technique for the production of pellets, a major drawback of this process is that it is a multi-step batch process. Hence, there is a scope for improvement in process or instrumental system so as to overcome this drawback of the multi-step batch process and also to achieve different goals, which may be economical, technical or commercial. There is also a scope for developing new methodologies for characterization of the pellets.

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