EXTRUSION/SPHERONIZATION

PELLETS AND PELLETIZATION TECHNIQUES

Pellets used in pharmaceutical industry are usually spherical particles with a size ranging between 100 and 2000 µm. They could be prepared by different agglomeration techniques and as semiproduct subsequently filled into hard capsules or compressed into tablets as final orally applied dosage forms. Recently in the pharmaceutical industry, they are usually produced by an extrusion/spheronization process by layering of drug dispersion on inactive core pellets from inner materials (lactose, starch, microcrystalline cellulose) or by pelletization process in a fluidized bed rotor chamber (roto-agglomeration) [1]. Pellets are usually used as film-coated with one or more layers of polymer film that provide protection of the active ingredient or control the release of the drug or could be formed as matrix type of formulation with homogeneously dispersed active ingredients [2]. Applications of pellets could be found not only in the pharmaceutical industry, but also in the agribusiness (e.g., fertilizer, fish food), ceramic industry, metallurgy, polymer industry, etc. [3].

Pelletization can be defined as an agglomeration process that converts fine powders or particles of bulk drugs and excipients into small, free-flowing, more or less spherical units [4].

Pellets could be formed by number of methods. The overview provide in Figure 1.

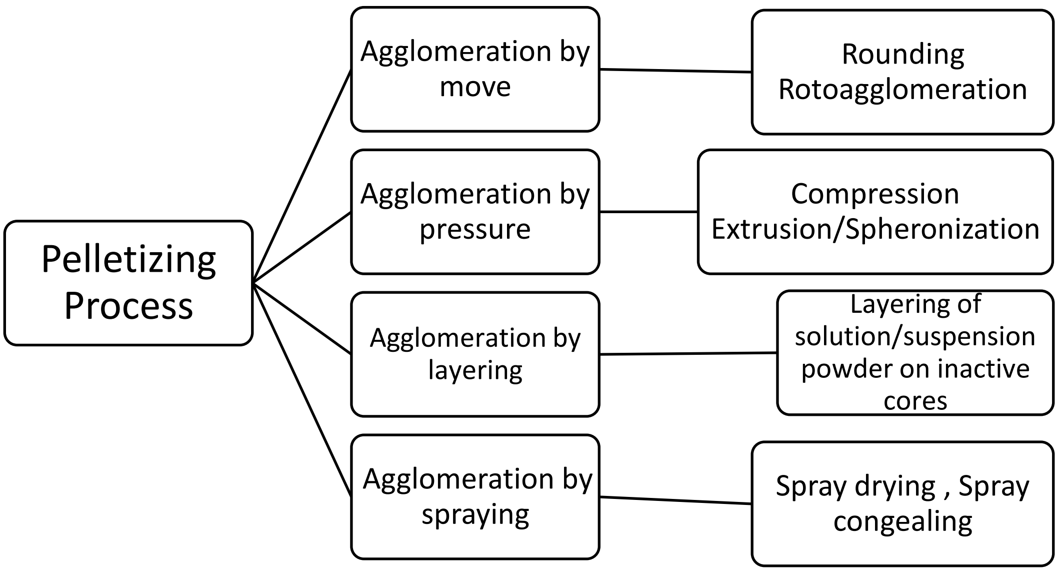

Figure 1: Methods used for pellets formation

MAIN ADVANTAGES AND DISADVANTAGES OF PELLETS

The pharmaceutical industry has developed a great interest in pelletization due to a variety of reasons: The main *technological advantages of pellets* are [5]:

- prevention of segregation of co-agglomerated components, resulting in an improvement of the uniformity of the content;
- prevention of dust formation, resulting in an improvement of the process safety;
- increasing bulk density and decreasing bulk volume – better filling into capsules and compression into tablets;
- the spherical shape of pellets improves the appearance of the product;
- improvement of the handling properties, due to the perfect flowing properties;
- improvement of the hardness and friability of pellets;
- Ideal low surface area-to-volume ratio that provides an ideal shape for the application of film coatings.

Additionally, the production of controlled-release multiparticulate oral dosage forms using spheroids, designed to deliver drugs at a specific site within the gastrointestinal tract or releasing drug over an extended period of time, leads to a series of *therapeutic advantages* over conventional oral dosage forms (tablets or capsules) such as [6,7]:

- pellets can disperse freely throughout an area of the gastrointestinal tract after administration and consequently the drug absorption is maximized as a large gastrointestinal surface can be involved in this process
- fluctuation (changes) of the drug plasma levels can be reduced by the use of spherical particles with different release rates; potential side effects are minimized without lowering drug bioavailability, modified-release multiparticulate delivery systems are less susceptible to dose dumping than single-unit dosage forms;
- the wide distribution of spherical particles in the gastrointestinal tract limits localized cumulation of the drug, avoiding the irritant effect of some drugs on the gastric mucosa;

But pellets also present some disadvantages [7]:

- pellets often cannot be pressed into tablets because they are too hard and rigid. In that case, pellets have to be filled into the final form of hard capsules;
- compressing into tablets of coated pellets may also lead to film damage potentially affecting its controlled release properties;
- the production of pellets is often an expensive process and requires highly specialized equipment; and well educated operators;
- the control of the production process is difficult, because of the multi-step character of the majority of pelletization techniques.

Extrusion/Spheronization

Extrusion/spheronization is a multi-step process, for the production of pellets. This technique was invented in 1964 by Nakahara in Japan. Extrusion/spheronization nowadays is considered more established and serves more advantages over the other methods for pellet production. These advantages are the ease of operation, high yield with low material wasting, narrower distribution of particle size and the low friability of the pellets. Also pellets produced by this technique are characterized with improved drug-release profiles, when compared with pellets of other techniques [18].

Extrusion/spheronization technique was not often used by pharmaceutical industries before 1970, when first articles were published by employees of Eli Lilly and Co. Conine and Hadley. These articles described the movement of the particles within the spheronizer, the mechanics of the particles creation, and provided also a detailed description of the equipment and steps used. The stages of the process involve (1) dry mixing (2) wetting (granulation) (3) extrusion (forming of rod shaped extrudate) (4) spheronization (conversion of the rod shaped extrudate to spherical particles) (5) and drying of the spherical particles resulting in final pellet production [14].

Dry mixing

On the first stage of extrusion/spheronization process the powders that being used must be dry mixed in order to achieve a uniform blend before to wetting (granulation) step. These powders are usually blends of drugs with suitable excipients (fillers, disintegrants, release-modifying agents, colors, etc.). This step is important, because the uniformity of the dry mixture can have important effect on the final pellets in terms of their: size, shape, quality and drug content uniformity. Insufficient powder uniformity could result to adverse effects during extrusion and spheronization step, even in the total failure of the production process. This stage usually takes place in the same homogenization equipment (low or high-shear mixer, fluid-bed equipment) that the wetting step takes place. This arrangement ensures the reduction of the risk of the product contamination during transferring [14].

Wetting

On that step the wet mass is prepared by mixing the uniform blend, of the previous step, with the wetting liquid. Basically, it is a process very similar to wet granulation (only higher amounts of wetting liquids are usually needed). This process takes parts in mixers of various types, like batch-type mixers (planetary mixer, high-shear mixer, sigma blade mixer) and continuous granulators. The most commonly used is the planetary mixer [18].

Critical in this step is the selection of the suitable liquid and liquid/solids ratio. Proper ratio can be achieved by maintaining steady input of powder and fluid into the mixer. Small changes in the powder feed and wetting process, can affect the final pellets' quality. Also important for the properties of the product is the proper movement of the mixing paddles and blades. This parameter is very important especially in cases of high energy mixers (high-shear), where also cooling of the mixing bowl is often needed, because of significant increasing of the product temperature, affecting the wet mass. This can lead to evaporation of the wetting liquid (if the system is not closed) and degradation of thermo-labile components in the mixture [14].

Extrusion

Extrusion, the third stage of extrusion/spheronization technique, takes place in an extruder, which is usually consisted by a platform, barrels, screws arranged on a screw shaft, a die and a connection to utilities and controls. During the process of extrusion, the extrudate, in the form of cylindrical rods is formed, by forcing the wetted mass through an orifice or extrusion die under controlled conditions. This technique has been widely used also in other industries (ceramic, metallurgy) and not only in the case of pharmaceutical industry [39].

There are four basic types of extruders that can be used in extrusion/spheronization techniques: **screw**, **sieve**, **basket** and **roll**. Ram extruders which are experimental are also worth to be noticed (Figure 1) [18].

Industrially the most often used are *screw extruders*, which can be fitted with one or twin Archimedes screws. The role of the screw is to feed the wetted mass towards one of two different types of extrusion screens/dies. The first one is *axial* type, in which the screen is at the end of the screw, vertically placed to the axis of the screw. The second type is *radial* position, in which the screen is placed around the screw, discharging the extrudate vertically to the axis of the screw (Figure 1). The main advantages of this type of extruders are: continual process, possible control of all the process parameters, high performance and good quality final extrudate [67].

Sieve and *basket extruders* both have an extrusion chamber which is fed with wetted mass either by a screw or by gravity. Commonly, in the chamber of the extrudater, there is a rotating device pushing the mass through an extrusion screen. For basket extruders the walls of the chamber are also the extrusion screen, whereas for the sieve extruders, the extrusion screen is on the bottom side of the chamber [18].

Roll extruders can be divided in two types. The one type is a roll extruder with a perforated cylinder rotating around one or more rollers. The extrudate is discharged outside the cylinder. The other type is a roll extruder with two contra-rotating wheels. It is possible that both of the wheels are perforated or only the one of them. The main difference with the other roll extruder is that the extrudate feds between these two wheels and the mass is collected inside them [14].

Ram extruders are composed by a barrel, with a piston inside it and extrusion screen at the end of it. The wet mass is being moved and pushed by the piston to the screen of the barrel [67].

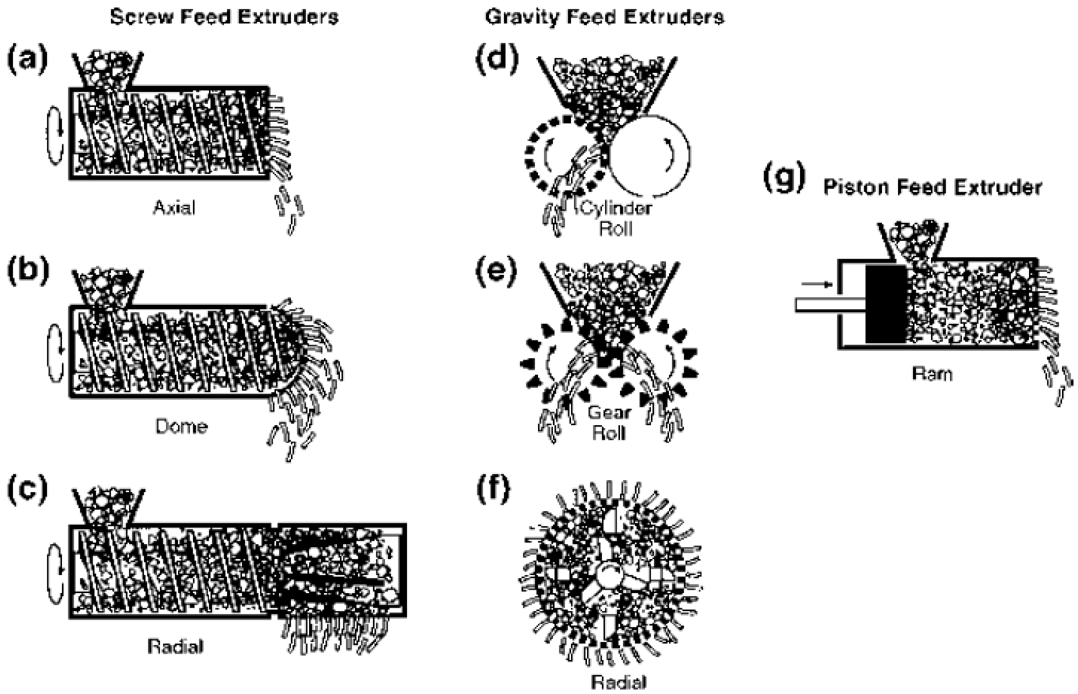

Figure 1: Schematic diagrams of extruder types used in extrusion/spheronization [14]

The quality of the extrudate yielded from the process of extrusion is critical for the spheronization process. Extrudates with insufficient plasticity, have increased risk to be broken up or to be rounded off within the spheronizer. The quality of extruded is usually inseparable from the quality of wetted mass used and also from the quality of final pellets [10].

Spheronization

The fourth step of extrusion/spheronization technique is the spheronization, which takes place in a relatively simple equipment, the spheronizer (marumerizer in the past) (Figure 2). It consists of a horizontal rotating disk (friction plate), within a hollow cylinder. The rotating disk is rapidly rotating, forcing the extrudate to move within the cylinder. Friction forces generated by particle-particle and particle-equipment interactions are responsible for the conversion of extrudate to pellets. The disk has grooved surface and this morphological characteristic, induces the forces of the particle-equipment interaction [14].

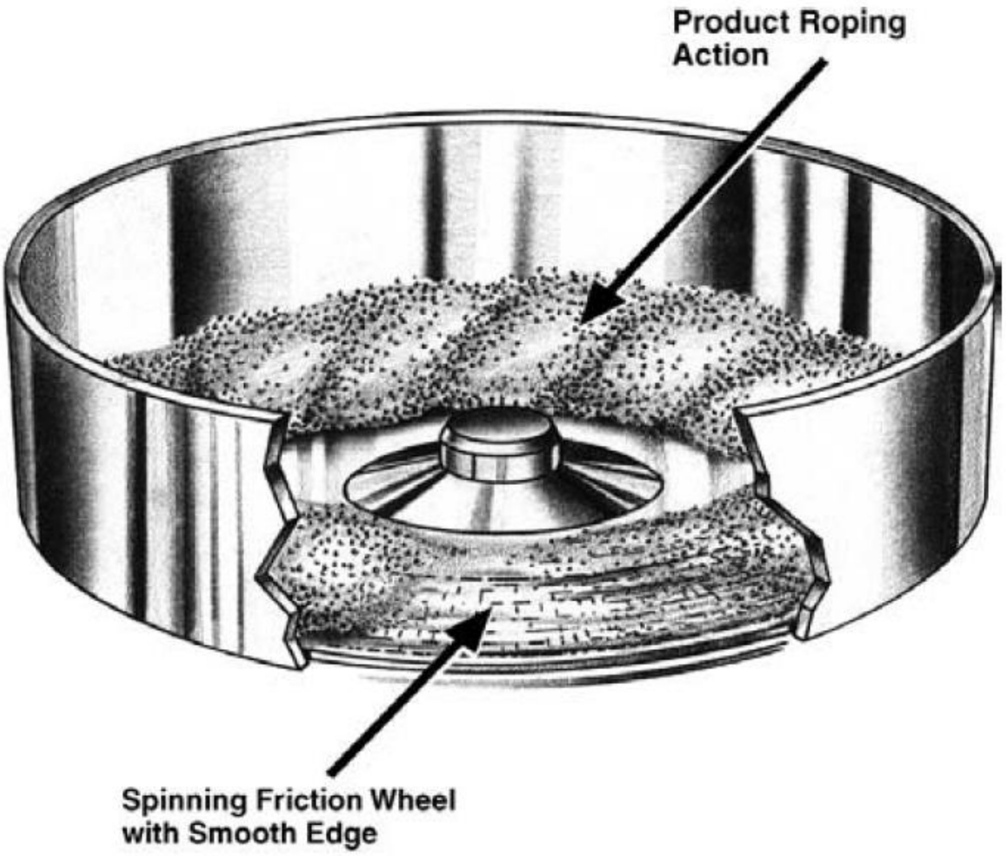

Figure 2: Graphical representation of a spheronizer bowl during the formation of ropelike movement of particles [14]

The *friction plates* are classified in two types, according to their geometry. The one is the cross-hatch geometry, which is the most common. On this type the grooves of the disk intersect each other at 90 degrees. The other type is the radial geometry in which the grooves come from the centre of the disk [18].

There are several concepts about the pellet formation during spheronization. The first concept came from Rowe, who proposed that the extrudates during spheronization are initially broken up into small cylinders. These cylinders can be of the more or less equal length. Then the edges of those cylinders start to be rounded, followed by dumb bells, egg shape and at the end spherical pellets [54]. Another concept was proposed by Baert et al., according to which the short cylinders experienced rope-folding and rope-shaped cylinders with round edges. Following that they would be shaped to dumb bell, which after their breakage would form the pellets (Figure 3) [4].

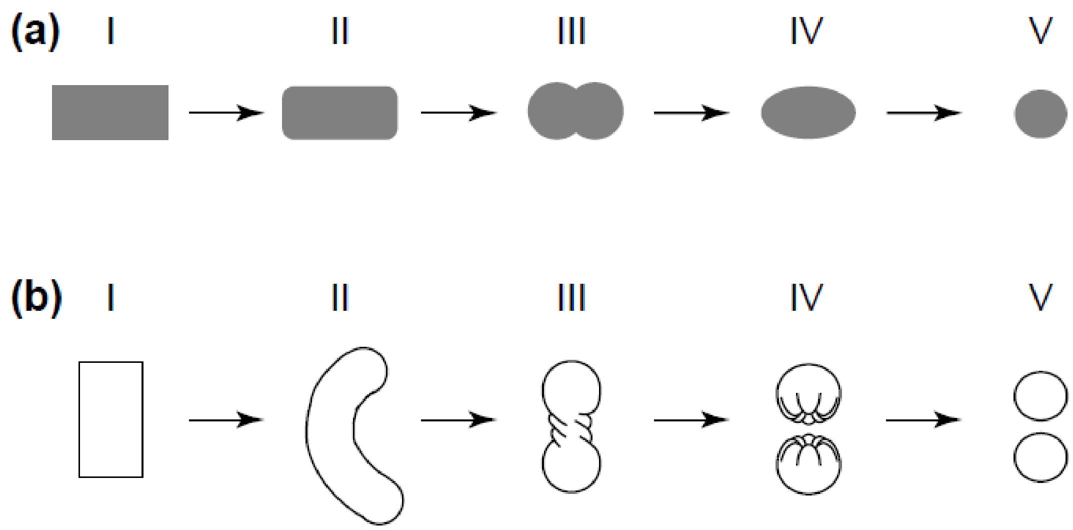

Figure 3: Pellet-forming mechanism according to Rowe (a) and Baert (b) [18] (a): I. Cylinder, II. Cylinder with rounded edges, III. Dumbbell, IV. Ellipse, V. Sphere (b): I. Cylinder, II. Rope, III. Dumbbell, IV. Sphere with a cavity outside, V. Sphere

Spheronization needs usually 2-10 minutes with rotation speed of the friction plate at 200-1000 rpm. Although that these numbers are generally accepted, statements for higher speed needed have been made. It has been found that one important parameter for good spheronization is the diameter of the friction plate which should be considered for the calculation of the appropriate speed [67].

Drying

Drying is the last phase of the extrusion/spheronization pellets preparing technique. By drying it is meant the application of heat or energy for the removal of liquid added to the powder blend during wetting step of the process. The result is more stabilized product with improved mechanical durability. Also chemical reactions can be avoided [40].

Pellets can be dried at *room temperature* or at any dryer that can be used for conventional-type granulations. This includes *fluidized-bed driers*, *forced circulation oven*, *vacuum driers* and *microwave ovens* [18].

Parameters influencing the final pellets' properties

Extrusion/spheronization is a multistep technique for pellet production. During such a technique, various factors, in each step, may affect the quality of the final product. The parameters can be either formulating (influenced by used materials) or processing factors (influenced by process steps). Having so many parameters to consider during extrusion/spheronization technique makes it difficult to predict the behavior and properties of final pellets [57].

Formulation factors

Moisture content of the wetted mass

The moisture content is an important parameter for the whole technique. It is closely connected to the proper plasticity of the powder mass, in order to be extrudable and have the proper shape following the spheronization. There is a certain limit of moisture content for the production of acceptable pellets, with proper properties (shape and mechanical properties). High ratio of dust may be produced, during the spheronization step, if the moisture content is below the lower limit and the result will be increased yield of fines [67].

On the other hand, if the moisture content is over the upper limit, the wetted mas could be over-wetted and agglomeration of individual pellets could cause, because of an excess of liquid on pellet's surface. Also particle-size distribution, internal porosity, mechanical strength and friability of pellets may be influenced by the moisture content in wetted mass [67][58].

In general, it could be concluded that underwetted powder blend led to production of pellets with smaller size, higher porosity and worse mechanical durability in comparison to overwetted material which forms pellets of bigger size and higher hardness [5][32].

The main problem is the prediction of the optimal amount of liquid, which should be used for specific formulation. This parameter is usually tested experimentally despite the possibility of measuring the blender resistance during adding of wetting liquid or using a specific equipment called mixer torque rheometer [55][35].

Starting material

Particle size, hardness and sphericity of pellets produced, are highly influenced by the physical properties of the starting material. Also the release rates of the drug included may change when different starting materials are used. More specifically the composition of pellets, the types of the same product or even the supplier, can be factors affecting the quality and characteristics of the final pellet product [18].

The solubility of the drug and also excipients, in the wetting liquid, is also a factor to be considered. This parameter has crucial effect on the plasticity of wetted mass, because when using soluble substances, the volume of the liquid phase can be increased, causing over-wetting of the system, when the drug dissolves in the liquid [14].

Type of wetting liquid

The most commonly used wetting liquid for granulation and pelletization processes is water. Although that, cases that alcohol or alcohol-water mixtures are used, have been also reported [13]. Water causes a big contribution to mechanical properties of pellets, like hardness and the release rate of the drug. The increasing water content will increase the hardness and make the release rate of the drug slower. For example, it has been proposed that a minimum 5 % of the wetting liquid should be water, when pellets with Avicel PH-101 and theophylline are processed [17][38].

Processing factors influencing the final pellets' properties

Dry mixing equipment

Dry mixing represents an important step in many pharmaceutical processes, because the uniformity of the dry mixture can have important effect on the final dosage form quality. Mixing process is intended to lead to a blend internal structure of acceptable quality. The feeding of the material to the mixer and the behavior of the mixer may have crucial effect to the quality of mixture [7]. Mixing of powders usually takes place in the same equipment that the wetting step takes place. That fact ensures the reduction of the risk of the product contamination during transferring. Except of homogenization equipment like low and high shear mixers, fluid bed equipment and sigma blenders for the mixing of powders rotary drums, v-mixers, planetary mixers and three-axial homogenizers (turbula) can be used [14].

Extruder type

Although the missing comparison between different types of extruders, their influence during extrusion step of extrusion/spheronization technique has been described in several studies and is considered well documented. It has been observed that the final product pellets, showed differences in size distribution, sphericity and density, when different type of extruder were used for their formation [18][11].

According to studies of Reynolds and Rowe, more dense material is produced by the axial screw extruder, when compared with the radial screw type. The radial screw extruder showed higher output and the mass had higher temperature during extrusion [53][54].

Comparisons between a gravity feed with two perforated rolls versus a screw extruder, and between a roll extruder with one perforated roll versus a ram extruder, have been made in order to find the influence of the type of extruder to the final product pellet. Comparisons showed that the pellets obtained from the two types of extruders differed in sphericity and in particle size distribution. That differ was due to a shift of the optimal amount of wetting liquid needed with each extruder or to differences in the 'length to radius' ratio (L/R ratio) of the extrusion screen used or to differences in parameters determining the quality of the extrudate and the final pellets, like 'shear stress' or 'shear rate' [67].

Extrusion screen properties

The thickness of the extrusion screen or die and the diameter of the perforations (pores), are parameters that play important role in the pellet quality. Any change of these two parameters, result in the change of the quality of the extrudate, therefore pellets' quality is usually also affected [18].

When processed under the same conditions, it could be stated that pellets' diameter is analogous to the diameter of the extrusion screen perforations [66][67].

The second parameter of extrusion screen that has effect on the pellets' quality is its thickness. It has been found that the surface roughness of the pellet product is strongly related to the thickness of extrusion screen. The screen with high thickness is about to produce smooth and well-bounded extrudate, whereas a screen with low thickness produces a rough and loosely-bound extrudate. The reason for this relation has basis in the densification of the wet mass in the screen. Higher densification occurs when a screen with higher thickness is used [3][67].

Extrusion speed

Extrusion speed is a parameter that regulates the total output of the extrusion process and influence also the quality of prepared extrudate. It is advised that the output should be as high as possible, for economic reasons. With elevated speed during the extrusion process the extrudate output rises [67]. However the higher speed leads to final product pellets with reduced properties. Surface impairments, roughness, shark skinning and pellet size are influenced by the increase extrusion speed [18].

It was shown that when the extrusion speed is low, the water moves towards the die wall interface and acts as a lubricant. This phenomenon results in reduced extrusion forces. On the other hand, when the speed is high, the water cannot move rapidly through the mass and the result are increased forces. By this report, it was indicated that the water content and its distribution is crucial for pellets' properties. Low water content accompanied with increased speed, results into reduced size and sphericity of the final product. It could be concluded that for the desired pellet quality, adjustment of water content and extrusion speed should be made [46].

Spheronization speed and time

Speed of the friction plate, during the spheronization process is another crucial parameter that plays important role for obtaining high-quality pellets. Changes in spheronization speed affect the mean diameter, hardness, roundness, bulk and tapped density, porosity, friability, flow rate and surface structure of prepared spherical particles [18]. Significant changes in the shape of the extrudate cannot be observed, when the friction plate is at too low speed, while round, but small particles with high dust ratio will be the result of applied too high speed [42].

Diameter of the spheronizer plate is almost as important as the rotating speed of it, because it represents the main factor that regulates the linear peripheral velocity of the plate. When the speed is increased, during scale up from smaller friction plate, to larger diameter plate, but the linear peripheral velocity remains the same, the pellets produced should be of the same properties. Therefore in some cases, it could be more appropriate to mention the peripheral velocity at the characterization of the spheronizer plate, than just the rotational speed of the plate [47].

The residence time of the extrudate in the spheronizer (spheronization time), is another important factor, influencing the size distribution, bulk and tapped density, sphericity and other parameters of final pellets [42]. It was observed that with extended spheronization time, particles get more spherical, have increased diameter, with narrower particle size distribution [4]. Friability of pellets can also be affected by increasing of spheronization time [18].

Several studies have been made to show the changes that these two factors (friction plate speed and residence time in the spheronizer) cause to the semi-product during the spheronization process. When spheronization speed and time increase, the coarse fraction and the mean diameter are increasing, but the fine fraction is decreasing. When using high spheronization speed and long time, there could occur moisture loss in the material, which could have a significant effect on decreased plasticity of the particles. Result can be unchanged particles in the form of deformed cylinders or dumbbells [23].

Increased plate speed, but with low spheronization time results in creation of small rounded pellets. It has also been suggested that by these parameters the pellets result to be more rounded than without the increased speed [24][68].

It has been stated that the number of rotations of the spheronizer plate is also very important factor. The total number of rotations is regulated by the plate's speed and the duration of the procedure. When there is a change of one of these variables inversely proportional to the other variable, it is possible to have no different effect to the final product [23].

Spheronization load

Important parameter for the quality of the spheronization process, therefore for the pellet quality, is the load of spheronizer. This parameter is closely related to the speed and time of the procedure, and can influence the particle size distribution, bulk and tapped density, hardness as well as the roundness of final pellets [18].

It has been found that by increasing the spheronizer load, the mean diameter, bulk and tapped density and hardness are increasing. On the other hand the size and the sphericity of the pellets were decreased, during that change of variable [67].

2.2.2.6 Drying method

The method used for the last step of the extrusion/spheronization technique can also have significant contribution to the properties and quality of the pellets. The drying process can have an important influence on the morphology of the pellets and dissolution of the drug, by differentiation of the porosity [40].

The crystallization and migration of soluble materials during the process, the mechanism of heat transfer and generation, the rate of moisture removal and contraction forces have been mentioned as the main variables when using different drying method[6].

When pellets are dried by microwaves, they show rougher surface than the ones dried in a hot air ventilated oven. Moreover, these pellets are more porous and with lower hardness [67]. During tray drying, which is considered as a slow process, there are more possibilities that there will occur migration of a drug towards surface and to recrystallize there. On the other hand, the more rapid heat rate in a fluid-bed is more likely to minimize the effects of this migration. Due to this phenomenon the rate of dissolution can be increased in pellets dried using the first method because there is higher active substance concentration on the surface of the pellets [14].