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Invited Review

Extrusion-spheronisation A literature review

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Abstract

This review article deals with the aspects of the extrusion-spheronisation process. The different steps in the production process of pellets are described. In a second part the parameters which can influence the pellet quality are discussed. Finally, an overview of the methods available for analysis of the quality of the pellets is given.

Keywords: Extrusion; Spheronisation; Pellet

1. Introduction

Pellets are spheres of varying diameter depending on the application and the wish of the producer. Applications are found not only in the pharmaceutical industry but also in the agribusiness (e.g., fertiliser, fish food) and in the polymer industry. This article reviews the pharmaceutical aspect of pellets produced by extrusion-spheronisation.

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 (Bechgaard and Hegermann Nielsen, 1978) but also technological advantages, for example, better flow properties, less friable dosage form, narrow particle size distribution, ease of coating and uniform packing (Reynolds, 1970). The reproducibility of the drug blood levels (Bechgaard and Hegermann Nielsen, 1978; Eskilson, 1985) is an additional advantage to the use of a pellet formulation. Pellets, manufactured in the pharmaceutical industry, are sized between 500 and 1500 μm (Ghebre-Sellassie, 1989) and are commonly filled into hard gelatine capsules but can also be compressed to tablets (Conine and Hadley, 1970; Jalal et al., 1972; Malinowski and Smith, 1974; Sandberg et al., 1988; Millili and Schwartz, 1990; Béchard and Leroux, 1992). The commercially available pellet formulations are mainly coated with a polymer film in order to obtain a controlled release effect. The thickness (Bianchini and Vecchio, 1989; Zhang et al., 1991; Yuen et al., 1993) and composition (Eerikäinen and Lindqvist, 1991; Yuen et al., 1993) of the film influence the release pat-

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tern, so by mixing different types of coated pellets the desired release profile can be obtained.

Pellets can be produced in different ways: spraying a solution or a suspension of a binder and a drug onto an inert core, building the pellet layer after layer (Gamlen, 1985; Chambliss, 1989; Li et al., 1989); spraying a melt of fats and waxes from the top into a cold tower (spray-congealing) forming pellets due to the hardening of the molten droplets (Ghebre-Sellassie, 1989); spray-drying a solution or a suspension of the drug forming pellets due to the evaporation of the fluid phase (Ghebre-Sellassie, 1989); spraying a binder solution into the whirling powder using a fluidized bed (Gamlen, 1985; Olsen, 1989). The most popular method of producing pellets is by the extrusion-spheronisation technique. This process was first reported by Reynolds (1970) and by Conine and Hadley (1970) and involves four steps: preparation of the wet mass (granulation), shaping the wet mass into cylinders (extrusion), breaking up the extrudate and rounding of the particles into spheres (spheronisation) and finally drying of the pellets. The most recent method for the production of pharmaceutical pellets is by means of the fluid-bed rotogranulator or by the centrifugal granulator (Gajdos, 1984; Gamlen, 1985; Ghebre-Sellassie et al., 1985; Goodhart, 1989; Robinson and Hollenbeck, 1991; Béchard and Leroux, 1992; Maejima et al., 1992; Niskanen, 1992) performing the whole cycle in one closed system (Fig. 1). The binder solution and the powder mix are added at a fixed rate onto the plate of a kind of spheroniser so that the particles are stuck together and spheronised at the same time. The rotating plate is mounted in a fluidized bed making it possible to dry the pellets when they have reached the appropriate size because of the

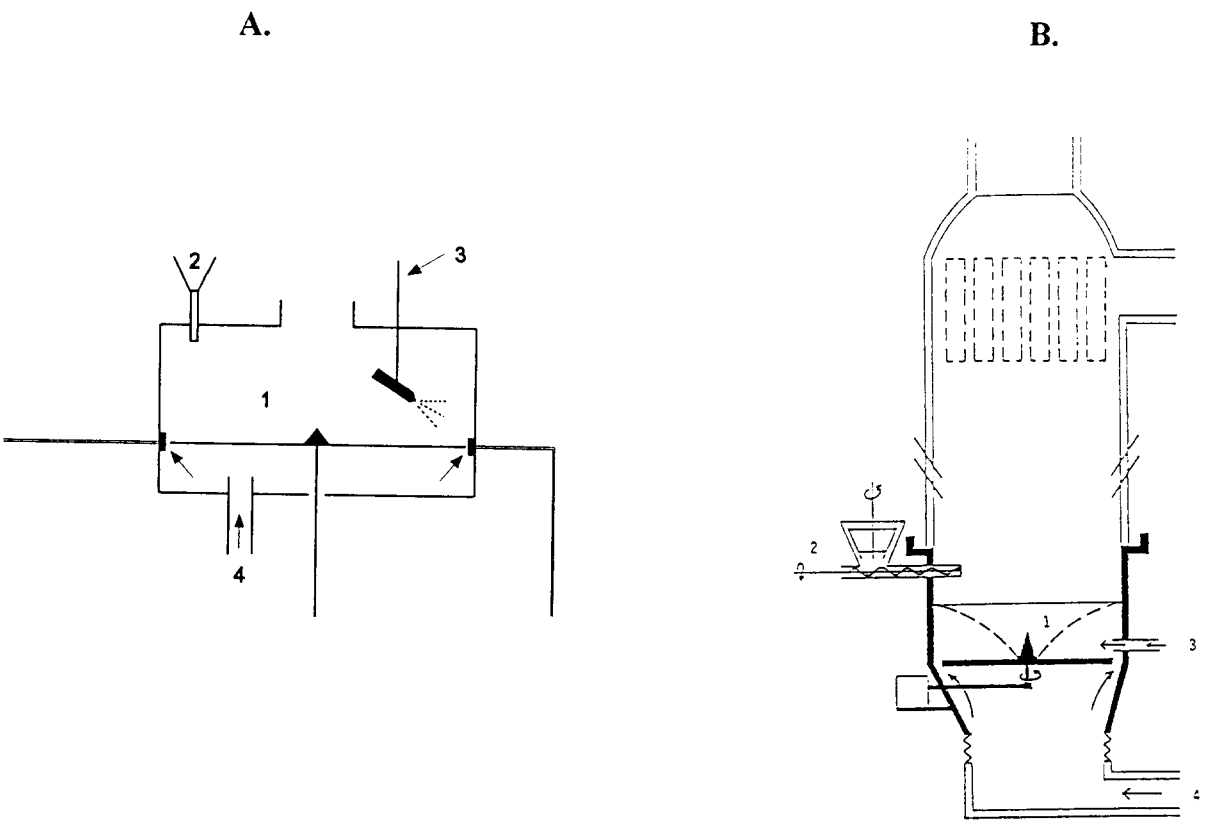

Fig. 1. (A) Centrifugal granulator. (B) Fluid-bed rotary granulator. 1, fluid bed; 2, powder feed; 3, binding solution feed; 4, air supply.

air blown through the small opening between the rotating plate and the vertical wall of the fluidized bed. With each production technique pellets with specific characteristics are obtained (Zhang et al., 1990, 1991; Robinson and Hollenbeck, 1991). For example, pellets formed by extrusion-spheronisation show a slower release profile compared to those made by the layer building technique (Zhang et al., 1990, 1991).

2. Equipment used during an extrusion-spheronisation cycle

2.1. Granulation

The first step of an extrusion-spheronisation cycle consists of the preparation of the plastic mass. Different types of granulators are used to perform the mixing of the powder blend and the granulation liquid. The first three types of processors mentioned below are also used to mix the different constituents of the powder blend. The most commonly used granulator is a planetary mixer (Harrison et al., 1984, 1985a,b, 1987; O'Connor et al., 1984; Chien and Nuessle, 1985; O'Connor and Schwartz, 1985; Chapman et al., 1986; Chariot et al., 1987; Fielden et al., 1988, 1989, 1992a,b, 1993; Herman et al., 1988; Ghali et al., 1989; Bataille et al., 1990a,b, 1991, 1993; Millili and Schwartz, 1990; Zhang et al., 1990, 1991; Baert et al., 1991, 1992a,b, 1993a,b; Bains et al., 1991; Ligarski et al., 1991, 1992; Rahman et al., 1991a,b; Robinson and Hollenbeck, 1991; Barrau et al., 1992, 1993; Newton et al., 1992; Baert and Remon, 1993; Goskonda and Upadrashta, 1993; Hileman et al., 1993; Mesiha and Vallés, 1993; Pinto et al., 1993; Tapia et al., 1993, Yuen et al., 1993) although the use of high shear (Dietrich and Brausse, 1988; Lövgren and Lundberg, 1989; Baert et al., 1991; Elbers et al., 1992; Ku et al., 1993) or sigma blade (Woodruff and Nuessle, 1972) mixers has also been reported. Bianchini and Vecchio (1989), Hellén et al. (1992, 1993a,b,c,d) and Hellén and Yliruusi (1993) used a continuous granulator to prepare the wet powder mass.

During the granulation step the evaporation of the fluid phase should be restricted to a minimum. This could especially be a problem with the high shear mixers as they introduce a large amount of energy into the mass which is partly transformed into heat. This rise in temperature will induce the evaporation of the granulation liquid (Baert et al., 1991), thus influencing the extrusion behaviour of the wet mass. Cooling of the granulation bowl might avoid this problem. A special feature of the granulation step is the homogeneous distribution of the liquid phase throughout the granulated mass. Some authors assumed that the water would equilibrate throughout the complete mass when the wet mass was left for 12 h in a sealed polyethylene bag (Fielden et al., 1989, 1992a,b, 1993; Bains et al., 1991; Pinto et al., 1993). Thus far, no comparative study has been performed examining the possible effect of the type of granulator on the final quality of the pellets.

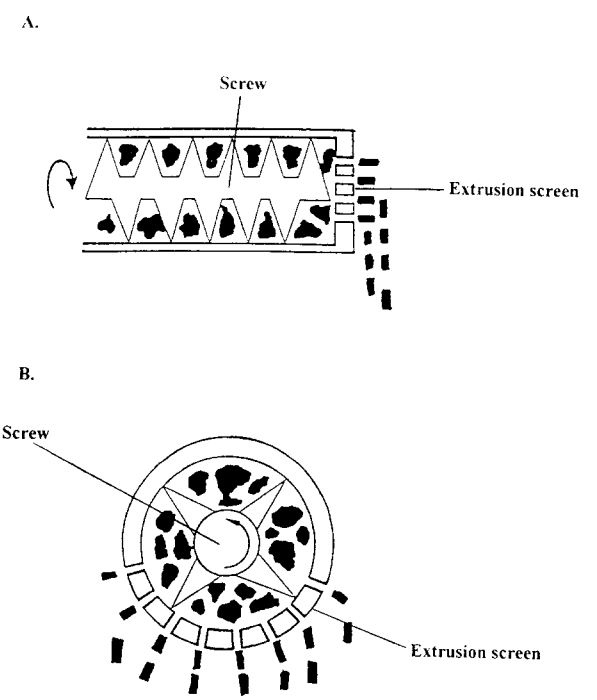

Fig. 2. Schematic view of a screw extruder. (A) Axial type, (B) radial type.

2.2. Extrusion

The second step of the process is the shaping of the wet mass into long rods during extrusion. The extrusion process, used not only in the pharmaceutical industry but also in the food, ceramics and polymer industries, can be performed using four main classes of extruders: screw, sieve and basket, roll, and ram extruders.

The screw extruder consists of one or two (twin-screw) Archimedes screws feeding the plastic mass to an axial or radial extrusion screen (Reynolds, 1970; Rowe, 1985; Hicks and Freese, 1989) (Fig. 2). In the axial type, the screen is placed at the end of the screw, perpendicularly with the axis of the screw in contrast to the radial type where the die is placed around the screw, discharging the extrudate perpendicularly to the axis of the screw.

In the sieve and basket extruders (Hicks and Freese, 1989) (Fig. 3) the granulate is fed by a screw or by gravity into the extrusion chamber, where a rotating or oscillating device pushes the plastic mass through the screen. The difference between the sieve and basket extruders is similar to that between the radial and axial screw extruders. In a sieve extruder the screen is positioned at the bottom of the extrusion chamber, while in the case of a basket-type extruder the vertical walls of the extrusion chamber make up the extrusion screen.

A third class of extruders are the roll extruders (Hicks and Freese, 1989). Two types can be distinguished: an extruder equipped with two con-

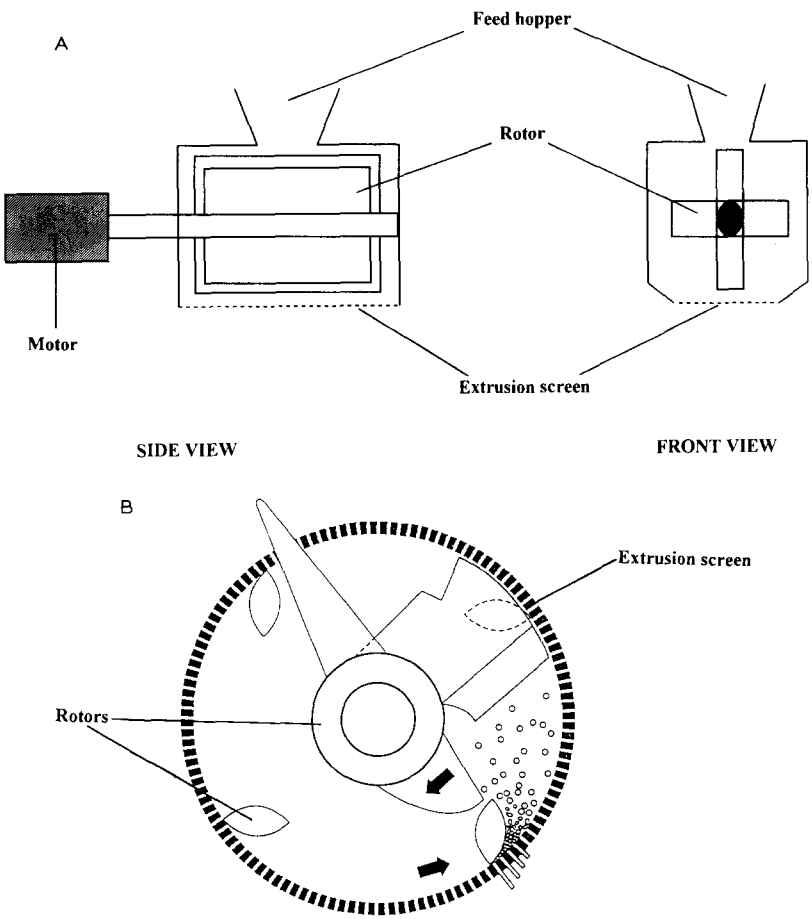

Fig. 3. (A) Schematic view of a sieve extruder; (B) schematic view of a basket extruder.

trarotating wheels of which one or both are perforated. Using this type of extruder the mass is fed between the two wheels and the extrudate is collected inside the extrusion wheels (Fig. 4A and B). The second type of roll extruder has a perforated cylinder which rotates around one or more rollers, discharging the material to the outside of the cylinder (Fig. 4C). The last type of extruder is an experimental one, called the ram extruder (Hicks and Freese, 1989). The principle of this extruder is based on a piston which pushes the wet mass through the screen situated at the end of the barrel (Fig. 5).

Another method of classifying the extruders is according to the feed mechanism of the plastic mass to the extrusion screen, by means of screws or by means of gravitational forces (Rowe, 1985).

The extrusion process can also be used to prepare extrudate which will not be further processed. Using this method it is possible to prepare granules in a continuous way with a screw extruder where the mixing of the powder and the granulation liquid is performed inside the barrel of the extruder (Goodhart et al., 1973; Gamlen and Eardley, 1986; Lindberg et al., 1987, 1988).

In recent years, more attention has been paid to the instrumentation of the extruder (Goodhart et al., 1973; Harrison et al., 1985b, 1987; Dietrich and Brausse, 1988; Fielden et al., 1989; Baert et al., 1991; Bains et al., 1991; Elbers et al., 1992; Kleinebudde and Lindner, 1993; Mesiha and Vallés, 1993). Due to these modifications of the standard equipment, the authors were able to gain a better insight into the extrusion process. Baert et al. (1991) reported on the instrumentation of a roll extruder with two perforated cylinders, where it was possible to measure the forces during extrusion. This kind of instrumentation allowed an in-process control as the extrusion forces recorded could be correlated to the final quality of the pellets (Baert et al., 1992a). Harrison et al. (1985b, 1987) measured the force applied on the piston of a ram extruder necessary to maintain the set extrusion speed. Other types of

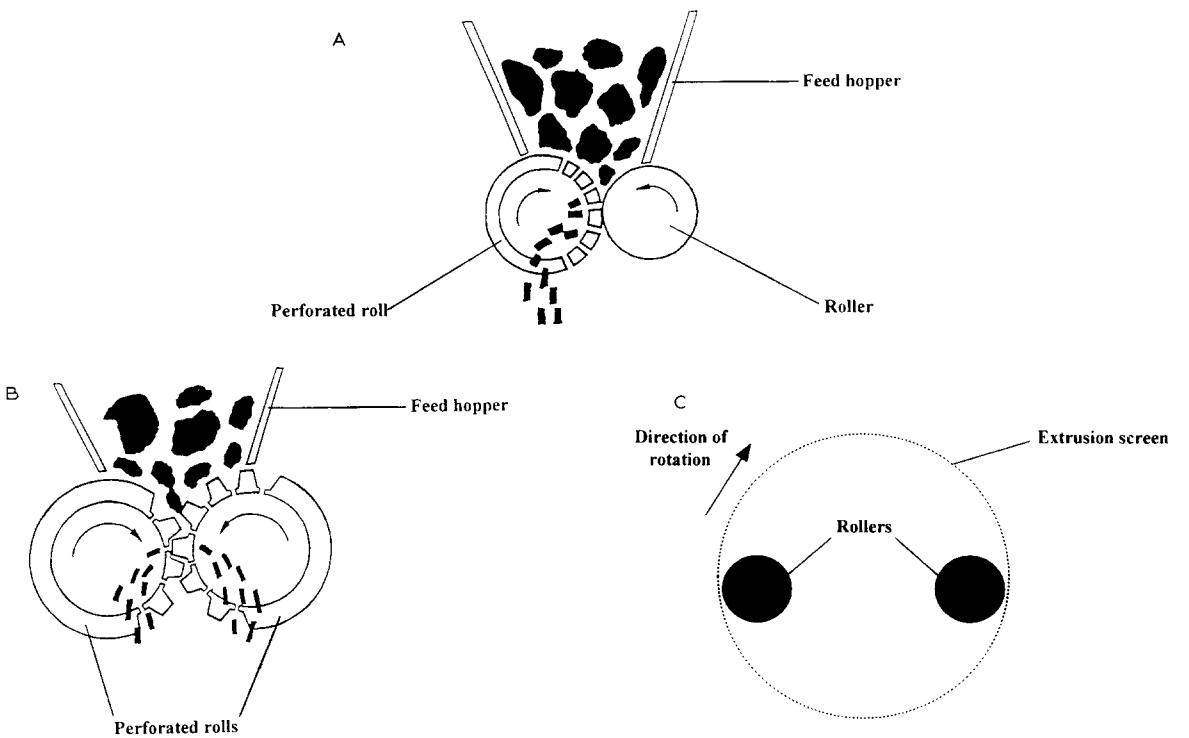

Fig. 4. Schematic view of the roll extruders. (A) Roll extruder with one perforated roll, (B) roll extruder with two perforated rolls, (C) roll extruder with the extrusion screen rotating around rollers.

instrumentation are the measurement of the pressure at the extrusion screen using a screw extruder (Goodhart et al., 1973; Dietrich and Brausse, 1988; Kleinebudde and Lindner, 1993) or the recording of the power consumption of the motor driving the extruder (Dietrich and Brausse, 1988; Elbers et al., 1992; Kleinebudde and Lindner, 1993; Mesiha and Vallés, 1993).

2.3. Spheronisation

During the third phase of the extrusion-spheronisation process the cylinders are dumped onto the spinning plate of the spheroniser (Nakahara, 1964), called the friction plate, where the extrudate is broken up into smaller cylinders with a length equal to their diameter (Conine and Hadley, 1970). According to Rowe (1985), those plastic cylinders are rounded due to frictional forces. In the spheronisation 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, dumb-bells and elliptical particles to eventually perfect spheres (Fig. 6A). Baert and Remon (1993) suggested that another pellet-forming mechanism might exist (Fig. 6B). 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 spheronisation process the edges of the flat side fold together like a flower forming the cavity observed in certain pellets.

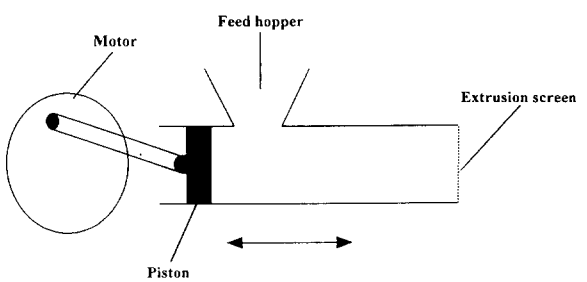

Fig. 5. Schematic view of a ram extruder.

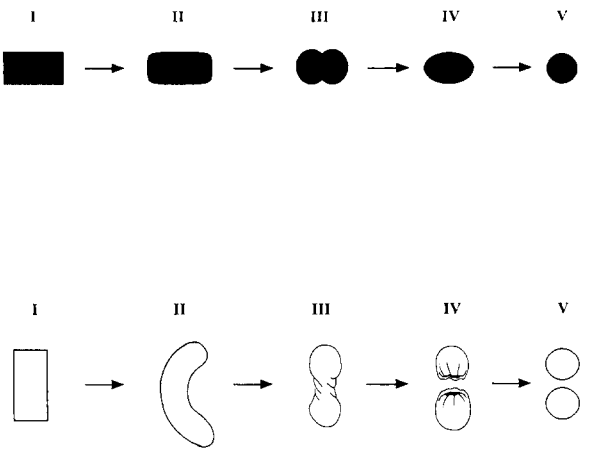

Fig. 6. Pellet-forming mechanism according to: (A) Rowe: I, cylinder; II, cylinder with rounded edges; III, dumb-bell; IV, ellipse; V, sphere; (B) Baert: I, cylinder; II, rope; III, dumb-bell; IV, sphere with a cavity outside; V, sphere.

The spheronisation of a product usually takes 2–10 min (Gamlen, 1985). A rotational speed of the friction plate in the range between 200 and 400 rpm would be satisfactory to obtain a highly spherical pellet according to West and Rowe (1988). This statement is in sharp contrast with most reports indicating the use of spheronisation speeds exceeding 400 rpm. This contradiction can be explained by the fact that not the absolute speed is important but the speed in combination with the diameter of the friction plate. From those two parameters the plate peripheral velocity can be calculated and these data should be compared instead of the absolute rotational speed of the friction plate (Lövgren and Lundberg, 1989). The friction plate has a grooved surface to increase the frictional forces. Two types of geometry of the grooves exist (Rowe, 1985), cross-hatch geometry where the grooves form right angles and radial geometry where a radial pattern is used (Fig. 7).

A special kind of spheroniser was designed by NICA-Systems with a lip around the rim of the friction plate which claims to reduce the milling effect of the friction plate resulting in a smaller amount of fines (Hellén et al., 1992).

Depending on the composition of the formulation, substances soluble in the granulation liquid

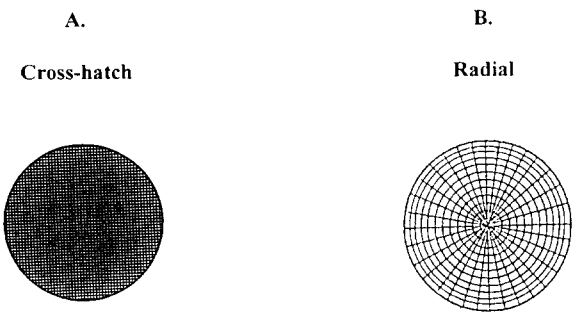

Fig. 7. Geometry of the spheronisation plate. (A) Cross-hatch, (B) radial.

might migrate to the outside of the pellets during spheronisation, leading to an inhomogeneous distribution of the substance throughout the pellet (Chien and Nuessle, 1985).

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 (Hasznos et al., 1992; Hellén et al., 1992, 1993a,b,c,d; Hellén and Yliruusi, 1993) or at elevated temperature in a fluidized bed (Briquet et al., 1986; Chapman et al., 1986; Bianchini and Vecchio, 1989; Lövgren and Lundberg, 1989; Bains et al., 1991; Robinson and Hollenbeck, 1991; Baert et al., 1992a,b, 1993a,b; Bianchini et al., 1992; Elbers et al., 1992; Fielden et al., 1992a,b, 1993; Newton et al., 1992; Baert and Remon, 1993; Hileman et al., 1993; Kleinebudde, 1993; Ku et al., 1993; Pinto et al., 1993; Tapia et al., 1993; Yuen et al., 1993) or in an oven (Woodruff and Nuessle, 1972; Malinowski and Smith, 1974; O'Connor et al., 1984; O'Connor and Schwartz, 1985; Dietrich and Brausse, 1988; Herman et al., 1988; Ghali et al., 1989; Bataille et al., 1990a,b, 1991, 1993; Millili and Schwartz, 1990; Zhang et al., 1990, 1991; Eerikäinen and Lindqvist, 1991; Ligarski et al., 1991, 1992; Rahman et al., 1991a,b; Barrau et al., 1992, 1993; Goskonda and Upadrashta, 1993; Mesiha and Vallés, 1993; Wan et al., 1993). Bataille et al. (1993) reported the use of a microwave oven as the final phase in the production process of pellets.

3. Parameters influencing the final pellet quality

3.1. The moisture content of the granulated mass.

The moisture, necessary to give the powder mass its plasticity so that it can be extruded and shaped afterwards, is an extremely important parameter in the extrusion-spheronisation process. The extent of the influence of the moisture content has been the subject of many research articles (Malinowski and Smith, 1975; Harrison et al., 1984, 1985a; Gamlen, 1985; Briquet et al., 1986; Heng and Staniforth, 1988; Lövgren and Lundberg, 1989; Bataille et al., 1990a; Baert et al., 1991, 1993a; Bains et al., 1991; Barrau et al., 1992; Bianchini et al., 1992; Hasznos et al., 1992; Hellén et al., 1992, 1993c; Newton et al., 1992; Baert and Remon 1993; Fielden et al., 1993; Kleinebudde and Lindner, 1993; Kleinebudde, 1993; Ku et al., 1993; Pinto et al., 1993; Wan et al., 1993). It was shown that the moisture content can range between a lower and an upper limit and still produce pellets of an acceptable quality (Gamlen, 1985; Bains et al., 1991; Rahman et al., 1991a; Ligarski et al., 1992; Fielden et al., 1993; Kleinebudde, 1993). If the moisture content is less than the lower limit, a lot of dust will be formed during spheronisation resulting in a large yield of fines. Exceeding the range of the moisture content leads to an overwetted mass and agglomeration of the individual pellets during spheronisation due to the excess of water at the surface of the pellets. A feature closely related to the moisture content of the mass is its plasticity. Harrison et al. (1987) showed that the rheological characteristics of the wet mass are important for achieving good properties for the extrusion process. Elbers et al. (1992) proved that by measuring the plasticity of a mixture after granulation at different moisture contents the optimal moisture content for a specific composition could be determined.

3.2. The type of granulation liquid

In most cases water is used as the granulating liquid although the use of alcohol or water/alcohol mixtures has also been reported (Goodhart

et al., 1973; Briquet et al., 1986; Lindberg et al., 1987, 1988; Millili and Schwartz, 1990; Elbers et al., 1992).

The effect of this parameter was clearly shown by Millili and Schwartz (1990); a minimum of 5% of the granulation liquid had to be water in order to produce pellets when processing a formulation of Avicel® PH101 and theophylline (90:10, w/w). Increasing the water content in the granulation liquid lead to an increase in the hardness of the pellets. This increase in the hardness was correlated with a slower in vitro release rate of theophylline.

3.3. The physical properties of the starting material

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 (O'Connor and Schwartz, 1985; Herman et al., 1988; Ghali et al., 1989). O'Connor and Schwartz (1985) demonstrated the effect of the Avicel® type on the quality of the pellets (pellet size, sphericity as well as release rate of an included drug). The RC and CL types slowed the release rate of drugs because a gel-like structure was formed in water due to the presence of sodium carboxymethylcellulose whereas the pellets containing Avicel® PH101 remained unchanged in the aqueous dissolution medium, resulting in a greater release rate. This phenomenon was also described by Ghali et al. (1989) who reported that the release rate of theophylline or chlorpheniramine maleate in water was dependent on the Avicel® PH101/RC581 ratio; a larger amount of the RC type slowed the release rate.

Herman et al. (1988) reported about the difference in release rate in different types of dissolution fluids between pellets containing only microcrystalline cellulose and those containing a blend of microcrystalline cellulose and sodium carboxymethylcellulose.

The use of similar products but from different *suppliers* could change the characteristics of the pellets (Heng and Staniforth, 1988; Barrau et al., 1992; Newton et al., 1992). Avicel® PH 101, Emcocel® and Unimac® MG are three examples of microcrystalline celluloses from different manufacturers. Pellets prepared with these materials had differences in size and in roundness when processed under the same conditions (Newton et al., 1992).

The *particle size* of the starting material has a profound influence on the extrusion characteristics of the wet mass (Fielden et al., 1989) and on the size (Bianchini and Vecchio, 1989; Barrau et al., 1992; Fielden et al., 1992a,b, 1993; Newton et al., 1992; Wan et al., 1993) and the roundness (Fielden et al., 1992a,b, 1993; Newton et al., 1992; Wan et al., 1993) of the resulting pellets. Fielden et al. (1993) found that pellets containing a mixture of microcrystalline cellulose and lactose and prepared with the coarser lactose agglomerated at a lower water content. It was assumed that it was due to the lower capillarity inside the pellets compared to the pellets prepared with the fine lactose. These lower capillary forces could lead to an excess of water at the surface of the pellets during spheronisation. Due to the moisture at the surface these pellets tend to stick together whereafter this bunch of pellets is densified into one large agglomerate.

The *solubility* of the products in the granulation liquid has a dramatic influence on the amount of granulation liquid needed to obtain the proper plasticity. A soluble drug will dissolve in the granulation liquid increasing the volume of the liquid phase. This could lead to an overwetting of the system in contrast with a formulation containing a non-soluble drug (Baert et al., 1991).

3.4. The type of extruder

Several authors have reported on the influence of the type of extruder on the quality of the pellets (Reynolds, 1970; Rowe, 1985; Baert et al., 1992b, 1993b; Fielden et al., 1992b). According to Reynolds (1970) and Rowe (1985), an axial screw extruder produced a more dense material compared to a radial screw extruder which had a higher output but also a greater temperature rise of the mass during processing. Baert and coworkers compared a gravity feed with two perforated rolls versus a screw extruder (Baert et al., 1993b) and versus a ram extruder (Baert et al.,

1992b). Fielden et al. (1992b) compared a roll extruder with one perforated roll versus a ram extruder. These authors showed that the pellets obtained from the two types of extruders differed in sphericity and in particle size distribution. These observations were due to a shift of the optimal amount of granulation liquid needed with each extruder or to differences in the 'length-to-radius' ratio (L/R ratio) of the extrusion screen used (Baert et al., 1992b, 1993b) or to differences in 'shear rate' or 'shear stress' (Fielden et al., 1992b), two parameters determining the quality of the extrudate and of the final pellets (Fielden et al., 1989).

3.5. The extrusion speed

The total output of the extrudate is mainly governed by the extrusion speed (Hellén et al., 1992). The output should be as high as possible for economical reasons but several authors stated that an increase in extrusion speed influenced the final pellet quality (Goodhart et al., 1973; Harrison et al., 1985a,b, 1987; Dietrich and Brausse, 1988; Bianchini et al., 1992; Hellén et al., 1993b; Ku et al., 1993; Pinto et al., 1993).

Harrison et al. (1985a) showed that the surface impairments such as roughness and sharkskinning became more pronounced with increasing extrusion speed. These surface defects of the extrudate lead to pellets of lesser quality because the extrudate will break up unevenly during the initial stages of the spheronisation process, resulting in a lot of fines and a wide particle size distribution. Mesiha and Vallés (1993) evaluated a series of lubricants as to their ability to reduce surface impairments in order to obtain higher quality pellets. They found that surfactants with a high HLB value were suitable to reduce the surface defects of the extrudate. This was correlated with a reduced power consumption during extrusion as the friction at the die wall of the extrusion screen was lowered. These findings are in contradiction with other research reports, where no influence of the extrusion speed on the size of the pellets was detected (Chariot et al., 1987; Hasznos et al., 1992; Hellén et al., 1993a; Hileman et al., 1993).

3.6. The properties of the extrusion screen

The extrusion screen is characterised by two parameters, the thickness of the screen and the diameter of the perforations. Changing one of these two parameters influences the quality of the extrudate hence of the pellets (Malinowski and Smith, 1975; Harrison et al., 1985a; Chariot et al., 1987; Dietrich and Brausse, 1988; Hellén et al., 1992; Baert et al., 1993b; Hellén et al., 1993a,b; Hileman et al., 1993; Pinto et al., 1993). The diameter of the perforations determines the size of the pellets, a larger diameter of the perforations will produce pellets with a larger diameter when processed under the same conditions.

Baert et al. (1993b) described the difference in extrudate quality between an extruder equipped with a screen of a length-to-radius ratio (L/R ratio) of 1.8 and one of L/R ratio of 4. The screen with the lowest L/R ratio formed a rough and loosely bound extrudate while the screen with an L/R ratio of 4 formed a smooth and well-bound extrudate. This observation can be explained by the higher densification of the wet mass in the screen with the greatest thickness. Hellén et al. (1992) also observed that the surface of the extrudate was much rougher when the granulate was extruded by means of an extrusion screen with a low thickness.

Baert et al. (1993b) determined the zone where pellets of the desired quality were obtained with a screw extruder and with a gravity feed extruder. Using the gravity feed extruder, equipped with an extrusion screen with an L/R ratio of 4, the zone was larger compared to that outlined with the screw extruder, equipped with an extrusion screen with an L/R ratio of 1.8. A restricted number of mixtures had the desired quality when the mixtures were extruded with the screen with the lower L/R ratio. It remains unclear whether this phenomenon is screen or machine dependent. Harrison et al. (1985a) stated, as mentioned before, that the surface impairments of the extrudate such as roughness and sharkskinning should be avoided in order to get pellets of good quality. Those surface impairments will become more severe not only as the extrusion is performed at a higher speed but also as the stress at the wall of

the die perforations increases with increasing thickness of the extrusion screen or as the moisture content of the formulation decreases. Goodhart et al. (1973) observed an increase of the bulk density when the total area of the screen perforations increased related to the total area of the screen. The bulk density of the pellets increased when, for a given formulation, a screen with more perforations was used.

3.7. The extrusion temperature

The control of the temperature during extrusion is an important feature not only when a formulation with a thermolabile drug is processed but also in view of the importance of the moisture content. A rise in temperature during the extrusion cycle could dramatically alter the moisture content of the granulate due to evaporation of the granulation liquid. This could lead to a difference in the quality of the extrudate produced at the beginning of a batch and at the end of a batch. The evaporation of water during extrusion of formulations containing Avicel® PH101 is possible because most of the water is available as free water (Fielden et al., 1988).

In order to gain an idea about the temperature increase during extrusion some authors built in a temperature probe (Dietrich and Brausse, 1988; Baert et al., 1991; Kleinebudde and Lindner, 1993; Mesiha and Vallés, 1993). Other researchers used a screw extruder with a cooling jacket around the barrel in order to keep the temperature of a given formulation between predetermined limits (Dietrich and Brausse, 1988; Kleinebudde and Lindner, 1993). This jacket has a double function as it can be used to heat the mass in order to give products (e.g., a fat-wax mixture) their necessary plasticity.

Hellén et al. (1992) found that there was no substantial temperature rise during extrusion with the NICA extruder but this observation should not be generalised as the increase in temperature is highly dependent on the formulation.

3.8. The spheronisation speed

The spheroniser speed affected the particle size of the pellets (Malinowski and Smith, 1975; Chapman et al., 1986; Chariot et al., 1987; Bataille et al., 1990b; Ligarski et al., 1991; Rahman et al., 1991b; Bianchini et al., 1992; Hasznos et al., 1992; Baert et al., 1993a; Ku et al., 1993; Hellén et al., 1993d; Wan et al., 1993). An increase of the yield of the smaller fractions was seen, probably due to a greater degree of fragmentation during the initial stages of the spheronisation process. In contrast, a decreasing amount of fines and an increasing amount of large particles with increasing spheronisation speed correlating with an increased mean diameter were also observed. The hardness (Bataille et al., 1990a, 1993; Ligarski et al., 1991, 1992; Rahman et al., 1991b), roundness (Woodruff and Nuessle, 1972; Lövgren and Lundberg, 1989; Bianchini et al., 1992; Ligarski et al., 1992; Baert et al., 1993a; Hellén and Yliruusi, 1993; Hileman et al., 1993; Wan et al., 1993), porosity (Bianchini et al., 1992; Ligarski et al., 1992; Bataille et al., 1993), bulk and tapped densities (Malinowski and Smith, 1975; Chapman et al., 1986; Hellén et al., 1993c; Hileman et al., 1993), friability (Malinowski and Smith, 1975; Rahman et al., 1991b; Ligarski et al., 1992), flow rate (Malinowski and Smith, 1975) and surface structure (Bataille et al., 1993) of the pellets were also influenced by a change in the spheronisation speed. According to Rowe (1985), the spheronisation speed should be optimised to obtain the desired densification. He stated that a low spheronisation speed would not provide sufficient densification to obtain perfect spheres, as opposed to a spheronisation process at higher speed which could lead to agglomeration of the individual pellets.

3.9. The spheronisation time

A wide variety of effects was witnessed when assessing the importance of this parameter on formulations containing mixtures of microcrystalline cellulose: an increased diameter (O'Connor et al., 1984; Wan et al., 1993), a narrower particle size distribution (Bianchini et al., 1992), higher sphericity (Lövgren and Lundberg, 1989; Hellén and Yliruusi, 1993; Hileman et al., 1993; Wan et al., 1993), a change in the bulk and tapped densities (Malinowski and Smith, 1975;

Chapman et al., 1986; Hellén et al., 1993c; Hileman et al., 1993) and a change in the yield of a certain size range (Malinowski and Smith, 1975; Chariot et al., 1987; Hasznos et al., 1992; Ku et al., 1993) were observed with extended spheronisation time. Baert et al. (1993a) also found an increase of the sphericity of the pellets when a formulation containing only Avicel® PH101 was processed. In contrast, Bataille et al. (1990b) found no influence on the granulometry, the hardness and the friability when formulations containing only Avicel® PH101 were spheronised for different periods of time.

3.10. Spheroniser load

The importance of the spheroniser load was determined by means of an experimental design (Chariot et al., 1987; Hasznos et al., 1992; Hellén et al., 1993c,d). The yield of pellets of a specific range decreased with increased spheronisation speed at a low spheroniser load and increased with extended spheronisation time at higher spheroniser load (Chariot et al., 1987). Hasznos et al. (1992) demonstrated the influence of the spheroniser load on particle size distribution as the mean diameter increased with increasing spheroniser load. According to Hellén and coworkers, the size of the pellets decreased (Hellén et al., 1993d) and their bulk and tap density (Hellén et al., 1993c) increased with an increasing spheroniser load.

Barrau et al. (1993) found that an increasing spheroniser load increased the hardness and decreased the roundness of the pellets whereas the yield in the majority size range remained unchanged.

3.11. Drying method

The influence of the drying technique on the pellet quality was shown by Bataille et al. (1993) comparing a formulation dried in a microwave oven or in an ordinary oven, containing Avicel® PH101 and lactose. The pellets dried with microwaves differed from those dried in the oven as their surface was rougher and those pellets were more porous and of lesser hardness. To date, no further studies have been performed which include a fluid bed drier in the comparison.

4. Methods used to evaluate the quality of pellet

4.1. The determination of the size

The size of pellets can be determined using a variety of parameters: particle size distribution, mean diameter, geometric mean diameter, interquartile range, mean particle width and length.

Particle size analysis is in most cases carried out by a simple sieve analysis (Woodruff and Nuessle, 1972; Goodhart et al., 1973; Malinowski and Smith, 1975; O'Connor et al., 1984; O'Connor and Schwartz, 1985; Chapman et al., 1986; Dietrich and Brausse, 1988; Ghali et al., 1989; Lövgren and Lundberg, 1989; Millili and Schwartz, 1990; Zhang et al., 1990; Bataille et al., 1990a,b, 1991; Bains et al., 1991; Ligarski et al., 1991; Rahman et al., 1991a,b; Robinson and Hollenbeck, 1991; Baert et al., 1992a,b, 1993a,b; Barrau et al., 1992, 1993; Bianchini et al., 1992; Fielden et al., 1992a,b, 1993; Hasznos et al., 1992; Newton et al., 1992; Goskonda and Upadrashta, 1993; Hileman et al., 1993; Ku et al., 1993; Kleinebudde, 1993; Mesiha and Vallés, 1993; Pinto et al., 1993; Tapia et al., 1993; Wan et al., 1993) although the more advanced method of computer-aided image analysis (Dietrich and Brausse, 1988; Fielden et al., 1992a,b, 1993; Hellén et al., 1993a,d; Kleinebudde, 1993; Lindner and Kleinebudde, 1993; Wan et al., 1993) has also been reported.

4.2. 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 (Hellén et al., 1993c; Hileman et al., 1993; Ku et al., 1993); one-plane-critical-stability (OPCS), being the angle to which a plane has to be tilted before a particle begins to roll (Rowe, 1985; Chapman et al., 1986, 1988; Fielden et al., 1992a,b, 1993; Newton et al., 1992; Pinto et al., 1993); the ratio

of the largest and the smallest diameter of a pellet (Rahman et al., 1991a; Baert et al., 1992a,b, 1993a,b; Ligarski et al., 1992; Baert and Remon, 1993; Barrau et al., 1993); shape factors calculated by means of the projected area of the pellet and its perimeter measured with computer-aided image analysis (Woodruff and Nuessle, 1972; Dietrich and Brausse, 1988; Lövgren and Lundberg, 1989; Robinson and Hollenbeck, 1991; Fielden et al., 1992a; Hellén et al., 1993b; Hellén and Yliruusi, 1993; Kleinebudde, 1993; Lindner and Kleinebudde, 1993; Mesiha and Vallés, 1993; Wan et al., 1993).

An indirect indication of the sphericity of a pellet results from the determination of the repose angle ϕ (Woodruff and Nuessle, 1972; Hellén et al., 1993b). Tangent ϕ is the ratio of the pile height and the pile radius measured after a certain amount of pellets are allowed to fall from a given height onto a hard surface through a specified orifice.

4.3. Friability

The tendency of the pellets to flake off during handling resulting in the formation of dust is assessed by rotating the pellets in a friabilator (Malinowski and Smith, 1975, O'Connor et al., 1984; O'Connor and Schwartz, 1985; Millili and Schwartz, 1990; Zhang et al., 1990; Baert et al., 1992a,b, 1993b; Bianchini et al., 1992; Goskonda and Upadrashta, 1993; Hellén et al., 1993c; Mesiha and Vallés, 1993) or by shaking the pellets in a Turbula mixer (Dietrich and Brausse, 1988, Bataille et al., 1990b, 1991; Rahman et al., 1991a,b; Ligarski et al., 1992) for a fixed period of time. Both techniques make use of glass beads to increase the mechanical stress on the pellets.

4.4. Dissolution testing

The drug release profile from pellets is another main characteristic. Several authors correlated parameters such as hardness, composition and drug loading with the release profiles of a drug but it is difficult to take general conclusions from the published data since the work has been performed on different dissolution systems (O'Connor et al., 1984; O'Connor and Schwartz, 1985; Briquet et al., 1986; Herman et al., 1988; Bianchini and Vecchio, 1989; Ghali et al., 1989; Millili and Schwartz, 1990; Zhang et al., 1990, 1991; Rahman et al., 1991a,b; Eerikäinen and Lindqvist, 1991; Robinson and Hollenbeck, 1991; Bianchini et al., 1992; Baert and Remon, 1993; Goskonda and Upadrashta, 1993; Kleinebudde, 1993; Pinto et al., 1993; Tapia et al., 1993; Yuen et al., 1993).

A topic of growing interest is the production of matrix pellets. This could lead to a simplification of the production process as the coating can be avoided in that case. Goskonda and Upadrashta (1993) and Tapia et al. (1993) incorporated chitosan in their formulation, achieving slower release of the drug in acid medium. The addition of carnauba wax and Cutina® HR slowed the release rate of KCl of a pellet formulation (Briquet et al., 1986).

4.5. The pellet strength

This characteristic of the pellets can be correlated with the friability according to Reynolds (1970) or can be measured directly (Bataille et al., 1990a,b, 1991, 1993; Ligarski et al., 1991, 1992; Rahman et al., 1991a,b; Robinson and Hollenbeck, 1991; Baert and Remon, 1993; Barrau et al., 1993; Mesiha and Vallés, 1993). 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 (Ligarski et al., 1991).

4.6. Scanning electron microscopy

Scanning electron microscopy (SEM) pictures are taken to examine the microstructure of the pellet surface (Eerikäinen and Lindqvist, 1991; Robinson and Hollenbeck, 1991; Hellén et al., 1992, 1993c; Baert and Remon, 1993; Bataille et al., 1993; Goskonda and Upadrashta, 1993). Eerikäinen and Lindqvist (1991) took SEM pictures to observe the influence of the different fillers in the extrusion-spheronization process. The formulations prepared with microcrystalline cellulose and corn starch as excipients resulted in

the best quality pellets and SEM pictures showed that those pellets had a smooth surface. The pellets with glucose, lactose and calcium hydrogen phosphate dihydrate as excipients resulted in pellets of lesser quality with a much rougher surface.

4.7. Density

The bulk and tap densities of pellets are determined to gain an idea of the homogeneity of the particle size distribution (Woodruff and Nuessle, 1972; Goodhart et al., 1973; O'Connor et al., 1984; O'Connor and Schwartz, 1985; Dietrich and Brausse, 1988; Heng and Staniforth, 1988; Ghali et al., 1989; Bataille et al., 1990b; Millili and Schwartz, 1990; Robinson and Hollenbeck, 1991; Bianchini et al., 1992; Goskonda and Upadrashta, 1993; Hellén et al., 1993b,c, Hileman et al., 1993). The true density of pellets evaluates the porosity of the pellets and can be determined by the displacement with He or Hg (Millili and Schwartz, 1990; Rahman et al., 1991a; Bianchini et al., 1992; Baert and Remon, 1993; Bataille et al., 1993) or by a pycnometer (Chapman et al., 1986; Dietrich and Brausse, 1988; Eerikäinen and Lindqvist, 1991; Rahman et al., 1991b; Ligarski et al., 1992).

4.8. Flow properties

A final characteristic of pellets is their free flowing capacity. Bataille et al. (1990b), Hellén et al. (1993b,c) and Malinowski and Smith (1975) determined the flow capacities of the pellets to assess whether a homogeneous filling of the gelatine capsules would occur.

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