DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 30, No. 1, pp. 43–51, 2004

RESEARCH PAPER

Development of 400 μm Pellets by Extrusion-Spheronization: Application with Gelucire 50/02 to Produce a ''Sprinkle'' Form

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ABSTRACT

The aim of this study was to develop monodimensional, spherical particles of 400 μm by extrusion-spheronization. An Alexanderwerk GA65 cylinder extruder with two counter-rotating rollers associated with a Caleva model 15 spheronizer were used. The study was made with an auxiliary substance of fatty consistency and with amphiphilic properties: Gelucire 50/02. The plasticity of the mass can be deduced using a piston extruder. Pellet quality can be determined by particle-size analysis and shape estimation by microscopy. Modifications to the cylinders and the extruder itself are required for feasibility studies of extruded materials of 400 μm. The horizontal plate of the spheronizer had to be adapted to take into account the small size of the extruded materials. For the chosen auxiliary substance, Gelucire 50/02, the formulation of the wet mass to be extruded and the conditions required to obtain this mass were defined. The results show the feasibility of 400 μm pellets with Gelucire 50/02. At least 90% of the pellets have a particle size of between 250 μm and 500 μm and particle shape is acceptable. In this form the dose can be adapted to individual patients. After proving the feasibility of 400 μm spheroids of Gelucire 50/02, the association of a drug with it was considered.

Key Words: Extrusion-spheronization; Gelucire; 400 μm pellets; Active drug.

INTRODUCTION

Extrusion-spheronization is an agglomeration technique used to obtain micropellets.[1–7] Although extensive work on extrusion-spheronization has been underway for quite a number of years, it has not been possible as yet to produce any formulation methodology for obtaining by extrusion-spheronization 400 μm

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DOI: 10.1081/DDC-120027510
0363-9045 (Print); 1520-5762 (Online)

spheroids that could be used in a ''sprinkle'' form. The ''sprinkle'' form consists of a multiparticle granulometry system very much smaller than 1 mm that is used to facilitate observations. The dosage unit can easily be absorbed by sprinkling on food stuffs or swallowing in a glass of water. These small-sized spheroids could be considered as ''solid drops,'' enabling doses to be adapted to the patient by using a distributor. Other advantages are uniform distribution of the active principle in the gastrointestinal tract and improved compliance.[8–10]

The extrusion-spheronization technique is convenient when adapted to formulations: it is rapid and implies complete control of parameters. Technological parameters that could influence the quality of the extruded materials are orifice characteristics, extrusion speed, and the cooling system.

Increasing orifice dimensions results in increased mean spheroid size[11,12] and decreased pressure level.[13,14] For ibuprofen/microcrystalline cellulose/lactose mixtures, Bianchini and Vecchio obtained a more homogeneous granulometric distribution with 0.8 mm diameter orifices than with 1 mm diameter.[15]

Increasing orifice depth decreases the presence of water at the extrudate surface, increases the extrusion force, and then has a negative effect on granulometric distribution and on shape.[16] On the other hand, Newton[4] showed that insufficient depth did not densify extrudates enough, leaving them with a rough texture. The critical parameter is the L/R ratio, L being the orifice depth and R its radius.[13,14,17–20] Harrison, Newton, and Rowe[13] and Benbow, Oxley, and Bridgwater[19] noted that increasing this ratio increases the pressure level. When L/R decreases, extrudate density decreases[18] and flakes appear on the extrudate surface.[21] According to Harrison, Newton, and Rowe, who worked on a piston extruder, the L/R ratio must be above 4 to avoid the appearance of flakes.[13]

Another parameter influencing extrusion is the number of orifices per surface unit, as this controls the pressure level and compaction degree of the extrudate.[22]

In a previous work, a methodology to evaluate the capacity of a wet mass to produce 400 μm spheroids was developed.[23] This methodology requires a piston extruder to select wet masses that have the qualities necessary for both extrusion and spheronization. Gelucire 50/02 was selected as a suitable excipient, and our purpose was to evaluate formulation and process parameters in order to assess the capacity of only Gelucire 50/02 formulation. In the present work, the objective is to test the capacity of the excipient selected during experiments made on the piston extruder to yield 400 μm pellets on a cylinder extruder and then to assess the proposed selection method. It will then be necessary to modify the equipment so that it is better suited to the production of smaller-sized spheroids.

MATERIALS

Gelucire 50/02 (Gattefossé, Saint Priest, France) is used as starting materials. This is a saturated polyglycolyzed glyceride with a hydrophilic-lipophilic balance (HLB) value of 2 and melting point of 50° C. It is prepared in solid block form. Theophylline monohydrate (Boehringer Ingelheim, Ingelheim, Germany) was used as the active drug. An aqueous solution of sodium lauryl sulfate at 0.5% is used as the wetting liquid. A piston extruder consisting of a hollow steel cylinder in which the steel piston slides was used for extrusion. Dies with one or several holes of different diameters can be fitted into the end of the cylinder. This extruder is attached to a steel stand by four bolts. For the feasibility experiments, an Alexanderwerk GA 65 cylinder extruder fitted with two counter-rotating rollers was used. One of them was bored with holes of varying diameters. For our study the diameter was 0.4 mm. The mass was carried toward the die by gravity. Rotation speed varied. Spheronization was realized with the Caleva model 15 spheronizer that consisted of a horizontal plate of 38 cm diameter that rotated at high speed inside a vertical cylinder fitted with a door to enable discharge of the spheroids. Rotation speed varied from 346 to 1980 rpm. The spheroids were dried in a fluidized bed dryer at 25° C for 30 minutes. The type of mixer used depended on the quantities involved. For quantities less than 500 grams, mixing was carried out very carefully using a mortar. For larger quantities a Lodïge mixer and a planeting Erweka AR 400 mixer were used.

METHOD

Preparation of Gelucire in Powder Form

Previous works carried out in our laboratory made it possible to define a particular method to prepare the wet mass because of the presentation of Gelucire 50/02 in a solid and waxy block form.

To avoid heating that could lead to polymorphism, conditions to transform Gelucire into powder form without fusion were defined: Gelucire 50/02, after storage at 7° C, was rasped with a rotative rasp and

then frozen for 12 hours at −15° C. The frozen shavings were then sieved through an oscillating Frewitt granulator (sieve openings 1 mm). Gelucire 50/02 in powder form was then stored at a temperature of +5° C.

Feasibility of 400 μm Micropellets of Gelucire

Gelucire 50/02 in powder form was wetted with an aqueous solution of 0.5% sodium lauryl sulfate because of its lipophilic characteristics. The wet mass was tested on the piston extruder, and then on the cylinder extruder. The criteria required for study were determined.

Assessment of Wet Mass on the Piston Extruder

Plasticity of the wet mass was necessary to enable it to deform when going through the extruder orifice so as to form correctly extruded material, then spheres, during spheronization.

The minimum load required to obtain a flow through the piston extruder gave an indication of the plasticity of the mass. A low load level showed that the wet mass could easily deform. Absence of variations in this load meant constant flow with a homogenous mass.

100 grams of the wet mass was placed in the cylinder fitted with a 0.4 mm orifice. To extrude the wet mass through the orifice, a load was applied to the piston using a hydraulic press fitted with a force detector to measure the minimum load required. Any variation in this load was determined in relation to time. If the results were satisfactory, the wet mass was tested on the cylinder extruder, then spheronized.

A test to quantify the cohesion of the wet mass was developed. The samples tested were obtained by the compression of a constant volume of wet mass (2/3 of the total volume of the cylinder) at a force of 5000 N introduced into the piston extruder fitted with a full die. Then the sample was removed from the piston extruder. A force was applied in the middle of the sample, the two ends of the cylinder being laid on a support. The force required to break the sample was determined. The type of breaking was also examined. If it was a clean break, it was considered brittle.

Assessment of Extruded Materials

Cohesion of the extruded materials was assessed by its resistance at the extruder exit. If the extruded materials crushed in the collecting container, they were considered unacceptable.

Nonsticking was assessed by observing the extruded materials collected. These materials had to remain separated from each other. Formulations that produced sticky extruded materials were excluded.

Brittleness was assessed by self-breaking at the extruder exit, which indicated that the extruded material easily broke into identically sized pieces during spheronization. Extruded materials should have a smooth appearance; surface unevenness may lead to irregular breaking.

Adequation Between Equipment Geometry and Particle Size

The materials constituting the cylinders and the geometry of the orifices were chosen according to particle size.

Extrusion and Spheronization on Modified Material

Three thousand grams of wet mass was extruded at a speed of 0.285 m/s. Spheronization speed and duration were defined during the experiments. The presence of fine particles and the agglomeration of particles, observed by the formation of a bed losing its homogeneity, illustrated the need to reduce spheronization speed and duration.

Analysis of the Pellets

Tests related to the requirements of pellets for distribution as a unit dose were retained. Volumetric dosage must be reproducible. If drug content is homogeneous, the dose will be proportional to the volume of pellets and the patient will be able to take the appropriate dose from a volumetric distributor.

To obtain a reproducible volumetric dosage, flowing must be satisfactory and reproducible as well as the filling volume of the final product, which should not be influenced by tapping. It depends on granulometric distribution and shape. The former must be narrow, the latter spherical. Both also influence drug liberation.

Assessing Dose Reproducibility

Flow time and tapping capacity are determined according to the method described in the European Pharmacopoeia. One hundred grams of pellets was

introduced through a 12 mm diameter funnel with 60° angle into a test tube that underwent tapping. The flow time, the volume after 10 taps (V10), and the volume after 500 taps (V500) were noted. Tapping capacity was represented by the V10 − V500 difference. Reproducibility of the volume was estimated by analyzing the results of the V10 volume.

Granulometric Analysis

This was carried out on 400 particles after dispersion in paraffin oil using an optical microscope fitted with a micrometer. L was the largest size measured.

Assessing Shape

One hundred particles were examined through a microscope. The Heywood L/l factor was calculated, ''L'' being the largest size and ''l'' the smallest size, measured perpendicularly.

Dissolution Assay

It was performed according to the method described in the European Pharmacopoeia using a cylindrical basket rotating at a speed of 60 rpm. The dissolution medium was 900 mL of distilled water at 37° C. The dosage unit was 1 g of pellets. Samples of 1 mL were taken every 30 min for 1 hour and then every hour for 7 hours. These were filtered with 0.22 μm Millipore filters before dosing with a U.V. spectrophotometer at a wavelength of 264 nm.

RESULTS AND DISCUSSION

First of all, the wet mass wetted with various percentages of sodium lauryl sulfate was extruded through the piston extruder fitted with 400 μm die. These experiments with the piston extruder are necessary to assess the capacity of the wet mass to be extruded and make a first selection of formulations. Previous trials have already shown that when formulations are satisfactorily extruded through a 1-mm orifice, they are not systematically extruded through a 400 μm orifice.[23]

A test to quantify the cohesion of the wet mass was developed. This can be assessed after compression of the wet mass in a closed system. It represents the solid capacity to make bindings in the presence of a liquid when a force is applied. This parameter is important to assess wet mass capacity to give extruded materials.

Table 1 presents the results of cohesion, plasticity, and quality of extrudates through the 400 μm orifice for Gelucire 50/02.

For all the mixtures, the extrusion force does not vary. Whatever the percentage of wetting liquid, the type of breaking of the wet mass is clear-cut and complete during the experiments carried out to quantify cohesion of the wet mass. A comparison of the results for extrusion force and cohesion shows that when the quantity of wetting liquid increases, the extrusion force decreases and is associated with a decrease in wet mass cohesion. For low percentages of wetting liquid, 20% and 25%, the extruded materials are not smooth, which supposes a wide distribution of

Table 1. Cohesion of the wet mass and extrusion characteristics through the 400-μm orifice of the piston extruder with Gelucire 50/02 wetted with various percentages of LS Na.

	Extrusion capacity		Extruded material characteristics			
Mixture	Extrusion force in Newtons	Cohesion of the wet mass (N)	Smooth appearance	Cohesion	Self-breaking	Non-sticky
Gelucire 50/02/LS Na (100/20)	6,000	41.5 (cv=1.2%)	−	+	+	+
Gelucire 50/02/LS Na (100/25)	3,500	20.35 (cv=2.84%)	−	+	+	+
Gelucire 50/02/LS Na 100/30)	3,000	18.166 (cv=5.83%)	+	+	+	+
Gelucire 50/02/LS Na (100/40)	2,000	9.04 (cv=5.11%)	+	+	+	+

The quantity of sodium lauryl sulfate solution is indicated in brackets for 100 g of Gelucire 50/02.
Key: +, presence of the characteristic; −, absence of the characteristic.

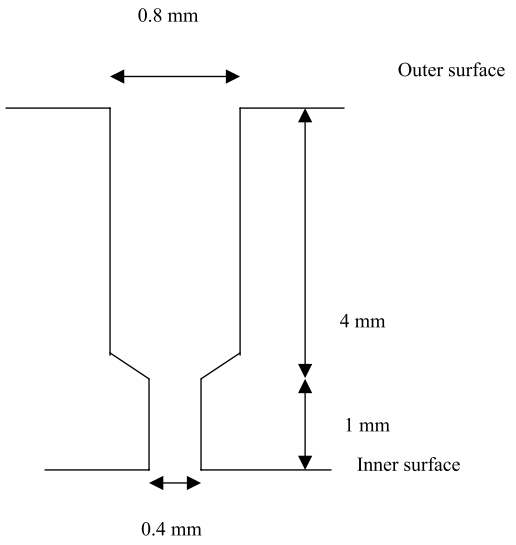

Figure 1. Orifice geometry used for the cylinder extruder.

spheroid granulometry. With a percentage of 40%, wet mass cohesion is lower. In this case, wet mass behavior is plastic, leading to an absence in force variation. As the minimum force obtained is for 40% of LS Na and as the extruded materials have all the required characteristics, this percentage of 40% of wetting liquid was retained.

Secondly, the chosen formulation was tested on a cylinder extruder and a laboratory spheronizer. This equipment was selected because, if feasibility is proven, similar devices can be used for industrial manufacturing.

The material for extrusion and spheronization is classically used to manufacture pellets of at least 800 μm. Wet mass penetration through orifices depends on the pressure applied. The smaller the orifices, the higher the pressure must be. When the pressure is too low, the mass slips between the two cylinders without being extruded. On the commercialized cylinder extruders, both cylinders are made of steel and never come in contact with each other. To increase the pressure level, a different thrust cylinder whose diameter is increased to reduce the space between the two cylinders to a minimum was developed. The pressure on the perforated cylinder is therefore increased. This modification in cylinder dimension must be made with nonrigid materials to induce contact between the two cylinders. A cylinder made of nylon called Ertalon was retained. The passage of wet mass through 400-μm orifices is made easier by the geometry and number of orifices. The shape of the orifices plays an important role in the rheological behavior of the wet mass. As for the piston extruder, the orifice geometry is cone-shaped (Fig. 1); its diameter is 0.8 mm on the outer edge and 0.4 mm on the inner edge. A maximum number of orifices—35.5 orifices per cm^2—was chosen.

Self-breaking of the extrudates is a quality parameter of the wet mass. In the case of extrudates obtained through a 0.4 mm orifice, self-breaking is all the more necessary. Indeed, the use of a cutting system, even if slight, is not possible because of the fragility of extrudates of 400 μm diameter.

The first experiments showed us that the extrudates tended to accumulate inside the cylinder and then

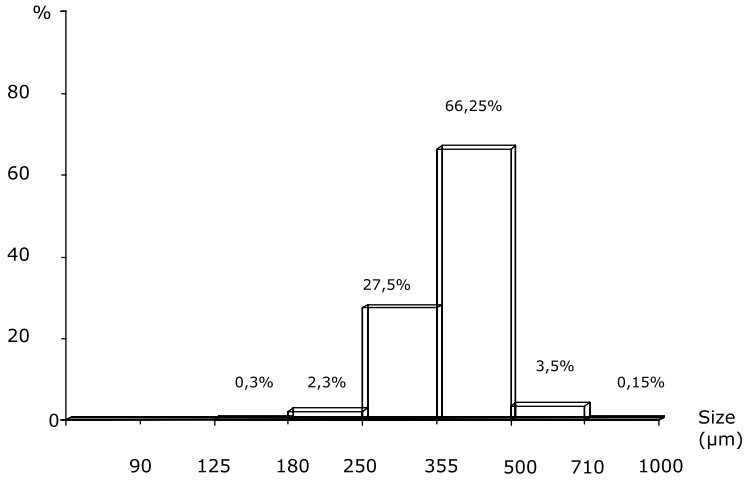

Figure 2. Granulometric repartition of Gelucire 50/02 micropellets.

Table 2. Extrusion characteristics through the 400-μm orifice of the piston extruder for Gelucire 50/02 associated with various percentages of drug wetted with 40% LS Na.

	Extrusion capacity		Extruded material characteristics			
% Theophylline	Extrusion force in Newtons	Nonvariation of the force	Smooth appearance	Cohesion	Self-breaking	Nonsticky
0	2,000	+	+	+	+	+
10	2,500	+	+	+	+	+
15	2,500	+	+	+	+	+
30	3,000	+	±	±	+	−
35	3,000	+	±	±	+	−
40	3,000	+	±	±	+	−
45	3,000	+	±	±	+	−
50	3,000	+	±	±	+	−

Key: +, presence of the characteristic; −, absence of the characteristic; ±, slight presence of the characteristic.

to agglomerate there. The extruder was inclined at a 10° angle to make the spheroid flow more easily and to avoid agglomeration. The height of the plate in which the extrudates were collected was standardized and fixed at 75 cm in relation to extruder output, making individual flowing of particles possible.

The choice of a mixer to prepare the wet mass was important. Results showed that with Gelucire 50/02, densification during wetting is associated with an increase in temperature, leading to a part of the Gelucire sticking to the inner wall of the mixer. This occurred in a Lodige-type mixer that was first used because of the high efficiency of this type of mixer. The temperature rises from 19° C to 30° C after 10 minutes of mixing in the Lodïge.

To avoid too much densification and stickiness in the mixer, a planetary mixer was chosen. Agitation was performed with a beater plus a scraper. Speeds were chosen to take account of the requirements of the mass. It is in fact important to work without developing too much energy as Gelucire 50/02 is heat-sensitive, and so the beater and the scraper rotated in the tank at 34 rpm and the beater turned on its own axis at 175 rpm.Forty percent of wetting liquid was used, as was decided during piston extruder trials. The wetting liquid was added at a speed of 25 mL/min.

Spheronization conditions of the extruded materials obtained are of prime importance. Two speeds selected after several trials were used successively: 3 minutes at 1368 rpm to ease breaking, and 4 minutes at 817 rpm to avoid agglomeration.

To avoid excessive breaking of the extruded materials and the forming of over-fine particles we chose to use a smooth rather than a grooved plate. The specified operating conditions gave spheroids of homogenous appearance.

The results of the particle-size analysis of pellets of Gelucire 50/02 wetted with 40% sodium lauryl sulfate solution are shown in Fig. 2. The elongation

Table 3. Extrusion characteristics through the 400–μm orifice of the piston extruder for Gelucire 50/02 and theophylline wetted with 35% LS Na.

	Extrusion		Extruded material characteristics			
% Theophylline	Extrusion force in Newtons	Nonvariation of the force	Smooth appearance	Cohesion	Self-breaking	Nonsticky
30	3,000	+	+	+	+	+
35	3,000	+	+	+	+	±
40	3,000	+	+	+	+	±
45	3,500	+	+	+	+	±
50	3,500	+	+	+	+	±

Key: +, presence of the characteristic; −, absence of the characteristic; ±, slight presence of the characteristic.

Table 4. Granulometric analysis of Gelucire 50/02 pellets containing different percentages of theophylline.

	Percentage of theophylline						
Particle size (μm)	10%	15%	30%	35%	40%	45%	50%
<250	4.25%	0%	0.24%	2.25%	4.5%	0.98%	13.18%
250–500	91.5%	80.2%	80.57%	77%	86.5%	88.23%	61.52%
>500	4.25%	19.8%	19.19%	20.75%	9%	10.79%	25.3%

factor of these micropellets is 1.17 (cv=1.8%) and shows that the spheroids obtained are nearly sperical. The low coefficient variation value indicates that the results are reproducible.

The microgranules are not free flowing because of the consistency of spheroids that tend to agglomerate. The apparent V_{10} is 184.5 mL and the tapping capacity $V_{10}-V_{500}$ is 15 mL.

The slight difference between the apparent V_{10} and V_{500} volumes led us to conclude that tapping will have little influence on dosage.

The feasibility of 400 μm spheroids by extrusion-spheronization was demonstrated by checking parameters, showing that granulometric distribution, average diameters, and shapes were all satisfactory and reproducible.

The association of drug to Gelucire 50/02 for obtaining 400 μm pellets was then considered. Theophylline, slightly soluble in water, was chosen.

Extruded materials were obtained by adding 10% to 50% of theophylline to Gelucire 50/02. Table 2 presents the extrusion characteristics of these formulations wetted with 40% LS Na using the piston extruder and the 400 μm die. Beyond 30% of theophylline, sticking appears and cohesion decreases. This is explained by the poor solubility of theophylline that leads to a lower absorption of the wetting liquid. It is necessary to decrease the quantity of LS Na.

Table 3 reports the assays performed with 35% LS Na. Results are more satisfactory, as sticking is decreased and only a slight tendency to agglomerate persists. These formulations were then tested on the cylinder extruder. Table 4 presents the granulometric analysis of the pellets obtained. For theophylline percentages below 45%, 77% to 91% of pellets were between 250 and 500 μm in size. Beyond that, size homogeneity decreases. Elongation factor, flow time, and tapping aptitude of these micropellets are presented in Table 5.

Elongation factor increases with the percentage of theophylline. Flow time and tapping capacity are satisfactory regardless the percentage of theophylline.

The liberation profiles of theophylline from Gelucire 50/02 pellets containing 10% and 50% of theophylline were established. In both cases, theophylline is released rapidly: 90% in 1 hour and 100% in 3 hours. Drug liberation is not delayed by lipophilic excipient because of the small size of pellets.

CONCLUSION

Preparation of 400-μm-diameter spheres by extrusion-spheronization has been shown to be possible. It requires a suitable excipient. Measurement of the extrusion load through a piston extruder and an examination of the extruded materials are good indicators of feasibility for cylinder extruders.

Setting up a laboratory cylinder extruder that can also be used in an industrial setting requires adequation between equipment geometry and particle size.

Table 5. Characteristics of Gelucire 50/02 pellets containing various percentages of theophylline.

% Theophylline	Elongation factor	Forced flowing (sec)	V10 (mL)	Tapping aptitude (mL)
10%	1.148	13	180	V10 – V500 = 180 – 166 = 14
15%	1.174	12	172	V10 – V500 = 172 – 163 = 9
30%	1.196	12,5	170	V10 – V500 = 170 – 158 = 12
35%	1.239	14	170	V10 – V500 = 170 – 157 = 13
40%	1.24	12.5	165	V10 – V500 = 165 – 156 = 9
45%	1.268	13	167	V10 – V500 = 167 – 155 = 12
50%	1.654	15	166	V10 – V500 = 166 – 155 = 11

Gelucire 50/02 has suitable properties for obtaining 400 μm micropellets. The choice of mixer proved to be of prime importance in obtaining a satisfactory wet mass and thus the production of acceptable extruded materials and spheroids. A planetary mixer, in our trial conditions, yielded a mass with adequate qualities without a cooling system. It was homogenous with no increased densification patches. Self-breaking took place at the extruder exit. The wet mass must have sufficient plasticity to obtain correct extrusion output. An increase in wetting liquid increases plasticity if there is a plastic substance such as Gelucire 50/02 in the mass but to a certain extent induces stickiness. On the other hand, spheronization can be limited because of a too much wetted mass. To avoid agglomeration even with a correct mass, it is necessary to use a high speed at the beginning to facilitate cutting and then to reduce speed.

If these spheres are to be used as solid drops, their properties must not be modified in transportation and transfer. These spheres have to be tested for their tendency to deform. We plan to proceed with this study, taking a close look at the hardening processes on the surface of these minipellets.

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