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Developing a study method for producing 400 μm spheroids

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Abstract

The aim of this work was to obtain 400 μm spheroids that can be sprinkled on food to improve patient compliance particularly in the case of children and old people. A methodology to select wet masses for extrusion-spheronization through a 400 μm orifice was developed. The first step was to define the parameters that make it possible to assess the qualities required by the wet mass and the extrudates and evaluation norms: plasticity, cohesiveness, brittleness of the mass and the extrudates, and appearance of extrudates. A feasibility assay was then performed on the cylinder extruder, showing that extrusion of the lactose/Avicel PH 101/water (50/50/60) mass is not feasible through the 400 μm orifice. Precirol ato 5 and Gelucire 50/02 wetted with a sodium lauryl sulfate solution at 0.5% show plastic flow through the 400 μm diameter orifice. The presence of Avicel PH 101 does not improve plasticity for this orifice. Micropellets of 400 μm have been proved feasible as long as excipients with suitable pharmaceutical technological properties are used. After proving the feasibility of 400 μm spheroids of Gelucire 50/02, we considered the association of a drug with it.

Keywords: Cohesiveness; Extrusion-spheronization; Gelucire; Plasticity; 400 μm spheroids

1. Introduction

Ease of medicinal administration is of particular importance for infants and elderly people. Liquid drops via the mouth are convenient for adapting posology to the patient but may be difficult to implement, and lead to confusion. A "solid drop" form would improve reproducibility of the administered dose which would nevertheless remain adaptable to the patient (Kjellman et al., 1988).

The "sprinkle" form is a recent galenic form consisting of a multiparticle granulometry system very much smaller than 1 mm that is used to facilitate observations. The dosage unit can easily be absorbed after sprinkling on foodstuffs, or swallowed in a glass of water. These small-sized minipellets can be considered as "solid drops" that enabling doses to be adapted to the patient by using a distributor. The manufacturing procedures may use crystals that are mounted in a turbine or

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in a fluidized bed dryer. Nebulization of the active principle dispersion, together with cooling in the dispersion phase, make it possible to prepare sprinkles with excipients that can melt.

The other main features favouring divided rather than undivided forms, whatever their size, are reduced effects on the alimentary bolus, gastric emptying, active principle activities and possible adapted releasing of the active principle (Carrigan et al., 1990; Follonier and Doelker, 1992).

Although extensive work on extrusion-spheronization has been going on for quite a number of years, it has not been possible as yet to produce any formulation methodology for the obtention by extrusion-spheronization of 400 μm spheroids that could be used in a "sprinkle" form.

The extrusion-spheronization technique is a spheroid-obtaining procedure that proves to be faster when the formulation is adapted to the procedure. It is used to produce minipellets of about 1 mm (Newton, 1990; Newton et al., 1992, 1995; Raines and Newton, 1987; Gayot and Leterme, 1990; Gayot et al., 1985; Mouton and Gayot, 1988).

Newton's works deal with the study of the capacity of a lactose/Avicel blend to give 1 mm spheroids. In our study, we examined the possibility of adapting this technique to the production of 400 μm spheroids, with various types of vehicles in mind.

The excipients used were only wetted with an aqueous solution to avoid the problems of deflagration and toxicity related to the use of organic solvent. The excipients were not melted because of a problem of heat stability.

In this work, we have two objectives. Both are relating to feasibility, the first one is to evaluate it by choosing adequate excipients and the second by testing if association of these excipients and drugs will give 400 μm spheroids. Two drugs of different solubilities were used: theophylline, slightly soluble in water and diltiazem chlorhydrate, soluble in water. Drugs have to be blended with the excipients before the wetting of the mass. The possibility to produce 400 μm spheroids containing drugs will be related to the influence of the drug on plasticity and cohesion of the wet mass. The drug behaviour during extrusion-spheronization will restrict the percentage of drug that could be incorporated.

2. Materials and methods

We developed an methodology for the evaluation of the capacity of a wet mass to give 400 μm spheroids.

2.1. Materials

The excipients used are those used in the techniques of extrusion alone, of extrusion-spheronization, or those acknowledged to be plastic.

- Avicel PH 101 (microcrystalline cellulose) (Seppic, Paris, France).
- Fine lactose powder (60–80 μm) (H.M.S., Sains du Nord, France).
- Metolose 65 HS 400 (hydroxypropylmethyl cellulose) (Shin Etzu, Tokyo, Japan).
- Gelucire 50/02 (Gattefossé, Saint Priest, France). This is a saturated polyglycolyzed glyceride with an HLB of 2 and melting point at 50 °C. It is in the form of a solid block.
- Precirol ato 5 (Gattefossé). This is a glycerol palmitostearate also known as Gelucire 54/02. It is a white atomized powder.
- Purified water.
- Theophylline monohydrate (Boehringer Ingelheim, Ingelheim, Deutschland).
- Diltiazem chlorhydrate (Teva, Petah-Tiqua, Israel).
- 0.5% Sodium lauryl sulfate aqueous solution (LS Na).
- Piston extruder consisting of a hollow steel cylinder with a sliding steel piston inside. Dies with one or more holes of different diameters can be fitted in the end of the cylinder. This extruder is fixed to a steel stand by four bolts.
- An Alexanderwerk GA 65 cylinder extruder with two counter-rotating rollers. One of them is bored with holes of varying diameters. For our study, the diameter was 0.4 mm. The mass is carried towards the die by gravity.
- The Caleva model 15 spheronizer consists of a horizontal plate that rotates at high speed inside

a vertical cylinder fitted with a door to enable discharge of the spheroids. The spheroids are dried in a fluidized bed dryer at 25 °C for 30 min.

2.2. Developed methodology

The wet mass must have qualities that meet both extrusion and spheronization operation requirements. We assessed the parameters necessary to appreciate the essential qualities that the wet mass and the extruded materials must have:

- Plasticity of the mass and the extruded materials: plasticity of the extruded materials is related to that of the wet mass; we shall examine only the latter by studying its capacity to extrude through a piston extruder. Measurement is made of the minimum force to be applied to obtain an extrudate and the variation of this force in time is determined. Absence of variation in this force means there is a constant flow and homogenous mixing. A low level of force, of the order of 2000 N, proves the ease with which the wet mass deforms under low stress levels.
- Smooth appearance of extruded materials: this ensures the breaking in particles of regular size.
- Cohesion of the mass and the extruded materials: we developed a test to quantify the cohesion of the compressed mass. The samples tested were obtained by the compression of a constant volume of wet mass at a force of 5000 N introduced into the piston extruder fitted with a full matrix. The force required to break the sample is measured.

  The cohesion of the extruded materials is assessed by its resistance at the extruder exit. If the extruded materials crush in the collecting container, they are considered unsuitable.
- Brittleness: it is assessed both on the extruded materials and on the wet mass sample used for the cohesion test by breaking. If it is a clear-cut and complete division, it is considered brittle. Assessment of extruded materials is based on their ability to self-break at the extruder exit.
- Non-sticking: it is assessed by observing the extruded materials collected. These materials must remain separated from each other.

The ability of the wet mass to be extruded is assessed on the piston extruder in the following conditions:

- 100 g of wet mass is introduced into the cylinder, and the wet mass is extruded through the matrix by a load applied to the piston by a hydraulic press fitted with a captor to measure the force applied during extrusion.

The excipients, whether alone or combined with Avicel PH 101 because of its binding non-stick plastic qualities, are first tested with a 1 mm diameter matrix. These experiments enable us to make a first selection. Will be only retained mixtures, which are perfectly extrudable using a low force through a 1 mm diameter orifice. The lactose/Avicel PH 101/water mixture (50/50/60) is considered as a mixture that presents adequate properties to be extruded through a 1 mm orifice.

A second selection is then performed using the 400 μm matrix. We appreciated the characteristics of the wet mass and of the extruded materials.

3. Results and discussion

Tables 1 and 2 show the results of extrusion through the 1 mm diameter matrix, and the experiments carried out on the wet mass.

The results of extruding the lactose/Avicel PH 101/water (50/50/60) mixture through the 1 mm matrix show that the wet mass of this mixture meets all the required criteria and that the extrusion force is weak. The extruded materials have all the required characteristics, unlike those obtained using Metolose which do not cut clearly and tend to stick. The addition of Avicel PH 101 to Metolose only slightly improves results. It never satisfactorily makes better the breaking capacity.

Laboratory experiments have shown the need to wet Precirol and Gelucire 50/02 with 0.5% LS Na because of their lipophilic characteristics.

Table 1
Extrusion characteristics using a 1 mm matrix (LS Na, 0.5%)

Mixture	Extrusion capacity		Experiments carried out on the wet mass		
	Extrusion force (N)	Non-variation of the force	Cohesion (N)	Type of break	
				Clear-cut	Complete
Lactose/Avicel PH 101/water (50/50/60)	1500	+	5.8 (cv = 4.36%)	+	+
Metolose/water (100/100)	3000	+	30 (cv = 2.66%)	−	+
Metolose/Avicel PH 101/water (50/50/95)	2500	+	27.34 (cv = 2.11%)	−	−
Precirol/LS Na (100/20)	$4000 < x < 1500$	−	Not realized		
Precirol/LS Na (100/35)	3000	+	3.4 (cv = 2.94%)	+	+
Precirol/LS Na (100/55)	1000	+	Not realized		
Precirol/Avicel PH 101/LS Na (75/25/53)	2000	+	1.96 (cv = 2.93%)	+	+
Gelucire 50/02/LS Na (100/20)	5000	+	41.5 (cv = 1.2%)	+	+
Gelucire 50/02/LS Na (100/30)	1750	+	18.166 (cv = 5.834%)	+	+
Gelucire 50/02/LS Na (100/40)	1500	+	9.04 (cv = 5.113%)	+	+
Gelucire 50/02/Avicel PH 101/LS Na (80/20/32)	2000	+	14.90 (cv = 5.067%)	+	+

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

For Precirol alone wetted at 35%, the extrusion force was 3000 N and did not vary but the extruded materials tended to stick. We observed that for Precirol, a reduction in wetting liquid increased the extrusion force and gave unsmooth extruded materials. On the other hand, an increase in wetting liquid reduced the extrusion force but increased the sticky character of the extruded materials and prevented their self-breaking.

Adding Avicel PH 101 reduced the necessary extrusion force and improved the characteristics of the wet mass and of the extruded materials by eliminating the stickiness and increasing brittleness.

Table 2
Extruded material characteristics using a 1 mm matrix

Mixture	Characteristics of the extruded materials			
	Smoothness	Cohesion	Self-breaking	Non-sticky
Lactose/Avicel PH 101/water (50/50/60)	+	+	+	+
Metolose/water (100/100)	+	+	−	±
Metolose/Avicel PH 101/water (50/50/95)	+	+	−	±
Precirol/LS Na (100/20)	−	+	±	±
Precirol/LS Na (100/35)	+	+	+	±
Precirol/LS Na (100/55)	±	−	−	−
Precirol/Avicel PH 101/LS Na (75/25/53)	+	+	+	+
Gelucire 50/02/LS Na (100/20)	−	+	+	+
Gelucire 50/02/LS Na (100/30)	+	+	+	+
Gelucire 50/02/LS Na (100/40)	+	+	+	±
Gelucire 50/02/Avicel PH 101/LS Na (80/20/32)	+	+	+	+

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

The extrusion force of 2000 N with the previous is close to that obtained for the lactose/Avicel PH 101/water (50/50/60) formula.

For Gelucire 50/02, with and without Avicel PH 101, the wet mass and the extruded materials have all the characteristics required. The effect of the quantity of wetting liquid is the same as for Precirol. With the mixture Gelucire 50/02/LS Na (100/30), the results are the best.

For all the tested formula, results of cohesion and breaking on the wet mass sample and on the extruded materials are comparable.

Since the formulas lactose/Avicel PH 101/water (50/50/60), Precirol/Avicel PH 101/LS Na (75/25/50), Gelucire 50/02/LS Na (100/30), Gelucire 50/02/Avicel PH 101/LS Na (80/20/32) give satisfactory results, they were extruded through the 400 μm orifice. The results relative to the extrusion force and to the quality of the extruded materials are shown in Table 3.

Extrusion of the lactose/Avicel PH 101/water (50/50/60) mass is not feasible. The components separate and we could not obtain extruded materials in spite of a force of 30 000 N.

The extrusion force for Precirol, under test conditions, was not constant. It varied between 1500 and 3000 N. The extruded materials agglomerate and are difficult to break.

The Gelucire 50/02/Avicel PH 101/LS Na (80/20/32) formulation produced extruded materials with all the required characteristics but the extrusion force was 5000 N. The Gelucire 50/02/LS Na (100/30) formula required a lower extrusion force of 3000 N. The extruded materials were non-sticky, smooth and self-breaking. Increasing the wetting liquid to 40% reduced the extrusion force to 2000 N and the extruded materials had all the required characteristics.

Experiments showed that the formulas that give satisfactory results when extruded through an orifice of 1 mm do not systematically do so through an orifice of 0.4 mm.

For the formulas tested, extrusion through 0.4 mm led to a loss of plasticity. Removing Avicel PH 101 from the formulas containing Precirol ato 5 and Gelucire 50/02 improved this plasticity. The Gelucire 50/02 formula wetted with 40% of wetting liquid was chosen because it enabled extruded materials of good quality to be obtained with a minimum force, just 2000 N. The extruded materials self-break and are not sticky.

This formula was retained for the feasibility assay in a cylinder extruder associated to a spheronizer. 500 g of wet mass was extruded through the Alexanderwerk GA 65 cylinder extruder and spheronized on the Caleva model 15. Because of the low melting point of excipients, axial extruder is not suitable. It induces heating.

We obtained 400 μm spheroids with granulometric distribution, average diameters and shapes that were all satisfactory and reproducible: 93.75% of the particles had a size between 250 and 500 μm

Table 3
Extrusion and extruded material characteristics for the 400 μm matrix

Mixture	Extrusion capacity		Characteristics of the extruded materials			
	Extrusion force (N)	Non-variation of the force	Smoothness	Cohesion	Brittleness	Non-sticky
Lactose/Avicel PH 101/water (50/50/60)	30000	Not available, No extruded materials obtained				
Precirol/Avicel PH 101/LS Na (75/25/53)	1500–3000	−	±	±	±	−
Precirol/LS Na (100/35)	4000	+	+	±	±	±
Gelucire 50/02/Avicel PH 101/LS Na (80/20/32)	5000	+	+	+	+	+
Gelucire 50/02/LS Na (100/30)	3000	+	+	+	+	+
Gelucire 50/02/LS Na (100/40)	2000	+	+	+	+	+

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

with 66.25% between 355 and 500 μm. The Heywood factor L/l assessed by microscopy was 1.17 (cv: 1.8%) with L being the biggest size and l the smallest size, measured perpendicularly. That shows that the spheroids obtained are closed to a spherical shape. The low coefficient variation value indicates that the results are reproducible.

The feasibility of 400 μm spheroids of Gelucire 50/02 being demonstrated, we considered the association of a drug with it.

Extruded materials are obtained by adding 10–50% of theophylline to Gelucire 50/02 wetted with 35% LS Na using the piston extruder and the 400 μm die. Results are described in Table 4.

They show that extrusion force is slightly higher than for Gelucire 50/02 wetted with 40% lauryl sulfate sodium solution. The behaviour of the Gelucire 50/02–theophylline mixture is plastic. Whatever the percentage of theophylline, the extruded materials have adequate characteristics.

Pellets were obtained when these different mixtures are extruded through cylinder extruder. For theophylline percentages below 45%, 77–91% of pellets have a size between 250 and 500 μm.

Whatever the percentage of theophylline, 90% is dissolved in 1 h. This confirms that as specific surface area is high, dissolution even with an excipient such as Gelucire 50/02 is not delayed. It will be possible to satisfy our objective that is to say to use pellets as a solid dosage drop form. This allows to adapt doses to the therapeutics and will be particularly interesting for infants.

On the piston extruder, diltiazem chlorhydrate alone wetted with water gives a non self-breaking, sticking and cohesive mass.

Decreasing the wetting reduces the importance of those three characteristics. Wetting with ethanol decreases cohesiveness and sticking and improves cutting. Lack of cutting was observed for a mixture of 30% diltiazem chlorhydrate and 70% Gelucire 50/02 wetted with a 0.5% aqueous solution of sodium lauryl sulfate whatever the quantity of wetting liquid.

With only Gelucire 50/02 and diltiazem chlorhydrate, it was not possible to obtain 400 μm spheres. Other experiments will be done taking into consideration the results of feasibility with other excipients.

4. Conclusion

The feasibility of 400 μm micropellets has therefore been demonstrated with a cylinder extruder associated to suitable pharmacotechnical properties.

A feasibility trial using an Alexanderwerk GA 65 cylinder extruder with 400 μm orifices coupled to a Caleva model 15 spheronizer showed that our methodology offered correct feasibility forecasting.

There is a relationship between formulation and apparatus. Setting up a cylinder extruder required some modifications. The spheres obtained using Gelucire 50/02 alone and associated with theophyl-

Table 4
Extrusion characteristics through the 400 μm orifice of the piston extruder for Gelucire 50/02 and theophylline wetted with 35% LS Na

Mixture		Extrusion		Extruded material characteristics			
% Theophylline	% LS Na	Extrusion force (N)	Non-variation of the force	Smooth appearance	Cohesion	Self-breaking	Non-sticky
30	35	3000	+	+	+	+	+
35	35	3000	+	+	+	+	±
40	35	3000	+	+	+	+	±
45	35	3500	+	+	+	+	±
50	35	3500	+	+	+	+	±

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

line wetted with a solution of sodium lauryl sulfate have all the required characteristics.

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