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CAPACITY OF LIPOPHILIC AUXILIARY SUBSTANCES TO GIVE SPHERES BY EXTRUSION - SPHERONIZATION

A. Edimo [1], P. Leterme [1], J. Denis [2], M. Traisnel [1], A.T. Gayot [1]

[1] Laboratoire de Pharmacotechnie Industrielle, Faculté de Pharmacie, rue du Professeur Laguesse,
59045 LILLE Cédex

[2] Gattefosse, Chemin de Genas, 68 - SAINT PRIEST

ABSTRACT

The authors consider the preparation of spheroids by extrusion-spheronization with Precirol ato 5 and Gelucire 50/02. The material is a ram extruder and a cylinder extruder associated to a spheronizer. Spheroids are obtained by adding an auxiliary substance such as microcrystalline cellulose. A comparison of the results obtained on the two types of extruder allows a better understanding of the pressure/displacement

profile and emphasizes the necessary qualities of the wet mass and extrudates.

INTRODUCTION

This work concerns the feasibility of pellets by extrusion-spheronization with lipophilic auxiliary substances such as Precirol ato 5[1] and Gelucire 50/02[1].

MATERIALS AND METHODS

Materials

Precirol ato 5 is a palmito-stearate of glycerol obtained by spray-drying. It is a powder for which 85 % of particles are smaller than 100 μm. Its melting point is between 52° and 55°, its H.L.B. is 2. (1)

Gelucire 50/02 associates a mixing in definite proportions of mono, di, triglycerides of fatty acids of C_8 to C_{18}. Its melting point is between 48° and 53°,
the H.L.B. value is 2. It is a waxy solid. (2)
The wetted mass is prepared in a planetary mixer.
For extrusion, material is the following (3)
- a ram extruder made up of a hollow steel cylinder in which slides a steel piston. Dies with one or several

holes of different diameter can be set in the extremity of the cylinder.

This extruder is fixed with four screws onto a steel stand. This unit is set under the load cell of a universal testing machine. This machine is composed of a rigid frame between which moves a cross-head and of a load cell.

The load required to extrude the material was monitored and recorded depending on the displacement on an X-Y recorder. Different ram speeds can be selected.

For our study, the ram speed is 5 cm/mm, the die diameter is 1 mm, the lenght to radius ratio of the die (L/R) is 8.

- a cylinder extruder (Alexanderwerk GA 65)[2] made up of two contra-rotating rollers. One of them is bored with holes whose diameter can vary. For our study, the diameter is 1 mm. The feed machanism to transport the mass towards the die is gravity. The speed of rotation can vary. For our study, the speed is constant 95 rpm.

- The spheronizer (Caleva model 15)[3] consists of a grooved horizontal plate rotating at high speed within a stationary vertical cylinder fitted with a door to allow the discharge of the spheroids. The geometry of the stainless steel plate is made up of pyramids whose height is 1,9 mm and side 5,8 mm.

Spheroids are dried in a fluidized bed dryer at a temperature of 30° during 20 min.

Method

The study of the pressure-displacement profile obtained from the ram extruder associated to the universal testing machine and the study of the aspect of the extrudate allows the selecting of formulae whose characteristics are good for extrusion-spheronisation.

The plasticity of the mass can be inferred by the study of the profile when the pressure is independent of the displacement during the flow stage (4). Extrusion mass and extrudates must not be sticky. Besides, the latter must be smooth. (5,6)

In our study, to evaluate the feasibility of pellets with these lipophilic components and also to connect the results obtained on the one hand with the ram extruder, on the other hand with the cylinder extruder, we must test wetted masses at first on the ram extruder, then on the cylinder extruder and the spheronizer.

RESULTS AND DISCUSSION

As Gelucire 50/02 is a waxy solid, it must be changed into powder to get a homogeneous wet mass.

The inclusion method is the one we use :

Gelucire 50/02 in a jacketed kettle of a planetary mixer is heated at 70°.

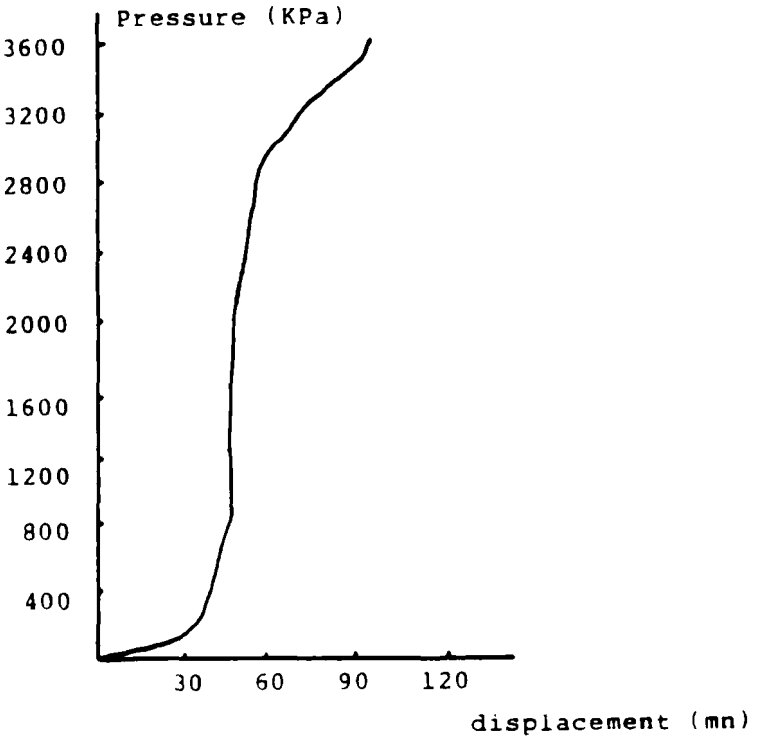

FIGURE 1 : Pressure-displacement profile for precirol ato 5 - 22 % aqueous solution of 0,5 % sodium lauryl sulfate

The other components are added under agitation which takes place during 5 minutes. The temperature of the kettle containing homogeneous mixing is progessively decreased. When the content has a temperature of 60°, it is spread out on trays. When the mass is 25°, it is passed through sieves of an oscillating granulator whose openings are successively 1,5 mm and 1 mm.

As Gelucire 50/02 and Precirol ato 5 have a H.L.B. value of 2, the wetting liquid that we choose is an aqueous solution of 0,5 %

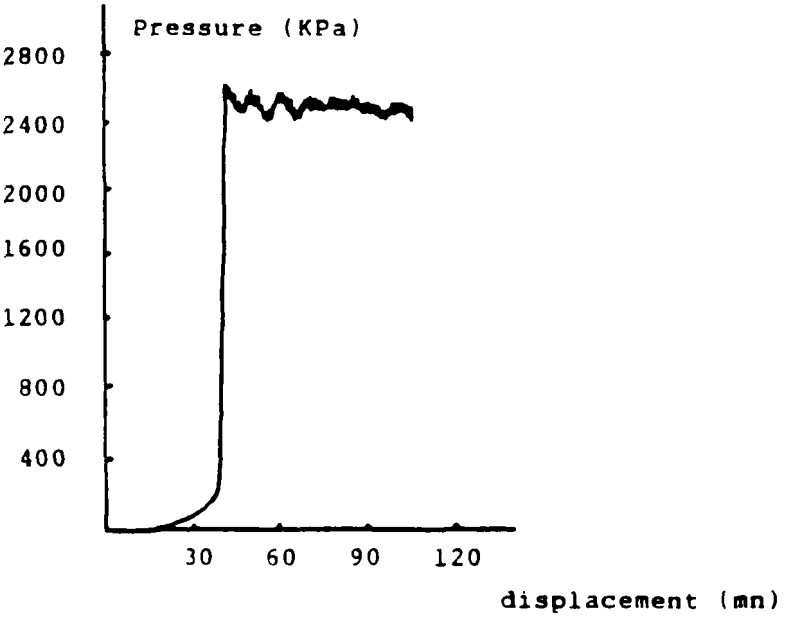

FIGURE 2 : Pressure-displacement profile for gelucire 50/02 - 17 % aqueous solution of 0,5 % sodium lauryl sulfate

sodium lauryl sulfate. In these conditions, the wetting mass is homogeneous.

The pressure-displacement profiles for the Precirol ato 5 wetted with 22 % (v/w) of an aqueous solution of 0,5 % sodium lauryl sulfate and for the Gelucire 50/02 wetted with 17 % (v/w) of the same solution are represented on the figures 1 and 2.

For both cases, the pressures are high. Gelucire 50/02 shows a steady state flow stage. For Precirol, this stage does not exist. The extrudates of Precirol ato 5 and Gelucire 50/02 in the spheronizer do not give spheres, they change into powders.

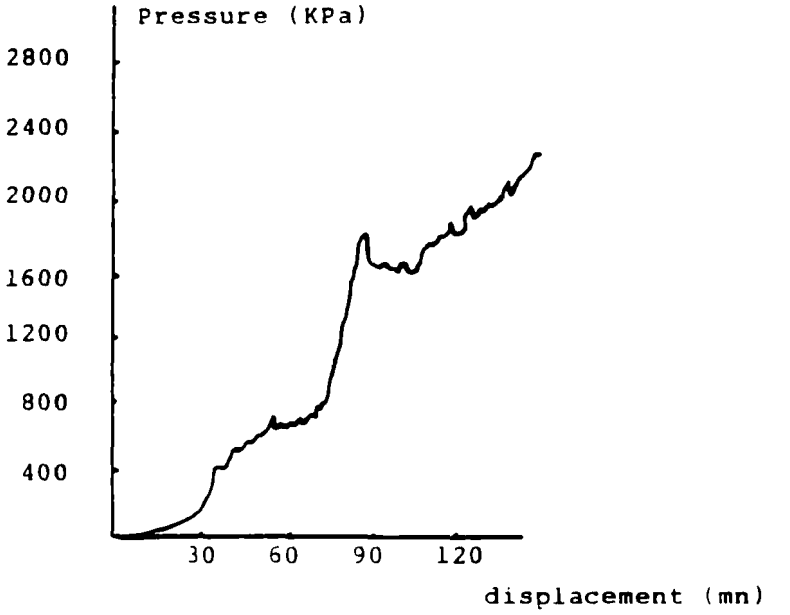

FIGURE 3 : Pressure-displacement profile for microcrystalline cellulose-precirol ato 5 : 27/73 wetted with 31 % (v/w) aqueous solution of 0,5 % sodium lauryl sulfate

We consider if the adding of microcrystalline cellulose (Avicel PH 101[4]) can improve the results.

Percentages between 27 and 33,5 (w/w) of microcrystalline cellulose are added to Precirol ato 5. The quantities of the wetting liquid are adapted to each mass (7). The pressure/displacement profiles when adding microcrystalline cellulose show a decrease in the pressure necessary to flow, a very short steady state flow stage. Figure 3 gives the profile with 27 % microcrystalline cellulose.

The same masses are tested on the cylinder extruder and the spheronizer. Whatever the percentage of microcrystalline cellulose, the extrudates are smooth, not sticky, able to give spheres.

As the feasibility of pellets with Precirol ato 5 associated to cellulose microcrystalline is proved, we consider decreasing the percentage of microcrystalline cellulose and defining the conditions which give good results.

Percentages of 15, 17,5 , 20 microcrystallne cellulose have been tested with an adjusted volume of wetting liquid. The pressure/displacement profiles do not show a steady state flow stage. The pressures are lower than the one obtained with the only Precirol and do not change with the percentage of microcrystalline cellulose (figure 4).

The cylinder extrusion with the same speed as for higher percentages of microcrystalline cellulose (95rpm) gives non sticky extrudates, which are capable of spheronizing.

The spheronizer speed is decreased in comparison with experiments with higher percentages of microcrystalline cellulose and adjusted to each formula. The spheronization duration increases with the percentage of Precirol in the formula. The compositions and the operating conditions are listed in the table I.

The extrudates obtained are smooth, non-sticky and give spheroids when spheronized. The particle size distribution is

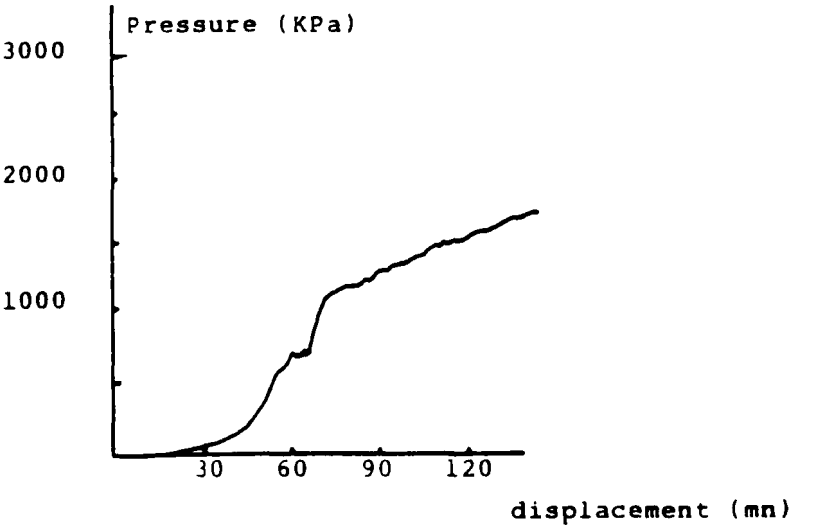

FIGURE 4 : Pressure-displacement profile for microcrystalline cellulose-precirol ato 5 : 15/85 wetted with 34 % (v/w) aqueous solution of 0,5 % sodium lauryl sulfate

TABLE 1

Compositions and operating conditions for Precirol ato 5

Microcrystalline cellulose (g)	15	17,5	20	25
Precirol ato 5 (g)	85	82,5	80	75
Wetting liquid (ml)	33,6	39	40	53
Spheronization speed (rpm)	700	800	800	1000
Spheronization duration	12mn30s	10mn	10mn	7mn30s

TABLE 2

Particle size distribution of Precirol ato 5 associated to 20 % or 15 % microcrystalline cellulose.

Screen opening (μm)	% retained	
	20 % microcrystalline cellulose 80 % Precirol ato 5	15 % microcrystalline cellulose 85 % Precirol ato 5
2000	2	0,5
1600	14	7
1250	81,5	88
1000	2	3
800	0,5	1
630	0	0,5
Pan	0	0

unimodal with a maximum percentage for particle sizes between 1000 and 1250 μm.

Table 2 gives the particle size distribution of mixtures with 15 % and 20 % microcrystalline cellulose.

All the particles whatever the percentage of microcrystalline cellulose, when examined under the microscope, are not very different from spheres, with a smooth surface.

For Gelucire 50/02, a maximum quantity of microcrystalline

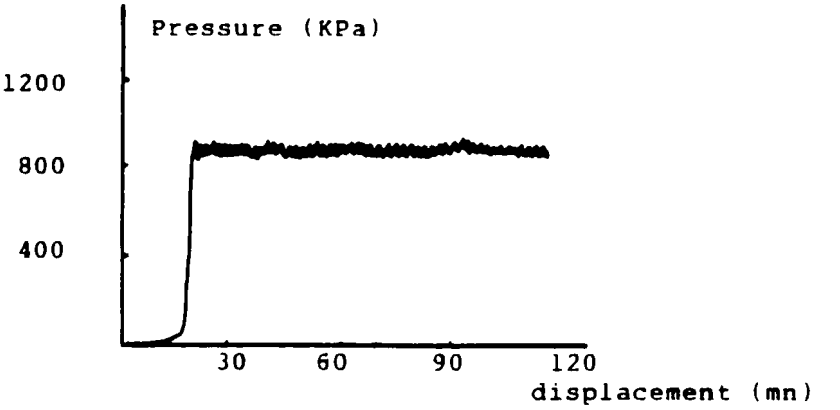

FIGURE 5 : Pressure-displacement profile for microcrystalline cellulose-gelucire : 37/63 wetted with 28,2 % aqueous solution of 0,5 % sodium lauryl sulfate

cellulose (37 %) can be mixed with the melted Gelucire. For this percentage and for 30 %, the pressure/displacement profiles show a steady state flow stage with a lower pressure than the one got with the only gelucire (figure 5).

The extrudates obtained with the cylinder extruder are smooth, non-sticky and give spheroids.

We are planning to decrease the concentrations of microcrystalline cellulose. Percentages of 15, 17,5 , 20 are tested. The quantities of wetting liquid and the spheronization conditions are adjusted and are described on the table 3.

The pressure/displacement profiles show a decrease in the pressure of the steady state flow stage when microcrystalline cellulose is added and/or when the wetting liquid increases

TABLE 3

Compositions and operating conditions for Gelucire 50/02

Microcrystalline cellulose (g)	15	17,5	20
Gelucire 50/02 (g)	85	82,5	80
Wetting liquid (ml)	30	32	32
Spheronization speed (rpm)	650	700	750
Spheronization duration	12mn30s	12mn30s	12mn30s

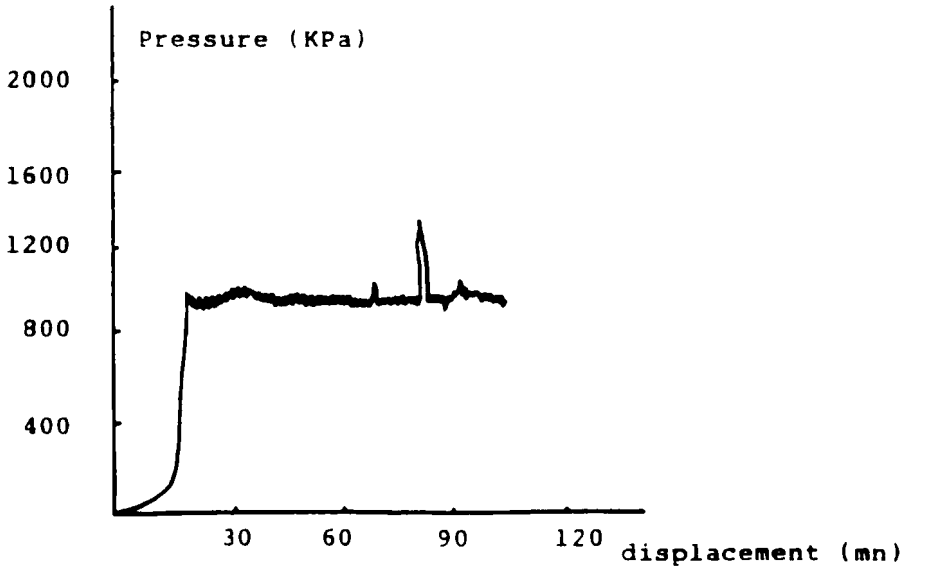

FIGURE 6 : Pressure-displacement profile for microcrystalline cellulose-gelucire : 17,5/82,5 wetted with 26 % aqueous solution of 0,5 % sodium lauryl sulfate

TABLE 4

Particle size distribution of Gelucire ato 5 associated to 20 % or 17,5 % microcrystalline cellulose

Screen opening (µm)	% retained	
	20 % microcrystalline cellulose 80 % Gelucire ato 5	17,5 % microcrystalline cellulose 85 % Gelucire ato 5
2000	1	0,5
1600	6	4,5
1250	84	74
1000	8	17
800	0,5	3
630	0,5	1
Pan	0	0

(figure 6). The extrudates are smooth and non-sticky. With 15 % microcrystalline cellulose, the shape of particles is very varied with only some spheroids.

With higher percentages, we get spheroids. The particle size is unimodal (Table 4). At least, 74 % of particles have sizes between 1000 and 1250 µm.

Spheres of Gelucire 50/02 and Precirol ato 5 can be obtained by extrusion-spheronization when adding an auxiliary substance such as microcrystalline cellulose. The latter has the advantage of bringing two properties: plasticity and cohesiveness. For Precirol ato 5, the choice of microcrystalline cellulose is

advantageous because this component compensates the lack of plasticity and cohesiveness of the mass wetted with an aqueous solution of sodium lauryl sulfate. In the case of Gelucire 50/02, the addition of microcrystalline cellulose intends to increase the cohesiveness of the mass wetted with the same liquid. On the other hand, it also decreases the pressure required for extrusion seeing that the pressure for obtaining flow decreases with the addition of microcrystalline cellulose.

We are considering the substition of microcrystalline cellulose by a drug. The chosen one is theophylline (8). The dissolution profile shows that 85 % of theophylline is dissolved in 4 h 30 mn if the particle size of pellets with Gelucire 50/02 is between 1000 and 1600 μm.

This study shows the feasibility of pellets with lipophilic auxiliary substances as Gelucire 50/02 and Precirol ato 5. It also gives a better understanding of the pressure/displacement profiles.

The lack of a steady state flow stage such as with Precirol ato 5 wetted with an aqueous solution of sodium lauryl sulfate does not mean that this material will not give spheres by extrusion-spheronization. The high pressure required for the flow of material through the ram extruder, is inauspicious and requires addition of components which decrease this pressure.

The cohesiveness of the mass which is not evaluated by the

consideration of the pressure/displacement profile, is also preponderant on the capacity of a wetted mass to give spheres by extrusion-spheronization. This characteristic depends on the quality and quantity of the wetting liquid. For some excipients, it is unfortunately associated to stickiness. The stickiness of the mass and of the extrudates is a major fault. If there is a long steady state flow stage on the pressure/displacement profile, if the pressure at this stage is low, if the extrudates are not sticky and with enough cohesiveness the probability of obtaining spheres by extrusion-spheronization is high.

NOTES

1 Gattefossé, 36 Chemin de Genas, B.P. 603, 69804 SAINT PRIEST CEDEX

2 Machines Euraf, 55 à 65 rue Emile Deschanel, 92400 COURBEVOIE

3 G.B. Caleva Ltd

Butts Pond Industrial Estate

Sturminster Newton Dorset DT 10 1A2

Angleterre

4 F.M.C. Corporation

Food and pharmaceutical products division

2000 Market Street, Philadelphia PA 19103 USA

distribué par Seppic, 75 Quai d'Orsay, 75321 PARIS.

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