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RESEARCH PAPER

Small-Scale Characterization of Wet Powder Masses Suitable for Extrusion–Spheronization

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ABSTRACT

The method of compresso-rheology with an Instron 5567 was used for flow assessment of wet powder mass in order to improve its formulation. In our experiments, the method was efficient for selection of the excipient (Avicel CL611) able to improve the extrusion behavior of the high-dose wet powder mass. The method also allowed the determination of the minima and maxima of the wetting agent volume necessary to identify the correct moisture content for extrusion (20%). The results were not discriminative for the choice of the Avicel CL611 amount in the formulae even if an average amount necessary to improve extrudability of the active ingredient could have been estimated at about 10%. Nevertheless, this method appeared to be a rapid and easy small-scale method for studying wet powder mass. cause only a few grams of solids are required, this rheometer should prove useful in formulation research.

INTRODUCTION

To develop a high-dose multiunit oral dosage form of a very hydrosoluble active ingredient (sodium butyrate), pellets produced by the extrusion–spheronization technique (1) were envisaged.

This work describes a method that enables both a qualitative and quantitative assessment of wet mass of materials used in extrusion–spheronization to be made. This small-scale method assessment is interesting for particular drugs (i.e., expensive or toxic), and outlines any pertinent properties exhibited in the wet powder extrusion that may be important in the extrusion–spheronization process.

In our experiments, various excipients known to impart plastic consistency to wet masses were tested to enable selection of the best product. Then, formulae containing 0–25% of the selected excipient were tested

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at different moisture contents in order to determine whether the extrudability of the active ingredient was improved.

MATERIALS

Chemicals

Sodium butyrate (ref 817500, pharmaceutical grade, Merck-Clevenot, France), three grades of Avicel® Seppic (France) microcrystaline cellulose (MCC) either containing or not containing sodium carboxymethylcellulose (NaCMC) (Table 1), and distilled water were used.

Compresso-Rheometer Description

The apparatus was an Instron 5567 (Instron Ltd., UK) with a type 5500 interface coupled to a computer system (Series IX Automated Material Testing System 7.23.00) for data entry and data processing. A scheme of the apparatus is shown in Fig. 1.

The apparatus had a recording modulus (I) coupled to a computer system, a central structure (II) [with the sample tray (4) mounted on the static cross piece (5) and the load cell (3) mounted on the mobile cross piece (2) pulled by the driving screw (1)] and a control board (III). A standardized syringe was completely filled with the wet powder to be tested and was put upside down in the sample tray.

The load cell supported a 30 kN maximal load and the measurement precision was 0.5%. Experiments were carried out in an air conditioned room at 23 ± 1°C with 50 ± 5% relative humidity. The standardized syringes were 10 ml Plastipak syringes (Becton-Dickinson, France). The total volume of the syringe was 14.5 ml because of an additional broadening 1 cm above graduation.

Tested Formulae

At first, different types of Avicel (Table 1) were screened. They were wetted with water at different moisture contents (45, 50, 55, and 60%). Second, mixtures of the active ingredient (sodium butyrate) with 5, 10, 15, and 25% of Avicel CL611 were prepared. Each mixture contained a small quantity of active ingredient (5 g).

Table 1

Avicel Grades and Composition

Avicel grades	MCC	NaCMC
Avicel PH101	100%	-
Avicel RC591	86.2–91.7%	8.3–13.8%
Avicel CL611	81.2–88.7%	11.3–18.8%

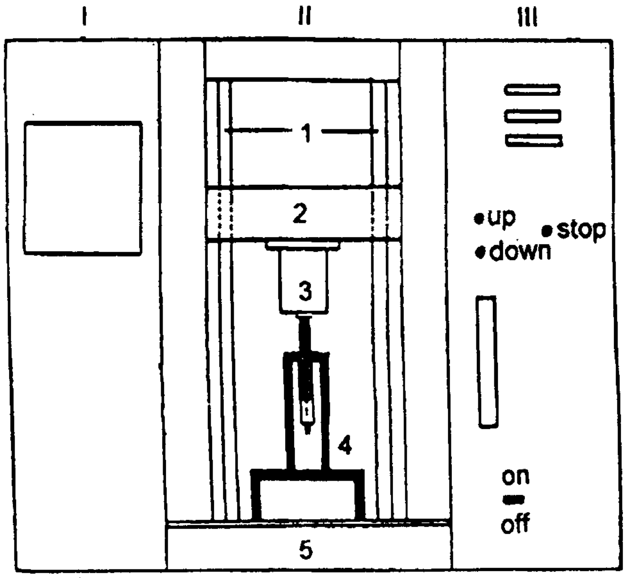

Figure 1. Compresso-rheometer (Instron 5567).

Various quantities of water were added to obtain different moisture contents (ranging from 16 to 25%). The moisture content can also be expressed as a ratio related to Na^+ butyrate according to following calculation: R = water (g)/Na butyrate (g). R ranged from 0.24 to 0.37.

METHODS

Principle

The wet mass was put into a syringe which allowed flow through the aperture. External forces were applied through the piston on the wet mass in order to simulate forces involved in the extrusion process. The load cell mounted on the mobile cross piece depressed the piston of the full syringe. The forces applied were recorded as a function of the displacement of the mobile cross piece.

Powder Moisturizing

Chemicals were weighed and put in a small beaker. They were mixed together and water accurately measured was added all at once. Homogenization was done by manual mixing with a glass stick.

Sample Preparation

The piston was taken out of the syringe which was completely filled with the wet powder (14.5 ml). A new syringe was used for each measurement. Then, the piston was put in the syringe and lowered 1 cm (additional broadening). The full syringe was put upside down in the sample tray. The mobile cross piece was lowered until the load cell lightly touched the piston. Therefore, the starting reference (zero) of the displacement was the same for each measurement.

Sample preparation is shown in Fig. 2.

Measurements

When the compresso-rheometer was set in motion, the mobile cross piece moved down automatically at 25 mm · min^{-1} and depressed the piston. The applied force was recorded (kN) as a function of the displacement (mm). The maximal displacement was set at 60 mm and the maximal force recorded was 600 N. Above this force, the wet powder mass in the syringe was more resistant than the plastic material of the piston. Thus, the piston twisted before or while the extrusion of the wet mass occurred. In this case, the recorded forces were not representative of the real force necessary to extrude the wet mass but were actually less.

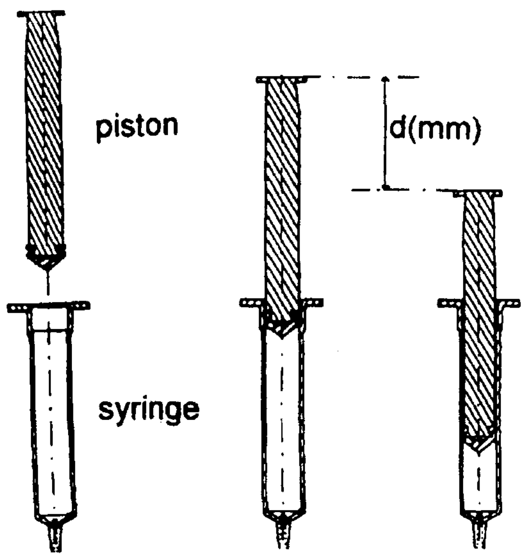

Figure 2. Sample preparation.

One measurement was done for each formula at each moisture content.

Theoretical Analysis of Force–Displacement Profile

The aim of this part of the study was to point out the pertinent information given by the small-scale method used to characterize wet powder masses suitable for extrusion. In practice, the extrusion process can be performed using two main classes of extruders, according to the feed mechanism of the plastic mass to the extrusion screen: by means of screws and by means of gravitational forces, for which required extrusion forces are different (2). In our experiments, the force–displacement profile was analyzed considering the extrusion–spheronization equipment intended to be used in practice: a gravity-feed extruder composed of a full and a perforated cylinder.

The force (F)–displacement (d) profile shown in Fig. 3 consists of three distinct regions (3): compression, steady-state flow, and forced flow.

Compression Stage (Initial Ascending Part)

The piston moves down and eliminates interparticulate voids. Densification of the wet mass occurs before the wet powder mass flows. The characteristics of this first stage do not depend on the operating conditions (speed of the mobile cross piece, size of the syringe aperture), but they depend on moisture content and formulation. In general, the best formulae for extrusion show a minimal compression stage: a slope as near as 90° and a low plateau that is readily reached. These kinds of profiles allow extrudates to be easily obtained.

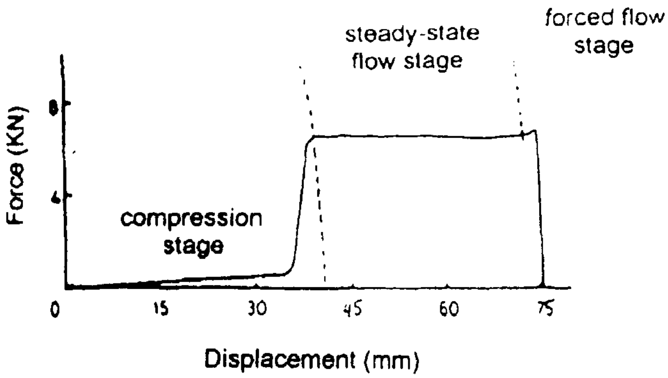

Figure 3. $F = f(d)$.

Steady-State Flow Stage (Horizontal Plateau)

When the wet mass in the syringe has begun to flow, the pressure required to maintain the flow remains constant provided that the flow pattern created in the syringe remains constant. The magnitude of the constant force at the plateau is the most important information; it represents extrudability capacities of the wet powder mass. The characteristics of this stage depend on the syringe size (length and diameter of the aperture) and on operating conditions.

At this stage, the quality of extrudates can also be observed (whether the wall is smooth, rough, or shark-skinned). If the wet powder is too dry, the extrusion forces are high and the extrudates show shark-skinning or roughness (4). If the wet powder is overwetted, water in excess is extruded before and separately from the rest of the wet mass. This is called "overwetting." The forces are very low and extrudates do not remain molded. Both situations are not favorable to product extrudates of good quality. Thus, the method allows a range of moisture contents to be defined. However, the forces involved in compresso-rheology are almost the same as in a ram extruder, whereas in a perforated cylinder extruder, shear stress and friction forces (5) are reduced and the temperature increase is limited (6). Formulations that succeed with this kind of extrusion process require less critical processing conditions. Therefore, tested formulae for which there is extrusion but no overwetting may fit with our particular equipment.

Forced-Flow Stage (Final Ascending Part)

At this stage, increasing forces are required to maintain extrusion from the syringe. A moisture gradient appears in the wet mass in the syringe. The extrudate always has a higher moisture content than the material remaining in the syringe. The applied forces increase. The ideal extrusion profile should exhibit no forced-flow stage and formulations should be designed to minimize the extent of the forced-flow stage to maximize the steady flow region. However, the maximal force recorded is about 600 N, whereas forced-flow stage requires higher forces. Therefore, forced-flow stage was not analyzed in our experiments.

In summary, the analysis of the force–displacement profile including slope and its position in the compression stage, force necessary to obtain steady-state flow, and quality of extrudate should permit us to estimate processability of formulations and/or of various moisture contents. At first, various excipients known to impart plastic consistency were tested to select the best product. Second, formulae containing 0–25% of the selected excipient were tested at different moisture contents in order to determine whether the extrudability of the active ingredient was improved and to find the best formula that could be used in the extrusion–spheronization process.

RESULTS AND DISCUSSION

Choice of Avicel Grade

The basis of most pharmaceutical formulations for extrusion–spheronization is the inclusion of MCC containing or not containing NaCMC to impart the plastic consistency required for the process (7–9). Therefore, at first, various grades of Avicel were screened (Table 1). Avicel PH101 (MCC), usually used for direct compression, is an essential ingredient in the preparation of wet powder masses suitable for extrusion–spheronization (3, 9–13). Avicel RC591 and CL611, which contain about 11 and 15% NaCMC, respectively, improve plasticity and have the ability to absorb large amounts of water and thus to maintain the moisture content during the extrusion–spheronization process. They are especially useful in the production of high-dose pellets (1, 7–9, 14, 15).

For each Avicel, only the first two first regions of the graph $F =' f(d)$ (or only the compression stage for Avicel RC591 at 45 and 50% moisture contents) were described. Conditions of forced flow were not generated. Nevertheless, the comparison of those parts of the profile allow us to make the following remarks.

The slope of Avicel PH101 was less vertical than both other grades of Avicel: the compression stage was longer. No real plateau was reached. Extrusion and overwetting occurred whatever the total moisture content. But, steady-state flow was not reached below 600 N. Although Avicel PH101 is a reference in preparation of wet masses, it gave the worst force–displacement profile.

For Avicel RC591 and CL611, compression stages were shorter. The slopes were more vertical than Avicel PH101 and the plateau was reached. Higher than 50% moisture content, the wet masses were extruded without overwetting. Both Avicel grades with NaCMC seemed to have good flow properties and the NaCMC improved the water uptake in the wet powder mass.

Moreover, Avicel CL611 steady-state flow stage was reached with lower forces than Avicel RC591 at the same moisture contents. Extrudability was easier with

Avicel CL611. Thus, the grade was selected to improve the extrudability of the active ingredient.

Determination of the Optimal Avicel CL611 Percentage in the Mixture and the Optimal Moisture Content

Force-displacement graphs for sodium butyrate are reported in Fig. 4, with corresponding data in Table 2. The total moisture content (total MC) expressed as a percentage and the moisture content related to sodium butyrate (MC/Na^+ butyrate) are expressed as a ratio according to the following calculation: R = water (g)/ Na butyrate (g).

The average magnitude of the force at the steady-state flow was determined graphically by the horizontal mean line. The upper limit recorded was 600 N. The presence (+) or absence (-) of extrudates is noted, and when necessary, a remark on the quality of extrudates is included.

To facilitate understanding, graphs were unwedged on the displacement axis. The superimposed graphs are not represented here but no slope unwedging has been noticed for each type of formula, whatever the moisture content. Nevertheless, when the composition of the mixture varied, the positions of the slope were different and could be compared.

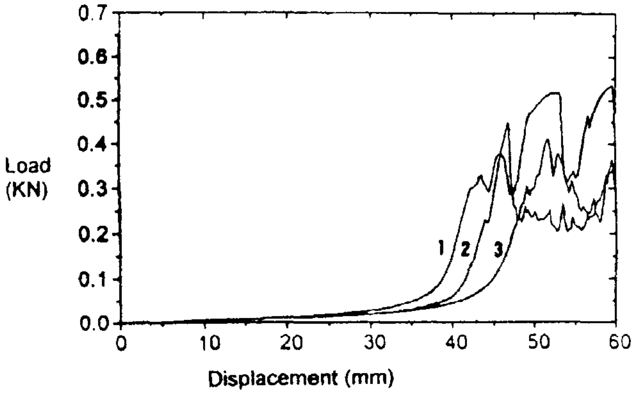

Figure 4. $F = f(d)$ for sodium butyrate; see Table 2.

For sodium butyrate alone (Fig. 4, Table 2), graphs were not smooth. This was probably due to the heterogeneous wetting of the powder which did not correctly fill the syringe.

At 20.6% moisture content, the syringe twisted before the plateau was reached, whereas at 21.9% moisture content, extrusion occurred without overwetting for a 300-N force. At 23.1% moisture content, extrusion was easier: the required force was lower but overwetting occurred. The sodium butyrate moisturizing zone, allowing a good extrusion, was tight: R strictly ranged from 0.26 to 0.30. For sodium butyrate, the middle of the slope was positioned at about a 40-mm displacement (see graph no. 1, which is not unwedged).

For the mixtures, the more Avicel CL611, the smaller the displacement of the position of the slope (i.e., the displacement of the slope was about 35 mm for mixture containing 25% of Avicel CL611). The compression stage was slightly shortened. But for any mixture, the graphs were a little smoother than the sodium butyrate graph.

To point out the influence of Avicel CL611 on extrusion behavior of sodium butyrate, graphs recorded for mixtures characterized by the same content of water [R = water (g)/Na butyrate (g) = 0.30] and increasing Avicel CL611 amounts were compared. The extrudability characteristics are reported in Table 3.

For small total moisture content changes (4.7%, between 23.1 and 18.4%), forces applied on wet mass were different, ranging from 255 N to more than 600 N. The larger the amount of Avicel CL611 in the mixture, the higher the steady-state force. Moreover, the overwetting phenomena was suppressed by Avicel CL611, the hygroscopicity characteristics of which allowed the mixture to absorb water.

The increasing steady-state flow force could be due to the swelling of Avicel and/or the loss of mass lubrication because of water absorption by Avicel CL611. Nevertheless, those increasing forces should not be sig-

Table 2

Sodium Butyrate Extrusion Characteristics

Graph No.	Total MC (%)	MC/Na + Butyrate R	Steady-State Force (N)	Extrusion	Remark
1	21.9	0.28	300	+	
2	23.1	0.30	225	+	Overwetting
3	20.6	0.26	>600	-	

Table 3

Extrudability Characteristics for Various Mixtures [R = water (g)/Na Butyrate (g) = 0.30]

Avicel CL611 (%) in the Mixture	Extrusion	Overwetting	Steady-State Force (N)	Total MC (%)
0	+	+	225	23.1
5	+	–	275	22.2
10	+	–	300	20.3
15	+	–	300	19.4
25	±	–	>600	18.4

nificant in practice, except for two mixtures: that containing 25% Avicel CL611 and 18.4% moisture content, the wet powder of which seemed too dry and which gave the worst extrusion profile, and sodium butyrate alone with 23.1% moisture content for which overwetting occurred.

Table 4 summarizes extrusion characteristics for various mixtures with approximately the same total moisture content (20%).

At 20.6% total moisture content, sodium butyrate could not be extruded by a force below 600 N. As soon as the mixture contained Avicel CL611, the wet mass was extruded for a force above 300 N. The variations of steady-state flow forces (±50 N) were not significant because the precision of the measurement and of the determination of the force value was weak. However, Avicel CL611 improved the extrudability of sodium butyrate, although it was not possible to determine its optimal ratio. But, in order to produce high-dose pellets, not more than 10% Avicel CL611 in formula seemed to be sufficient to improve extrudability and to maintain moisture content of the wet mass during processing. This property could be very important to control unavoidable fluctuations of moisture content during the process. Moreover, 20% moisture content seemed to provide good extrudability characteristics.

For each mixture, the strict minimal and maximal total moisture contents are reported in Table 5.

The strict minimal total moisture content corresponded to the smallest water amount necessary to prohibit the steady-state flow force from exceeding 600 N. The maximal moisture content corresponded to the largest water amount that allowed extrusion to occurr without overwetting. Whatever the Avicel CL611 amount in the mixture, a mean total moisture content of 20.0% seemed to be sufficient to obtain extrusion with extrudates of a good quality. Tested moisture contents have been deliberately chosen after preliminary assays (data not shown). However, to determine more accurately the upper and lower limits of moisture content that allow the correct extrusion of wet powder mass, a wider range of moisture contents should be tested. Nevertheless, the tight moisturizing zone (±1.7%) delimited in this work is of real interest for the realization of extrusion–spheronization process in practice.

Table 4

Extrusion Characteristics for Wet Masses with 20% Total Moisture Content (MC)

Avicel CL611 (%) in the Mixture	Total MC (%)	Steady-State Force (N)	Extrusion
0	20.6	>600	–
5	21.0	300	+
10	20.3	300	+
15	20.4	250	+
25	20.0	350	+

Table 5

Strict Minimal and Maximal Moisture Content for Extruded Wet Masses

Avicel CL611 (%) in the Mixture	Total Moisture Content (%)	
	Minimum	Maximum
0	20.6	21.9
5	17.3	22.2
15	18.3	20.4
25	18.4	21.6

CONCLUSIONS

In our experiments, the method was efficient to select the excipient (Avicel CL611) able to improve the extrusion behavior of the high-dose wet powder mass as well as to determine the minima and maxima of the wetting agent volume necessary to get a correct moisture content for extrusion (20 ± 1.7%). However, the results were not discriminative for the choice of the Avicel CL611 amount in the formulae. The amount necessary to improve extrudability of the active ingredient was estimated at about 10%. The amplitude of the measurement was limited to 600 N. Conversely, the speed of the mobile cross piece and/or the measurement accuracy were not adapted to the wet mass heterogeneity. Thus, the method did not allow the choice of one optimum formula. Studies continue to optimize the apparatus utilization by adapting the operating conditions (recording limits, speed of the mobile cross piece) and especially by testing its ability to reproduce data.

Nevertheless, the compresso-rheometer (Instron 5567) appears to be a useful instrument for studying wet powder mass. It is a small-scale technique for assessment of the flow. By monitoring the forces applied on a wet powder mass, it is possible to assess the formulation by examining the resultant force–displacement profile. Measurements are relatively easy and rapid to undertake. Since only a few grams of solids are required, this rheometer should prove useful in formulation research. The method of compresso-rheology, therefore, provides a system which can be used on a small scale to develop and improve formulation for extrusion–spheronization.

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