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RESEARCH PAPER

Effect of Microcrystalline Cellulose Grade and Process Variables on Pellets Prepared by Extrusion–Spheronization*

L. Alvarez, A. Concheiro, J. L. Gómez-Amoza, C. Souto, and R. Martínez-Pacheco†

Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Santiago de Compostela, 15706 Santiago de Compostela, Spain

ABSTRACT

This study evaluated the effects of spheronizer load and speed on the size, circularity, microporosity, compressibility, and friability of pellets prepared by extrusion–spheronization of wet microcrystalline cellulose (MCC) masses with a water content shown by mixer torque rheometry to ensure maximum consistency. Two MCC grades with different mean particle size were used. Both gave pellets with good particle size, sphericity, and compressibility, under a wide range of spheronization conditions. Modification of pellet properties of interest (including size and porosity) was possible by adjustment of spheronization conditions and MCC grade; in particular, pellet porosity was greater with MCC of larger particle size.
Key Words: *Extrusion–spheronization; Microcrystalline cellulose; Mixer torque rheometry*

INTRODUCTION

Mixer torque rheometry has proved to be one of the most useful techniques for establishing the optimal proportion of wetting agent during wet granulation processes (1–4). Furthermore, several studies have demonstrated the utility of this technique for characterizing wetting kinetics (5) and substrate–binder interactions (6,7), for detecting inter-lot and inter-manufacturer variability in raw materials (8), and for scale-up (9). However, little information is available about the usefulness of

*These results were presented in part at the 8th International Conference on Pharmaceutical Technology, Paris, 1998.
†Corresponding author. Fax: +34-981-547148; E-mail: fframapa@usc.es

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mixer torque rheometry in extrusion–spheronization processes.

In this study we used mixer torque rheometry to determine the water content necessary to achieve wet microcrystalline cellulose (MCC) masses with greatest consistency, and then determined the effects of spheronization conditions (load and speed) on the properties of pellets manufactured from these masses by extrusion–spheronization. Two MCC grades, with different mean particle size, were used.

MATERIALS AND METHODS

Materials

The microcrystalline celluloses (Avicel® PH101, nominal mean particle size 50 μm, batch 6643C and Avicel® PH102, nominal mean particle size 100 μm, batch 010) were purchased from FMC Corp. Initial moisture contents, determined by thermogravimetric analysis in a Shimadzu TGA-50 with heating to 105°C at 10°C min^{-1}, were 4.06% for Avicel PH101 and 4.44% for Avicel PH102.

Rheological Characterization of the Wet Powder Masses

Wet masses of water and microcrystalline cellulose in various proportions were prepared by mixing for 10 min at 300 rpm in a Heidolph RZR50 mixer, and the consistency of 30-g samples was measured in triplicate in a Caleva mixer torque rheometer at shaft speeds of 52, 40, and 100 rpm (52 rpm is the default speed of the apparatus, and speeds of 40 and 100 rpm were chosen as representative of slower and faster speeds).

Pellet Preparation

For both MCC grades, the extrusion–spheronization process was as follows.

1. Preparation of the wet mass found, as above, to have maximum consistency (greatest mean torque).
2. Extrusion of the mixture in a Caleva Model 10 extruder at 60 rpm, through a 1-mm aperture screen.
3. Spheronization of the extruded mass in a Caleva Model 120 spheronizer, for 10 min. Six different spheronization conditions were evaluated (spheronization load 100 or 150 g, spheronization rate 800, 1200, or 1600 rpm).
4. Drying in a hot-air oven at 40°C for 24 hr.

Characterization of Pellets

Shape and Size

Pellet shape and size were evaluated with an Olympus SZ60 microscope connected to a video camera. Size was estimated as mean Feret diameter obtained from four different angles, for a total of 600 pellets per lot; in all cases, the size data were best fitted by a normal distribution. Pellet shape was characterized by the parameter circularity, as defined by Exner and Link (10). In addition, photomicrographs of pellets were obtained with a scanning electron microscope (Leo Electron Microscopy VP Ltd.).

Pellet Porosity

Pellet porosity was evaluated by mercury-intrusion porosimetry with a Micromeritics 9305 pore sizer, using the 3-mL powders penetrometer. Working pressures were over the range 0.6–25,000 lb $inch^{-2}$. Micropore volume was estimated as the total volume of pores with diameter greater than 0.1 μm (11).

Flow Properties

Compressibility was evaluated as per Thomson (12) on the basis of bulk density before and after compaction in a Hosokawa PT-E powder tester (20 min, 50 taps min^{-1}; triplicate determinations).

Friability

Friability was assayed with an Erweka TAB apparatus for 30 min at 20 rpm. For each assay, 20 g of pellets was mixed with 30 g of glass beads. Friability was estimated as the increase in the percentage of sample weight due to pellets with diameter less than 250 μm.

Experimental Design and Statistical Treatment of Results

Pellets were prepared in accordance with a three-way factorial design (2 MCC grades × 2 spheronization loads × 3 spheronization rates).

Quantification of the effects of these variables on pellet properties was done by stepwise multiple linear regression (13), with MCC grade as dummy variable (0 for Avicel PH101, 1 for Avicel PH102).

RESULTS AND DISCUSSION

Figure 1 shows the mean torque values obtained for each MCC/water mixture at each shaft speed. Although mean torque clearly differed with shaft speed, as reported previously (14), and at some speeds was not measured for mixtures with very low or very high water content, the maximum value was in all cases obtained for the mixture containing 1.2 mL of water per gram of MCC. These mixtures were therefore selected for spheronization. This maximum-torque water content ($1.2\,mL\,g^{-1}$) is similar to that reported in previous studies of Avicel PH101 (5,15). In the present study, Avicel PH101 and Avicel PH102 showed similar behavior, in accordance with previous studies which have likewise found that rheometric behavior differs little between MCC grades (15). However, the sharp-peaked mean-torque profile obtained for the MCC grade with lower particle size (PH101) (Fig. 1) suggests that there is a greater risk of over-wetting this grade.

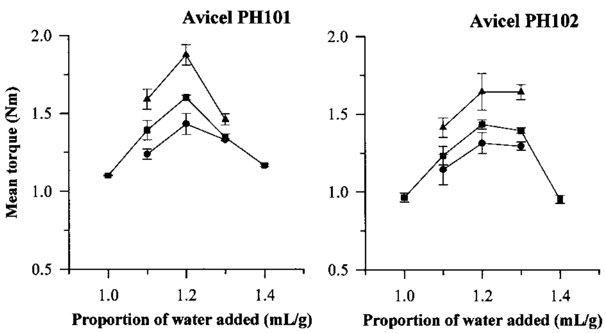

Figure 1. Mean torque profiles for the two microcrystalline grades at each of the shaft speeds tested (● 40 rpm, ■ 52 rpm, ▲ 100 rpm).

Table 1 summarizes the size, shape, and functional properties of pellets prepared with each of the MCC grades under each of the spheronization conditions.

Except for one of the PH102 preparations, all the spheronization conditions used gave pellets with sizes within the range 710–1180 μm (16–18), without excess small particles or agglomeration during the spheronization process. Stepwise multiple regression with mean pellet size as response variable and MCC grade (G), spheronization rate (SR), and

Table 1

Mean Results (SD) Obtained in the Characterization of the Pellets[a]

Cellulose Grade	Spheronization Rate (rpm)/Load (g)	Size (μm)[b]	Circularity	Micropore Volume (cm^3/g^{-1})	Compressibility (%)
Avicel PH101	800/100	814.8±77.0	0.945 (4.2×10^{-3})	0.0203 (5.7×10^{-4})	2.94 (0.82)
	800/150	728.5±114.8	0.944 (6.9×10^{-3})	0.0211 (3.1×10^{-3})	4.93 (0.30)
	1200/100	898.4±69.2	0.951 (1.2×10^{-3})	0.0164 (4.2×10^{-4})	4.29 (0.71)
	1200/150	859.9±77.9	0.952 (2.5×10^{-3})	0.0141 (1.3×10^{-3})	4.39 (0.85)
	1600/100	1067.3±95.5	0.954 (4.8×10^{-3})	0.0124 (9.9×10^{-4})	3.17 (0.67)
	1600/150	873.2±103.6	0.946 (4.9×10^{-3})	0.0130 (1.4×10^{-4})	2.29 (0.28)
Avicel PH102	800/100	776.0±182.4	0.930 (8.3×10^{-3})	0.0338 (0.0115)	3.12 (0.34)
	800/150	634.0±63.7	0.939 (9.2×10^{-3})	0.0433 (9.4×10^{-3})	4.98 (0.61)
	1200/100	837.3±95.5	0.940 (5.1×10^{-3})	0.0290 (0.0103)	3.87 (0.82)
	1200/150	760.3±27.2	0.946 (3.0×10^{-3})	0.0339 (0.0137)	4.34 (0.07)
	1600/100	1071.6±208	0.908 (18×10^{-3})	0.0271 (5.3×10^{-3})	3.19 (0.10)
	1600/150	898.4±122	0.936 (4.7×10^{-3})	0.0309 (7.8×10^{-3})	4.75 (1.52)

[a]In all the conditions, pellet friability was zero.
[b]Mean diameter±standard deviation of the size distributions.

spheronization load (SL) as candidate predictors gave the following equation:

$$\text{Mean pellet size } (\mu\text{m}) = 492.7 + (5.4 \times 10^{-1})\ \text{SR} - (1.9 \times 10^{-3})\ \text{SR} \times \text{SL} \quad (r = 0.9459)$$

The absence of G from this equation indicates that mean pellet size was not significantly affected by the MCC grade used. The magnitudes of the effects of spheronization rate and spheronization load (Fig. 2) are in agreement with previous reports (19).

Although pellet shape was in all cases close to spherical (Figs. 3 and 4), multiple regression with the parameter circularity as response variable revealed significant effects of cellulose grade (though not spheronization conditions):

$$\text{Circularity} = 0.945 - (8.83 \times 10^{-3})\ \text{G} \quad (r = 0.6595)$$

The poor fit of this equation is of little practical importance, since the effects on pellet circularity are of very low magnitude.

The microporous structure of the pellets is of particular interest, in view of potential biopharmaceutical implications. The results of mercury-intrusion porosimetry (Table 1) show that pellets prepared with Avicel PH102 have markedly higher intra-particular porosity than pellets prepared

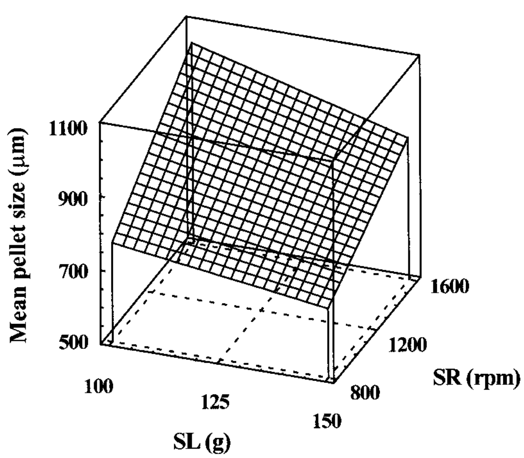

Figure 2. Response–surface plot illustrating the effects of spheronization load (SL) and spheronization rate (SR) on mean pellet size (μm).

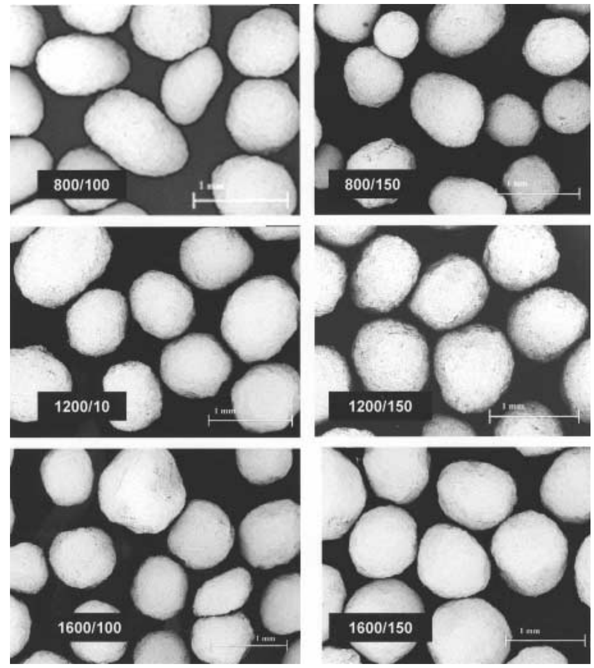

Figure 3. Photomicrographs of pellets obtained with Avicel PH101 using the six spheronization rate/load combinations indicated.

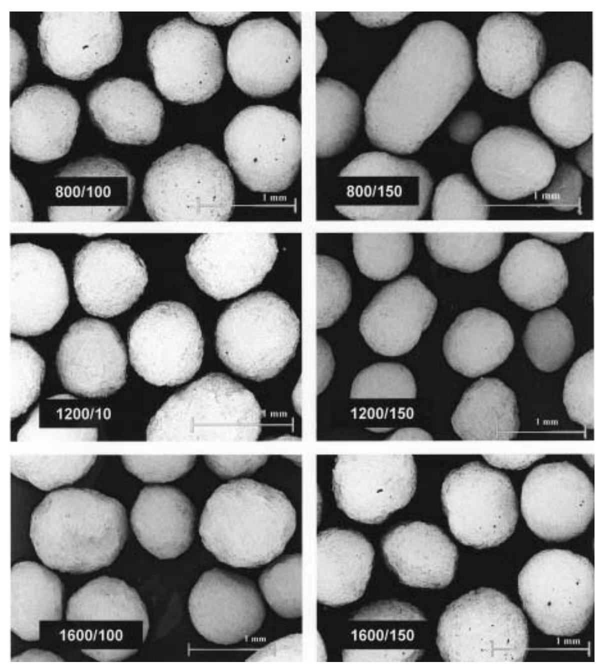

Figure 4. Photomicrographs of pellets obtained with Avicel PH102 using the six spheronization rate/load combinations indicated.

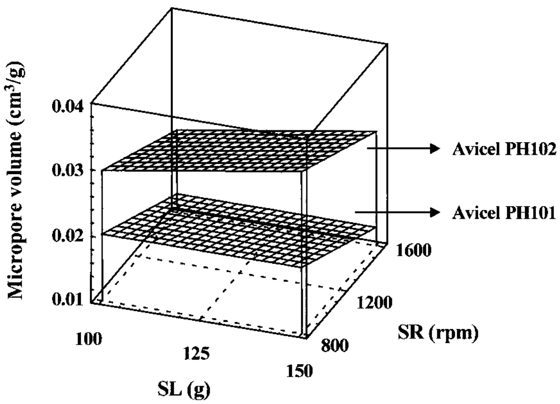

Figure 5. Response–surface plot illustrating the effects of spheronization load (SL) and spheronization rate (SR) on micropore volume ($cm^3\,g^{-1}$).

with Avicel PH101. This is as expected given the differences in mean particle size between the two grades. Multiple regression with micropore volume as response variable gave the following equation:

$$\text{Micropore volume } (cm^3 g^{-1}) = 0.0272 + (9.6 \times 10^{-5})\ G \times SL - (9.0 \times 10^{-6})\ SR \quad (r = 0.9470)$$

This equation indicates a significant effect of spheronization rate and a significant interaction between grade and spheronization load (reflecting the fact that SL had a significant effect only for pellets made with Avicel PH102). The magnitudes of these effects are represented graphically in Fig. 5.

All pellet formulations tested showed excellent compressibility (in all cases less than 5%). None of the formulation variables (G, SL, SR) were selected as significant predictors of compressibility in multiple regression.

Finally, all pellet formulations tested showed zero friability.

In conclusion, wet microcrystalline cellulose masses of maximum consistency, as determined by mixer torque rheometry, give pellets of acceptable size, shape, flow properties, and mechanical resistance. Some control over pellet size and porosity can be exerted by selection of the cellulose grade used and by modification of spheronization rate and load.

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REFERENCES

1. Harrison, P.J.; Newton, J.M.; Rowe, R.C. Application of Capillary Rheometry to the Extrusion of Wet Powder Masses. Int. J. Pharm. **1987**, *35*, 235–242.
2. Parker, M.D.; Rowe, R.C.; Upjohn, N.G. Mixer Torque Rheometry: A Method for Quantifying the Consistency of Wet Granulations. Pharm. Tech. Int. **1990**, *2*, 50–62.
3. Rowe, R.C.; Parker, M.D. Mixer Torque Rheometry. An Update. Pharm. Tech. Eur. **1994**, *6*, 24–27.
4. Delalonde, M.; Baylac, G.; Bataille, B.; Jacob, M.; Puech, A. The Rheology of Wet Powders: A Measuring Instrument, the Compresso-Rheometer. Int. J. Pharm. **1996**, *130*, 147–151.
5. Hancock, B.C.; York, P.; Rowe, R.C. Characterization of Wet Masses Using a Mixer Torque Rheometer: 2. Mixing Kinetics. Int. J. Pharm. **1992**, *83*, 147–153.
6. Parker, M.D.; York, P.; Rowe, R.C. Binder–Substrate Interactions in Wet Granulation. 1: The Effect of Binder Characteristics. Int. J. Pharm. **1990**, *64*, 207–216.
7. Parker, M.D.; York, P.; Rowe, R.C. Binder–Substrate Interactions in Wet Granulation. 2: The Effect of Binder Molecular Weight. Int. J. Pharm. **1991**, *72*, 243–249.
8. Parker, M.D.; York, P.; Rowe, R.C. Binder–Substrate Interactions in Wet Granulation. 3: The Effect of Excipient Source Variation. Int. J. Pharm. **1992**, *80*, 179–190.
9. Landín, M.; York, P.; Cliff, M.J.; Rowe, R.C.; Wigmore, A.J. Scale-up of a Pharmaceutical Granulation in Fixed Bowl Mixer-Granulators. Int. J. Pharm. **1996**, *133*, 127–131.
10. Exner, H.E.; Link, E. Image Analysis for Characterization of Size and Shape Distribution of Lead Powders Powder Metall. Int. **1977**, *9*, 131–133.
11. *Micromeritics Instruction Manual Pores Size 9305*. Micromeritics: Norcross, GA, 1984.
12. Thomson, F.M. Storage of Particulate Solids. In *Handbook of Powder Science and Technology*, Fayed, M.E. and Otten, L., Eds.; Van Nostrand Reinhold: New York, 1984; 365–463.
13. Statgraphics, Version 7.0. Manugistics Inc., Statistical Graphics Corp., Los Angeles, 1993.

14. Landín, M.; Rowe, R.C.; York, P. Characterization of Wet Powder Masses with a Mixer Torque Rheometer. 3. Nonlinear Effects of Shaft Speed and Sample Weight. J. Pharm. Sci. **1995**, *84*, 557–559.
15. Rowe, R.C.; Sadeghnejad, G.R. The Rheology of Microcrystalline Cellulose Powder/Water Mixes—Measurement Using a Mixer Torque Rheometer. Int. J. Pharm. **1987**, *38*, 227–229.
16. Law, M.F.L.; Deasy, P.B. Use of Hydrophilic Polymers with Microcrystalline Cellulose to Improve Extrusion–Spheronization. Eur. J. Pharm. Biopharm. **1998**, *45*, 57–65.
17. Thoma, K.; Ziegler, I. Investigations on the Influence of the Type of Extruder for Pelletization by Extrusion–Spheronization. II. Sphere Characteristics. Drug Dev. Ind. Pharm. **1998**, *24*, 413–422.
18. Umprayn, K.; Chitopras, P.; Amarekajorn, S. Influence of Process Variables on Physical Properties of the Pellets Using Extruder and Spheronizer. Drug Dev. Ind. Pharm. **1999**, *25*, 45–61.
19. Vervaet, C.; Baert, L.; Remon, J.P. Extrusion–Spheronization. A Literature Review. Int. J. Pharm. **1995**, *116*, 131–146.