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Research paper

Powdered cellulose as excipient for extrusion–spheronization pellets of a cohesive hydrophobic drug

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Abstract

This study compared a powdered cellulose (PC) and a microcrystalline cellulose (MCC) as sole excipients in the preparation of furosemide pellets by extrusion–spheronization. Pellets prepared with PC and 25 or 50% furosemide showed smaller mean size, a broader particle size distribution, similar sphericity, greater surface roughness and higher friability than equivalent pellets prepared with MCC. Furosemide release rate was markedly higher from PC pellets, which may be attributable to their higher micropore volume.

Keywords: Microcrystalline cellulose; Powdered cellulose; Furosemide; Extrusion–spheronization; Mixer torque rheometry

1. Introduction

Microcrystalline cellulose (MCC) is undoubtedly the most widely used excipient in pellet production by extrusion–spheronization. Its capacity to retain very large quantities of water internally means that wet masses made with MCCs have rheological properties that are very suitable for extrusion–spheronization [1].

However, drug release from MCC extrusion–spheronization pellets is for some drugs very slow, particularly for drugs with low water solubility [2]. This has been attributed to the low porosity of MCC extrusion–spheronization pellets due to contraction during drying [3]. To overcome this limitation, various options have been proposed and evaluated, including (a) the incorporation of water-soluble excipients, surfactants or disintegrants [3,4]; (b) the use of water-alcohol mixtures instead of water as wetting agent [5]; (c) modification of the proportions of diluent and drug [2,6]; and (d) partial or total replacement of MCC with other excipients [6]. As regards this latter option, Lindner and Kleinebudde [7] have observed that paracetamol dissolution rate is markedly higher from powdered cellulose (PC) extrusion–spheronization pellets than from MCC extrusion–spheronization pellets. However, the deficient mechanical properties of pellets made with PC mean that it is necessary to incorporate a binding agent.

In line with the above, the aim of the present study was to evaluate the utility of powdered cellulose as sole excipient in pellets of a poorly hydrosoluble and highly cohesive drug. Specifically, we compared the properties of furosemide pellets made with a PC grade and a MCC grade. Additionally, we evaluated the utility of torque rheometry for the identification of PC/drug mixtures giving wet masses with highest consistency.

2. Materials and methods

2.1. Materials

2.1.1. Excipients

Microcrystalline cellulose (Avicel PH101, nominal mean particle size 50 μm, batch 6643C, FMC Corp., Philadelphia, PA) and powdered cellulose (Elcema P100, particle size approx. 50–150 μm, batch 078060603, Degussa Ibérica S.A, Barcelona, Spain). Initial moisture contents, determined by thermogravimetric analysis in a Shimadzu TGA-

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50 (Kyoto, Japan) with heating to 105 °C at 10 °C min^{-1}, were 4.24% for Avicel PH101 and 5.97% for Elcema P100.

2.1.2. Drug

Furosemide, supplied by U.T.E.F.S.A. (batch 9907177, Valencia, Spain). Mean particle size (determined as in Section 2.4.1) 43.6 μm, compressibility (determined as in Section 2.4.3) 62.6%, and water solubility [8] 0.5 g/l.

2.2. Rheological characterization of the wet powder masses

Wet masses of water-drug-MCC and water-drug-PC in various proportions were prepared by mixing for 10 min at 300 rpm in a Heidolph RZR50 mixer (Schwabach, Germany), and the consistency (mean torque) of 30-g samples was measured in triplicate in a Caleva Mixer Torque rheometer (Dorset, UK) at shaft speeds of 52 rpm.

2.3. Pellet preparation

Pellets were prepared from those wet masses showing highest mean torque. The extrusion–spheronization process was as follows: (a) extrusion of the wet mass in a Caleva Model 10 extruder (Dorset, UK) (at 60 rpm, through a 1-mm-aperture screen); (b) spheronization of the extruded mass in a Caleva Model 120 spheronizer (Dorset, UK) (spheronization time 10 min, spheronization load 100 g, spheronization rate 1200 rpm); (c) drying in a hot-air oven at 40 °C for 24 h.

2.4. Characterization of pellets

The pellets of the different formulations (properties summarized in Table 1) were characterized as follows.

2.4.1. Shape and size

Pellet shape and size were evaluated with an Olympus SZ60 microscope (Tokyo, Japan) 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, calculated as $4\pi A/p^2$, where A is projection area and p projection perimeter [9]. In addition, photomicrographs of pellets were obtained with a scanning electron microscope (Leo Electron Microscopy VP Ltd., Cambridge, UK).

2.4.2. Micropore volume

Micropore volume was evaluated by mercury-intrusion porosimetry with a Micromeritics 9305 pore sizer (Norcross, GA), using the 3-ml powders penetrometer, in triplicate. Working pressures were over the range 0.04–170 MPa. Micropore volume was estimated as the total volume of pores with diameter greater than 0.1 μm [10].

2.4.3. Flow properties

Compressibility was evaluated as per Thomson [11] on the basis of bulk density before and after compaction in a Hosokawa PT-E Powder Tester (Osaka, Japan) (20 min, 50 taps min^{-1}; triplicate determinations).

2.4.4. Friability

Friability was assayed with an Erweka TAB apparatus (Hensenstamm, Germany) 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 or pellet fragments with diameter less than 250 μm.

2.4.5. Dissolution test

Drug release profiles for 200 mg of pellets were determined (six replicates) using a USP 24 type II apparatus (Turu Grau, Barcelona, Spain) (50 rpm, 900 ml of pH 5.8 buffer, 37 °C). The release of furosemide was analysed spectrophotometrically at 274 nm. Furosemide dissolution rate was characterized on the basis of dissolution efficiency over 0–180 min [12].

3. Results and discussion

Fig. 1 shows consistency profiles obtained for the four wet masses tested. As can be seen, the consistency of the wet masses prepared with PC was much lower than that of wet masses prepared with MCC. In addition, the consistency profiles for wet masses prepared with PC were much flatter. Both aspects make it difficult to identify the peak (i.e. to decide which proportion of water will give highest consistency). In fact, the presence of the poorly water-soluble drug furosemide meant that the volume of water

Table 1
Mean results (SD) obtained in the basic characterization of the pellets

Cellulose variety	Proportion of drug (%)	Particle size[a] (μm)	Circularity	Micropore volume (cm^3/g)
Avicel PH101 (MCC)	25	712.5 ± 152.6	0.955 (3.1×10^{-3})	0.0427 (7.7×10^{-3})
	50	782.9 ± 137.7	0.954 (2.0×10^{-3})	0.1373 (1.3×10^{-2})
Elcema P100 (PC)	25	546.2 ± 218.4	0.938 (2.8×10^{-3})	0.4787 (0.0252)
	50	601.5 ± 178.5	0.933 (0.012)	0.4433 (0.0270)

[a] Mean diameter ± standard deviations of the size distributions.

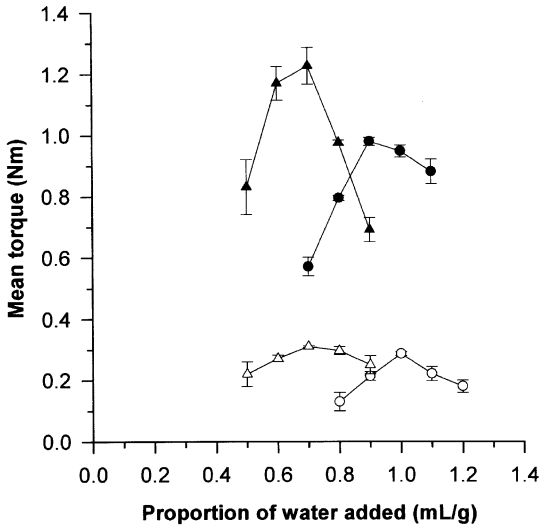

Fig. 1. Mean torque profiles for wet masses prepared with MCC (Avicel PH101) and 25% (●) or 50% (▲) furosemide, or with PC (Elcema P100) and 25% (○) or 50% (△) furosemide.

required to obtain masses of maximal consistency was similar for PC and MCC. Consistency peaks for pure PC and MCC were obtained with 1.2 ml/g [13] and 2.2 ml/g of water, respectively. That PC requires a larger volume of wetting agent has been reported previously by El Saleh et al. [14] on the basis of measurements of power consumption during the extrusion phase. These authors attributed this difference to absorption by the amorphous regions of PC of large amounts of water which remain in unbound among the fibres.

Table 1 shows the results obtained in the morphological and microstructural characterization of pellets produced from the maximum-consistency wet masses identified by torque rheometry. Pellets produced with PC showed smaller mean size and a broader size distribution than pellets produced with MCC. Sphericity differed little between PC and MCC pellets, and was in both cases acceptable (Fig. 2). This figure also shows the higher surface roughness of PC pellets, in particular in the formulation that contained the smallest proportion of drug.

Micropore volume was markedly higher in PC pellets than in MCC pellets. This difference has been noted previously, and has been attributed to the different behaviour of the two types of excipient during drying [7, 14]. The pore size distributions (Fig. 3) indicate that PC pellets have a very considerable pore volume due to pores of about 1 μm. Only in MCC pellets were microstructural characteristics significantly affected by the proportion of drug (Table 1), because of the presence of small micropores (< 0.2 μm) in 50% furosemide pellets (Fig. 3).

Table 2 summarizes the results of the functional characterization of the formulations evaluated. MCC pellets showed clearly better flow properties, attributable to their larger particle size, lower micropore volume, and lower surface roughness. However, the compressibility of all four formulations was as expected for free-flowing products [15].

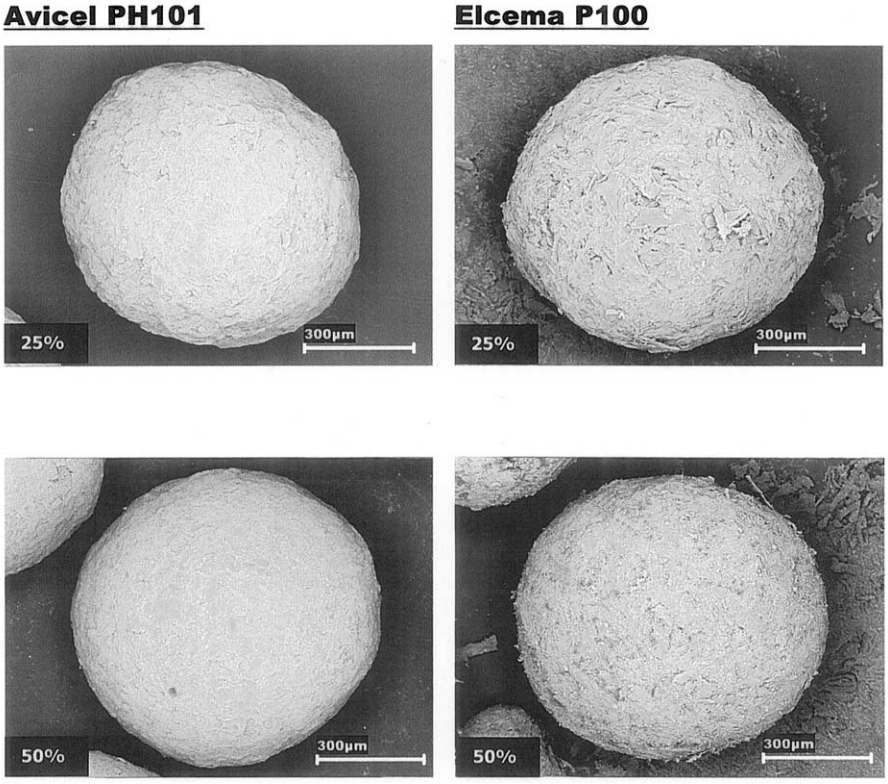

Fig. 2. Scanning electron micrographs of the four different pellet types.

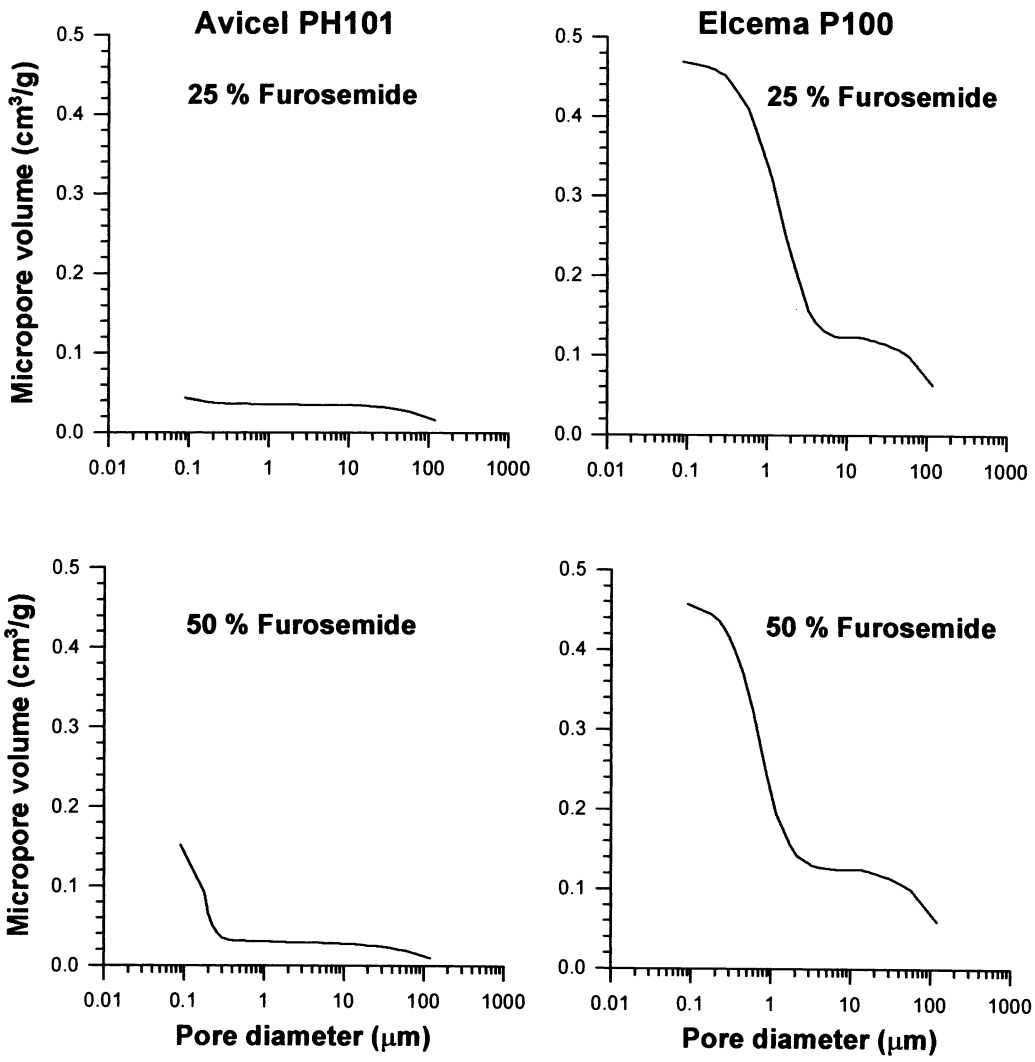

Fig. 3. Cumulative pore-diameter distribution plots for the four different pellet types.

One of the most problematic aspects of PC pellets is their reduced mechanical resistance [14]. In line with this, weight loss in friability tests was higher for PC pellets than for MCC pellets, although the results for PC pellets (particularly for pellets containing 25% drug) were acceptable (Table 2).

Drug release profiles (Fig. 4) and 180-min dissolution efficiency values (Table 2) indicate that furosemide release from PC pellets was markedly more rapid than from MCC pellets. This difference – noted previously for paracetamol and propiophenazone [7,16] – may be attributable to the higher micropore volume of the PC pellets. The proportion of furosemide in the pellets had negligible effect on dissolution rate. This may be because an increase in furosemide proportion (from 25 to 50%) was associated with an increase in the micropore volume of MCC pellets; in addition, only PC pellets with 50% furosemide showed disintegration during the release assays.

In conclusion, powdered cellulose is an attractive alternative to microcrystalline cellulose as sole excipient (i.e. no binding agent) in rapid-release extrusion/spheronization pellets of highly cohesive poorly water-soluble drugs

Table 2
Mean results (SD) obtained in the characterization of the functional properties of the pellets

Cellulose variety	Proportion of drug (%)	Compressibility (%)	Friability (%)	Dissolution efficiency 180 min (%)
Avicel PH101 (MCC)	25	5.83 (0.57)	0.0	30.3 (0.6)
	50	3.72 (0.45)	0.0	30.4 (0.4)
Elcema P100 (PC)	25	8.24 (2.65)	0.7 (0.3)	71.2 (1.1)
	50	11.23 (3.53)	1.3 (0.3)	73.2 (2.0)

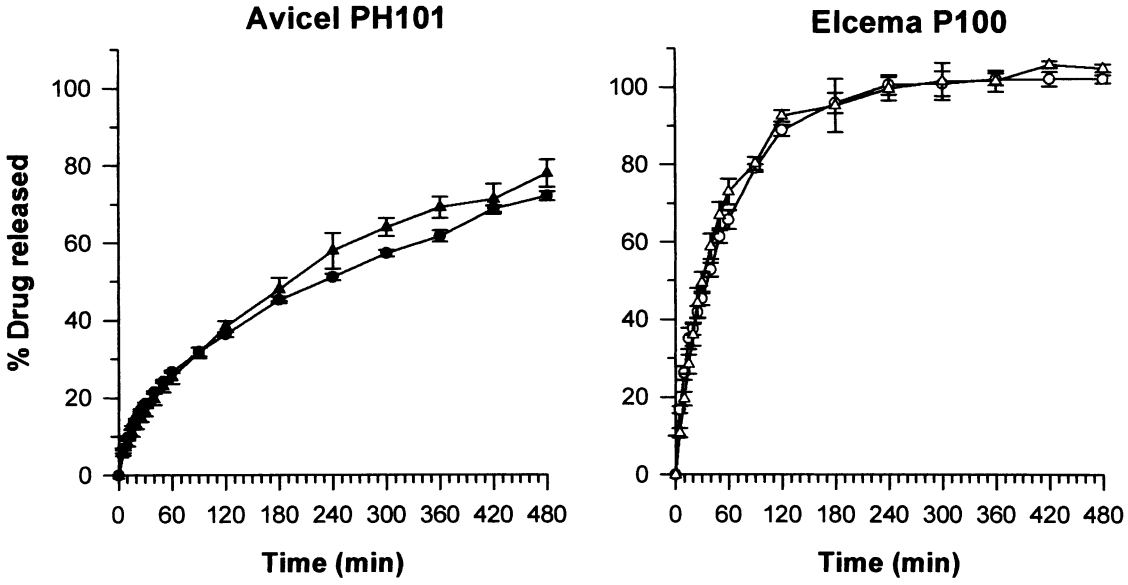

Fig. 4. Furosemide release profiles for the four different pellet types. (●, ○) 25% furosemide; (▲, △) 50% furosemide.

like furosemide. It should however be noted that the mechanical properties, size and size distribution of pellets prepared with powdered cellulose are less appropriate than those of pellets prepared with microcrystalline cellulose.

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