A Comparison of Cellactose with Two *ad hoc* Processed Lactose–Cellulose Blends as Direct Compression Excipients

Marta Casalderrey, Consuelo Souto, Angel Concheiro, José L. Gómez-Amoza, and Ramón Martínez-Pacheco*

*Departamento de Farmacia y Tecnología Farmacéutica. Facultad de Farmacia, Universidad de Santiago de Compostela, 15706, Santiago de Compostela, Spain. Received July 21, 1999; accepted December 9, 1999

Three processed lactose–cellulose blends of similar composition, particle size and true density were compared as direct compression excipients: one was prepared by dry granulation, one by extrusion–spheronization, and the commercial product Cellactose. Differences among their flow properties depended solely on their different sphericities. Unlike those of the other blends, Cellactose particles exhibited numerous macropores. The mean yield pressures of all three blends were similar to those of direct compression lactoses. Cellactose tablets prepared at a punch pressure that largely eliminated macropores (pores $>1\,\mu m$) had better mechanical properties but much poorer disintegration than tablets of the other blends prepared at the same punch pressure. However, the tensile strength and disintegration time of Cellactose tablets both fell rapidly as macropore volume was increased by reducing punch pressure, while the enthalpy of wetting/dissolution rose. The strength and water-resistance of well-compacted Cellactose tablets is attributed to the spatial distribution of lactose and cellulose in Cellactose particles, rather than to $\beta$-lactose content or extra-particular structural features.

**Key words** coprocessed excipients; Cellactose; direct compression

Since the 1980s, considerable attention has been paid to direct compression excipients prepared by co-processing two or more components by means of powder engineering techniques such as coating or controlled agglomeration.\(^1\) For direct compression tableting, processed blends of this kind have been shown to be superior to both traditional single-component excipients\(^2\)–\(^7\) and simple mixtures of single-component excipients.\(^8\)–\(^9\) It is therefore striking that practically nothing has been published concerning the influence of particle structure and morphology on the behaviour of processed blends. As a step towards filling this gap, in this work we compared the properties of Cellactose, a typical processed blend for direct compression, with those of two granulates of similar composition and particle size, one prepared by dry granulation and the other by extrusion–spheronization.

**Materials and Methods**

**Materials** Cellactose (a processed 3 : 1 (w/w) mixture of lactose monohydrate and powdered cellulose), from Meggle, was supplied by Fher S.A. (lot 919). $\alpha$-Lactose monohydrate Ph. Eur., was from Merck (lot 2444543). Avicel PH 101, from FMC Corp., was supplied by C. Barcia S.A. (lot 5648). Magnesium stearate B.P., was supplied by C. Barcia S.A. (lot 548).

**Preparation of Excipients** Cellactose was used as supplied. Fig.1 shows its particle size distribution, as determined by sieving a sample taken with a Quantachrome rotary microriffler through 500, 400, 315, 200, 105, 75 and 45 $\mu m$ meshes in a Retsch Vibro sifter.

The dry-granulated blend (hereinafter excipient B) was prepared by blending a 3 : 1 mixture of $\alpha$-lactose monohydrate and Avicel PH 101 in a Tubula T2C mixer for 15 min at 30 rpm, compacting the blend in 300 mg tablets in a sensorized Bonals B/MT eccentric tableting machine\(^10\) using 9 mm flat punches and a pressure of 50 MPa, fragmenting the tablets in an Erweka AR400 apparatus, separating the resulting granules in size fractions as described above for Cellactose, and blending suitable amounts of the various fractions in a Tubula T2C mixer for 15 min at 30 rpm so as to reproduce the particle size distribution of Cellactose.

The third blend (hereinafter excipient C) was prepared by blending a 3 : 1 mixture of $\alpha$-lactose monohydrate and Avicel PH 101 in a Tubula T2C mixer as described above for excipient B, mixing 100 g samples of the blend with 25 ml of distilled water in a Heidolph RZR 50 planetary mixer for 10 min at 300 rpm, extruding the wet mass through 500 $\mu m$ meshes in a Caleva Model 10 extruder, spheronizing the extruded pellets in a Caleva Model 120 for 10 min at 3000 rpm, drying the resulting granules under a current of hot air (40 °C) for 24 h, and separating and recombining particle size fractions as described for excipient B so as to reproduce the particle size distribution of Cellactose.

**Characterization of the Blends** $\alpha$-Lactose and $\beta$-Lactose Contents: Powder X-Ray Diffraction. The excipient was pressed into a sample holder and the surface was smoothed with a glass slide. Room temperature X-ray diffractograms were recorded between 5 and 50°2h in a Phillips PW1710 powder diffractometer using monochromatic CuKα radiation and a scan rate of 1.2°2h/min.

Gas Chromatography (GC). $\alpha$-Lactose and $\beta$-lactose were determined by GC as per Dwivedi and Mitchell\(^11\) as follows. A sample of excipient was derivatized in 19.5 : 22.0 : 58.5 (v/v) dimethylsulphoxide/N-trimethylsilylimidazole/pyridine. Aliquots of this solution were injected into a Perkin Elmer 3700 GC apparatus equipped with the column described by Dwivedi and Mitchell.\(^11\) The carrier gas was nitrogen (flow rate 20 ml/min), and the injector and column temperatures were 260 and 205 °C, respectively. The proportions of $\alpha$- and $\beta$-lactose were calculated from the areas of the corresponding peaks ($t_R$=6—7 and 10—11 min, respectively). Final results (%) are the means of triplicate determinations.

Differential Scanning Calorimetry (DSC). DSC thermograms of 2—3 mg samples of excipient hermetically sealed in aluminium pans were recorded at a heating rate of 10 °C/min in a Shimadzu DSC-50 instrument. Dehydration enthalpy was estimated from the area of the endothermic peaks near 150 °C, and the enthalpy of the melting of lactose from that of the peak in the 215—235 °C region.

*To whom correspondence should be addressed.
**Results and Discussion**

The X-ray diffractograms of all the excipients (Fig. 2) showed the expected peak for α-lactose at 12.6° 2θ, but not the characteristic β-lactose peak at 10.5° 2θ.\(^{21,22}\) However, gas chromatography showed β-lactose contents ranging from 8.35 (0.91) to 1.11 (0.01). The X-ray diffractogram of Cellactose is shown in Fig. 2.

**Preparation of Tablets**

Using the same mixtures and tabletting machine as described above and a punch pressure of 160 MPa, 250 mg tablets of each blend were prepared at a rate of 8 tablets/min. In addition, 250 mg Cellactose tablets were prepared under the same conditions using punch pressures of 5, 50 and 100 MPa.

**Characterization of Tablets**

Tensile Strength: The crushing strengths of Cellactose tablets were determined using an Erweka T2B apparatus; mean tensile strengths were then calculated from these results and the dimensions of each tablet,\(^{26}\) which were measured using a Mitutoyo digital micrometer (measuring range, 0—25 mm; precision, ±0.001 mm).

Friability: Friability was determined by measuring the weight lost in 15 min by 10 tablets in an Erweka TAP apparatus operated at 20 rpm.

Disintegration Time: Tablet disintegration time in distilled water was determined in a Turu-Grau apparatus conforming to the specifications of USP23 (1995). Results are the means of values for six tablets.

Specific Surface Area and Microporous Structure: The specific surface areas of the tablets, and their pore size distributions, were determined by the same methods used for the untabletted excipients (section 2.3.7). The pore size distributions were used to obtain the total volume of pores >1 μm in diameter.

---

**Table 1. Properties of Cellactose and Two ad hoc Processed Cellulose/Lactose Blends**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cellactose</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration temperature, °C</td>
<td>152</td>
<td>151</td>
<td>151</td>
</tr>
<tr>
<td>Dehydration enthalpy, J·g⁻¹</td>
<td>107.5 (1.54)</td>
<td>114.9 (1.80)</td>
<td>109.3 (1.25)</td>
</tr>
<tr>
<td>Lactose melting temperature, °C</td>
<td>219</td>
<td>219</td>
<td>217</td>
</tr>
<tr>
<td>Lactose melting enthalpy, J·g⁻¹</td>
<td>79.3 (1.1)</td>
<td>95.5 (1.6)</td>
<td>91.5 (1.3)</td>
</tr>
<tr>
<td>β-Lactose content, %</td>
<td>8.35 (0.91)</td>
<td>1.11 (0.05)</td>
<td>2.91 (0.67)</td>
</tr>
<tr>
<td>True density, g·cm⁻³</td>
<td>1.5278 (0.0075)</td>
<td>1.5273 (0.0039)</td>
<td>1.5316 (0.0017)</td>
</tr>
<tr>
<td>Hydration water, %</td>
<td>3.02 (0.03)</td>
<td>3.39 (0.26)</td>
<td>3.23 (0.01)</td>
</tr>
<tr>
<td>Sorbed water, %</td>
<td>1.55 (0.04)</td>
<td>1.56 (0.04)</td>
<td>1.32 (0.19)</td>
</tr>
<tr>
<td>Wetting/dissolution enthalpy, J·g⁻¹</td>
<td>33.60 (0.90)</td>
<td>35.31 (1.26)</td>
<td>33.47 (2.01)</td>
</tr>
<tr>
<td>Circularity</td>
<td>0.754</td>
<td>0.735</td>
<td>0.817</td>
</tr>
<tr>
<td>Specific surface area, m²·g⁻¹</td>
<td>1.14 (0.00)</td>
<td>1.19 (0.01)</td>
<td>0.49 (0.01)</td>
</tr>
<tr>
<td>Compressibility, %</td>
<td>23.54 (0.11)</td>
<td>36.83 (0.13)</td>
<td>14.64 (0.77)</td>
</tr>
<tr>
<td>Flow factor, %</td>
<td>11.07</td>
<td>6.07</td>
<td>27.24</td>
</tr>
<tr>
<td>Mean yield pressure, MPa</td>
<td>125.79 (1.10)</td>
<td>138.55 (4.56)</td>
<td>189.48 (7.66)</td>
</tr>
</tbody>
</table>

Mean values, with standard deviations in parentheses.
1.1% for excipient B to 8.4% for Cellactose (Table 1). Because of the close correlation ($r = 0.9934$) between $\beta$-lactose content and the enthalpy of the melting of lactose as determined from the area of the lactose melting peak in DSC thermograms, the enthalpy of the melting of lactose was significantly lower for Cellactose than for excipients B and C (Table 1). The DSC peak for $\alpha$-lactose dehydration appeared, as expected, near 145 °C.

Its greater $\beta$-lactose content may also be held responsible for the hydration water content of Cellactose being slightly lower than that of the other excipients (Table 1). $\beta$-lactose being anhydrous. All three excipients had very similar sorbed water contents and very similar enthalpies of wetting/dissolution (Table 1).

SEM photomicrographs show Cellactose particles to be highly spherical and to possess pores of considerable size (Fig. 3). The circularity of the spheronized blend was rather higher than that of Cellactose, and that of the dry-granulated excipient rather lower (Table 1); unlike Cellactose, neither B nor C exhibited large pores at the particle surface (Fig. 3). In consonance with the latter observation, the total pore volume of Cellactose particles, as determined by mercury intrusion and nitrogen adsorption porosimetry, was more than double that of the other excipients as the result of the much greater abundance of large pores in Cellactose particles (Fig. 4). In both Cellactose and the dry-granulated blend, the pore volume due to pores $<1 \mu$m in diameter was significantly greater than in the extruded/spheronized blend (Fig. 4), a circumstance that explains parallel differences in specific surface area (Table 1).

The values of compressibility and flow factor reflect the free-flowing nature of Cellactose and, in particular, the extruded/spheronized blend, while the dry-granulated blend had
deficient flow. As these findings and Fig. 3 suggest, and as might be expected in view of the similar particle size, true densities and sorbed water content of the three excipients, flow factor was in fact determined by circularity, as is reflected by the perfect correlation between the two ($r = 1.0000$).

The mean yield pressures of all three excipients (Table 1) were similar to those of direct compression lactoses, and suggest that particle fragmentation makes a major contribution to their densification under pressure. We note that the value obtained for Cellactose is very similar to that reported by Garr and Rubinstein.

The enthalpy of wetting/dissolution, which was quite similar for all three untabletted blends (Table 1), was significantly reduced by tabletting at 160 MPa in the case of Cellactose but not in the cases of blends B and C (Table 2). This was tentatively attributed to the elimination of macropores by compression at 160 MPa (Fig. 5), which was marked for Cellactose (which before compression had a very large macropore volume) but relatively insignificant for B and C (which before compression had small macropore volumes). Likewise, in spite of similarities among the mean yield pressures of the untabletted excipients (especially between Cellactose and B), Cellactose tablets produced using a punch pressure of 160 MPa (hereinafter “Cellactose-160 tablets”) were both stronger and less friable than the tablets of B and C, which were produced under the same conditions (Table 2). In this case the difference was especially marked for the spheronized blend, possibly because the large circularity and small specific surface area of its particles (Table 1) make for better coating with the lubricant, and hence for weaker interparticle bonding. Cellactose-160 tablets also had a much longer disintegration time than B or C tablets, 836 s vs. 13 or 19 s (Table 2).

To investigate further the influence of macropore volume on the wetting/humectation enthalpy and other properties of Cellactose tablets, we characterized tablets in which the volume of pores $>1 \mu m$ was varied from 0.02 to 0.15 cm$^3$·g$^{-1}$ by varying the punch pressure used in the tabletting process (5, 50 or 100 MPa). Figure 6 shows the cumulative pore volume distributions of these tablets. The results of characterization (Table 2) clearly show that for Cellactose tablets tensile strength falls and wetting/humectation enthalpy rises with increasing macropore volume (Fig. 7), while disintegration time falls roughly exponentially. The properties of the more porous Cellactose tablets were quite similar to those of tablets of B and C. The fact that these latter fail to comply with the correlations observed for Cellactose tablets is of course expected, since the structures of B and C particles differ from Cellactose in many respects, regardless of macropore volume.

### Table 2. Properties of Tablets Prepared by Direct Compression from Cellactose and Two ad hoc Processed Cellulose/Lactose Blends

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Excipient</th>
<th>Cellactose</th>
<th>BC</th>
<th>5 MPa</th>
<th>50 MPa</th>
<th>100 MPa</th>
<th>160 MPa</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tensile strength, MPa</td>
<td></td>
<td>0.10 (0.02)</td>
<td>0.93 (0.30)</td>
<td>2.05 (0.07)</td>
<td>3.09 (0.05)</td>
<td>1.28 (0.07)</td>
<td>0.39 (0.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friability, %</td>
<td></td>
<td>1.90 (0.09)</td>
<td>1.92 (0.07)</td>
<td>2.05 (0.09)</td>
<td>0</td>
<td>0.33</td>
<td>0.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific surface area, m$^2$·g$^{-1}$</td>
<td>0.15 (0.03)</td>
<td>0.11 (0.05)</td>
<td>0.02 (0.06)</td>
<td>2.19 (0.08)</td>
<td>1.89 (0.06)</td>
<td>1.83 (0.06)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disintegration time, s</td>
<td></td>
<td>7 (1)</td>
<td>51 (2)</td>
<td>97 (3)</td>
<td>836 (34)</td>
<td>13 (1)</td>
<td>19 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wetting/dissolution enthalpy, J·g$^{-1}$</td>
<td>33.06 (0.23)</td>
<td>30.86 (0.51)</td>
<td>28.77 (0.39)</td>
<td>27.14 (0.76)</td>
<td>35.29 (1.99)</td>
<td>34.45 (0.10)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean values, with standard deviations in parentheses.
The above findings suggest that, in the absence of marked macroporosity, the remaining structural characteristics of Cellactose tablets markedly impede the weakening and disintegrating action of water. The extremely poor disintegration of Cellactose-160 tablets in comparison with B and C tablets cannot be attributed simply to their greater β-lactose content, since β-lactose content by itself has little effect on disintegration time. Rather, it seems likely that, as hypothesized by Schmidt and Rubensdörfer, the poor disintegration of well-compacted Cellactose tablets is due to the very feature that is also thought to be responsible for their excellent mechanical properties, namely, the fact that Cellactose particles consist basically of a cellulose core coated in lactose. With this structure, the disintegrating action of the cellulose must await the prior dissolution of the lactose, and even then it is hindered by the viscosity of lactose solutions, which slows the access of water to the cellulose. By contrast, the spatial distribution of lactose and cellulose in particles of blends B and C must be much more random, allowing easier access of water to cellulose.

In conclusion, when compressed at the same punch pressure, Cellactose afforded tablets with better mechanical properties but much poorer disintegration than those of the ad hoc cellactose/lactose blends of similar composition prepared in this study. However, the tensile strength and disintegration time of Cellactose tablets both fell rapidly as the volume of pores >1 μm rose, while the enthalpy of wetting/dissolution rose. The strength and water-resistance of well-compacted Cellactose tablets is attributed to the spatial distribution of lactose and cellulose in Cellactose particles, rather than to β-lactose content or extra-particular structural features.

Acknowledgments This work was supported by grant SAF 96-1706 CICYT, from the Spanish Ministry of Education and Science. We thank Quimidroga for providing us with Cellactose samples.

References