A Comparison of Drug Loading Capacity of Cellactose with Two *ad hoc* Processed Lactose–Cellulose Direct Compression Excipients

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This study compares the drug loading capacity of Cellactose and two excipients of similar composition and similar particle size, prepared by dry granulation and extrusion-spheronization respectively. The drugs evaluated were acetaminophen and furosemide. Acetaminophen did not significantly affect the flow properties of any of the excipients, whereas furosemide markedly worsened flow properties, eliminating the differences initially existing among the three excipients. For both drugs, tablet mechanical properties were clearly better with Cellactose than with the other excipients. Acetaminophen dissolution rate was very similar regardless of the excipient used, but furosemide dissolution rate was lower from Cellactose tablets than from tablets prepared with the other excipients. This important difference is discussed in terms of micropore structure, specific surface area, and wettability of tablets, and is attributable to the special structure of Cellactose particles.

Key words coprocessed excipient; Cellactose; direct compression; drug-loading capacity; acetaminophen; furosemide

In a previous study[1] we performed a comparative analysis of the properties of Cellactose, a coprocessed excipient for direct compression, and of two cellulose–lactose excipients (prepared by dry granulation and extrusion-spheronization respectively) of similar composition and particle size. We found major differences among the three excipients in particle structure and rheological properties, and in the mechanical properties and disintegration behaviour of the corresponding tablets.

In the present study, as a follow-up to our previous study,[1] we evaluate the drug-loading capacities of these three excipients, since drug loading is one of the major limitations of excipients of this type.[2] The model drugs used were acetaminophen (which is problematic at the compression stage[3,4]) and furosemide (which is highly cohesive[5]). Drug-loading capacity was evaluated in terms of the flow and compression properties of different drug–excipient mixtures, and the mechanical, microstructural and drug release properties of tablets prepared from these mixtures.

Experimental

Materials Cellactose, from Meggle, was supplied by Fher, S.A. (lot 919), and was used as supplied. Alpha-lactose monohydrate Ph. Eur. was from Merck (lot 2444543). Avicel PH-101 (FMC Corp.) was supplied by C. Barcia, S.A. (lot 5648). Magnesium stearate B.P. was likewise supplied by C. Barcia, S.A. (lot 548). Acetaminophen (lot 841) and furosemide (lot 97) were supplied by UTEFSA. The cellulose–lactose excipients were prepared by us by dry granulation (excipient B) and extrusion-spheronization (excipient C).[1]

Characterization of the Drugs Particle Size: Particle size distribution was evaluated in triplicate in a Coulter LS100 laser diffraction apparatus, using water as dispersal medium. For both drugs, mean diameter and standard deviation were estimated after fitting a log-normal distribution.

Flow Properties: Bulk density was determined over 20 min in a Hosokawa PT-E Powder Tester operating at 50 taps/min. Compressibility was calculated from the initial and final bulk densities.[6]

Compression Properties: 99.5 : 0.5 (w/w) mixtures of drug and magnesium stearate were prepared over 5 min in a Turbula T2C mixer operating at 30 rpm, and samples were tabletted in a Bonals B/MT eccentric apparatus equipped with 9-mm flat punches and a compression data acquisition system.[7] Mean yield pressures (Py) were estimated from Heckel plots of the upper punch force-displacement data for three punch cycles.[8]

Preparation of Drug–Excipient Mixtures Mixtures (Turbula T2C, 30 rpm, 15 min) of each excipient with each drug were prepared with 12.5 and 37.5% w/w acetaminophen or furosemide.

Characterization of the Drug–Excipient Mixtures Flow properties and compression properties of mixtures were characterized by the same methods as for drugs.

Tablet Preparation Using the same mixtures and tabletting machine as described above, and a punch pressure of 160 MPa, 250-mg tablets were prepared at 8 tablets/min.

Characterization of Tablets Tensile Strength: The crushing strengths of six tablets of each formulation were determined using an Erweka TB2A apparatus; mean tensile strengths were then calculated from these results and the dimensions of each tablet[9] which were measured using a Mitutoyo digital micrometer (measuring range, 0—25 mm; precision, ±0.001 mm).

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

Microporous Structure and Specific Surface. Mercury Intrusion Porosimetry: Tablet samples were placed in a 3-ml sample holder and intruded mercury volume was determined over the pressure interval 0.6—25000 psi in a Micromeritics 9305 Pore Sizer. The pore size distributions (pore size $>0.1\,\mu$m) were determined from these data following the manufacturer's instructions.[10] All determinations were done in triplicate.

Nitrogen Adsorption: Tablet samples were degassed by heating at 70 °C and 10^{-3} mmHg for 24 h. Nitrogen adsorption was determined in triplicate in a Micromeritics ASAP 2000 instrument at 77 K and at relative pressures of 0.01—0.98. Specific surface areas were estimated by means of the BET model.[11] Pore size distributions (pore size $<0.1\,\mu$m) were determined from the nitrogen adsorption isotherms of the BHJ method.[11]

Disintegration Time: Tablet disintegration time in distilled water was determined in a Turu-Grau apparatus conforming to the specifications of USP24 (2000). Results are the mean values for 6 tablets.

Dissolution Rate: Drug dissolution rates were determined in a Turu-Grau apparatus conforming to USP24 specifications (method II, 50 rpm, 900 ml of phosphate buffer pH 5.8). Acetaminophen or furosemide concentrations in samples from the dissolution assays were determined by direct spectrophotometry (Shimadzu UV-240) at 243 nm (acetaminophen) or 274 nm (furosemide). Dissolution rate was characterized as 30-min (acetaminophen) or 60-min dissolution efficiency (furosemide).[12]

Results and Discussion

Table 1 summarizes the results obtained in the characterization of furosemide and acetaminophen. These results confirm the marked differences in flow properties and compression behaviour,[3,5] and in mean particle size.

Acetaminophen and furosemide had rather different effects on the properties of the different excipients (Table 2). Thus

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the incorporation of acetaminophen (a drug with excellent flow properties) had no important effects on the compressibilities of either excipient, whereas furosemide (a highly cohesive drug) had negative effects on flow properties. These negative effects were more pronounced in the excipients with initially good flow properties: thus the incorporation of 37.5% furosemide produced mixtures with similarly high compressibilities (around 50%), even though the initial compressibilities of the excipients ranged from 15% (excipient C) to 37% (excipient B). By contrast, both drugs had basically additive effects on mean yield pressure.

Table 1. Summarized Physical Properties (Means±S.D.) of Acetaminophen and Furosemide

Drug	Mean particle size, μm	Compressibility, %	Mean yield pressure, MPa
Acetaminophen	298 (0.55)	8.47 (0.00)	213.6 (2.13)
Furosemide	81 (0.46)	62.63 (2.21)	117.4 (3.2)

Table 2. Summarized Physical Properties (Means±S.D.) of the Three Excipients and 12 Drug–Excipient Mixtures Tested

Blend			Compressibility, %	Mean yield pressure, MPa
Excipient	Drug	Drug content, %		
Cellactose	—	0	23.54 (0.11)	125.8 (1.1)
	Acetaminophen	12.5	22.62 (0.29)	163.6 (7.5)
		37.5	22.22 (0.95)	179.3 (2.8)
	Furosemide	12.5	29.74 (0.47)	145.4 (3.9)
		37.5	47.75 (0.48)	123.0 (5.7)
B	—	0	36.83 (0.13)	138.6 (4.6)
	Acetaminophen	12.5	36.21 (0.69)	123.5 (0.7)
		37.5	30.99 (0.13)	202.7 (5.9)
	Furosemide	12.5	41.15 (0.52)	141.2 (2.3)
		37.5	56.98 (0.32)	134.4 (5.7)
C	—	0	14.64 (0.77)	189.5 (7.7)
	Acetaminophen	12.5	15.85 (0.23)	174.3 (5.9)
		37.5	17.03 (1.00)	209.9 (8.2)
	Furosemide	12.5	33.45 (1.47)	178.7 (3.3)
		37.5	53.28 (0.01)	131.7 (2.3)

As expected, tablet mechanical properties were likewise affected in different ways by the two drugs (Table 3). Thus, by comparison with tablets prepared from the excipient alone, tablets including acetaminophen showed marked reductions in tensile strength and increased friability, in line with the known difficulties in acetaminophen tablet formulation. The effects of furosemide on tablet properties can be considered the opposite of those of acetaminophen, particularly with regard to tensile strength. In fact, the high cohesiveness of furosemide gives rise to improvements in the mechanical properties of tablets prepared with excipient B or C, particularly when used at the higher proportion 37.5%. In addition, our results clearly show that Cellactose gives tablets with markedly better mechanical properties than excipient B or C.

The slow disintegration of tablets prepared with Cellactose, which we have reported previously,[1)] is not seen in acetaminophen tablets but is accentuated in furosemide tablets. The rapid disintegration of acetaminophen tablets, regardless of excipient, is attributable to the relatively high hydrosolubility of acetaminophen, and the lower tensile strength values of acetaminophen tablets. In the case of furosemide tablets, marked differences were observed between Cellactose and the other two excipients when furosemide content was 37.5%: tablets prepared with Cellactose required more than 90 min for disintegration, whereas tablets prepared with excipient B or C showed complete disintegration in less than 70 s. These differences are attributable a) to the low hydrosolubility of furosemide; b) to the high tensile strength of tablets prepared with Cellactose, a consequence of the high cohesiveness of this drug; and c) to the disappearance (as a result of the compression process) of the large pores characteristic of Cellactose particles and their special structure, *i.e.* cellulose core and lactose outer layer.[13)] With this structure, cellulose disintegration only begins after the lactose outer layer has dissolved, giving rise to aqueous solutions of considerable viscosity, which further hinders water access to the

Table 3. Summarized Mechanical, Microstructural and Drug Release Properties (Mean±S.D.) of Tablets Obtained at 160 MPa from the Three Excipients and 12 Drug–Excipient Mixtures

Formulation			Tensile strength, MPa	Friability, %	Disintegration time, s	Dissolution efficiency, %[a)]	Wetting/dissolution enthalpy, −J/g	Specific surface, m^2/g
Excipient	Drug	Drug content, %						
Cellactose	—	0	3.09 (0.05)	0	836 (34)	—	27.14 (0.76)	2.19 (0.08)
	Acetaminophen	12.5	1.78 (0.04)	0.23	66 (7)	77.13 (2.53)	—	1.83 (0.11)
		37.5	0.96 (0.07)	0.50	31 (3)	77.51 (2.05)	—	1.55 (0.03)
	Furosemide	12.5	2.48 (0.05)	0.71	450 (20)	67.76 (3.54)	31.96 (0.09)	2.31 (0.15)
		37.5	2.64 (0.19)	0.40	5618 (1844)	3.96 (0.17)	3.31 (0.09)	2.73 (0.07)
B	—	0	1.28 (0.07)	0.33	13 (1)	—	35.29 (1.99)	1.89 (0.06)
	Acetaminophen	12.5	0.70 (0.15)	0.72	16 (3)	77.57 (3.93)	—	1.69 (0.08)
		37.5	0.29 (0.06)	2.82	13 (1)	77.53 (2.47)	—	1.51 (0.01)
	Furosemide	12.5	1.04 (0.28)	0.82	10 (0)	87.23 (0.70)	34.49 (0.17)	2.25 (0.05)
		37.5	1.50 (0.19)	0.71	62 (11)	84.25 (1.07)	24.82 (0.86)	2.71 (0.01)
C	—	0	0.39 (0.03)	0.67	19 (1)	—	34.45 (0.10)	1.83 (0.06)
	Acetaminophen	12.5	0.29 (0.02)	4.25	27 (3)	75.41 (4.34)	—	1.56 (0.20)
		37.5	0.17 (0.04)	29.70	260 (53)	75.99 (2.72)	—	1.31 (0.12)
	Furosemide	12.5	0.84 (0.06)	0.59	13 (1)	97.17 (1.07)	34.21 (0.27)	1.93 (0.04)
		37.5	1.12 (0.10)	0.65	69 (17)	68.01 (5.27)	25.55 (2.28)	2.35 (0.11)

a) 0—30 min for acetaminophen and 0—60 min for furosemide.

cellulose nucleus.[14] These limitations do not occur in tablets prepared with excipients B and C, made up of agglomerates of randomly distributed lactose and cellulose particles.

These marked differences among the different formulations are clearly reflected in drug dissolution rates. Acetaminophen dissolution rates did not vary appreciably among tablets prepared with the different excipients; by contrast, furosemide dissolution rates—especially in formulations with 37.5% furosemide—showed dramatic differences (Fig. 1). In addition to these differences in dissolution rate, comparison of the dissolution profiles suggests that the mechanism of furosemide release from Cellactose tablets is different from that for release from tablets prepared with excipient B or C. This is supported by the slow disintegration of the Cellactose-furosemide tablets.

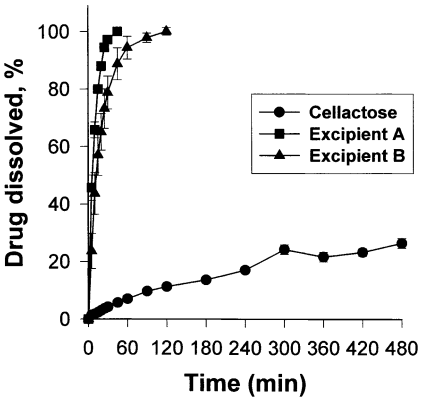

Fig. 1. Cumulative Drug Dissolution Curves for Tablets Containing 37.5% Furosemide

To further investigate these marked among-excipient differences in the rate of dissolution, we evaluated pore size distribution, specific surface area and (for furosemide formulations only) tablet wetting/dissolution enthalpy.

Pore size distributions (Figs. 2, 3) clearly show that the incorporation of acetaminophen had no important effects on porosity, whereas incorporation of 37.5% furosemide greatly reduced total porosity and increased the proportion of smaller pores. However, this effect of furosemide on porosity differed little between tablets prepared with the three excipients. However, this effect of furosemide on porosity differed little between tablets prepared with the three excipients: in other words, there were no appreciable differences between the three excipients as regards tablet structure.

The effects of acetaminophen and furosemide on specific surface area differed little among tablets prepared with the three excipients, and are attributable to differences in particle size of the two drugs, and to the greater tendency for frag-

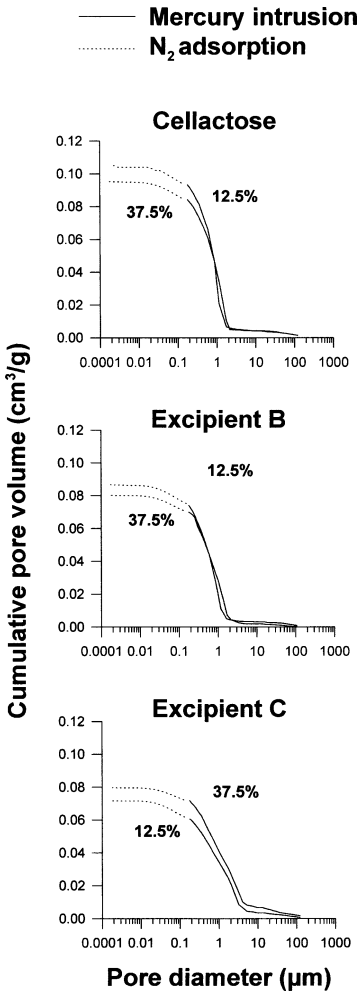

Fig. 2. Cumulative Pore Size Distributions in Tablets Containing 12.5 or 37.5% Acetaminophen

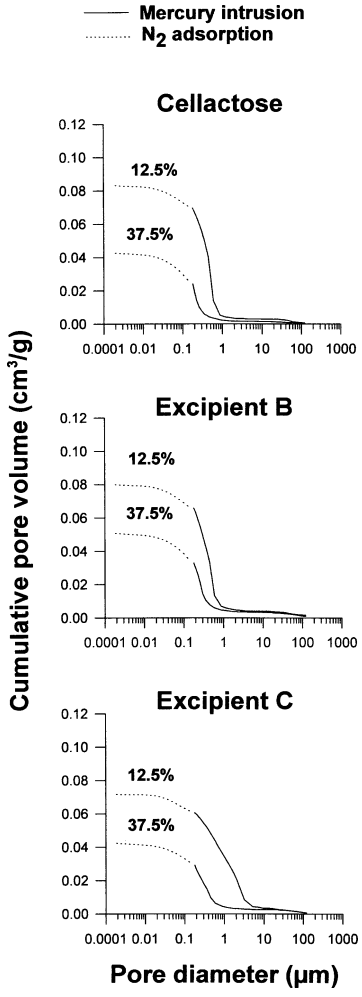

Fig. 3. Cumulative Pore Size Distributions in Tablets Containing 12.5 or 37.5% Furosemide

mentation of acetaminophen particles (as indicated by yield pressure values, Table 2). In any case, the observed among-excipient differences in furosemide dissolution rate are not attributable to a lower specific surface area of tablets prepared with Cellactose.

Finally, the data obtained for the furosemide-containing formulations by immersion calorimetry indicate that the wetting/dissolution capacity of Cellactose tablets with 37.5% furosemide is markedly reduced, without this being attributable to reduced porosity, or to lower specific surface area than that of equivalent tablets prepared with excipient B or C.

It thus seems clear that the sensitivity of Cellactose tablets to the marked reduction in porosity when furosemide content is increased from 12.5 to 37.5% is attributable to the structure of Cellactose particles (see above).

In conclusion, if we consider tablet mechanical properties, Cellactose clearly incorporates both of the drugs considered in this study better than excipients B and C. However, the release of poorly hydrosoluble drugs like furosemide from Cellactose tablets may be very slow, because the porosity-reducing effects of these drug have a particularly marked impact on drug release from tablets prepared with this excipient, in view of the structure of Cellactose particles.

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