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International Journal of Pharmaceutics 129 (1996) 253–261

international journal of pharmaceutics

Effects of hydration on the properties of a roller-dried β-lactose for direct compression

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Received 10 August 1995; accepted 16 October 1995

Abstract

The effects of partial and full hydration on the properties of a roller-dried β-lactose for direct compression were evaluated. Gas chromatography, X-ray diffraction and differential scanning calorimetry all indicated that the β-lactose was progressively transformed into α-lactose as hydration increased. Mercury intrusion porosimetry and nitrogen adsorption experiments indicated that the intraparticular porous volume of the β-lactose was considerably increased by full hydration of the excipient; this increase was accompanied by a marked increase in the specific surface of the fully hydrated excipient. The flow properties of the excipient deteriorated progressively as hydration increased, while its compression properties and the mechanical properties of derived tablets were not appreciably affected. Nonetheless, tablets of the fully hydrated excipient had disintegration times very much shorter than those of tablets of the anhydrous and partially hydrated lactose. Finally, incorporation of a small dose of an active principle (4% w/w diazepam) in tablets prepared from the fully hydrated β-lactose had a significant negative effect on their mechanical properties. This effect, together with the above-mentioned increase in the specific surface of the fully hydrated excipient, caused rapid dissolution of the diazepam from these tablets.

Keywords: Anhydrous lactose; Hydration; Direct compression; Microstructure; flow properties; Compaction properties; Tablets

1. Introduction

In recent years there has been considerable research into the interactions between water and the pharmaceutical excipients used in solid dosage forms, particularly those prepared by direct compression (Malamataris et al., 1991; Landín et al., 1994a,b; Mollan and Celik, 1995). In the case of lactoses for direct compression, Sebhatu et al. (1994) have examined the effects of trapped moisture on the structure of spray-dried α-lactose and on the properties of its tablets; Angberg et al. (1991) have intensively studied the hydration of

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SSDI 0378-5173(95)04360-M

β-lactose using immersion microcalorimetry; and Shukla and Price (1991) have determined the effects of hydration on the compression behaviour of a roller-dried β-lactose, and also on the mechanical resistance of tablets of this excipient.

In this work we compared the effects of partial and total hydration on the structural and rheological properties of a roller-dried β-lactose for direct compression. The effects of hydration on the mechanical and microstructural properties of derived tablets and the rate of release of diazepam from these tablets were also evaluated.

2. Materials and methods

2.1. Materials

The anhydrous roller-dried β-lactose for direct compression (DCL-21 lactose; Batch no. 301103 from DMV, Netherlands) was used as supplied. This material (excipient A) was partially and totally hydrated (affording excipient B and excipient C, respectively) by storing it at 100% relative humidity for appropriate periods (the water content of these excipients was later determined by thermogravimetry; see below).

2.2. Thermogravimetric analysis

Thermograms of samples (2–3 mg) of each excipient were determined in a Shimadzu TA-50 instrument at a heating rate of 10°C/min. The mass lost between 130 and 160°C was considered to correspond to the total mass of the hydration water (Otsuka et al., 1991).

Additionally, samples (2 g) of each excipient were heated at 70°C in a Shimadzu Libror EB-250 Moc thermobalance until their mass was constant; the mass lost corresponded to the mass of adsorbed water in each excipient (Handbook of Pharmaceutical Excipients, 1991).

2.3. Gas chromatography (GC)

α and β-lactoses were determined by GC using the method of Dwivedi and Mitchell (1989). A sample of each of excipients A–C was firstly derivatized in a 19.5:22.0:58.5 (v/v) mixture of dimethylsulphoxide/*N*-trimethylsilylimidazole/pyridine. Then aliquots of this solution were injected into a Perkin-Elmer 3700 GC apparatus equipped with the column described by Dwivedi and Mitchell (1989). 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 α and β-lactose were calculated from the areas of the corresponding peaks (t_R were 6–7 and 10–11 min, respectively). Final results (%) are the means of triplicate determinations.

2.4. Differential scanning calorimetry (DSC)

DSC thermograms of 2–3 mg samples of each excipient hermetically sealed in aluminium pans were recorded at a heating rate of 10°C/min in a Shimadzu DSC-50 instrument. Dehydration enthalpies were estimated from the areas of the endothermic peaks at 140°C. Additional peaks at 215–220°C and 230–235°C, corresponding to the fusion of α and β-lactose, respectively (Ford and Timmins, 1989), were also monitored.

2.5. Powder x-ray diffraction

The powdered excipients were pressed into a sample holder and the surface was smoothed with a glass slide. Then, their room-temperature X-ray diffractograms were recorded between 5 and 40°2θ in a Philips 1710 instrument using monochromatic Cu-K_α radiation and a scan rate of 1.2°2θ/min.

2.6. True density

True densities were determined in triplicate in a Quantachrome model PY2 helium pycnometer.

2.7. Scanning electron microscopy (SEM)

Photomicrographs (350 ×) of the three excipients were obtained using a Jeol JSM T-220A instrument.

2.8. Particle size analysis

Particle size analysis was performed on samples suspended in a current of air in a Malvern 2600 laser scattering instrument. In all cases, the particle volume distributions obtained were best fitted by normal probability-size distribution functions, from which the mean volume diameters (d_v) and corresponding standard deviations were estimated (Allen, 1978).

2.9. Mercury intrusion porosimetry

For each excipient in triplicate, a sample was placed in a 3 cm^3 powdered-sample holder and the intruded mercury volume was determined over the pressure interval 0.6–25000 psi in a Micromeritics 9305 Pore-sizer. The pore volume distribution and corresponding total porosity were then evaluated from these data (Micromeritics, 1984).

2.10. Nitrogen adsorption

Excipient samples were degassed by heating them at 70°C and 10^{-3} mm Hg for 16 h. Duplicate nitrogen adsorption experiments were carried out in a Micromeritics ASAP 2000 instrument at 77 K and relative pressures of 0.01 to 0.98. Specific surfaces were estimated by means of the BET model (Stanley-Wood, 1983). The pore-size distribution were determined from the nitrogen adsorption isotherms by the BJH method (Stanley-Wood, 1983).

2.11. Flow properties

Shear strengths were determined using an IPT RO-200 automatic apparatus equipped with a rotational split-level shear cell (Svarovsky, 1987a). Duplicate samples of each excipient were subjected to three consolidating loads, thus allowing obtention of a family of three yield loci with final normal stresses corresponding to 50, 150 and 250 g/cm^2. Regression of the unconfined yield stress (f_c) for the three different levels of consolidation on the corresponding major consolidation stress (σ_1) gave a straight line plot whose slope was the inverse of the flow factor (Brown and Richards, 1970; Svarovsky, 1987b).

2.12. Compression properties

Prior to compression, each excipient was mixed with 0.5% (w/w) magnesium stearate (5 min at 30 revs/min in a Túrbula T2C mixer) to prevent it sticking to the punch or die. Subsamples of each material were then compressed in a Bonals model B/MT excentric press equipped with flat-faced 9 mm punches and a data acquisition system (Martínez-Pacheco et al., 1985). Mean yield pressures (P_y) were estimated from Heckel plots of the data for three compression force-displacement cycles of the upper punch (Humbert-Droz et al., 1982).

2.13. Preparation of tablets

Using the apparatus described above, adjusted for preparation of 250 mg tablets, six formulations of each excipient (mixed with 0.5% w/w magnesium stearate as above) were obtained by applying all possible combinations of three maximum compaction forces (4, 8 and 12 kN) and two compression rates (8 and 42 tablets/min). For each excipient, a single formulation containing 4% (w/w) diazepam (10 min at 30 revs/min in a Túrbula T2C mixer) was prepared using a compression force of 12 kN and a compression rate of 8 tablets/min.

2.14. Characterization of tablets

Each formulation was subjected to the following tests.

2.14.1. Tensile strength

The crushing strength of six tablets of each formulation was determined using an Erweka TB 2A apparatus; mean tensile strengths were then calculated from these results and the dimensions of each tablet (Fell and Newton, 1971), which were measured using a Mitutoyo digital micrometer (measuring range, 0–25 mm; precision ± 0.001 mm).

Table 1
Mean values (± standard deviation) of several properties of the three uncompressed excipients

Property	Excipient		
	A	B	C
Hydration water (%)	0.80 (0.04)	2.78 (0.05)	4.95 (0.10)
Adsorbed water (%)	0.11 (0.05)	0.13 (0.02)	0.08 (0.01)
α-lactose content (%)	27.05 (2.45)	50.95 (1.48)	97.41 (0.51)
ß-lactose content (%)	72.92 (2.51)	49.00 (1.47)	2.59 (0.51)
Dehydration enthalpy (−J/g)	9.82 (2.61)	98.54 (5.79)	190.33 (3.26)
True density (g/cm^3)	1.587 (3.3×10^{-3})	1.556 (2.8×10^{-3})	1.541 (2.6×10^{-3})
Total porosity (%)	45.97 (1.29)	48.35 (0.55)	56.04 (3.68)
Specific surface (m^2/g)	0.3406 (0.011)	0.4301 (0.071)	1.1733 (0.004)
Particle mean volume diameter (μm)	221.03	219.59	203.06
Flow factor (FF)	11.54	8.75	5.57
Mean yield pressure (MPa)	149.9 (1.5)	141.7 (1.4)	148.4 (3.4)

2.14.2. Disintegration time

Determinations were carried out in a Turu Grau apparatus conforming to the specifications exacted in USP 23 (1995). Mean values were calculated from the disintegration times of six tablets of each excipient. Distilled water was the attacking medium except in the case of the diazepam-containing tablets, for which 0.1N HCl was used.

2.14.3. Dissolution rate

Only the diazepam-containing tablets were subjected to this test, which was carried out in a Turu Grau apparatus conforming to the specifications exacted in USP 23. The rates of dissolution of six replicate tablets prepared from each excipient were determined by USP method I (the basket method). The dissolution medium was 900 ml of 0.1 N HCl, which was continuously stirred at 100 revs/min. At five-min intervals, an aliquot of the dissolution medium was withdrawn, filtered, diluted with 0.1 N HCl when necessary and assayed spectrophotometrically at 240 nm. Analysis of the dissolved-diazepam/time curve (Khan and Rhodes, 1972) allowed evaluation of the 0–20 min dissolution efficiency.

2.14.4. Specific surface

This was determined for selected formulations as described in section 2.10 for the uncompressed excipients.

2.15. Experimental design and statistical treatment of results

A complete factorial design was used to study the effects of three controlled factors — hydration level of the β-lactose, compression force and compression rate, at 3, 3 and 2 levels, respectively on the tensile strengths and disintegration times of the tablets (Cochran and Cox, 1978). Firstly, ANOVA was used to identify the controlled factors most influencing the dependent properties being studied. Then, functions for prediction of the dependent properties from these factors and their interactions were obtained by stepwise multiple regression. Finally, response surfaces were constructed from the regression equations obtained (Statistical Graphics System, 1992).

3. Results and discussion

The results of the analysis of the three uncompressed excipients are listed in Table 1. There were considerable differences between the amounts of hydration water in excipients A, B and C, while the adsorbed water content was effectively the same for all three. The gas chromatographic studies indicated that, as has been previously observed (Shukla and Price, 1991; Angberg et al., 1991), progressive incorporation

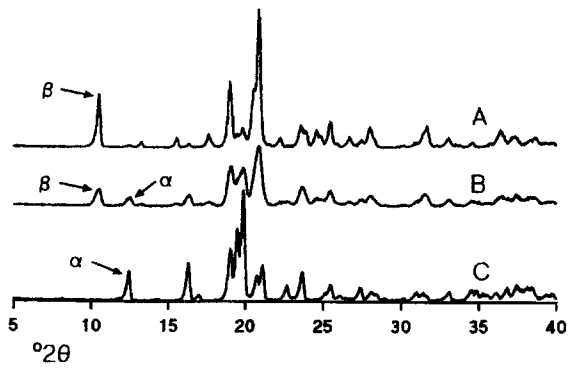


Fig. 1. X-Ray diffractograms of the three excipients studied; the peaks due to α and ß-lactose are indicated.

of hydration water causes anomerization of the β-lactose until, at about 5% (w/w) hydration, only the α-form is present. Indeed, the α-lactose contents of the excipients increased parallel with their hydration water contents. The anomerization of β- to α-lactose was also evident in the X-ray diffractograms (Fig. 1): as hydration increased, the peak due to α-lactose at 12.6°2θ increased in intensity at the expense of the peak due to β-lactose at 10.5°2θ, in keeping with the results of Otsuka et al. (1991) and Di Martino et al. (1993). Likewise, the DSC thermograms of the excipients (Fig. 2) showed the same variation of α and β-lactose content with hydration. The final proportions of each anomer cannot be determined from the DSC curves due to the existence of heat-induced anomerization during the DSC experiment (Lerk, 1983; Olano et al., 1983; Angberg et al., 1991). However, if the derived dehydration enthalpies are expressed per unit mass (Table 1),

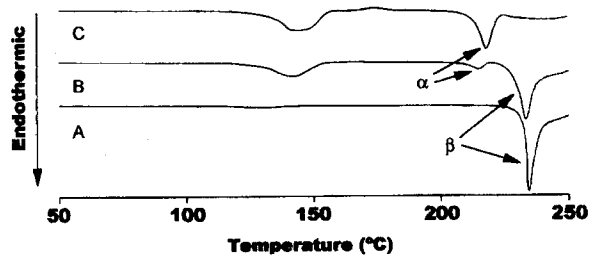


Fig. 2. DSC thermograms of the three excipients studied; the peaks due to fusion of α and ß-lactose are indicated.

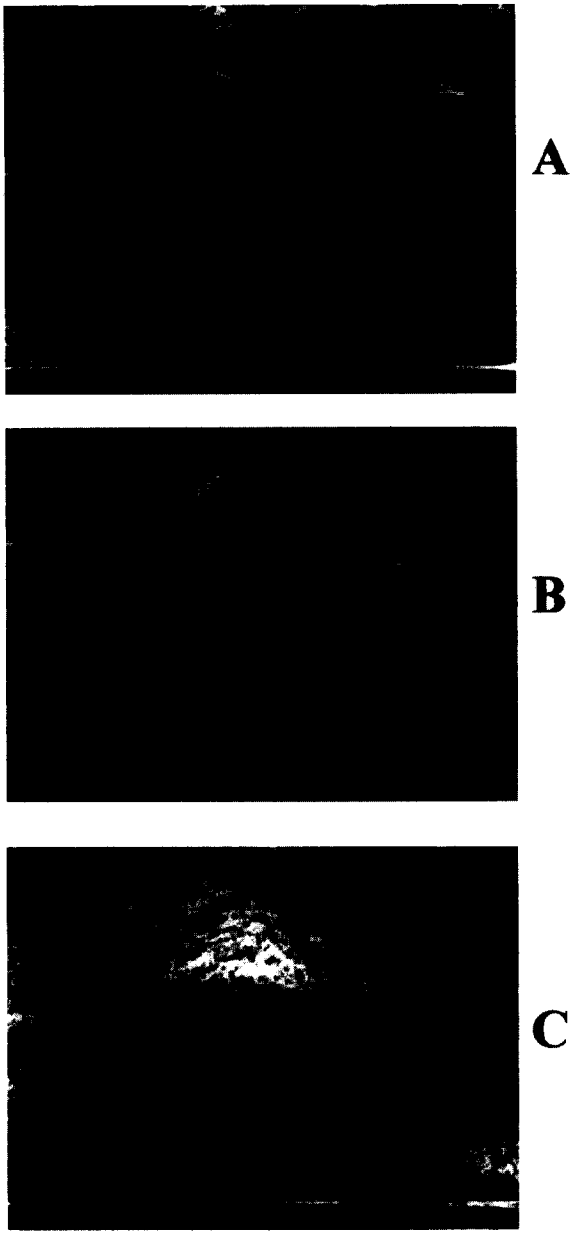


Fig. 3. Scanning electron photomicrographs of the three excipients used: (A) anhydrous; (B) partially hydrated and (C) fully hydrated lactose.

they can be easily related to the proportion of α-lactose determined by GC.

The photomicrographs (Fig. 3) show that important changes in particle structure accompany hydration and produce a clear increase in the surface porosity. We tentatively attribute these

changes to the dissolution of small amounts of lactose by the sorbed water and their subsequent precipitation when that water becomes occluded in the crystal lattice. Not withstanding these changes, hydration had little effect on the mean volume diameter or the particle size distribution of the excipients (Fig. 4).

The important changes in the particles' surface structure observed using SEM called for an intensive evaluation of the porous structures of the excipients. Mercury intrusion porosimetry clearly indicated that hydration-induced increases in the porous volume (1–10 μm pores) were appreciable only for the fully hydrated lactose (Fig. 5). Likewise, the porous volume (0.01–0.1 μm pores) of the fully hydrated lactose increased markedly, while that of the partially hydrated lactose showed only a very slight increase (Fig. 6). These increases in porous volume produced clear increases in the excipients' specific surfaces (Table 1).

The flow factors (FF) of the excipients decreased with increasing hydration, such that the free-flowing anhydrous lactose (FF > 8) became only moderately free-flowing (4 < FF < 8) when fully hydrated (Svarovsky, 1987b). Two factors may have contributed to this deterioration of the flow properties as hydration increased: the concurrent decrease in the true density of the excipients, and the changes in the surface texture discussed above.

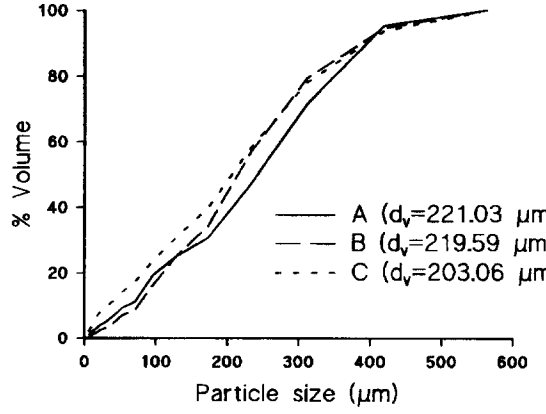


Fig. 4. Cumulative particle size distributions (determined by laser scattering) for (A) the anhydrous lactose, (B) the partially hydrated lactose and (C) the fully hydrated lactose; mean volume diameters (d_v) are given.

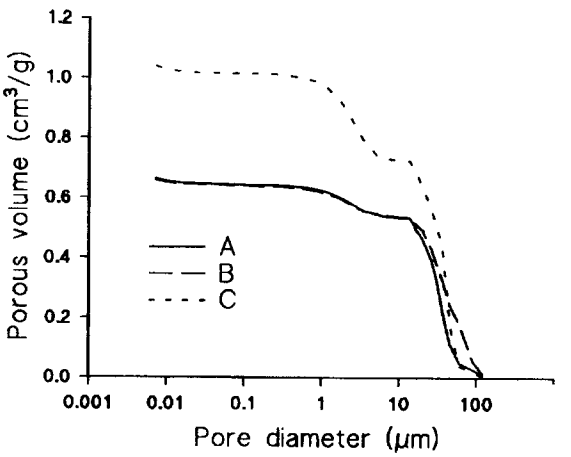


Fig. 5. Pore volume distributiors (1–10 μm pores; determined by mercury intrusion porosimetry) for the anhydrous (A), partially hydrated (B) and fully hydrated (C) lactose excipients studied.

The mean yield pressure of the partially hydrated lactose was significantly different from those of the anhydrous and fully hydrated lactoses. In quantitative terms, however, the differences between the values for the three excipients were small, as has previously been found by Shukla and Price (1991). This suggests that hydration has hardly any effect on the consolidation mechanism of this excipient.

With regard to the tablets, their mechanical properties (tensile strengths) were not appreciably

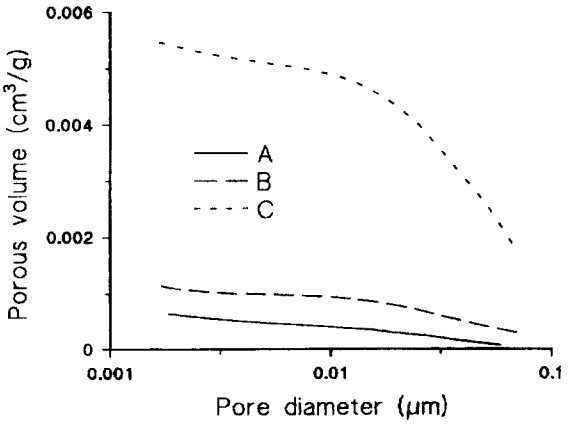
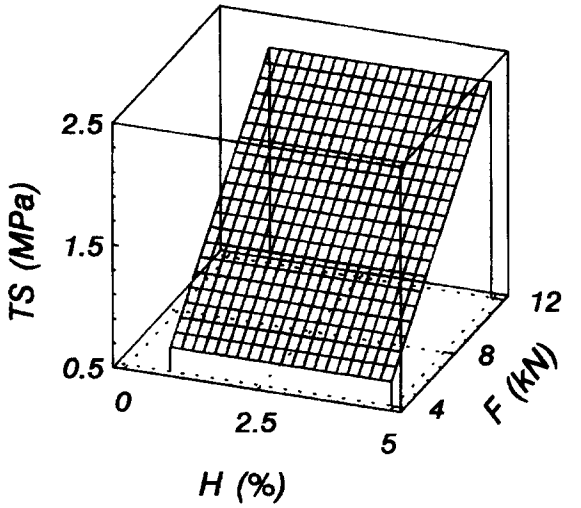


Fig. 6. Pore volume distributions (0.01–0.1 μm pores; determined by nitrogen adsorption) for the anhydrous (A), partially hydrated (B) and fully hydrated (C) lactose excipients studied.

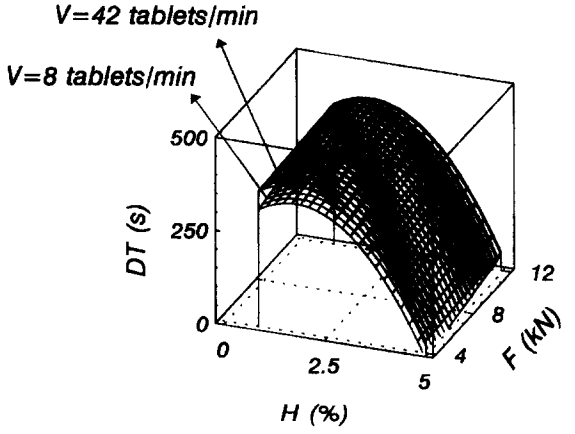


$$TS = -8.92\ 10^{-2} + 0.20\ F$$
$$(r = 0.9265;\ p>0.99)$$

Fig. 7. Response surface showing the variation of the tensile strength (TS) of tablets of the lactose excipient studied with its degree of hydration (H) and the compression force (F) used to prepare the tablet.

affected by their degree of hydration or the compression rate, but were affected by the compression force, as can be appreciated from the response surface in Fig. 7. This observation confirms the assertion above that hydration had only minor effects on the mean yield pressures of the excipients.

The response surfaces showing the effects of the controlled factors on the disintegration times of the tablets (Fig. 8) indicate that full hydration drastically reduced this parameter; smaller effects due to the compression force and rate are also evident. This result is surprising given the poorer water-solubility of α compared to β-lactose (Handbook of Pharmaceutical Excipients, 1986) and the fact that, in all cases, disintegration occurred by progressive dissolution of the lactose without crumbling of the tablets. We therefore attribute the much reduced disintegration times of tablets of the fully hydrated lactose to the hydration-induced changes observed in its porous structure and specific surface. This assertion is



$$DT = 193.07 + 120.19\ H - 34.80\ H^2 +$$
$$+ 2.11\ V + 8.79\ F - 0.16\ V\ F$$
$$(r = 0.9783;\ p>0.99)$$

Fig. 8. Response surface showing the variation of the disintegration time (DT) of tablets of the lactose excipient studied with its degree of hydration (H), the compression force (F) and the compression rate (V) used to prepare the tablet.

supported by the observation that full but not partial hydration of the lactose drastically increased the specific surfaces of the tablets, while compression force and compression rate had only

Table 2
Mean ($\pm$ standard deviation) values of the indicated properties of tablets of the three excipients prepared using the indicated compression forces (kN) and rates (tablets/min)

Excipient	Compact (compression force/velocity)	Specific surface (m^2/g)
A	4/8	0.8769 (0.007)
	12/8	0.8852 (0.036)
	4/42	1.0282 (0.039)
	12/42	1.1862 (0.150)
B	4/8	1.2854 (0.014)
	12/8	1.2931 (0.014)
	4/42	1.2537 (0.051)
	12/42	1.3112 (0.010)
C	4/8	2.3179 (0.062)
	12/8	2.4336 (0.241)
	4/42	1.8309 (0.104)
	12/42	2.4698 (0.228)

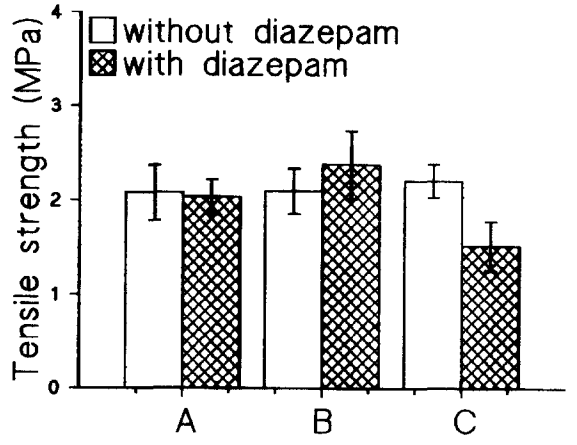


Fig. 9. Comparison of the TS of tablets of the anhydrous (A), partially hydrated (B) and fully hydrated (C) lactose excipients with those of the corresponding tablets containing 4% (w/w) diazepam.

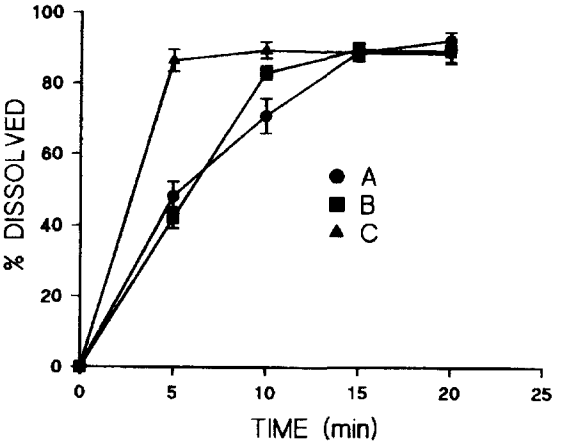


Fig. 10. Dissolution profiles for diazepam in tablets of the anhydrous (A), partially hydrated (B) and fully hydrated (C) lactose excipients studied.

minor effects on this property (Table 2). This increase apparently counters, indeed reverses, the effect on the disintegration time of the increased proportion of poorer water-soluble α-lactose in tablets of the fully hydrated lactose.

The effects of introducing a small dose (4% w/w) of diazepam into the tablets prepared using a 12 kN compression force and a compression rate of 42 tablets/min were also determined. Fig. 9 compares the tensile strengths of these tablets with those of tablets of the three excipients alone prepared using the same conditions. Bearing in mind that, in the absence of diazepam, hydration of the lactose barely affected tablet tensile strength (Fig. 7), the observation that the diazepam-containing tablets had significantly lower tensile strength than those without diazepam only when they were prepared from fully hydrated lactose suggests that the diazepam somehow weakens interparticular union within the tablet, most notably in those almost exclusively composed of α-lactose.

The diazepam-containing tablets prepared from the fully hydrated lactose also had anomalous properties as regards dissolution of the diazepam (Fig. 10). The higher dissolution efficiency (Table 3) obtained for the tablets prepared from the fully hydrated lactose is attributed to the increased intraparticular porosity of the excipient and the weakened interparticular union within its tablets. The importance of the latter effect was manifest in the disintegration times determined for the diazepam-containing tablets: tablets of the fully hydrated lactose disintegrated considerably faster than those of the anhydrous or partially hydrated lactose; indeed, these tablets were the only ones that truly disintegrated (i.e., crumbled) in the course of this test.

In summary, full hydration induced significant changes in the properties (most notably the porous structure) of the roller-dried β-lactose for direct compression evaluated, while partial hydration had little effect. Likewise, full hydration decreased the disintegration times of tablets of this excipient and increased the rate of dissolution of an active principle (diazepam) added to them.

Table 3
Mean ($\pm$ standard deviation) values of the indicated properties of tablets of the three excipients with 4% (w/w) diazepam; which wereprepared using a compression force of 12 kN and compression rate of 8 tablets/min

Excipient	Dissolution efficiency (0–20 min) (%)	Disintegration time (s)
A	63.55 (2.30)	363 (10)
B	64.86 (1.80)	383 (11)
C	77.18 (1.68)	69 (4)

Work aimed at confirming the origins of some of these effects by comparing the properties of the fully hydrated lactose with those of spray-dried α-lactose monohydrate for direct compression is under way.

Acknowledgements

This work was supported by grant SAF 91-0630 CICYT, Ministerio de Educación y Ciencia, Spain. We are thankful to Quimidroga and Laboratories Roche for providing us with lactose and diazepam samples, respectively.

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