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Comparison of a spray-dried α-lactose monohydrate with a fully hydrated roller-dried β-lactose

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Abstract

We compared the properties of two lactoses chiefly composed of α-lactose monohydrate: one was a spray-dried α-lactose (DCL-11), the other a roller-dried β-lactose that had been fully hydrated and then sieved and reconstituted (DCL-21(H)) so that its particle size was similar to that of the first. As regards their structural properties, the lactoses were similar; however, their particles differed in that those of DCL-21(H) had greater specific surface and intraparticular porosity, and those of DCL-11 had higher sphericity, which afforded this lactose flow properties very much superior to those of DCL-21(H). As regards the compressed lactoses, the above-mentioned differences in the porosity and specific surface, together with their lower mechanical resistance, caused DCL-21(H) tablets to disintegrate very much faster than DCL-11 tablets. Incorporation of a small dose (4% w/w) of diazepam in tablets of DCL-11 caused both their tensile strengths and disintegration times to decrease to values close to those of DCL-21(H) tablets, which were not significantly altered by incorporation of diazepam. Finally, due to the greater specific surface of the DCL-21(H) tablets, the rate of dissolution of diazepam from them was significantly faster than from the DCL-11 tablets.

Keywords: Lactose monohydrate; β-Lactose hydration; Direct compression; Flow properties; Compaction properties; Microstructure; Tablets

1. Introduction

In a recent paper (Cal et al., in press), we described the effects of partial and full hydration on the properties of a roller-dried β-lactose for direct compression. The major changes noted were that full hydration considerably increased the intraparticular porous volume and specific surface of the excipient, and drastically decreased the disintegration times of derived tablets, with corresponding increases in the rates of dissolution of an incorporated active principle (4% w/w diazepam). Also, as had previously been reported (Angberg et al., 1991; Shukla and Price, 1991), it was observed that hydration of β-lactose causes

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its progressive transformation into α-lactose monohydrate. Given the latter, in this work we undertook a comparison of the properties of a fully hydrated roller-dried β-lactose and a spray-dried α-lactose monohydrate, with a view to establishing the origins and importance of some of the above-mentioned hydration effects.

The excipients to be compared both chiefly comprise α-lactose; however, owing to the different processes used in their manufacture, these lactoses will differ a priori as regards particle structure (Lerk, 1993; Vromans, 1987) and due to the presence of a significant proportion (ca. 15%) of amorphous lactose in the spray-dried excipient (Sebhatu et al., 1994). To eliminate further differences that might affect their properties (Riepma et al., 1990; De Boer et al., 1986), the particle size distribution of the roller-dried lactose was modified so that it was similar to that of the spray-dried lactose.

2. Materials and methods

2.1. Materials

Spray-dried α-lactose monohydrate (DCL-11, Batch 10264 from DMV, The Netherlands). This excipient, hereinafter referred to as DCL-11, was used as supplied.

Roller-dried β-lactose (DCL-21, Batch 30113 from DMV, The Netherlands). This excipient was hydrated by exposing it to a water-saturated atmosphere, and the particle size distribution of the hydrated material was modified by separating eleven fractions (using 40, 60, 75, 105, 120, 140, 150, 200, 250 and 355 μm sieves) and then recombining them in the proportions (% w/w) determined for these particle-size fractions of DCL-11. The mean sieving diameter of this lactose, hereinafter referred to as DCL-21(H), and that of DCL-11 were thus both around 130 μm.

Diazepam (Batch 9402000292 from Roche Laboratories, Switzerland).

Magnesium stearate BP (Batch 548 from C. Barcia, Spain).

Table 1
Mean values (standard deviation) of several properties of the two uncompressed lactoses

Property	Excipient	
	DCL-11	DCL-21(H)
Hydration water (%)	5.05 (0.06)	4.95 (0.10)
Adsorbed water (%)	0.18 (0.05)	0.08 (0.01)
α-lactose content (%)	89.71 (1.01)	97.41 (0.51)
β-lactose content (%)	10.29 (1.01)	2.59 (0.51)
Dehydration enthalpy (-J/g)	162.15 (13.39)	190.33 (3.26)
True density (g/cm^3)	1.548 (6.8 × 10^{-3})	1.541 (2.6 × 10^{-3})
Total porosity (%)	47.98 (0.84)	58.56 (1.09)
Specific surface (m^2/g)	0.4628 (0.068)	1.1952 (0.112)
Flow factor (FF)	34.90	6.65
Mean yield pressure (MPa)	116.84(2.51)	133.68(2.68)

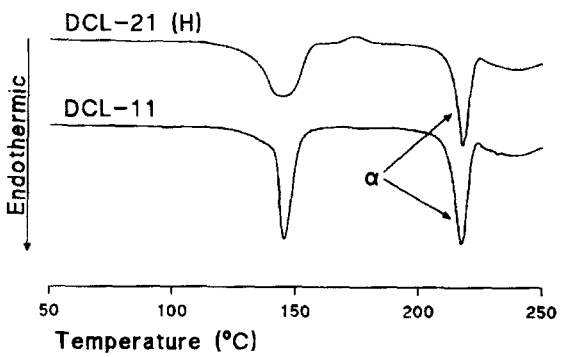


Fig. 1. DSC thermograms of the two lactoses studied; the peaks due to fusion of α-lactose are indicated.

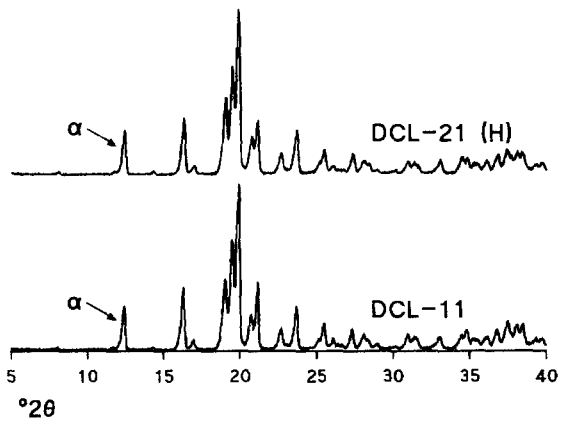


Fig. 2. X-Ray diffractograms of the two lactoses studied; the peaks due to α-lactose are indicated.

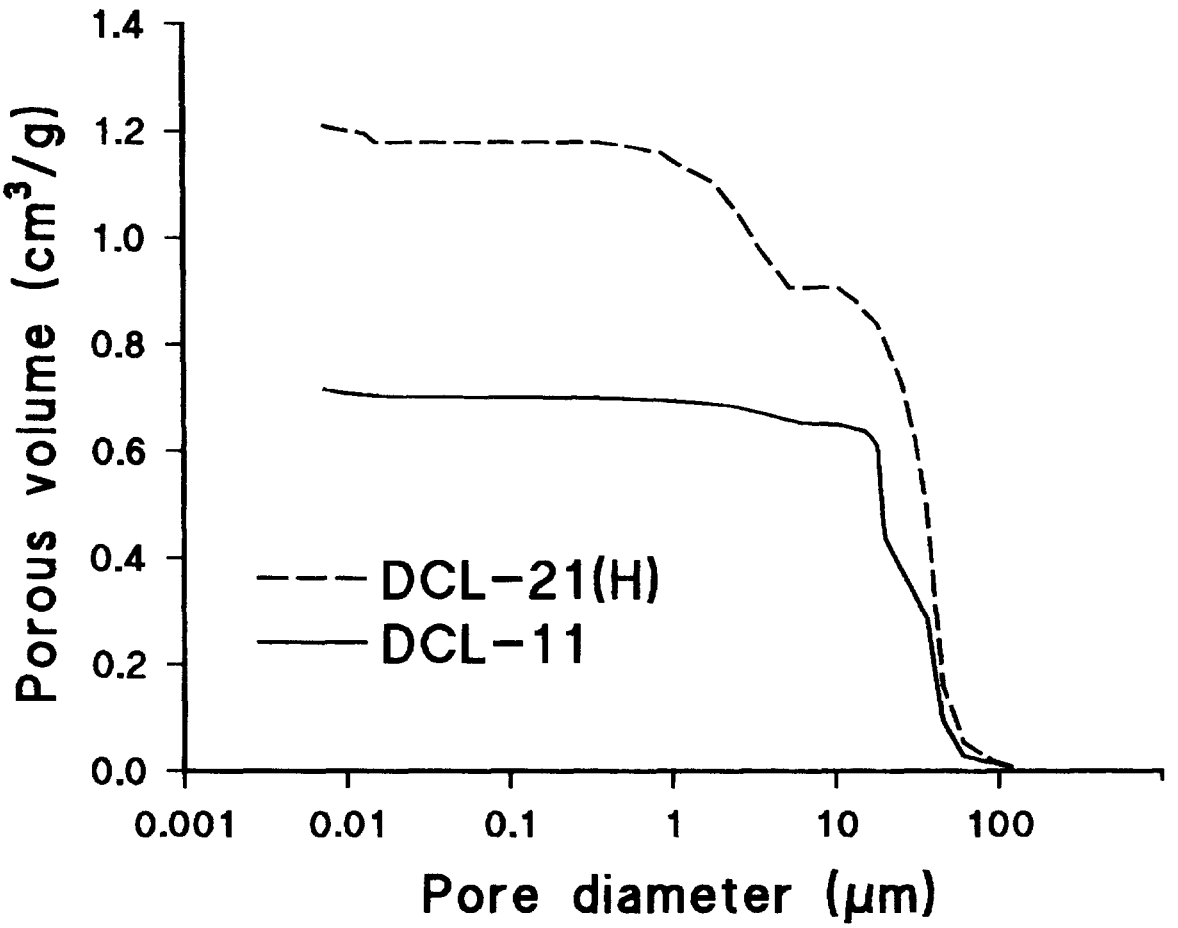


Fig. 3. Pore volume distributions for the two lactoses studied, determined by mercury intrusion porosimetry.

2.2. Methods

The procedures used to characterize the excipients, the methods and conditions used for elaboration and evaluation of tablets of each excipient and of each excipient with 4% (w/w) diazepam, and the statistical methods used to analyse the results, have all been described in a previous paper (Cal et al., in press).

3. Results and discussion

The results of analysis of the two uncompressed lactoses are listed in Table 1, and the DSC thermograms and X-ray diffractograms from which the hydration data were evaluated are shown in Figs. 1 and 2, respectively. As regards structural properties and, bearing in mind the higher content in α-lactose of DCL-21(H), dehydration enthalpies, the two excipients are very similar. Notwithstanding, their specific surfaces differ considerably, doubtless because of the greater porous volume of DCL-21(H) (Figs. 3 and 4). The greater intraparticular porosity of DCL-21(H), which is a direct consequence of full hydration (Cal et al., in press), was reflected in the electron photomicrographs of the substrates (Fig. 5), which also show

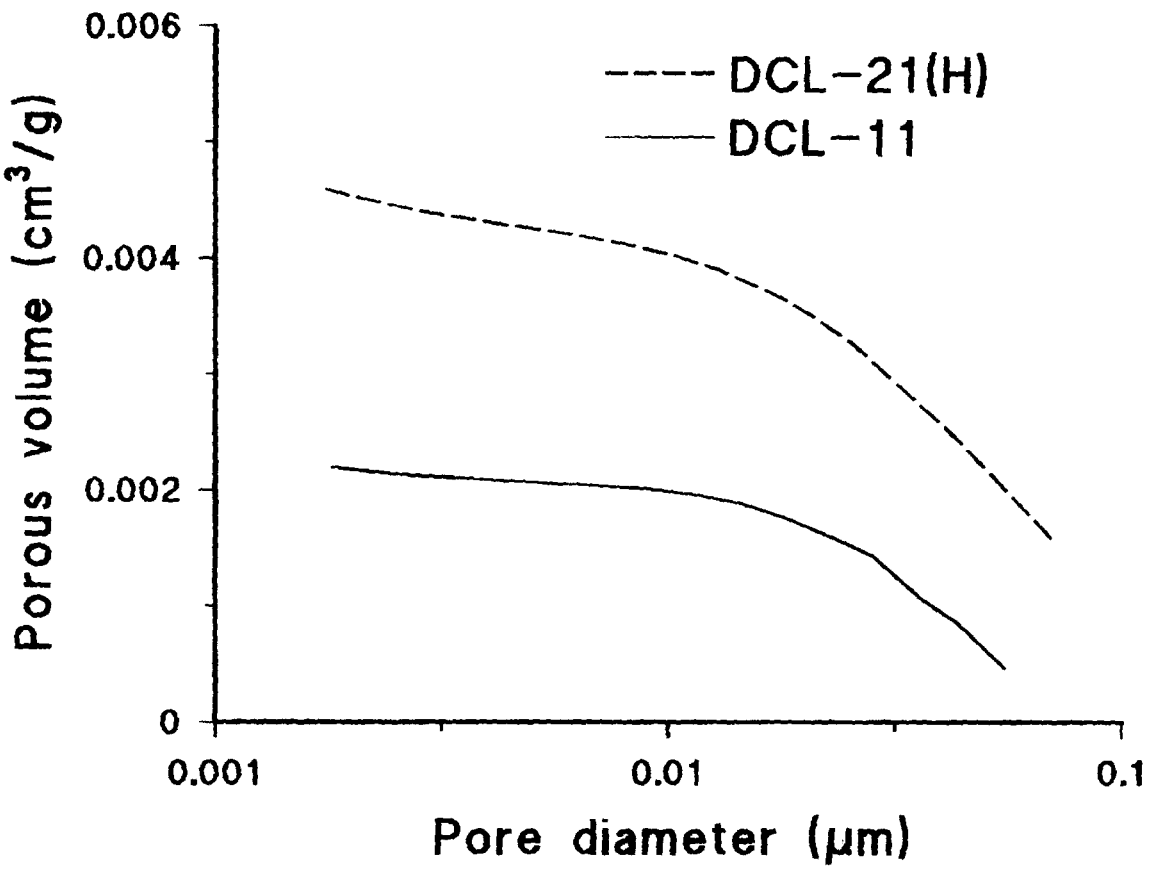


Fig. 4. Pore volume distributions for the two lactoses studied, determined by nitrogen adsorption.

that DCL-11 particles have higher sphericity than those of DCL-21(H).

As regards the rheological properties of the two lactoses (Table 1), DCL-11 had a much higher flow factor than DCL-21(H), which was attributed to the higher sphericity of the DCL-11 particles. The slightly lower mean yield pressure recorded for DCL-11 was doubtless due to the presence of amorphous lactose, which would impart plasticity to the excipient (Vromans et al., 1986).

The above-noted differences in the intraparticular porosities and rheological properties of the uncompressed excipients were clearly reflected in the properties of derived tablets. For each lactose, Fig. 6 shows the response surface describing the variation of the mean tensile strength (TS) of tablets with the compression force (F) and velocity (V) used to prepare them; Fig. 7 shows the corresponding response surfaces for the disintegration time (DT) of those tablets. For the entire range of compression conditions used, tablets of DCL-11 had superior mechanical resistance and considerably longer disintegration times. Since both excipients are chiefly composed of α-lactose, the rapid disintegration of the DCL-21(H) tablets is almost certainly due to their lower tensile strengths and, in particular, to the greater microporous volume and specific surface of DCL-21(H) particles (Cal et al., in press). To establish the extent to which the latter differences in the uncompressed excipients were affecting the mi-

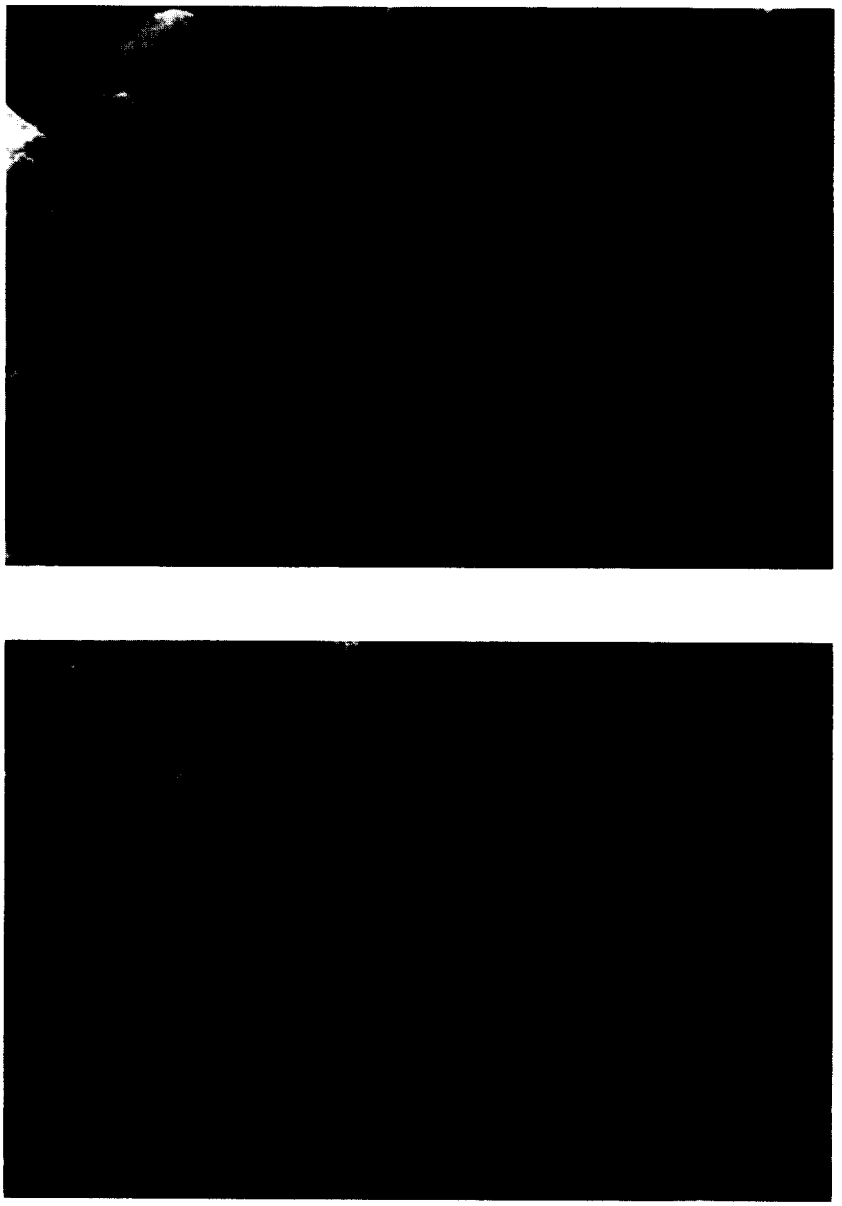
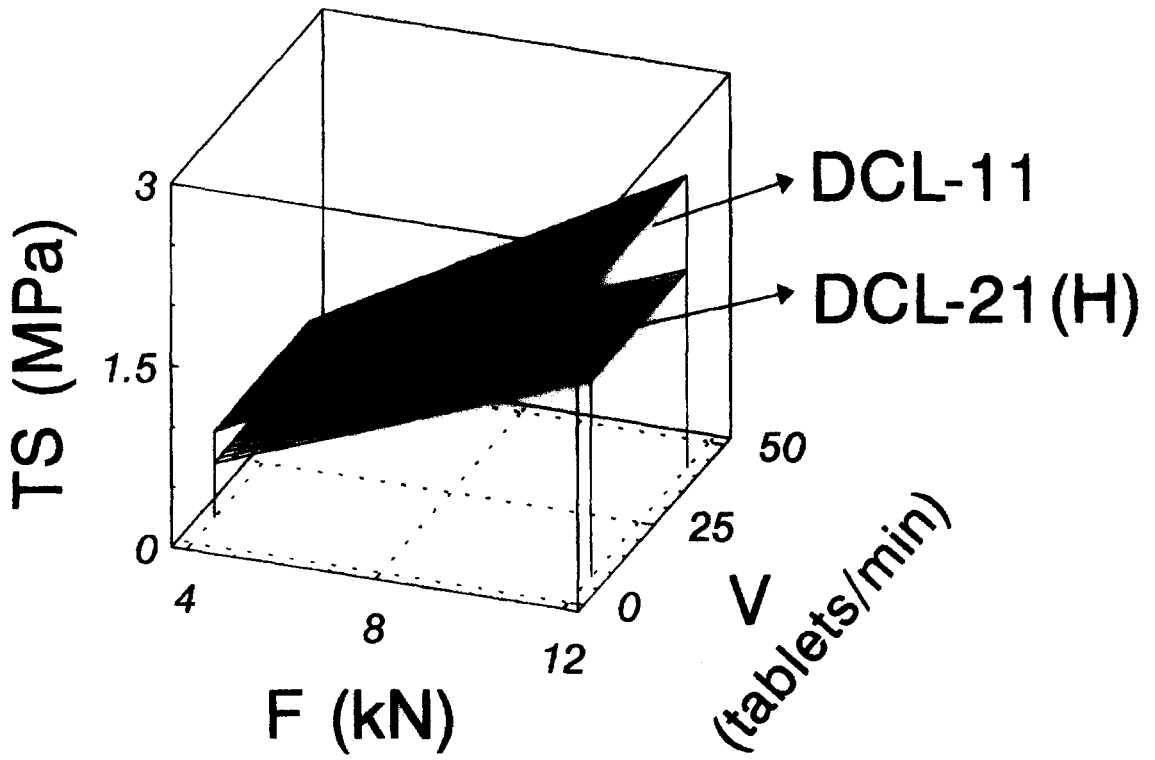


Fig. 5. Scanning electron photomicrographs (175 ×) of the two lactoses studied.

crostructure of derived tablets, the specific surface of selected tablets were determined by nitrogen adsorption (Table 2). The results clearly show that, like bulk DCL-21(H), tablets of DCL-21(H) have greater specific surface than those of DCL-11 prepared using the same compression conditions. Finally, it is noteworthy that only the DCL-21(H) tablets underwent crumbling during disintegration, while the DCL-11 tablets disintegrated fundamentally by dissolution of the disaccharide.

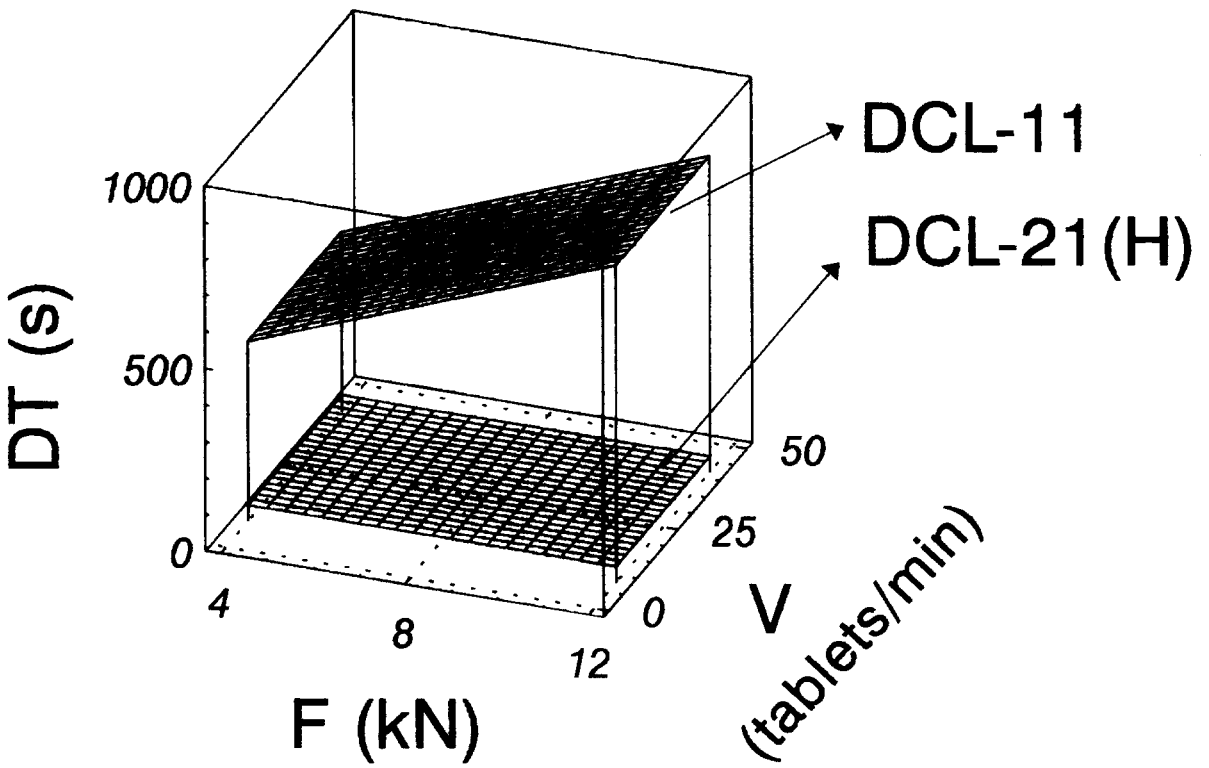
The effects of incorporating a small dose (4% w/w) of the anxiolytic diazepam into tablets pre-



$$TS\ (MPa) = -0.13 + 0.15\,F + 6.5*10^{-2}\,L\,F$$
$$(r = 0.9235;\ p>0.99)$$

Fig. 6. Response surface showing the variation of the tensile strength (TS) of tablets of the two lactoses studied (L = 1 for DCL-11 and L = 0 for DCL-21(H)) with the compression force (F) and rate (V) used to prepare them.

pared using a 12 kN compression force and a compression rate of 8 tablets/min were also determined. Fig. 8 compares the tensile strengths of diazepam-containing tablets with those of tablets of each excipient prepared using the same compression conditions. Only for DCL-11 tablets did incorporation of diazepam reduce the tensile strength by a quantitatively and statistically significant amount. This reduction can be attributed to weakening of interparticular union between excipient particles due to interposition of diazepam particles. Note that a similar but smaller effect has been observed previously for tablets of diazepam with fully hydrated roller-dried β-lactose that had not been subjected to sieving (Cal et al., in press), suggesting that the contrary result obtained here for DCL-21(H) is due to its smaller mean particle size compared to the unsieved excipient. In fact, the mean tensile strengths of tablets of DCL-21(H) with or without diazepam (Fig. 8) are very similar to the value of 1.5 MPa obtained in Cal et al. (in press) for tablets of the



$$DT\ (s) = 43.83 + 259.56\ L + 46.86\ L\ F$$

$$(r = 0.9923;\ p > 0.99)$$

Fig. 7. Response surface showing the variation of the disintegration time (DT) of tablets of the two lactoses studied (L = 1 for DCL-11 and L = 0 for DCL-21(H)) with the compression force (F) and rate (V) used to prepare them.

unsieved fully hydrated excipient with diazepam. It can therefore be inferred that the weakening of interparticular union due to interposition of diazepam (to which the reduction in tensile strength is attributable) does not occur in tablets of DCL-21(H) with diazepam.

Fig. 9 compares the disintegration times for tablets with and without diazepam that were prepared using the same compression conditions (12 kN and 8 tablets/min). These results clearly show the extent to which tablet disintegration time is influenced by tensile strength and by specific surface. Specifically, weakening of interparticular union induced disintegration by crumbling of tablets of DCL-11 with diazepam, and thus considerably shortened their disintegration times compared to tablets of DCL-11 alone. In contrast, tablets of DCL-21(H) with and without diazepam had similar disintegration times which, owing to the greater surface area of these tablets (Table 2), were very much shorter than those for the corresponding DCL-11 tablets. Finally, these surface area effects and the different effects of the diazepam on the tablet disintegration times were

Table 2
Mean values (standard deviation) of the specific surface area of tablets of the two lactoses prepared using the indicated compression forces (kN) and rates (tablets/min)

Excipient	Compact (compression force/velocity)	Specific surface (m^2/g)
DCL-11	4/8	1.0786 (0.021)
	12/8	1.4664 (0.087)
	4/42	1.3494 (0.308)
	12/42	1.5172 (0.156)
DCL-21(H)	4/8	2.0139 (0.109)
	12/8	2.1626 (0.220)
	4/42	1.9367 (0.124)
	12/42	2.1528 (0.089)

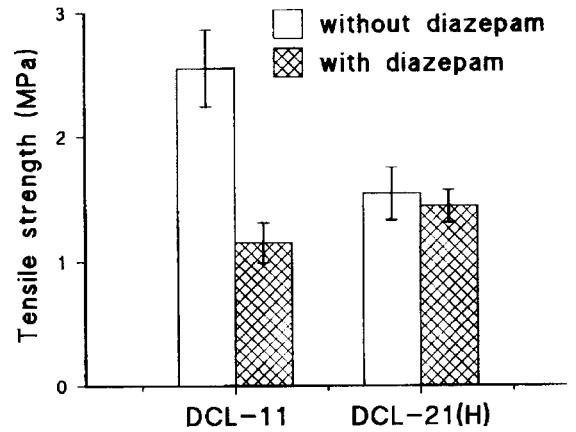


Fig. 8. Comparison of the tensile strengths of tablets of the two lactoses studied with those of tablets containing 4% (w/w) diazepam that were prepared using the same compression conditions.

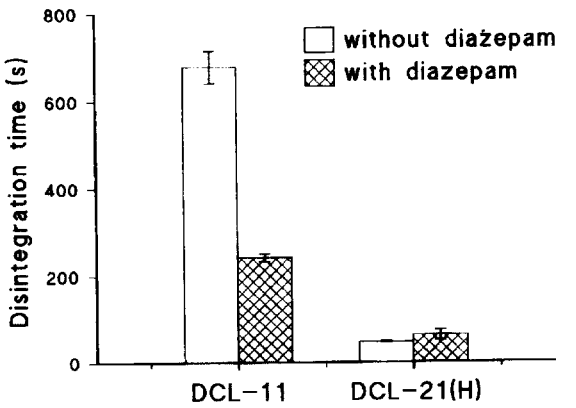


Fig. 9. Comparison of the disintegration times of tablets of the two lactoses studied with those of tablets containing 4% (w/w) diazepam that were prepared using the same compression conditions.

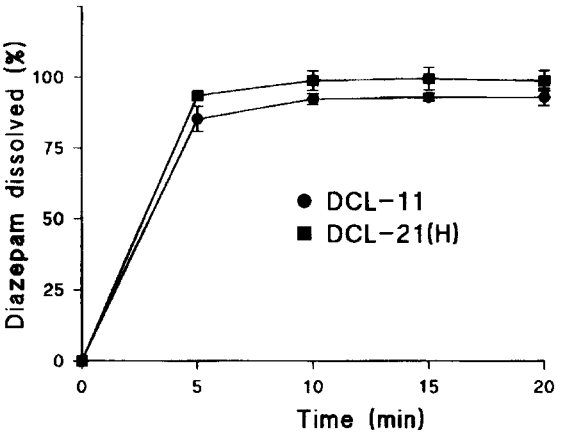


Fig. 10. Dissolution profiles for diazepam in tablets of the two lactoses studied.

Table 3
Mean values (standard deviation) of the indicated parameters of tablets of the two lactoses with 4% (w/w) diazepam, wich were prepared using a compression force of 12 kN and compression rate of 8 tablets/min

Excipient	Dissolution efficiency (0–20 min) (%)	Disintegration time (s)
DCL-11	79.17 (1.67)	242 (9)
DCL-21(H)	85.22 (2.31)	62 (12)

reflected in its dissolution rate (Fig. 10), with the result that there were significant differences between the 0–20 min dissolution efficiencies for the two diazepam formulations (Table 3).

In summary, the marked sphericity of particles of spray-dried α-lactose monohydrate (DCL-11) afford it flow properties far superior to fully hydrated roller-dried β-lactose (DCL-21(H)). By contrast, because of the greater intraparticular porosity and specific surface of DCL-21(H) particles, and the lower mechanical resistance of DCL-21(H) tablets, these disintegrate very much faster than DCL-11 tablets. However, when a small dose of an active principle (4% w/w diazepam) was incorporated in tablets of each excipient, the differences in their tensile strengths were practically eliminated, and their disintegration and dissolution parameters approached one another, although there were still significant differences between the corresponding values for each formulation.

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