Studies on tableting properties of lactose

Part 2. Consolidation and compaction of different types of crystalline lactose

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Introduction

Many different attempts have been reported to explain the difference in tableting behaviour of the various types of excipients used for direct compression of tablets. The consolidation of powdered material is frequently described in a mathematical way. The most generally used principle is to derive quantitative data from curves relating volume reduction to applied compaction load. Though numerous equations have been proposed,[1] only a few are generally used.

With the aid of the Heckel equation[2,3] several authors have studied different direct compression excipients. With this it appeared possible to differentiate between consolidation by brittle fracture and consolidation by plastic deformation.[4,5] This has been confirmed by others.[6,7] There is considerable evidence,[8,9] however, that the type of Heckel plots obtained for many materials will vary depending on the experimental compaction technique used. Furthermore, different particle size fractions of the same material may exhibit changes in the predominant compaction mechanism.[8,10,11]

Another approach to study the process of powder consolidation is to observe the compactability of the material by means of hardness determinations. In this way equations were obtained relating the deformation hardness of the compact with the applied pressure and relative density,[12] or relating the compact strength with the porosity.[13,14]

Qualitative data of the consolidation process can be acquired by methods which express the fragmentation tendency of the material.

- Brittle fracture can be visualized by means of a scanning electron microscope (SEM). It appeared, however, that the extent of fragmentation is difficult to specify with this method.[7]
- Binding properties of excipients with a high degree of fragmentation are found to be less influenced by mixing with lubricants than materials undergoing mainly plastic deformation. This effect is attributed to the extent to which clean lubricant free surfaces are formed during compression.[6,7]
- Changes of the specific surface area of tablets compacted at different loads have been measured by gas adsorption[7,15,16] and by permeametry.[17-20] The latter method proved to be a fairly good indication of the fragmentation propensity of the material under study.
- Particle size analysis after disintegration of compacts demonstrated that the initial particle size distribution had changed during compression.[21-23]

The tableting characteristics of materials with similar chemical compositions can vary widely. Visualization of tablet filler-binders by means of SEM illustrated that chemically equivalent materials from alternate sources often showed large differences in particle structure, which was manifested in different tableting properties.[24]

Lactose is one of the most widely used excipients in direct compression tableting. It is available in hydrous and anhydrous crystalline forms, which both occur in aggregated form or as separate crystals. Spray-dried lactose consists of aggregates of α-lactose monohydrate crystals bonded together by amorphous 'glass'.

Several studies have been reported on the consoli-

Vromans H, De Boer AH, Bolhuis GK, Lerk CF, Kussendrager KD, Bosch H. Studies on tableting properties of lactose. Part 2. Consolidation and compaction of different types of crystalline lactose. Pharm Weekbl [Sci] 1985;7:186-93.

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Abstract

Lactose is available in several crystalline forms, which differ in binding properties. A new method of estimating the fragmentation propensity was applied to investigate the consolidation and compaction behaviour of this excipient for direct compression. Mercury porosimetry was used to demonstrate that crystalline lactose fragments during compaction. Tablet strength was found to be dependent on the degree of fragmentation only. This finding indicates that the nature of the actual binding must be the same for the different types of crystalline lactose.

dation of α-lactose monohydrate and of spray-dried lactose. Examination by means of the Heckel equation indicates that these materials consolidate mainly by brittle fracture.[5 10 11 25-27] Recent work, however, showed for both anhydrous and hydrous α-lactose strongly increasing tablet strength with decreasing particle size of the starting material.[28] The result indicates that fragmentation obviously is not intensive enough to level large differences in initial particle size.

A totally different approach to studying lactose tableting is to characterize the starting material instead of examining the consolidation process during compaction. Solid density measurements[29] as well as the X-ray diffraction patterns[30 31] have been used to determine the degree of crystallinity of the substance. It has been suggested that a decrease in crystallinity of the lactose would cause an increase in tablet strength.[29]

Mercury porosimetry showed tablets of anhydrous α-lactose to exhibit a large number of small pores. From this it has been concluded that the tremendous increase in tablet strength is caused by increased fragmentation.[32]

The purpose of the present work has been to investigate the role of fragmentation on the consolidation and compaction of crystalline lactose. The results of a study on amorphous lactose will be presented in a forthcoming paper.

Methods

PRODUCTION AND CHARACTERIZATION OF LACTOSE

All lactose samples were supplied by DMV (Veghel, The Netherlands). Crystalline α-lactose monohydrate was produced by crystallization from a supersaturated solution at temperatures below 93°C, whereas crystalline β-lactose was obtained by crystallization at temperatures above 93°C. Anhydrous α-lactose was manufactured by thermal dehydration of α-lactose monohydrate. Roller-dried anhydrous β-lactose was used in the commercially available form (DCLactose® 21). In all cases sieve fractions of 100-125 μm were used. The α/β ratio of the samples was determined by gas liquid chromatography (GLC). Before injection the lactose was transformed into the corresponding trimethylsilyl derivative to make it sufficiently volatile.[33 34] The α-lactose content of the different types of crystalline lactose used in this study is given in Table I.

The other excipients used were microcrystalline cellulose NF (Avicel® PH 101, FMC Europe SA, Brussels, Belgium) and dicalcium phosphate dihydrate NF (Emcompress®, Edward Mendell, New York, USA).

Electron micrographs were made using a scanning electron microscope (Jeol JSM-U3, Jeol Ltd., Tokyo, Japan). Prior to investigation, the samples were coated with gold, using a direct current sputter technique.

COMPACTION AND CHARACTERIZATION OF TABLETS

Compaction of tablets was carried out using a hydraulic press (Mooi/Peekel, Appingedam, The Netherlands). A weighed quantity of 500 mg was compressed at 55% relative humidity in a prelubricated die, with flat-faced punches, having a diameter of 13 mm, at a compression speed of 2000 N/s. The crushing strength of the tablets was measured 15 min after compaction with a Schleuniger 2E instrument (Dr. Schleuninger Productronic AG, Solothurn, Switzerland).

TABLE I

α-Lactose content of the four types of crystalline lactose used in this study

Crystalline α-lactose monohydrate	95%
Crystalline β-lactose	3%
Roller-dried β-lactose	17%
Anhydrous α-lactose	80%

Tablet dimensions were determined using an electronic micrometer (Mitutoyo MFE Co., Ltd., Tokyo, Japan) with an accuracy of 0.001 mm. The calculated porosity of the tablet was derived from data of its weight, volume and from the solid density of the material, being 1.54 g/cm^3 for both α-lactose monohydrate and anhydrous α-lactose. Within 48 h after compaction the samples were subjected to mercury porosimetry measurements, which were carried out with the aid of a Carlo Erba Porosimeter series 200 (Carlo Erba Strumentazione SpA, Milano, Italy). The tablets were evacuated at about 10 Pa prior to the measurements for at least half an hour.

Results and discussion

Figure 1 illustrates the increase in crushing strength with compaction load of both hydrous and anhydrous α-lactose. The depicted results express the strongly increased binding capacity of anhydrous

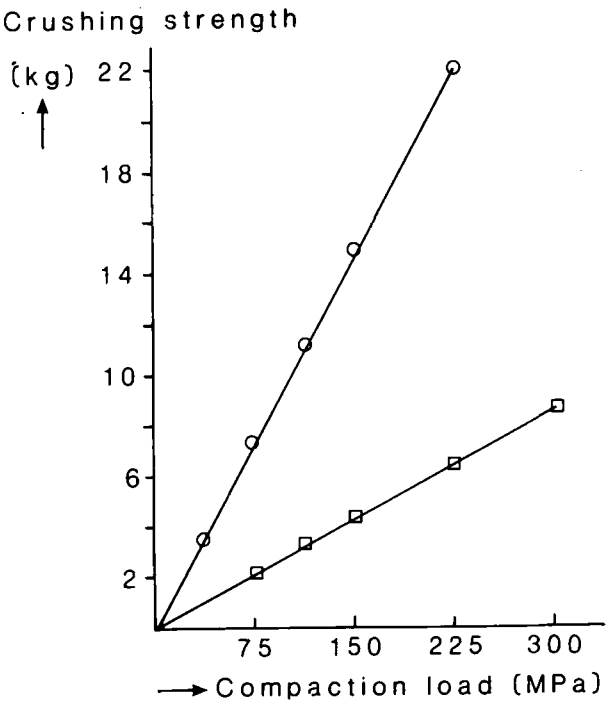

FIGURE 1

Crushing strength versus applied compaction load for tablets of α-lactose monohydrate (□) and anhydrous α-lactose (○), respectively

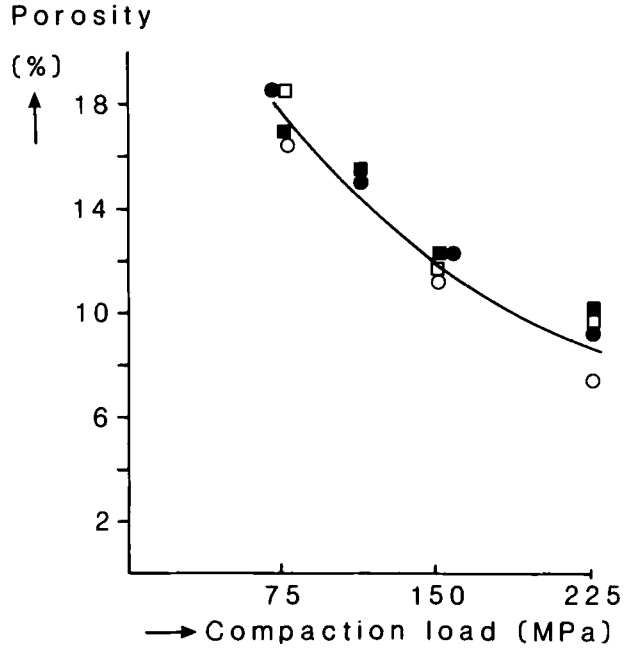

FIGURE 2
Porosity versus compaction load for tablets of α-lactose monohydrate (□,■) and anhydrous α-lactose (○,●), respectively. The porosity data were obtained by calculation (○,□) and mercury porosimetry measurements (●,■), respectively

α-lactose. In spite of the great difference in tablet strength between the two types of α-lactose, the compacts exhibited almost equal overall porosities at the same compaction load (Fig. 2). The porosity data were calculated from the tablet dimensions, using a solid density of 1.54 g/cm^3. For both materials this value was chosen as an average of the values reported in literature.[35,36] This is supported by the observation that no significant differences in solid density between α-lactose monohydrate and anhydrous α-lactose could be detected.[35,36] Morphologic studies showed, however, great differences in texture between both types of lactose.[37] Visualization by means of scanning electron microscopy showed a change from rather smooth crystals of α-lactose monohydrate on thermal or chemical dehydration into microporous aggregates of anhydrous α-lactose. The tremendous increase in binding capacity with increasing dehydration was suggested to be caused by a strongly increased fragmentation propensity.[32] As no quantitative data on extent of fragmentation are available, however, it is quite possible that other factors can play a role in determining the tablet strength, like the presence of water of crystallization or the α/β-ratio in the particles.

Different methods have been applied to estimate the degree of fragmentation during compaction. It is not likely that Heckel plots will discriminate between consolidation of α-lactose monohydrate and anhydrous α-lactose. Since tablets of both types of lactose showed equal porosities at the same compaction load, the equal solid densities of the materials will result in equal relative densities of the compacts, *i.e.* the Heckel plots for both α-lactose monohydrate and anhydrous α-lactose will coincide. For the same reason other mathematical approaches probably will not give much more information either.

It is apparent, that a difference in consolidation and compaction behaviour is also expressed by a difference in susceptibility of the binding properties of powder mass to the presence of and the mixing

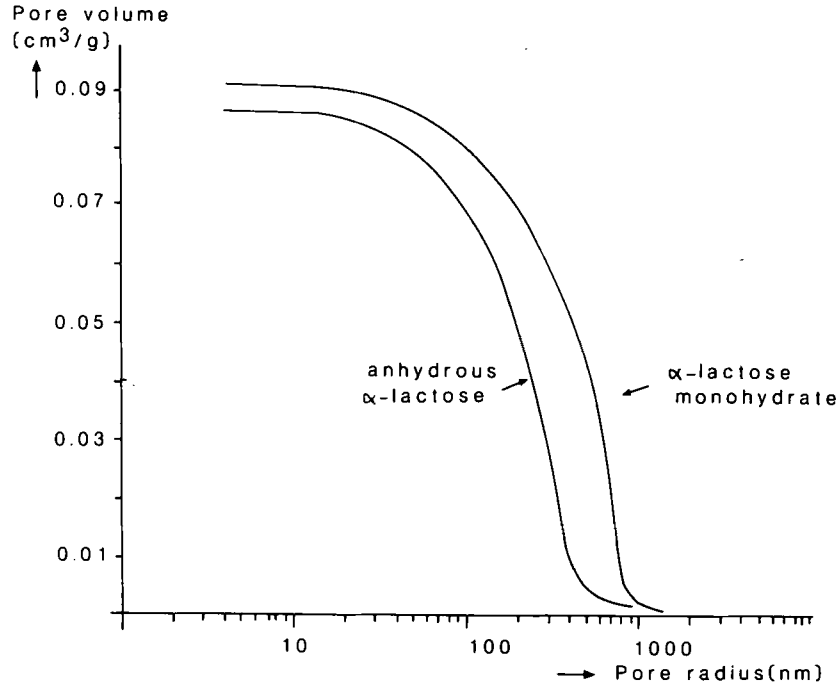

FIGURE 3
Cumulative pore volume of α-lactose monohydrate and anhydrous α-lactose compacts, compressed at 151 MPa, as measured by mercury porosimetry

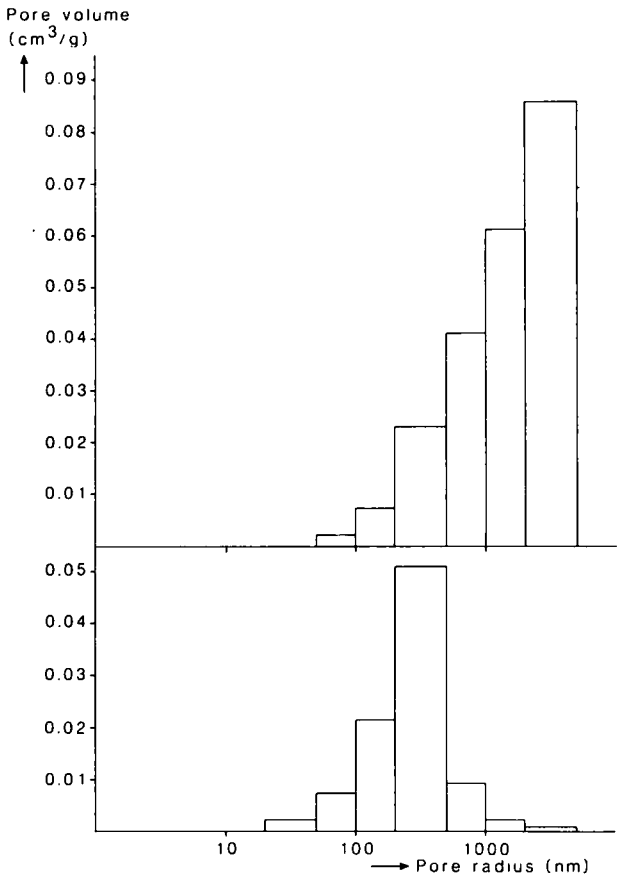

FIGURE 4
Comparison of pore volumes at different pore sizes of tablets compressed from roller-dried β-lactose at a compaction load of 37.8 (upper part) and 151 MPa (lower part), respectively

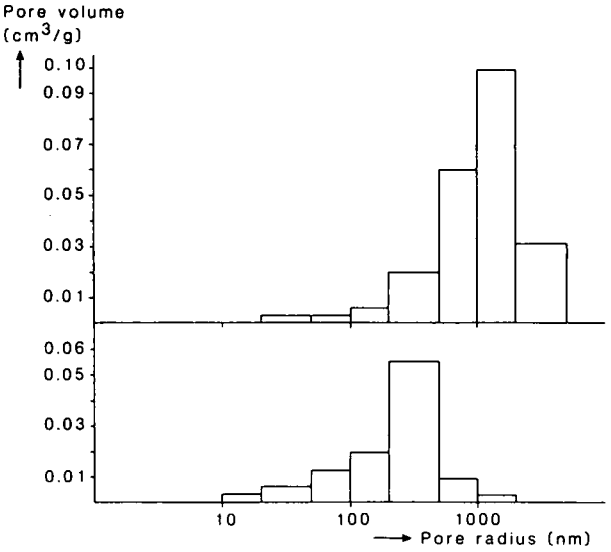

FIGURE 6
Comparison of pore volumes at different pore sizes of tablets compressed from dicalcium phosphate dihydrate at a compaction load of 37.8 (upper part) and 302 MPa (lower part), respectively

with a film-forming lubricant, like magnesium stearate. For tablets compressed without magnesium stearate the binding properties of anhydrous α-lactose were found to be somewhat higher than those of roller-dried β-lactose.[38] This may possibly be caused by a more intensive fragmentation of the first. It was shown, however, that the tablet hardness values were levelled on mixing with 0.5% magnesium stearate. This relatively low sensitivity of roller-dried β-lactose was explained to be caused by the rougher texture of this product.

The application of mercury porosimetry on tablets of α-lactose monohydrate and anhydrous α-lactose, respectively, showed completely different pore size distributions for the two tablets (Fig. 3), as reported earlier.[32] The pore size distribution is also dependent on the compaction load, as illustrated for roller-dried β-lactose in Figure 4.

These results do not support the theory of Bockstiegel,[39,40] which states that at increasing compaction load, the pores of a compact disappear strictly in order of size, starting with the largest pores. Meanwhile, the remaining voids will show no change in number. Thus the change in porosity of a compact is related to the disappearance of the largest pores. As

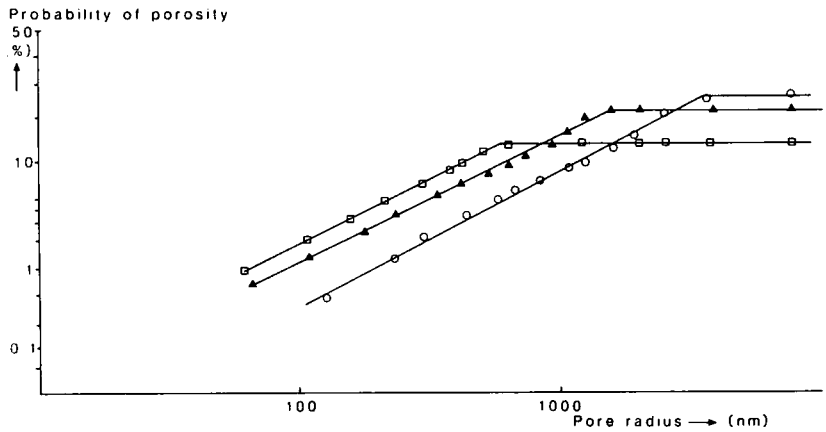

FIGURE 5
Cumulative porosities of compacts of roller-dried β-lactose compressed at 37.8 (○), 75.5 (▲) and 151 MPa (□), respectively, calculated from mercury porosimetry measurements

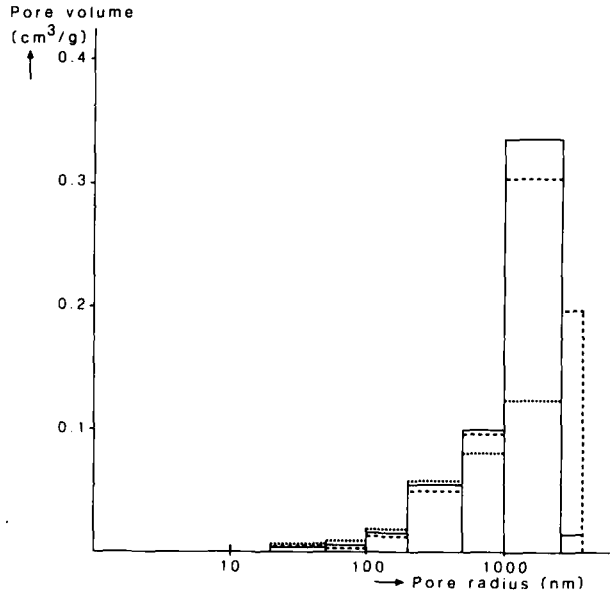

FIGURE 7
Comparison of pore volumes at different sizes of tablets compressed from microcrystalline cellulose at compaction loads of 7.6 (-----), 18.9 (———) and 37.8 MPa (.....), respectively

seen from Figure 5 a totally different kind of consolidation behaviour was found for roller-dried β-lactose compaction. Considering the consolidation mechanism of lactose, this can easily be understood. As lactose fragments during compaction, this will result in an increase in the number of small particles and consequently a new pore size distribution will arise. On the other hand, when compressing a material which only deforms plastically under compaction, no new pores will be created and in this situation the change in pore distribution might follow the theory of Bockstiegel.

To confirm this assumption, two (model) excipients with well-known properties were chosen. Dicalcium phosphate dihydrate (DCP, Emcompress®) is known to fragment intensively under

TABLE II
Some data of tablets compressed from microcrystalline cellulose and dicalcium phosphate dihydrate. Values for pore volume and specific surface area were obtained by mercury porosimetry

Compaction load (MPa)	Pore volume (cm^3/g)	Crushing strength (kg)	Specific surface area (m^2/g)
Microcrystalline cellulose			
7.6	0.663	4.7	1.21
18.9	0.529	13.4	1.37
37.8	0.290	~ 26	1.31
Dicalcium phosphate dihydrate			
37.8	0.221	1.1	0.66
75.8	0.168	2.2	0.88
151	0.135	4.3	1.10
226	0.116	6.2	1.26
302	0.104	8.5	1.65

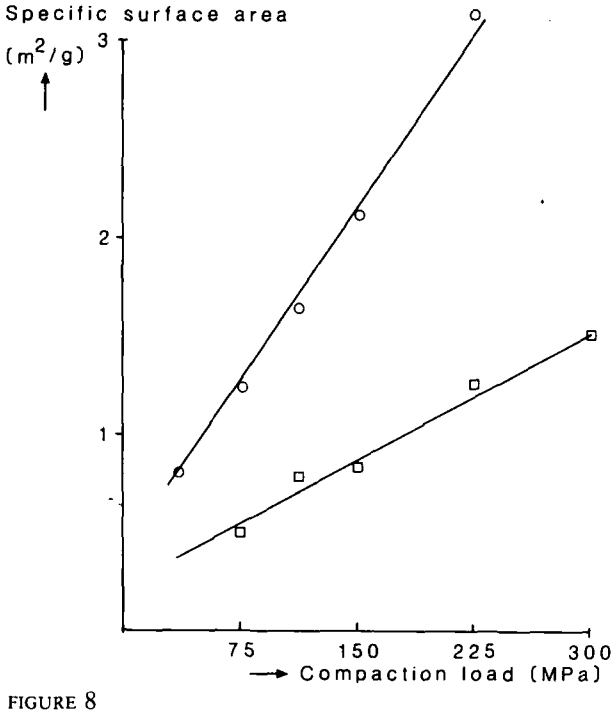

FIGURE 8
Specific surface area, measured by mercury porosimetry, versus compaction load, for tablets of α-lactose monohydrate (□) and anhydrous α-lactose (○)

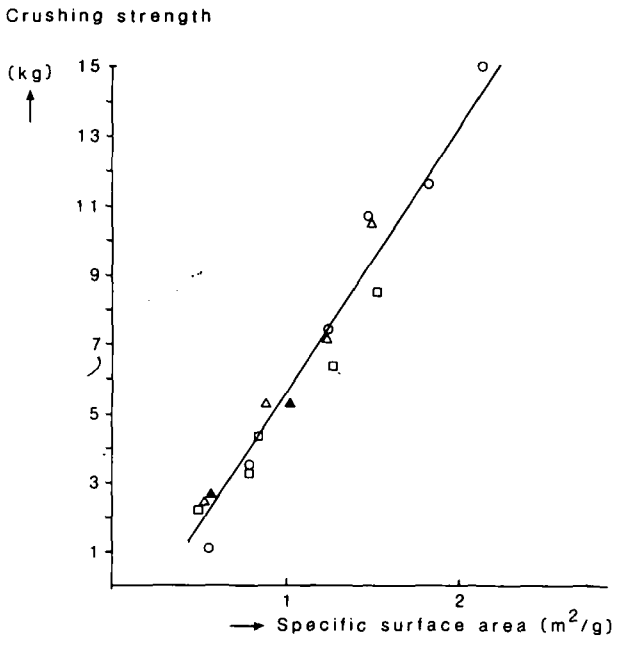

FIGURE 9
Crushing strength versus specific surface area for tablets compressed from different types of crystalline lactose: α-lactose monohydrate (□), anhydrous α-lactose (○), roller-dried β-lactose (△), crystalline β-lactose (▲)

FIGURE 10
Scanning electron micrographs of different types of crystalline lactose. Magnitude 65 ×. Values between brackets represent the crushing strength of tablets compressed from these materials at a compaction load of 151 MPa. Top left: α-lactose monohydrate (4.3 kg); top right: texture of a particle of α-lactose monohydrate (2000 ×); middle left: anhydrous α-lactose (15.0 kg); middle right: texture of a particle of anhydrous α-lactose (2000 ×); bottom left: roller-dried β-lactose (10.6 kg); bottom right: crystalline β-lactose (5.1 kg)

compression,[6 7] whereas the plastic deformation of microcrystalline cellulose (MCC, Avicel®) is also well documented.[25 41] As expected, there was found an increase in the number of small pores when compressing DCP (Fig. 6), proving the brittle nature of this material. MCC showed, on the contrary, no important alteration in the quantity of small pores of the tablets at different compaction loads (Fig. 7). As a matter of fact this agrees well with the findings of Bockstiegel, for the material used by him was described to have deformation characteristics. On the other hand, the results as obtained here do not agree with those presented earlier.[42] In this earlier report, DCP was described as behaving according to the theory of Bockstiegel.

Assuming cylindrical pores, the specific surface area S_m can be calculated by

$$S_m = 4\,\Sigma_i \frac{\Delta V_i}{d_i}$$

where V_i is the volume of pores filled with mercury and d_i is the diameter of a certain pore, which can be roughly estimated by $S = 4\Delta V/\bar{d}_{50}$ where $\bar{d}_{50}$ is the median diameter which means that 50% of the volume is taken by pores smaller than $\bar{d}_{50}$. Figure 3 shows different pore size distributions at the same compaction load for tablets of α-lactose monohydrate and anhydrous α-lactose. For tablets having about the same porosity, a smaller $\bar{d}_{50}$ gives a larger pore surface area. Plotting the specific surface area of tablets, measured by mercury porosimetry, versus compaction load, a linear relationship was found for both α-lactose monohydrate and anhydrous α-lactose (Fig. 8).

In this respect it is most interesting to notice that the two model excipients used, showed totally different relations between the specific surface area of tablets having comparable crushing strength, and the compaction load (Table II). The specific surface area of tablets compressed from DCP increased on increasing compaction load, whereas this was not the case with compression of MCC. Thus the increase in crushing strength is coupled with an increase in specific surface area for the fragmenting material, which is not the case for the plastic deformable substance. This agrees with a study estimating the fragmentation propensity of different tablet additives by means of the measurement of tablet surface area by permeametry.[20] In that study it was found that the slope of the surface area–pressure curves can be used as a measurement of the fragmentation propensity of a material. As a consequence, it can be concluded from Figure 8 that the degree of fragmentation of α-lactose monohydrate must be smaller than that of anhydrous α-lactose.

From Figures 1 and 8 it can be deducted that a higher pore surface area is accompanied by a higher tablet strength. Assuming proportionality between a change in binding surface area with an alteration in pore surface area, the tablet strength is plotted in Figure 9 versus the measured pore surface area for different types of crystalline lactose. Figure 9 shows a linear relationship. Apparently the crushing strength is dependent on the extent of fragmentation during compaction only. Most important is the conclusion that neither the presence of water of crystallization, nor the α/β ratio has any influence on the binding properties of lactose. Moreover, there seems to be a relationship between the manufacturing conditions and the tableting properties: slow crystallization of lactose produces single crystals with plane faces as illustrated in Figure 10. Rapid crystallization by roller-drying or dehydration results in aggregates of microcrystals. These particles undergo, as discussed before, intensive fragmentation under compression.

It may be concluded that the good binding properties of these types of lactose are caused by morphological properties. In literature it has been suggested that the degree of crystallinity of the material would determine the mechanical characteristics of the compacts.[29-31] Furthermore, it has been demonstrated in these studies that the crystallinity of the substance is influenced by the manufacturing conditions. It is most important to recognize from Figure 9, however, that the actual binding mechanism is likely to be the same for all types of crystalline lactose and that this consequently is independent of the degree of crystallinity of the material.

In conclusion, it has been shown by mercury porosimetry, that lactose consolidates mainly by fragmentation. The binding properties are found to be independent of the presence of water of crystallization or of the α/β ratio. The binding mechanism seems to be identical for all types of crystalline lactose used, while the crushing strength of tablets depends apparently on the extent of fragmentation only.

The fragmentation propensity is related to the morphology of the particles under compaction, which in turn is affected by the way of manufacturing the lactose.

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Received March 1985.
Accepted for publication June 1985.