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STUDIES ON TABLETING PROPERTIES OF LACTOSE;
THE EFFECT OF INITIAL PARTICLE SIZE ON BINDING PROPERTIES AND DEHYDRATION CHARACTERISTICS OF α-LACTOSE MONOHYDRATE.

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Summary

Unmilled particle size fractions of α-lactose monohydrate were used to study its dehydration and tableting characteristics. It appeared that the speed of dehydration of the substance was de-pendent on both the powder surface area and the temperature.
The results made it possible to explain changes in thermograms which are observed after milling or compacting the material, by pointing to the surface enlargement due to these mechanical treatments.
Tablet pore surface areas were derived from mercury porosimetry measurements. By plotting tablet strength against tablet pore surface area a linear relationship was obtained for different sieve fractions. This was concluded to point to a similar proportionality between tablet pore surface area and binding surface area for the fractions used. It was observed that only fractions which intensively fragment fitted this line. From this it was suggested that in general the tablet

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strength of compacts of α-lactose monohydrate is mainly determined by fragmentation. For small particles counts however, that other mechanisms of consolidation play a predominant role so that the proportionality between tablet pore surface area and binding surface area gets another value.

Introduction

Lactose exists in a α and β-form and can be either crystalline or amorphous. In the crystalline α-form it occurs both as monohydrate and anhydrate. The crystalline β-form exists as anhydrate only, whereas amorphous lactose can contain varying amounts of water. α-lactose monohydrate can be desiccated to stable and unstable anhydrous α-lactose, respectively. All these types of lactose exhibit different compaction properties. The aim of the studies on tableting properties of lactose is to determine the role of both consolidation and actual binding mechanism on the compactability characteristics of the compound. The work has been started with the crystalline lactoses (1,2,3). In this paper only α-lactose monohydrate is concerned.
Several reports have been published dealing with the effect of particle size on the tensile strength of tablets compressed from different particle size fractions of α-lactose monohydrate (e.g. 4,5,6). Although in one study (7) only a slight effect of initial particle size on tablet hardness was found, most studies indicate that the compact strength generally tends to increase as the particle size decreases. Moreover, the compaction speed has been found (8) to play an important role in determining the effect of the initial particle size on tensile strength, because differences in the mechanical strength of tablets obtained from different sieve fractions levelled out when the compaction speed was increased. This was presumed to be caused by the greater extent of particle fragmentation of the starting material, thus eliminating initial size differences.
Various mechanisms of consolidation have been proposed in order to explain the variations in binding properties. While it has been suggested (6,9) on the one hand that a decrease in particle size would cause an increase in cohesive and frictional forces, resulting in

stronger tablets, it has been presumed on the other hand that tablet strength would be a function to the total bond area (5).

In accordance with the "Activation Theory" (9,10) it has been postulated that the fractions consisting of smaller particles are activated under compression to a greater extent than the fractions consisting of larger particles, which was observed as a decrease in density of the compacted material, indicating an increase in lattice defects.

Activation was also observed when milling the material, reducing the particle size as well as the degree of crystallinity (11), thus improving the binding properties of the substance. The increased rate and extent of removal of water of crystallization during the drying of milled samples of α-lactose monohydrate at a certain temperature was suggested to confirm this activation theory (12).

Another detection of mechanical activation by milling α-lactose monohydrate has been demonstrated by means of differential thermal analyses (13). The effect of mechanical treatment of the material on the thermograms of lactose has already been reported in earlier studies, in which it was recognized, however, that the thermograms are affected by experimental conditions such as heating rate and type of container (14). Grinding of organic hydrates, including α-lactose monohydrate, resulted in a broadening of the dehydration, peak in the thermogram (15), while intensive grinding even resulted in the total disappearance of the peak (16).

The aim of this study was to investigate the role of the particle size of the starting material on the tablet strength of α-lactose monohydrate and to study the dehydration characteristics of α-lactose monohydrate.

Materials and methods

Preparation of sieve fractions.

Unmilled sieve fractions of α-lactose monohydrate were supplied by DMV (Veghel, the Netherlands). Particles over 32 μm were fractionated using an Alpine Air Jet Sieve and the smaller sizes were obtained by sieving with the help of a windsifter (Alpine Multi-Plex Labor Zickzacksichter 100 MZR). No other operations, such as milling, were used to obtain smaller particles.

Compaction and characterization of tablets.

Compaction of tablets was carried out using a hydraulic press (Mooi/Peekel). 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 diametral compression test apparatus (Schleuniger 2E). The data given are the mean of at least eight measurements.

Thermal analysis.

Thermal analysis was performed by means of a DuPont Thermal Analyzer 990 with DSC cell 910. Open aluminium pans were used. The samples, weighing 5 mg each, were flushed with nitrogen during the measurements. Thermogravimetric analysis was carried out with a Linseis Thermobalance (series 2000), using samples of 50 mg.

Mercury porosimetry measurements.

Within 48 h. after compaction the tablets were subjected to mercury porosimetry measurements, which were carried out with the aid of a Carlo Erba Porosimeter series 200. The tablets were evacuated at about 10 Pa prior to the measurements for at least half an hour.

Tablet pore surface areas were derived from the mercury penetration data, using the calculation method as previously described (2).

Results and discussion

Thermal analysis has been shown to be an appropriate method to characterize the different types of lactose (e.g. 17). It has frequently been reported that the shape of the dehydration peak in the thermogram of α-lactose monohydrate was changed after milling or compacting the substance (13-16). From fig. 1 it can be seen that there is a broadening of the dehydration peak when the material is compacted at increasing loads. Similar thermograms were obtained after short milling. It

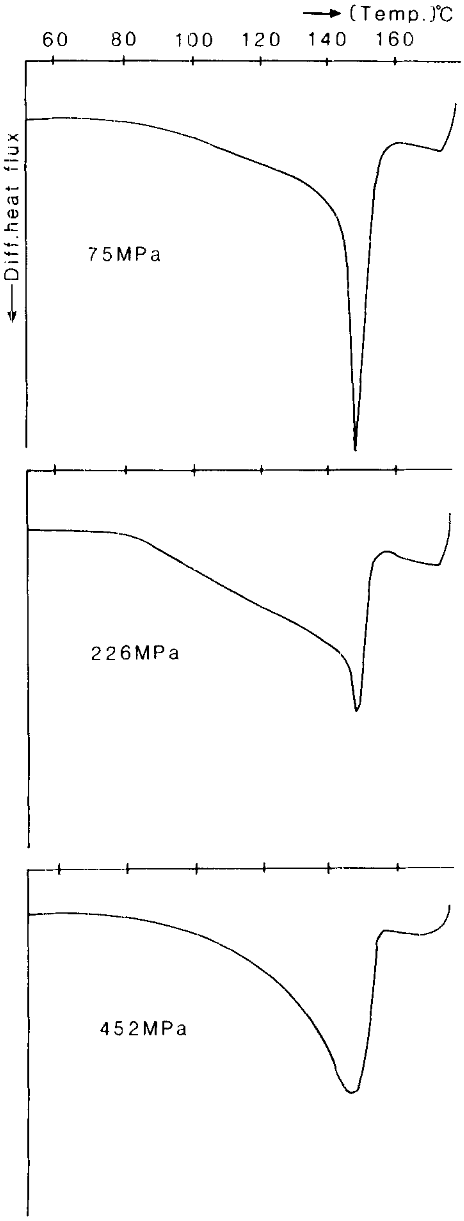

Figure 1
Dehydration peaks of α-lactose monohydrate 100 Mesh, compacted at different compaction loads, as recorded by DSC at a heating rate of 10^0C/min.

has been postulated (13) that after mechanical treatment, there would be a quantity of water bound by a high energy form of lactose. Using unmilled sieve fractions of α-lactose monohydrate, it appeared however, that the shape of the dehydrationpeak changed at decreasing particle size. From fig. 2 it can be deducted that smaller particles lose already considerable amounts of water of crystallization at relative low temperatures. With the aid of a thermobalance the speed of desiccation was examined for the different particle size fractions. Fig. 3 illustrates that dehydration is obviously determined by both temperature and particle size.

At a fixed temperature of 113°C the speed of desiccation was measured for the different particle size fractions (fig. 4). From this figure it can be concluded that dehydration is also a function of the powder surface area. Thus it can be proposed that the observed broadening of the dehydration peak after mechanical treatment might be caused by the creation of smaller particles. For instance, comparing the thermograms of compacted (fig. 1) or milled (13) α-lactose monohydrate with a mixture of two untreated sieve fractions of the substance (fig. 5) respectively, it is likely to explain the changes in the shape of the peak by an increase in surface area.

Thus it seems not to be necessary to refer to (surface) activation processes.

The formation of smaller particles under load is known to be an important contribution to the consolidation process of the compound. The fragmentation properties of α-lactose monohydrate have frequently been reported in literature (e.g. 5,18). It is known, however, that fragmentation of this type of lactose is less intensive than for products such as e.g. dicalcium phosphate dihydrate. Moreover, plastic deformation is thought to play a certain role in the compaction of lactose (8,19,20). Although α-lactose monohydrate exhibits brittle fracture on compaction, initial differences in particle size are not levelled out; In fig. 6 it can be seen that from smaller particles stronger tablets could be obtained. The effect of the particle size on the crushing strength is dependent on the applied compaction load; at 77 MPa the differences in compact strength are small, whereas with increasing load differences become more and more pronounced.

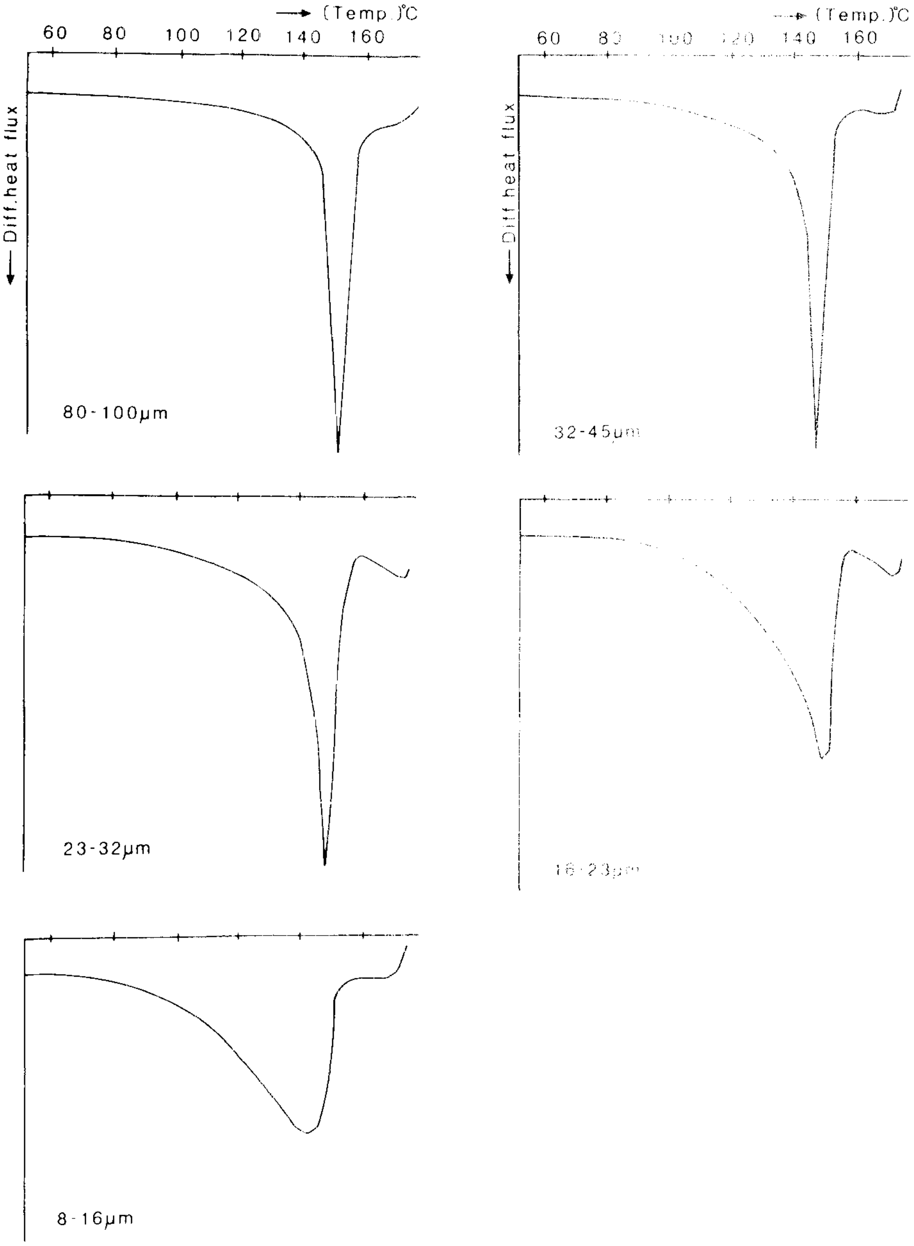

Figure 2
Dehydration peaks of particle size fractions of α-lactose monohydrate, recorded by DSC at a heating rate of 10°C/min.

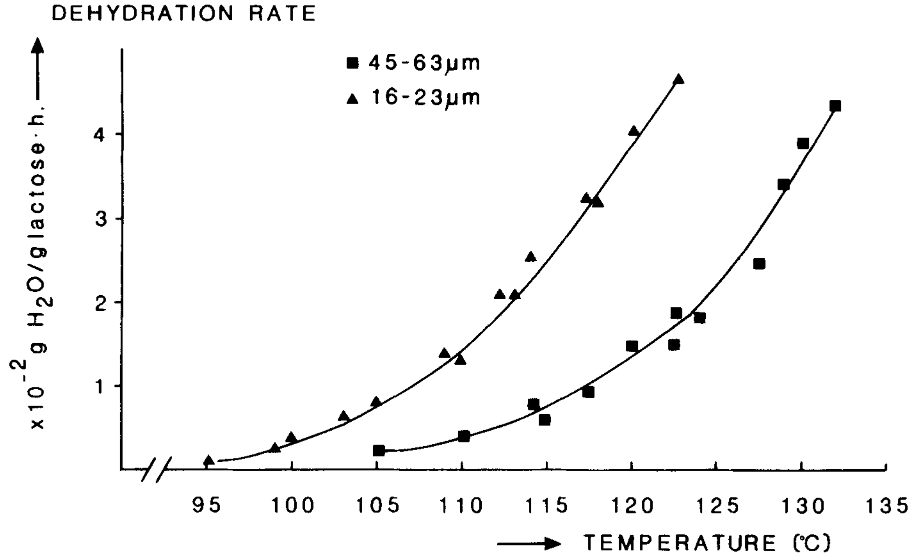

Figure 3
Dehydration rate of particle size fractions of α-lactose monohydrate, measured by thermobalance at fixed temperatures.

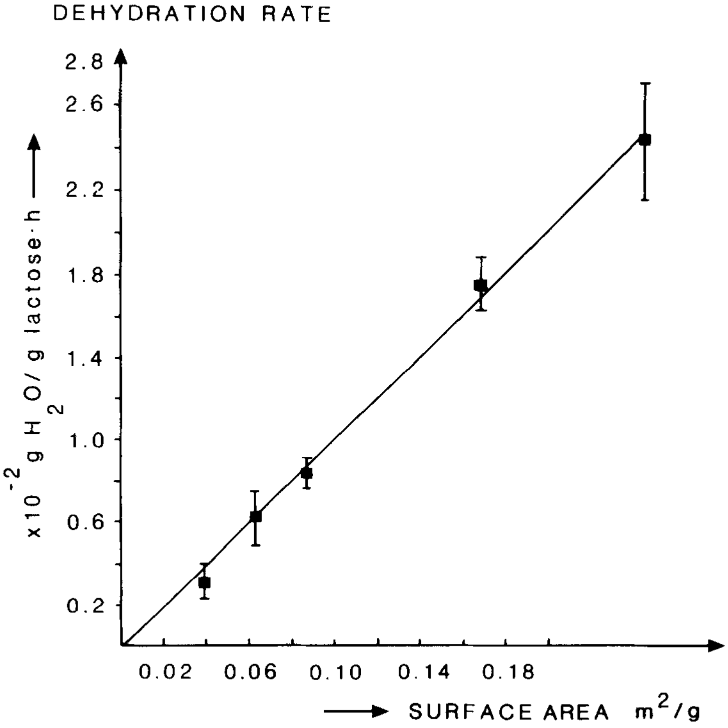

Figure 4
Dehydration rate of particle size fractions of α-lactose monohydrate at a constant temperature (113^{0}C) as a function of the lactose particle surface area.

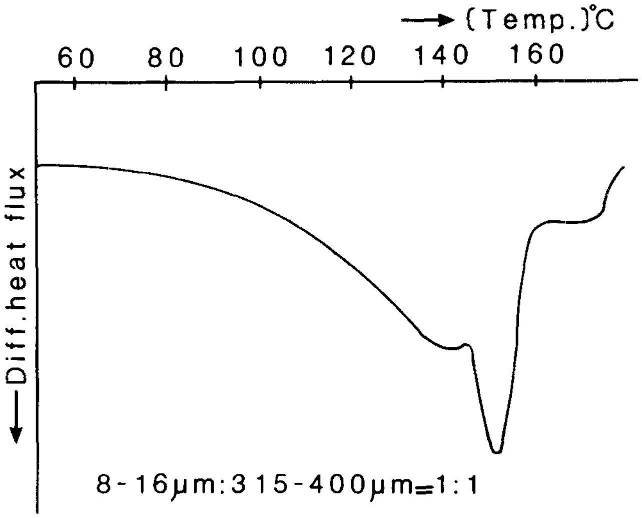

Figure 5
Dehydration peak of a mixture containing equal parts of two particle size fractions of α-lactose monohydrate, recorded by DSC at a heating rate of 10^0C/min.

In our studies mercury porosimetry measurements have been used to investigate tablets compacted from different types of lactose. Fig. 7 illustrates the pore volume distribution of tablets compressed from 32-45 and 315-400 µm fractions of α-lactose monohydrate, respectively, compacted at a load of 152 MPa. Assuming cilindrical 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 (2).

It is clear that the pore surface area of the smaller particles is somewhat larger than that of the large particles. One has to notice, however, that initial differences in powder surface area, which have a ratio of approx. 10:1, are not brought out in the pore surface areas of the tablets. This probably may mean that there is a difference in degree of fragmentation between the two sieve fractions. This is illustrated in fig. 8, where the ratio between pore surface area of

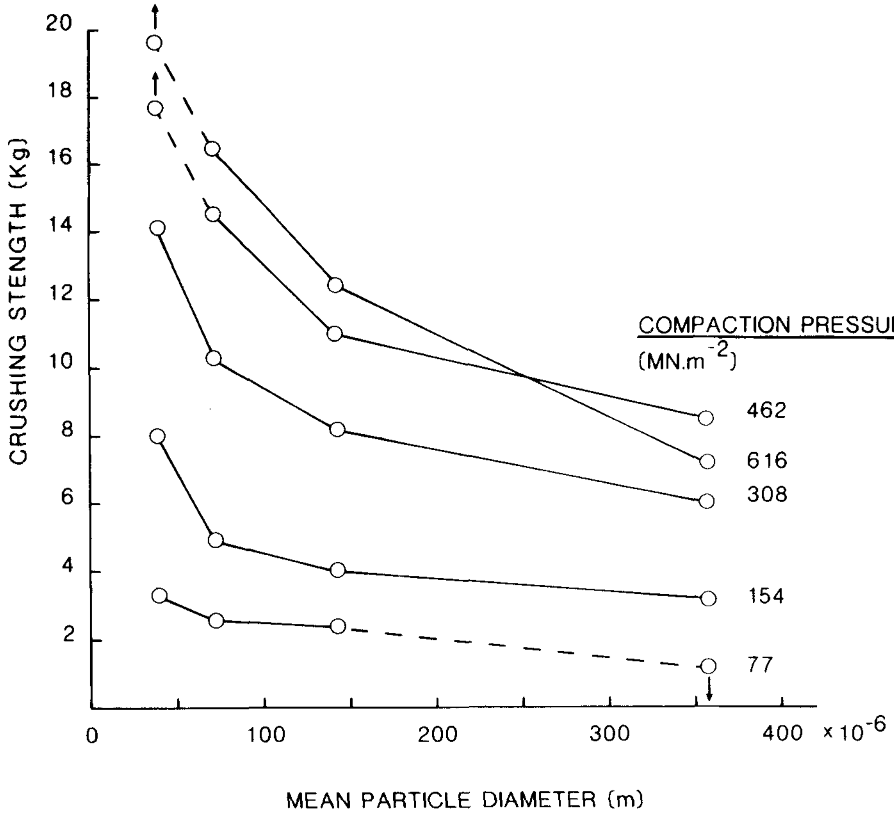

Figure 6
Compact strength versus mean original particle diameter for tablets compressed from sieve fractions of α-lactose monohydrate at different compaction levels.

tablets compacted at a pressure of 75 MPa and the calculated initial powder surface area is used as a measurement of the degree of fragmentation.

From this figure it can be concluded that the fragmentation tendency strongly decreases with decreasing particle size. This has already been reported in a study using permeametry as a method to estimate the tablet surface area (21). The observation that the degree of fragmentation is a function of the particle size is not very surprising. It is known from literature (22) that the strength of a crystalline

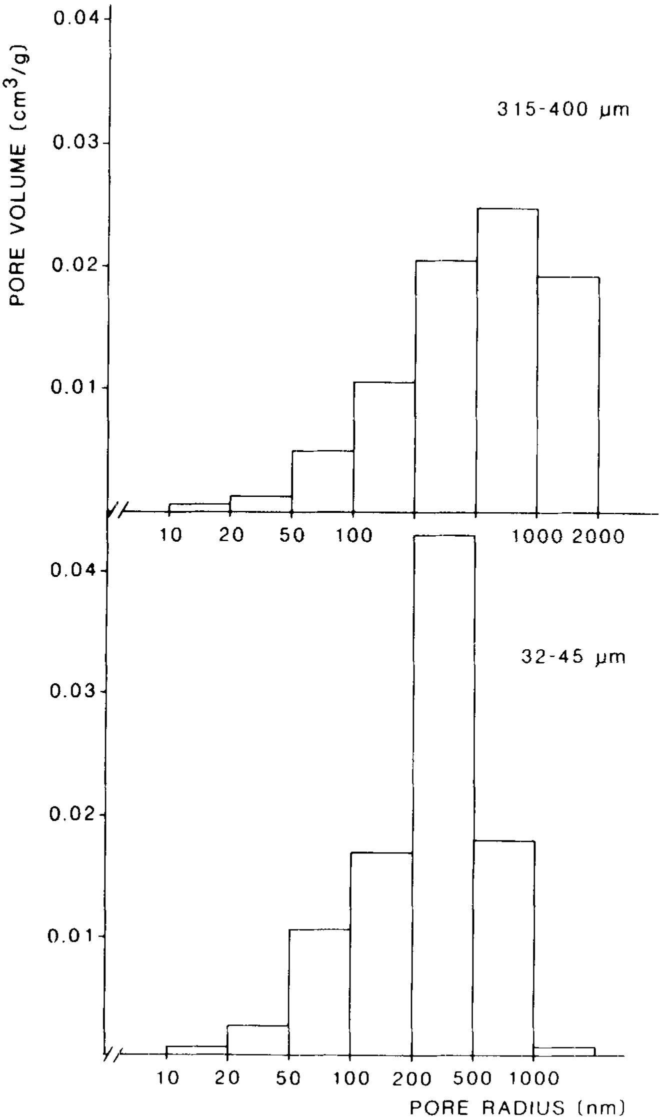

Figure 7
Pore volume distributions of tablets compacted from 32-45µm and 315-400µm fractions of α-lactose monohydrate, respectively, compressed at a load of 152MPa.

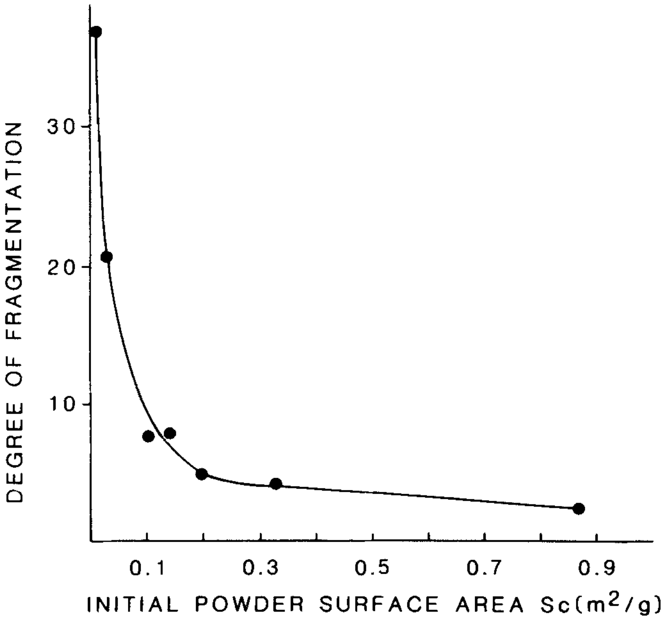

Figure 8
Degree of fragmentation, expressed as the ratio between the surface area of tablets compressed at 75MPa and the initial surface area (Sc), respectively, as a function of the initial particle surface area (Sc)for sieve fractions of α-lactose monohydrate.

material is dependent on the mean grain size: smaller particles require a higher load for fracture.

In fig. 9 the crushing strength is plotted as a function of the pore surface area for different sieve fractions of α-lactose monohydrate (32-45 μm, 125-160 μm, 315-400 μm) and for different types of crystalline lactose (anhydrous α-lactose, roller dried β-lactose, crystalline β-lactose, all 100-125 μm fractions).

From this linear relationship it can be concluded that there exists an equal proportionality between the actual binding surface area and the measured pore surface areas. Consequently it is apparent that the tablet strength is mainly determined by the actual (bonding) surface area. It appeared, however, that for extremely small particles the relationship was not valid (fig. 10).

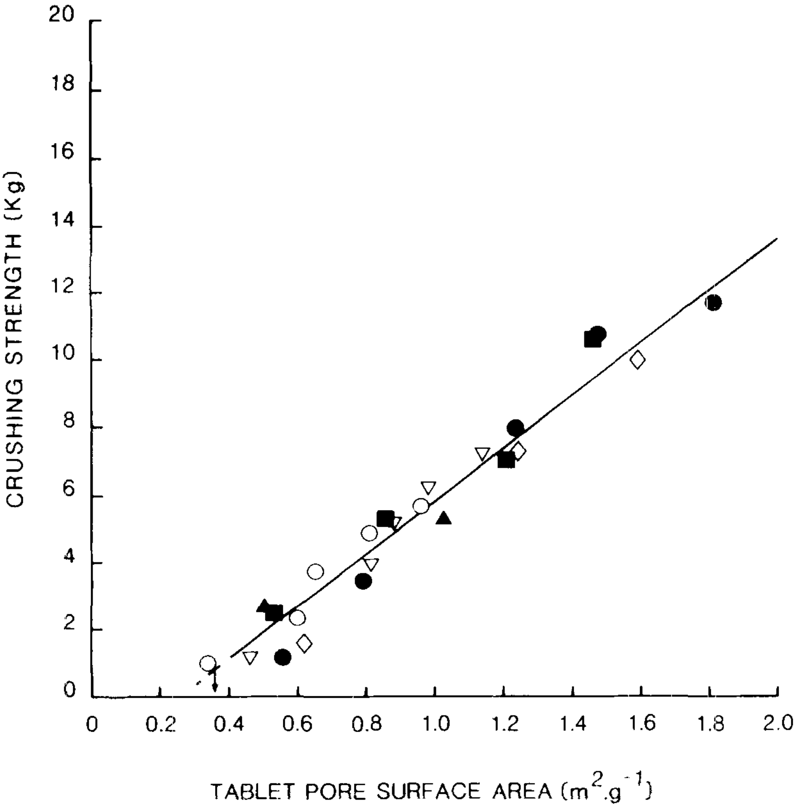

Figure 9
Compact strength versus tablet pore surface area, derived from mercury porosimetry, for sieve fractions of crystalline α-lactose monohydrate: (○) 315-400μm, (▽) 125-160μm, (◇) 32-45μm and anhydrous α-lactose (●), roller dried β-lactose (■) and crystalline β-lactose (▲), respectively, all 100-125μm fractions.

This might be explained by pointing to fig. 8.
In this figure it can be seen that small particles fragment only slightly. Densification of these fractions must occur by particle rearrangement and by plastic and elastic deformation, respectively. Because of the large number of contactpoints within the powder bed an important amount of friction must exist. This is undoubtedly the reason why tablet thickness increases considerably with decreasing particle size (1). One can suggest form this that because of the poor densification of small particles, the available large potential bon-

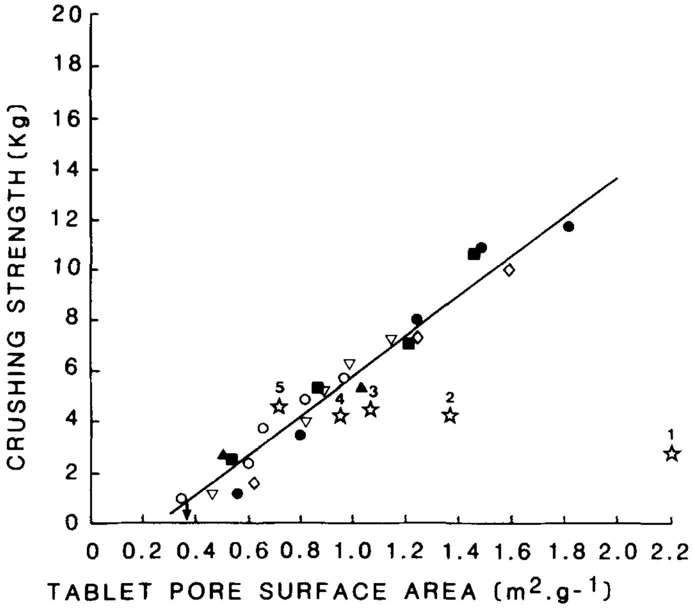

Figure 10
Crushing strength of tablets compressed from different crystalline lactoses at various compaction pressures, as a function of the pore surface area, calculated from mercury porosimetry measurements. Symbols as in figure 9. The values of α-lactose monohydrate samples indicated with figures, are obtained from tablets compressed at 75MPa: (☆^{1}) 1-8μm, (☆^{2}) 8-16μm, (☆^{3}) 16-24μm, (☆^{4}) 24-32μm and (☆^{5}) 32-45μm.

ding surface areas cannot come to close contact. This means in fact that the proportionality between tablet pore surface area and binding surface area changes at small particle sizes. One can argue that obviously a prerequisite for obtaining the unique relationship (fig.9) is the existence of a large degree of particle fragmentation; i.e. brittle fracture must be the predominant mechanism of consolidation.

In conclusion, a strong dependence of the compaction behaviour of crystalline α-lactose monohydrate on the original particle size can be explained by pointing to the differences in extent of particle fragmentation.
The speed of dehydration at a certain temperature increases with increasing powder surface area. The broadening of the dehydration peak

in the thermogram of the substance after mechanical treatment can be considered to be due to a surface area enlargement.

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