Studies on tableting properties of lactose

Part III. The consolidation behaviour of sieve fractions of crystalline α-lactose monohydrate

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Introduction

The complex nature of the consolidation of particulate solids can be deduced from the number of papers about the subject. It can also be related to the number of methods used to study this matter. Almost from the start of this century a great number of powder densification relationships has been introduced to estimate the major factors contributing to powder bed consolidation under pressure, such as particle rearrangement, fragmentation and plastic flow.[1]

More recently some new approaches were added to the list of techniques to study particle behaviour and interaction processes during the formation of pharmaceutical compacts under load, such as

- scanning electron microscopic (SEM) investigations of fracture planes in broken tablets;[2]
- particle size analysis on the fragments of disintegrated tablets;[3,4]
- pore surface area measurements in tablets by various means;[5-7]
- determination of the isotropy ratio of tablets.[8]

In the meantime the compaction mechanisms of some pharmaceutical model excipients are well-documented and classifications have been made in terms of brittle material (*e.g.* dicalcium phosphate dihydrate and paracetamol), material with plastic behaviour (*e.g.* microcrystalline cellulose and starch) or a combination of the two (*e.g.* saccharose and lactose).[5,9-12]

Most of the studies to reveal these mechanisms were carried out well-defined with regard to initial particle size, compaction pressure and compression speed, respectively. Only a few authors, however, studied the influence of particle size on compaction for a considerable compression range. Moreover, the number of materials used in such studies is small. This may be the reason why the influence of initial particle size on consolidation mechanism and compact strength is a subject submitted to discussion. It has been claimed that when the interparticulate bonds in a compact are weak (*e.g.* for lactose) little influence of initial grain size on tablet strength is to be expected.[13] Where the interparticulate bonds are strong, however, fracture occurs across the grains and the strength of the tablet is a simple function of the particle size. On the other hand it has been stated that various experiments have proved that smaller particles give stronger tablets as a general rule.[14] It has been found for sulfathiazole,[3] dicalcium phos-

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Abstract

The consolidation and compaction behaviour of sieve fractions of crystalline α-lactose monohydrate were studied. From mercury porosimetry measurements tablet pore surface areas were derived. At a certain compaction load it appeared that tablets compressed from small particles were generally stronger and showed a larger surface area than compacts prepared from coarse sieve fractions. By plotting compact strength against pore surface area, a unique linear relationship was obtained. From these results it can be concluded that the actual tablet surface area, being a function of both the initial particle size and applied compaction pressure, is responsible for the compact strength.

phate dihydrate,[4] phenacetin and prednisolone,[15] by various methods, that smaller particles tend to aggregate under compaction, whereas larger particles are fractured. A number of authors confirm that the fragmentation propensity of a substance under load increases with its particle size.[5 13 16 17] For this reason changes in mean particle diameter may alter the predominant consolidation mechanism of a substance.

Various authors performed their studies on the same model excipients, such as sodium chloride and crystalline lactose. It has been found for sieve fractions of sodium chloride that the tablet strength increases with decreasing mean particle diameter over the whole compression range applied.[13 18] However, other results showed a reverse dependence for the same material.[8] It was shown for crystalline lactose that initial particle size has very little effect on the compact strength for all compaction pressures used,[19] whereas on the other hand also an increase in strength with decreasing particle size for this substance has been reported.[8 20] With respect to this, it should be noted that the circumstances under which compression is performed can have great influence on the results.[11 16]

The results presented in previous papers in this series point out that crystalline lactose consolidates mainly by fragmentation.[6 20] It was also indicated that for both α-lactose monohydrate and anhydrous α-lactose, there is an effect of initial particle size on tablet strength, the effect being influenced by the compression force. From that, it was concluded that, although fragmentation is the main consolidation mechanism, this is insufficient to eliminate differences in initial potential bonding areas of the fractions used. These findings support the idea that the consolidation mechanism of a substance is not merely a function of its physicochemical properties alone, but a rather complex matter in which physical and geometrical factors, including particle rearrangement and process conditions can play an important role.

In this paper an explanation for the differences in behaviour with regard to consolidation of different sieve fractions of crystalline α-lactose monohydrate is given on the basis of differences between mechanical strength and tablet porosity for these fractions. Pore surface area calculations from mercury intrusion data are used to estimate distinctions in degree of fragmentation depending upon particle size and compaction load.

Methods

LACTOSE

Sieve fractions of unmilled crystalline α-lactose monohydrate were supplied by DMV (Veghel, The Netherlands). All size fractions were derived from the same batch of crystallization and were therefore chemically identical, with a β-content of approximately 5%. Sieving was performed by hand with ASTM standard sieves (BV Metaalgaasweverij Twente, Hengelo, The Netherlands): the smaller size fractions obtained were verified with the Coulter Counter method. No greater deviations than 16% at most of particles beyond the lower particle size limit were found.

COMPACTION AND CHARACTERIZATION OF TABLETS

Tablets were compressed on a programmable hydraulic press (Hydro Mooi/Automation, Peekel, Appingedam, The Netherlands). The applied load rate for all tablets made was 2 kN/s. It should be noted that this rather slow compression speed – which is the standard for all compression studies in this series – does not correspond to the high speed compaction procedures of common tablet production machines. Compressions were performed at a constant air humidity of about 55% relative humidity. Room temperature was kept constant during tableting at 20±1 °C.

Plane tablets with a weight of 500 mg and a diameter of 13 mm were produced for mercury penetration measurements. The results obtained by this are comparable to all data revealed in previous papers in these series for the same type of tablets, which is also standard for our studies.

In order to obtain the higher compression pressure data, as presented in this paper, with the same hydraulic press and under the same conditions, the use of a lower tablet surface area was necessary. For this reason all compact strength and compact porosity measurements were performed on flat-faced tablets with a diameter of 9 mm and a weight of 300 mg. It may be possible that both types of tablets show differences in pore structure after compression at the same compaction pressure. This will not interfere with the discussion, however, as no direct comparison between the two types has been made.

No lubricant was used, except for die prelubrication (magnesium stearate). Mercury intrusion measurements were carried out within 48 h after compression 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.

Compact strength and tablet dimensions were measured after a constant relaxation time of 15 min, using a Schleuniger model 2E instrument (Dr. Schleuniger Productronic AG, Solothurn, Switzerland) and an electronic micrometer with an accuracy of 0.001 mm (Mitutoyo MFE Co., Ltd., Tokyo, Japan) respectively. Overall porosity of the tablets was calculated from data concerning weight, outer dimensions and solid density of the substance. A solid density value of 1.54 $g \cdot cm^{-3}$ for α-lactose monohydrate was used.

The Coulter Counter data for all sieve fractions showed a good symmetry with regard to particle size distribution. For this reason the arithmetical mean particle diameter was used to calculate the initial particle surface area on the basis of spherical particles. Tablet pore surface areas were derived from mercury penetration data, using the calculation method as described previously.[6]

Results and discussion

In Figure 1 the relationship between compact strength and the mean diameter of different sieve fractions of α-lactose monohydrate are presented for

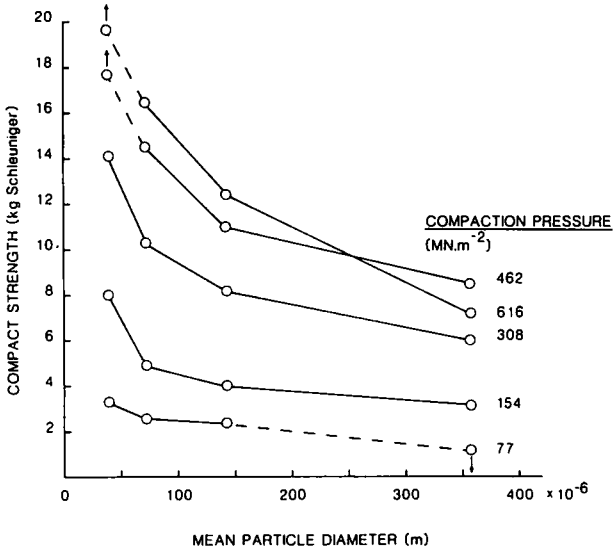

FIGURE 1
Compact strength versus mean original particle diameter for tablets compressed from sieve fractions of crystalline α-lactose monohydrate at different compaction pressure levels (n = 10 for each point)

a series of compaction pressures. The curves clearly indicate that from smaller particles stronger tablets can be obtained, while the differences in tablet strength become more pronounced with increasing load. In Figure 2 the compaction profiles for four sieve fractions are shown, which exhibit clearly defined maximum values in compact strength. The fall in strength at high compaction load for the coarsest fractions is caused by lamination of the

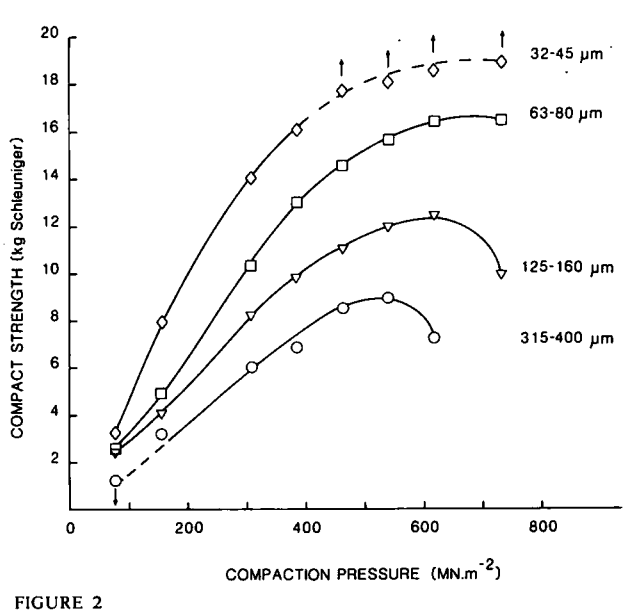

FIGURE 2
Comparison of compact strength versus applied compaction load for tablets from sieve fractions of crystalline α-lactose monohydrate

tablets, probably due to the effect of elastic recovery. Obviously, for smaller particles the maximum is reached at higher pressures.

The lamination tendency of the tablets at higher compaction pressures is the main reason why calculation of tensile strength values for these tablets does not give a better presentation of the results. Even before laminar cracks were visible, some deviations in tablet thickness were found. The failure mechanism for the different sieve fractions, however, stayed rather uniform up to the ultimate points as presented in Figure 2.

Although fragmentation is considered to be important in the consolidation process, this apparently does not occur to a sufficient extent to level out initial differences in powder surface areas completely.[20] The initial powder surface areas of the ultimate fractions, being 32-45 μm and 315-400 μm respectively, have a ratio of approximately 1:10.

With an equal degree of fragmentation for both fractions one would expect from previous work to obtain values for the tablet strength having about the same ratio.[6] From the Figures 1 and 2 it can be seen, however, that the difference in compact strength reaches at most a factor 3 at any pressure. This could indicate that fragmentation of the coarsest fractions in the lower compression regions occurs to a far greater extent than that of smaller particles. On the other hand it is also quite well possible that in the case of smaller particles there is a larger contribution of plastic deformation in the compaction process.

It can be concluded that the effect of differences in initial particle sizes remain, notwithstanding the existence of brittle fracture during compaction. Using a SEM technique, the fragmentation of two size fractions of crystalline lactose has been visualized.[2] It was concluded that even at compaction pressures of 240 MN·m^{-2}, differences between the two fractions can still be seen, in spite of a considerable reduction of the number of particles of original dimensions. Also the occurrence of plastic flow was observed.

In a previous study it has been reported that there exists a linear relationship between the pore surface area, derived from mercury porosimetry, and the crushing strength of tablets compressed from sieve fractions of 100-125 μm of different types of crystalline lactose, being α-lactose monohydrate, anhydrous α-lactose, roller-dried -β-lactose and crystalline β-lactose.[6] From this it was concluded that the crushing strength mainly depends upon the extent of fragmentation during compaction. Starting from a certain minimum pore surface area level, necessary to form a compact at all, the creation of new internal tablet surface area is required to increase tablet strength. The results showed an almost direct proportionality between the pore surface area and the tablet strength. It was demonstrated that neither the α/β ratio nor the amount of water of crystallization influences the binding mechanism.

Figure 3 shows a linear relationship between the pore surface area and the crushing strength for tablets compressed from different fractions of crystalline α-lactose monohydrate as well. This result indicates that original differences in particle surface area do not result in distinctive relationships. Assuming a proportionality between bonding surface area and measured pore surface area it can be concluded that it is the actual surface area being responsible for the tablet strength. To depict the agreement with data as found for other types of crystalline lactose, previously reported values are marked in Figure 3 with closed symbols.[6]

In Part 1 of our series on tableting properties of lactose it was argued that the effect of mechanical activation of particle surfaces with respect to binding properties of lactose should not be overestimated.[20] In fact, a similar conclusion can be drawn from Figure 1, as it seems not to be necessary to refer to such an activational effect.

To estimate the degree of particle size reduction during compaction from pore surface area values, a better description should be given for the fragmentation process. Fragmentation has been defined as the formation of smaller, discrete particles from an initial grain.[21] This implies that the characterization method should give direct information about the number of cleavages created in a particle after submission to stress. As sieve fractions of various substances with equal initial particle size were concerned,[21] the proposed method based upon the measurement of changes in tablet pore surface area with compaction pressure by permeametry seems to answer the purpose. An increase in pore surface area is a direct and proportional consequence of the number of cleavages in the original grains. However, if the initial mean particle diameters are dissimilar, some considerations have to be made.

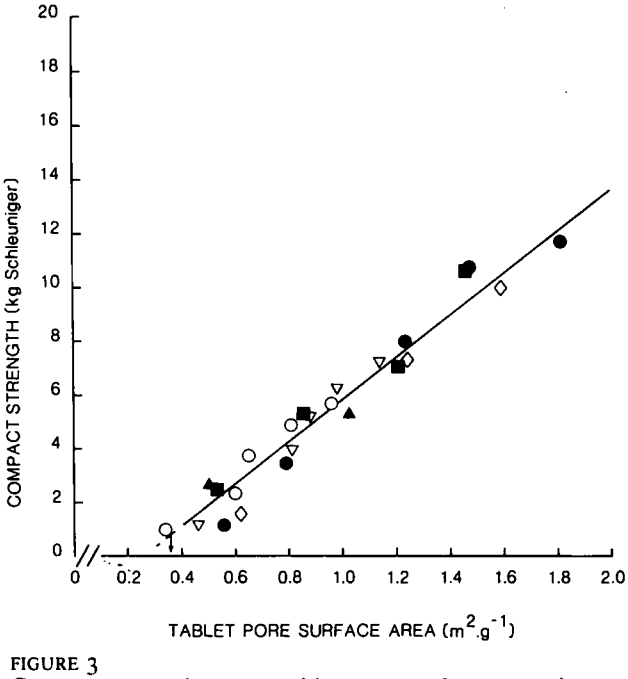

FIGURE 3
Compact strength versus tablet pore surface area, derived from mercury porosimetry, for sieve fractions of crystalline α-lactose monohydrate: (○) 315-400 μm; (▽) 125-160 μm; (◇) 32-45 μm; and anhydrous α-lactose (●), roller-dried β-lactose (■) and crystalline β-lactose (▲) respectively. The closed symbols represent data discussed in a previous paper[6]

It is obvious that to achieve an equal absolute increase in surface area, larger particles with a lower initial surface area have to fracture much more intensively than smaller particles with a higher starting surface area. If changes in surface area are related to fragmentation propensity, an increase of this for a tablet during consolidation should therefore be related to the starting surface area.

In Table 1 initial powder surface areas (S'), calculated from the mean sieve particle diameter and pore surface area data derived from mercury porosimetry (S) for tablets from three different sieve fractions of crystalline α-lactose monohydrate, compressed at 55, 147 and 221 $MN \cdot m^{-2}$ respectively, are presented.

In principle the pore surface areas by mercury porosimetry and the initial powder surface areas by calculation from the mean particle diameter cannot be related to each other directly, both data being the result of different techniques. However, since it is known from gas adsorption measurements on crystalline α-lactose monohydrate as a powder that the crystals show no important internal porosity, such a comparison might provide a better insight into the extreme differences in degree of fragmentation for the sieve fractions at low compaction pressures.

As can be calculated from the data presented in Table 1, the absolute increase in pore surface area (S–S') for the smallest fraction is approximately 0.5 $m^2 \cdot g^{-1}$, whereas this increase for the fraction 315-400 μm is only approximately 0.3 $m^2 \cdot g^{-1}$. Related to the starting powder area values (S'), however, the total pore surface area after fragmentation for the largest particles is approximately thirty times the initial value, whereas the size fraction 32-45 μm fragments to a surface area extension of only a factor 5.

Similar calculations can be made for the higher compression regions. From this it can be concluded directly that the degree of fragmentation decreases strongly with increasing compaction load. Some authors reported not only the effect of particle size, but also the influence of compaction speed on density changes in tablets of crystalline lactose.[22] Under the circumstances used for compaction, we cannot report a significant dependence on this although some tendencies were found.

To explain the differences in compaction behaviour for the size fractions of crystalline α-lactose monohydrate, the influence of particle size on both

TABLE I
Initial powder surface area (S') and tablet pore surface area (S) with crushing strength to match at different compaction pressures for three sieve fractions of crystalline α-lactose monohydrate

Sieve fraction (μm)	Initial powder surface area S' (m^2/g)	Compaction pressure ($MN \cdot m^{-2}$)					
		55		147		221	
		S (m^2/g)	crushing strength (kg)	S (m^2/g)	crushing strength (kg)	S (m^2/g)	crushing strength (kg)
32-45	0.102	0.62	1.7	1.24	7.4	1.59	10.0
125-160	0.027	0.46	1.1	0.88	5.2	1.14	7.3
315-400	0.011	0.34	< 1.0	0.65	3.8	0.96	5.7

mechanical strength of an individual grain and compact porosity has to be considered. Although lactose is described as a brittle material, the participation of particle rearrangement and plastic flow in the densification process has been reported too.[2 12 16]

The relative efficiencies of these mechanisms, however, were found to be dependent upon compression force. In the lower compaction regions, rearrangement and fragmentation appear to be dominant, whereas with increasing load plastic and subsequently elastic flow start to become important. Various authors reported that the predominant consolidation mechanism in a restricted compaction pressure range can vary with the particle size of a substance as well.[10 12 22] To give this a better understanding for brittle material like crystalline lactose, it should be realized that fragmentation of a single particle is influenced by its size and shape and its configuration in the compact in regard to porosity and pore distribution.

Results found for lactose as well as for other materials show that compacts of smaller size fractions exhibit higher overall porosities for all compression forces.[13 17 20 22] Therefore the effect of particle rearrangement on consolidation to be expected for these fractions at low compaction pressures is more important than that for coarse particles.[22] Next to higher overall porosities, smaller size fractions have a greater number of particles, *i.e.* number of contact points in the compact, resulting in a smaller load per unit contact area. Furthermore it is known that the strength of a crystalline material is dependent on the mean grain size; smaller particles require a higher load for fracture.[23]

Considering all these factors, it may be expected that the degree of fragmentation cannot be the same for the sieve fractions in the compaction pressure range investigated. It is also unlikely that the extent of fragmentation would be constant with increasing compaction load. Particle size reduction will be reduced as porosity draws near zero and subsequently elastic behaviour will start to dominate the consolidation process. It is obvious that differences in extent of fragmentation for the sieve fractions will reflect in the crushing strength values, regarding the fact that fragmentation is the creation of new pore surface area. The proportionality between surface area and compact strength has already been discussed (Fig. 3).

These phenomena will of course show in the porosity profiles of the sieve fractions. Figure 4 shows the relationships between compact porosity and compaction pressure for three different sieve fractions. The depicted differences are significant for the individual points up to and including 150 $MN \cdot m^{-2}$, but the tendency is continued up to higher pressures. In this Figure it is to be seen that starting with about the same porosity the densification is the highest for the coarse material. It is reasonable to assume that the greater degree of fragmentation of this fraction is an important contributory factor. At all compaction pressures at least two factors are important in determining the degree of brittle fracture; fragmentation propensity and

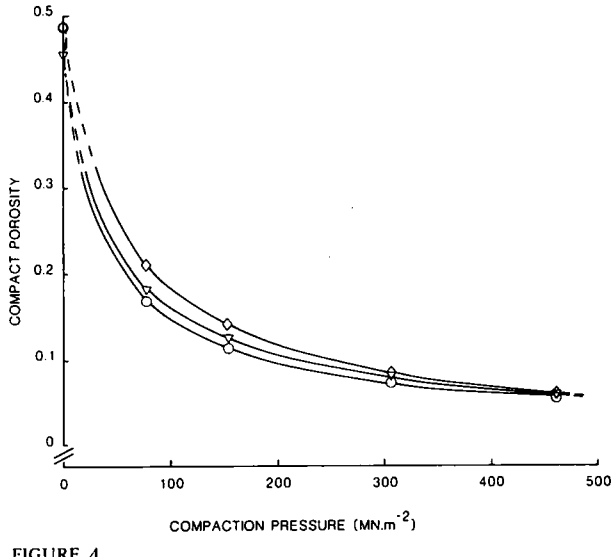

FIGURE 4
Tablet porosity, as measured 15 min after ejection, versus compaction pressure for sieve fractions of crystalline α-lactose monohydrate: (○) 315-400 μm; (▽) 125-160 μm; (◇) 32-45 μm (n = 3 for each point)

fragmentation potential. It is obvious that for a certain particle size, the higher the compaction load, the more fragmentation will occur.

On the other hand one should not forget that fragmentation cannot take place when porosity draws near zero. Thus considering fragmentation to be a function of particle size and porosity, it is clear from Figure 4 that at increasing compaction load the smaller particles can continue to fragment up to higher pressures. This is probably the reason why the maximum values for compact strengths for smaller fractions are obtained at higher pressures.

In conclusion, fragmentation can be considered to be the predominant mechanism of consolidation in the compaction of the studied sieve fractions of α-lactose monohydrate. However, fragmentation does not occur to an equal extent for all fractions used. The tablet strength is determined by the actual surface area, which is dependent on initial particle size and compaction pressure.

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