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Studies of tableting properties of lactose. IX. The relationship between particle structure and compactibility of crystalline lactose

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Summary

In order to study the relation between the compactibility and particle texture of crystalline lactose, a wide variety of samples, differing in particle size, texture, water content and α/β ratio, was investigated. It appeared that the binding capacity of the products was directly related to the powder surface area, determined by gasadsorption measurements. By this technique, it could be established that the values of the tablet surface areas obtained were very unreliable. A plausible explanation for this seems to be the occurrence of capillary condensation in the pores of the tablets. By taking this aspect into account, a relation was obtained between tablet strength and tablet surface area. From this it is concluded that the mechanism of consolidation and the mechanism of binding must be the same for all products.

Introduction

In a wide range of industrial applications, powders are compressed in order to yield compacts with desired mechanical properties, size and shape. Although powder compaction has been subjected to research work for many years, the matter is still not well understood. It is, for example, often unclear why chemically equivalent materials exhibit totally different compactibility properties (Shah et al., 1983; Shangraw et al., 1981).

Lactose occurs in several types, which distinguish themselves by different tableting characteristics. In the series entitled "Studies on tableting properties of lactose" (De Boer et al., 1986; Van Kamp et al., 1986a and b; Vromans et al., 1985a and b, 1986, 1987a and b) compactibility, dissolution, disintegration, etc., of different types of lactose are studied in order to get an insight into the fundamental parameters that are responsible for its compaction behaviour.

The purpose of the present paper was to investigate the relation between the state of the starting material and its compactibility.

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Materials and Methods

Characterization of the materials

All lactose samples were supplied by DMV (Veghel, The Netherlands). Desiccation of α-lactose monohydrate with dry methanol was carried out by refluxing the material in the liquid for

2 h at 60 °C. Rehydration occurred in a climate chamber at a relative humidity of 85% at 20 °C. The α/β-ratio of the samples was determined by GLC, as described in a previous paper (Vromans, 1985b). The water content of the samples was determined by a semi-micro method, using Merck's Karl Fischer reagents (Merck, Darmstadt, F.R.G.). The specific surface area, S_{N_2}, was measured with a Quantasorp gasadsorption apparatus (Quantachrome, Syosset, U.S.A.) using nitrogen as adsorbent. Outgassing occurred at 120 °C in a nitrogenous atmosphere for at least 18 h prior to analysis. As this procedure would more or less dehydrate the α-lactose monohydrate, for this substance an alternative method of outgassing was used, which includes repetitive adsorbing and desorbing of the adsorbate at a relative pressure of 0.3 (Lopez-Gonzalez et al., 1955).

Compression of tablets

Compaction of 500 mg tablets with a diameter of 13 mm was carried out on a programmable hydraulic press (Hydro Mooi/Automation, Peekel, Appingedam, The Netherlands). The applied compaction load rate was 2 kN/s for all tablets. The crushing strength of the tablets was measured after a relaxation time of about 15 min, using a Schleuniger 2E instrument (Dr. Schleuniger Productronic, Solothurn, Switzerland). In this paper the compactibility is defined as the slope value of the tablet strength–compaction pressure curve. Tablet dimensions were estimated with an electronic micrometer (Mitutoyo MFE Co., Tokyo, Japan) having an accuracy of 0.001 mm.

Results and Discussion

Crystalline α-lactose monohydrate can be dehydrated into stable anhydrous α-lactose either by thermal treatment (Berlin et al., 1972) or by desiccation with suitable liquids such as dry methanol (Lim et al., 1973). Both methods result in an increased binding capacity of the material (Lerk et al., 1983). The anhydrous form has been demonstrated to have an expanded powder surface area as determined by low temperature gas adsorption (Berlin et al., 1972). Rehydration of the anhydrous lactose by exposure to water vapour resulted in a partial reduction in surface area. Similar results were found by Sekiguchi et al. (1968, 1978), who used a solvation–desolvation method to enlarge the surface area of several medicinal compounds.

In Table 1 the effect of repeated methanol desiccation and rehydration on the specific powder surface area (S_{N_2}) of α-lactose monohydrate is demonstrated. It is clear that dehydration increases the surface area of the lactose while by rehydration the reverse occurs. The net result is an enlargement, however. It is of interest to notice that the compactibility of the substance is related to its specific powder surface area. When it is realized that there are only minor changes in the particle size distribution, obviously there is a gradual increase in the irregularity of the particle structure. In order to elucidate whether the binding capacity of crystalline lactose is in general related to its particle structure, a variety of samples was examined, differing in specific powder surface area, water content, particle size and α/β-ratio, respectively (Table 2). In Fig. 1 the compactibility of these different types of lactose is plotted in relation to the powder surface area. At low values there exists a direct proportionality between the two parameters. At high values, i.e. in the case of highly porous materials, the curve starts to decline. From Fig. 1 it may be concluded that the ease to form a coherent tablet apparently increases with increasing powder surface area. This is not infinite, however. Clearly there exists a maximum obtainable compactibility.

TABLE 1

α-lactose content, water content, specific powder surface area (S_{N_2}) and crushing strength of tablets compacted at 75 MPa, respectively, of a α-lactose monohydrate starting material and of its methanol desiccated and subsequently rehydrated products

	α-Content (%)	Water content (%)	Spec. surf. area (m^2/g)	Cr. str. 75 MPa (kg)
starting material	96	5.2	0.12	2.7
anhydrous 1	96	0.3	1.35	12.4
rehydrated 1	97	5.0	0.69	6.1
anhydrous 2	97	0.3	2.62	16.9
rehydrated 2	97	5.0	1.00	7.7

TABLE 2

Survey of the samples used in this study. The conditions to manufacture a compound crystalline lactose are indicated by Lerk et al. (1984a and b). T = thermally dehydrated; M = dehydrated with dry methanol.

	Particle sizes (μm)	Water content (%)	α-Lactose content (%)	Spec. powder surface area (m^2/g)
α-lactose monohydrate	24– 315	5	96	0.06–0.26
anhydrous α-lactose (T)	24– 315	< 0.5	80	0.27–1.07
anhydrous α-lactose (M)	< 63– > 180	< 0.5	96	1.10–2.43
crystalline β-lactose	32– 315	< 0.5	4	0.04–0.20
roller dried β-lactose	32– 315	< 0.5	17	0.28–0.63
compound crystalline lactose	< 63– 400	< 0.5	52	0.43–1.00

In previous studies (Vromans et al., 1985b; De Boer et al., 1986) a linear plot between the compact strength and the specific surface area of the tablet was demonstrated for different types of crystalline lactose compacted at various compaction levels. The specific surface area was determined with the aid of mercury porosimetry. It was concluded that, although binding properties of the different lactoses vary considerably, the binding mechanism must be the same. In an attempt to determine the tablet surface area with gas-adsorption, it was noticed that the measurements were very poorly reproducible; It appeared that tablets which were measured immediately, i.e. without any sample preparation, showed considerably larger surface areas than those which had undergone a pretreatment. This is illustrated in Fig. 2 from which it is clear that there is an increasing deviation when increasing the compaction pressure. The phenomenon appeared to be directly related to the atmospheric humidity. In Fig. 3 the tablet surface area is plotted in relation to the storage conditions at which the tablets have

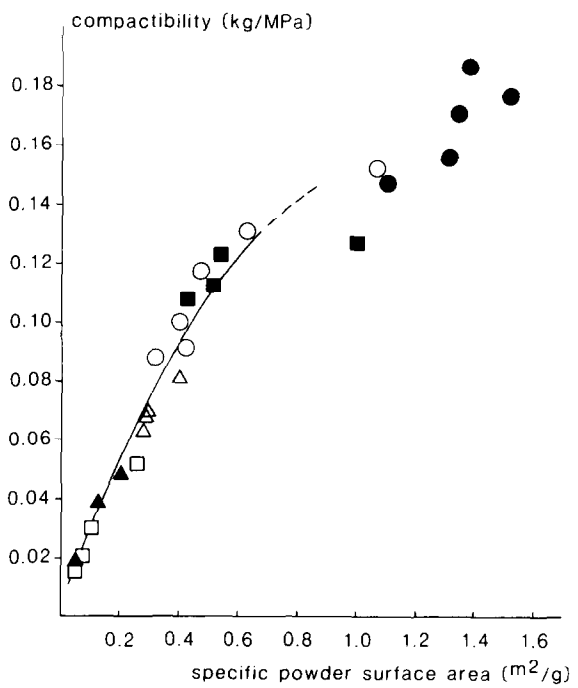

Fig. 1. Compactibility of samples of crystalline lactose plotted versus the powder surface area (S_{N_2}). □, α-lactose monohydrate; ○, anhydrous α-lactose (T); ●, anhydrous α-lactose (M); △, roller-dried β-lactose; ▲, crystalline β-lactose; ■, compound crystalline lactose.

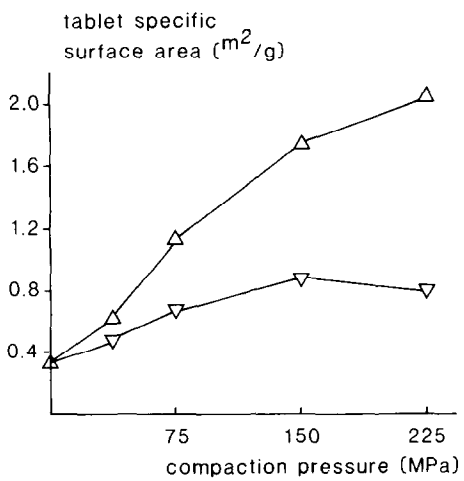

Fig. 2. Specific surface area (S_{N_2}) of tablets compacted from roller-dried β-lactose (100–160 μm) versus the compaction pressure. The tablets were measured immediately after compaction (△) or after outgassing at 120 °C (▽).

been stored for at least 24 h. In fact these results point to capillary condensation being the cause of the change in surface area. This seems to be very likely because there exists a gradual shift to smaller pores on compaction (Vromans et al., 1985b). Along with this, the influence of capillary condensation must theoretically increase, which is illustrated in Fig. 2. It was not possible to remove the water from the tablet under any condition without disturbing the structure of the lactose tablet itself. Moreover, the phenomenon seems to occur very quickly, which means that it takes place before the tablet is heated up. As a consequence of this the application of gasadsorption on tablets is considerably limited. In spite of this the method has been used to estimate tablet surface areas already for many years. Surveying literature, it is obvious that quite different surface area–compaction pressure plots have been found (e.g. Alderborn, 1985; Armstrong and Griffiths, 1970; Higuchi et al., 1953; Stanley-Wood and Johansson, 1978). Undoubtedly one of the reasons for this is the wide variety of materials studied, which distinguish themselves by, for example, mechanism of consolidation and particle structure. However, it seems reasonable to speculate that at least some of the controversy will be eliminated by taking also the aspect of capillary condensation into account.

It was not possible to determine tablet surface areas by gasadsorption before any condensation could take place. A better approach appeared to be to study the tablets which exhibit only minor capillary condensation because of the absence of small pores. Arbitrarily, a compaction pressure of 37.5 MPa was chosen. Fig. 2 shows that at this compaction load no dramatic influence of capillary condensation is to be expected. In Fig. 4 the crushing strength of the samples listed in Table 2 is depicted versus the tablet surface areas (S_{N_2}). It can be seen that the same relationship exists for all samples. One should realize that the measured value represents the total non-bonding surface area, while in fact only the bonding surface area is wanted. From the equal proportionality between compact strength and tablet surface area it can be concluded that apparently there also exists a proportionality between the measured and the bonding surface area. At high surface area values the curve deflects to the abscissa. It is clear that in this case the materials cannot use the available surface area for bonding to an optimum extent. This means that the ratio between the measured and the bonding surface area has become another value.

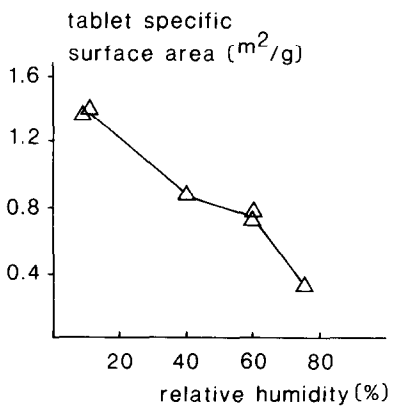

Fig. 3. Specific surface area (S_{N_2}) of tablets compacted from roller-dried β-lactose at 225 MPa plotted in relation to the storage conditions, being the relative humidity at 20 °C.

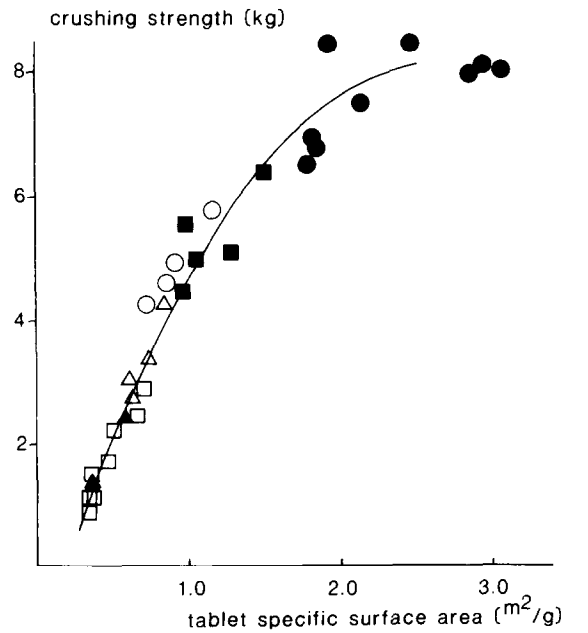

Fig. 4. Crushing strength of tablets compressed from samples of crystalline lactose at 37.5 MPa versus the tablet specific surface area (S_{N_2}). Symbols as in Fig. 1.

From the results obtained so far it can be concluded that the differences in compactibility of the several types of lactose can be explained by pointing to the differences in size of the available surface areas. Since there exists a unique relationship between the powder/tablet surface area and the compactibility/compact strength, respectively, it is clear that the mechanism of bonding must be the same. With respect to the mechanism of consolidation it is of interest to note that all samples fit the same relationship, existing between the surface area of tablets compacted at 37.5 MPa and the surface area of the starting material, respectively (Fig. 5). Obviously the extent of the surface area enlargement, caused by compaction at a pressure of 37.5 MPa, is determined by the initial powder surface area only.

Several theories have been proposed to explain the variations in compactibility observed for chemically equivalent compounds. They have been referred to in previous papers (Vromans et al., 1985a and b). One of the theories points to the importance of disorder and lattice defects for the compactibility (Hüttenrauch, 1978; Morita et al., 1984). Although this has been discussed in parts 1 and 2 of our series (Vromans et al., 1985a and b), it is still of interest to add the results presented here because of the growing amount of samples involved. It is known that in an α-lactose monohydrate crystal, the presence of the β-anomer in the lattice can be considered as a disorder (Fries et al., 1971). The results presented in this paper indicate, however, that no essential difference in the mechanism of binding can be observed by this. Apparently neither the α/β-ratio nor the water of crystallization is of significance for the binding capacity of crystalline lactose. It has been noted that the β-form is accommodated in the lattice with no apparent sacrifice in the number of hydrogen bonds (Fries et al., 1971). Consequently the stability of the lattice is not diminished by the presence of this lattice disorder. This is probably the reason for the finding that compactibility of lactose powder is simply related to its specific surface area (S_{N_2}) and that the fragmentation of all samples seems to follow the same trend (Fig. 5).

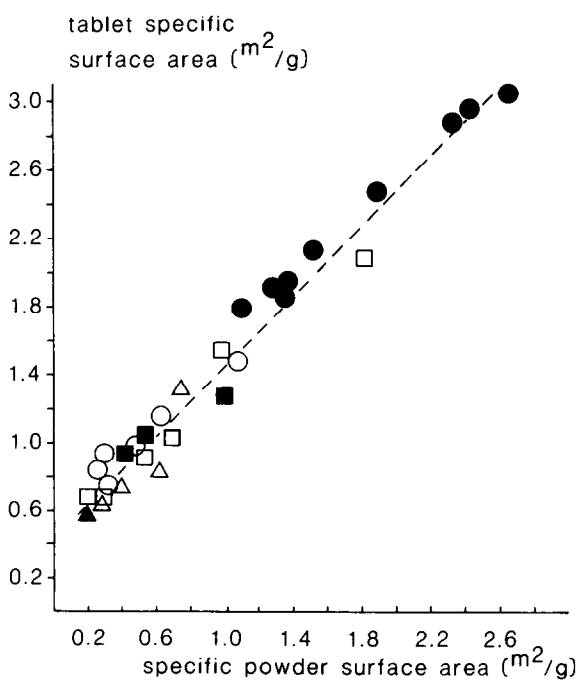

Fig. 5. Specific surface area of tablets compacted at 37.5 MPa versus specific powder surface area of the starting material. Symbols as in Fig. 1.

In conclusion, it is found that the compactibility of crystalline lactose is predisposed in the particle texture. Irregular particles yield a better binding capacity than smooth crystals. The compactibility as well as the extent of fragmentation are found to be directly related to the powder surface area. Therefore, the actual mechanism of binding is likely to be the same.

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