DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(17&18), 2359-2398 (1993)

CONSOLIDATION AND COMPACTION OF LACTOSE

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Introduction

It is well known that lactose is the most wide used excipient in tablet formulation. It is, however, less known that lactose occurs in one amorphous and different crystalline forms. What is more, same types of lactose can be processed under different process-conditions into different products.

The purpose of this presentation is (1) to focuss the attention on the different properties for direct compression of the different types and products of lactose and to explain the common mechanism of consolidation and compaction of all crystalline types of lactose, differing from the consolidation and compaction of amorphous lactose. Next (2), the phenomenon will be reported of interaction between different particle size fractions of different types of lactose during the process of consolidation. Further (3), the mechanism of consolidation and compaction of lactose granules will be discussed, prepared by dry granulation. Moreover (4), a coherent matrix model will be presented explaining magnesium stearate sensitivity. Finally (5), attention will be paid to the effect of moisture sorption on the strength and internal surface area of tablets.

Lactose types

Lactose is a natural disaccharide and occurs only in the milk of mammals, in which it is the only carbohydrate.

Chemically lactose consists of one galactose and one glucose unit, and exists in two isomeric forms, the so-called α- and ß- form.

Solid α-lactose monohydrate is produced by crystallization from a supersaturated solution at temperatures below 93°C, whereas the ß-form is obtained at temperatures above 93°C. During crystallization of ß-lactose, no water is incorporated in the crystal lattice. Solid ß-lactose exists therefore in the non-hygroscopic anhydrous form only. This in contrast to α-lactose, which occurs in both the hydrous and anhydrous form. Thermal dehydration, or desiccation with suitable liquids like methanol, of α-lactose monohydrate converts the crystals into the anhydrous form. A very hygroscopic product, called unstable anhydrous α-lactose, is formed when α-lactose hydrate crystals are heated at temperatures of 100-130°C. Thermal treatment above 130°C produces a non-hygroscopic product, called stable anhydrous α-lactose. Quick drying of a lactose solution produces amorphous lactose. Absorption of moisture under atmospheric conditions changes amorphous lactose into crystalline lactose. Amorphous lactose is converted into a stable α/ß-compound crystalline product when heated at elevated temperatures (1).

Solid lactose thus exists as:

α-lactose monohydrate,
unstable anhydrous α-lactose,
stable anhydrous α-lactose,
(anhydrous) ß-lactose,
α/ß-compound crystals and as
amorphous lactose.

Pharmaceutical application of lactose products

Powdered α-lactose monohydrate is commonly applied as filler in the preparation of tablets by the process of wet granulation. Sieved crystalline fractions of lactose monohydrate (see Figure 1) are merely used in direct compression systems. Coarse crystalline fractions of α-lactose monohydrate have very good flow properties, but exhibit relatively poor binding. This poor binding challenged the interest in the properties of the other types of lactose and in the application of the different lactose products in formulations for the direct compression of tablets.

Anhydrous α-lactose (see Figure 1) is produced by thermal dehydration of crystalline fractions of α-lactose monohydrate. This process results into a product with dramatically increased binding capacity, but keeping the (excellent) flow properties of the original material. The phenomenon of increased binding will be discussed later. It should, however, already be noted that the surface texture of the particles of anhydrous α-lactose has changed as compared to the original α-lactose monohydrate crystals.

The commercially available so-called anhydrous lactoses (see Figure 2) merely contain about 80% of (anhydrous) ß-lactose, next to about 20% of anhydrous α-lactose. These products are mostly produced by roller drying of a lactose solution and should be called 'high ß-content anhydrous lactose'. So-called roller dried ß-lactose exhibit good binding but moderate fluidity.

Spray dried lactose was introduced in 1956 and is produced by spray drying a suspension of lactose crystals in a solution of lactose. This process results into a final product which is build up of α-lactose monohydrate crystals, glued together with amorphous lactose, or lactose glass (see Figure 2). Spray dried lactose is mostly characterized as a direct compression excipient with both good binding and good fluidity. Storage of the product under humid conditions is, however, troublesome because of conversion of

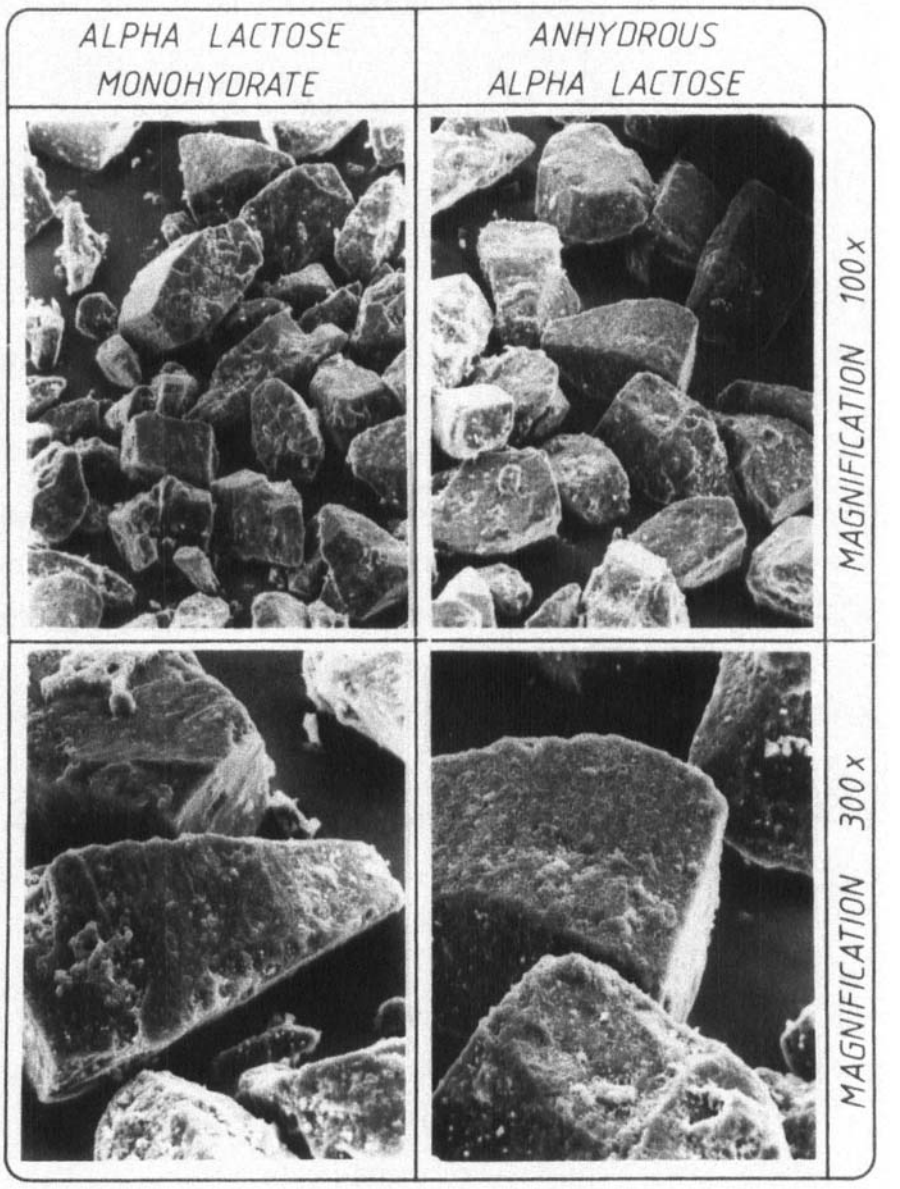

FIGURE I
SEM of α-lactose monohydrate and of anhydrous α-lactose

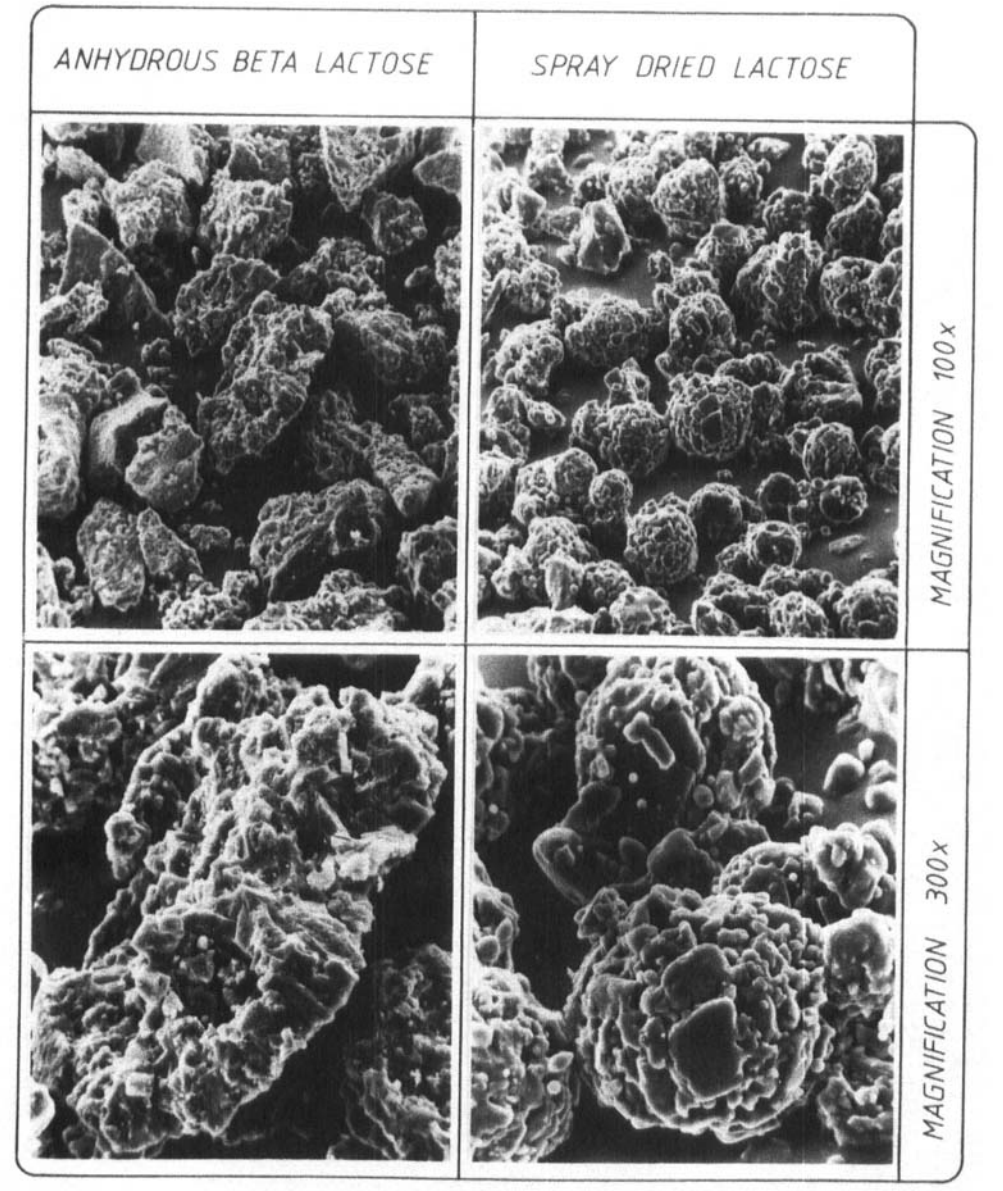

FIGURE 2
SEM of roller dried β-lactose and of spray dried lactose

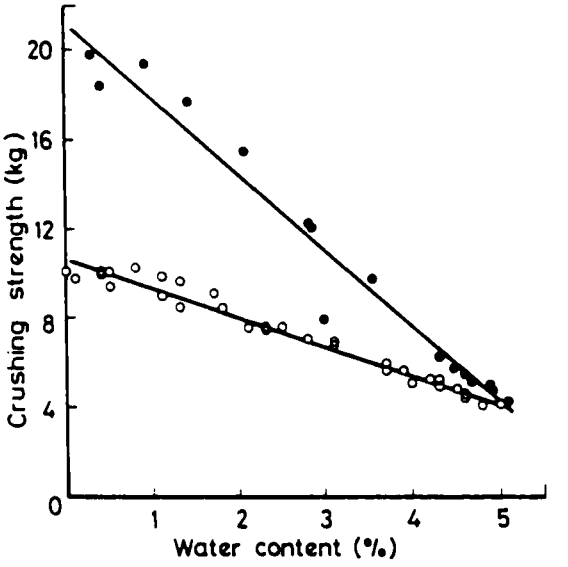

FIGURE 3
Effect of thermal (○) and chemical (●) dehydration of α-lactose monohydrate

the amorphous lactose into the crystalline form, resulting into clumping of the powder mass.

From this survey it is concluded that the different commercially available lactose products all differ in properties for direct compression.

Mechanism consolidation and compaction of lactose

Crystalline lactose

All these different properties can successfully be reduced to one denominator, because of the existence of one coherent mechanism for the consolidation and compaction of the different types of lactose (2).

Figure 3 illustrates the dramatic increase in binding capacity of α-lactose monohydrate with decreasing water content (3). It should be noted that the binding capacity is much more increased by chemical desiccation of the α-monohydrate crystals than by thermal dehydration. This difference in

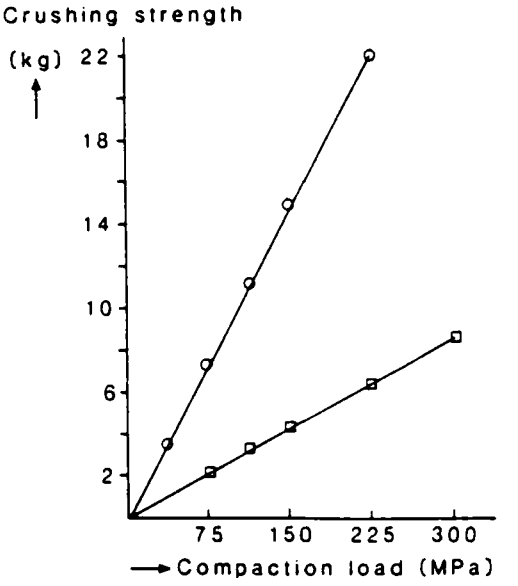

FIGURE 4
Binding profile of α-lactose monohydrate (□) and of anhydrous α-lactose (○)

behaviour goes with a difference in surface texture of the two fully dehydrated products; the chemically dehydrated crystals show a much more pronounced surface roughness than the thermally dehydrated lactose crystals.

Figure 4 shows the crushing strength profile of tablets compressed from 100-125 μm sieve fractions of α-lactose monohydrate and of fully dehydrated (anhydrous) α-lactose, respectively. The results point to a binding capacity for the anhydrous α-lactose which is almost 4 times higher as compared to the corresponding α-lactose monohydrate crystals.

In contrast to this great difference in compactibilty the two types of tablets exhibited almost equal porosities with compaction load.

Application of mercury porosimetry (see Figure 5) on both tablets of α-lactose monohydrate and of anhydrous α-lactose resulted, however, into

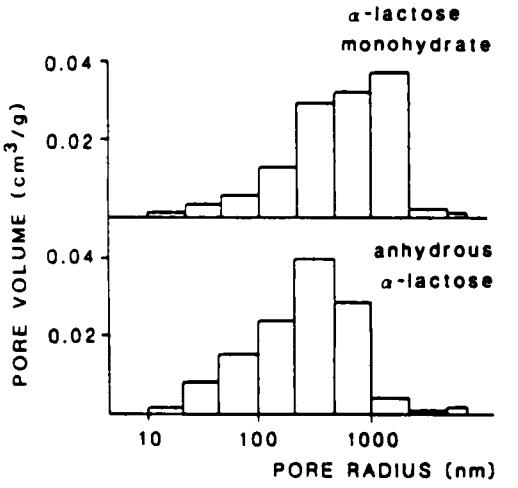

FIGURE 5
Pore volume distribution of tablets, compressed from 100-125 μm fractions of different types of lactose. Compaction load 113 MPa

totally different pore size distributions. The figure shows much smaller pores for the tablets compressed from the anhydrous α-lactose as compared to the α-lactose monohydrate.

Assuming cylindrical pores, the tablet pore surface area (S_m) is related to the pore volume (δV) and pore diameter (d) according to the equation given: $S_m = 4.\Sigma\ \delta V / d$

Applying mercury porosimetry the pore surface area of a tablet can be calculated from the volume of the pores with diameter d, filled with mercury. From this equation it can be seen that the pore surface area of the tablets, having the same total porosity, will increase with decreasing pore size. The observation of much smaller pores for the anhydrous α-lactose tablets, imply much higher internal pore surface area for the anhydrous tablets than for the monohydrate tablets.

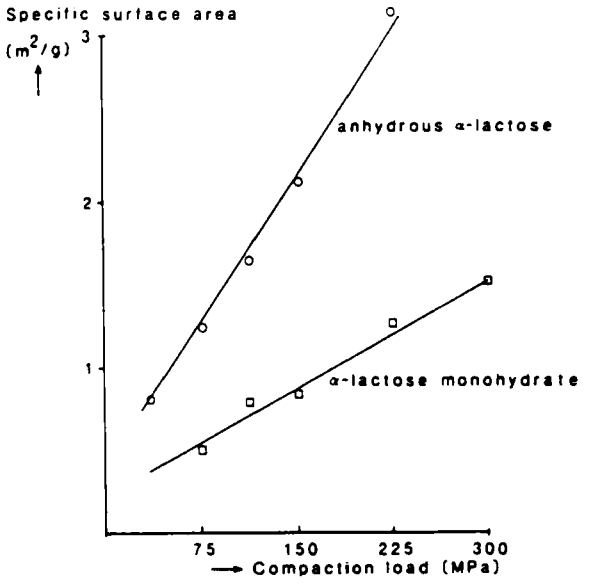

FIGURE 6
Specific surface area of tablets, compressed from 100-125 μm fractions of two different types of crystalline lactose, calculated from mercury porosimetry measurements

The differences in internal pore surface area between the tablets of anhydrous α-lactose and α-lactose monohydrate, respectively, are illustrated in Figure 6, expressing the relation between internal pore surface area of the tablet and compaction load. The tablets of anhydrous α-lactose indeed exhibit a much faster increase in internal pore surface area than the tablets of α-lactose monohydrate (4).

The more interesting is the observation of a similarity between the increase in crushing strength with the compaction load (see Figure 4) and the increase in tablet pore surface area with the compaction load (see Figure 6). The results clearly show a much faster increase for both the crushing strength and the tablet pore surface area of the anhydrous lactose as compared with the hydrous lactose. This similarity points to a correlation between tablet pore surface area and the crushing strength of the tablets.

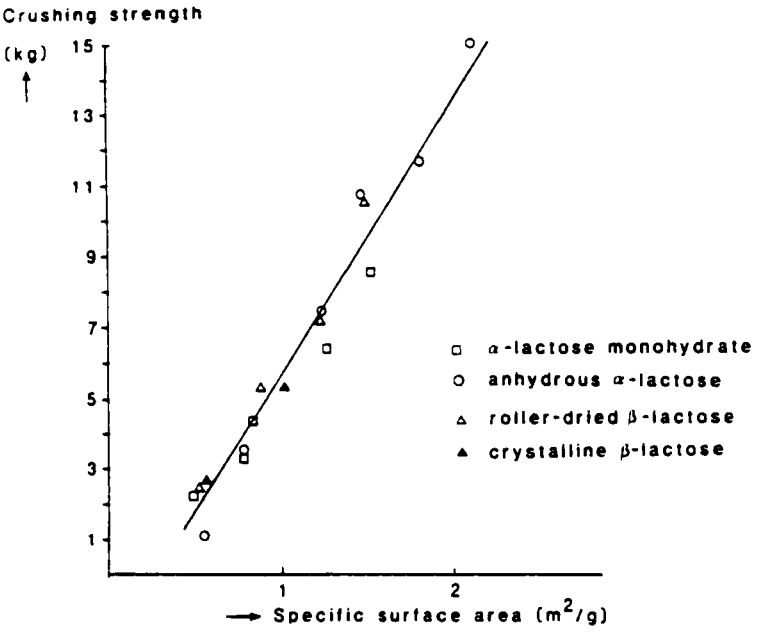

FIGURE 7
Relation between surface area and crushing strength of tablets compressed from different types of crystalline lactose

Indeed a unique relationship (see Figure 7) was found between the crushing strength of the tablets and the tablet pore surface area. The tablets were compressed at different compaction loads from sieve fractions of 100-125 μm. As seen the relationship was found to hold for all types of crystalline lactose: α-lactose monohydrate, anhydrous α-lactose, roller dried ß-lactose and crystalline ß-lactose.

Moreover (see Figure 8), the unique relationship proved to be valid for the whole range of particle sizes (32 - 400 μm) tested (5).

These results point to the conclusion that neither the presence of water of crystallization nor the α/ß-ratio has any influence on the bonding properties of the (crystalline) lactoses tested. The bonding mechanism seems to be the same for all different types of crystalline lactose. The crushing

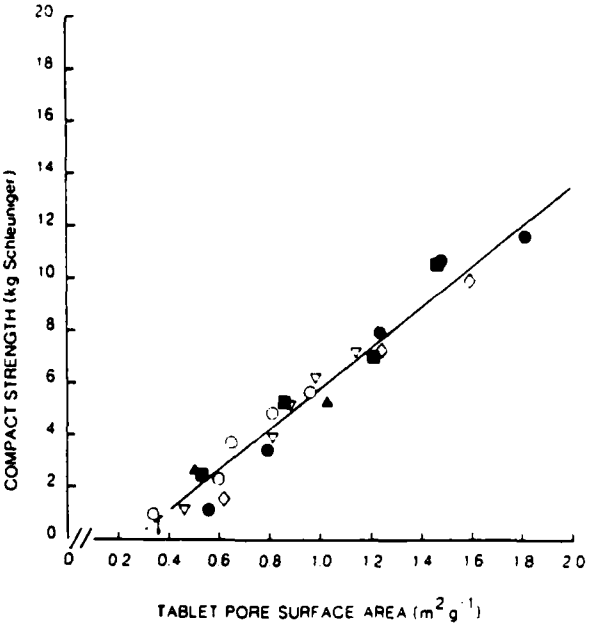

FIGURE 8
Relation between surface area and crushing strength of tablets compressed from different types of crystalline lactose and different particle sizes

strength of the tablets is only determined by the pore surface area of the tablet, initially present and created by fragmentation during the consolidation process.

The relationship found is recently explained by Leuenberger (6). He presented a theoretical model for the calculation of the tensile strength of tablets. Assuming that a tablet is made up of spherical isometric particles and that the strength of all types of crystalline lactose tablets is caused by Van der Waals dispersion forces, acting at the coordination points of the particles, a proportionallity is obtained between the tensile strength and the internal specific surface of the tablet. This theoretical approach enables the calculation of coordination numbers of the particles in a tablet and illucidates the unique relationship between the crushing strength and the internal

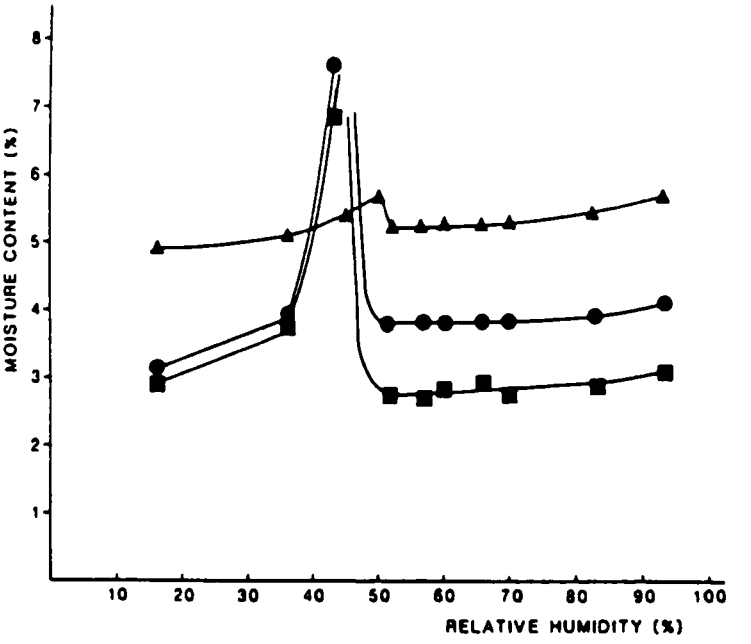

FIGURE 9
Moisture content of spray dried lactose (▲), of amorphous lactose (●) with α/β ratio 70/30 and of amorphous lactose (■) with α/β ratio 50/50

specific surface area of a tablet, as found experimentally for all types of crystalline lactose.

It is to be noted, that the internal specific surface area of a tablet is the ultimate result of both the initial specific surface area of the powder and the process of fragmentation during consolidation.
Realizing that the specific area of a tablet is directly related to its crushing strength, it is concluded that a high specific surface area of the powder to be compressed is a precondition for a good compactibility of a crystalline lactose product.

Amorphous lactose

The consolidation and compaction properties of amorphous lactose differ from those of crystalline lactose (7).

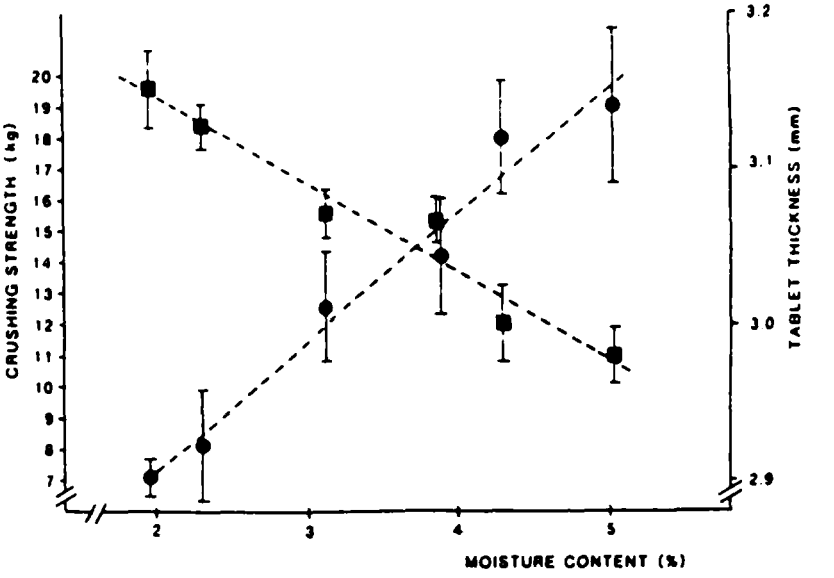

FIGURE 10
Compact strength (•) and tablet thickness (▪) of amorphous lactose at 75 MPa compaction load (13 mm tablets)

Amorphous lactose is instable when exposed to atmospheric conditions; the extend of water uptake is dependent upon the relative humidity and temperature. Figure 9 shows the water equilibrium content at 20°C as a function of the relative humidity for fully amorphous lactose and for commercially available spray dried lactose containing 15% amorphous lactose. On increasing relative humidities, amorphous lactose absorbs moisture up to about 9%. Next, it crystallizes under the loss of water. The α-part of the amorphous lactose is converted into crystalline α-lactose monohydrate, whereas the ß-part of the amorphous lactose is transferred into crystalline (anhydrous) ß-lactose. The ultimate water content is consequently determined by the amount of α-lactose present in the original amorphous product.

The compactibility of fully amorphous lactose is found to be strongly dependent on the moisture content of the product. This is illustrated in

TABLE 1

Specific surface area and crushing strength of amorphous lactose tablets

compaction pressure (MPa)	pore volume (cm^3/g)	specific surface area (m^2/g)	crushing strength (kg)
38	0.195	0.53	< 1
55	0.180	0.64	6.9
75	0.157	0.66	10.9
95	0.155	0.55	17.3
115	0.095	0.61	20
150	0.060	0.56	>20
225	0.030	0.54	>>20

Figure 10 for tablets, compressed at 75 MPa. The tablets showed increasing crushing strength with increasing water content, but decreasing thickness. These results suggest an increasing compactibility, caused by an increasing consolidation of the amorphous lactose, with increasing water content.

Mercury porosimetric measurements showed, however (see Table 1), no significant change in pore surface area, but a very strong increase in crushing strength of the tablets with increasing compaction load. This result disagrees with the validity of a relationship between the internal specific surface area and crushing strength of tablets compressed from all types of crystalline lactose. The phenomenon, as found for the amorphous lactose tablets, of no increase in tablet surface area with increasing compaction load points to plastic deformation of fully amorphous lactose under compression.

The difference in consolidation between amorphous and crystalline lactose agrees with the specific behaviour of plastic deformation of microcrystalline cellulose and of fragmentation of dicalcium phosphate under compression.

In Table 2 both the tablet surface areas, determined by mercury porosimetry, and the crushing strengths of the tablets are given at different compac-

TABLE 2

Crushing strength and specific surface area of microcrystalline cellulose and of dicalcium phosphate dihydrate tablets (13 mm)

compaction load (MPa)	pore volume (cm^3/g)	crushing strength (kg)	specific surface area (m^2/g)
microcrystalline cellulose			
7.5	0.663	4.7	1.21
19.0	0.529	13.4	1.37
37.5	0.290	26	1.31
dicalcium phosphate dihydrate			
37.5	0.221	1.1	0.66
75	0.168	2.2	0.88
150	0.135	4.3	1.10
225	0.116	6.2	1.26
300	0.104	8.5	1.65

tion loads. The data clearly show for Avicel an almost constant tablet pore surface area, but a very strong increase in crushing strength with increasing compaction load. This result is consistent with the generally accepted behaviour of plastic flow under load for microcrystalline cellulose. Dicalcium phosphate dihydrate, on the contrary, is known to consolidate by brittle fracture. This product indeed showed an increase in tablet pore surface area with increasing crushing strength of the tablets.

In conclusion, fragmentation is the predominant mechanism of consolidation for both dicalcium phosphate dihydrate and all crystalline lactoses. In contrast to this, both microcrystalline cellulose and amorphous lactose consolidate rather more by plastic deformation than by particle fragmentation.

Spray dried lactose

So-called spray dried lactose is produced by spray drying a suspension of α-lactose monohydrate crystals in a solution of lactose. As a result the

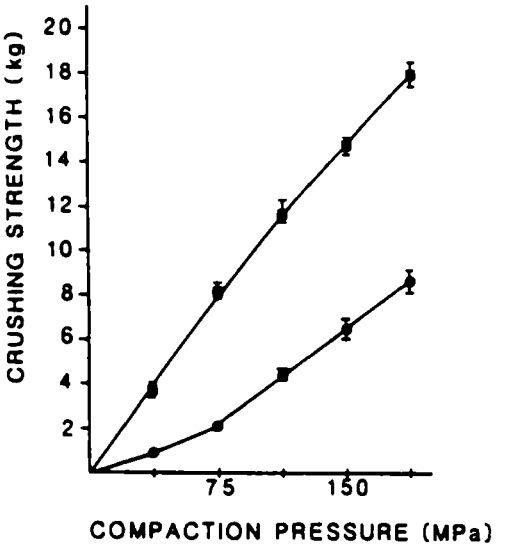

FIGURE 11
Binding profile of α-lactose monohydrate (●) and of spray dried lactose (■)

product is build up of primary α-lactose monohydrate crystals glued together by amorphous lactose into spherical agglomerates (see Figure 2). Commercially available spray dried lactose contains only about 15% of amorphous lactose. The other 85% consists of α-lactose monohydrate crystals.

Knowing the difference in consolidation behaviour between crystalline and amorphous lactose, the binding properties of spray dried lactose was expected to differ from that of the fully crystalline product (7).

Comparison (see Figure 11) of the crushing strength of tablets compressed from a sieve fraction of loose α-lactose monohydrate crystals, with tablets compressed from the same fraction worked up with 15% of amorphous lactose indeed showed a strongly increased compactibility for the spray dried product.

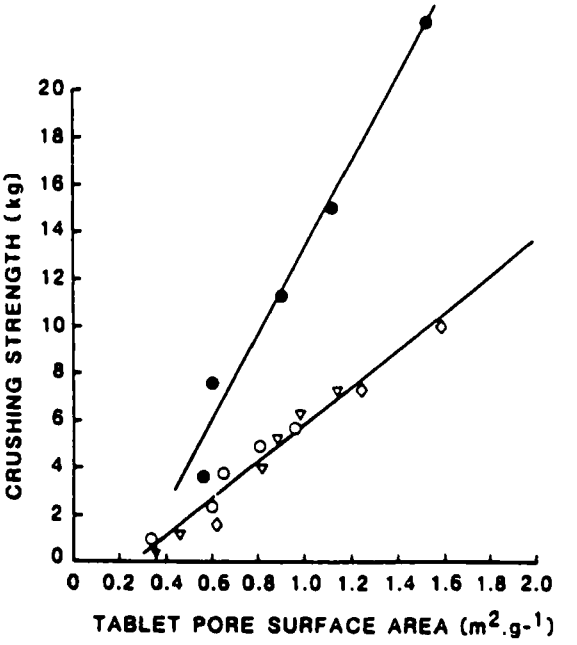

FIGURE 12
Relation between specific surface area and crushing strength of tablets compressed from different fractions of α-lactose monohydrate (open symbols) and from spray dried lactose (closed symbols)

It was self-evident to correlate the crushing strength with the pore surface area of the tablets.

The results are illustrated in Figure 12. As was expected, the data for the spray dried samples did not fit the unique relationship found for all fractions of crystalline lactose. The tablets from the spray dried samples, containing 15% amorphous lactose, all exbibited about the same tablet pore surface area as compared to the tablets compacted at the same compaction load from the referring original loose α-lactose monohydrate powder, but showed much higher crushing strengths.

From the previous results it may be assumed, that the **number** of binding points will increase with increasing fragmentation of the α-lactose monohydrate crystals under compression. Additionally, the binding **surface** will be

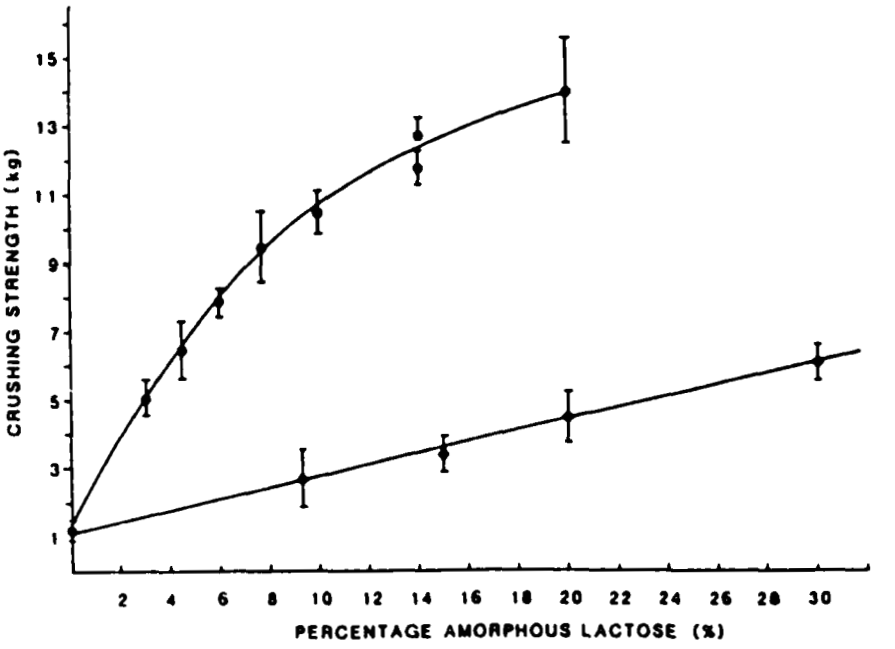

FIGURE 13
Effect amorphous lactose present in a physical mixture with dicalcium phosphate dihydrate (♦) and as spray dried product (●)

increased at the binding points by plastic deformation of the amorphous lactose present. Fragmentation and plastic deformation will consequently result into an increased binding capacity of spray dried lactose, as compared to the corresponding α-lactose monohydrate crystals only.

This conclusion agree with the theory of Leuenberger, mentioned earlier. Calculation of the coordination numbers in tablets of spray dried lactose indeed result into values which point to the phenomenon of plastic deformation under compression.

The effect of increased compactibility by the presence of amorphous lactose on the surface of crystalline lactose particles can be practized on other excipients as primary particles.

Figure 13 shows the relation between crushing strength and amount of amorphous lactose present next to dicalcium phosphate dihydrate. The

results show for the physical mix of DCP with amorphous lactose only slightly increasing crushing strength with increasing lactose content. The spray dried products exhibited, however, a dramatic increase in binding capacity with increasing amount of amorphous lactose. The flattening of the binding profile points to saturation of the surface of the primary DCP particles with the glassy lactose.

These results illustrate the possibility of increasing the compactibility of an excipient by fixing a bounded layer of a plastically deforming material on to the surface of the primary particles.

Consolidation and compaction of powder mixtures of lactose

These and many other studies have been performed on narrow sieve fractions of the powders tested. Commercially available excipients for direct compression generally show, however, a broad range of particle diameters. The study on the consolidation and compaction of lactose has therefore been extended to the study of binary powder mixtures (8).

To start with, binary powder mixtures of same particle size fractions of four different types of crystalline lactose were compressed into tablets and tested on crushing strength and specific surface area (9).

Figure 14 illustrates the profiles of both crushing strength and specific surface area of the tablets versus the composition of the six different binary blends. The profiles show for all blends and for both, the crushing strength and the specific surface area of the tablets, an almost linear relation with the composition of the blend. This result imply no interaction between the different types of lactose concerning consolidation and compaction, when compressed from binary mixtures of same particle size fraction.

This conclusion is endorsed by the plot (see Figure 15) of crushing strength versus specific surface area of all the tablets tested. As seen, all data from

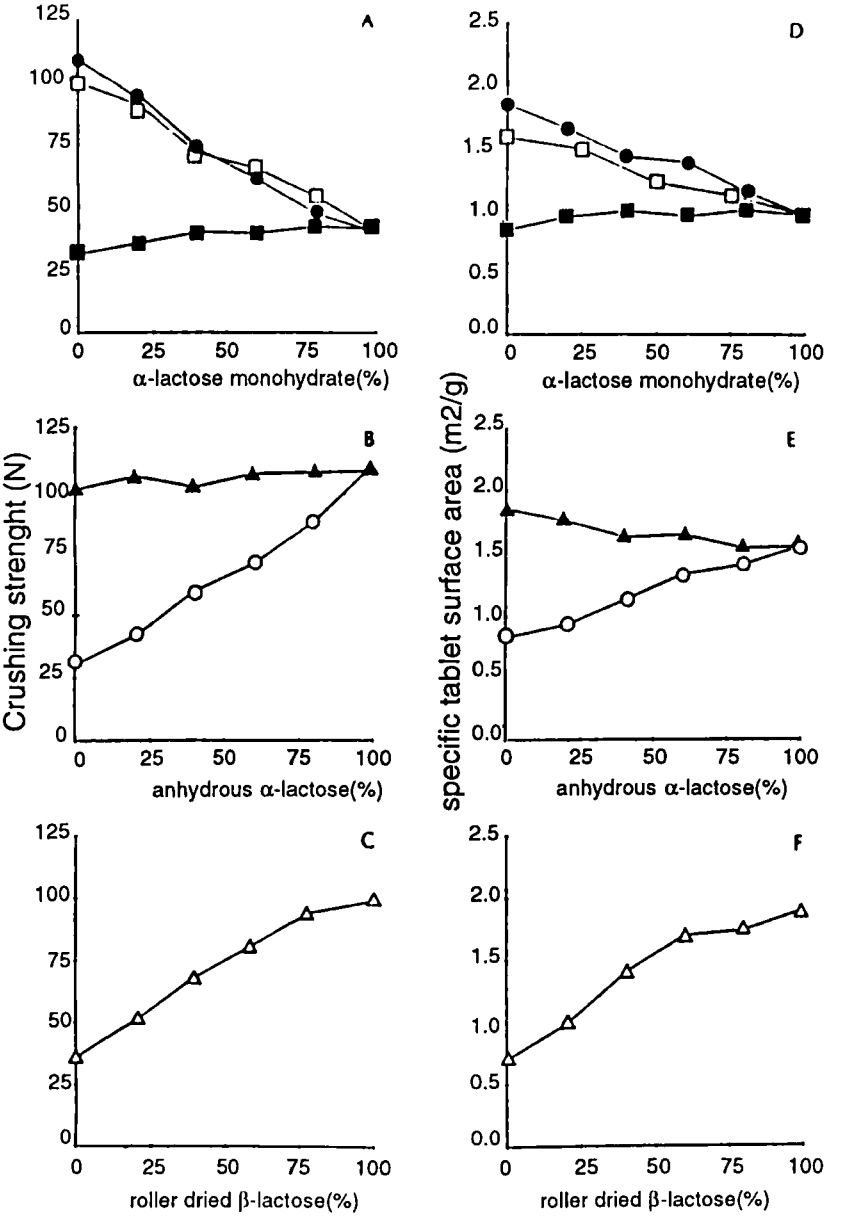

FIGURE 14
Binary blends of same particle size fractions of different crystalline lactoses

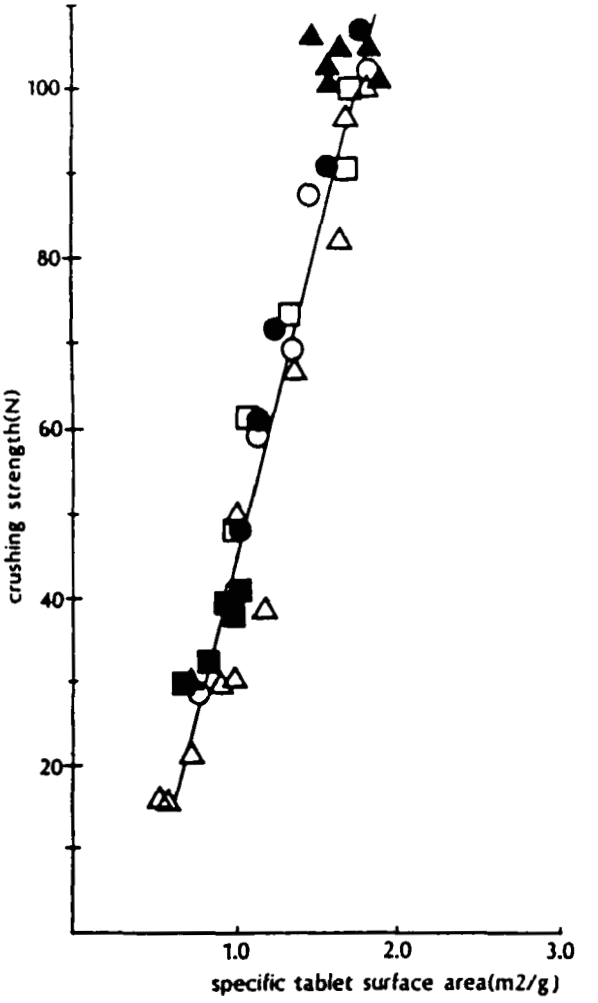

FIGURE 15
Relation between specific surface area and crushing strength of tablets compressed from binary blends of same particle size fractions of different crystalline lactoses

Figure 14 fit the unique relationship between crushing strength and specific surface area of the tablets.

It is therefore concluded that binary mixtures of **same** particle size fractions of different types of crystalline lactose exhibit no interaction between the components during consolidation and compaction.

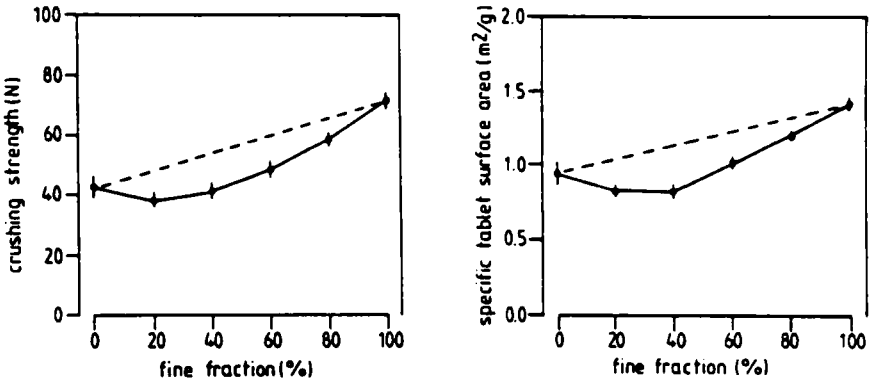

FIGURE 16
Binary blends of coarse (250-315 μm) with fine (32-45 μm) size fractions of α-lactose monohydrate

Interaction between the components is found on compression of **different** particle size fractions of each of the four lactose types (10). Figure 16 illustrates the profiles of both crushing strength and specific surface area of tablets compressed from binary mixtures of course (250-315 μm) and a fine (32-45 μm) fraction of α-lactose monohydrate, versus the weight % of the fine fraction. As seen, the tablets compressed from the blends exhibit lower crushing strengths as compared to the values obtained by linear interpolation of the strength of the tablets compressed form the single sieve fractions. A similar deviation from linearity is shown by the profile of pore surface area of the tablets versus the composition of the blends. The decreased surface areas of the tablets compressed from the blends point to decreased fragmentation under compression.

This is evident from the profiles (see Figure 17) of both specific powder and specific tablet volume versus weight % of the fine fraction in the blend. The profiles show decreased specific volumes, corresponding with decreased porosities, of both the powder beds and the tablets compressed from the powder beds. The decreased powder volumes, corresponding with

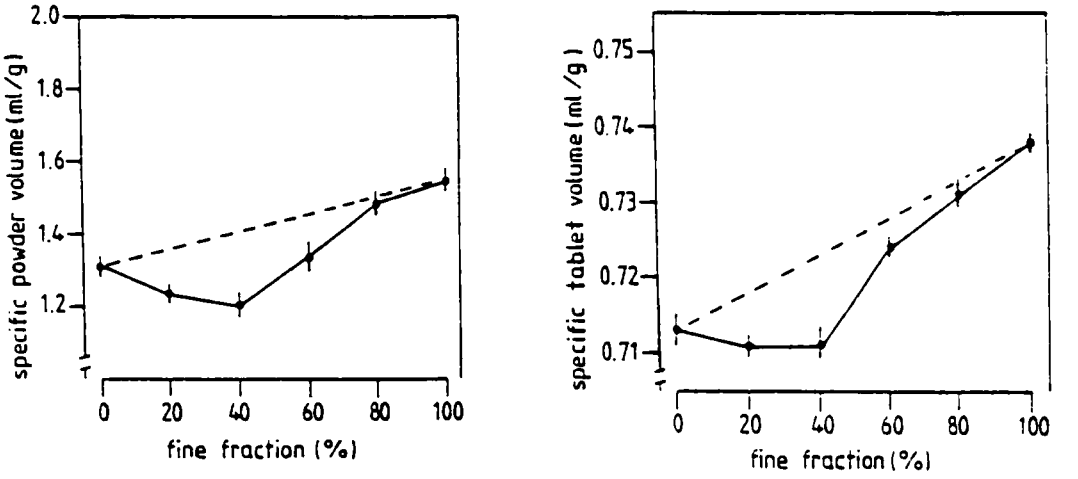

FIGURE 17
Binary blends of coarse (250-315 μm) with fine (32-45 μm) size fractions of α-lactose monohydrate

increased packing densities, are caused by percolation of smaller particles into the voids between the coarse particles. Next, it is to be realized that packing of small particles in between coarse particles, and reversed coarse particles in between fine particles, decreases the fragmentation potential of the particles in a particulate system. Knowing from literature that the packing density of a powder bed increases with the diameter ratio between large and small particles, it was to be expected that the crushing strength of tablets compressed from blends of coarse and fine particles would decrease with increasing diameter ratio. This is indeed shown by the results as illustrated in Figure 18. Tablet strengths are expressed in the figure, for reason of comparison, as relative deviation from the linear interpolated values of the strength of the tablets compressed from the corresponding single fractions. It is noted, that maximum deviations from linearity are found at 40% finer fraction in the blends. The results obtained showed for both the crystalline types, α-lactose monohydrate and crystalline ß-lactose, up to 30% lower crushings strengths and specific surface areas of the

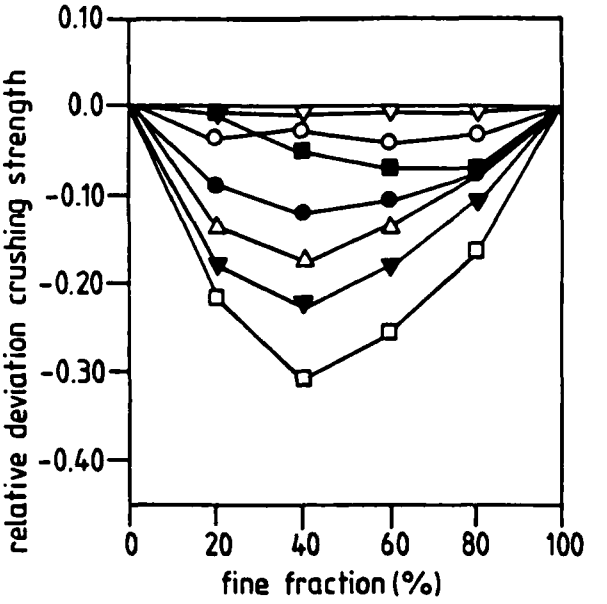

FIGURE 18
Binary blends of coarse (250-315 μm) with finer (from (▽) 200 down to 32 μm (□)) size fractions of α-lactose monohydrate

tablets, as compared to the values calculated by linear interpolation of the data obtained for the corresponding single powder fractions, when compressed from binary mixtures of 60% coarse (250-315μm) with 40% fine (32-45 μm). Much smaller deviations from the interpolated values were found for the the granular types, roller dried ß-lactose and anhydrous α-lactose.

Roller dried ß-lactose is manufactured, as mentioned before, by rapid crystallization of a lactose solution on two steam heated rollers, exceeding a temperature of 93°C. After drying the anhydrous product is scraped from the rollers, ground and sieved, producing a 'granular' product, consisting of aggregates of many small crystals. A 'granular' type of product is also obtained by thermal dehydration of α-lactose monohydrate, producing anhydrous α-lactose. The original product α-lactose monohydrate is, on the

TABLE 3

Degree of particle fragmentation of a coarse (250 - 315 μm) and a fine (32 - 45 μm) fraction of four crystalline lactose types on compaction into tablets (13 mm) at a compression force of 10 kN

	S_p (m^2/g)	S_t (m^2/g)	$(S_t - S_p)/S_p$
Roller dried β-lactose			
Coarse	0.17	1.15	5.8
Fine	0.38	1.46	2.8
Anhydrous α-lactose			
Coarse	0.21	1.31	5.2
Fine	0.62	1.93	2.1
Crystalline β-lactose			
Coarse	0.06	0.65	9.8
Fine	0.17	0.95	4.6
α-Lactose monohydrate			
Coarse	0.07	0.74	9.6
Fine	0.18	1.05	4.8

S_p, specific powder surface area; S_t, specific tablet surface area; $(S_t - S_p)/S_p$, degree of fragmentation

contrary, non-granular and is produced, just like crystalline ß-lactose, by slow crystallization.

The granular types differ in particle morphology from the non-granular types (11). Table 3 depicts that the granular types, roller dried ß-lactose and anhydrous α-lactose, exhibit much higher powder specific surface areas than the non-granular types, crystalline ß-lactose and α-lactose monohydrate. Moreover, the granular types demonstrate less fragmentation during consolidation, where the degree of fragmentation (St-Sp)/Sp is expressed as relative increase in surface area when compressing a powder with surface area Sp into a tablet with surface area St. Realizing that the granular types

of lactose exhibit much higher binding capacities than the non-granular types, it is evident that the greater compactibility potentials are caused rather more by the higher powder specific surface areas than by the lower degrees of fragmentation of the granular types of lactose.

Effect of dry granulation on consolidation and compaction of lactose

Tablet formulation often involves the preparation of granulations by dry, but mostly by wet granulation. The main purpose of granulation is to improve fluidity by enlarging the particle size of the particulate mass. Although it is realized that granulation may affect the properties of the powder (blend) with regard to consolidation and compaction, relative few studies, as compared to the great number of studies on direct compression, have been performed concerning the relation between the primary properties of the powder(s), the characteristics of the granulation and the properties of the final tablets (12).

Table 4 lists the effect of dry granulation, slugging, on the compressibility and compactibility of α-lactose monohydrate. Both a coarse (250-300μm) and a fine (<63 μm) sieve fraction of ungranulated α-lactose monohydrate were compresssed at different compaction forces into 13 mm tablet-slugs and analysed on crushing strength and porosity. These slugs were subsequently crushed and sieved into a coarse fraction (212-425 μm) of granules, compresssed at 20 kN into 13 mm tablets, and analysed again on crushing strength and porosity. The results show for the slugs compressed from the ungranulated powder, as expected, increasing crushing strengths and decreasing porosities with increasing compaction forces. Compaction of the granulates, produced from these different slugs resulted, unexpectedly, into tablets with almost equal crushing strength and porosity. This imply that strength and porosity of the granules seem to have almost no effect on the strength and porosity of the tablets compressed form these granules. Moreover it is to be noted that almost equal crushing strengths and

TABLE 4

Strength and porosity of slugs compacted from coarse (250 - 300 μm) and fine (< 63 μm) fractions, respectively, of α-lactose monohydrate and of tablets compacted from a granule fraction (212 - 425 μm) prepared from the slugs

Fraction (μm)		Cf (kN)	Cs (N)	ε
α-Lactose monohydrate				
	Slugs			
250 - 300	A	5	6(1)	0.23
	B	20	40(2)	0.12
	C	40	65(9)	0.08
< 63	D	5	5(1)	0.25
	E	40	100(9)	0.10
	Tablets			
From:	A	20	32(1)	0.12
	B	20	35(4)	0.13
	C	20	33(6)	0.13
	D	20	44(2)	0.15
	E	20	45(4)	0.15

Cf, compaction force; Cs, crushing strength; ε, porosity

porosities were obtained for both the slugs and the tablets, compresssed at the same compaction force (20 kN) from ungranulated powder and the granules, respectively.

Analysing the specific pore surface areas of the tablets, slugging evidently results into increased surface areas but no increase in crushing strength of the tablets compressed from these slugs. This is illustrated in Figure 19 for both α-lactose monohydrate and roller dried ß-lactose by plotting crushing strength versus specific pore surface area of tablets, first compressed into slugs from ungranulated powder and next compressed from the granulated

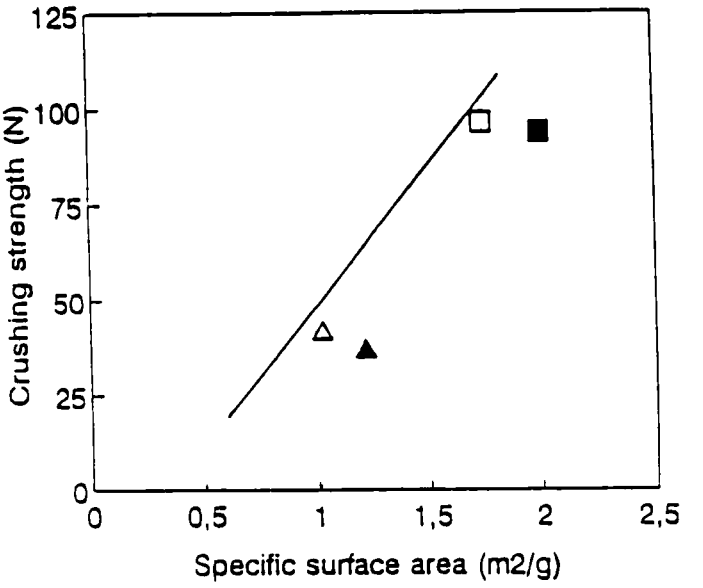

FIGURE 19
Relation between specific surface area and crushing strength of tablets compressed from non-granulated (open symbols) and from dry-granulated (closed symbols) lactose

slugs. The increased surface area of the tablets compressed from the slugs apparently do not contribute to increased bonding. This result points to differences in consolidation mechanism between ungranulated and granulated crystalline lactose and endorses again that dry granulation, or slugging, seems to have little influence on the compactibility of crystalline lactose. Bonding strength shows to be more affected by the size of the granules to be compresssed (see Table 5).

Increasing size fractions of the granules result into decreasing crushing strengths of the tablets compresssed from the granules, prepared by slugging of α-lactose monohydrate and roller dried ß-lactose, respectively. There seems to be a relation between compactibility and size of the granules to be compressed. Next, it may be suggested that differences in granule size may result on compression into differences in pore size

TABLE 5

Specific permeametry surface area, calculated with granule density, and strength of tablets (13 mm) compacted at 5 kN from granule fractions prepared from 40 kN slugs of α-lactose monohydrate and roller dried β-lactose, respectively

Fraction (μm)	Sv_g (m2/g)	Cs (N)
α-Lactose monohydrate		
63 - 106	0.44	11
106 - 212	0.41	10
212 - 425	0.39	6
425 - 850	0.31	6
850 -1400	0.23	5
Roller dried β-lactose		
63 - 106	0.62	26
106 - 212	0.33	20
212 - 425	0.26	16
425 - 850	0.18	18
850 -1400	0.10	16

Sv_g, specific permeametry surface area; Cs, crushing strength

distribution of the tables. Determination (see Figure 20) by mercury porosimetry of the pore size distribution of tablets compacted at 5 kN from a coarse (212-425 μm) and a fine (63-106 μm) fraction, respectively, of granules prepared from 5 kN slugs of roller dried ß-lactose, indeed showed finer pores for the tablets compressed from the finer fraction of granules. It is obvious that decreasing granule sizes will yield tablets with finer pore stuctures and higher crushing strengths. This suggests a relation between strength and pore size distribution. However, (see Figure 21) different pore size distributions were found for tablets with equal crushing strength, compacted from granules (212-425 μm), prepared from 5 kN and 40 kN

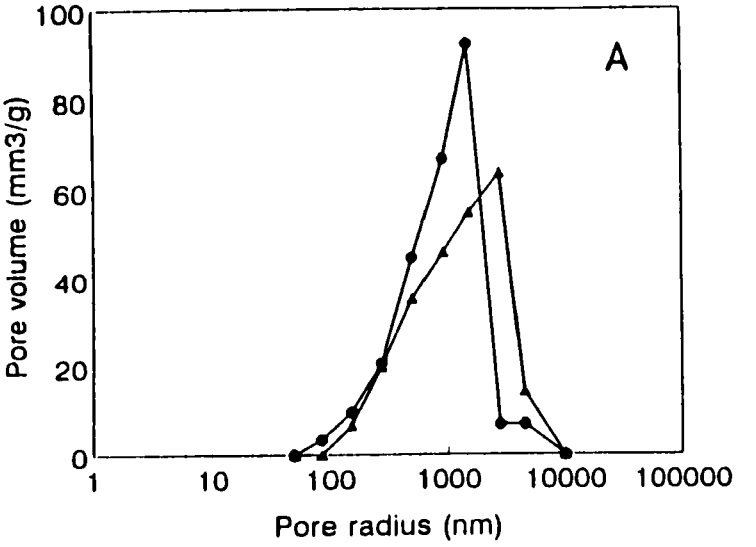

FIGURE 20
Pore size distribution of tablets compressed from coarse (▲) and fine (●) fractions of dry-granulated β-lactose

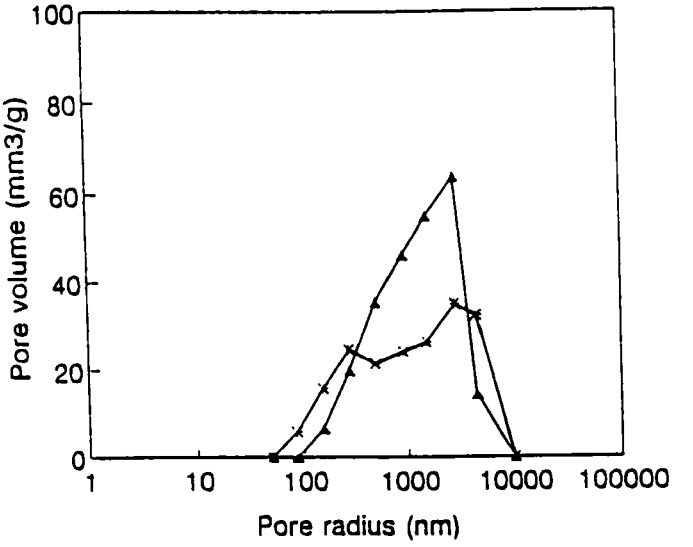

FIGURE 21
Pore size distribution of tablets with equal crushing strength compressed from dry-granulated β-lactose

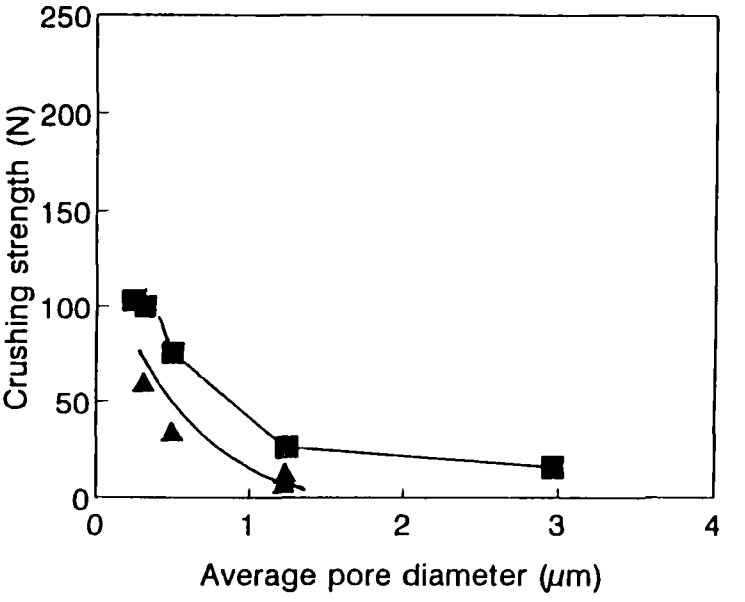

FIGURE 22
Tablets compressed from dry-granulated α-lactose monohydrate (▲) and from dry-granulated β-lactose (■)

slugs of roller dried ß-lactose, respectively. The pore size distribution demonstrates that a duality in intra- and inter-granular pore system is sustained for the tablets compressed from the 40 kN slugs, but is lost for the tablets compresssed from the 5 kN slugs. Obviously, the structural properties of the granules influence the pore structure of the tablets, although no direct relationship between pore size distribution and tablet strength is shown. However, when the strength of the tablets is plotted versus the average pore diameter within the tablets (see Figure 22), decreasing tablet strengths correlate with increasing pore diameters.

Moreover, it is shown that the two different lactose types exhibit different courses between strength and average pore diameter of the tablets.

Considering the results discussed, it is apparent that the compactibity of granules prepared by dry granulation, or slugging, of crystalline lactose is

neither affected by the strength nor the porosity of the slugs, but is principally determined by the properties of the lactose powder, the size of the granules and the compaction pressure. Differences in structure of the granules, such as porosity and strength, are eliminated during compaction and do not affect the compactibility of the granule particles. The granule particles seem to sustain their integrity to some extend during compression. However, consolidation of the granules involves both intra- and intergranular porosity changes. Mercury porosimetry reveals that the whole pore system determines tablet strength. The observed differences in compactibility between the granules of α-lactose monohydrate and roller dried ß-lactose are suggested to be caused by differences in internal granular structure.

A coherent matrix model for magnesium stearate sensitivity

Lubricants, magnesium stearate in particular, are notorious for its deteriorating effect on the crushing strength of tablets.

Magnesium stearate interferes bonding by the formation of a lubricant film around particulate solids during the process of dry blending. It is generally accepted that fragmenting particles are less sensitive or even insensitive to magnesium stearate, as compared to plastically deforming solids, like sodium chloride and starch. This is attributed to the creation of clean magnesium stearate free excipient surfaces by the process of fragmentation during consolidation of the particulate mass. Magnesium stearate sensitivity is even applied as an indication of the fragmentation propensity of particulate solids. Table 6 presents the degree of fragmentation, (St-Sp)/Sp, and the lubricant sensitivity ratio, (LSR), of both α-lactose monohydrate and roller dried ß-lactose. Lubricant sensitivity ratio is defined as the ratio between the decrease in crushing strength of the tablets due to mixing with the lubricant and the crushing strength of the unlubricated tablets. According to the model of the creation of lubricant free surfaces by fragmenta-

TABLE 6

Specific surface area, extent of fragmentation and Lubricant Sensitivity Ratio of tablets (13 mm) compacted at different forces from a fraction (250 - 315 μm) of α-lactose monohydrate and roller dried β-lactose, respectively

Fraction	Cf	S_t	$(S_t-S_p)/S_p$	LSR
α-lactose monohydrate				
250 - 315 μm	0	0.08 (=S_p)	-	-
	15	0.76	8.5	0.38
	20	0.88	10	0.43
	30	0.96	11	0.56
roller-dried β-lactose	0	0.17 (=S_p)	-	-
	5	0.70	3.1	0.29
	10	1.15	5.8	0.39
	15	1.42	7.4	0.39
	20	1.68	8.9	0.42

Cf, compression force; S_p, specific powder surface area; S_t, specific tablet surface area; $(S_t - S_p)/S_p$, extent of fragmentation, LSR, Lubricant Sensitivity Ratio

tion of the particles during consolidation, lubricant sensitivity should decrease with increasing degrees of fragmentation. In contrast to this, the data show both increasing degrees of fragmentation and increasing lubricant sensitivities with increasing compression forces (13). Moreover, it is to be noted that a LSR of only 0.4 is in no way consistent with an almost 10-times increase in solid surface area. The suggestion of magnesium stearate migration throughout the powder mass during consolidation is neither tenable. Table 7 demonstrates the effect of decanoic acid coating on different excipients on lubricant sensitivity of the excipients on compression into tablets. The data show almost equal sensitivities for all three strongly

TABLE 7

The effect of lubrication with magnesium stearate (0.5%) and decanoid acid (0.5%), respectively, on the strength of tablets (13 mm) compacted at 20 kN from a fraction (250 - 300 μm) of several materials

Material	magnesium stearate			decanoic acid		
	Cs_u	Cs_l	LSR	Cs_u	Cs_l	LSR
α-lactose monohydrate	42	24	0.43	42	21	0.50
sodium citrate	23	5	0.78	23	11	0.52
dicalcium phosphate dihydrate	32	29	0.09	32	16	0.50

Cs_u, crushing strength of unlubricated tablets; Cs_l, crushing strength of lubricated tablets; LSR, Lubricant Sensitivity Ratio

fragmenting materials. These and other results, including photomicrographs of fractures of lubricated tablets, originate the suggestion that if a coherent three-dimensional matrix of magnesium stearate is present in a particulate mass, created by dry blending, this coherent matrix is largely sustained during the process of powder consolidation (see Figure 23). Fragmentation of the excipient particles during consolidation occurs within the areas surrounded by the magnesium stearate network. Therefore, the increase in internal surface area will contribute only little to the crushing strength of the tablets. The strength of a compact is principally determined by the amount of lubricant matrix formed during dry mixing. Lubricated tablets indeed demonstrate to fail mainly along the interfaces of the original particles.

Effect of moisture sorption by lactose tablets

Finally the attention is focussed on the phenomenon of moisture sorption by tablets (14). It is well known both to general practice and from literatu-

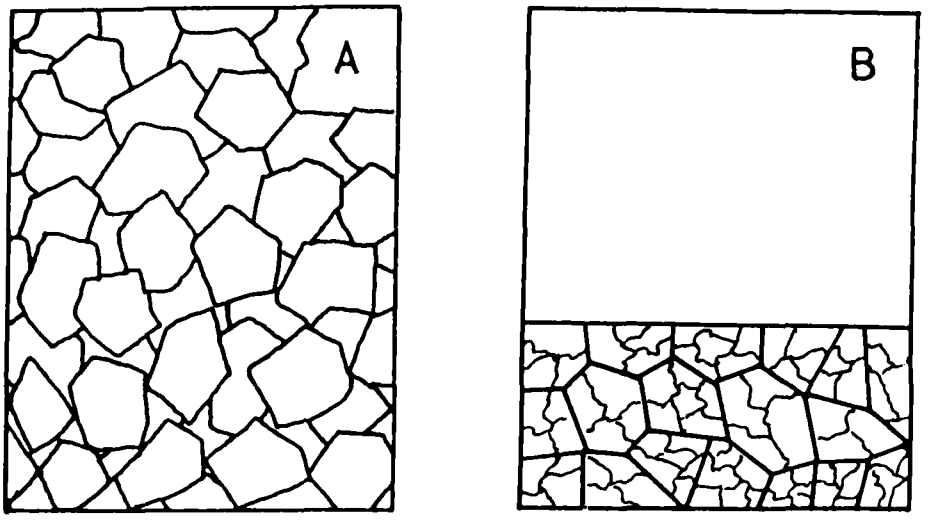

FIGURE 23
Coherent magnesium stearate model on powder consolidation

re that tablets may change in properties on storage. However, very little attention is paid to the consequences of this behaviour.

Figure 24 demonstrates moisture sorption by tablets compacted from both α-lactose monohydrate and roller dried ß-lactose, when exposed to atmospheric humidity. It is to be noted that the tablets did not increase in weight when stored over silica gel. Moreover, it is interesting to note that the sorption profiles were found to be different for the two different crystalline lactose types. This difference in behaviour is also shown (see Figure 25) by plotting the amount of moisture sorbed in 24 hours versus tablet surface area. There seems to be a direct relation between moisture sorption and the initial (BET)-surface area of the tablets determined immediately after ejection from the die. This result indicates moisture uptake by adsorption of water vapour on the internal surface area of the lactose tablets. However, it is interesting to note that the sorption profiles were found to be different for the two different crystalline lactose types, α-lactose monohy-

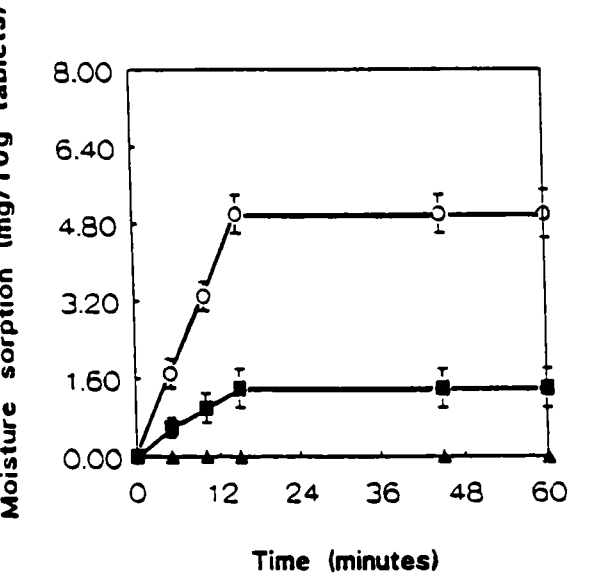

FIGURE 24
Moisture sorption of α-lactose monohydrate (■) and of roller dried β-lactose (○) tablets; (▲) when stored over silica gel

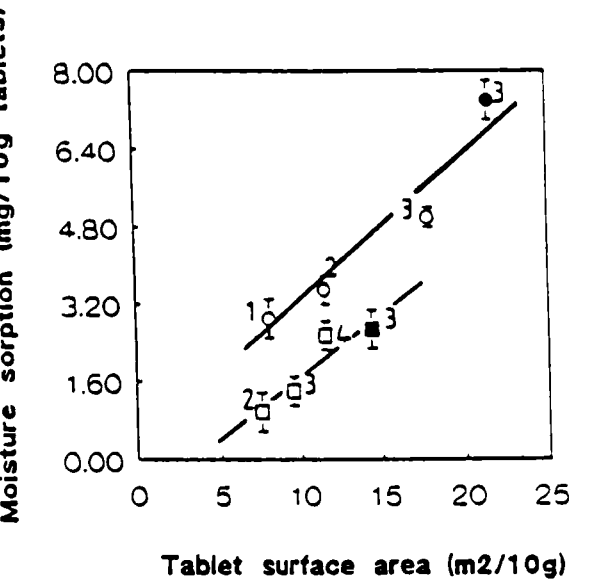

FIGURE 25
Relation between moisture sorption and surface area of tablets of α-lactose monohydrate (□) and of roller dried β-lactose (○)

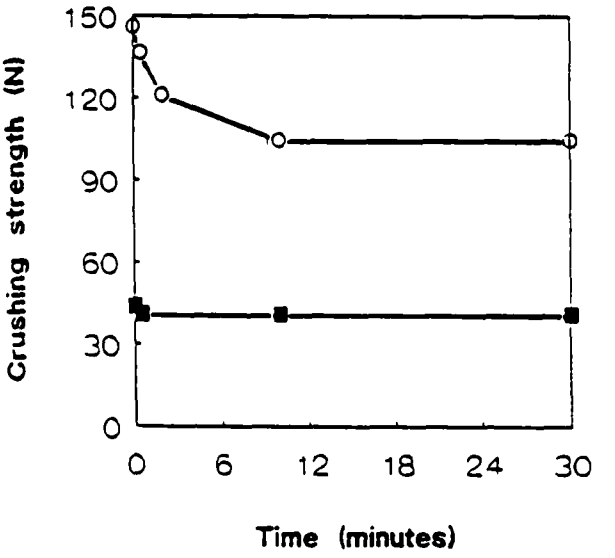

FIGURE 26
Course of crushing strength of tablets of α-lactose monohydrate (▪) and of roller dried β-lactose (o), when exposed to atmospheric humidity

drate and roller dried ß-lactose. It was therefore expected that changes in crushing strength on storage would be different for the two types of lactose tablets tested.

Figure 26 indeed shows different crushing strength versus storage time profiles of tablets, compresssed at 20 kN from a sieve fraction (250-315 μm) of α-lactose monohydrate and roller dried ß-lactose, respectively, stored at 20±1°C and 45±1% RH.

As seen, tablet strength decreases rapidly and tends to reach a plateau within 10 min after compaction. To distinguish any influence of the specific surface area of the tablets on compact strength, tablets were compressed from different sieve fractions of α-lactose monohydrate and roller dried ß-lactose, repectively, and stored at low humidity (over silica gel), and at ambient (45% RH) and high (70% RH) humidity, respectively. The 'initial' tablet strength was measured as soon as possible, in practice within 10 sec;

TABLE 8

Effect of humidity on the strength of tablets (13 mm) compacted at 20 kN from sieve fractions of α-lactose monohydrate and roller dried β-lactose, respectively

Fraction (μm)	Tablet strength (N)[a]			
	A	B	C	D
α-Lactose monohydrate				
250 - 315	44(2)	45(1)	41(1)	40(1)
63 - 90	73(4)	75(2)	64(5)	50(3)
Roller dried β-lactose				
250 - 315	144(8)	134(7)	104(6)	100(5)
63 - 90	154(5)	140(6)	100(7)	99(7)

A, within 10 s after compaction; B, stored for 30 min over silica gel; C, stored for 30 min at 45% RH; D, stored for 30 min at 70% RH.
[a]Standard deviations are given between parentheses

additional tablets were tested after a time interval of 30 min. The results are summarized in Table 8 and demonstrate no significant change in crushing strength of the tablets when stored over silica gel, but for all tablets a decrease in strength when exposed to 45 or 70% RH. This result indicates that atmospheric moisture affects the strength of crystalline lactose tablets. These changes in crushing strength endorse the need to standardize the time between ejection and strength measurement. Concerning the BET-specific surface area, it is recommended to suppress blocking of pores by transferring the tablets immediately after ejection from the die in a dry nitrogen atmosphere for transport to the gas-adsorption apparatus.

Summary

Summarizing the results presented it may be concluded that:

- all types of crystalline lactose, α-lactose monohydrate, anhydrous α-

lactose, roller dried ß-lactose and crystalline ß-lactose, consolidate primarely by particle fragmentation;

- the crushing strength of tablets compressed from all types of crystalline lactose is linearly related to the number of binding points in the tablet, which, on its turn, is linearly related to the specific surface area of the tablet;
- compression of binary blends of different sieve fractions show increased consolidations and decreased fragmentation potentials, caused by percolation of the smaller particles in the voids between the coarse particles;
- the crystalline types of lactose can be differentiated into the non-granular types, α-lactose monohydrate and crystalline ß-lactose, and the granular types, anhydrous α-lactose and roller dried ß-lactose;
- same sieve fractions of the granular types of lactose show higher specific surface areas, less fragmentation on compression and higher binding capacities than the non-granular types;
- amorphous lactose consolidate by plastic deformation, resulting into increased binding surfaces and thus increased binding capacities;
- dry granulation (slugging) of lactose powders result into decreased compactibility of the granules with reference to the specific surface area of the tablets;
- magnesium stearate sensitivity is not directly related to the degree of fragmentation on compression;
- lactose tablets show time-dependent moisture uptake when exposed to an ambient humid atmosphere, resulting into decreased crushing strength and decreased surface area of the tablets.

It may be concluded that lactose is a most fascinating excipient!

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