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Consolidation and compaction of powder mixtures: III. Binary mixtures of different particle size fractions of different types of crystalline lactose

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Summary

Tablets were compacted from a coarse fraction (250–315 μm), a fine fraction (32–45 μm) and from binary blends of a coarse and a fine fraction of different types of crystalline lactose. The results showed differences in consolidation and compaction between the granular lactose types, i.e., roller-dried β-lactose and anhydrous α-lactose, and the non-granular lactose types, namely, crystalline β-lactose and α-lactose monohydrate. Equal particle size fractions of the granular types of lactose exhibited greater specific powder surface areas, less fragmentation on compression, and higher binding capacities than the non-granular types. Slight increases in consolidation were demonstrated on compression of binary blends of the coarse and fine fraction of the different types of lactose. Differences in morphology between the lactose types were shown by increasing true densities of the granular types when examined on tablets compacted with increasing compression force. No change in true densities on compaction were demonstrated by the non-granular types.

Introduction

The first paper in this series on the consolidation and compaction of powder mixtures discussed the behaviour of binary blends of equal particle size fractions of different types of crystalline lactose: α-lactose monohydrate, anhydrous α-lactose, crystalline β-lactose and roller-dried β-lactose (Riepma et al., 1990). The results showed that both crushing strength and (internal) specific surface area of the tablets were linearly related to the weight ratio of the binary blends compressed. All data were found to fit the unique relationship between crushing strength and specific surface area as observed for tablets compressed from single particle size fractions of different crystalline lactose types (Vromans et al., 1985). It was therefore concluded that binary mixtures of two different types of crystalline lactose of equal particle size fractions exhibit no interaction with respect to consolidation and compaction.

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Nevertheless, commercially available excipients for direct compression generally show a broad range of particle size diameters. The second article in the series on the consolidation and compaction of powder mixtures was therefore focussed on the behaviour of binary blends composed of different sieve fractions of α-lactose monohydrate (Riepma et al., 1991). The results demonstrated decreases in both crushing strengths and specific surface areas of the tablets as compared with the values calculated via linear interpolation of the data obtained for the corresponding single sieve fractions. The extent of the decreases in crushing strength and specific surface area of the tablets was found to depend upon the weight ratio of the finer fraction in the blend and to increase with the particle diameter ratio between the coarse and finer fractions. All data on crushing strength and specific surface area of the tablets fitted the previously determined linear relationship between these parameters. This phenomenon of interaction with respect to consolidation and compaction was explained on the basis of decreased fragmentation potentials, due to increased packing densities of the binary mixtures of the two particle size fractions of α-lactose monohydrate.

This paper presents the results of an extended study on the consolidation and compaction of a coarse fraction, a fine fraction and binary blends of the coarse and fine fraction, respectively, of four different types of crystalline lactose: roller-dried β-lactose, anhydrous α-lactose, crystalline β-lactose and α-lactose monohydrate.

Materials and Methods

The materials used were different sieve fractions of α-lactose monohydrate, crystalline β-lactose, roller-dried β-lactose and anhydrous α-lactose, all supplied by DMV, Veghel, The Netherlands. All handling was performed at constant temperature (20 ± 1°C) and constant relative humidity (45 ± 5%). The powders were stored under the same conditions for at least 1 week before mixing and compression.

Different weight ratios of a coarse sieve fraction (250–315 μm) with a finer fraction (32–45 μm) of the same crystalline lactose type were blended over a period of 30 min in a Turbula mixer model 2P (W.A. Bachofen, Basle, Switzerland) at 90 rpm. Compaction of 500 mg flat-faced tablets with a diameter of 13 mm was carried out using a programmable hydraulic press (ESH Testing, Brierley Hill, U.K.). If necessary the die was prelubricated with magnesium stearate.

Tablet strengths were determined 30 min after compaction with a Schleuniger 4 M tester (Dr. Schleuniger Production AG, Solothurn, Switzerland). The data given are the means of at least five measurements.

Tablet porosities were calculated from the weight and the dimensions of the tablets, using

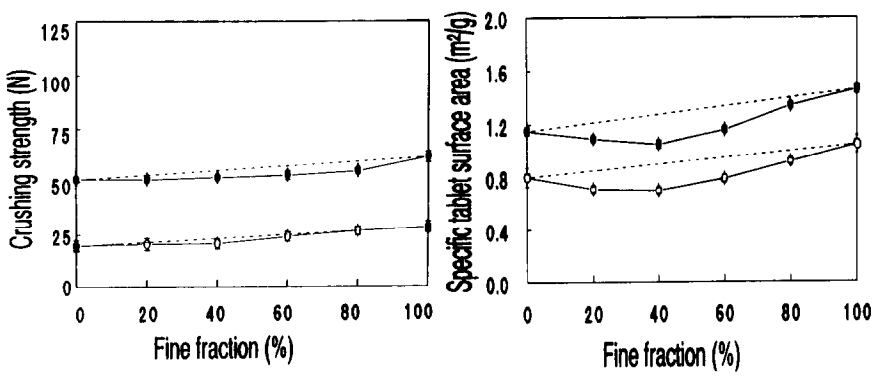

Fig. 1. Crushing strength (a, left) and specific surface area (b, right) of tablets compressed from binary mixtures of a coarse (250–315 μm) and a fine (32–45 μm) fraction of roller-dried β-lactose plotted vs the weight percentage of the fine fraction in the blend. The mixtures were compacted at 5 kN (○) and 10 kN (●) compression force into 500 mg, 13 mm diameter tablets.

values after the true densities of 1.54 g/cm^3 for α-lactose monohydrate and anhydrous α-lactose and 1.59 g/cm^3 for roller-dried β-lactose and crystalline β-lactose. The tablet dimensions were measured with an electronic micrometer (Mitutoyo, Tokyo, Japan).

True densities of the different types of lactose were determined on both the powders and tablets, using a (He)-pycnometer model MVP-1 (Quantachrome Corp., Syosset, U.S.A.). Immediately after compaction the tablets were stored under an atmosphere of nitrogen to suppress moisture sorption.

Porosities of powder beds were calculated from the apparent densities of the powder packings, employing the true densities as mentioned before. The apparent powder densities were determined by pouring 100 g of the powder into a glass measuring cylinder.

The (BET-)specific surface areas of both the powders and the tablets were evaluated with a Quantasorb gas adsorption apparatus (Quantachrome Corp., Syosset, U.S.A.) using nitrogen as adsorbate. Immediately after compaction the tablets were stored under a nitrogen atmosphere to suppress moisture sorption. The data given are the means of four tablets.

Results and Discussion

Fig. 1a illustrates the relation between the crushing strength of tablets compressed from binary blends of a coarse (250–315 μm) and a fine (32–45 μm) sieve fraction of roller-dried β-lactose and the composition of the blend. The results refer to compression forces of 5 and 10 kN, respectively. As demonstrated, the profiles show no significant deviation from a linear relationship between crushing strength and composition of the tablets. However, a different profile is found for the relation between the specific pore surface

TABLE 1

Crushing strength and specific pore surface area of tablets compressed from a coarse (250–315 μm) fraction, a fine (32–45 μm) fraction and from binary blends of 60% coarse and 40% fine fraction, respectively, of four crystalline lactose types

Fraction	C_s (N)	C_s^* (N)	$(C_s^* - C_s)/C_s^*$	S_t (m^2/g)	S_t^* (m^2/g)	$(S_t^* - S_t)/S_t^*$
Roller-dried β-lactose						
Coarse	51	–	–	1.15	–	–
Blend	52	55	−0.06	1.05	1.27	−0.18
Fine	62	–	–	1.46	–	–
Anhydrous α-lactose						
Coarse	73	–	–	1.31	–	–
Blend	84	87	−0.03	1.30	1.56	−0.17
Fine	108	–	–	1.93	–	–
Crystalline β-lactose						
Coarse	16	–	–	0.65	–	–
Blend	16	22	−0.27	0.57	0.77	−0.26
Fine	31	–	–	0.95	–	–
α-Lactose monohydrate						
Coarse	18	–	–	0.74	–	–
Blend	17	24	−0.30	0.59	0.86	−0.32
Fine	34	–	–	1.05	–	–

The powders were compacted at 10 kN compression force into 500 mg, 13 mm diameter tablets. C_s, tablet strength; C_s^*, tablet strength calculated by linear interpolation of the values found for the tablets compressed from the single sieve fractions; $(C_s^* - C_s)/C_s^*$, relative deviation from the linearly interpolated tablet strengths; S_t, specific tablet surface area; S_t^*, specific tablet surface area calculated by linear interpolation of the values found for the tablets compressed from the single sieve fractions; $(S_t^* - S_t)/S_t^*$, relative deviation from the linearly interpolated tablet surface areas.

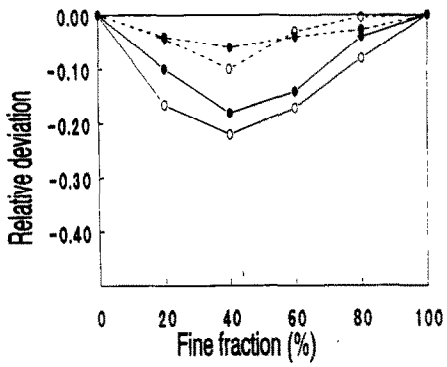

Fig. 2. Crushing strength (- - - - -) and specific tablet surface area (———), expressed as relative deviation from the linearly interpolated values of the strength and the specific surface area of tablets compressed from the single sieve fractions vs the weight percentage of the fine fraction in the blend. Binary mixtures of a coarse (250–315 μm) and a fine (32–45 μm) fraction of roller-dried β-lactose were compacted at 5 kN (○) and 10 kN (●) compression force into 500 mg, 13 mm diameter tablets.

area of the tablets, measured by nitrogen adsorption, and the composition of the blends (Fig. 1b). As seen, the tablets compressed from the blends exhibited lower pore surface areas than those calculated by linear interpolation of the values obtained for the single sieve fractions. The dissimilarity of the profiles of Fig. 1a and b is illustrated in Fig. 2 by plotting the relative deviation from the linearly interpolated values of both crushing strength and specific pore surface area of the tablets vs the composition of the binary blends. It should be noted that the maximum deviation from linearity is found for the tablets compressed from blends containing 40% of the finer fraction. The data on crushing strength and specific surface area of the roller-dried β-lactose tablets, compacted at 10 kN from the coarse (250–315 μm) and the fine fraction (32–45 μm), respectively, are summarized in Table 1 together with those as found for the blends containing 40% of the fine fraction. In addition, Table 1 includes the data as obtained for the other three lactose types, i.e., anhydrous α-lactose, crystalline β-lactose and α-lactose monohydrate. For both roller-dried β-lactose and anhydrous α-lactose, the only slightly lower crushing strengths (3–6%) for the tablets compressed from the blends, as compared to those obtained by linear interpolation of the data found for the coarse and the fine fraction, respectively. Greater deviations (17–18%) from the linearly interpolated values were observed for the specific surface areas of these tablets. The other two lactose types, crystalline β-lactose and α-lactose monohydrate, showed both much lower crushing strengths (27–30%) and considerably smaller surface areas (26–32%) of the tablets compacted from the blends, again as compared to the linearly interpolated values. These results are indicative of differences in consolidation and compaction behaviour between roller-dried β-lactose and anhydrous α-lactose, on the one hand, and crystalline β-lactose and α-lactose monohydrate, on the other.

It has been stated by several workers that the differences in consolidation and compaction properties between crystalline lactose powders are a reflection of the differences in diameter and morphology of the particles (Fell and Newton, 1971; Hersey et al., 1972; Alderborn and Nyström, 1982; Vromans et al., 1985; De Boer et al., 1986). Both α-lactose monohydrate and crystalline β-lactose are produced via a slow crystallization process yielding single crystals with rather regular shapes and smooth surfaces. Roller-dried β-lactose is manufactured by rapid crystallization of a lactose solution on two steam-heated rollers, at temperatures exceeding 93°C. After drying the anhydrous product is scraped from the rollers, ground and sieved, producing 'granular' particles, which can be considered as being aggregates of many small crystals. Anhydrous α-lactose is manufactured by thermal dehydration of α-lactose monohydrate. We have previously reported that the process of thermal dehydration, or chemical desiccation with organic solvents, (gradually) changes single crystals of α-lactose (Lerk et al., 1983). The anhydrous product was characterized by a strongly increased binding capacity, as compared to the original non-dehydrated product. Moreover, it was shown that compaction of a sieve fraction (100–125 μm) of α-lactose monohydrate and of anhydrous α-lactose, respectively, produced tablets with almost equal overall porosities, but with totally different pore size distributions. The observed differences in com-

paction characteristics have been demonstrated by Wong et al. (1988), who studied the deformation characteristics of α-lactose monohydrate and anhydrous α-lactose monocrystals. Indentation testing showed that the crystals of the anhydrous form were much softer, less elastic, weaker and less anisotropic than those of the monohydrate. It appears that, during the dehydration process, the removal of water of crystallization results in the partial disruption of crystalline order. Such disruption could explain the difference in the degree and nature of the fragmentation mechanism between the two crystal types. The anhydrous crystals undergo fragmentation into very small particles rather than into large splinters as does the monohydrate.

The differences in particle morphology between the granular and non-granular types of lactose are characterized by differences in powder specific surface area of equal particle size fractions of the four lactose products (Table 2). The granular types, roller-dried β-lactose and anhydrous α-lactose, exhibited much higher powder specific surface areas than the non-granular types, crystalline β-lactose and α-lactose monohydrate. The related differences in degree of fragmentation, $(S_t - S_p)/S_p$, have been expressed as the relative increase in surface area when compressing a powder with surface area S_p into a tablet with surface area S_t. The calculations show less fragmentation for the granular than for the non-granular lactose types. On consideration of the fact 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 more likely the result of the higher powder specific areas rather than the lower degrees of fragmentation of the granular types of lactose.

TABLE 2

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 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.

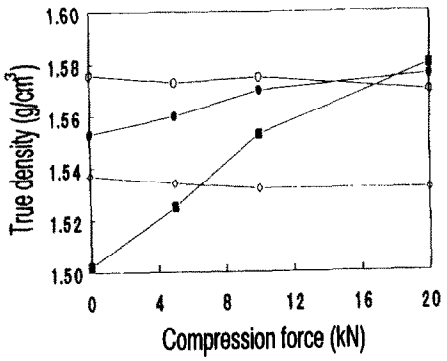

Fig. 3. True density of (●) roller-dried β-lactose, (■) anhydrous α-lactose, (○) crystalline β-lactose and (◇) α-lactose monohydrate, measured on tablets compressed from one sieve fraction (250–315 μm), vs compression force.

The differences in particle morphology between the granular and non-granular types of lactose are also apparent from true density determinations performed on tablets compressed at different compaction forces from same sieve fractions (250–315 μm) of the four different lactose types. Fig. 3 illustrates the profiles of true density vs compaction force. As can be observed, the non-granular types, α-lactose monohydrate and crystalline β-lactose, did not show any significant change in true density on compaction. In contrast, the granular types, roller-dried β-lactose and anhydrous α-lactose, exhibited increasing true densities with increasing compaction forces. This phenomenon of increasing true densities may be attributed to distortion of the (micro)

porous structure of the granular lactose types on compression.

Previous studies on the consolidation and compaction properties of lactose demonstrated a unique relationship between the crushing strength and internal specific surface area of different types of crystalline lactose tablets (Vromans, 1987). The experimentally found relationship has been elucidated by a theoretical model for the calculation of the tensile strength of compacts, as presented by Leuenberger et al. (1989). Assuming that a tablet is made up of spherical isometric particles and that the strength of all types of crystalline lactose is caused by Van der Waals dispersion forces, acting at the coordination points of the particles, a proportionality is obtained between the tensile strength and the pore specific surface area of the tablet. The theoretical model permits the calculation of coordination numbers of the particles within a compact. Conversely, a proportionality between the crushing strength and specific surface area of the tablets implies that the coordination numbers remain constant for the particles within the compacts. Close examination of the plot of crushing strength vs specific surface area of the tablets from Table 1 shows, for the tablets compressed from the fine fraction, relatively lower crushing strengths and for those from the blends of the coarse and fine

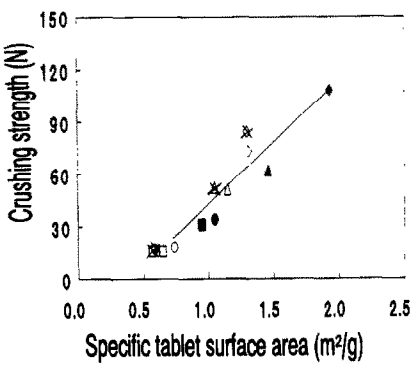

Fig. 4. Crushing strength vs specific surface area of tablets compressed from a coarse (250–315 μm) fraction, a fine (32–45 μm) fraction and blends of a 60% coarse and a 40% fine fraction of (△) roller-dried β-lactose, (◇) anhydrous α-lactose, (□) crystalline β-lactose and (○) α-lactose monohydrate. Open symbols: coarse fractions; closed symbols; fine fractions; open symbols with cross: binary blends.

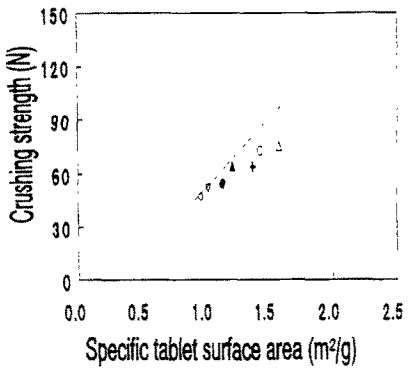

Fig. 5. Crushing strength vs specific surface area of α-lactose monohydrate tablets, compressed at 20 kN from different sieve fractions into 500 mg tablets having a diameter of 13 mm (◇) 180–200 μm, (▽) 125–160 μm, (●) 100–125 μm, (▲) 63–80 μm, (+) 45–63 μm, (○) 32–45 μm and (△) 24–32 μm.

fractions, relatively higher crushing strengths than expected on the basis of the linear relationship (Fig. 4).

Deviations from linearity of the relationship between strength and specific pore surface area have been reported previously by Vromans et al. (1987) for tablets compacted from very fine particle size fractions of α-lactose monohydrate. The lower crushing strengths were accompanied by higher porosities of the compacts and were therefore explained as being due to poor densification of the fine powder fractions. The present results are consistent with this observation and indeed show increasing deviations from the linear relation between crushing strength and specific surface area of α-lactose monohydrate tablets when compacted from powder fractions with decreasing particle size (Fig. 5). The porosities of the tablets are compiled in Table 3 and show, as was expected, increasing values with decreasing particle size of the powders compacted.

The differences in consolidation behaviour are demonstrated by a differentiated presentation of the relation between crushing strength and specific surface area of the tablets from Table 1. Fig. 6a depicts the data as found for the tablets compressed from the coarse fraction (250–315 μm) of the four different lactose types: roller-dried β-lactose, anhydrous α-lactose, crystalline β-lactose and α-lactose monohydrate. Fig. 6b and c pre-

TABLE 3

Porosity of tablets compressed from different sieve fractions of α-lactose monohydrate

Fraction (μm)	ε
180–200	0.119
125–160	0.113
100–125	0.129
63– 80	0.132
45– 63	0.139
32– 45	0.148
24– 32	0.158

The powders were compacted at 20 kN compression force into 500 mg, 13 mm diameter tablets. ε, tablet porosity.

sents the experimental data as obtained for the tablets compacted from the fine fraction (32–45 μm) and from the blends of coarse and 40% of the fine fraction, respectively, together with the linear relation as derived from the data obtained for the tablets compacted from the coarse fraction. As seen, all tablets exhibited lower crushing strengths as compared to the reference line when compacted from the fine fraction, whereas higher crushing strengths were shown by tablets compacted from the blends. These results provide confirmatory evidence of the decrease in consolidation for the fine fraction, and of increased consolidation for the blends. The tablets compacted from the fine fractions indeed showed higher porosities than those compacted from the coarse fraction and from the blends of coarse with fine fraction, respectively (Table 4). In-

TABLE 4

Porosity of tablets compressed from a coarse (250–315 μm) fraction, a fine (32–45 μm) fraction and from binary blends of 60% coarse and 40% fine fraction, respectively, of four crystalline lactose types

Fraction	ϵ^1	ϵ^*	ϵ^2
Roller-dried β-lactose			
Coarse	0.233	–	0.597
Blend	0.230	−0.237	0.533
Fine	0.244	–	0.637
Anhydrous α-lactose			
Coarse	0.159	–	0.516
Blend	0.164	0.169	0.445
Fine	0.184	–	0.590
Crystalline β-lactose			
Coarse	0.124	–	0.505
Blend	0.126	0.141	0.467
Fine	0.166	–	0.597
α-Lactose monohydrate			
Coarse	0.169	–	0.504
Blend	0.172	0.190	0.459
Fine	0.221	–	0.581

The powders were compacted at 10 kN compression force into 500 mg, 13 mm diameter tablets. ϵ^1, tablet porosity; ϵ^*, tablet porosity, assuming a linear relationship between the porosity and the composition of the blend; ϵ^2, porosity of the powder bed.

creased consolidation for the blends is also demonstrated by lower porosities of the tablets as compared to the values obtained by linear interpolation of the porosities of the tablets compressed from the coarse and fine sieve fraction, respectively (Table 4). Finally, it should be noted

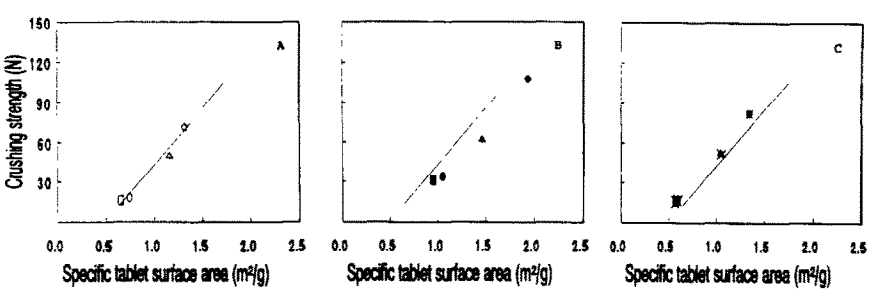

Fig. 6. Crushing strength vs specific surface area of tablets compressed from coarse (a, left) fine (b, middle) and binary blends of 60% coarse and 40% fractions (c, right) of roller-dried β-lactose, anhydrous α-lactose, crystalline β-lactose and α-lactose monohydrate. The line refers to the relation as found for tablets compressed from the coarse fractions of the four crystalline lactose types. Symbols as in Fig. 4.

that the highest porosities were found for both the powder beds and the tablets compressed from roller-dried β-lactose.

In conclusion, on compaction, the four different types of crystalline lactose, roller-dried β-lactose, crystalline β-lactose, anhydrous α-lactose and α-lactose monohydrate, demonstrate decreasing consolidation with decreasing particle sizes of the powders to be compacted, resulting in tablets with increasing porosities. Slight increases in consolidation are shown on compression of binary blends of a coarse and a fine sieve fraction of the different lactose types.

Differences in morphology between the lactose types are demonstrated by increasing true densities of the granular types, roller-dried β-lactose and anhydrous α-lactose, when performed on tablets compacted with increasing compression forces. No changes in true densities on compaction were exhibited by the non-granular types, crystalline β-lactose and α-lactose monohydrate.

Same sieve fractions of the granular types of lactose show higher specific powder surface areas, less fragmentation on compression, and higher binding capacities than the non-granular types.

Compression of binary powder blends of a coarse and a fine fraction of the non-granular lactose types demonstrates decreases in both crushing strengths and specific surface areas of the tablets, as compared to the data obtained via linear interpolation of the values found for the tablets compressed from the coarse and the fine fraction, respectively. Less interaction on compression is demonstrated by the granular types of lactose.

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