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The compression properties of lactose

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The tabletting characteristics of crystalline and spray dried lactose under direct compression have been examined together with the effect of particle size, shape and storage of the powders. The results indicated that the particle size had little effect, although there was a general tendency for the compact strength to increase as the particle size decreased. On the other hand, the particle shape and storage of the powder influenced the strength of the tablets and the force lost to the die wall. The 22 μm and 35 μm fractions of spray dried lactose—especially the latter—were almost entirely very regular spherical particles which resulted in the strongest tablets, whereas fractions below or above contained many more angular particles resulting in weaker tablets. Storage of the small particle size fraction of the crystalline material appeared to induce aggregation, and on compaction, a harder tablet was formed, accompanied by a decrease in the force lost to the die wall.

Lactose is widely used in tablet formulations, but little work has been reported in the literature on its compression characteristics. Higuchi, Elowe & Busse (1954) using a grade of crystalline lactose, measured the surface area, porosity, hardness and disintegration times of tablets compressed at various pressures. Subsequently, Gunsel & Lachman (1963) compared the use of similarly sized crystalline lactose and spray dried lactose in various formulations. They were able to demonstrate an increase in the tablet hardness when prepared from the formulation containing spray-dried lactose. Fell & Newton (1968) measured the tensile strength of tablets prepared from the two forms of lactose and showed that, for particles of 150–210 μm, the conventional crystalline lactose tablets were harder; for smaller sized fractions, the spray dried lactose tablets were harder. For both forms, the tablet strength increased as the particle size decreased.

Hersey, Bayraktar & Shotton (1967) previously reported on the effect of particle size on the strength of sodium chloride tablets prepared at several different pressure levels and it was anticipated that a similar approach would be useful in a comparison of the spray-dried and crystalline forms of lactose.

EXPERIMENTAL

Crystalline lactose and spray-dried lactose, which were hydrated, were size fractionated using a Lavino Alpine Air-Jet Sieve. For each material, a sub-sieve fraction

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was obtained by feeding the original material through a Gem fluid energy mill operating at 100 psig using a feed rate of about 5 g min^{-1}.

The size fractions were subjected to microscopic size analysis, moisture determination, apparent density and angle of repose determinations. Microscopic size analysis was by the British Standard method (No 3406 Part A, 1963). After allowing the fraction to equilibrate with the atmosphere, the moisture content was determined immediately before compression using the Cahn Gram Electrobalance as described by Shotton & Rees (1966). The bulk density of the powders was determined by pouring a sample, at 45°, into a tared 25 ml measuring cylinder. The angle of repose, was measured with reseived material by the tilting table method described by Train (1958).

After sieving, some material from each size fraction was immediately examined as above and then compressed, whilst an aliquot of the crystalline sample was stored in a screw-capped jar for twelve months before testing. The stored material was subsequently resieved before testing as the crystalline lactose had caked badly. Comparative experiments with stored spray dried lactose showed no visible caking had occurred. Material sufficient to produce a 0·4 cm long tablet in the 1 cm diameter die at zero porosity, 0·6895 g, was introduced into the die cavity by hand and compressed using a power driven tablet machine instrumented in a manner similar to that described by Shotton & Ganderton (1960). The apparent density of the tablet was obtained from the dimensions of the ejected tablet and the crushing strength of the tablet immediately determined by the method of Shotton & Ganderton (1960).

RESULTS

For the sieved fractions, the moisture content and the mean size obtained by microscopic examination is given in Table 1 and these were unaffected by storage. The relative densities of tablets prepared under different pressures is given in Table 2.

Table 1. *Particle size of fractions and moisture content.* Average of three determinations

Aperture size of sieves (μm) Milled		Crystalline lactose Mean particle size (μm)	Moisture content % Stored	Moisture content % Fresh	Spray dried lactose Mean particle size (μm)	Moisture content %
		2	4·65	4·81	2	4·74
—32		22	3·15	5·00	22	5·00
+32	—40	34	4·92	5·01	35	4·92
+40	—45	43	—	4·47	41	4·58
+45	—63	59	4·57	4·47	54*	—
+63	—76	69*	—	—	71	4·66
+76	—105	82	4·35	—	90*	—
+105	—125	110	4·14	4·50	119	4·60

* Mean sieve aperture
(Lactose monohydrate contains 5·0014% Water)

To compare die wall friction effects of the different materials, two of the fractions of spray dried, freshly sifted and stored crystalline lactose were chosen. These were the +32/−40 μm size fraction and the +105/−125 μm size fraction. Results of force lost to die wall for these powders are plotted respectively in Fig. 1A and B. Results of ejection force for the former size are given in Fig. 2A and for the latter size in Fig. 2B.

Table 2. *Bulk densities of powders and relative* densities of tablets.* Average of 5 results at arbitrary pressures PI–PIV.

Substance	Lactose														
	S.D.	Crystalline Fresh	Crystalline Stored	S.D.	Crystalline Fresh	Crystalline Stored	S.D.	Crystalline Fresh	Crystalline Stored	S.D.	Crystalline Fresh	Crystalline Stored	S.D.	Crystalline Fresh	Crystalline Stored
Aperture size of sieves (μm)	Bulk density of powder			PI			PII			PIII			PIV		
							Average compression force (kg) †								
	0	0	0	666	494	592	895	782	874	1362	1213	1328	1800	1763	1859
Milled	0·49	0·31	0·36	0·74	0·74	0·74	0·79	0·78	0·77	0·83	0·83	0·83	0·86	0·86	0·87
−32	0·56	0·44	0·40	0·71	0·74	0·75	0·76	0·79	0·77	0·81	0·82	0·82	0·84	0·85	0·86
+32 −40	0·64	0·65	0·61	0·75	0·75	0·74	0·79	0·78	0·78	0·83	0·82	0·82	0·85	0·86	0·86
+40 −45	0·70	0·71	—	0·75	0·75	—	0·80	0·79	—	0·84	0·82	—	0·87	0·87	—
+45 −63	—	0·73	0·66	—	0·75	0·74	—	0·79	0·78	—	0·83	0·82	—	0·88	0·86
+63 −76	0·70	—	—	0·74	—	—	0·79	—	—	0·83	—	—	0·87	—	0·87
+76 −105	—	—	0·67	—	—	0·75	—	—	0·79	—	—	0·83	—	—	—
+105 −125	0·70	0·74	0·72	0·75	0·75	0·75	0·79	0·79	0·80	0·83	0·84	0·85	0·88	0·88	0·89

S.D. = Spray dried
Stored = Powders stored for 12 months
Fresh = Powders used immediately after sieving
* = Apparent densities of tablets based on physical measurements of tablets.
(True density of lactose = 1·525)
†Comparative range in S.I. ≈ 4·5 — 17·5 kN

In Fig. 3A-C results for the strength of the tablets prepared from the different particle size fractions at the four pressure levels are given for freshly sifted crystalline lactose, the stored crystalline lactose and for the spray-dried material respectively. In each case, the result given in the mean of five determinations.

DISCUSSION

The method of moisture determination of Shotton & Rees (1966) used measures the free and bound water in the lactose sample. Since lactose is in the form of the monohydrate, it contains about 5% bound water. The results in Table 1 indicate that there was no free water in the lactose samples used and the lower percentages indicate a content of anhydrous lactose in many of the fractions consistent with the findings of Gunsel & Lachman (1963).

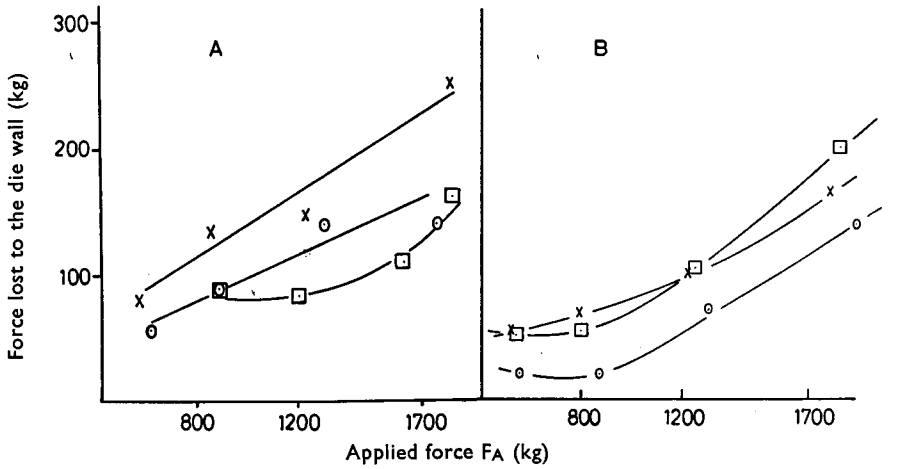

FIG. 1. Effect of applied force on the force lost to the die wall. A. Size fraction +32/−40 μm. B. Size fraction +105/−125 μm. × Crystalline lactose—freshly sieved. ○ Crystalline lactose—stored. □ Spray dried lactose.

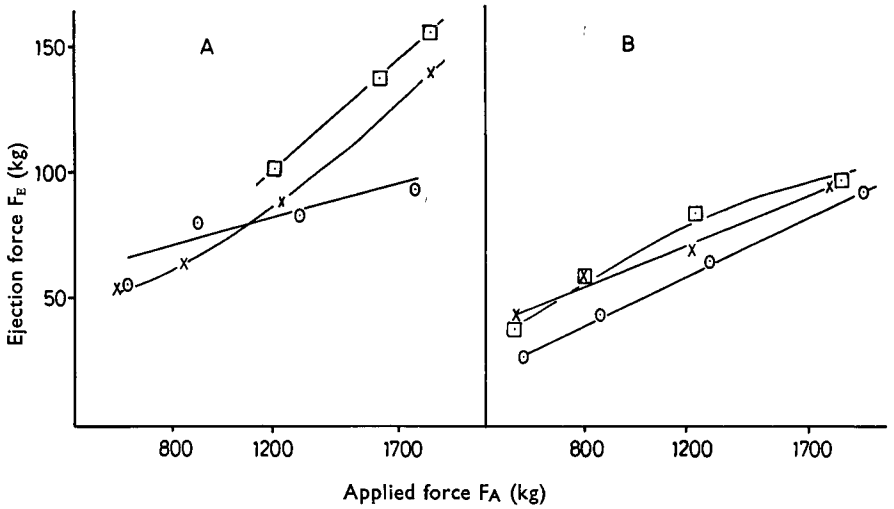

FIG. 2. Effect of applied force on the ejection force. A. Size fraction $+32/-40\,\mu$m. B. Size fraction $+105/-125\,\mu$m. × crystalline lactose—freshly sieved. ○ Crystalline lactose—stored. □ Spray dried lactose.

The bulk density before compaction is dependent upon the previous history of the lactose. The stored crystalline lactose fractions after sieving exhibited a lower density than the freshly sifted crystalline material. This suggests that the material formed loose aggregates during storage and which were not completely broken down by sieving. Evidence of aggregation is also inferred from the generally higher angles of repose of the stored material compared with the freshly sifted crystalline lactose. When the stored material was mounted in liquid paraffin aggregation was not seen under the microscope, indicating that the process completely destroyed the aggregate structure.

Comparison of Fig. 1A and 1B shows that spray dried lactose has a lower die wall friction at $+32/-40\,\mu$m size fraction than the freshly sieved crystalline material whereas at $+105/-125\,\mu$m size fraction there is little difference between the two materials. At both chosen particle size levels, the die wall friction is lower using stored material than when using freshly sieved crystalline material. These observations may also be explained by the shape difference between the particles. At 35 μm, the spray dried material consists almost entirely of spherical particles (Fig. 4). This fraction, which gives the lowest angle of repose, Table 3, will have a small contact area with the die wall and thus frictional resistance will be smaller than for the irregular crystalline variety. At the higher size range, the spray-dried material is largely crystalline and there is therefore little difference between the two fractions. The stored crystalline fractions consisting of loosely bound agglomerates will also have less die wall contact and therefore has a lower frictional resistance than the freshly-seived material at both size fractions.

Results similar to those occuring and the die wall during compression occur on ejection of the compacts (Fig. 2A and B) except that the 35 μm spray-dried fraction has a much higher ejection force than might be expected. This may be due to the fact that the spherical particles on compaction will fracture, thereby increasing the frictional resistance on subsequent ejection.

Figs 3A-C show the effect of particle size on the strength of lactose compacts

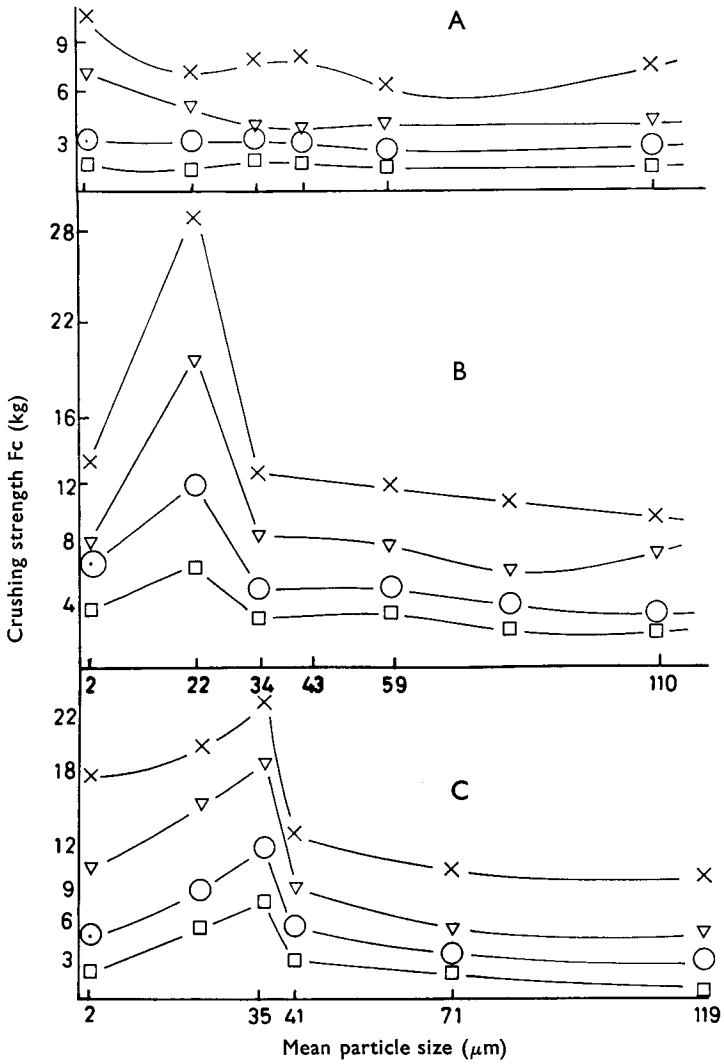

FIG. 3. Effect of mean particle size on the crushing strength of A, freshly sieved, and B, stored crystalline and C, spray dried lactose tablets, Machine setting to arbitrary pressures of □ PI. ○ PII. ▽ PIII. × PIV.

Table 3. *Angles of repose of various lactose fractions (Means of 7 experiments)*

Aperture size of sieves (μm)		Angle of repose °		
		Crystalline stored	Crystalline fresh	Spray dried
Milled		(no flow)	(no flow)	(no flow)
—32		(no flow)	(no flow)	40
+32	−40	50	46	37
+40	−45	—	42	39
+45	−63	65	41	—
+63	−76	—	—	38
+76	−105	45	—	—
+105	−125	42	44	40

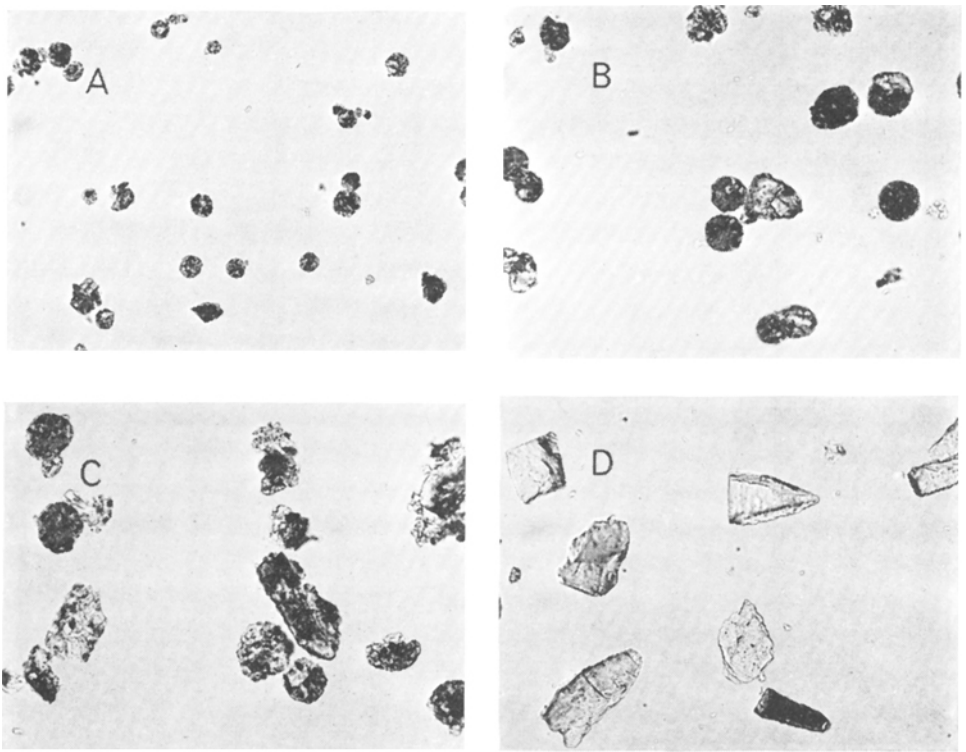

FIG. 4. Photomicrographs of lactose: spray dried 22 μm (A), 35 μm (B), 41 μm (C) and crystalline 34 μm.

prepared at different pressures. Fig. 3A shows that with the freshly-sieved material, particle size has little effect, although there is a general tendency for the compact strength to increase as the particle size is reduced. This tendency is also shown in Fig. 3B for stored lactose and Fig. 3C for spray-dried material, however, in both of these cases, a maxima is observed. The strength of tablets prepared from spray-dried material (Fig. 3C) is greater than that of tablets prepared from freshly sieved crystalline lactose, as found by Gunsel & Lachman (1963) and Fell & Newton (1968), but is less than the strength of tablets prepared from stored, crystalline material (Fig. 3B).

This increase of strength shown by the stored-lactose may be due to the weak agglomerate formation as shown by bulk-density and angle of repose determinations. These loose agglomerates are deemed equivalent to weak granules, which occupy a larger volume of the die with fewer contacts at the die wall. On compression, these aggregates must break down and there will be much local shear within the particle mass leading to a stronger tablet. Since there are also fewer die wall contacts, the effective frictional force will also be reduced (Fig. 1A and B) and the compression force will be more advantageously utilized. The very high value for the crushing strength of the 22 μm stored fraction is an exaggeration of these effects possibly due to the tendency of this fraction to agglomerate more readily than the other size fractions. In Table 2, it can be seen that this fraction has a lower bulk density than either of the other two powders examined, however, on compaction, this material forms, at least, equally dense tablets.

Further examination of Table 2 shows that the 2 μm fraction of stored material is in fact more dense than the freshly sieved variety, which suggests that this material does not aggregate, or conversely, that the freshly sifted material is more readily agglomerated and on storage, these agglomerates break down. Thus it should be anticipated that there will be little difference between these two fractions at the 2 μm level, as shown by Fig. 3A and B. Loss of aggregate structure on milling spray-dried material, also accounts for the fact that similar strength values for 2 μm spray-dried fraction material.

Examination of the effect of mean compaction force on the crushing strength of the 2 μm fraction of freshly sieved lactose produced the strongest tablets possibly due to the high surface area available for bonding. On storage it would appear that with the 22 μm size fraction, and to a decreasing extent with increasing particle size, the tendency to form loose aggregates is manifest in a stronger compact. With the spray-dried material, departures from sphericity either above or below the 35 μm spherical particle used in this batch is consistent with a decrease in tablet strength. Fig. 4A–D is included so that the extent of the change of particle shape between the different fractions can be seen. The 22 μm (Fig. 4A) and 35 μm (Fig. 4B) spraydried particles are almost entirely spherical, but the 41 μm spraydried particles (Fig. 4C) contained a large proportion of angular material similar to the crystalline lactose shown in Fig. 4D.

With lactose powder, it appears that particle shape, whether as spheres or angular crystals, or weak aggregates formed on storage, has a considerable effect upon tablet strength.

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REFERENCES

FELL, J. T. & NEWTON, J. M. (1968). *J. Pharm. Pharmac.*, **20**, 657–658.
GUNSEL, W. C. & LACHMAN, L. (1963). *J. pharm. Sci.*, **52**, 178–182.
HERSEY, J. A. and BAYRAKTAR, G. & SHOTTON, E. (1967). *J. Pharm. Pharmac.*, **19**, 24S–30S.
HIGUCHI, T. ELOWE, L. N. & BUSSE, L. W. (1954). *J. Am. pharm. Ass.*, **43**, 685–689.
SHOTTON, E. & GANDERTON, D. (1960). *J. Pharm. Pharmac.*, **12**, *Suppl.*, 87T–92T.
SHOTTON, E. & REES, J. E. (1966). *Ibid.*, **18** Suppl., 160S–167S.
TRAIN, D. (1958). *Ibid.*, **10**, 127T–135T.