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VARIATIONS IN LACTOSE NF FROM TWO DIFFERENT SOURCES AND THEIR INFLUENCE ON TABLET PROPERTIES

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ABSTRACT

Samples of Lactose NF obtained from one supplier in the UK and one in the USA were examined in terms of their compaction properties. The materials were studied in a model formulation and also in a development formulation. Differences in properties between the samples were shown to depend principally on the particle size, size distribution and specific surface area. The source of lactose can have significant deleterious effects on a multicomponent formulation even when lactose is not the major component.

INTRODUCTION

There have been several studies in the literature reporting variations between different batches of active and inactive formulation components (1-3). The quality of the finished product may be affected to a greater or lesser degree, depending on the extent of such variations and the proportion of the material in the dosage forms.

Many international companies have research and development establishments in both North America and Europe, and there is frequently a need to transfer a manufacturing process between sites so that, for example, clinical trial supplies may be manufactured or stability studies performed. Recently in these laboratories, during transfer of a tablet formulation, problems of reduced tablet crushing strength were found and related to differences in the source of Lactose NF. The purpose of this investigation was to examine the physical and mechanical properties of the two lactose products involved, and to study the influence of each material on the properties of selected tablet formulations.

MATERIALS AND METHODS

Materials

(A) Lactose NF, powdered hydrous 100 mesh (Zimmerman-Hobbs Ltd, Milton Keynes, UK).

(B) Lactose NF, powdered hydrous grade 310 (Foremost, Wisconsin, USA).

Microcrystalline Cellulose NF (Honeywill and Stein, Wallington, UK).
Crospovidone NF (BASF, Cheadle, UK).
Sodium Starch Glycolate NF (Forum Chemicals Ltd, Redhill, UK).
Magnesium Stearate BP (Durham Raw Materials Ltd, London, UK).

Methods

Sieve analysis was performed on (A) and (B) using ASTM E11 8-inch test sieves arranged in a $\sqrt{2}$ series. The geometric mean particle size was determined in each case from the log-normal size distribution. The true densities of (A) and (B) were determined using a helium-air pycnometer (Micromeritics, Norcross, GA, USA) and the bulk and tapped densities were also determined. The latter two measurements were used to calculate the Carr compressibility index (4). Loss on drying was determined for (A) and (B) using an infra-red moisture balance (Sartorious Instruments Ltd, Belmont, UK) at 74°C for 10 minutes.

To determime differences in performance between the two sources of lactose, blends containing 3.3% w/w crospovidone and 0.5% magnesium stearate per 400 g batch were prepared in a planetary mixer and compressed at a range of different compaction pressures on an instrumented Manesty F3 single-punch tablet machine operating at 75 strokes per minute, with 10 mm flat-faced tooling. Tablets were prepared at a compression weight of 300 mg, then stored in sealed containers for twenty-four hours before physical testing was performed.

Tablet weight variation and friability were determined for twenty tablets from each batch. Crushing strength was determined using an Erweka TBH tablet tester; disintegration time was measured using a

Pharmatest PTZ disintegration tester with water at 37°C (without discs) and tablet thickness was measured using a dial micrometer. These determinations were performed on six tablets from each batch. Tensile strength was calculated as described by Fell and Newton (5).

To confirm that the source of Lactose NF was the major cause of differences in the properties of tablets made in the UK and USA, one batch of tablets was made in the UK using each type of lactose, according to the formula:- Development Compound 14%; Microcrystalline Cellulose NF 50%; Sodium Starch Glycolate NF 3.0%; Lactose NF, powdered hydrous 32.6%; Magnesium Stearate NF 0.4%.

The properties of these tablets were compared with those of tablets made in the USA. Tablets were manufactured on a Stokes RB2 tablet machine in the USA, while in the UK a Manesty F3 was used. All other processes and equipment were alike at both sites.

Finally, to determine whether any differences in performance between the two sources of lactose were caused by differences in particle size and size distribution, each sample was sieved to provide a 125-180 μm size fraction. The size-fractions were re-sieved on a 125 μm sieve to remove as many of the fine particles as possible. Particle size and size distribution were then determined using a Coulter Counter model PCAI, (Coulter Electronics Ltd, Luton, UK) with a 560 μm orifice tube. Samples were dissolved in a 5% w/v solution of ammonium thiocyanate in isopropanol, saturated with lactose. Specific surface area was measured using a Flowsorb II nitrogen adsorption apparatus (Coulter Electronics Ltd, Luton, UK). The prepared samples were then mixed with

TABLE I : PHYSICAL PROPERTIES OF LACTOSE NF, SAMPLES (A) AND (B)

	(A)	(B)
True Density (g cm^{-3})	1.53	1.52
Loose Bulk Density (g cm^3)	0.740	0.710
Tapped Density (g cm^3)	0.825	0.900
Carr's Index (%)	10.3	21.1
Loss on Drying (%)	0.4	0.4
Geometric Mean Particle Size (μm)	160	118
Geometric Standard Deviation	1.32	1.39

crospovidone and magnesium stearate as before and compressed at a range of pressures. Physical testing was carried out as described above.

RESULTS

The physical properties of lactose (A) and (B) are summarised in Table I. (B) has a smaller particle size than (A), and this is reflected in the higher tapped density for (B) which indicates closer packing. The loose-poured bulk density of (B) is lower than that of (A), probably because of arching and bridging within the powder bed. From the Carr's Indices we can see that (A) would be expected to have superior flowability to (B) - "excellent" as opposed to "fair".

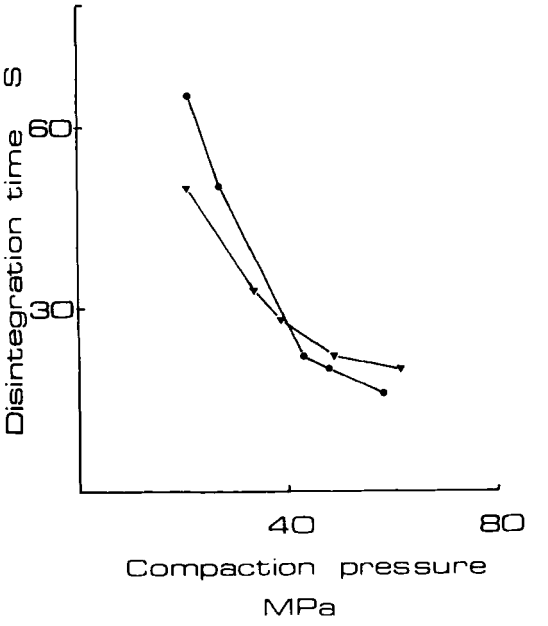

Fig. 1 Tensile strength as a function of mean compaction pressure for tablets made from bulk lactose samples. ●, (A); ▼, (B).

The relationship between tablet tensile strength and compaction pressure is shown for each type of lactose in Figure 1. It is clear that for a given compaction pressure, (A) gives weaker tablets than (B).

Compaction pressure had little effect on the disintegration times of tablets containing (B), but disintegration time increased sharply with increasing pressure for tablets made with (A) (Figure 2). Tablets made from (A) had longer disintegration times than those made from (B). Friability is plotted against compaction pressure in Figure 3, from which we can see that (A) gave more friable tablets than (B).

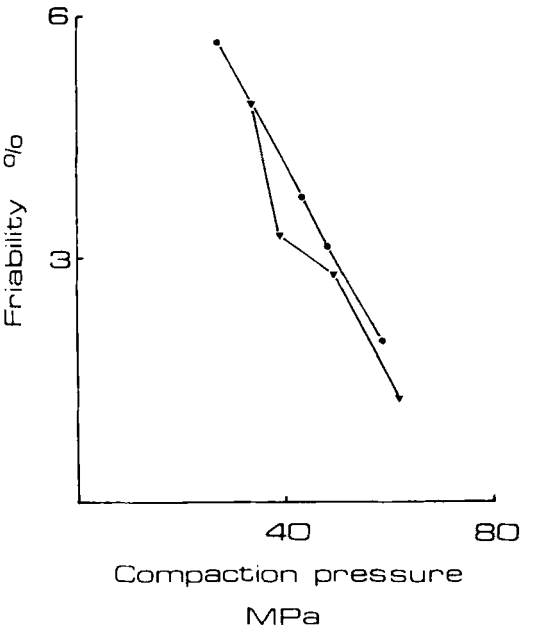

Fig. 2 Disintegration Time as a function of mean compaction pressure for tablets made from bulk lactose samples. ●, (A); ▼, (B).

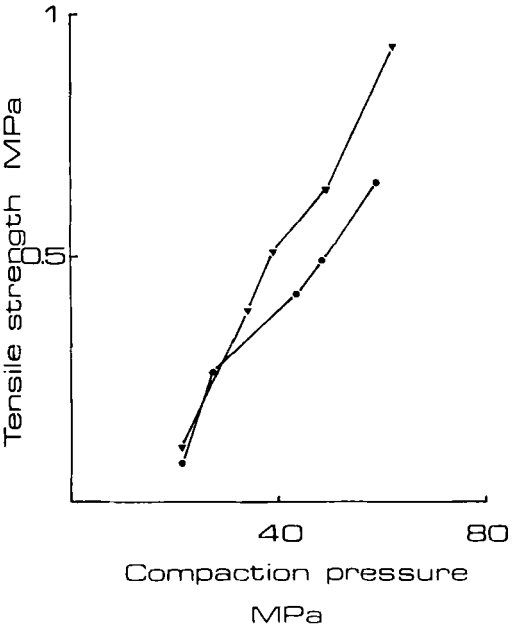

Fig. 3 Friability as a function of mean compaction pressure for tablets made from bulk lactose samples. ●, (A); ▼, (B).

TABLE II : PHYSICAL PROPERTIES OF FORMULATED TABLETS

BATCH	1	2	3
Crushing Strength (Strong Cobb Units)	11.3	7.2	10.3
Disintegration Time (minutes)	3¼-5¼	6-7	4-6
Friability (% w/w)	0.09	0.30	0.13
Tablet Weight (mg)	400.7	403.0	397.7
Coefficient of Weight Variation (%)	1.4	1.1	1.1

The results of studies using a selected development formulation containing several ingredients as well as lactose are shown in Table II. Three batches of tablets were examined; Batch 1 was made in the USA using (B), Batch 2 was made in the UK using (A) and Batch 3 was made in the UK using (B). For Batch 2, the figures are for the highest tablet strength it was possible to achieve, while for Batch 3 the tablet machine was adjusted to produce tablets resembling as closely as possible those from Batch 1. As Table II shows, it was not possible to produce tablets similar to Batch 1 using (A), but when lactose (B) was used tablets were obtained which had similar properties to Batch 1.

Table III shows the particle size distribution and specific surface areas for the 125-180 μm size fractions of (A) and (B). The distributions were similar, as were the modal sizes, but the mean and median sizes for (B) are less than those for (A) due to the greater

TABLE III : PHYSICAL PROPERTIES OF 125-180 μm SIEVE FRACTIONS OF (A) AND (B)

	A	B
Mean Size	133 μm	106 μm
Median Size	141 μm	129 μm
Modal Size	144 μm	140 μm
Specific Surface Area	0.26 $m^2 g^{-1}$	0.34 $m^2 g^{-1}$

proportion of fines in (B). This was also the main reason for the greater surface area of (B).

Strength-pressure profiles for the 125-180 μm fractions are shown in Figure 4. The profiles for (A) and (B) are much closer together than for the unsized materials (Figure 1), but (B) still gives slightly stronger tablets than (A).

Friabilities (Figure 5) and disintegration times (Figure 6) were also much closer together than for the bulk samples and both decreased with increasing pressure. Thus the differences in physical properties of (B) over (A) have been largely eliminated by the use of closely matched size fractions.

DISCUSSION

The differences in tensile strength between tablets made from the two types of lactose are probably due at least in part to differences in

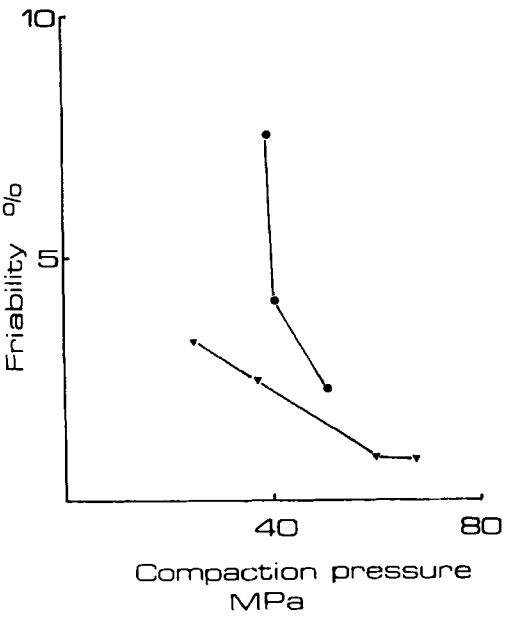

Fig. 4 Tensile strength as a function of mean compaction pressure for tablets made from 125-180 μm sieve fractions. ●, (A); ▼, (B).

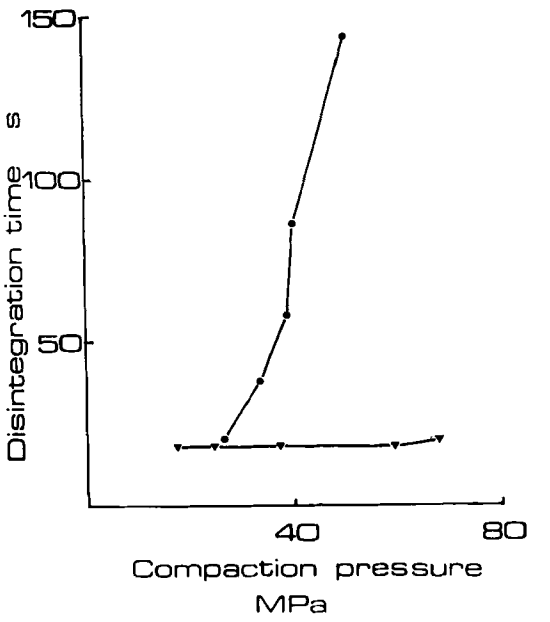

Fig.5 Friability as a function of mean compaction pressure for tablets made from 125-180 μm sieve fractions. ●, (A); ▼, (B).

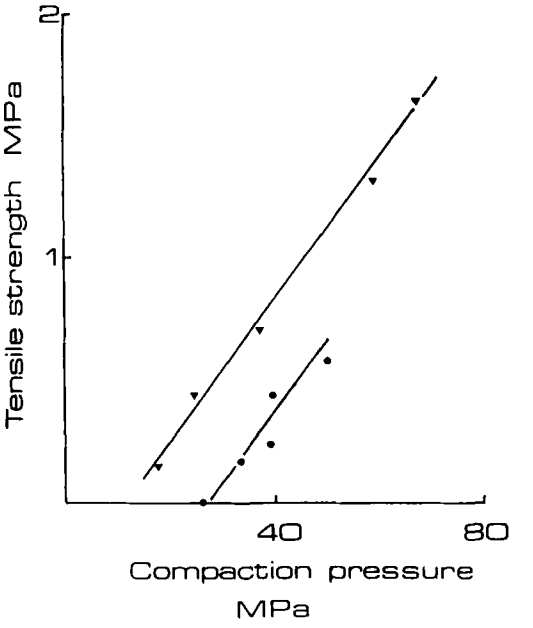

Fig. 6 Disintegration Time as a function of mean compaction pressure for tablets made from 125-180 μm sieve fractions.
●, (A); ▼, (B).

particle size and size distribution. It is generally accepted that the strength of tablets made from lactose increases as particle size decreases (7-9). The reason for this is thought to be the extent of fragmentation which the lactose particles exhibit on compaction. De Boer et al (8) stated that while fragmentation is the predominant compaction mechanism for α-lactose monohydrate, the same degree of fragmentation is not shown at all particle sizes. Tablet strength depends on surface area which is in turn dependent on the initial particle size and the compaction pressure.

In the present study, it was possible to reduce the differences between the properties of tablets made from different brands of lactose by preparing samples having similar particle size distributions. The fact that (B) still gave slightly stronger tablets than (A) is probably due to the greater proportion of fines in (B) and hence its greater surface area.

These results serve to confirm previous work, but the results for the development formulation are more interesting because they demonstrate the extent of the effects of using the different lactoses. Microcrystalline cellulose is renowned for its binding properties and so it is perhaps surprising that the compression characteristics of a formulation containing 50% Microcrystalline cellulose and 33% lactose should be so severely affected by differences in the lactose used.

Although different tableting machines were used at the two sites, this does not explain the discrepancies in tablet properties, because the batches made in the UK with (A) and (B) behaved very differently to each other.

The conclusion must be that when transferring processes between sites, identical sources of supply should be used where possible. Where this cannot be done, the materials should be fully characterised, so that the best possible match can be obtained.

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