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THE EVALUATION OF SIX LACTOSE-BASED MATERIALS AS DIRECT COMPRESSION TABLET EXCIPIENTS.

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ABSTRACT

Six lactose-based products have been evaluated as direct-compression tableting excipients in a simple formulation. Anhydrous Lactose, NF was the best material overall, with Fast-Flo lactose and Ludipress also being very good. The compaction properties of these products changed to varying degrees when tablets were made on a rotary press instead of a single punch press, and when machine speed was increased on the rotary machine.

Compendial specifications cannot adequately differentiate between products with differing compaction properties.

INTRODUCTION

Direct compression tableting first came to prominence a quarter of a century ago, when excipients with sufficiently good flow and compaction properties became available. The advantages of direct compression are well-known, the most important of them being a smaller number of processing stages and the elimination of heat and moisture. The main disadvantages are the requirements that powder blends flow freely and compress satisfactorily at speed. The tableting properties of direct compression blends are much more dependent on the properties of the raw materials than is the case with wet-granulated systems and so the choice of excipients is critical to the quality of the final product. This is particularly important in the case of the filler or binder, which can constitute over 95% of the weight of a direct compression formulation.

The particle size, size distribution, shape and texture must be kept within the tightest possible limits to minimise variations in the flow properties and compressibility. Differences in particle size between excipients and drug can lead to poor mixing.

If the direct compression technique is to be used with confidence, it is vital that the raw material specifications extend well beyond pharmacopoeial limits and include particle size data, compaction force/strength profiles and information on the flowability of the excipients and drugs.

There is a single monograph for lactose in the British Pharmacopoeia, despite the fact that α-lactose monohydrate can be obtained as almost any desired size fraction, and there are numerous sources of anhydrous, spray-dried or physically-modified lactose available. The properties of the various types and grades of lactose can vary widely: Lerk et al. (1) reported that α-lactose monohydrate is a poor binder, whereas anhydrous lactose (mainly β-lactose) is a superior binder but has borderline flowability. Even for pure α-lactose, the binding capacity is dependent on the extent of dehydration (2). Particle size, as well as affecting flowability and segregation, has been shown to influence the strength of tablets made from spray-dried and anhydrous lactose (3,4).

The aim of the work presented here is to evaluate six lactose products as direct compression excipients in order that excipient selection and inventory control can be rationalised.

EXPERIMENTAL

Materials

1. Fast-Flo Lactose (Foremost/K & K Greeff Ltd., Croydon, England): spray-dried α-lactose monohydrate.
2. Lactose NF, powdered hydrous (DMV/Zimmerman-Hobbs Ltd, Milton Keynes, England): α-lactose monohydrate.
3. Lactose NF, powdered anhydrous, direct tableting (Sheffield/ Moreham Ltd., Lewes, England): mainly β lactose.

4. Tablettose (Meggle/Forum Chemicals Ltd., Redhill, England): physically-modified α-lactose monohydrate.
5. Zeparox (Dairy Crest Ltd., Harlington, England): spray-dried α lactose monohydrate.
6. Ludipress (BASF, Cheadle, England): α-lactose monohydrate + 2.2% PVP C-30 + 3.4% crospovidone.

Disintegrant: Kollidon C.L 3.4% was added to each material except Ludipress.

Lubricant: Magnesium Stearate BP 0.5% was added to each material.

400g batches of the materials were mixed for 5 minutes in a Hobart planetary mixer prior to compression.

Methods

Sieve analysis was performed on each sample and the geometric mean particle size was determined from the log-normal size distribution. The true density of the blends was determined using a Micromeritics' helium-air pycnometer.

Bulk (ρB) and tap (ρT) densities were also determined and the Carr compressibility index calculated (5).

Loss on drying was determined using a Sartorius 7093 01 infra-red moisture balance (75°C/10 min).

The blended powders were compressed on an instrumented Manesty F3 single punch tablet machine operating at 75 strokes per minute, with 10mm flat-faced tooling. The target tablet weight was 300mg.

For each type of lactose, tablets were made at five different compaction pressures. After compaction, the tablets were stored in sealed containers for 48 hours before physical testing.

Tablet weight variation and friability were determined for 20 tablets from each sample: Crushing force/tensile strength was determined using an Erweka TBH 28 tablet tester, disintegration time was determined using a Pharmatest disintegration tester with water at 37°C. Tablet thickness was measured using a Mercer dial gauge. Each of these determinations was performed on six tablets from each sample.

The tensile strength of the tablets was calculated as described by Fell and Newton (6).

RESULTS AND DISCUSSION

The physical characteristics of each material are summarised in Table 1. The main differences are that hydrous lactose, NF has a greater bulk density than most of the others, and Ludipress has a lower bulk density. Ludipress also has a greater loss on drying (NB. water of hydration was not driven off.)

Using the Carr's Index to predict flowability, Ludipress, hydrous lactose, Zeparox and Fast-Flo could be classified as "excellent", Tablettose as "good" and anhydrous lactose as "fair". Examination of Table 2 reveals that all of the systems

TABLE 1

Physical Characteristics of Samples

	TRUE DENSITY (g cm^{-3})	LOOSE BULK DENSITY (g cm^{-3})	TAPPED[1] BULK DENSITY (g cm^{-3})	CARR'S INDEX (%)	LOSS ON DRYING (%)	GEOMETRIC MEAN PARTICLE SIZE (μm)	GEOMETRIC STANDARD DEVIATION
Fast Flo	1.50	0.593	0.676	12.3	0.6	140	1.36
Lactose NF, hydrous	1.53	0.740	0.825	10.3	0.4	160	1.32
Lactose NF, anhydrous	1.53	0.570	0.699	18.5	0.4	180	1.59
Tablettose	1.53	0.595	0.704	15.8	0.3	215	1.60
Zeparox	1.51	0.595	0.666	10.8	0.5	155	1.32
Ludipress	1.47	0.521	0.543	4.0	1.5	240	1.50

[1] 100 taps at 240 min^{-1}, drop height 3mm.

TABLE 2

Coefficients of Tablet Weight Variation

Material	Mean Applied Pressure (MPa)	C.O.V. (%)
Fast Flo	15.6	0.22
	21.5	0.54
	28.0	0.88
	36.1	0.43
	62.9	0.71
Lactose NF, powdered hydrous	26.5	2.15
	33.7	1.50
	39.2	0.30
	40.3	0.62
	50.6	0.28
Lactose NF, powdered anhydrous	12.0	0.36
	20.5	0.40
	28.4	0.27
	34.7	0.37
	59.9	0.52
Tablettose	20.5	0.46
	29.5	0.51
	43.6	0.56
	50.5	0.39
	63.1	0.42
Zeparox	12.4	0.89
	23.7	0.26
	31.5	0.33
	44.8	0.39
	60.4	0.28
Ludipress	12.9	0.94
	24.2	1.09
	35.4	0.61
	40.0	0.58
	54.3	0.69

flowed well, giving quite low coefficients of tablet weight variation. The high values for Lactose NF, powdered hydrous are due to the high friability of these tablets, causing weight loss during handling. The slightly high values for Ludipress could be due to the larger particle size of this material compared with the other products.

Tensile strength varied linearly with applied pressure for each excipient, and there were great differences in the tablet strengths for each excipient at any given pressure (Fig 1). Lactose NF, powdered anhydrous gave the strongest tablets, followed by Ludipress and Fast Flo. Zeparox and Tablettose produced much weaker tablets and Lactose NF, powdered hydrous gave such weak tablets that it should not be considered as a direct compression excipient in spite of its excellent flow properties. The maximum pressure used for each material approximates to the point at which the tablet machine began to overload.

The differences in tensile strength (σx) are not completely explained by differences in particle size or moisture content, although these factors are known to influence tablet strength. It seems that, as suggested by de Boer et al. (4), the consolidation process is complex and depends on chemical, physical and spatial factors.

Log σx varied linearly with porosity (Fig 2). For tablets of equal porosity, anhydrous lactose would give the strongest tablets, followed by Ludipress and Fast Flo, followed by

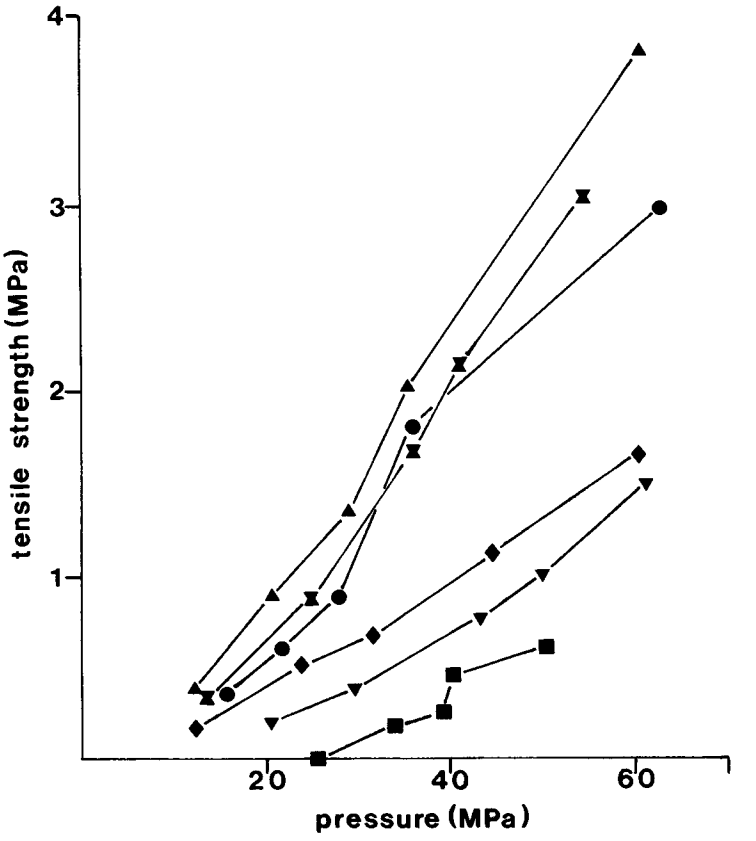

FIGURE 1

Tensile strength of compacts prepared with lactose from different suppliers, at selected compaction pressures.

- ● Fast Flo
- ■ Lactose NF, hydrous
- ▲ Lactose NF, anhydrous
- ▼ Tablettose
- ◆ Zeparox
- ⧗ Ludipress

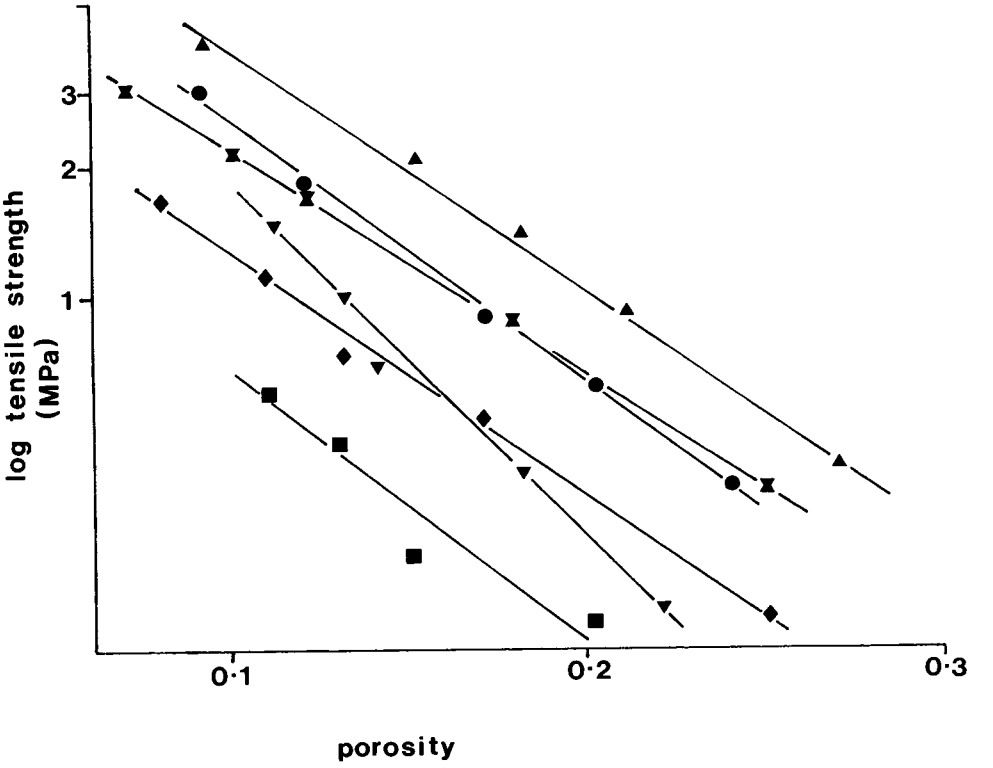

FIGURE 2

Relationship between porosity and tensile strength for compacts prepared with lactose from different suppliers.

- ● Fast Flo
- ■ Lactose NF, hydrous
- ▲ Lactose NF, anhydrous
- ▼ Tablettose
- ◆ Zeparox
- ⧗ Ludipress

Zeparox and Tablettose, with hydrous lactose giving the weakest tablets.

Anhydrous lactose, Ludipress and Fast Flo tablets showed roughly the same degree of friability. Zeparox was a little worse than these, Tablettose was worse still and hydrous lactose did not yield satisfactory tablets at any of the pressures used (Fig 3).

The disintegration times were generally low (Fig 4) and compaction pressure had little effect on disintegration except for hydrous lactose and for anhydrous lactose at the highest pressure used. Disintegration of the Ludipress tablets took longer than for the others because of the presence of poly-vinylpyrrolidone in the formulation.

From the results obtained, it appeared that Lactose NF, powdered anhydrous, Ludipress and Fast Flo were superior direct compression excipients to the others studied and so 2.5kg batches of each blend were prepared and tableted on a Manesty Betapress rotary tablet machine with 9.5mm flat, bevel-edged tooling. All three blends were tableted at the same precom-pression setting.

The results are given in Table 3. These show that Fast Flo lactose, which gave weaker tablets than the other materials on the single-punch machine, gave the strongest tablets on the Rotary machine. All three products gave weaker tablets on the rotary machine than on the single-punch press, although the difference was obviously least for Fast Flo.

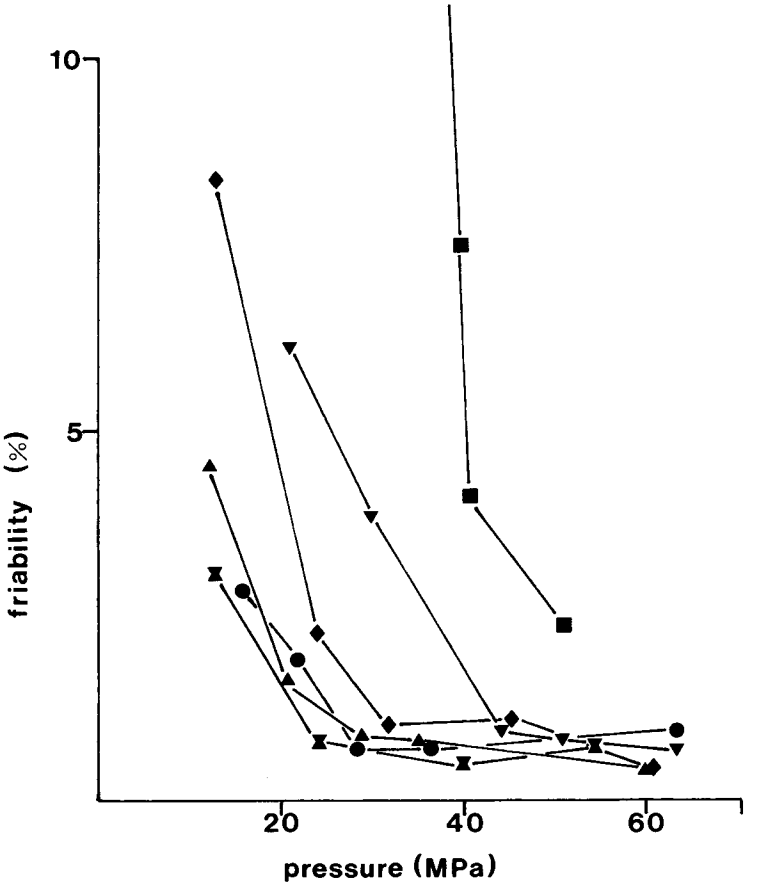

FIGURE 3

Friability of compacts prepared with lactose from different suppliers, at selected compaction pressures.

- ● Fast Flo
- ■ Lactose NF, hydrous
- ▲ Lactose NF, anhydrous
- ▼ Tablettose
- ◆ Zeparox
- ⧗ Ludipress

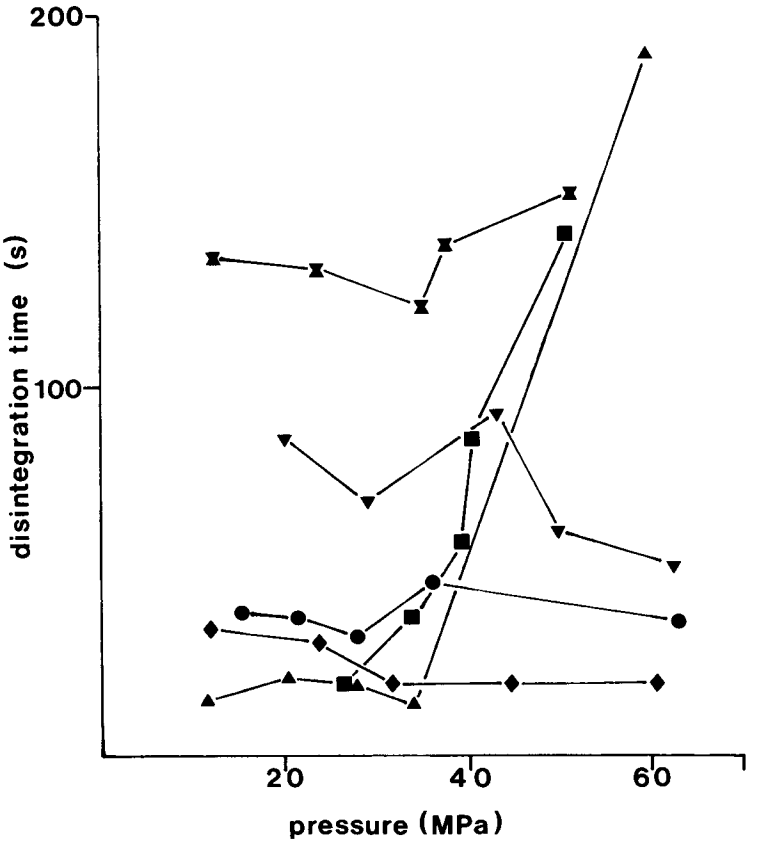

FIGURE 4

Disintegration of compacts prepared with lactose from different suppliers, at selected compaction pressures.

● Fast Flo
■ Lactose NF, hydrous
▲ Lactose NF, anhydrous
▼ Tablettose
◆ Zeparox
⧗ Ludipress

TABLE 3

Physical Properties of Tablets Produced on a Rotary Tablet Machine

Material	Machine Speed (tabs/min)	Crushing Strength (kp)	Coefficient of Tablet Weight Variation (%)	Disintegration Time (min)
Fast Flo	770	6.95	1.91	0.5
	1500	6.31	3.58	0.5
Anhydrous Lactose	770	4.48	0.91	0.5
	1500	4.11	1.53	2.5
Ludipress	770	4.36	0.77	3.0
	1500	3.54	0.98	3.0

Crushing strength decreased with increasing machine speed for each material, but only the anhydrous lactose sample showed any change in disintegration time with increasing speed. While the variations in tablet weight were reasonably low for anhydrous lactose and Ludipress, the values for Fast Flo were rather high; the coefficient of tablet weight variation increased with increasing machine speed for each material.

Table 4 shows the approximate price for 1kg of each material relative to the price of Lactose NF, powdered hydrous. (Prices obtained March 1987). The table shows Ludipress is twice as expensive as Fast Flo or Anhydrous Lactose NF, although this would have to be balanced against the possible advantages of having an excipient which has a binder and disintegrant incorporated into it.

The borderline flowability of anhydrous lactose is often given as one of the material's main drawbacks, but the results presented here show that the level of tablet weight variation was satisfactory on both single-punch and rotary machines. The variation shown by Fast-Flo lactose on the rotary machine was surprising, given its excellent flow properties and the low variation observed on the single-punch machine, and no reason for this behaviour was identified.

Ludipress performed well on both types of machine and would appear to be an excellent direct compression excipient. The samples of Zeparox and Tablettose were poor by comparison with Anhydrous Lactose NF, Fast Flo and Ludipress with the

TABLE 4

Relative Costs of Excipients
(March 1987), based on 1 tonne order)

Material	Relative Cost
Lactose NF, powdered hydrous	1.0
Tablettose	1.9
Anhydrous Lactose NF	2.8
Fast Flo	3.3
Ludipress	6.7
Zeparox	No longer available

sample of Lactose NF, powdered hydrous being completely unsuitable as a direct compression excipient despite its very good flow properties.

It is important to consider not only the type and composition of excipients but also the source. Two samples of spray-dried lactose were used in this work - Fast Flo and Zeparox - each having very different properties. Similarly, recent manufacturer's literature (7) indicated that Tablettose produced stronger tablets for a given pressure than spray-dried lactose, which conflicts with the results presented here.

It seems logical and necessary to include an evaluation of compaction properties into the specifications for directly compressible raw materials rather than rely on compendial standards.

Most of the excipients currently used in pharmaceutical manufacture have been 'borrowed' from other industries, and it is only recently that excipients designed specifically for direct compression tableting have become available, so it is encouraging that Ludipress performed well against some of the more established products. It is to be hoped that more manufacturers take up the challenge to produce the ideal excipient.

CONCLUSIONS

1. Six lactose-based excipients have been evaluated as direct compression excipients. Anhydrous Lactose NF (Sheffield) proved to be the best, followed closely by Fast Flo and Ludipress.
2. Samples of spray-dried lactose from different suppliers had very different properties and hence would not necessarily be interchangeable in direct compression formulation.
3. For manufacturers employing direct compression formulations, the adoption of compaction profiles into raw material specifications would be advantageous.
4. Rate of compaction and type of compaction machine can affect the compression properties of lactose-based excipients.

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