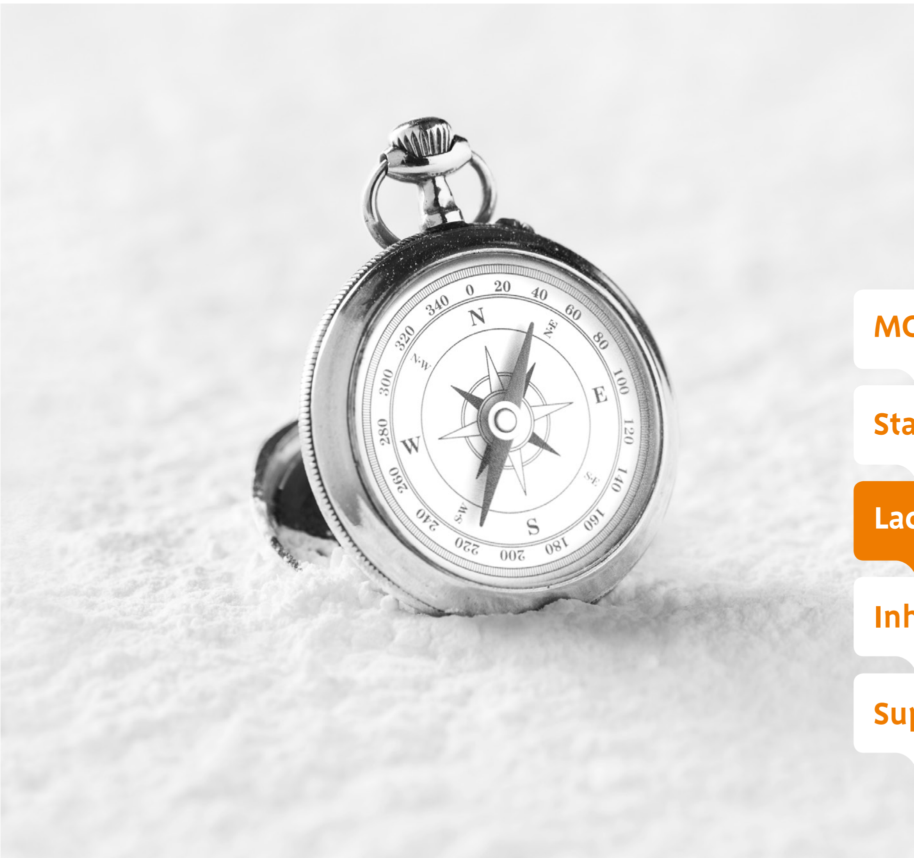
DFE pharma

Use of lactose in hard gelatin capsules



MCC

Starch

Lactose

Inhalation

Superdisintegrants

The pursuit of excipient excellence

Summary

SuperTab® 21AN, SuperTab® 30GR and sieved grades of Pharmatose® are all suitable for encapsulation in hard gelatin capsules based on their flowability (Carr's Index).
SuperTab® 21AN gave the strongest plugs of all grades of lactose tested, and SuperTab® 30GR gave the strongest plugs of the grades of lactose monohydrate.

1 Introduction

Hard gelatin capsules are a common oral solid dosage for immediate release formulations. Compared to tablets they are easy to formulate and manufacture, formulations can be developed with minimal amounts of active pharmaceutical ingredient (API) and they are easily blinded for clinical trial purposes. Additionally they provide a ready means of identification through the choice of capsule shell colour and printing, and they are patient friendly being easy to swallow and providing taste masking for unpleasant actives.

Lactose is a common diluent in hard gelatin capsules. Figure 1 shows the frequency of use of 5 common diluents in hard gelatin capsule formulations based on analysis of the FDA Inactive Ingredients Database (June 2011).

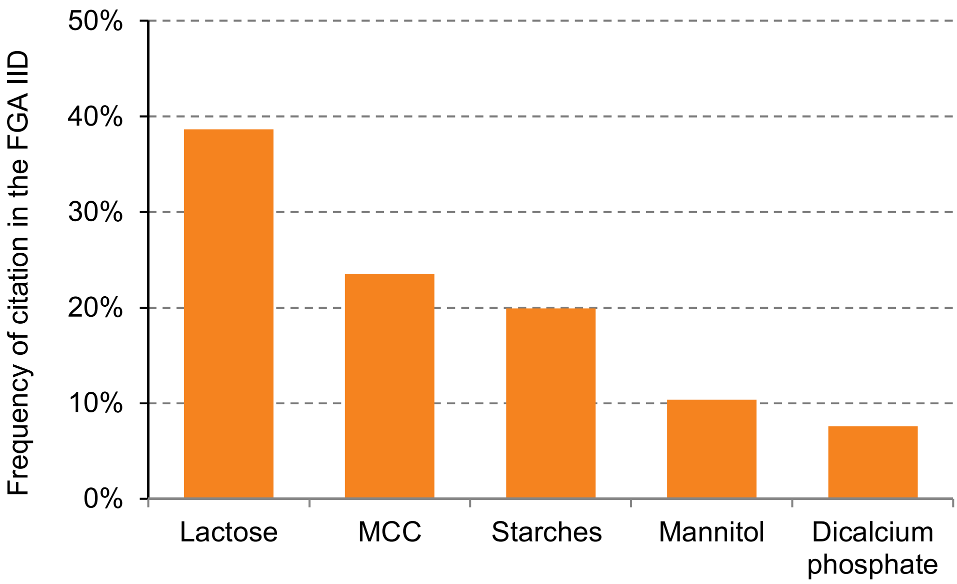


Figure 1: *Estimated usage of excipients in hard gelatin capsules*

There are several beneficial properties of lactose that make it suitable in hard gelatin capsule formulations.

- It has very low aldehyde levels. Aldehydes have been implicated in the cross linking reactions that cause insolubility of hard gelatin capsule shells resulting in extended dissolution times. An extensive review of the affect of aldehydes on gelatin capsules can be found in reference 1.

Table 1 shows the measured formaldehyde and acetaldehyde content of a range of capsule diluents [(2)].

__Table 1:__ Measured aldehyde content of certain excipients (adapted from ref 2)

Excipient	Formaldehyde	Acetaldehyde	Other aldehydes
Lactose	0.1 ppm	ND	ND
Microcrystalline Cellulose	0.4 ppm	0.1 ppm	ND
Partly pregelatinised corn starch	2.5 ppm	0.1 ppm	ND
Mannitol	0.2 ppm	ND	ND
Dibasic Calcium Phosphate	ND	ND	ND

- Lactose monohydrate and anhydrous lactose both exhibit very low hygroscopicity (see the dynamic vapour sorption (DVS) plots in figure 2). Lactose monohydrate absorbs only about 0.2% water at 90% RH, and anhydrous lactose absorbs approximately 1%. The hysteresis in the anhydrous lactose plot is attributable to crystallisation of the anhydrous α-lactose component to α-lactose monohydrate.

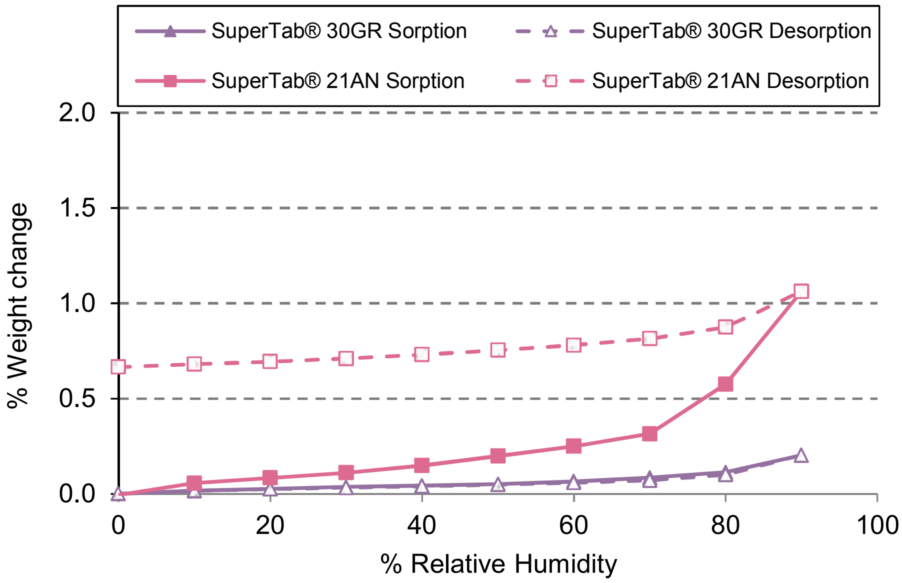


__Figure 2:__ DVS isotherms of lactose monohydrate and anhydrous lactose

- Lactose is water soluble and does not contribute to the blockage of some sinkers used in capsule dissolution testing.

Lactose is available in a wide number of types (milled & sieved with different particle sizes, anhydrous, agglomerated and spray dried) for various applications. The purpose of the work in this paper was to assess the most suitable types of lactose for use in simple dry blended capsule formulations. The assessment is based on two key physical properties (Carr's Index and plug strength) which have previously been identified as key properties for a powder for encapsulation [3], using both dosing disc and dosator type machines (H&K GKF400 and Zanasi LZ64 respectively).

For different grades of MCC it was found that 101 grades with Carr's Index of 37% or 102 grades with Carr's Index of 27% gave the least variability of fill weights on both types of filling machine.
For blends of ascorbic acid and MCC, with Carr's Index values ranging from 12% to 21% it was found that the lowest Carr's Index was associated with the highest variability of fill weight. The variability in this instance was associated with separation of the base of the unsupported plug of powder during transfer to the capsules.

Thus, for good weight uniformity it appears that it is necessary to form strong cohesive plugs at the low forces used to form plugs during encapsulation, and intermediate values of Carr's Index are preferred. A Carr's Index range of 20% to 40% was the target for the studies in this paper.

2 Experimental section

2.1 Materials

All lactose products are available from DFE Pharma.
Magnesium stearate was supplied by Mallinckrodt Inc., St Louis, MI.
Acetaminophen (APAP) was supplied by Spectrum Chemicals, New Brunswick, NJ.

2.2 Formulations

All functional tests (flowability, plug formation and plug strength) were performed two formulations. These were (a) 99.5% lactose / 0.5% magnesium stearate and (b) 10% acetaminophen / 89.5% lactose / 0.5% magnesium stearate.

2.3 Particle size analysis

Particle size analysis of lactose was performed by laser diffraction (Malvern Mastersizer; Malvern Instruments Ltd., UK) using the 3-RF lens, the small-volume sample presentation unit (capacity 150 ml) and powder dispersion pressure of 60 psi.

2.4 Flowability

Flowability of formulations containing 0.5% magnesium stearate was assessed using Carr's Index (CI). Bulk density (BD) and tapped bulk density (TBD) were measured using Scott and Stampf Volumeters respectively.

2.5 Capsule plug formation

Capsule plugs were prepared on a Harro Höfliger KFM/3 dosing disc machine using a size 1 piston with 150 Newton force, 35 rpm speed and 40 mm powder bed height.

2.6 Plug strength measurement

Plug strength was measured using a P/10 10 mm Delrin cylindrical probe attached to TA.XT2i Texture Analyser (Texture Technologies Corp., Scarsdale, NY / Stable Micro Systems, Godalming, Surrey, UK). Data were collected using the Texture Expert Exceed1 (version 2.50) software supplied with the instrument. The acquisition rate was 200 points per second at test speed and target deformation distance of 0.25 mm/s and 1 mm respectively.

3 Results and discussion

3.1 Powder flow

The relationship between lactose median particle and Carr's Index of lubricated lactose and blends with acetaminophen is shown in Figure 3.

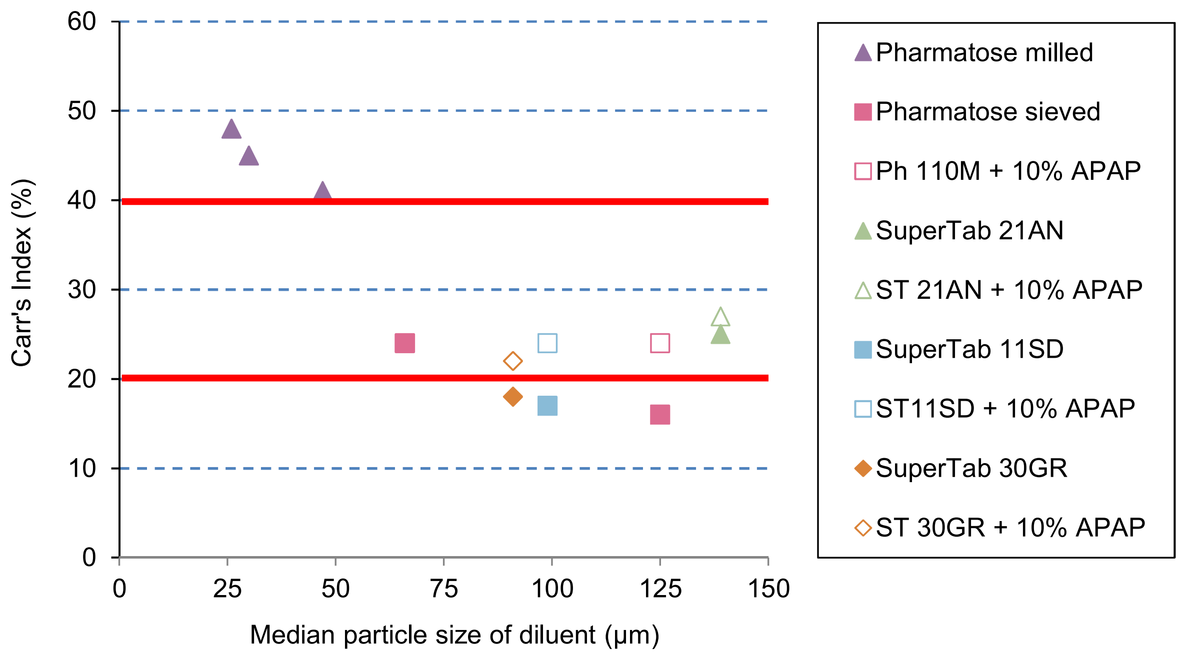


***Figure 3:** Particle size of lactose and Carr's Index of lactose and lactose / acetaminophen blends*

The samples of milled lactose (Pharmatose® 350M, Pharmatose® 200M and Pharmatose® 150M with median diameters of 26 µm, 30 µm and 47 µm respectively all exhibited higher Carr's Indices higher than the target of this study.

One sample of sieved lactose (Pharmatose® 125M with median diameter 66 µm) had Carr's Index within the target range and the other sample (Pharmatose® 110M with median diameter 125 µm) was outside the target range.

Of the three grades of SuperTab® assessed, the anhydrous lactose sample (SuperTab® 21AN) has Carr's index within the target range, despite this sample having the largest median diameter. This is probably a result of the relatively high proportion of fine particles (approximately 18% < 45 µm) in this product.

Addition of 10% acetaminophen to Pharmatose® 110M and SuperTab® products increased Carr's Index to within the target range.

3.2 Plug strength

Figure 4 shows the plug strength of size 1 plugs compressed with a force of 150 N.

The milled and sieved Pharmatose products form plugs whose strength appears independent of particle size. Of the SuperTab® products, the granulated lactose monohydrate (SuperTab® 30GR) and especially the anhydrous product (SuperTab® 21AN) give the strongest plugs.

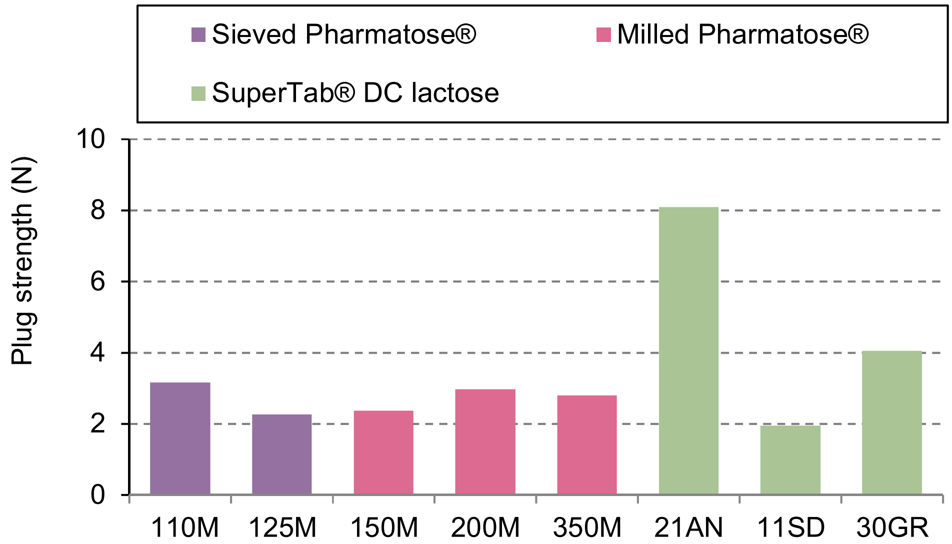


***Figure 4:** Strength of lactose plugs*

4 Conclusions

On the basis of these data, SuperTab® 21AN appears to have the optimum properties of flowability and the ability to form strong coherent plugs, and is the preferred form of lactose for hard gelatin encapsulation.
Granulated lactose (SuperTab® 30GR) is the preferred form of granulated lactose because of its ability to form stronger plugs than milled or sieved lactose.
Sieved lactose grades are suitable for encapsulation, and have the advantage of being available in a wide range of particle sizes. Thus it is possible to manipulate the Carr's Index value of the formulation blend by selection of the appropriate grade.

References

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Acknowledgements

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