DFE pharma

Re-compaction properties of lactose and microcrystalline cellulose

Individual excipients

MCC

Starch

Lactose

Inhalation

Superdisintegrants

The pursuit of excipient excellence

Summary

SuperTab® 21AN (anhydrous lactose) is the preferred form of lactose for use in dry granulated formulations, because it does not suffer from reduction in tabletability after densification. Microcrystalline cellulose forms very strong compacts, despite the reduction in tabletability after densification.

1 Introduction

Dry granulation, and especially roller compaction, is being used increasingly as a means of granulation of pharmaceutical products. The granulation process improves powder flowability and helps to "lock" the active substance in the granule thus reducing the risk of segregation and poor tablet or capsule content uniformity.

Compared to wet granulation, roller compaction has the advantages that it uses no water or solvent, it is readily scaled up and it can offer lower capital and running costs.

Many excipients have been evaluated for their suitability for roller compaction, but microcrystalline cellulose has been the most studied. However, MCC suffers from a drawback in that it tends to exhibit reduced tabletability after the initial densification step (*see footnote*). Such reduced tabletability is usually attributed to work hardening [1], although a subsequent study proposes that granule size enlargement is responsible for the phenomenon [2].

Irrespective of the cause, reduced tabletability may be regarded as an unwanted property of dry granulated powders, and this technical paper shows the importance of selecting an appropriate grade of lactose for dry granulation.

Footnote: Definitions
To avoid confusion, in this bulletin the term "densification" is used to mean the first compaction step by roller compaction or by slugging, and "tableting" is used to mean tableting of the granules formed by the densification process as in the schematic process below.

Relative density (used to describe the degree of densification) is calculated as

RD = density of the compact / true density of the components of the compact.

Porosity (used to describe the porosity of the final tablets) is calculated as

*Porosity = 100 * (1 – RD)*

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2 Experimental Section

2.1 Materials

Pharmatose® 125M (sieved α-lactose monohydrate), SuperTab® 21AN (anhydrous β-lactose), SuperTab® 11SD (spray dried lactose) and Pharmacel® 102 (microcrystalline cellulose / MCC) are all supplied by DFE Pharma.

2.2 Densification and milling

Samples of lactose and MCC were densified by compaction on a single punch tablet machine (Korsch EK0) fitted with 13 mm punches. The materials were densified to target relative densities (RD) of 0.6, 0.7, 0.8 and 0.9.
Tablets so produced were milled using a rotary granulator fitted with a 1.6 mm screen and operating at 50 rpm. Granules densified to 0.9 RD were also milled again through a 0.8 mm screen to further reduce the granule size. In the discussion these granules are given the suffix “fs”.

2.3 Particle size analysis

Samples of granules (20 g) were sieved over 1400 µm, 1000 µm, 710 µm, 500 µm, 355 µm, 250 µm 125 µm and 63 µm screens using Retsch sieving apparatus for 5 minutes. Median particle sizes were calculated.

2.4 Density measurement

Poured and tapped bulk densities were measured on a 30 ml sample of granules in a 100 ml measuring cylinder. The measuring cylinder was tapped 1250 times using a Jel STAV tap bulk density tester.

2.5 Tableting

All powders and all granules of 0.9 RD passed through the fine screen (fs) were tableted. Additionally one further granule of each material was selected, this being the granule closest to a target median particle size of 200 to 300 µm.
The powders and granules were lubricated by blending with 0.5% magnesium stearate for 5 minutes using an Erweka AR400 cube mixer.
The lubricated powders and granules were tableted using a single punch tablet machine fitted with 11 mm punches to target porosities of 20%, 15%, 10% and 5%.
Tablet strength was determined after 10 days using an Erweka TBH 30 tester.

3 Results and discussion

3.1 Granule particle size

The median particle size of the granules is shown in Figure 1.

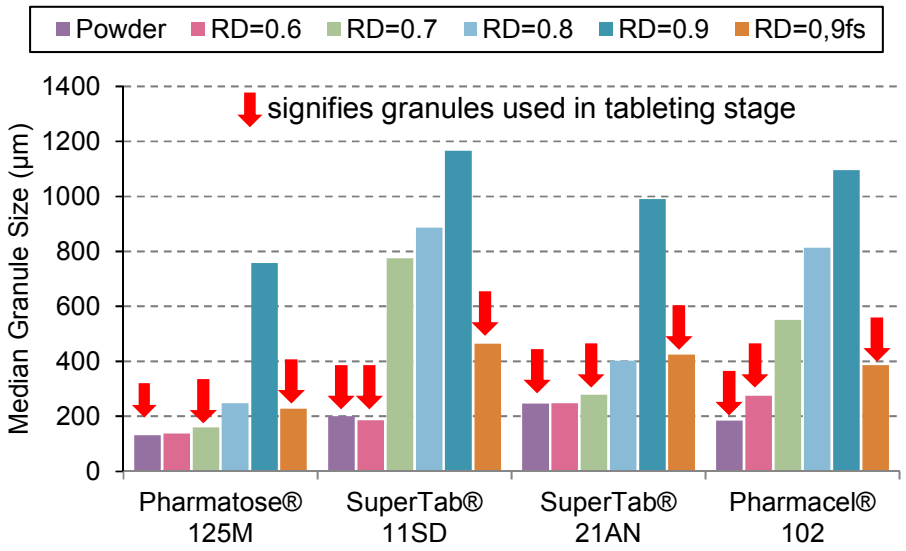

Figure 1: *Median particle size of granules*

Crystalline Pharmatose® 125M, which has very little tabletability, needed to be densified to a 0.9 RD before there was any substantial granule size increase. Spray dried SuperTab® 11SD, which has much better tabletability, formed large granules when densified to just 0.7 RD and anhydrous lactose SuperTab® 21AN showed intermediate behaviour.
Pharmacel® 102 on the other hand gave a smooth increase in granule size as RD increased.

3.2 Granule density

Increasing the extent of densification for all lactose types had relatively little effect on either poured or tapped bulk density (figures 2 & 3). However for Pharmacel® 102 the bulk density increased smoothly with increasing densification and the bulk density at 0.9 RD was 50% higher than that of the powder. A similar pattern was evident for tapped density with an overall increase of 33% for Pharmacel® 102.

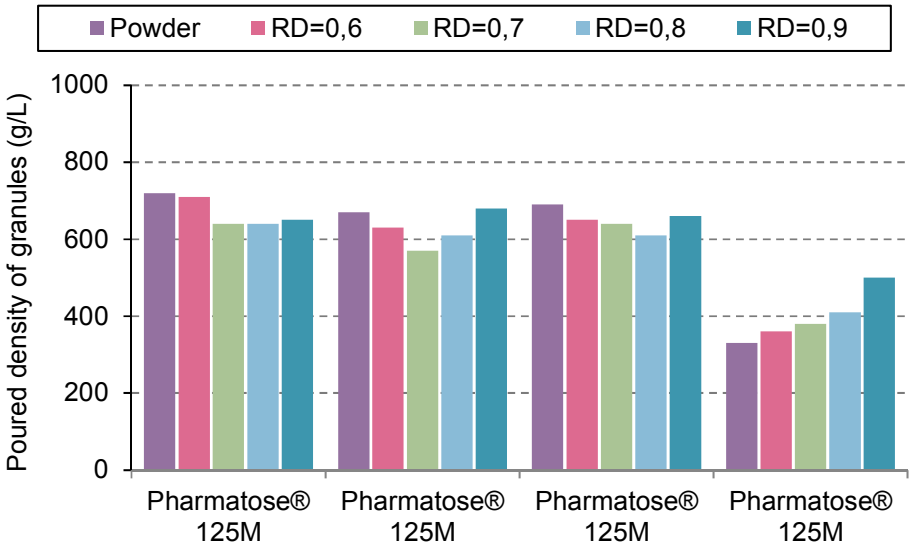

Figure 2: *Poured density of granules*

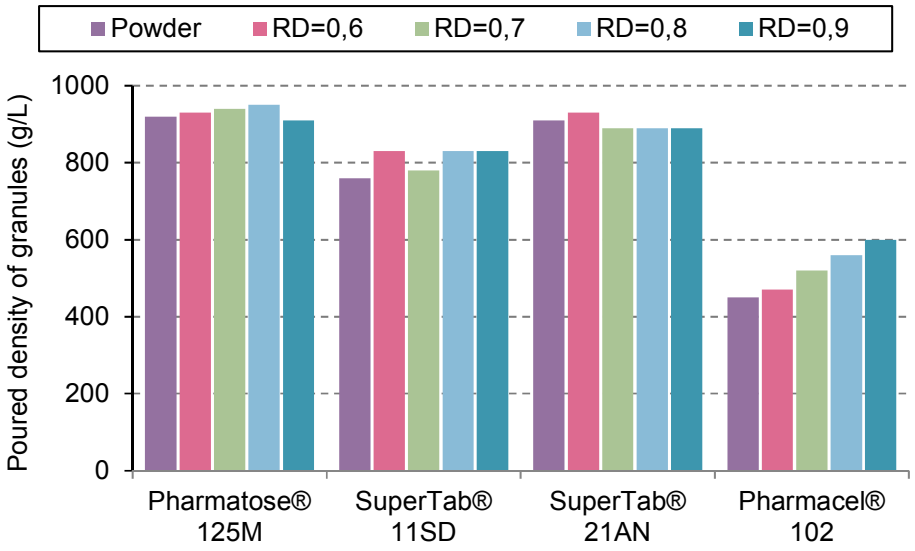

Figure 3: *Tapped density of granules*

3.3 Tableting

The tableting profiles of the excipients “as supplied” (powder) and as densified granules are shown in figures 4a to 4d.

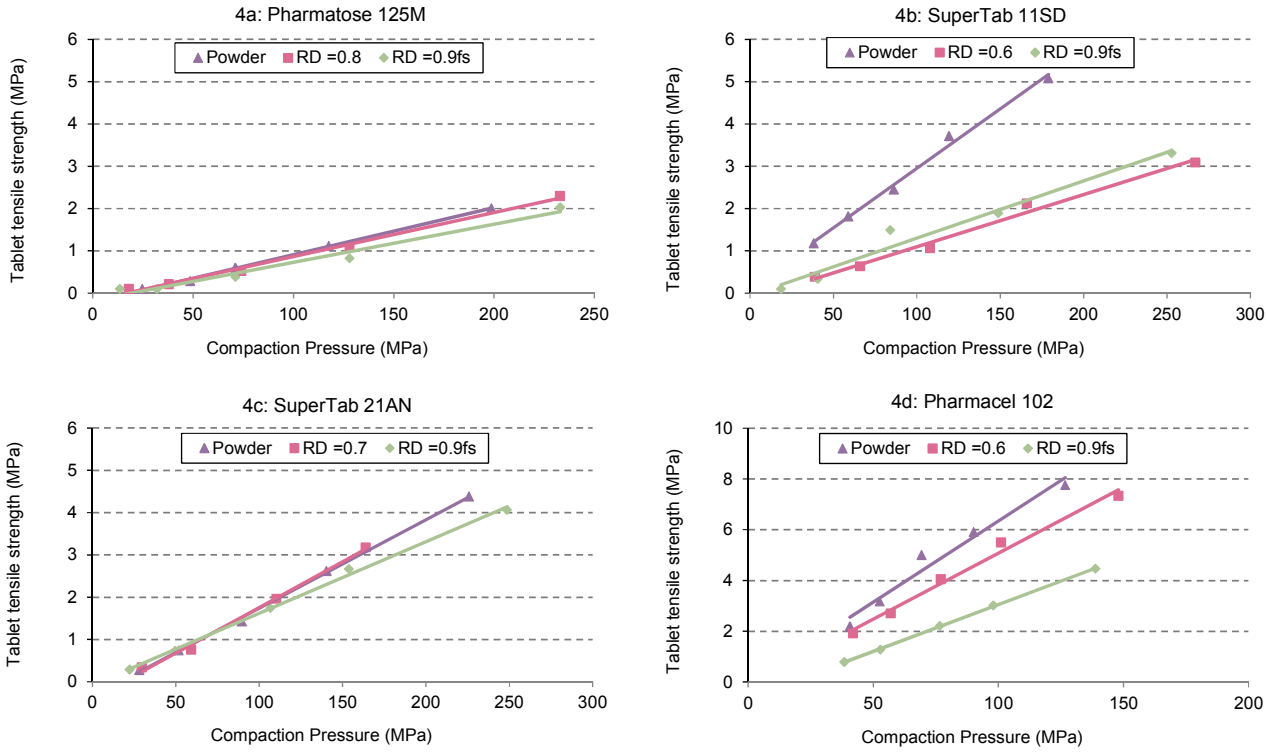

Figure 4: *Tabletability profiles of the excipients*

Pharmatose® 125M (crystalline α-lactose monohydrate) is not designed for direct compression and this is evident in figure 4a. Weak tablets were formed from the powder and from both sets of granules.

SuperTab® 11SD (spray dried lactose) forms strong tablets when tableted as supplied (figure 4b). However tabletability after densification is substantially reduced, and there appears to be no progressive loss of tabletability with increasing densification.

SuperTab® 21AN (anhydrous lactose) again forms strong tablets (figure 4c), but with this material there is little loss of tabletability even after it has been densified to 0.9 RD. The majority of its tabletability, as assessed by the slopes of the tableting profiles, is retained.

Pharmacel® 102 (figure 4d) forms very strong tablets, typical of microcrystalline cellulose. There is a progressive reduction in tabletability with increasing densification, but even the 0.9 RD granules form strong tablets.

The behaviour of the different materials can be explained in terms of brittle or plastic deformation. It is known that brittle and plastic materials exhibit different re-compaction properties.

Both lactose monohydrate and anhydrous lactose compact by brittle fracture, and the particle size of Pharmatose® 125M is above the value of 27 µm usually given as the brittle – ductile transition point for lactose monohydrate [3]. Hence we would expect that Pharmatose® 125M and SuperTab® 21AN will not exhibit much loss of tabletability. Lactose monohydrate has a low fragmentation propensity (that is, although it is brittle, the crystals are not easily fractured), and therefore it does not form strong tablets.

Spray dried lactose consists of very fine crystals of alpha-lactose monohydrate in a plastic matrix of amorphous lactose, and it is likely that loss of the plasticity of the matrix accounts for the changes in tabletability of spray dried lactose.

Microcrystalline cellulose deforms plastically, and the reduction of tabletability is well known.

5 Conclusion

SuperTab® 21AN is the preferred form of lactose for dry granulation applications because it forms strong tablets with little loss of tabletability after densification.
Microcrystalline cellulose loses tabletability, but nevertheless retains the ability to form strong tablets after densification.

References

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2. Reduced Tabletability of Roller Compacted Granules as a Result of Granule Size Enlargement, C Sun and WH Himmelspach, J. Pharm. Sci., 2006, 95(1), 201 – 206.
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Acknowledgements

These studies were performed at the University of Halle by Professor Katherina Picker-Freyer and Stephanie Hein. The data are summarised from reference 4.

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