DFE pharma

Roller compaction of anhydrous lactose and microcrystalline cellulose

Fitzpatrick Chilsonator studies

The pursuit of excipient excellence

Summary

Blends of anhydrous lactose and MCC in the ratio 65/35 to 55/45 give granules with the optimal properties for roller compaction.
Inclusion of MCC tends to decrease the roller compaction throughput rate and to increase the ribbon temperature during roller compaction.
However, granule size and flow, and tablet weight uniformity are improved with the inclusion of MCC.
In this ratio, the loss of tabletability of MCC after roller compaction is minimal and inconsequential.

1 Introduction

Earlier DFE Pharma technical papers on dry granulation [1,2] showed that anhydrous lactose is the preferred form of lactose for dry granulation because it exhibits minimal loss of compactability after densification.
Additional studies with blends of anhydrous lactose and microcrystalline cellulose indicated that inclusion of about 35% to 45% of MCC with the anhydrous lactose was an optimal starting point for formulation. Inclusion of the MCC tended to reduce the compaction force required to tablet the granules, although above this optimal level loss of tabletability attributed to the MCC became very noticeable.

In this paper blends of anhydrous lactose and MCC are examined using a Fitzpatrick Chilsonator IR520 roller compactor.

2 Experimental Section

2.1 Materials

SuperTab® 21AN (anhydrous lactose) and Pharmacel® 102 (microcrystalline cellulose) are available from DFE Pharma.
Magnesium stearate was supplied by BUFA, The Netherlands.

2.2 Formulations Assessed

The formulations assessed are shown in table 1. Magnesium stearate was included in blend A to prevent sticking to the rollers during densification. The level of 0.75% was determined empirically.

Table 1: *Placebo formulations assessed*

Component	Formulation A	Formulation B	Formulation C
SuperTab® 21AN	99,25%	65%	55%
Pharmacel® 102	-----	35%	45%
Magnesium stearate	0,75%	-----	-----

2.3 Densification and Milling

Formulations were densified using a Fitzpatrick Chilsonator IR520 roller compactor fitted with knurled beveled rolls fed by a horizontal and a vertical feed screw rotating at 12 and 200 rpm respectively. The rolls rotated at a minimum speed of 6 rpm (range 6 to 22 rpm) and were cooled with water at 15ºC. The temperature of the ribbons was measured using an infrared thermometer. Roll pressure was varied from 2.1 to10.5 kN/cm.
The time needed to process a certain weight of powder was measured to calculate the throughput of each powder blend at a roll pressure of 4.2 kN/cm.
Subsequent in-line milling was performed using a FitzMill model D6A with knives forward at 800 rpm and a 1 mm screen.

2.4 Powder Blends

Direct compression powder blends of equivalent composition to the roller compacted granules were prepared by blending in a Turbula T2 mixer.

2.5 Particle size distribution

The particle size distribution (PSD) of the granules was assessed by laser diffraction using a Sympatec Helos system.

2.6 Poured and tapped bulk density

Granule poured and tapped bulk densities were assessed using a weighed sample of approximately 230 ml powder in a 250 ml graduated cylinder. The powder volume was determined before and after 1250 taps.

2.7 Tableting

Powders and granules were lubricated with 0.5% magnesium stearate before tableting into 250 mg tablets using a rotary press (Rotab-T, Luxner, Germany) fitted with 9mm flat bevel edge punches. Target compaction pressures were 75, 150, 225 and 300 MPa.

2.8 Tablet crushing strength

The tablet strength was tested on 10 tablets the day following compaction.

2.9 Tablet friability:

Tablet friability was tested according to USP chapter 1216.

2.10 Tablet weight uniformity:

The relative standard deviation (RSD) of ten tablets was calculated.

3 Results and Discussion

3.1 Roller compaction

The three blends all roller compacted well. Ribbons did not stick to the roll surface throughout the 20kg runs. The temperature of the ribbon was measured during roller compaction. Stabilisation of the temperature was achieved within 5 minutes for all three blends. Figure 1 shows the stabilized temperature for the three blends at the 5 different roll pressures used. The temperature increased with increasing pressure and was also slightly higher for the blends containing MCC. Increases in temperature are primarily caused by the densification process of the powder but also by work exerted by the vertical pre-compression screw. This effect may be a result of the different deformation mechanism of brittle anhydrous lactose and plastic MCC.

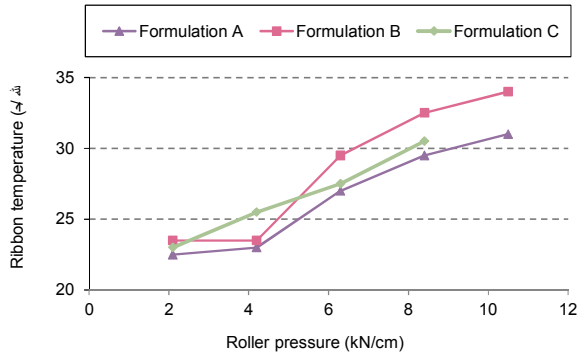


Figure 1: *Ribbon temperature for the formulations at different roll pressures*

The throughput of the blends was 46 kg/h, 39 kg/h and 41 kg/h for blends A, B and C respectively. The lower density of the MCC results in lower throughput. This means that, at a given roll speed, throughput can be increased by increasing the SuperTab® 21AN content in the formulation.

3.2 Granule particle size

Figure 2 shows the effects of formulation and roll pressure on particle size of the granules.

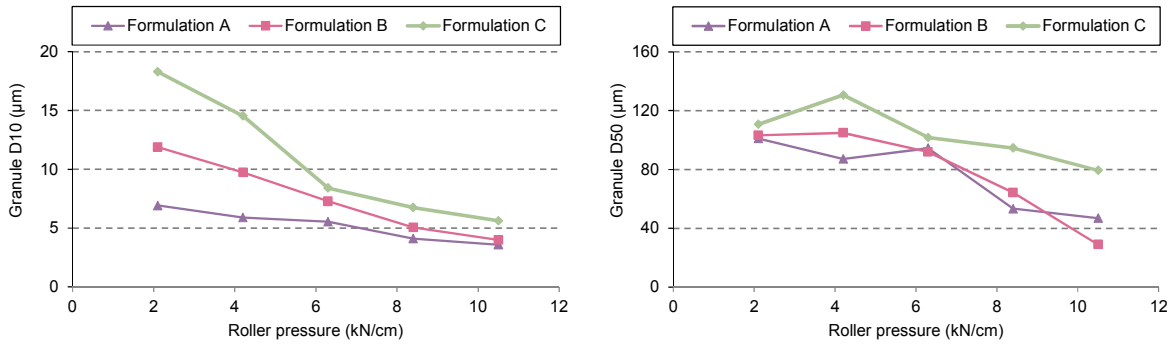


Figure 2: *D10 and D50 values for the densified and milled ribbons*

Ribbons made using the lightest roll pressures (2.1 and 4.2 kN/cm) showed the greatest differences in D10, and the inclusion of MCC resulted in granules with the fewest fines. D50 generally decreased with increasing roll pressure, and in general higher levels of MCC gave larger D50 values.
The particle size effects can, and do, have implications for flow on a tablet machine. A relationship between D10 and D50 with pharmaceutical powder flow has been developed [(3)], which suggests that D50 values of 80 µm or higher and D10 of 9 µm or higher provide excellent flow.
It is stressed that no optimisation of the milling conditions was performed in this study, and it is possible that improvements of the particle size distribution could be achieved by milling optimisation.

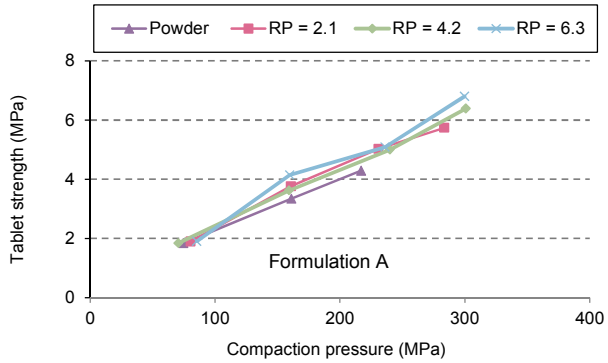
3.3 Tableting

The granules made with roll pressures of 2.1 kN/cm, 4.2 kN/cm and 6.3 kN/cm all tableted well. Granules made at 8.4 kN/cm had a tendency to cap, and granules made at 10.5 kN/cm could not be tableted because of poor flow. No attempt was made to improve flow by adding a flow aid.

3.4 Tablet testing

3.4.1 Tabletability

Figure 3 shows tableting profiles for the three formulations and the equivalent powder blends. A very slight loss of tabletability can be seen between powder blends containing MCC (B and C) and the granules of the same blend, but not for the granules made without MCC (A).



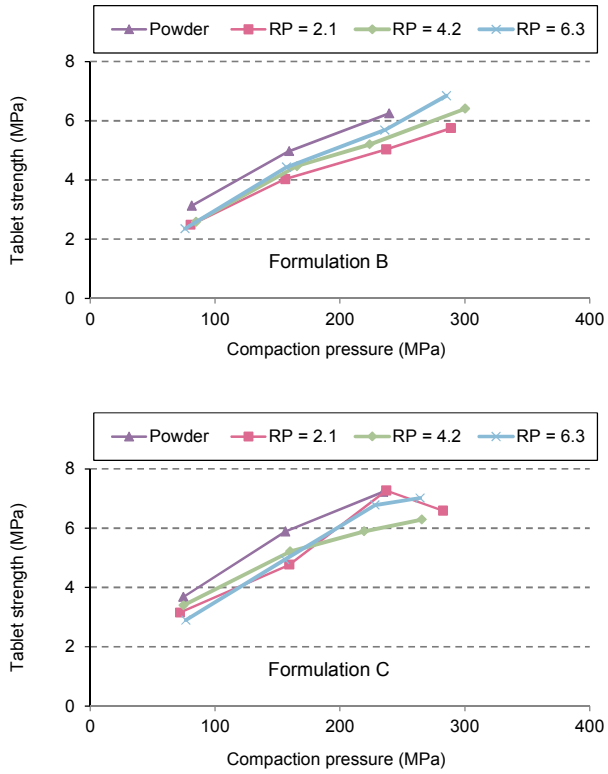


Figure 3: *Tabletability plots for powders and granules of formulations A, B and C.*

3.4.2 Friability

The friability of all tablets was consistently very good. The tablets of formulation A were 0.1% or less, and the tablets of formulations B and C were 0.05% or less.

3.4.3 Weight uniformity

The weight uniformity of the tablets made from the powders was always below 1%.
In general the weight uniformity of the tablets made from the granules reflect the relationship between particle size and flow [3].

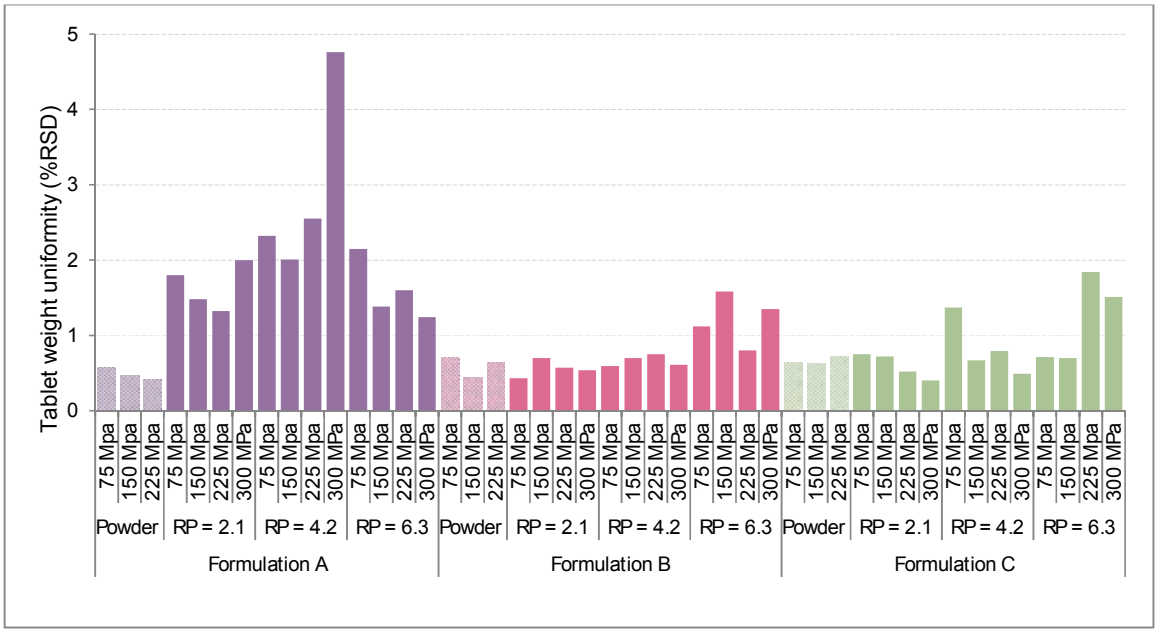


Figure 4: *Weight uniformity of tablets made from powders and granules. RP stands for roller pressure in kN/cm, and the target tablet compaction pressure is indicated below each bar.*

Based on the categorisation in reference 3, the granules of formulations B and C made with the two lowest roll pressures would be classified as having "excellent flow", and in general these granules give tablets with the best weight uniformity. The other tableted granules would be classified as having "good flow", although it is clear that the MCC containing granules of formulations B and C, which have the fewest fines, give more uniform tablets.

4 Conclusions

SuperTab® 21AN and blends of SuperTab® 21AN with MCC are very suitable for use in roller compaction.
When used in the range of 35% to 45% the loss of tabletability of MCC was inconsequential.
Addition of MCC decreased the throughput of the roller compactor and increased the temperature of the ribbon. However roller compaction could be performed without the addition of a lubricant when a blend of anhydrous lactose and MCC was used.
Also, inclusion of MCC slightly improved the tablet particle size properties with consequent improved flow and improved tablet weight uniformity.
For every formulation, increasing the roller pressure tended to give milled granules with more fines and a lower D50 values, and in these studies, where milling was not optimized, pressures of 2.1 and 4.2 kN/cm gave granules with the best overall tableting properties.

References

1. DFE Pharma Technical Paper: Recompaction properties of lactose and microcrystalline cellulose: individual excipients.
2. DFE Pharma Technical Paper: Recompaction properties of anhydrous lactose and microcrystalline cellulose: excipient blends.
3. Modelling pharmaceutical powder flow performance using particle size distribution data, MP Mullarney & N Leyva, Pharm Tech, March 2009, 126 – 135.

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