DFE pharma

Wet granulation of milled lactose

MCC

Starch

Lactose

Inhalation

Superdisintegrants

The pursuit of excipient excellence

Summary

Lactose is commonly wet granulated with microcrystalline cellulose in the preparation of pharmaceutical tablets. The studies reported in this article examine the effects of lactose / MCC ratio, lactose particle size and polyvinylpyrrolidone concentration on granule and tablet properties.

It was found that the breaking force of tablets made by high shear granulation of lactose and MCC is most affected by the lactose / MCC ratio and the particle size of the lactose. Harder tablets are achieved by reducing the proportion of MCC, and by use of finely milled lactose. In comparison, the PVP level had only a small effect.

Additionally, tablet disintegration times were not affected by the method of incorporation of Primojel® as a superdisintegrant.

1 Introduction

Wet granulation is a process in which a mix of powders is agglomerated with a liquid binder forming larger particles or granules. These granules normally have a size distribution in the range of 0.1 - 2 mm, and are mainly used for tablet compaction and capsule filling.Wet granulation is typically used to improve the flow, compressibility and homogeneity of the mixture used to produce solid dosage forms.
The most widely used excipientsfor granulation aremicrocrystalline cellulose, lactose and dibasic calcium phosphate. The three main types of wet granulation process are:

- low shear granulation, (planetary mixer),
- high shear granulation, (high speed mixer with an impeller and chopper)
- fluid-bed granulation, (fluid-bed drier).

This study describes how some formulation and process factors affect the properties of granules and tablets made by the high shear granulation process.

2 Experimental section

2.1 Granulation and compaction

Materials: milled lactose (Pharmatose® 150M, 200M, 350M and 450M, DFE Pharma), microcrystalline cellulose (MCC) (Pharmacel® 101, DFE Pharma), polyvinylpyrrolidone(PVP) (polyvidone K30, Bufabv), sodium starch glycolate(SSG) (Primojel®, DFE Pharma) and magnesium stearate (Bufabv).

Granulation: All granulations were performed on a laboratory scale high shear granulator (Formate 4M8, Proceptnv, Zelzate, Belgium).
After 5 minutes dry mixing (lactose, MCC and PVP), water was added to the mixing vessel during 8 to 10 minutes. After water addition the granulation was wet massed for 2 further minutes. The granules were dried in a Fluid bed dryer (Retsch TG-1, Retsch GmbH, Haan, Germany), passed trough a 500 µm screen using a sieve shaker (RetschVibro, Retsch GmbH, Haan, Germany) and stored in plastic bags.

Compaction: After conditioning the granules overnight in a climate chamber (HC2020, Heraeus Instruments, Hanau, Germany), at 30%RH and 20°C, the granules were mixed with 0,5% w/w magnesium stearate in a Turbula Mixer (T2C, W.A. Bachofen AG, Basel, Switzerland) for 5 minutes at 90 rpm. The mixtures were compressed on an instrumented rotary press (RLE 15 AM, Kilian& Co. GmbH, Cologne, Germany),at 10, 15 and 20 kN, and a targeted weight of 250 mg (± 3 mg).
The tablets were stored in air tight containers.

2.2 Granule and tablet testing

Granule Testing: The poured bulk density was measured by the weight of the granules in a 250 ml cylinder and expressed in g/l.

Tablet Testing: Tablet hardness and dimensions were determined 24 hours after compaction using an Erweka hardness tester (TBH 300 MD, Erweka GmbH, Heusenstamm, Germany). For each batch 10 tablets were tested.

Disintegration times were determined using an Erweka disintegration tester (ZT-3).Six tablets were tested (using no discs).
Friability was determined by taking a sample of whole tablets corresponding to 6.5 gram, using an Erweka friability tester (TA-UZ) operated according to the USP procedure.

3 Results and discussion

The results and discussion are divided in four separate parts:

- The effect of the lactose / MCC ratio on granule and tablet properties.
- The effect of particle size of milled lactose on granule and tablet properties.
- The effect of the amount of binder ongranule and tablet properties.
- The method of incorporation of the superdisintegrant (intragranular, extragranular or equally divided).

3.1 The effect of lactose / MCC ratio

Microcrystalline cellulose is frequently used in combination with lactose in wet granulation processes. Lactose compacts predominantly by brittle fracture while MCC exhibits plastic deformation. The ratio of these two filler binders can affect tablet properties, and these experimentsstudied MCC proportions in the range 0-50% of the total granulation mass as shown in Table 1.

Table 1: *Granule formulation to study the lactose/MCC ratio.In these batches the amount of water used for granulation was 0.83 times the amount of MCC, except the 0% MCC (4% water added).*

Component	% w/w
Pharmatose® 200M	48-98
Pharmacel® 101	0-50
Polyvidone K30	2

As shown in Table 2 and inFigure 1, the breaking force of the tablets decreaseswith increasing MCC content. Above 20% MCC the granule density also increases steeply.

Table 2: *Effect of % MCC on the poured bulk density and tablet properties.*

MCC (%)	Density (g/l)	Strength (N)*	Friability (%)*
0	570	109	0.12
5	505	103	0.14
10	497	103	0.12
15	485	96	0.12
20	477	88	0.13
30	616	63	0.12
40	618	66	0.10
50	655	35	0.29

*At 15 kN compaction force

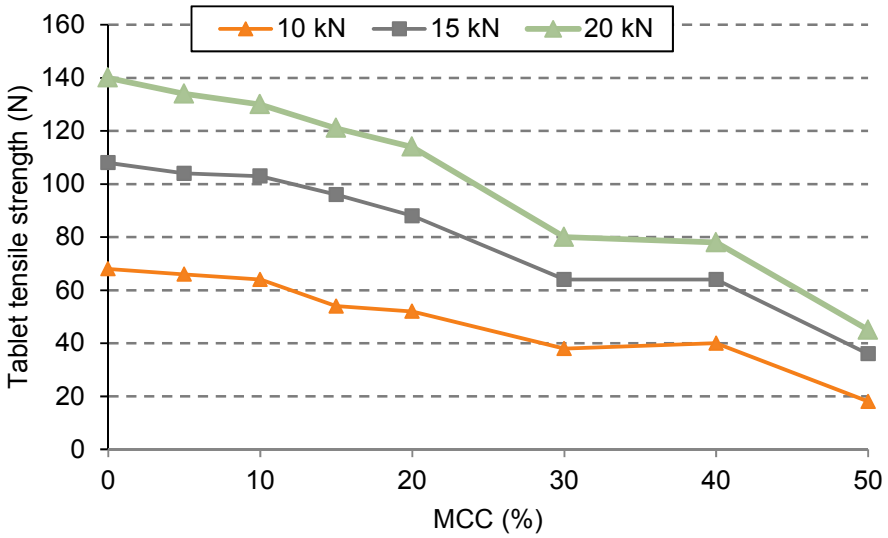

Figure 1: *Effect of lactose/MCC ratio on the compactibility profile.*

It is known that wet granulation of MCC leads to granule densification and loss of compactibility[(1)], and this mechanism is also thought to be responsible for the observed changes in breaking force when MCC is granulated with lactose.To test this theory, granules were prepared according to the formulation in Table 3 but using different amounts of granulating water (28%, 56% and 83% of the amount of MCC,). These granules were blended with 2% SSG (Primojel®) in addition to 0.5% magnesium stearate before compaction.

Table 3: *Granule formulation to study the effect of granulating water quantity.*

Component	% w/w
Pharmatose 200M	68
Pharmacel 101	30
Polyvidone K30	2

The results in Table 4 and Figure 2 show that decreasing the granulating water quantity causes a decrease in the granule density and an increase in the breaking force of the tablets, in accordance with the proposed explanation. Tablet disintegration times (15 and 20 kN compaction forces) increase with increasing granulating water, again as a consequence of increased granule density.

Table 4: *Effect of the amount of liquid binder on poured bulk density and tablet properties.*

Water	Density (g/l)	Strength (N)*	Disintegration time (s)*
28%	510	96	33
56%	586	62	38
83%	682	27	54

*At 15 kN compaction force

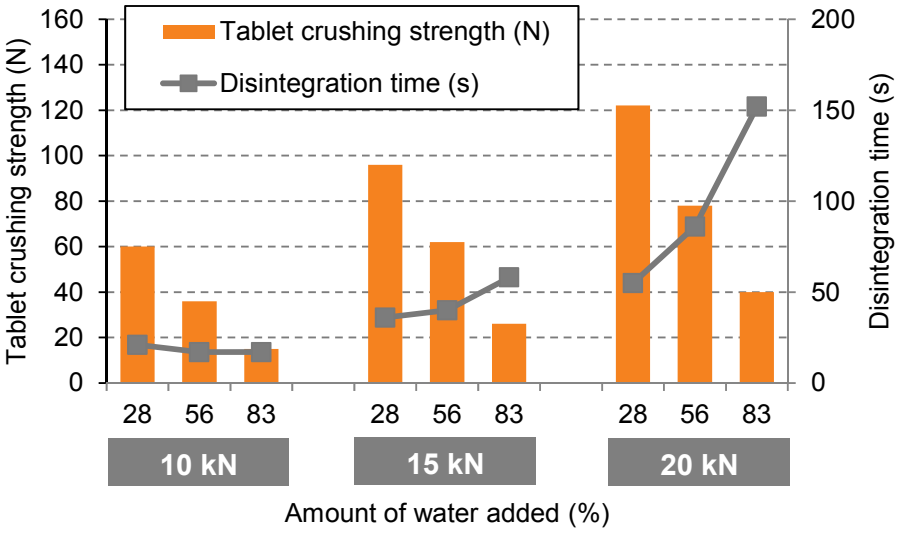

***Figure 2**: The effect of the amount of water (added to a 30% MCC mixture) on the compactibility and disintegration time.*

3.2 Effect of particle size of milled lactose

From published data[2] it is known that the breaking force of lactose tablets increases with decreasing particle size of the lactose crystals.The four milled lactose batches used in this study have different particle size distributions listed below in Table 5.

***Table 5**: PSD of the milled lactose products, as measured by Sympatec dry powder laser diffraction at 3.0 bar.*

Pharmatose®	D_{10} (µm)	D_{50} (µm)	D_{90} (µm)
150M	4.6	54	159
200M	3.4	35	108
350M	2.9	28	79
450M	2.7	21	49

In order to study predominantly the effect of lactose particle size on granule and tablet properties, the formulation used contained only 10% MCC as shown in Table 6.

***Table 6.** Granule formulation to study the effect of lactose particle size. In these batches the amount of water used for granulation was 0.86 times the amount of MCC.*

Component	% w/w
Pharmatose®	88
Pharmacel® 101	10
Polyvidone K30	2

The results are shown in Table 7 and Figure 3.

Table 7: *Effect of PSD of lactose on the poured bulk density and tablet properties.*

Pharmatose®	Density (g/l)	Strength (N)*	Friability (%)*
150M	563	65	0.15
200M	538	101	0.13
350M	545	110	0.14
450M	517	132	0.13

*At 15 kN compaction force

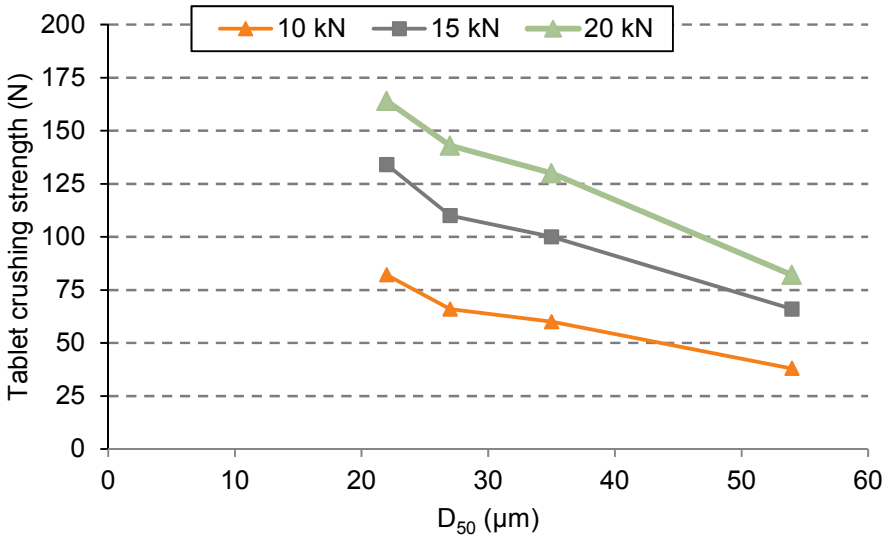

Figure 3: *Effect of lactose particle size on the compactibility of granules.*

Granule density is not greatly affected by lactose particle size distribution, but there is a strong effect on tablet breaking force. The effect of the lactose particle size on the breaking force can be explained by the fact that smaller crystals have a higher surface area available for bonding within the tablets[3].

3.3 Effect of amount of binder on compaction

A binder such aspolyvidone K30 is usually added in concentrations from 2-5%[4]. Table 8 shows the formulations used to study the effect of binder concentration.

Table 8: *Granule formulations to study the effect of binder concentration.*

Component (%w/w)	1	2	3	4
Pharmatose® 200M	89	86	69	66
Pharmacel® 101	10	10	30	30
PVP K30	1	4	1	4
Water	10	10	27	27

Figure 4 and 5 show the effect of the amount of PVP on granules with 10% and 30%MCC.

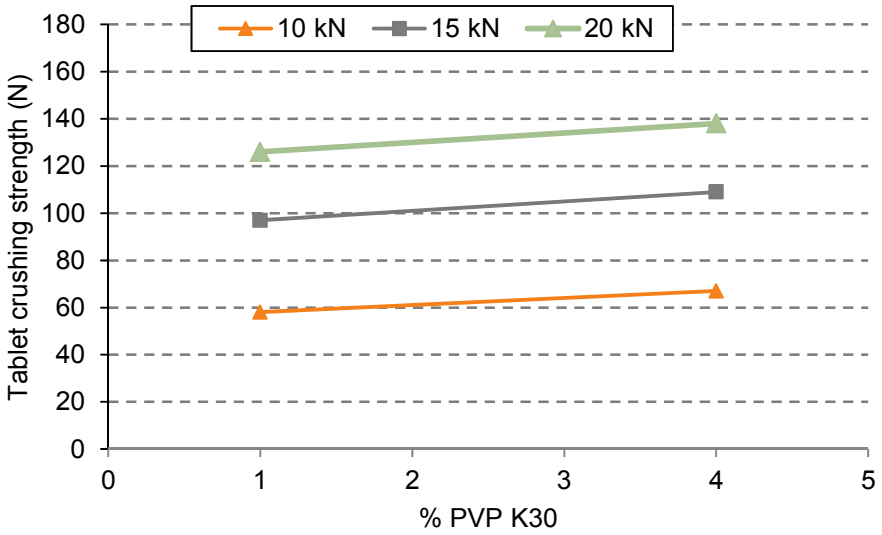

***Figure 4**: Effect of % PVP on compaction of lactose/MCC tablets (10% MCC).*

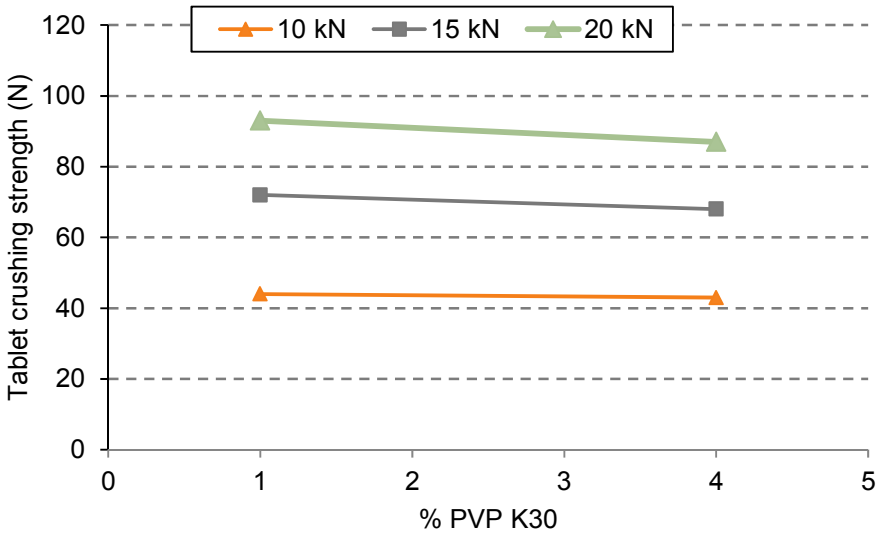

***Figure 5:** Effect of % PVP on compaction of lactose/MCC tablets (30%MCC).*

With 10% MCC in the granules MCC, increasing the PVP from 1% to 4% has a small beneficial effect on tablet breaking force, but this effect is not evident with 30% MCC granules.The data are also in general agreement with Figure 1,where it is shown that a higher amount of MCC gives tablets with a lower breaking force.

3.4 Method of incorporation of the super-disintegrant

The incorporation of the disintegrant into the granule can be performed in three ways.

- Intragranular: the disintegrant is dry mixed with the other components, wet granulated, dried, lubricated and compacted.
- Extragranular: The disintegrant is mixed with the granules before lubrication and compaction.
- Split: the disintegrant is distributed between the intra- and extragranular part.

In this study, 4% of Primojel® were incorporated in the formulation with an intra-/extra granular division as shown in Table 9.

Table 9: *Formulation to study the effect of superdisintegrant incorporation method.*

Component (%w/w)	1	2	3
Pharmatose® 200M	83	83	83
Pharmacel® 101	10	10	10
Polyvidone K30	3	3	3
Primojel® (intragranular)	4	2	0
Primojel® (extragranular)	0	2	4

Resulting tablet properties at 15 kN are shown in Table 10.

Table 10: *Effect of Primojel® incorporation method on the granule density and tablet properties.*

Location	Density (g/l)	Strength (N)*	Friability (%)*	DT (s)*
Intra	538	115	0.1	58
Equal	499	112	0.1	56
Extra	484	98	0.1	55

*At 15 kN compaction force

In this study the use of intragranularPrimojel® caused an increase in the granule density and in the tablet strength, but the effects are small in comparison to the effects of MCC / lactose ratio and lactose particle size. There was no effect on tablet disintegration time. Various previous studies show no consistent pattern in the effect of incorporation method on disintegration time[5 - 8].

4 Conclusions

From the data presented here, the breaking force of tablets made by high shear granulation of lactose and MCC is most affected by the lactose / MCC ratio and the particle size of the lactose. Harder tablets are achieved by reducing the proportion of MCC, and by use of finely milled lactose. In comparison, the level of PVP K30 used as a binder had only a small effect.In this study the tablet disintegration times were not affected by the method of incorporation of Primojel® as a superdisintegrant.

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DFE pharma

Head Office
Klever Strasse 187
P.O. Box 20 21 20
47568 Goch, Germany
T. +49 2823 9288 770
F. +49 2823 9288 7799
pharma@dfepharma.com

www.dfepharma.com

DFE Pharma (#code/month year)