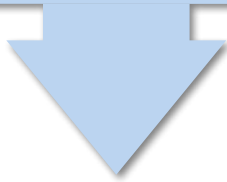


Wet granulation of milled lactose.

DMV-Fonterra Excipients
The ingredients of success

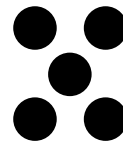


Summary

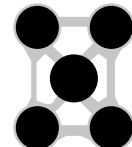
Lactose is commonly wet granulated with microcrystalline cellulose in the preparation of pharmaceutical tablets. The studies reported in this article examine the effects of lactose/MCC ratio, lactose particle size and polyvinylpyrrolidone concentration on granule and tablet properties.

It was found that the crushing strength 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.

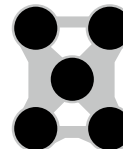
Additionally, tablet disintegration times were not affected by the method of incorporation of Primojel as a superdisintegrant.



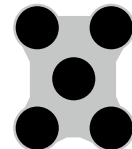
Dry state



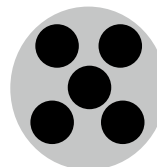
Pendular



Funicular



Capillary



Droplet

Different stages of saturation for liquid bonds in granules.

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 0.1-2mm, 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 excipients for granulation are microcrystalline cellulose, lactose and dibasic calcium phosphate.

The three main types of wet granulation processes 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.

Experimental section

Granulation and compaction

Materials: Milled lactose (Pharmatose 150M, 200M, 350M and 450M, DMV-Fonterra Excipients), microcrystalline cellulose (MCC) (Pharmacel 101, DMV-Fonterra Excipients), polyvinylpyrrolidone (PVP) (polyvidone K30, Bufa bv), sodium starch glycolate (SSG) (Primojel, DMV-Fonterra Excipients) and magnesium stearate (Bufa bv).

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

Compaction: After conditioning the granules overnight in a climate chamber (HC 2020, 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) fitted with 9mm round punches, at 10, 15 and 20 kN compaction force, and a targeted weight of 250mg (± 3 mg). The tablets were stored in tight containers.

Granule and tablet testing

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

Tablet testing: Tablet crushing strength 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 disks).

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.

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 on granule and tablet properties.
- The method of incorporation of the superdisintegrant (intragranular, extragranular or equally divided).

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 experiments studied MCC proportions in the range 0-50% of the total granulation mass as shown in table 1.

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

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).

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.

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

As shown in table 2, and in figure 1, the crushing strength of the tablets decreases with increasing MCC content. Above 20% MCC the granule density also increases steeply. 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 crushing strength 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.

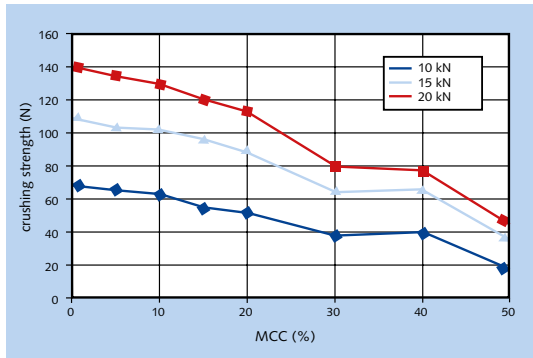


fig. 1: Effect of lactose/MCC ratio on the compactibility profile.

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

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

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

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.

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

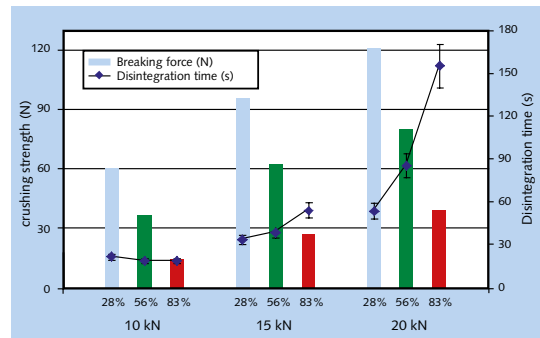


fig. 2: The effect of the amount of water (added to a 30% MCC mixture) on the compactibility and disintegration time.

Effect of particle size of milled lactose

From published data⁽²⁾ it is known that the crushing strength 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 distribution as listed in table 5.

Pharmatose	D10 (µm)	D50 (µm)	D90 (µm)
150M	4.6	54	159
200M	3.4	35	108
350M	2.9	28	79
450M	2.7	21	49

table 5: PSD of milled lactoses, measured by Sympatec dry powder laser diffraction at 3.0 bar.

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.

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

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.

The results are shown in table 7 and figure 3.

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.

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

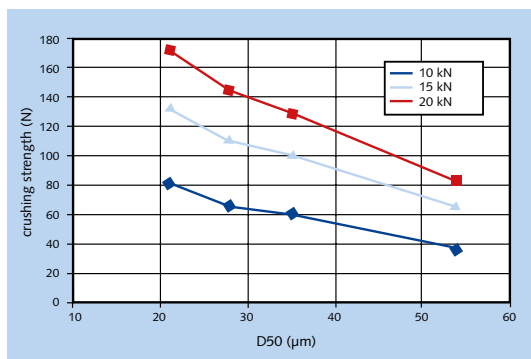


fig. 3: Effect of lactose particle size on the compactibility of granules.

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

Effect of amount of binder on compaction

A binder such as polyvidone K30 is usually added in concentrations from 2-5%⁽⁴⁾. Table 8 shows the formulations used 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

table 8: Granule formulations to study the effect of binder concentration. Granules were made using 100% or 81% of the MCC amount, for granulation containing 10% and 30% MCC respectively.

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

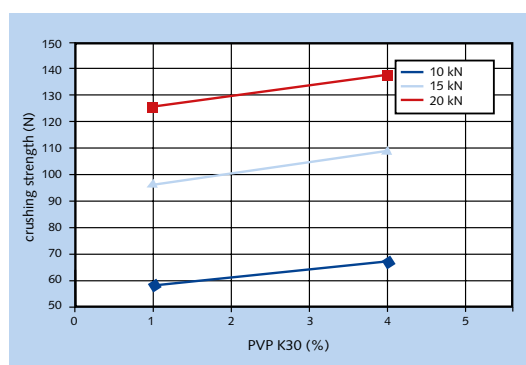


fig. 4: Effect of % PVP on compaction of lactose/MCC tablets (10% MCC).

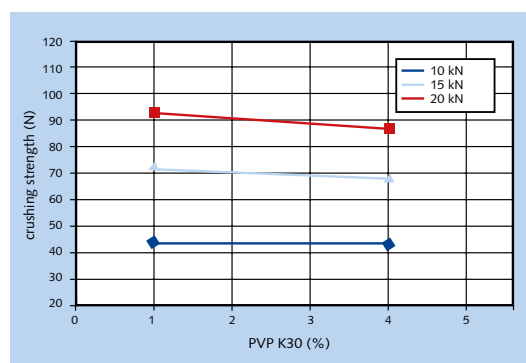


fig. 5: Effect of % PVP on compaction of lactose/MCC tablets (30% MCC).

With 10% MCC in the granules, increasing the PVP from 1% to 4% has a small beneficial effect on tablet crushing strength, but this effect is not evident with 30% MCC in the 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 crushing strength.

Method of incorporation of the superdisintegrant

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.

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

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

Results are shown in table 10.

Location	Density (g/l)	Strength (N)*	Friability (%)*	DT (s)*
Intra	538	115	0,1	58
Split	499	112	0,1	56
Extra	484	98	0,1	55

* At 15 kN compaction force.

table 10: Effect of Primojel incorporation method on the granule density and tablet properties.

In this study the use of intragranular Primojel caused a slight 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. In these predominantly soluble tablets, 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).

Conclusions

From the data presented here, the crushing strength of tablets made from high shear granulations of lactose and MCC is most affected by the lactose/MCC ratio the amount of granulating water and the particle size of the lactose. Stronger tablets are obtained by reducing the proportion of MCC, and by the use of finely milled lactose. In comparison, the level of PVP K30 used as a binder had only a small effect. In this study (predominantly lactose) the tablet disintegration times were not affected by the method of incorporation of Primojel as a superdisintegrant.

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