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Roll compaction/dry granulation: Effect of raw material particle size on granule and tablet properties

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Abstract

The influence of particle size of MCC, as a binder, and theophylline, as an active pharmaceutical ingredient on the process of roll compaction/dry granulation was investigated using a D-optimal design of experiments. Examined parameters were particle size of both starting materials, fraction of theophylline and ribbon porosity. Therefore, different binary mixtures were roll compacted, dry granulated and compressed into tablets. Flowability of powders and granules and tensile strength of tablets made from powders or granules were the focus of this study. This study showed that a decrease in particle size of MCC or theophylline resulted in an increase of tensile strength even after roll compaction/dry granulation. Comparing tensile strength of tablets made from powder using large size MCC with ones made from granules with small sized MCC revealed that the tensile strength of tablets produced from granules was equal or even higher than tensile strength from direct compressed tablets. Furthermore, using small sized MCC instead of large sized MCC led to larger granules with better flowability. It is shown that the fraction of binder can be reduced without a loss of tensile strength of the final tablets by size reduction of MCC.

Keywords: Roll compaction; Dry granulation; Tensile strength; Flowability; Microcrystalline cellulose; Theophylline

1. Introduction

Powders are often granulated to improve their flow behaviour. Roll compaction/dry granulation is a widely used process for granulation without water. This method allows the granulation of materials sensitive to moisture and heat. A major advantage is the continuous production of granules leading to a reduction of costs (Miller, 1994). However, the resulting tablets show inferior tensile strength compared with other granulation techniques. This is due to the limited binding potential which is partially consumed in the first compression step (Malkowska and Khan, 1983; Falzone et al., 1992; Kleinebudde, 2004). Materials with plastic deformation properties are particularly sensitive to this phenomenon.

Generally, during direct compression the tensile strength increases by decreasing the size of the MCC due to an increase in binding area available for bonding (McKenna and McCafferty, 1982). In pharmaceutical industry it is a common use to add small binders extragranularly after dry granulation to compensate this loss in tensile strength. However, this practise can negatively affect the powder flowability and can cause segregation of the final blend upon processing or storage (Sun and Himmelspach, 2006). Therefore the question is raised whether altering the particle sizes of raw powders in the dry granulation step will impact the tensile strength of the final tablets. In this study, powders were roll compacted to certain porosities, whereas, in other published papers, powders were roll compacted to certain forces resulting in different porosities of the ribbons (Inghelbrecht and Remon, 1998a).

Another disadvantage of roll compaction/dry granulation is the fine particle fraction. On industrial scale, fines are often re-granulated to improve the yield. However, a negative influence of recycling on API-conformity was reported (Sheskey et al., 1994). Therefore, the generation of fines should be minimized during roll compaction/dry granulation process.

Another important parameter is the flowability of granules. Therefore, a ring shear cell tester was used to describe the

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influence of altering the particle size in the origin mixture on the flowability of the granules.

Due to its excellent compression properties, microcrystalline cellulose (MCC) is a widely used excipient in the process of dry granulation (Inghelbrecht and Remon, 1998b). In the present study, a binary powder mixture was evaluated. MCC was used as binder in different particle sizes. Furthermore, the study aimed to examine the influence of the particle size of the used API (theophylline anhydrous) on the recompression process.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (MCC) was used in three different particle sizes. Vivapur 105 and Vivapur 101 were supplied by Rettenmaier, Germany and MCC102G was supplied by Pharmatrans Sanaq, Switzerland. Since the degree of polymerisation of MCC affects the workability (Shlieout et al., 2002), the investigated MCCs possessed the same degree of polymerisation (228 ± 3).

The active pharmaceutical ingredient, theophylline anhydrous, was used in two different particle sizes (theophylline anh. powder and theophylline anh. fine powder). Both powders were supplied by BASF, Germany.

Magnesium stearate was used as a lubricant during compression of tablets (Caelo, Germany).

Prior to investigations the materials were at least stored for 2 weeks at 21 °C/45% relative humidity (r.h.).

2.2. Preparation of powder mixtures

In order to achieve different fractions of theophylline based on real volumes, the particle densities of MCC and theophylline were determined with an AccuPyc 1330 Helium Pycnometer (Micromeritics, USA). Eq. (1) was used to determine the mass of the theophylline fraction.

$$m_{\text{Theo}} = \frac{\rho_{\text{Theo}} m_{\text{t}} X}{\rho_{\text{t}}} \tag{1}$$

m_{Theo} is the mass of theophylline (g), ρ_{Theo} the particle density of theophylline (g/cm^3), m_{t} the total mass (g), X the theophylline fraction (v/v), and ρ_{t} is the particle density of the mixture (g/cm^3).

Binary mixtures were prepared in a laboratory scale blender LM20 (Bohle, Germany). Mixing time was 15 min at 25 rpm. Twenty-five mixtures were prepared according to a D-optimal design of experiments.

During processing the powders were handled at 21 °C/45% r.h. Under these conditions, the water amounts were $0.05 \pm 0.01\%$ (w/w) and $5.36 \pm 0.15\%$ (w/w) for both theophylline powders and for MCCs, respectively. The determination of the water content was carried out by Karl-Fischer titration.

2.3. Roll compaction/dry granulation

All experiments were performed using an instrumented roll compactor (Mini-Pactor, Gerteis, Switzerland) equipped with smooth rim rolls. The rolls had a diameter of 25 cm and a width of 2.5 cm. The gap between the rolls was kept constant at 3 mm. Speed of rolls was set to 1 rpm. The way of powder addition was along feeding and tamping auger. The tamping auger was operated at twice the speed of the feeding auger. The roll compactor was operated in the automatic mode (Shlieout et al., 2000), where the speed of the temping auger is adjusted by a control circuit keeping the gap constant.

Ribbons were roll compacted to certain porosities, i.e. 20–40%. Granules were retained after reaching constant gap and force (steady state section) (Bultmann, 2002).

Because of continuous gap measurement it was possible to calculate the volume of the produced ribbon. Mass of the corresponding granules was weighted after each trial and processing time was recorded. The in-gap porosity of the ribbons was calculated after compaction according to Eqs. (2) and (3).

$$V_{\text{r}} = \pi d_{\text{r}} w_{\text{r}} v_{\text{r}} g t \tag{2}$$

$$\varepsilon_{\text{ribbon}} = \left(1 - \frac{m_{\text{gran}}/V_{\text{r}}}{\rho_{\text{t}}}\right) \times 100 \tag{3}$$

V_{r} is the volume (cm^3), d_{r} the diameter of rolls (cm), w_{r} the width of rolls (cm), v_{r} the speed of rolls (rpm), g the gap between rolls (cm), t the production time (min), $\varepsilon_{\text{ribbon}}$ the in-gap ribbon porosity (%), m_{gran} the mass of granules (g), and ρ_{t} is the particle density of the mixture (g/cm^3).

To achieve different porosities it was necessary to adjust the specific compaction forces between 0.7 and 5.9 kN cm^{-1} roll width.

Resulting ribbons were directly granulated with a pocket mould grooved granulator using a 1.25 mm sieve. The oscillating (150°/160°) granulator was operated at a rotor speed of 30 rpm clockwise and 40 rpm counter clockwise. Distance between sieve and rotor was set to 1 mm.

2.4. Compression of tablets

A hydraulic press (FlexiTab, Roeltgen, Germany) was used to compress tablets (Albers et al., 2006). Flat-faced tablets of 12 mm diameter and mass of 405 ± 5 mg were produced at three different compression levels (10, 18 and 25 kN). Because of poor flow properties, the powder mixtures were manually filled into the die. The duration of the compaction event was approximately 2000 ms from rest to peak pressure and approximately 150 ms back to rest, for a compression level of 18 kN. The lubricant was not added to the powder mixtures or granules. Instead a pure magnesium stearate tablet was pressed for lubrication of die and punches prior to compression of powders or granules (Adolfsson and Nyström, 1996).

2.5. Properties of the powder mixtures and granules

Prior to all analysis the powders and granules were divided using a rotary sample divider (PT, Retsch, Germany) in order to obtain representative samples of adequate amount.

2.5.1. Particle size

The distributions of the particle sizes of all raw-powders were determined by laser diffraction (Helos H1402/KF-Magic, Sympatec, Germany) using lenses of 50, 200 and 500 mm focal length. The powders were dispersed with a Rhodos dry disperser (Sympatec, Germany). For characterisation of each powder the average median particle size (d50) of three measurements was used.

For granules, the particle size distribution was determined by combined vibrating sieve analysis and air jet sieve analysis (Alpine 200LS-N, Hosokawa, Japan). The applied sieves for vibrating sieve analysis (180, 315, 500, 800, 1000, 1250 and 1400 μm) were shaken on the sieve tower (Vibrio, Retsch, Germany) for 5 min at an amplitude of 1 mm. The used air jet sieves were 32, 63, 90 and 125 μm. The median particle size and the part of fines, which was defined as the fraction of particles smaller than 90 μm (Freitag and Kleinebudde, 2003), were used as descriptive factors for sieve analysis.

2.5.2. Bulk- and tap-density

Bulk and tap densities of powder mixtures and granules were measured in duplicate according to DIN 53468 and European Pharmacopoeia, respectively.

2.5.3. Flowability

Flowability of powders and granules was measured using a computer controlled ring shear cell tester RST-01.pc with RST-CONTROL 95 (Schulze Schuettgutmesstechnik, Germany). Normal stress applied for pre-shearing was 5000 Pa resulting in a consolidation stress of about 11,000 Pa. To construct a yield-locus, the samples were sheared with four different normal stresses (1000, 2000, 3000 and 4000 Pa). At the end of a measuring cycle the first normal stress (1000 Pa) was repeated. The second measurement at 1000 Pa was compared with the first measurement to verify that the measurement procedure had not induced a change in the sample. Flowability (ff_c) is defined as the relationship of the consolidation stress (σ_1) to the unconfined yield strength (σ_c). Every powder mixture or granule sample was measured three times and the mean value of ff_c was calculated according to Eq. (4).

$$ff_c = \frac{\sigma_1}{\sigma_c} \tag{4}$$

The greater the value of ff_c is the better flowing are the powders or granules. Table 1 shows a classification of ff_c with the assessment of the flow behaviour similar to Jenike (1970).

The change of flowability after roll compaction was characterised by the ff_c-ratio according to Eq. (5). The lower the ff_c-ratio the better was the flowability improvement.

$$ff_c - \text{ratio} = \frac{ff_{c^{powder}}}{ff_{c^{granules}}} \tag{5}$$

Table 1
Correlation of ff_c values with flow behaviour

$ff_c < 1$	Non-flowing
$1 < ff_c < 2$	Very cohesive
$2 < ff_c < 4$	Cohesive
$4 < ff_c < 10$	Easy flowing
$10 < ff_c$	Free flowing

2.6. Properties of tablets

2.6.1. Tensile strength

The tablets were stored at least for 72 h at 21 °C/45% r.h. prior to the diameter and height measurements with a micrometer screw 29356130 (Mitutojo, Japan). Tablet volume was calculated from the dimensions of the flat-faced tablet. Tablet volume, tablet mass and the particle density of the powder mixture were used to calculate the porosity of each tablet. The mechanical strength of the tablets was measured with a diametral strength tester (HT-1, Sotax, Switzerland) at a constant speed of 1 mm/s. The tensile strength of the compacts was calculated according to Fell and Newton (Fell and Newton, 1970). The mean of 10 measurements was used.

2.6.2. Friability of tablets

Friability of tablets was determined by a friabilator (Erweka, Germany). For each measurement, 10 tablets were de-dusted and weighed prior and after rotation. Drum rotation was set to 100 times. The trials were replicated twice and the mean value was calculated.

2.7. Statistical evaluation

To evaluate the influence of particle size of MCC (MCC) and theophylline (Theo), fraction of theophylline (fraction), and porosity of the ribbons (porosity), a D-optimal design of experiments consisting of 25 trials was used. The levels of the design of experiments are presented in Table 2. The different factor settings of the trials with some of the results are shown in Tables 3 and 4.

All factor level combinations ($n = 1$) and the center point ($n = 3$) were carried out in a randomized order. The results were evaluated with the program MODDE (Umetrics, Sweden). Unless otherwise stated all confidence levels were 95%. The

Table 2
Levels for the design of experiments

Level	−1	−0.33	0	+0.33	+1
MCC (μm)	21	–	56	–	106
Theo (μm)	7	–	–	–	110
Fraction (%)	25	41.67	50	58.33	75
Porosity (%)	20	26.67	30	33.33	40

Table 3
Factor level combinations of the D-optimal design of experiments with results for non-compacted powder mixtures

MCC (μm)	Theo (μm)	Fraction[a] (%)	ff_c	TS_{powder} (N/mm^2)
106	110	25	5.77	5.42
106	110	25	5.77	5.42
21	110	25	2.78	7.64
21	110	25	2.78	7.64
106	110	50	5.91	3.99
106	110	50	6.18	4.04
21	110	50	3.08	5.35
106	110	41.67	6.43	4.36
106	110	58.33	6.55	3.62
21	7	41.67	2.17	5.34
106	7	25	4.48	4.47
106	7	41.67	3.41	5.92
21	7	58.33	1.94	4.98
21	7	25	2.50	7.47
21	7	75	1.85	4.13
106	110	50	6.38	4.13
106	110	75	6.52	2.96
106	110	75	6.51	2.96
56	7	25	3.78	6.95
56	7	75	2.06	3.87
56	110	58.33	4.95	4.57
21	110	75	3.57	3.51
106	7	58.33	2.51	4.03
106	7	75	1.73	3.47
21	110	75	3.45	3.51

[a] Theophylline fraction.

response Y was described as a regression model of the four variables (MCC, Theo, fraction and porosity) given by the general formula (Eq. (6)):

$$Y = \beta_0 + \beta_1 \mathrm{MCC} + \beta_2 \mathrm{Theo} + \beta_3 \mathrm{fraction} + \beta_4 \mathrm{porosity} + \beta_5 \mathrm{MCC\ Theo} + \beta_6 \mathrm{MCC\ fraction} + \beta_7 \mathrm{MCC\ porosity} + \beta_8 \mathrm{Theo\ fraction} + \beta_9 \mathrm{Theo\ porosity} + \beta_{10} \mathrm{fraction\ porosity} + \beta_{11} \mathrm{fraction}^2 + \beta_{12} \mathrm{porosity}^2 \quad (6)$$

with β_1 to β_{12} representing regression coefficients and β_0 the regression constant. The main factors or factor combinations were removed stepwise if their p-values were higher than 0.05 starting with the highest p-value. Main factors were only removed if neither their quadratic nor one of their interactions showed p-values higher than 0.05.

3. Results and discussion

3.1. Properties of powder mixtures and granules

3.1.1. Powder size

The median particle sizes of the MCC powders used in this study were 21, 56 and 106 μm. Theophylline powder and theophylline fine powder had median particle sizes of 110 and 7 μm, respectively.

Table 4
Factor level combinations of the D-optimal design of experiments with results for granules

MCC (μm)	Theo (μm)	Porosity[a] (%)	Fraction[b] (%)	d50 (μm)	Fine particle fraction (%)	ff_c	$TS_{granules}$ (N/mm^2)
106	110	35.0	25	240	26	6.44	4.52
106	110	19.9	25	516	15	6.58	3.69
21	110	40.5	25	588	24	5.32	6.92
21	110	22.1	25	757	10	6.57	5.21
106	110	31.4	50	278	24	5.90	3.74
106	110	31.4	50	280	24	5.92	3.67
21	110	30.6	50	606	21	5.10	4.74
106	110	39.7	41.67	186	27	6.42	4.20
106	110	38.0	58.33	217	27	6.35	3.51
21	7	36.7	41.67	518	31	3.52	5.93
106	7	41.1	25	208	35	4.99	4.81
106	7	19.4	41.67	503	18	5.85	3.71
21	7	39.3	58.33	498	29	3.58	5.08
21	7	20.9	25	782	10	7.39	5.40
21	7	19.1	75	733	12	6.69	3.56
106	110	31.4	50	257	23	5.84	3.65
106	110	31.9	75	234	26	5.89	2.78
106	110	18.8	75	507	17	5.26	2.75
56	7	27.9	25	574	17	5.25	5.11
56	7	33.0	75	360	33	3.06	3.77
56	110	20.5	58.33	584	22	5.14	3.61
21	110	26.1	75	400	25	4.54	3.39
106	7	19.4	58.33	595	15	5.54	3.30
106	7	40.9	75	282	41	–[c]	3.35
21	110	40.2	75	189	43	4.20	3.66

[a] Calculated according to Eq. (3).
[b] Theophylline fraction.
[c] No value obtained.

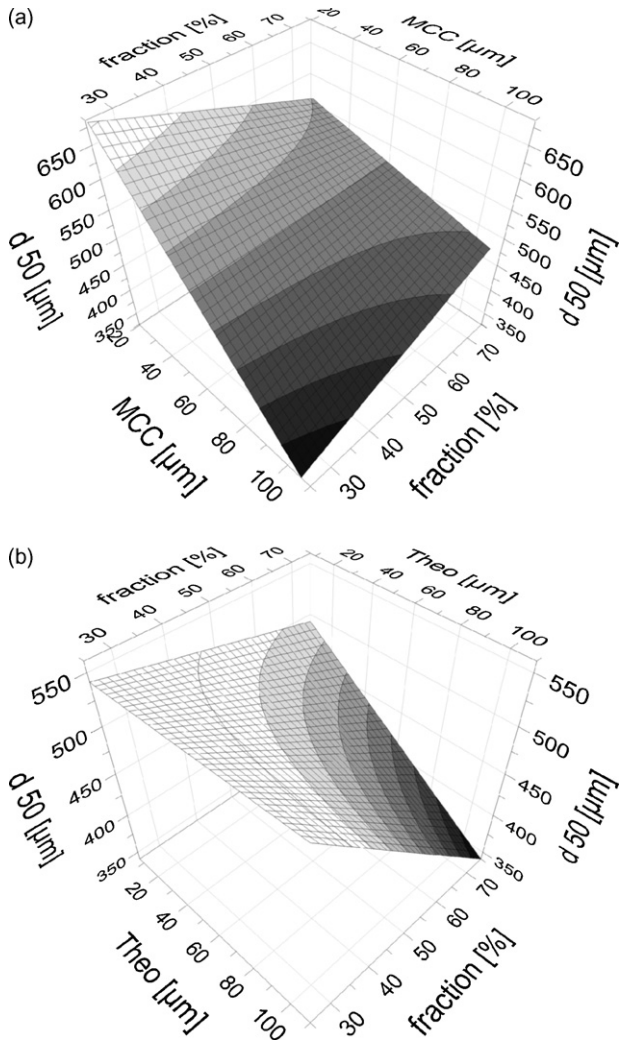

Fig. 1. (a) Surface plot for median granule size (porosity = 30%; Theo = 7 μm), $R^2_{adj} = 0.938$. (b) Surface plot for median granule size (porosity = 30%; MCC = 56 μm), $R^2_{adj} = 0.938$.

3.1.2. Granule size

Sieve analysis showed that median particle diameter of the granules varied from 186 to 782 μm. The median granule size increased with decreasing particle size of MCC and theophylline ($p < 0.01$), due to the larger area available for binding. Furthermore, granules resulting from ribbons compacted to lower porosities showed a significant higher granule size ($p < 0.01$). A higher fraction of theophylline in the mixture resulted in smaller granules ($p < 0.01$) as a result of the poor binding property of the theophylline compared to the MCC. Furthermore, there is an interaction between MCC and fraction of theophylline in the mixture. With higher fractions of theophylline, the influence of smaller sized MCC on the granule size enlargement is less but still significant (Fig. 1a).

The combination of high fractions theophylline and small particle sizes of theophylline showed larger values for granule size compared to theophylline with large size. At low fractions of theophylline, the variation of theophylline particle size resulted only in a smaller difference of granule size (Fig. 1b).

Fine particle fraction (9.5–41.2%) was lowered by decreasing the particle size of the MCC and the porosity of the ribbons ($p < 0.05$). Increasing the fraction of theophylline resulted in a higher fine particle fraction ($p < 0.01$).

3.1.3. Flowability of powder mixtures

Flowability of powder mixtures ($ff_{c^{powder}}$) varied between 1.73 (very cohesive) and 6.55 (easy flowing). The easy flowing of some powders can be explained by the large size of the starting raw materials (e.g., MCC102 and coarse theophylline powder). Decreasing particle size of both raw powders affected negatively the flowability ($p < 0.01$). In contrast, reducing the fraction of theophylline in the binary mixture improved the flowability ($p < 0.01$). These observations were in good agreement with the analysis of pure materials. Decreasing the size of MCC led to reduced flowability and the flowability of theophylline powder was lower compared to MCC. Using fine powder theophylline in the mixture reduced the flowability of the whole mixture regardless of the MCC type used.

Additionally, pure theophylline powder, fine powder and powder mixtures with theophylline fine powder fraction over 40% showed slip-stick behaviour. The slip-stick behaviour is an attitude characterised by self excited pulsating flow (Schulze, 2003). Further handling of powders showing this phenomenon is difficult and should be avoided. The insufficient flowability and slip-stick complicated the process control of roll compaction but processing was still possible.

3.1.4. Flowability of granules

After roll compaction the slip-stick behaviour of all powders disappeared with the exception of two granules prepared from powder mixtures containing 75% theophylline fine powder. These two powder mixtures were roll compacted to 33 and 40% porosity and the compaction force was too low for these two mixtures. At lower porosity levels the slip-stick effect vanished. For lower fractions of theophylline it was sufficient to roll compact to a porosity of 40% to avoid the slip-stick effect.

Flowability of the granules varied between 3.1 and 7.4. An alteration of particle size of MCC had no significant effect on the flowability. However, particle size of MCC accompanied with porosity showed a significant effect ($p < 0.01$) (Fig. 2).

At high in-gap ribbon porosities, the flowability of mixtures containing larger sized MCC was higher compared to smaller sized MCC. At porosity values higher than 27%, the increase of granule particle size during roll compaction was not sufficient to improve the flowability markedly. Flowability of the three types of raw MCC decreased with decreasing particle size. This rank order could be found as well for granules obtained from ribbons of high porosities. However, a change in rank order was observed with decreasing porosity of ribbons. At a porosity value below 27%, the flowability was higher using smaller sized MCC in the origin powder mixture. Flowability of Vivapur 105 and 101 roll compacted to porosity smaller 27% even exceeded the flowability of granules from large MCC102G produced at high porosities. Alteration of the in-gap ribbon porosity had the largest influence on flowability ($p < 0.01$). The lower the in-gap ribbon porosity the higher was flowability of the resulting

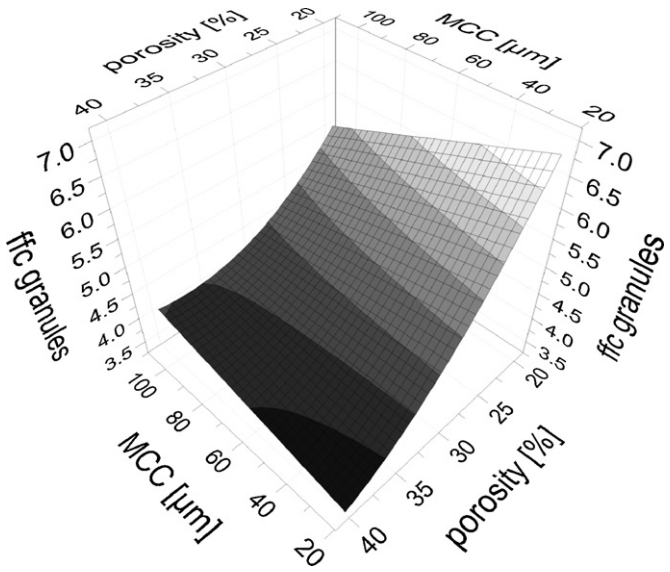

Fig. 2. Surface plot for flowability of granules (Theo = 7 μm; fraction = 50%), $R^2_{adj} = 0.901$.

granules. Explanation is given by the rise of granule size and reduction of fine particle fraction due to a decrease of porosity. Similar to powder mixtures higher fractions of theophylline resulted in a decreased flowability ($p < 0.01$).

3.1.5. Flowability ratio

The flowability was at largest enhanced using small size MCC blended with small sized theophylline roll compacted to ribbons to a porosity of 20% (ff_c-ratio = 0.28). In contrast, large sized MCC and theophylline powder at a ribbon porosity of 40% showed even an impairment of flowability (ff_c-ratio = 1.24). Smaller particles of MCC and theophylline in origin powder mixture resulted in lower values for ff_c-ratio and, consequently, higher improvement after roll compaction ($p < 0.01$). Higher values for ff_c-ratio were obtained for mixtures with a high theophylline fraction and large particles of MCC and theophylline. This could be the result of large granules produced with the small particle sizes of MCC or theophylline. A decrease of ribbon porosity as well as a decrease of fraction of theophylline led in turn to larger particles and, therefore, lower values for ff_c-ratio ($p < 0.01$). Values larger than 1 were obtained for mixtures containing large MCC and theophylline. These powder mixtures showed good flow properties even before roll compaction but the enlargement during roll compaction was low.

3.2. Properties of tablets

The results at the three different compression levels showed the same trends. Therefore only results of tablets compressed at 18 kN are presented and discussed.

3.2.1. Tablets from powder mixtures

The tensile strength (TS) of tablets compressed at 18 kN produced from powders ranged from 3 to 7.6 N/mm^2. A decrease in particle sizes of MCC or theophylline resulted in stronger

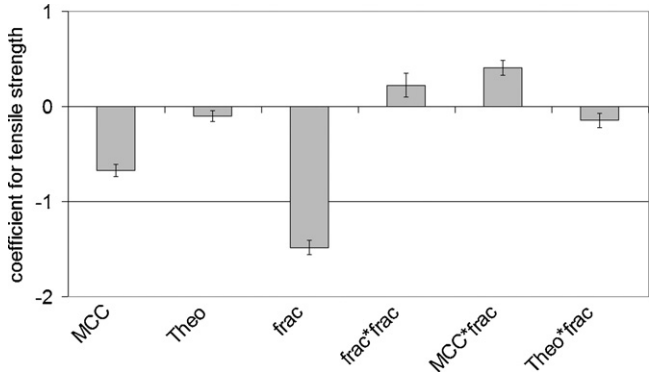

Fig. 3. Coefficient plot for tensile strength of tablets compressed from powder at 18 kN, $R^2_{adj} = 0.991$.

tablets (Fig. 3). However, an increase of fraction of theophylline resulted in weaker tablets for the same reasons as described for particle size of granules. Increasing the fraction of theophylline decreased the effect on tensile strength as indicated by a quadratic effect of the fraction of theophylline.

Using high theophylline fractions, the effect of MCC particle size on tensile strength was reduced. Lowering the fraction of MCC decreased the influence of this component on the tensile strength and a tendency towards tensile strength of pure theophylline tablets (1.9 N/mm^2 for theophylline powder and 2.3 N/mm^2 for theophylline fine powder at 18 kN) was observed. Using high theophylline fractions, the effect of theophylline particle size on tensile strength was more pronounced compared to low theophylline fractions.

3.2.2. Tablets from granules

The tensile strength of tablets produced from granules at 18 kN level varied between 2.8 and 6.9 N/mm^2.

The magnitude of tensile strength was lower than the tensile strength of tablets produced without prior roll compaction. However, reduction of particle size of MCC and theophylline in the origin powder mixture still resulted in stronger tablets even after roll compaction (Figs. 4 and 5). It seemed that there were still more binding points due to the larger specific surface area available.

Tensile strength was reduced by raising the fraction of theophylline in the mixture for the same reasons described for tablets made from powder. As observed in tablets from powder, by increasing the fraction of theophylline in granules the tensile strength value tended towards the value for pure theophylline tablets.

An increase of porosity of the ribbons was accompanied by an increase of the tensile strength of the tablets. At high porosities the effect of decreasing particle size of MCC was more distinct.

In contrast to a recently published paper (Sun and Himmelspach, 2006), larger granules did not result in a decreased tensile strength. Decreasing the particle size of the original MCC powder resulted in larger granules with a lower fraction of fines. These granules resulted in an increased tensile strength compared with smaller granules produced from powders containing large sized MCC.

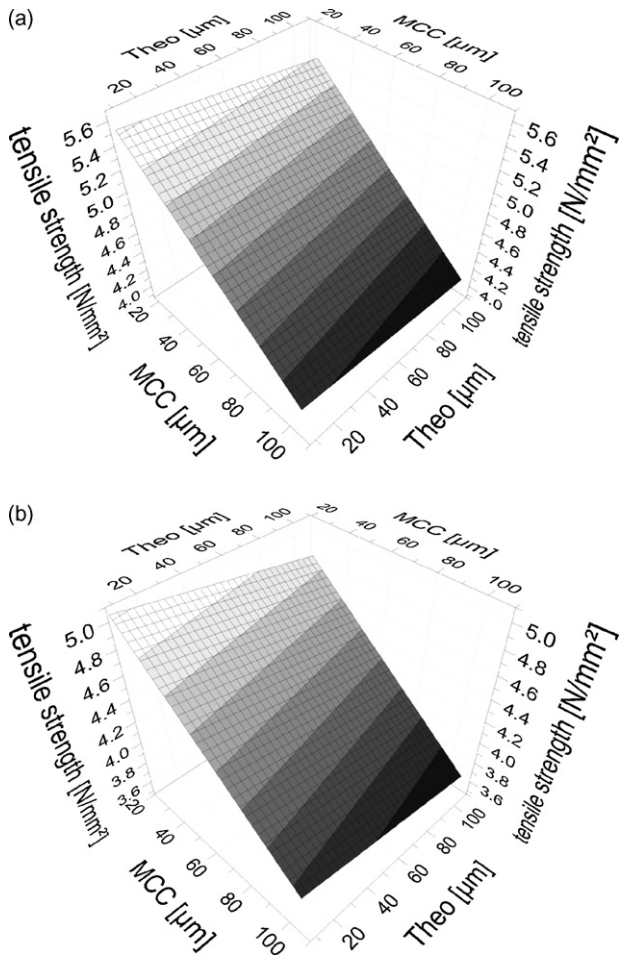

Fig. 4. (a) Surface plot for tensile strength of tablets made from powder at 18 kN (fraction = 50%), $R^2_{adj} = 0.991$. (b) Surface plot for tensile strength of tablets made from granules at 18 kN (porosity = 30%, fraction = 50%), $R^2_{adj} = 0.992$.

The friability of all tablets was below 0.4%. A decrease of particle size of MCC resulted in lower friability values ($p < 0.01$). Particle size of theophylline had no significant influence on friability. An increase of in-gap ribbon porosity led to reduced friability as well as a small fraction of theophylline. Again the inferior binding potential of theophylline was the reason.

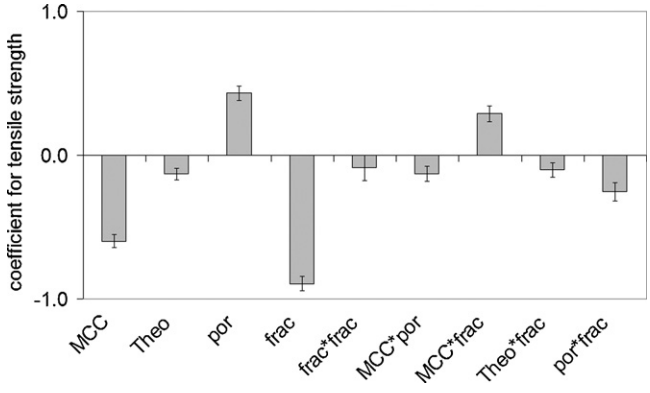

Fig. 5. Coefficient plot for tensile strength of tablets compressed from granules at 18 kN, $R^2_{adj} = 0.992$.

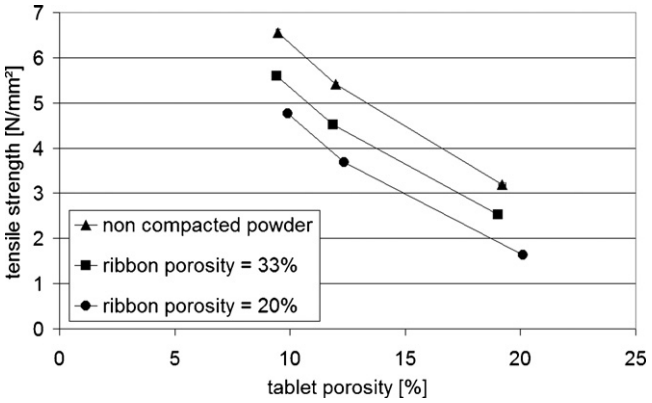

Fig. 6. Tensile strength as a function of porosity of tablets containing 75% MCC (106 µm) and 25% Theo (110 µm) roll compacted to different ribbon porosities, ($n = 10$, average ± confidence interval, $\alpha = 0.05$).

3.2.3. Comparison of tablets from powder with tablets from granules

Fig. 6 shows tablet porosity–tensile strength profiles for one formulation, which was either not compacted or compacted to different porosities. A compression level of 25 kN resulted in similar porosities of 8–9% independent of the pre-treatment during roll compaction. Only granules produced from ribbons of 20% porosity resulted in slightly higher tablet porosity. Similar results were found for the compression levels of 10 and 18 kN. However, tensile strength of tablets produced at the same compression level differed significantly in dependence of the pre-treatment procedure although tablet porosity was comparable (Fig. 6).

This decrease in re-working potential was described in literature as work hardening (Malkowska and Khan, 1983). In this paper, the ratio of tensile strength of tablets resulting from powder mixtures to tensile strength of tablets resulting from granules with the same composition is used to describe the extent of this phenomenon (Eq. (7)).

$$TS_{ratio} = \frac{TS_{granules}}{TS_{powder}} \quad (7)$$

A low TS ratio indicates a high loss in compactibility, i.e. a poor re-working potential. The values for TS ratio varied between 0.68 and 1.04. An alteration of particle size had no significant effect on the re-working potential. Ribbons with higher porosity and higher theophylline fraction resulted in higher TS ratio ($p < 0.01$). The impact of fraction of theophylline was mainly a result of the impaired compactibility of theophylline compared to MCC. The TS ratio compared the tensile strength before and after roll compaction. Theophylline in the mixture contributed less to the tensile strength in comparison with MCC. Therefore, increasing the fraction of theophylline raised the TS ratio.

A comparison of tensile strength of tablets made from powder using large size MCC (MCC102G) with tablets made from granules using small size MCC (Vivapur 105) and keeping the particle size and the fraction of theophylline constant revealed that the tensile strength of tablets resulting from granules was equal or even higher than the direct compressed tablets (Fig. 7).

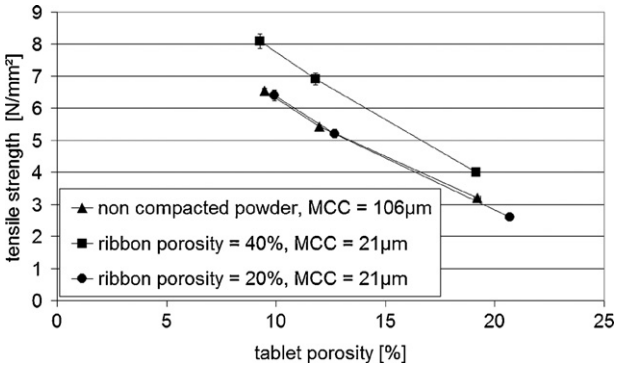

Fig. 7. Tensile strength as a function of porosity of tablets containing 75% MCC and 25% Theo (110 μm) roll compacted to different ribbon porosities, ($n = 10$, average ± confidence interval, $\alpha = 0.05$).

If the ribbons were roll compacted to a porosity of 40% tensile strength was significantly higher compared to the powder. For a ribbon porosity of 20% the tensile strength was still the same as tensile strength of non-compacted powder.

The flowability of the granules was similar to the non-compacted powder ($ff_c = 5.77$). Granules roll compacted to 20% ribbon porosity showed a slightly higher flowability ($ff_c = 6.57$). Granules roll compacted to 40% ribbon porosity resulted in a slightly lower flowability ($ff_c = 5.32$).

3.2.4. Formulation optimisation using statistical model

The use of small instead of large sized MCC allows the incorporation of a higher fraction of theophylline without a loss in the tensile strength. The statistical model derived from the D-optimal design was used to predict properties of tablets from dry granules. The starting point was the tensile strength of tablets resulting from a powder formulation containing 58.3% theophylline fine powder and large sized MCC. The model equation was used to predict the fraction of theophylline fine powder resulting in tablets of the same tensile strength using small sized MCC but after roll compaction to an in-gap ribbon porosity of 30%. The predicted fraction of theophylline fine powder was 75%. Granules with 75% of theophylline fine powder and 25% Vivapur 105 were roll compacted to 30% in-gap ribbon porosity and dry granulated. The granules were compressed to tablets at three compression levels. Fig. 8 presents the predicted values for tensile strength against the observed values.

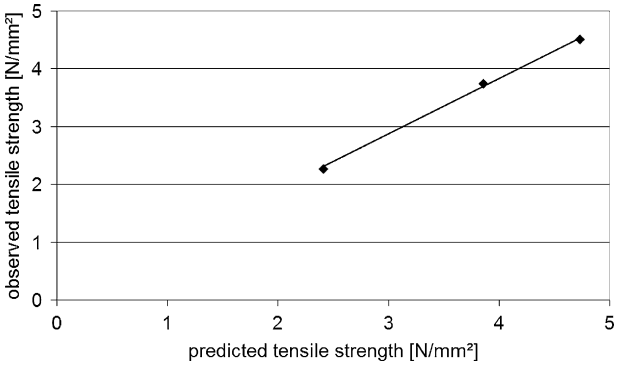

Fig. 8. Predicted vs. observed tensile strength of tablets containing 25% MCC (21 μm) and 75% Theo (110 μm) roll compacted to ribbon porosity of 30%, ($n = 10$), $R^2_{adj} = 0.999$.

The results indicate that the prediction capability of the statistical model is very good.

The largest residual was 0.22 N/mm^2. Therefore, it is possible to increase the fraction of theophylline by reducing particle size of MCC in the formulation. In this case a rise of 28.6% was achieved. The resulting granules showed a better flowability compared to the origin powder mixture.

4. Conclusion

The altering of particle size of MCC and theophylline changed the properties of the resulting tablets. These changes were not only observed by direct compression but also after roll compaction/dry granulation.

A decrease of particle size of MCC and theophylline resulted in higher values of tensile strength of directly compressed tablets as well as tablets made from granules obtained by dry granulation. The study showed that insufficient tensile strength after dry granulation can be compensated by decreasing particle sizes of MCC or theophylline. By roll compaction with smaller MCC particles larger granules with reduced fine particle fraction were obtained, which also showed a better flowability. Sufficient tensile strength after dry granulation can be utilized to increase the ratio of the active pharmaceutical ingredient. The drug load can be optimised by replacing large binder particles with smaller binder particles.

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