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Research paper

Studies on the reduction of tensile strength of tablets after roll compaction/dry granulation

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Abstract

Roll compaction/dry granulation is a widely used technique for granulation. A major drawback is the reduction of tablet tensile strength compared to other granulation methods. The purpose of this study was to determine the reasons for the partial loss in compactibility.

Microcrystalline cellulose of different particle sizes was roll-compacted/dry-granulated. The granules were sieved to obtain two sieve cuts and then compressed into tablets. The particle-size distribution within the sieve cut was determined using image analysis. The specific surface area of sieve cut was obtained by nitrogen adsorption. Heckel equation was used to determine the change in compressibility.

The work-hardening phenomenon was found to be caused by a combination of particle-size enlargement and hardening of material. Although particle size of granules was equal, the use of smaller particles as raw material resulted in tablets with higher tensile strength due to higher specific surface area.

Both work-hardening and particle-size enlargement cause the partial loss in compactibility. The reduction in tensile strength could be compensated by producing smaller granules or using raw materials with small particle sizes.

Keywords: Roll compaction/dry granulation; Tablets; Dry binder; Tensile strength; Particle size; Microcrystalline cellulose; Work Hardening; Compression; Compactibility

1. Introduction

Granulation is often a necessary step to improve the powder properties in pharmaceutical industry. Roll compaction/dry granulation and slugging are widely used techniques for granulation without water. Major advantages of roll compaction are the continuous production of granules and the lack of a drying stage leading to a reduction of costs [1]. However, dry granulation results in tablets with inferior tensile strength compared to direct compression.

In the literature this phenomenon was first described as work-hardening by Malkowska and Khan in 1983 [2]. It was explained with a limited binding potential which is partially consumed in the first compression step [3]. Materials with plastic deformation properties are particularly sensitive to this phenomenon. However, no evidence of direct hardening of powders was stated for this hypothesis. In a more recent paper by Sun and Himmelspach [4], the effect of reduced tensile strength was related solely to a particle-size increase during granulation. This resulted in a smaller binding area available for bonding. The authors used two sieve cuts (44–106 μm and 250–500 μm) with different types of microcrystalline cellulose (MCC) to avoid different particle-size distributions within the same sieve cut. Non-compacted and compacted materials were compared. The authors showed that there was a negative correlation between particle size of granules and tensile strength of tablets. The roll compaction was only performed at one compaction force level. In addition, according to Fig. 3 in their publication the same sieve cuts of granules made from different particle sizes of raw MCC resulted in different

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tensile strengths. The same amount of magnesium stearate (0.5%) was added independently of the particle size. This might explain partly the lower tensile strength of larger granules with a smaller surface area [5].

Recently, a significant correlation between particle size and tensile strength could not be observed by Herting and Kleinebudde [6]. In their study larger granules resulted in higher tensile strength values. Furthermore, in the study of Sun and Himmelspach [4] the values for tensile strength of tablets were not consistent with the values already reported in the literature [7]. Sun and Himmelspach did not provide detailed compression data and, therefore, statements about further changes of the material during roll compaction could not be stated.

Thus, the statement by Sun and Himmelspach explaining the reduction of tensile strength after roll compaction needs to be reconsidered. Therefore the purpose of this study was to examine if the reduction of tensile strength can solely be related to particle-size enlargement or, additionally, to a loss in binding potential due to double mechanical treatment. To investigate that, different types of MCC varying in particle size were roll-compacted/dry-granulated at various specific compaction forces. Two sieve cuts were obtained. Image analysis was performed to check the particle-size distribution within a certain sieve cut. The sieve cuts were then compressed into tablets using an instrumented tabletting press. The compression was performed using external lubrication and tensile strength of tablets was measured. The Heckel equation was used to determine the change and dimension of change in tabletting behaviour. The specific surface area of granules was measured using nitrogen adsorption.

2. Materials and methods

2.1. Materials

MCC was used in three different particle sizes. Vivapur 105 (MCC105) and Vivapur 101 (MCC101) were supplied by Rettenmaier, Rosenberg, Germany. MCC102G (MCC102) was supplied by Pharmatrans Sanaq, Basel, Switzerland. The investigated MCCs possessed the same degree of polymerisation (228 ± 3). The degree of polymerisation affects the compactibility of MCC [8].

Magnesium stearate was used as a lubricant (Caelo, Germany).

Prior to investigations, the materials were stored at least for 2 weeks at 21 °C and 45% relative humidity (rh).

2.2. Methods

2.2.1. Sampling

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

2.2.2. Particle density and particle-size measurement

The apparent particle density of all excipients was determined with an AccuPyc 1330 Helium Pycnometer (Micromeritics, Norcross, USA). For each excipient the determination was repeated 10 times and the mean value was reported.

The particle-size distributions of non-compacted MCCs were determined by laser diffraction analysis (Helos H1402/KF-Magic, Sympatec, Clausthal-Zellerfeld, 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 (d_{50}) 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, Osaka, 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, Haan, 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 amount of fines, which were defined as the fraction of particles smaller than 90 μm [9], were used as descriptive factors for sieve analysis.

2.2.3. Roll compaction/dry granulation

All experiments were performed using an instrumented roll compactor (Mini-Pactor, Gerteis, Jona, Switzerland) equipped with smooth rim rolls. The diameter and the width of the rolls are 25 and 2.5 cm, respectively. The gap between the rolls was kept constant at 3 mm. Speed of the rolls was set to 1 rpm. The roll compactor was set at the automatic mode [10], whereas the speed of the temping auger was adjusted by a control circuit keeping the gap constant.

Ribbons were roll-compacted to four (MCC102, MCC105) or five (MCC101) predefined specific compaction forces. The specific compaction force is applied force per width of rolls. Granules were retained after reaching constant gap and force (steady state section) [7].

The 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.

2.2.4. Image analysis

Each batch of granules was sieved into fractions 180–200 μm and 630–800 μm. Image analysis of these fractions was conducted using a system consisting of a stereomicroscope (MZ 75, Leica, Cambridge, UK), a ringlight with cold light source (KL 1500, Leica, Cambridge, UK), and a digital camera (CS 300F, Cambridge, UK). Software Leica Qwin (Cambridge, UK) was used to control and display data acquisition. Images of 500 particles of each sample at an adequate magnification [11] were translated into

binary images. Contacting particles were deleted manually. For each particle, 8 Feret diameters were determined and used to calculate the mean Feret diameter. The 10%, 50% and 90% quantile of the particle-size distribution were used for further characterisation.

2.2.5. Specific surface area

The specific surface area of granules was determined using the Surface Area and Porosity Analyzer Tristar (Micromeritics). The amount of the adsorbed nitrogen corresponding to a monolayer was measured at a temperature of 77 K to eliminate any temperature fluctuation effects. The evaluation of data was done using equation of Brunauer, Emmet and Teller (BET).

The mean of three measurements was used for characterisation.

2.2.6. Compression of tablets

An instrumented eccentric tablet press Korsch EKII (Korsch Pressen, Berlin, Germany) was used to compress tablets. Flat-faced tablets with 10 mm diameter and constant mass of 250 ± 1 mg were produced at a force of 12.5 ± 0.2 kN. The tabletting speed was set to 22 strokes/min. Granules were weighed and manually poured into the die. The lubricant was not added to the granules. Instead a pure magnesium stearate tablet was pressed for lubrication of die and punches prior to compression of powders or granules [12].

The upper punch was equipped with a digital incremental displacement transducer MT 2571 (Heidenhain, Traunreut, Germany) and strain gauges to measure compression force. Data were acquired using a MGC Plus system in combination with ML10B voltage amplifier (HBM Hottinger Baldwin Meßtechnik, Darmstadt, Germany). The sampling rate was 19200 data points/sec. For evaluation Catman 3.0 software (HBM) was used. For further detail see Dressler et al. [13].

2.2.7. Analysis of compression

The corrected upper punch displacement (for elastic deformation) was used to calculate the in-die Heckel plots [14]. The slope of the linear part of compression (K) was determined using univariate regression. The linear compression part included 300 data points. The mean apparent yield factor (P_y) was calculated according to Sonnergaard [15] by the following equation:

$$P_y = \frac{r^2}{K} \tag{3}$$

The coefficient of determination (r^2) was calculated from the linear regression curve.

2.2.8. Properties of tablets

The tablets were stored at least for 72 h at 21 °C/45% rh prior to the diameter and height measurements with a micrometer screw (Mitutoyo, Kawasaki, Japan). Tablet volume was calculated using the dimensions of the flat-faced tablet. Tablet volume, tablet mass and the particle density of the MCC 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, Basel, Switzerland) at a constant speed of 1 mm/s. The tensile strength of the compacts was calculated according to Fell and Newton [16]. The mean of six measurements was used.

3. Results and discussion

3.1. Characterisation of powders

Particle size decreased and specific surface area of the different used MCC types increased from MCC105 to MCC101 to MCC102 (Table 1).

3.2. MCC101 granules

3.2.1. Particle size of granules

Sieve analysis showed that median particle diameter of the granules varied from 482 to 784 μm. In general, the median granule size increased with higher specific compaction force (Fig. 1), whereas the amount of fines was decreased (28.2–7.5%). This was mainly due to stronger ribbons with lower porosity. There was no difference in particle-size distribution between granules produced at 7 and 9 kN/cm-specific compaction force.

3.2.2. Results of compression

The tensile strength (TS) of tablets compressed at 12.5 ± 0.2 kN produced from non-sieved granules consisting of MCC101 ranged from 5.8 to 8.3 N/mm^2 (Fig. 2). The higher the specific compaction force during roll compaction the lower was the TS of the tablets.

In the literature this phenomenon was explained by work hardening [2] or particle size increase [4]. With increasing particle size of granules the tensile strength of tablets was reduced in most cases (Fig. 3). The difference in tensile strength of tablets made from granules roll-compacted to 7 and 9 kN/cm was not significant ($p < 0.05$).

Table 1
d_{10}, Median particle size (d_{50}), d_{90}, particle density and specific surface area of different MCC types (means ± SD)

	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)	Particle density (g/cm^3)	Specific surface BET (m^2/g)
MCC105	7.40 ± 0.07	21.32 ± 0.09	50.89 ± 0.08	1.5698 ± 0.0036	2.35 ± 0.06
MCC101	20.11 ± 0.06	55.60 ± 0.07	125.35 ± 0.14	1.5738 ± 0.0012	1.47 ± 0.00
MCC102	23.91 ± 0.06	106.00 ± 0.07	218.84 ± 1.10	1.5719 ± 0.0009	1.31 ± 0.05

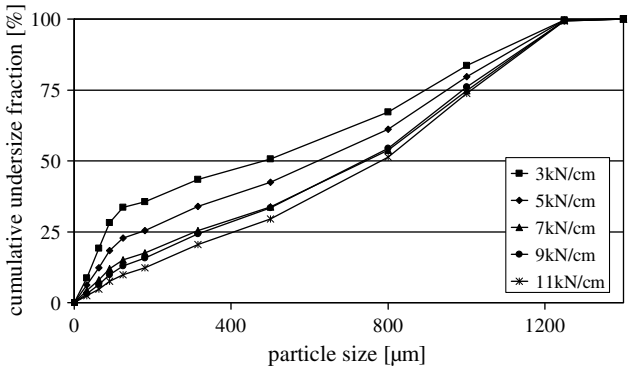

Fig. 1. Particle-size distribution of MCC101 roll-compacted with different specific compaction forces ($n = 2$, means ± SD).

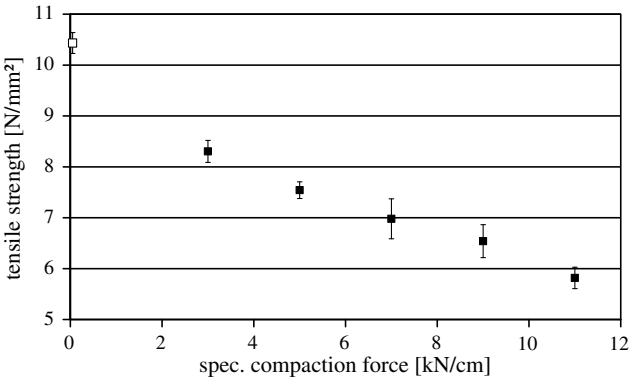

Fig. 2. Tensile strength of tablets made from raw powder (open symbol) or granule roll-compacted to different specific compaction forces (closed symbol) ($n = 6$, means ± confidence interval, $\alpha = 0.05$).

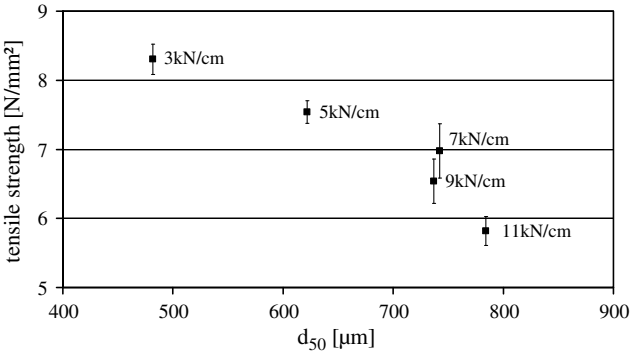

Fig. 3. Tensile strength of tablets made from granule roll-compacted to different specific compaction forces as a function of d_{50} sieve analysis diameter ($n = 6$, means ± confidence interval, $\alpha = 0.05$).

The resistance towards plastic deformation was higher with increasing specific compaction force during roll compaction as indicated by higher values of mean apparent yield pressure (Fig. 4). However, a relation was once again found between particle-size enlargement and stronger resistance towards plastic deformation.

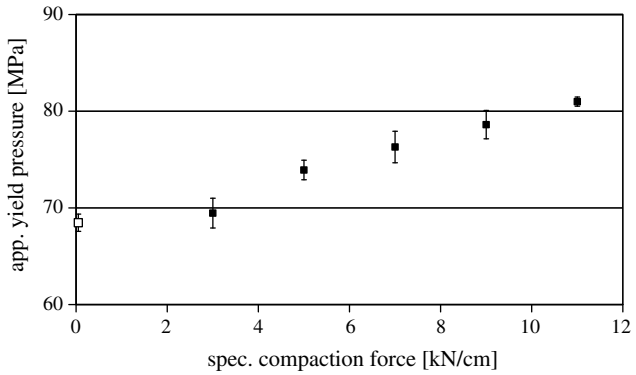

Fig. 4. Mean apparent yield pressure of tablets made from raw powder (open symbol) or granule roll-compacted to different specific compaction forces (closed symbol) ($n = 6$, means ± confidence interval, $\alpha = 0.05$).

3.3. Granule fractions of different MCCs

3.3.1. Particle-size distribution of granule fraction

Image analysis was performed to confirm that there was no difference in particle-size distribution within the different sieve cuts obtained at different specific compaction forces and different MCC types. Only a small increase of the median particle size with increasing specific compaction force was observed. However, considering the 10% and 90% percentile the difference found between the different sieve cuts in regard to the compaction force used for production was negligible. Thus, the particle-size distributions of granule fraction were regarded as equal for the fractions 180–200 µm. As an example, the results for the fraction 180–200 µm of MCC101 are shown in Fig. 5. The results for MCC105 and MCC102 are additionally stated in Tables 2 and 3. The fact that even the d_{10} was higher in size as the upper sieve (200 µm) can be explained by the shape of the granules (Fig. 6). They are longish-shaped and not spherical. Therefore, granules of larger particle size than 200 µm were able to pass the sieve.

There was a slight increase in median granule size with higher compaction forces for the particle-size distribution of the fraction 630–800 µm.

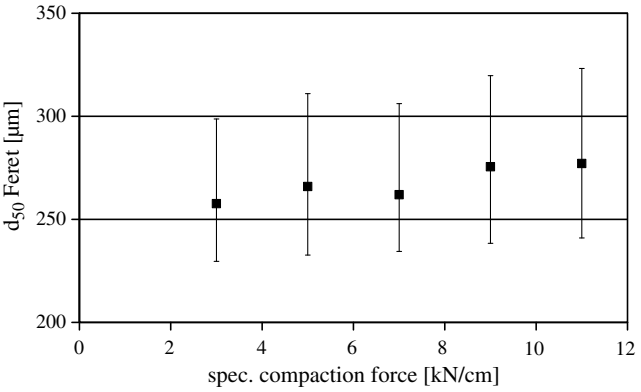

Fig. 5. Mean Feret diameter of MCC101 granule sieve fraction 180–200 µm roll-compacted to different specific compaction forces (d_{50}, d_{10}, d_{90}; $n = 500$).

Table 2
Specific compaction force, in-gap ribbon porosity, d_{10}, median particle size (d_{50}), d_{90}, specific surface area and tensile strength of tablets (TS) made from granules sieve cut 180–200 μm (means ± confidence interval, $\alpha = 0.05$)

	Specific compaction force (kN/cm)	In-gap ribbon porosity (%)	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)	Specific surface BET (m^2/g)	TS (N/mm^2)
MCC105	3	36	237	273	321	2.19 ± 0.02	10.88 ± 0.16
	5	27	241	276	320	2.01 ± 0.07	9.57 ± 0.22
	7	20	244	280	335	1.80 ± 0.02	9.12 ± 0.18
	9	16	245	290	345	1.67 ± 0.05	8.67 ± 0.12
MCC101	3	37	230	258	299	1.44 ± 0.03	9.03 ± 0.16
	5	28	233	266	311	1.36 ± 0.02	8.44 ± 0.11
	7	20	234	262	306	1.29 ± 0.05	8.26 ± 0.18
	9	15	238	276	320	1.18 ± 0.03	7.82 ± 0.17
	11	11	241	277	323	1.12 ± 0.05	7.49 ± 0.17
MCC102	3	37	228	256	295	1.27 ± 0.02	6.60 ± 0.10
	5	28	232	262	306	1.28 ± 0.05	6.25 ± 0.07
	7	21	230	257	293	1.19 ± 0.01	5.81 ± 0.11
	9	15	233	265	302	1.12 ± 0.04	5.63 ± 0.11

Table 3
d_{10}, Median particle size (d_{50}), d_{90} and tensile strength of tablets (TS) made from granules sieve cut 630–800 μm (means ± confidence interval, $\alpha = 0.05$)

	Specific compaction force (kN/cm)	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)	TS (N/mm^2)
MCC105	3	898	1047	1229	9.46 ± 0.25
	5	917	1080	1303	8.62 ± 0.24
	7	968	1126	1372	7.99 ± 0.27
	9	960	1114	1441	7.25 ± 0.21
MCC101	3	883	1027	1232	8.14 ± 0.15
	5	898	1043	1248	7.49 ± 0.20
	7	935	1077	1281	7.01 ± 0.25
	9	915	1050	1255	6.60 ± 0.20
	11	934	1095	1286	6.25 ± 0.22
MCC102	3	850	994	1155	6.28 ± 0.09
	5	898	1025	1200	5.77 ± 0.08
	7	923	1058	1264	5.32 ± 0.16
	9	887	1046	1275	4.49 ± 0.11

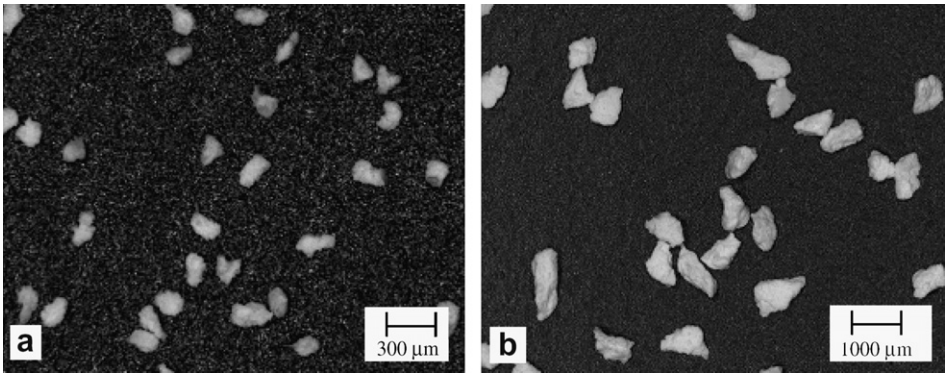

Fig. 6. SEM pictures of granule (MCC105, 9 kN/cm), (a) fraction 180–200 μm (b) fraction 630–800 μm.

A slight shift towards larger particles with smaller MCC as raw material was noticed when the particle sizes of both granule sieve cuts of the different MCC types were compared.

3.3.2. Results of compression

The tensile strength was different for tablets made from two fractions of the same MCC type produced at the same compaction force. Therefore, a size-dependent tensile

strength of tablets existed. This is not surprising as the area available for bonding is greater for small particles than for large ones. However, examination of tensile strength of tablets made from one type of MCC but at different compaction forces revealed differences. Although in this case an effect of different particle size distribution was excluded, there was still a decrease in tensile strength of tablets made from granules roll-compacted to a higher specific compaction force (Figs. 7 and 8). Therefore, reduction of tensile strength cannot be related solely to particle size enlargement as reported by Sun and Himmelspach [4]. This finding was supported by the fact that using smaller MCC led to slightly larger granules, which nevertheless resulted in stronger tablets.

Tablets consisting of MCC105 roll-compacted with 7 kN/cm possessed similar tensile strength compared to tablets produced using MCC101 at 3 kN/cm (Figs. 7 and 8). The tensile strength of tablets made with MCC102 at 3 kN/cm compaction force did not match the tensile strength of tablets of MCC105 or MCC101 at 9 or 11 kN/cm. To examine differences in compression behaviour the mean apparent yield pressure according to Sonnergaard [15] was used.

With increasing apparent yield pressure the resistance against permanent plastic deformation grows. According to Heckel [17] the plastic deformation is described by the linear part of the Heckel plot. In this study the elastic recovery was determined and differences between the different granules were not observed.

As seen in Figs. 9 and 10, the resistance of the granules against permanent plastic deformation increases with increasing the specific compaction force during roll compaction for all examined MCC types. There was no noticeable difference between apparent yield pressure values of MCC105 and MCC101 for fraction 180–200 μm. However, the values for MCC102 were lower compared to the values for the other two MCCs (Fig. 9). This might be related to some particles above 180 μm in the raw MCC102 (see Table 1). Therefore it might be possible that single particles of raw material existed in the examined fraction even after compaction.

Apparent yield pressure values of granule fraction 630–800 μm revealed the same trend for a specific MCC type as observed in the small fraction. However, in this fraction there existed a difference in apparent yield pressure between granules made from MCC105 and MCC101 (Fig. 10).

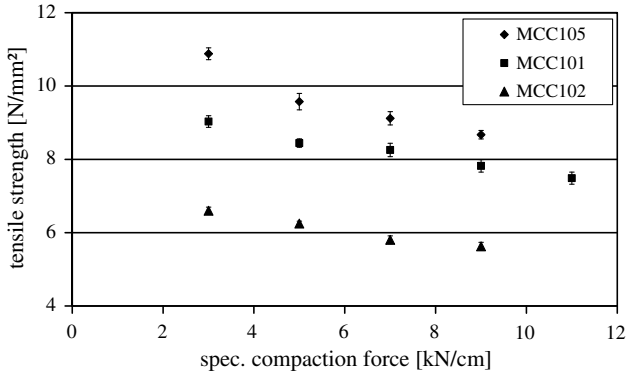

Fig. 7. Tensile strength of tablets made from granule fraction 180–200 μm roll-compacted to different specific compaction forces ($n = 6$, means ± confidence interval, $\alpha = 0.05$).

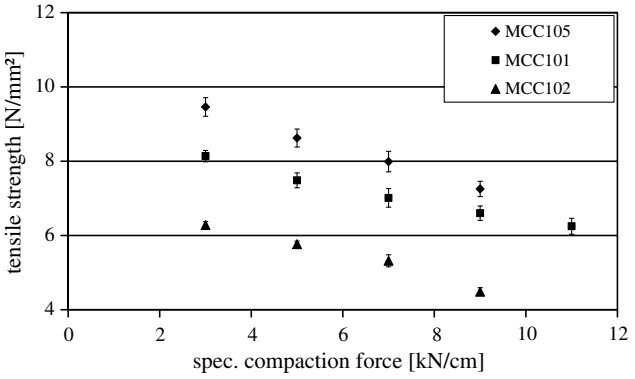

Fig. 8. Tensile strength of tablets made from granule fraction 630–800 μm roll-compacted to different specific compaction forces ($n = 6$, means ± confidence interval, $\alpha = 0.05$).

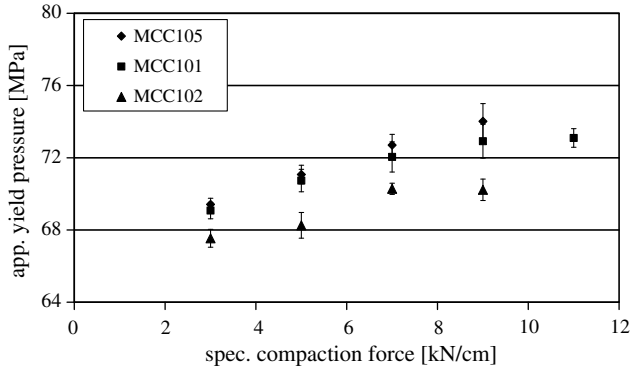

Fig. 9. Apparent yield pressure of granule fraction 180–200 μm roll-compacted to different specific compaction forces ($n = 6$, means ± confidence interval, $\alpha = 0.05$).

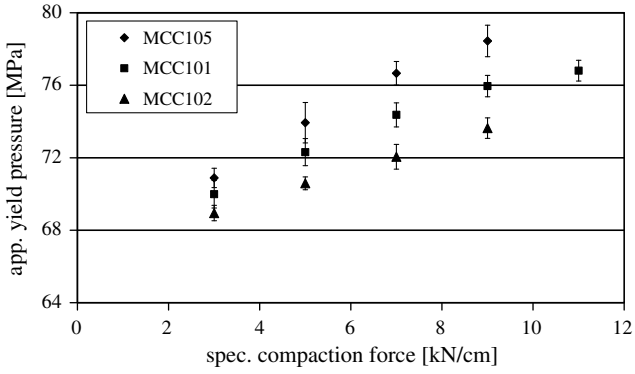

Fig. 10. Apparent yield pressure of granule fraction 630–800 μm roll-compacted to different specific compaction forces ($n = 6$, means ± confidence interval, $\alpha = 0.05$).

The process of roll compaction/dry granulation affected the compressibility of the examined materials. Although the same material was used and no difference of particle size was observed there was a trend of higher resistance towards permanent plastic deformation. Therefore the hypothesis of work-hardening seems to be right.

For each material a negative correlation ($R^2 > 0.93$) could be found between the apparent yield pressure and tensile strength of tablets (Fig. 11). This correlation can be used to describe the extent of work-hardening due to roll compaction/dry granulation.

However, compression of granules possessing the same apparent yield pressure did not result in equal tensile strengths of tablets. Although MCC105 showed the highest values for apparent yield pressure the tensile strength of tablets was highest. Therefore tensile strength cannot only be dependant on the particle size of granules but also on the higher resistance towards permanent plastic deformation.

The effect of moisture content on the mechanical properties was investigated by Khan et al. [18] and Malamataris et al. [19]. Both authors reported a negative correlation between moisture content and yield pressure. They observed an increase in yield pressure accompanied with a decrease in the moisture content. Therefore, the moisture content in the used MCCs was determined using Karl–Fischer titration. The result was 5.36 ± 0.15% (w/w) for all MCC types.

3.3.3. Results for surface area

The surface area of MCC cannot be determined using the geometric area based on the diameter as conducted by Sun because of the intra-particle porosity of the MCC. Comparing the geometric surface area with the surface area measured by nitrogen adsorption, the geometric surface area is only a tenth of the BET surface area [20].

The granule fraction 180–200 μm was used to determine the surface area using nitrogen adsorption. Within each type of MCC there was a decrease of specific surface area with increasing compaction force during roll compaction (Fig. 12). This can be explained by the diminishing porosity values at higher compaction forces. The inner granule surface is higher at higher porosity than at low porosity. This

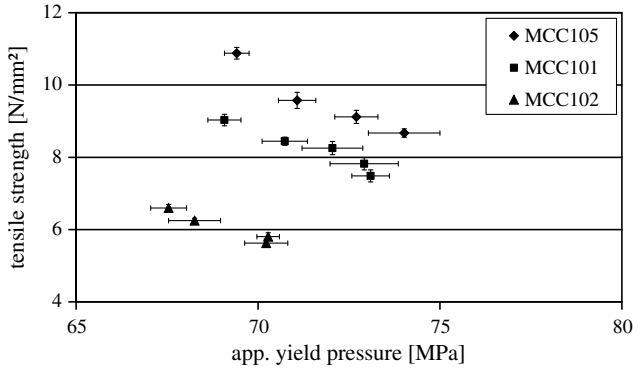

Fig. 11. Tensile strength of tablets as a function of apparent yield pressure of granule fraction 180–200 μm roll-compacted to different specific compaction forces ($n = 6$, means ± confidence interval, $\alpha = 0.05$).

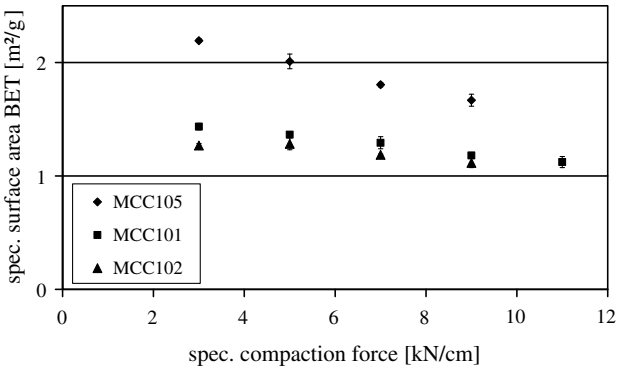

Fig. 12. Specific surface area of granule fraction 180–200 μm as a function of different specific compaction forces ($n = 3$, means ± standard deviation).

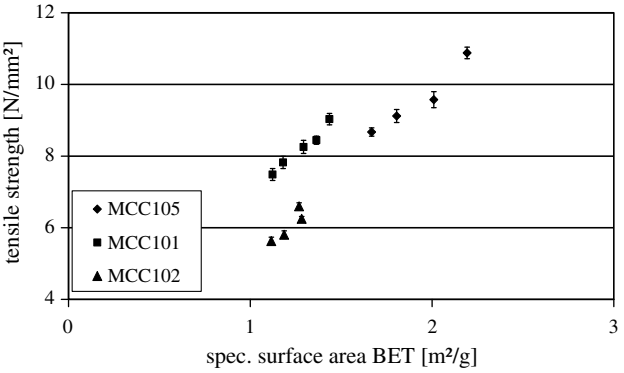

Fig. 13. Tensile strength of tablets as a function of specific surface area of granule fraction 180–200 μm roll-compacted to different compaction forces.

increase in surface might have an additional impact on tensile strength of tablets (Fig. 13).

Comparing specific surface area of different MCC types there was an increase of area with decreasing particle size of raw MCC (Fig. 12) although particle size of the granules did not differ. The significant higher surface area for MCC105 and MCC101 was responsible for the higher tensile strength of tablets. A higher surface area allows more bonding points between the particles during compression and thus a higher tensile strength of tablets [21]. The findings of surface area for MCC102 are unexpectedly high in regard to their tensile strength values. Although the surface area of unsieved raw MCC 101 and MCC102 differed less as expected from the particle size difference (1.47 ± 0.00 m^2/g to 1.31 ± 0.05 m^2/g), the tensile strength of tablets made from these two unsieved raw MCCs differed significantly (10.43 ± 0.21 N/mm^2 to 7.84 ± 0.10 N/mm^2). The surface area of MCC102 does not appear to be the only relevant factor to explain the variation in tensile strength.

4. Conclusion

The reduced tensile strength of tablets after roll compaction/dry granulation in comparison to direct compression

is based on different effects. One reason is the enlargement of particles during granulation. However, this enlargement applies for all granulation methods and not only dry granulation. The study proved that after mechanical pre-treatment (dry granulation) the resistance of the material towards plastic deformation is increased. These findings were observed for all three types of MCC. Nevertheless, the apparent yield pressure could not explain the different tensile strengths of tablets comparing different types of MCC at a certain specific compaction force. Although granule size did not differ between the different types of MCC there was a higher specific surface area found for smaller-sized raw MCC. In these cases the higher surface area was responsible for higher tensile strength values.

These findings could be used to minimize the reduction of tensile strength of tablets. Hence, either small-sized MCC could be used as a raw material for roll compaction/dry granulation or the granules can be decreased to a smaller particle size, e.g., by using a smaller sieve for dry granulation.

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