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Improving the compaction properties of roller compacted calcium carbonate

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Abstract

The effects of roller compaction process parameters, morphological forms of calcium carbonate and particle size of sorbitol on flow, compaction and compression properties were investigated. The morphology of the calcium carbonate and the sorbitol particle size were more influential on the compaction properties than the settings of the roller compactor. The roller compaction process was demonstrated to be robust and stable in regard to flowability and compactibility. The flowability of the granules was improved adequately to facilitate compression in a production scale rotary tablet press. By adding sorbitol to the calcium carbonate, the compressibility – characterized by the Walker coefficient W_{ID} – and the compactibility C_P were improved considerably. A correlation between the consolidation characteristics was demonstrated. Compactibility data from the compaction simulator correlated with the tablet press for two of the calcium carbonates, the cubic form and the ground quality.

Keywords: Roller compaction; Dry granulation; Compressibility; Compactibility; Morphology; Particle size

1. Introduction

Calcium carbonate tablets for nutrient supplement are manufactured in large batch quantities and thus an efficient manufacturing process is valuable. As the calcium carbonate particles in general have a mean particle size smaller than 70 μm, an agglomeration technique is required in order to obtain sufficient flow properties in a tablet press. Nowadays, the roller compaction has received much attention as a cheap and effective dry granulation method for pharmaceutical application. The process is simple and continuous as the powder is compressed between two counter-rotating rolls under pressure forming a dense ribbon, which is milled into granules.

The major rationale for granulation is to improve the material flow properties as the agglomerates are enlarged. Dry granulation of various morphological forms of magnesium carbonate succeeded in improving the flowability (Freitag and Kleinebudde, 2003). When testing the flow rate of inorganic materials through a funnel, the funnel generally became blocked and little or no effect of the roller compaction was reported from results of the repose angle (Parrott, 1981). In our experience, these flowability tests are often less functional and it might be necessary to include tests on a rotary tablet press.

The dry granulation process is expected to decrease the mechanical strength of tablets in comparison to tablets of the starting materials (Sheskey and Dasbach, 1995; Freitag et al., 2004; Weyenberg et al., 2005). However, the decrease in mechanical strength was limited by minimizing the compaction force during the roller compaction of magnesium carbonate (Freitag and Kleinebudde, 2003). In turn, differences in morphology and particle sizes of the magnesium carbonate caused a larger surface area of the starting materials, which was related to a larger mechanical strength (Freitag et al., 2004).

The tablet compaction characteristics are often determined as the diametral crushing force at a single compression force without consideration to the tablet dimension. Preferably the ability of a powdery material to form a mechanical resistant tablet should be characterized and quantified as the compactibility, which is defined as the material's ability to cohere as a function

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of applied compaction pressure (Leuenberger, 1982). The consolidation characteristics include also the compressibility which is defined as the ability of a powder bed to be reduced in volume due to the application of pressure (Leuenberger, 1982). The compressibility of pharmaceutical materials has frequently been estimated as the apparent mean yield pressure calculated from the Heckel equation (Heckel, 1961). However due to the severe estimation problems (Rue and Rees, 1978; Pedersen and Kristensen, 1994; Sonnergaard, 1999), the Heckel equation is considered to be obsolete for this investigation.

In this study, the aim was to investigate the improvement of the flowability and the influence on the compactibility and the compressibility of roller compacted granules of calcium carbonate. The study included the admixture of sorbitol as a binder. Initially, the effect of the process parameters of the roller compactor was evaluated. Second, the consolidation characteristics of different morphological forms of calcium carbonate and different particle sizes of sorbitol were investigated on a compaction simulator. Finally, industrial scale up to a rotary tablet press was performed in order to compare the compaction simulator and the tablet press.

2. Materials and methods

2.1. Materials

Calcium carbonate (Mikhart 65 (Provencale S.A., France), Scoralite (SCORA, France) and Sturcal L (Specialty Minerals Lifford, PA)).

Sorbitol (C*Sorbidex P166B0 (Cerestar, Belgium), C*Sorbidex P16656 (Cerestar, Belgium) and Neosorb P100T (Roquette, France)).

Magnesium stearate (Peter Greven C.V., The Netherlands) were used as starting materials.

The label codes Mikhart for Mikhart 65, Scoralite for Scoralite, Sturcal for Sturcal L, Sorbitol-45 for C*Sorbidex P166B0, Sorbitol-130 for Neosorb P100T and Sorbitol-236 for C*Sorbidex P16656 are applied. The sorbitol indexes refer to the mean particle size.

2.2. Preparing the powders for direct compression

Calcium carbonate (190.0 g) and sorbitol (60.0 g) were sieved manually (180 μm) and mixed in a 3.5 L cubic blender (Erweka KB 15/UG, Erweka, Germany) in the mass ratio 76:24. The cube was fixated at a 45° angle and the powder blends were mixed for 5 min at a speed of 33 rpm using a 100 g batch size.

2.3. Roller compaction

Calcium carbonate (61.0 kg) and sorbitol (19.0 kg) were sieved through an oscillating sieve (Frewitt Granulator MGI 312, Frewitt, Switzerland) with a sieve screen size of 600 μm. Calcium carbonate and sorbitol, in a 76:24 ratio, were mixed in a planetary blender (Bear Varimixer R 60, Bear Varimixer, Denmark) equipped with a 60 L container and a large mixing aggregate. A total of 80 kg of each blend were produced. For blends containing Scoralite or Mikhart the partial batch size was 40 kg while the lower bulk density of Sturcal required three partial batches of 26.7 kg. The partial batches were mixed for 10 min at 53 rpm.

Granules of calcium carbonate, sorbitol and calcium carbonate/sorbitol blends were prepared on an instrumented production scale roller compactor (GMP-Polygran Rollerpress 250/100/3, Gerteis, Switzerland). Preliminary eight batches of the Scoralite/Sorbitol-130 blend were granulated with different combinations of gap size (1.3–5.2 mm), roller force (6–12 kN/cm), roller speed (3–10 rpm) and tamp auger speed (TAS) (5.9–52.4 rpm) (Table 1). Based on these experiments, the following process and equipment variables were chosen for the final study: the hopper was equipped with a 10-blade lump breaker. The feed and tamp augers were operated at a speed of 4.2 and 5.9 rpm, respectively, thus the tamp/feed ratio was set to 140%. Since the gap size depends on the amount of delivered materials in the nip zone, it was automatically adjusted between 0.9 and 2.2 mm influenced by the bulk properties of the materials and the speed of the augers. The roller compactor was fitted with knurled rolls, operated at a compaction force of 12 kN/cm and a roller speed at 3 rpm (see Section 3.2). The ribbons were ground into granules in the oscillating pocket mould grooved rotor set at a speed of 80 rpm in each directions and a rotor angle of 360°/390°. The granulator screen was 2.0 mm.

2.4. Compression on the compaction simulator

All the powders and the granules were compressed on a compaction simulator described previously (Pedersen and Kristensen, 1994; Sonnergaard, 1999). The compaction simulator was adjusted to imitate the punch movement of a single tablet press. Six to eight samples of 1000 mg were compacted using

Table 1
Process parameters and granule size fractions for the eight experiments of the preliminary robustness test based on the Scoralite/Sorbitol-130 mixture

Experiment	Gap (mm)	Roller force (kN/cm)	Roller speed (rpm)	Tamp auger speed (rpm)	Fines < 125 μm (%)	Coarse > 1000 μm (%)
1	5.2	6	3	15.4	56.5	3.7
2	1.8	12	3	5.9	34.1	26.0
3	4.4	12	3	14.6	38.6	22.7
4	2.0	6	3	5.9	47.7	7.0
5	4.7	8	3	15.5	47.0	6.9
6	2.0	8	3	5.9	40.5	17.5
7	4.7	6	10	52.4	55.5	5.9
8	1.3	12	10	19.2	45.4	18.5

15 mm flat faced punches. For the sorbitol powders and granules, samples of 500 mg and 800 mg, respectively, were applied in order to fit the upper limit of the crushing force tester. The punches and die were cleaned with ethanol and lubricated with magnesium stearate before each compression. Each compression took 2.2 s in total which correspond to a contact time from 200 to 550 ms depending on the materials. Data were collected every 2.15 ms.

For calculating the compactibility and the compressibility, the tablets were characterized after storage of 24 h at ambient conditions. The tablet mass (Mettler Toledo AG204 DeltaRange, Mettler Toledo, Switzerland) and height (Digimatic indicator, Mitutoyo, Japan) were determined and the diametral crushing force was measured using a tablet crushing force tester (Schleuniger 8 M hardness tester, Dr. Schleuniger Pharmatron, Switzerland).

2.5. Compression on the rotary tablet press

Ten kilograms of the calcium carbonate/sorbitol granules were mixed with 0.34% magnesium stearate for 2 min and 53 rpm in a planetary blender (Bear Varimixer R 60, Bear Varimixer, Denmark) equipped with a 30 L container and a mixing aggregate.

The calcium carbonate/sorbitol granules were compressed on a 24-station rotary tablet press (Fette 1090 rotary tablet press, Fette GmbH, Germany). The tablet press was operated with 12 round, flat faced and beveled-edged punches with a diameter of 14 mm at 21.000 tablets/h corresponding to a contact time of 88 ms. Tablets with a mass of 1.75 g were produced at four or five compression forces differentiated by 10 kN with a fixed precompression of 10 kN.

The tablet mass variation was determined by measuring the weight of 20 randomly drawn tablets at each compression force (in total 80 tablets) using an automated in process control (Schleuniger AT4, Dr. Schleuniger Pharmatron, Switzerland).

2.6. Characterization of powders, granules and tablets

Scanning electron micrographs (JSM-5200 Scanning Microscope, Jeol, Japan) were prepared using samples spotted with gold (Bio-Rad Polaron Division E 5200 Auto Sputter, Bio-Rad, UK).

The median particle size of the starting materials was determined by a laser diffraction particle sizer (Malvern Mastersizer S 2601Lc, Malvern, UK) fitted with a dry powder feeder and operated at 3 bars. Triple determinations were performed.

The particle size distribution of the granules was performed as sieve analyses of samples of 100 g, which was withdrawn using a rotary cone sample divider (Laborette 27, Fritsch, Germany). A series of 10 ASTM standard sieves (Retsch, Germany) in the range of 75 and 2000 μm was vibrated (Analysette 3 Vibrator, Fritsch, Germany) for 2 min followed by a removal of the four top sieves and subsequent vibration of the remaining sieves for 5 further minutes. A single determination was performed.

The flow properties were evaluated by applying the test for flowability (European Pharmacopoeia, 2.9.16, 2005).

The compressibility index (CI) (Carr, 1965) was estimated from the bulk and tap volumes (V_{bulk} and V_{tap}) measured according to the test for apparent volume (European Pharmacopoeia, 2.9.19, 2005):

$$CI\% = \frac{V_{bulk} - V_{tap}}{V_{bulk}} \times 100 \quad (1)$$

The compactibility C_P was determined in terms of the specific crushing strength (SCS) as a function of the applied compaction pressure (P). The specific crushing strength for a cylindrical tablet is the crushing force (F) normalized by the cross sectional area (diameter (d) × height (h)):

$$SCS = \frac{F}{dh} \quad (2)$$

The compactibility C_P was calculated as follows (Sonnergaard, 2006):

$$SCS = C_P P + A \quad (3)$$

where C_P is the slope and A is the intercept. Six to eight tablets were compacted with varying pressures from the applicable minimum compaction pressures up to 200 MPa, which is the maximum relevant limit of the compaction simulator.

The compressibility of a tablet was determined as the specific volume in-die (V_{SID}) as a linear function of the logarithm of the compaction pressure (P). The specific volume is calculated from the in-die volume of the tablet and normalized by the mass of the tablet.

The in-die compressibility W_{ID} is defined as the numerical value of the slope of the Walker plot (Walker, 1923):

$$V_{SID} = -W_{ID} \log(P) + B \quad (4)$$

The compressibility W_{ID} is applied as a quantitative measure of the dynamic compressibility and calculated as an average of six to eight measurements from 5 MPa to maximum compression pressure.

The compressibility is also expressed as the out-of-die specific volume (V_{SOOD}) for 20 tablets at each compression pressure as a function of the logarithm of the maximum compression pressures. The out-of-die specific volume is calculated from the volume of the tablet ($r^2 \times \pi \times h$) and the mass of the tablet (M):

$$V_{SOOD} = \frac{r^2 \pi h}{M} \quad (5)$$

The out-of-die compressibility W_{OOD} is the numeric value of the slope from the plot and D is the intercept:

$$V_{SOOD} = -W_{OOD} \log(P) + D \quad (6)$$

2.7. Statistical data treatment

The standard deviation ($S.D._{slope}$) of the slope is calculated as (Draper and Smith, 1981):

$$R.S.D._{slope} = \frac{S_{res}}{\sqrt{SS_x}} \quad (7)$$

where S_{res} is the residual standard deviation about the regression line and SS_x is the sum of squares of the x-values. Subsequently, the relative standard deviation (R.S.D.$_{slope}$) of the slope is estimated as:

$$\text{R.S.D.}_{\text{slope}} = \frac{S_{\text{res}}}{\sqrt{SS_x}} \times \frac{100\%}{\alpha} \quad (8)$$

The slope α is the compressibility W_{OOD} and the compactibility C_P. Evaluating the quality of the estimates of the C_P and the W_{OOD}, the relative standard deviation of the slope was specified to be below 5%. If the relative standard deviation of the slope exceeded 5%, the outlier test Cook's distance was applied (Draper and Smith, 1981). Cook's distance expresses the difference between the computed values and the obtained values, when every point is excluded one by one. A Cook's distance above 1 was considered as an outlier which was eliminated and a new regression line with a new standard deviation was calculated. The regression analysis and Cook's distances were calculated in SigmaPlot 8.0. For W_{ID} all results were below 5%, whereas some of the curves of W_{OOD} and C_P exceeded the 5% limit. According to the Cook's distance, no points of W_{OOD} were outliers and therefore no elimination was performed. For half of the regressions of the C_P, one point was eliminated as a result of the outlier test.

In evaluating whether two slopes (W_{ID}, W_{OOD} and C_P) were significantly different, the t-test for comparison of slope α_1 and α_2 was applied (Hald, 1957):

$$t = \frac{\alpha_1 - \alpha_2}{S\sqrt{1/SS_{x1} + 1/SS_{x2}}} \quad (9)$$

In Eq. (9), S is the weighted average of the two residual standard deviation and SS_{x1} and SS_{x2} are the sums of squares of the x-values.

The analysis of variance (ANOVA, SigmaPlot 8.0) has been applied using the process parameters as response variables.

2.8. Outline of the experiments

Nine binary blends of three calcium carbonates and three sorbitol grades, in a 76:24 ratio, as well as each of the six starting materials were roller compacted. The 15 blends were characterized according to their flowability before and after dry granulation. Tablets were prepared from each of the 15 granule batches as well as the ungranulated starting materials, on a compaction simulator to evaluate the compressibility and the compactibility of the materials. Finally, the granule batches containing both calcium carbonate and sorbitol were compacted on a rotary tablet press in order to compare the results from the tablet press and the compaction simulator.

3. Results and discussion

3.1. Properties of the powders

The difference in morphology of the calcium carbonates is shown in the scanning electron micrographs (Fig. 1a–c). Calcium carbonate was applied as the ground limestone Mikhart, the cubic calcite Scoralite and the scalenohedral calcite Sturcal. The ground Mikhart consisted of rough and irregular particles with a mean particle size of 65 μm. The two precipitated calcium carbonates: Scoralite and Sturcal were smaller with a mean particle size of 10 and 8 μm. The three grades of sorbitol had very similar morphology, as shown in Fig. 2a–c, and differed only in particle size.

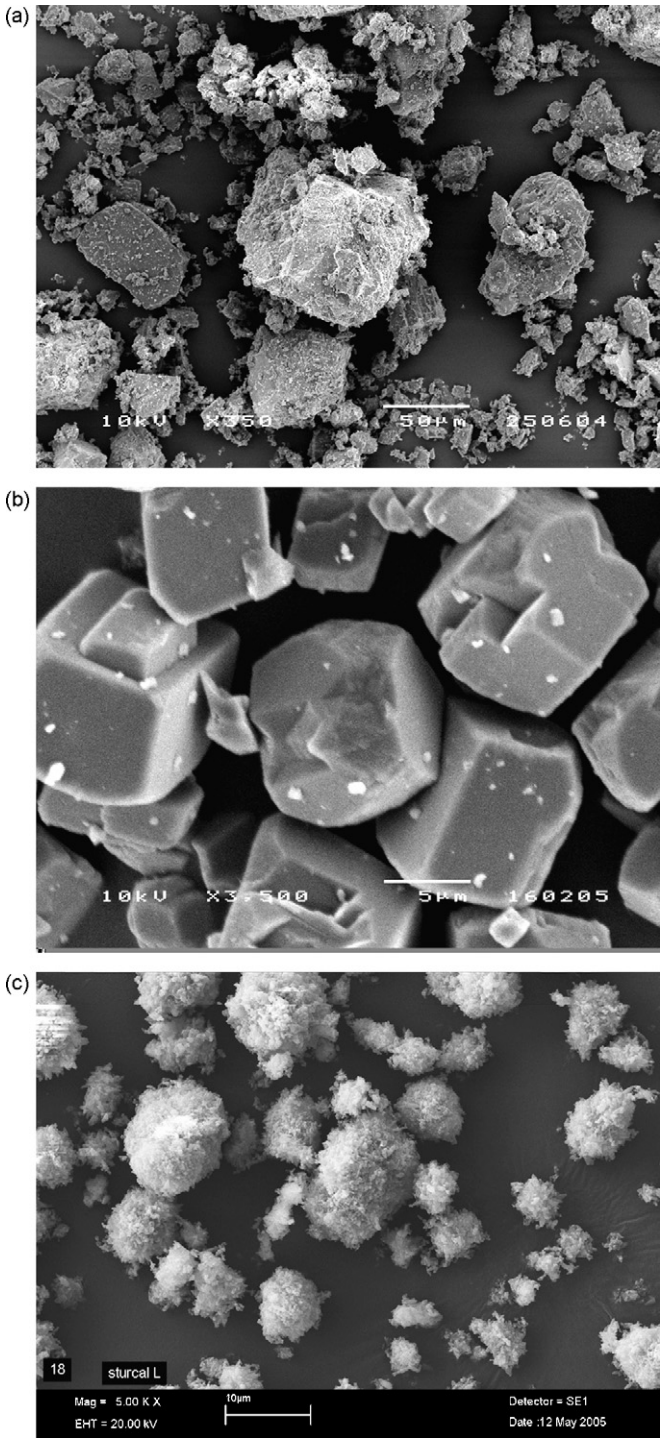

Fig. 1. Scanning electrons micrographs of (a) Mikhart, (b) Scoralite and (c) Sturcal.

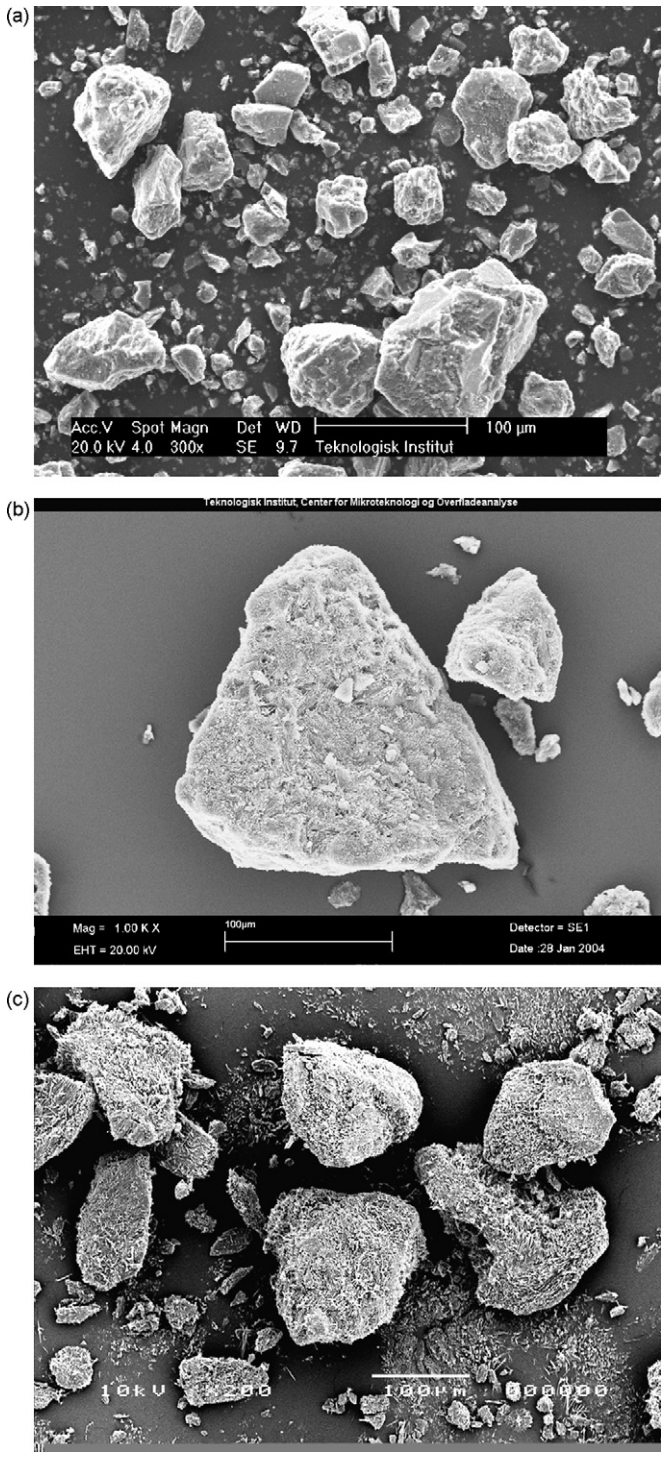

Fig. 2. Scanning electron micrographs of (a) Sorbitol-45, (b) Sorbitol-130 and (c) Sorbitol-236.

3.2. Evaluation of the roller compaction parameters

The compaction force of the roller compaction has been demonstrated to affect the mechanical crushing strength of tablets (Freitag and Kleinebudde, 2003; Freitag et al., 2004). Therefore the dry granulation process was evaluated in this study by investigating the effect of different combinations of gap, roller force, roller speed and tamp auger speed (TAS) on the flowability and the compactibility of the Scoralite/Sorbitol-130 granules. The investigated factors had no significant effect on the flowability which was estimated as the compressibility index and differed between 19% and 24% (see Section 3.3). Similar results were observed regarding the compactibility, which varied between 4.2 and 7.6×10^{-3}. Only a small significant difference was observed among the compression profiles, which was attributed to the most compressed granules. Therefore the process was considered robust in regard to the flowability and compactibility. However, large variations in the particle size distributions were obtained as the fines <125 μm varied between 34% and 57% and the coarse granules >1000 μm varied between 4% and 26% (Table 1). Since no important effect was observed on the compaction properties, the settings which resulted in granulates with the lowest amount of fines were chosen in the study.

These results of the preliminary experiments are in accordance with previous result; in which it was concluded that the impact of the process parameters on the mechanical strength of common pharmaceutical materials was limited (Sheskey and Hendren, 1999). Still, many authors have described the dependency of the roller pressure, roller speed and auger speed on the characteristics of the roller compacted granules. The effects are observed for the particle size (Falzone et al., 1992), friability (Inghelbrecht and Remon, 1998) and density (Parrott, 1981). The practical impact of these granule variables on the compaction process may however, be less significant.

All of the eight granules showed in general poor compaction properties (C_P: $4.2–7.6 \times 10^{-3}$) thus further improvement of the formulation was needed and the effect of the morphology of the calcium carbonate and the particles size of sorbitol were investigated.

3.3. Flowability

The flowability of calcium carbonate, sorbitol and calcium carbonate/sorbitol before and after dry granulation was initially examined accordingly to the test for flowability (European Pharmacopoeia, 2.9.16, 2005). However, since a majority of the samples were unable to flow through the funnel, the test was replaced by the indirect method of flowability—the compressibility index. In this test, a material having a compressibility index below 15% is considered to be free flowing whereas an index above 25% indicates that the material is cohesive (Carr, 1965).

As expected, the calcium carbonate powders had a poor flowability with a compressibility index between 31% and 32% (Table 2). Only the granulated Sturcal improved the compressibility index sufficiently to be considered as almost free flowing. This was attributed to the Sturcal's ability to agglomerate without a binder thus the granule consisted of many coarse granules >1000 μm and few fines <125 μm. The sorbitol powder and granules showed the expected decreasing values with an increase in particles size and the sorbitol granules were all free flowing. The compressibility index of the mixed powder blends were in the range 22–29%. The granulation process improved the flowability considerably to a compressibility index of 14–20%, thus the roller compacted granules had fair flow properties and

Table 2
The compressibility index for calcium carbonate and sorbitol as powder and granules

	Compressibility index (%)	
	Powder	Granule
Mikhart	31.4 (30.4–32.5)	23.7 (22.7–24.7)
Scoralite	30.9 (30.5–31.3)	34.0 (33.8–34.2)
Sturcal	32.4 (31.8–32.9)	16.5 (16.4–16.7)
Sorbitol-45	25.0 (24.4–25.6)	13.5 (12.9–14.1)
Sorbitol-130	20.5 (19.5–21.4)	12.1 (12.0–12.1)
Sorbitol-236	19.2 (19.1–19.3)	11.9 (11.6–12.3)
Mikhart/Sorbitol-45	24.5 (24.3–24.8)	16.5 (15.3–17.7)
Mikhart/Sorbitol-130	24.1 (23.7–24.4)	19.2 (17.0–21.3)
Mikhart/Sorbitol-236	25.3 (24.7–25.8)	20.4 (17.3–23.5)
Scoralite/Sorbitol-45	29.4 (27.0–31.8)	13.5 (12.6–14.3)
Scoralite/Sorbitol-130	22.4 (20.8–24.0)	19.9 (17.0–22.7)
Scoralite/Sorbitol-236	25.5 (25.3–25.8)	18.7 (17.2–20.2)
Sturcal/Sorbitol-45	28.9 (28.0–29.8)	14.2 (14.0–14.4)
Sturcal/Sorbitol-130	29.4 (29.3–29.5)	18.3 (17.2–19.3)
Sturcal/Sorbitol-236	31.3 (31.1–31.5)	17.7 (16.4–19.0)

The range is shown in the brackets. $N = 2$.

all the Sorbitol-45/calcium carbonate granules were free flowing or almost free flowing. The flowability of the Mikhart and Scoralite granules was improved sufficiently to facilitate a uniform dosing in the rotary tablet press, thus the mass variation was below 1.1% (Table 3). Even though the Sturcal granules were fairly free flowing according to the compressibility index, the mass variation reached 3.2%. The poor dosing was probably related to a low content of fines <125 μm below 9%, which could have been minimized by a softer compression on the roller compactor (Table 3). Fines in granules are presumed to fill up the voids during die-filling which ensures a uniform filling. In conclusion, the compressibility index gave a fair estimate of the flowability, though no direct relationship with the dosing in the tablet press could be established. This emphasized the need of testing in a rotary tablet press.

3.4. Compressibility

The roller compaction decreased the compressibility notably between 12% and 35% (Table 4) as a large W_{ID} indicates a large reduction in volume of a material. Some representative compression profiles are exemplified in Fig. 3. More void was obviously filled in the relative porous powders than in the granulated materials and in general the granules were compressed to a lower porosity.

Table 3
The relative standard deviations (R.S.D.) of the tablet masses of tablets obtained from a rotary tablet press and the fines < 125 μm

Granule	R.S.D. (%)	Fines < 125 μm
Mikhart/Sorbitol-45	1.1	14.7
Mikhart/Sorbitol-130	0.7	26.7
Mikhart/Sorbitol-236	1.0	44.2
Scoralite/Sorbitol-45	0.9	13.0
Scoralite/Sorbitol-130	1.0	34.1
Scoralite/Sorbitol-236	0.6	46.7
Sturcal/Sorbitol-45	3.2	9.2
Sturcal/Sorbitol-130	1.3	3.6
Sturcal/Sorbitol-236	2.5	1.8

Table 4
The compressibility W_{ID} of the powders and granules of calcium carbonate and sorbitol obtained from the compaction simulator

	Compressibility W_{ID} ($\times 100\,cm^3/g$)		Difference (%)
	Powder	Granule	
Mikhart	10.4 (0.30)	8.1 (0.44)	22.1
Scoralite	11.8 (1.08)	9.7 (1.23)	17.8
Sturcal	17.6 (0.12)	11.5 (0.62)	34.7
Sorbitol-45	35.0 (0.18)	25.3 (0.54)	27.7
Sorbitol-130	37.2 (0.22)	25.8 (0.46)	30.6
Sorbitol-236	30.7 (0.49)	25.8 (0.16)	16.0
Mikhart/Sorbitol-45	15.8 (0.20)	13.9 (0.28)	12.0
Mikhart/Sorbitol-130	15.2 (0.29)	13.0 (0.27)	14.5
Mikhart/Sorbitol-236	14.4 (0.30)	10.7 (0.34)	25.7
Scoralite/Sorbitol-45	16.7 (0.77)	13.0 (0.26)	22.2
Scoralite/Sorbitol-130	13.5 (1.46)	11.4 (1.00)	15.6
Scoralite/Sorbitol-236	13.1 (1.32)	9.7 (1.08)	26.0
Sturcal/Sorbitol-45	19.9 (0.34)	12.9 (0.40)	35.2
Sturcal/Sorbitol-130	18.7 (0.59)	12.3 (0.94)	34.2
Sturcal/Sorbitol-236	18.9 (0.29)	12.2 (0.49)	35.4

The R.S.D. (%) is shown in the brackets. $N = 6$–8.

Regarding the morphology, a large compressibility was obtained for Sturcal with and without sorbitol mainly as a result of the high initial porosity. The porosity has been reduced during roller compaction and the Sturcal granules have a marked lower compressibility than the corresponding powder blends. Powders and granules with Scoralite and Mikhart had almost the same compressibility and parallel compression curves. The curves are not identical since Scoralite had a higher bulk volume and higher final porosity. The admixture of sorbitol to the calcium carbonate powder improved the compressibility of calcium carbonate; however for the Sturcal only to a small extent (Table 4). The incorporation of the smallest sized sorbitol, Sorbitol-45, in the granules, improved the compressibility to the highest degree, followed by Sorbitol-130, whereas Sorbitol-236 did not affect the compressibility significantly.

While the W_{ID} is a measurement of the volume reduction during compression in-die, the W_{OOD} is the out-of-die measurement

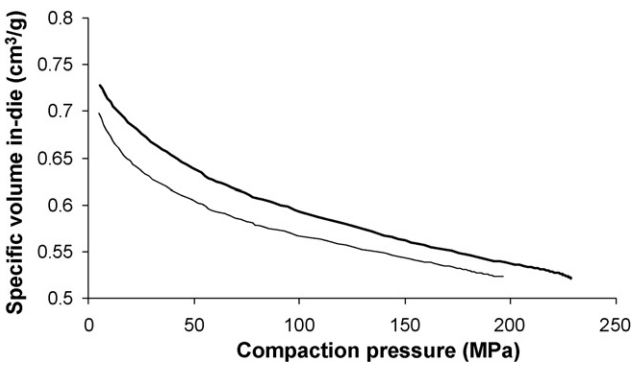

Fig. 3. An example of the compression profiles of Scoralite/Sorbitol-130. Powder (thick line): $W_{ID} = 13.5$ and granule (thin line): $W_{ID} = 11.4$.

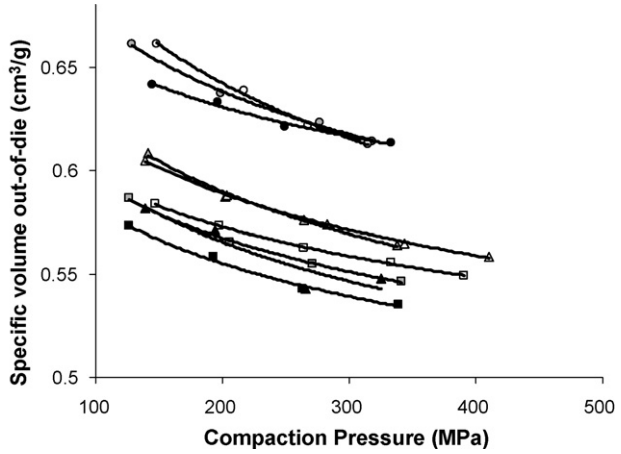

Fig. 4. The compression profiles of tablets produced of granules on a rotary tablet press. (■) Mikhart/Sorbitol-45, (■) Mikhart/Sorbitol-130, (□) Mikhart/Sorbitol-236, (▲) Scoralite/Sorbitol-45, (▲) Scoralite/Sorbitol-130, (△) Scoralite/Sorbitol-236, (●) Sturcal/Sorbitol-45, (●) Sturcal/Sorbitol-130 and (◯) Sturcal/Sorbitol-236. $N = 80$ for each granule. The lines are fitted according to Eq. (4).

including the elastic expansion after compression, which in general resulted in lower values of W_{OOD} than W_{ID}. In Fig. 4, the out-of-die compression profiles obtained from the tablet press are illustrated. The three morphological forms of the calcium carbonates affected the out-of-die specific volumes, since the tablets produced from Sturcal had a considerably larger specific volume than Scoralite and Mikhart tablets (Fig. 4). The large porosity in Sturcal tablets is caused by the reduced ability of the scalenohedral structure to pack closely as the internal friction during compression is high. In contrast to these observations, the volume differences for the sorbitols were less pronounced.

3.5. Compactibility

Characteristics compaction profiles from the compaction simulator are exemplified in Fig. 5. A large compactibility C_P expresses the ability of forming a relatively large mechanical strength at a relatively low compression force. Among the calcium carbonate powders and granules with and without sorbitol, the compactibility of Sturcal was significantly larger or similar to the compactibility of Mikhart, which was significant larger or similar to the compactibility of Scoralite (Table 5). However, this order did not apply for the addition of Sorbitol-45 in the calcium carbonate granules in which the compactibility of Mikhart and Scoralite are improved by the incorporation of the Sorbitol-45, whereas the Sturcal granules are unaffected by the presence of Sorbitol-45. The compactibility C_P of the smaller sized Sorbitol-45 in calcium carbonate powders and granules, was significantly larger than the compactibility of Sorbitol-130 which was significant larger the compactibility of the Sorbitol-236 (Fig. 5). The addition of sorbitol caused the overall highest increase in the compactibility. A high compactibility was related to a large area of bond formation which is associated with the surface area (Alderborn, 1996). Especially the bulky Sturcal had a large surface area and bonding by mechanical interlocking was likely to occur. The granules containing Sturcal have further reduced volume compared to Mikhart and Scoralite. Thereby it is likely that the material has reduced ability to mechanical interlock after dry granulation. The milled irregular particles of Mikhart had an advantage over the fairly smooth Scoralite; not only due to the larger surface area but could also be a result of higher electrostatic charges on the edges as claimed by Führer (1996). Decreasing sizes of sorbitol enlarged the area of bond formation, which explains the increase in compactibility of Mikhart/sorbitol and Scoralite/sorbitol powders and granules with decreasing sorbitol sizes. Yet, the smallest sized sorbitol did not benefit the Sturcal tablets, which could be due to Sorbitol-45 interferes with the packaging of the scalenohedral calcium carbonate during compression.

The compactibility in general was only influenced by the roller compaction to a small insignificant extent thus the

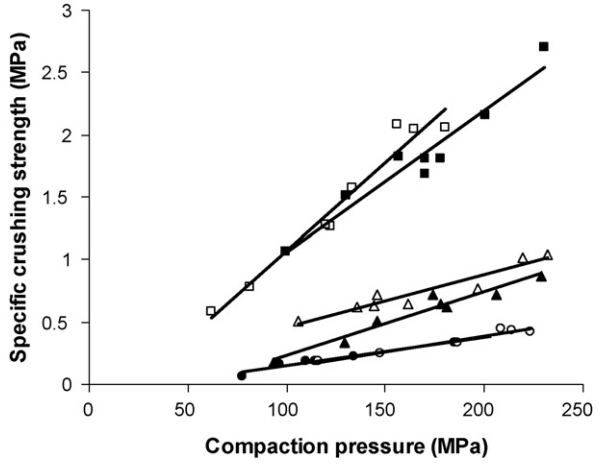

Fig. 5. Examples of compaction profiles. (■) Scoralite/Sorbitol-45 powder, (□) Scoralite/Sorbitol-45 granule, (▲) Scoralite/Sorbitol-130 powder, (△) Scoralite/Sorbitol-130 granule, (●) Scoralite/Sorbitol-236 powder and (◯) Scoralite/Sorbitol-236 granule.

Table 5
The compactibility C_P of the powders and granules of calcium carbonate and sorbitol obtained from the compaction simulator

	Compactibility C_P (×1000)		p-Value
	Powder	Granule	
Mikhart	3.5 (22.7)	2.9 (22.1)	N.S.
Scoralite	≈0 (N/A)	0.2 (8.9)	N/A
Sturcal	10.9 (5.2)	7.2 (9.4)	0.002
Sorbitol-45	66.0 (4.7)	39.3 (13.6)	0.001
Sorbitol-130	62.9 (9.3)	34.7 (21.7)	0.011
Sorbitol-236	42.3 (8.8)	31.2 (6.2)	0.013
Mikhart/Sorbitol-45	18.2 (5.4)	16.5 (8.1)	N.S.
Mikhart/Sorbitol-130	11.3 (4.5)	10.9 (17.2)	N.S.
Mikhart/Sorbitol-236	7.0 (5.9)	7.5 (12.0)	N.S.
Scoralite/Sorbitol-45	11.4 (11.1)	14.1 (7.7)	N.S.
Scoralite/Sorbitol-130	5.1 (10.1)	4.2 (12.8)	N.S.
Scoralite/Sorbitol-236	2.2 (14.2)	2.6 (9.6)	N.S.
Sturcal/Sorbitol-45	18.4 (7.5)	7.8 (10.5)	<0.001
Sturcal/Sorbitol-130	13.0 (4.7)	10.5 (5.9)	0.015
Sturcal/Sorbitol-236	9.0 (3.7)	8.0 (10.0)	N.S.

The R.S.D. (%) is shown in the brackets. N.S.: not significant.

compactibility of some granules was increased while the compactibility of others was decreased in comparison to the corresponding powder blend. Of the few granules which were shown to be significantly different than the powders, a decrease was observed. Similar results with a decrease of 20–50% in mechanical strength, were demonstrated of a primary brittle deformation consisting of theophyline anhydrous, MHPC, lactose and magnesium stearate (Sheskey and Hendren, 1999). The plastic deforming microcrystalline cellulose showed a reduction in tensile strength between 40% and 70% (Brudy and Bultmann, 2004). It appears that brittle materials are less reduced in mechanical strength as the materials are roller compressed than plastic materials. This may be caused by the fragmentation behavior as the brittle materials forms new surfaces during compaction, which are able to produce new bonds.

In contrast to this phenomenon, it is often observed that the comparable mechanical manipulation, the precompression in a rotary tablet press improves the compactibility. The recompression of pharmaceutical powders has been investigated by Al-Aghbar and Armstrong (1997) as the materials were compressed up to 10 times in a tablet press with varying time intervals. Interestingly, the mechanical strength of all the excipients was improved at low intervals of 1.2 s, whereas at increased time intervals of 1 and 5 min, the mechanical strength of some of the excipients decreased. This was explained as the elastic recovery caused a weakening of the interparticulate attractive forces (Al-Aghbar and Armstrong, 1997). For dry granules as well, the interparticulate attractive forces are weakened or even destroyed as the bond strength created during the roller compaction are reduced. It is likely that the interparticulate attractive forces are improved when the additional compaction force is applied from the same orientation while the bonds are destroyed when the force is added from a different angle. To some extent the roller compacted granules possibly behaves as larger particles with a smaller bonding area during tablet compression. Other research has indicated that granules to some extent sustain their integrity during compression, since a relation between the mechanical tablet strength and the granule surface area of dry granulated crystalline lactose was demonstrated (Riepma et al., 1993). Furthermore, larger pores were detected in the tablets of larger granules thus the pores in tablets of dry granules are less uniformly distributed than in tablets made of powders (Riepma et al., 1993).

3.6. Production scale compression

The compression of calcium carbonate/sorbitol granules has been scaled up on a rotary tablet press and these results have been compared with compactibility results from the compaction simulator in Fig. 6. A linear correlation existed between granules of Scoralite/sorbitol and Mihart/sorbitol while the Sturcal/sorbitol granules deviated from this trend. As expected the compactibility of the Scoralite and Mikhart granules was larger at the compaction simulator than the tablet press. This can be explained by the differences in the compression times; since the simulator had a contact time of 200–550 ms while each of the precompression and main compression at the tablet press lasted 88 ms. Other

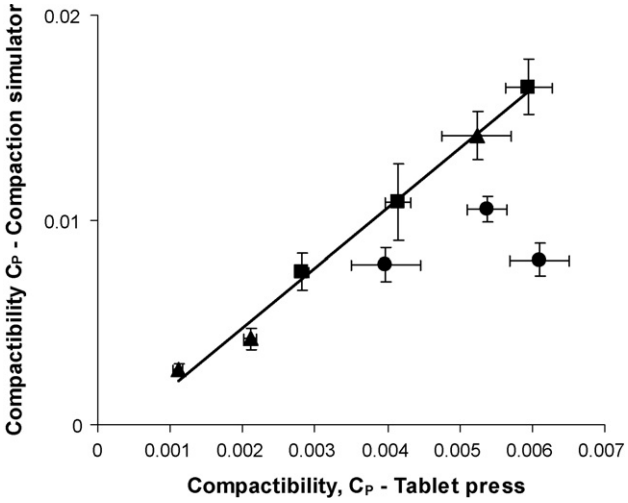

Fig. 6. Correlation between the compactibilities C_P at the tablet press and the compaction simulator. (■) Mikart/sorbitol granules, (▲) Scoralite/sorbitol granules and (●) Sturcal/sorbitol granules.

diversities between the tablet pres and the compaction simulator were the compression pressure range and the compression principle. The data from the simulator are obtained from the pressure interval: 50–200 MPa and the compression force is exerted from the upper punch whereas the compactibility at the tablet press originated from 100 to 400 MPa and the compression is supplied by both the upper and lower punches. The slower compression at the compaction simulator is not beneficial for the granules containing Sturcal, because Sturcal exhibits a large interparticle friction. This is expected to reduce the ability to relocate during compression and inhibit the decrease in porosity of Sturcal.

In conclusion, the compaction simulator provides an easy method for estimation of the compactibility at an early stage in the development process and thereby save experiments on production equipment.

3.7. Compressibility and compactibility

Encouraged by an observed correlation between the compressibility W_{ID} and compactibility C_P of pharmaceutical powders (Sonnergaard, 2006), results from this study is illustrated in Fig. 7, where the points represent powders and granules of calcium carbonate, sorbitol and calcium carbonate/sorbitol mixtures. Comparable results are obtained in spite of the narrow experimental area of this study. Previously, the compressibility expressed as the apparent mean yield pressure obtained from the Heckel plot failed to correlate with the tensile strength of roller compacted magnesium carbonate (Freitag and Kleinebudde, 2003). This lack of correlation is probably caused by confounding of the apparent mean yield pressure with the pycnometric density, which was shown by Humbert-Droz et al. (1983). Freitag and Kleinebudde (2003) found however, a correlation between the tensile strength and the degree of densification, expressed as the ratio between the relative density of the tablet and the relative density of the bulk material. During the compression of tablets, the particles slide past one another and create friction, which results in interparticulate contacts and thus inter-

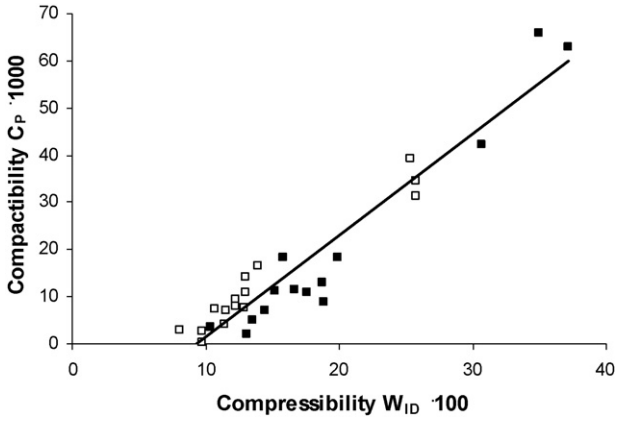

Fig. 7. Correlation between the compressibility W_{ID} and the compactibility C_P of investigated powders and granules. The relative standard deviation of the slope is 5.9%. (■) Powders and (□) granules.

particulate bonds may be created. Consequently the compression and compaction arise as inseparable and dependant phenomenon and it is anticipated that the compression behavior affects the compactibility. However, if a material has a pronounced elastic recovery, the relationship between the compressibility and the compactibility may be severely disturbed.

4. Conclusion

In order to produce calcium carbonate tablets from dry granules with an acceptable mechanical strength, it is essential to choose the right morphological form of the calcium carbonate and add a small sized dry binder. These formulation factors are far more important than any change or regulation of the process parameters of the roller compactor. Taking this into consideration, it was possible to improve the flowability satisfactorily to facilitate a proper dosing in the rotary tablet press as long as the granule contained a sufficient amount of fines to fill up the voids during die-filling. The compaction simulator appeared to be suitable for performing preliminary experiments. A correlation between the compactibility of the Mikhart and Scoralite granules on the tablet press and the compaction simulator was demonstrated. The friction of the Sturcal granules inhibited a fast volume reduction and consequently the results of Sturcal did not correlate as the Mikhart and Scoralite results.

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