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Compressibility and compactibility of granules produced by wet and dry granulation

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ABSTRACT

The bulk properties, compactibility and compressibility of granules produced by wet and dry granulation were compared applying a rotary tablet press, three different morphological forms of calcium carbonate and two particle sizes of sorbitol. Granules from both granulation methods possessed acceptable flow properties; however, the ground (Mikhart) and cubic (Scoralite) calcium carbonate demonstrated better die-filling abilities in the tablet press than the scalenhedral calcium carbonate (Sturcal). The wet processed granules showed in general larger compression properties. This was explained as these granules were mechanical stronger and had a higher initial porosity. In some cases, a large particle surface area of calcium carbonate and sorbitol resulted in a small, insignificant improvement of the consolidation characteristics. A correlation between the compression and compaction characteristics was demonstrated.

1. Introduction

In the field of pharmaceutical powder compaction, it is often necessary to improve the material flow properties in order to obtain a uniform die-filling in a tablet press. The flow properties can be enhanced by converting fine powders into larger agglomerates. Wet granulation is traditionally applied because the equipment and knowledge are available. In wet granulation, a fluid binder is distributed on a powder blend and subsequently the granules are dried. A more cost efficient alternative is the dry process—roller compaction where the material is densified between two counter rotating rolls under pressure forming a compact ribbon, which is milled into granules. This fairly simple technique is especially applicable for voluminous materials as it enhances the bulk density greatly. The disadvantages of the roller compaction comprise the formation of a relative large amount of dust and fines (Inghelbrecht and Remon, 1998) and the decrease in the compaction properties of powders (Bacher et al., 2007a; Sheskey and Hendren, 1999; Freitag et al., 2004).

Differences in compression of wet and dry granulated material are observed as wet processed granules often are more voluminous and roller compacted granules more dense than the original powder mixture (Sheskey and Hendren, 1999). Large granule porosity in wet processed granules has been related to a large fragmentation during compaction, resulting in mechanical stronger tablets (Wikberg and Alderborn, 1991). Similar results were obtain by Zuurman et al. (1994) who reported a positive relationship between the mechanical strength and the total porosity in the granule powder bed before compaction.

The geometric shape of the granules influences the volume occupied by intergranular voids in the powder bed before compaction; thus the granule morphology may affect the compression properties. Tablets made of rounded pellets, having the same intra-agglomerar porosity as irregular granules had a lower tensile strength due to a smaller interagglomerar void of the rounded pellets (Johansson and Alderborn, 2001). Agglomerates of different morphology are generated from wet and dry processing, thus Sheskey and Hendren (1999) characterised granules made in a high shear mixer as being rounded and course surfaced while granules from a roller compactor appeared smooth surfaced. In addition, Bacher et al. (2007a) described the roller compacted granules as edgy shaped.

The morphology of primary particles in granules has been demonstrated to affect the compressibility and the compactibility (Bacher et al., 2007a; Freitag et al., 2004). Generally, it is assumed that a decreased primary particle size increases the tablet strength

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(Alderborn, 1996). However, this assumption is provided that the particles stay intact during compaction.

In this study, the aim was to investigate and characterize granules from a wet and a dry process and compare the compressibility and compactibility. The granules were composed of three different morphologic forms of calcium carbonate and two particle sizes of sorbitol.

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) and Neosorb P100T (Roquette, France)).

Povidone (Povidone 30, BASF, Germany).

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 and Sorbitol-130 for Neosorb P100T are applied. The indexes of sorbitol refer to the mean particle size. Details about morphology and particles size are published in Bacher et al. (2007a).

2.2. Methods

2.2.1. Roller compaction

Calcium carbonate and sorbitol 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 mixed for 10 min at 53 rpm. 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.

Granules were prepared on an instrumented production scale roller compactor (GMP-Polygran Rollerpress 250/100/3, Gerteis, Switzerland). 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 automatic adjusted between 0.9 and 2.2 mm depending on 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. 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.

2.2.2. Wet granulation

5 kg calcium carbonate and sorbitol were sieved manually (300 μm) and dry mixed in a 25 l high shear mixer (Fielder PMA 25, T.K. Fielder, Denmark) in the mass ratio 76:24 for 1 min at an impeller speed of 120 rpm. The granulating fluid was produced by adding 100 g povidone slowly into stirring hot water (70–80 °C) and cooled down to room temperature before use. Keeping the binder content constant, the amount of water in the granulating fluid was varied according to the variation in the surface areas: Hence the povidone concentration was 34% for Mikhart/Sorbitol-45 and Scoralite/Sorbitol-45, 32% for Mikhart/Sorbitol-130 and Scoralite/Sorbitol-130, 20% for Sturcal/Sorbitol-45 and 19% for Sturcal/Sorbitol-130. The granulating fluid was atomized through a nozzle with an opening of 1 mm over 2 min while the impeller speed was set to 280 rpm and the chopper was activated. Wet massing was continued for 3 min at the same settings. The wet granules were transferred to a fluid bed dryer (Aeromatic MP 1, Aeromatic-Fielder AG, Switzerland) where the granules were dried at an inlet air temperature of 50 °C to a product temperature of 40 °C. The air volume was adjusted to reach a differential pressure over the perforated bottom from 2000 Pa at start to 300 Pa in the end of the drying. Loss on drying was performed at 80 °C (HR73 Halogen moisture analyzer, Mettler Toledo, Switzerland) in order to assure that the water content was below 0.5% w/w.

2.2.3. Compaction

The granules were mixed with 0.34% magnesium stearate for 5 min at 25 rpm in an 8 l cubic blender (Erweka AR400, Erweka, Germany) with an affixation angle of 45°.

The lubricated granules were compacted on an instrumented 6-station rotary tablet press (Korsch PH106, Korsch AG, Germany). The tablet press was operated with 3 round, flat faced and edged punches with a diameter of 14 mm at 8.000 tablets per hour. Tablets with a mass of 1.75 g were produced at five compaction forces in the compaction range: 1–25 kN.

The tablet mass variation was determined by measuring the weight of 10 randomly drawn tablets at each compression force (in total 50 tablets) using an automated in process control equipment (Schleuniger tablettester 8 M, Dr. Schleuniger Pharmatron, Switzerland).

Additionally, tablets were manufactured on a compaction simulator as described in Bacher et al. (2007a).

2.2.4. Characterization of 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). Samples consisted of granules from the size fraction: 180–1000 μm.

The bulk density was evaluated by applying the test for apparent volume (European Pharmacopoeia, 2.9.15, 2005).

The intragranular porosity of the agglomerates was estimated by a mercury immersion method as described by Strickland et al. (1956). A sample of 3–4 g granules from the size fraction: 180–1000 μm was placed in a glass pycnometer and degassed to a pressure of 80 mmHg. The pycnometer was filled with mercury and the apparent volume of the sample was estimated by mercury displacement at an intrusion pressure of 740 mmHg. At this intrusion pressure, mercury will penetrate into pores with a diameter greater than 20 μm (Johansen and Schæfer, 2001). Duplicate measurements of the apparent volume were performed. The intragranular porosity was determined on basis of the apparent volume and the volume of the ground material from the same size fraction. The granules were ground in a coffee mill (Braun 4041, Braun AG, Germany) for 1 min. The volume of the ground material was determined in a helium pycnometer (Accupyc 1330, Micromeritics instrument corporation, USA).

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):

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

The specific crushing strength (SCS) of the tablets is determined for a cylindrical tablet where the crushing force (F) is normalized by the cross-sectional area (diameter (d)·height (h)).

$$SCS = \frac{F}{d \cdot h} \quad (2)$$

The compactibility C_P was estimated from linear regression as (Sonnergaard, 2006):

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

Where C_P is the slope, P is the maximum compaction pressure and A is the intercept.

The out-of-die compressibility W_{OOD} was determined as the absolute value of the slope of the Walker plot {Walker E.E, 1923) where the specific volume out-of-die (V_{SOOD}) is plotted as a linear function of the logarithm of the maximum compaction pressures (P):

$$V_{SOOD} = -W_{OOD} \cdot \log(P) + B \quad (4)$$

Where B is the intercept and the out-of-die specific volume is calculated from the volume ($r^2 \cdot \pi \cdot h$) and the mass of the tablet (M):

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

In the calculation of V_{SOOD}, the volume of the edges is included. This results in a small but negligible deviation for all the tablets.

The compactibility C_P and compressibility W_{OOD} are calculated from 50 tablets from five compaction pressures.

2.2.5. Statistical data treatment

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

$$S.D._{slope} = \frac{S_{res}}{\sqrt{SS_x}} \quad (6)$$

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 calculated as:

$$R.S.D._{slope} = \frac{S_{res}}{\sqrt{SS_x}} \cdot \frac{100\%}{\alpha} \quad (7)$$

The slope α is the compressibility W_{OOD} and the compactibility C_P, respectively. Previously in a similar study of compressibility and compactibility (Bacher et al., 2007a), the relative standard deviation of the slope was specified to be below 5% otherwise the outlier test Cook's distance was applied (Draper and Smith, 1981). In this study, almost all of the W_{OOD} and C_P results exceeded the 5% limit while no single points of W_{OOD} and C_P were outliers according to Cook's distance and therefore no elimination was performed. These criteria were not estimated to be applicable in this study.

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

$$t = \frac{\alpha_1 - \alpha_2}{S \cdot \sqrt{1/SS_{x1} + 1/SS_{x2}}} \quad (8)$$

In Eq. (8), S is the weighted average of the two residual standard deviations and SS_{x1} and SS_{x2} are the sums of squares of the x-values.

The repeatability of the double measurements of the compressibility index, the granule porosity and the bulk density was expressed as the standard deviation (s) (Harsaae, 1966):

$$s^2 = \frac{1}{2k}\sum_{i=1}^{k} d_i^2 \quad (9)$$

Where k is the number of double measurements and d is the difference between the double measurements.

3. Results and discussion

The bulk properties, the compressibility and the compactibility are compared for wet and dry processed granules, manufactured from three different shapes of calcium carbonate and two different particle sizes of sorbitol.

3.1. Bulk properties

Examples of shapes and surfaces of the granules are shown in Fig. 1a–d. The roller compacted material was irregular with a coarse surface; whereas the wet granulated material was rounded also having a coarse surface though surrounded by small threads of PVP.

The flow properties of the agglomerated materials are indirectly evaluated as the compressibility index; thus below 15% a material is considered free flowing and above 25% the material is cohesive (Carr, 1965). The compressibility index of the roller compacted granules varied between 14 and 20% and the wet processed granules differed in the similar range: 16–20%; thus all the granules were flowing acceptably from a manufacturing point of view (Table 1). For the roller compacted granules, the flow properties were improved by reduced particle size of sorbitol; however this effect was not seen for the wet processed granules. No morphological influences of calcium carbonate are detected for either of the granulation methods. Compressibility indexes in a similar range as these results were obtained by Sheskey and Hendren (1999); thus roller compacted granules and a high shear granule had compressibility indexes of 13–17% and 14%, respectively. In a study of roller compacted granules of different morphological forms of magnesium carbonate, the average compressibility index for the most flowable morphological form was 18% whereas the least flowable was 23% (Freitag and Kleinebudde, 2003). This indicates that the particle morphology could affect the bulk properties in granules.

In an earlier study of calcium carbonate/sorbitol roller compacted granules on a 24-station rotary tablet press equipped with a force-feeder, the relative standard deviation of the tablet masses was used as a measure of the processability of the granules in the tablet press (Bacher et al., 2007a). Results below 1.1% were obtained for the irregular calcium carbonate, Mikhart and the cubic calcium carbonate, Scoralite whereas the mass variation of the scalenohedral calcium carbonate, Sturcal reached 3.2% which was expected to be due to the low content of fines. In this study of the roller compacted granules performed on a 6-punch rotary tablet press, no systematic effect of the morphology was seen as the variation was between 1.8 and 3.2% (Table 1). A larger variation was expected on the lab scale tablet press because the feeding system was a gravimetric feed frame. The wet processed granules of Mikhart and Scoralite had a mass variation of 0.3–1.6% while the granules with Sturcal had a poor die-filling, resulting in relative standard deviations up to 4.6% (Table 1). The poor dosing is probably due to the marked enhanced porosity at 44.3–55.4% and reduced bulk density at 0.455–0.504 g/ml of the wet granulated scalenohedral calcium carbonate (Table 1), since a larger filling dept is needed to be filled by gravity in the same short time with a lighter granule.

3.2. Compressibility

The out-of-die compressibility results in Fig. 2 show that the wet granulated materials have a remarkably higher compressibility than the roller compacted granules. The wet processed granules contained 2% povidone. This binder is not expected to account for the increase in compressibility since it only possesses weak agglomerating properties. From the exemplified in-die compression profiles in Fig. 3 of Scoralite/Sorbitol-130, the general difference in the compressibility of the wet and the dry granu-

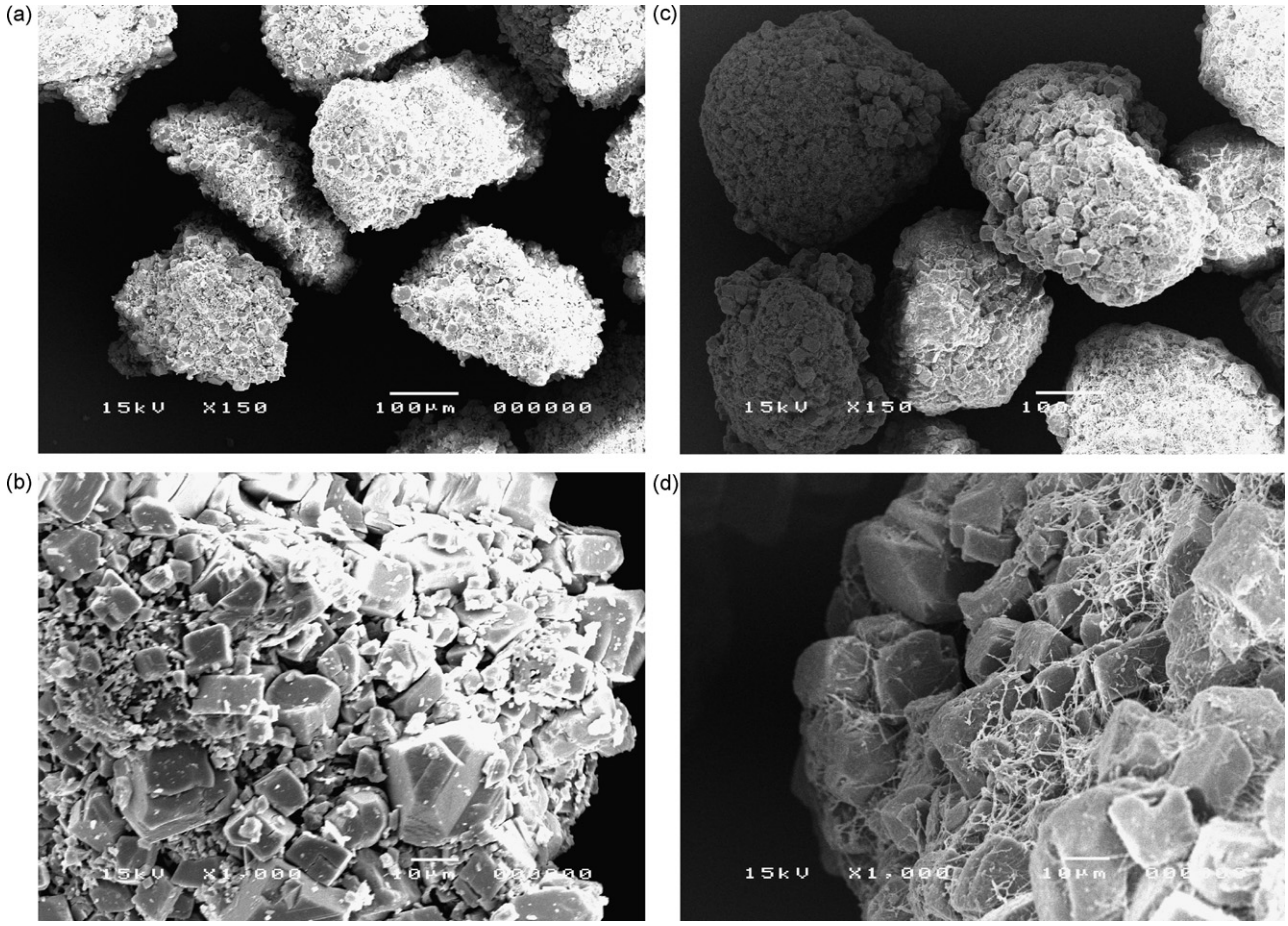

Fig. 1. Scanning electrons micrographs of Scoralite and Sorbitol-130. (a + b) Dry granulated material, (c + d) wet granulated material.

lated materials is elucidated in the following. At the pressures below 50 MPa, the specific volume of the wet granulated materials was larger and the dry granulated materials were denser than the original powder blend. At increasing compaction pressures, the granules were compressed into a more compact tablet than the corresponding power blend. The powder bed of the larger initial bulk volume of the wet granulated materials showed a larger resistance against deformation/fracturing during compression, indicating stronger granulates (Table 1). The higher resistance of the wet granulated materials resulted in a longer contact time and thus a longer mechanical processing since the upper punch reached the powder bed 50–110 ms earlier than the roller compacted granules (compared at 1 MPa). This is a remarkably increase considering the total contact time of the roller compacted granules varying from 280 to 400 ms. The larger initial in-die volume and the longer compression time are expected to enable the wet granulated materials to rearrange more easily during compression, resulting in a larger compressibility of the wet granulated materials. The roller compacted granules, on the other hand, were relatively soft and dense, resulting in a shorter compaction time and lower in-die volume during compression; accordingly the dry processed granules showed a lower compressibility.

A significant larger compressibility was obtained for the granules containing the scalenohedral calcium carbonate, Sturcal than the ground quality, Mikhart and the cubic Scoralite (Fig. 2). This is mainly ascribed to the large intra- and intergranular porosity, causing the upper punch to touch the granule powder bed 20–50 ms earlier (compared at 1 MPa) than the wet and dry granulated Mikhart and Scoralite, which had a contact time of 280–420 ms. However, the scalenohedral structure also caused a reduced ability to rearrange as the internal friction during compression was high, resulting in a larger tablet porosity.

Table 1
Granule characteristics of roller compacted granules (RC) and wet processed granules (WG) are listed

	Bulk density (g/ml)		Compressibility index (%)		Granule porosity (%)		R.S.D. of the tablet masses (%)	
	RC	WG	RC	WG	RC	WG	RC	WG
Mikhart/Sorbitol-45	1.130	1.081	16.5	17.3	3.2	21.9	1.130	1.081
Mikhart/Sorbitol-130	1.206	0.873	19.2	19.6	1.9	16.8	1.206	0.873
Scoralite/Sorbitol-45	1.136	0.905	13.5	18.6	2.1	18.3	1.136	0.905
Scoralite/Sorbitol-130	1.170	0.866	19.9	16.0	3.0	22.5	1.170	0.866
Sturcal/Sorbitol-45	0.890	0.455	14.2	19.8	2.0	55.4	0.890	0.455
Sturcal/Sorbitol-130	0.868	0.504	18.3	17.1	1.8	44.3	0.868	0.504

The estimated standard deviation based on Eq. (8) of the compressibility index is 1.90, for the granule porosity 1.06 and for the bulk density 0.0268 ($N = 2$). The R.S.D. of the tablet masses: $N = 50$.

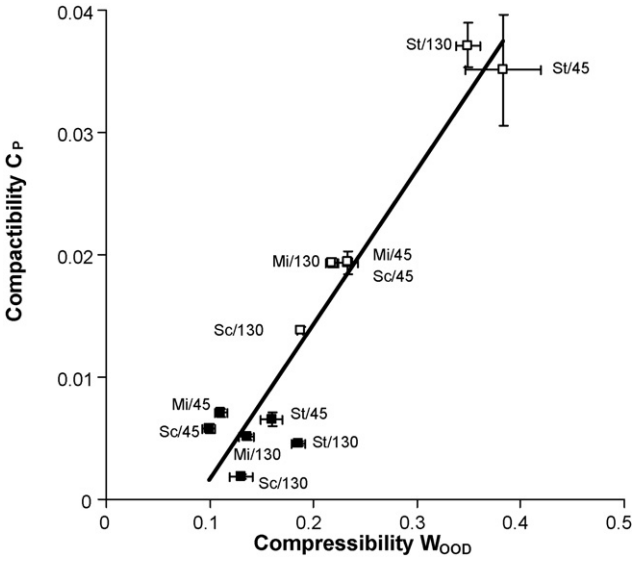

Fig. 2. Relationship between the compressibility W_{OOD} and the compactibility C_P of compacted granules. The relative standard deviation of the slope is 10.4%. ■: Roller compacted granules (RC), □: Wet processed granules (WG). The label codes are: Mi: Mikhart, Sc: Scoralite, St: Sturcal, 45: Sorbitol-45 and 130: Sorbitol-130. The error bars show the standard deviation.

The particle sizes of sorbitol had no systematic affect on the compressibility of the granulated materials. In a previously in-die compressibility study, a decreasing particle size of sorbitol improved the compressibility of roller compacted calcium carbonate granules (Bacher et al., 2007a). Similar relationship was also expected for the roller compacted granules in this study, but due to a less precise semiautomatic out-of-die measurement of the tablet thickness, the influence of sorbitol became less pronounced.

3.3. Compactibility

By analogy with the compressibility but more pronounced; the wet processed granules were more compactable than the dry granulated materials (Fig. 2). Apparently, the difference in compactibility is not caused by the porosity in these granules as suggested for agglomerates in earlier studies (Wikberg and Alderborn, 1991). An explanation for the decreased compactibility of the roller compacted granules has prior been given by the same authors (Bacher et al., 2007b). It is hypotized that the roller compacted granules are covered with the weakest bonding area on the granule surface as a result of the grinding process which splits the ribbon in the weakest particulate bonds. The fracturing of a tablet of roller compacted granules, is expected to occur between the granules in weak bonding zones. This fracturing is probably facilitated easier than if the weakest bonding areas were uniform distributed as it is presumed to be in a tablet made from direct compression. These theoretical considerations are supported by the scanning electron micrograph of the roller compacted granules, where only the weak bonding areas, the cubic calcium carbonate granules are visible (Fig. 1b). In the wet processed granules, the weak and strong bonds are expected to be distributed more evenly. However, from the scanning electron micrograph of the granule surfaces (Fig. 1d), only calcium carbonate and small threads of PVP appear. The wetted granules are likely to have a hydrophilic surface with a higher affinity to form interparticulate bonds. During compaction, the wet processed granules keep up a larger resistance towards deformation or fragmentation which enables a better rearrangement of particles and due to the enhanced internal friction, more contact points are formed.

A larger compactibility was obtained for the wet processed granules containing Sturcal than for granules of Mikhart and Scoralite. Strucal had a larger surface area and therefore most likely also a larger area of bonding which facilitated an enhanced compactibility. Therefore, to obtain tablets of wet processed Sturcal with acceptable mechanical strength, only a low compaction force has to be applied, resulting in large and porous tablets. For the roller compacted Sturcal, on the other hand, the bulk volume and compressibility were reduced sufficient to compact tablets of acceptable mechanical strength and height. For the roller compacted granules, the compactibility of all the calcium carbonates were very similar. Further, a low particle size of sorbitol increased the compactibility of the dry processed granules and the wet processed Scoralite granules due to the larger surface area, which makes it possible to form more contact points in a tablet. This indicates that the particle size of sorbitol only has a limited influence on the compactibility.

A correlation between the compressibility and the compactibility exists (Fig. 2) as previously shown for roller compacted granules (Bacher et al., 2007a). However, in this study the roller compacted granules do not show a clear relationship between the compressibility and the compactibility of the roller compacted granules as expected. This is probably mainly caused by the out-of-die measurements as the semiautomatic out-of-die measurements of the tablet thickness are less precise and contribute to a small variability.

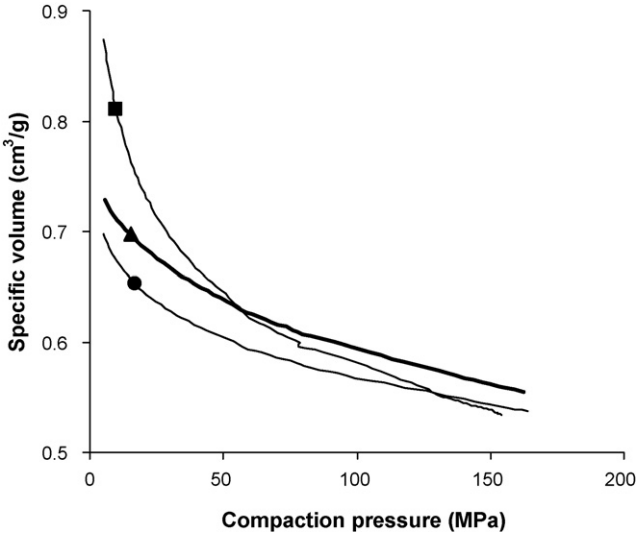

Fig. 3. Example of in-die compression profiles of Scoralite/Sorbitol-130 as ■: wet granulated material, ▲: powder blend and ● roller compacted granules.

4. Conclusion

Dry granulation/roller compaction produced irregular granules with higher density than the traditional wet granulation method, the high shear mixer. All the granules had flow properties which enabled compression on a rotary tablet press. The wet processed granules were more compressible and compactable than the roller compacted granules. However, tablets with an acceptable mechanical strength and satisfactory die-filling property in a tablet press were only manufactured for both the granulation methods when the proper morphological form of calcium carbonate and particle size of sorbitol were chosen.

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References

Alderborn, G., 1996. In: Alderborn, G., Nystrom, C. (Eds.), Particle Dimensions, vol. 71. Marcel Dekker, New York, pp. 256–257.

Bacher, C., Olsen, P.M., Berthelsen, P., Kristensen, J., Sonnergaard, J.M., 2007a. Improving the compaction properties of roller compacted calcium carbonate. Int. J. Pharm. 342, 115–123.

Bacher, C., Olsen, P.M., Berthelsen, P., Sonnergaard, J.M., 2007b. Granule fraction inhomogeneity of calcium carbonate/sorbitol in roller compacted granules. Int. J. Pharm. 349, 19–23.

Carr, R.L., 1965. Evaluating flow properties of solids. Chem. Eng. 72, 163–168.

Draper, N.R., Smith, H., 1981. Applied Regression Analysis, 2nd ed. Wiley, New York.

European Pharmacopoeia, 2005. European Pharmacopoeia, 5th ed. Council of Europe, Strasbourg, pp. 241–242.

Freitag, F., Kleinebudde, P., 2003. How do roll compaction/dry granulation affect the tableting behaviour of inorganic materials? Comparison of four magnesium carbonates. Eur. J. Pharm. Sci. 19, 281–289.

Freitag, F., Reincke, K., Runge, J., Grellmann, W., Kleinebudde, P., 2004. How do roll compaction/dry granulation affect the tableting behaviour of inorganic materials? Microhardness of ribbons and mercury porosimetry measurements of tablets. Eur. J. Pharm. Sci. 22, 325–333.

Hald, A., 1957. In: Shewhart, W.A., Wilks, S.S. (Eds.), Comparison of Two Regression Lines. Wiley, New York, pp. 571–573.

Harsaae, E., 1966. In: Harsaae, E. (Ed.), Middeltal af s^2-værdier. Dobbeltbestemmelser. Teknisk forlag, Copenhagen, pp. 102–105.

Inghelbrecht, S., Remon, J.P., 1998. Reducing dust and improving granule and tablet quality in the roller compaction process. Int. J. Pharm. 171,195–206.

Johansen, A., Schæfer, T., 2001. Effect of interactions between powder particle size and binder viscosity on agglomerate growth mechanisms in a high shear mixer. Eur. J. Pharm. Sci. 12, 297–309.

Johansson, B., Alderborn, G., 2001. The effect of shape and porosity on the compression behaviour and tablet forming ability of granular materials formed from microcrystalline cellulose. Eur. J. Pharm. Biopharm. 52, 347–357.

Sheskey, P.J., Hendren, J., 1999. The effects of roll compaction equipment variables, granulation techniques and HPMC polymer level on a controlled-release matrix model drug formulation. Pharm. Technol. 23, 90–106.

Sonnergaard, J.M., 2006. Quantification of the compactibility of pharmaceutical powders. Eur. J. Pharm. Biopharm. 63, 270–277.

Strickland, W.A., Busse, L.W., Higuchi, T., 1956. The physics of tablets compression XI. Determination of porosity of tablet granulations. J. Am. Assoc. Sci. Ed. 45, 482–486.

Walker, E.E., 1923. The properties of powders. Part VI. The compressibility of powders. Trans. Faraday Soc. 19, 73–82.

Wikberg, M., Alderborn, G., 1991. Compression characteristics of granulated materials. IV. The effect of granule porosity on the fragmentation propensity and the compactibility of some granulations. Int. J. Pharm. 69, 239–253.

Zuurman, K., Riepma, K.A., Bolhuis, G.K., Vromans, H., Lerk, C.F., 1994. The relationship between bulk density and compactibility of lactose. Int. J. Pharm. 102, 1–9.