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Investigating the effect of particle size and shape on high speed tableting through radial die-wall pressure monitoring

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ABSTRACT

Investigating particle properties such as shape and size is important in understanding the deformation behavior of powder under compression during tableting. Particle shape and size control the pattern of powder rearrangement and interaction in the die and so the final properties of the compact. The aim of this study was to examine the effect of particle size and shape on compactability. Particle friction and adhesion were investigated through radial die-wall (RDW) pressure monitoring. To fulfill this aim, powders and granules of different sizes and shapes of materials with different compaction behaviors were used. Compaction simulation using the Presster™ with an instrumented die was applied. Small particle size increased residual die-wall pressure (RDP) and maximum die-wall pressure (MDP) ($p < 0.05$) for plastic and viscoelastic materials, respectively, while big particle size had an opposite effect. No effect was found on brittle material, however big particle size showed higher friction for such materials. Regarding morphology, fibrous elongated particles of microcrystalline cellulose had less friction tendency to the die-wall in comparison to rugged surface mannitol particles. RDW pressure monitoring is a useful tool to understand the compactability of particles in respect to size and shape.

1. Introduction

Tablet formation depends on particle rearrangement or densification then interaction between these particles by bonding. Compaction steps (Bogda, 2007) include: particle rearrangement, fragmentation, deformation and finally fusion. Deformation may be elastic e.g. paracetamol (Garr and Rubinstein, 1991), plastic e.g. mannitol (Zhang et al., 2003), brittle e.g. dibasic calcium phosphate dihydrate (Gohel and Jogani, 2005), viscoelastic e.g. microcrystalline cellulose and pregelatinized starch (Doelker, 1993; Van der Voort Maarschalk et al., 1997), or plastic/brittle e.g. spray dried lactose (Ilić et al., 2009). The size of particles plays a role in this interaction regarding the available surface area and bonding propensity. There are international guidelines regarding acceptance of particle size distributions of new drug substances (ICH Q6A, 1999). Particle size was reported to have an influence on the compression process during tableting (McKenna and McCafferty, 1982; Yajima et al., 1996; Patel et al., 2007). For direct compression, usually particle size in the range of 100–200 μm is used (Shekunov et al., 2007). Granulation is often added as unit operation before the compaction step not only to enlarge particle size of the starting material but also to improve the mechanical properties under pressure (Betz et al., 2003; Leuenberger et al., 2009). Particle size is related to deformation behavior like plastic/fragmentation transition (Roberts et al., 1989; Sebhatu and Alderborn, 1999). Patel et al. (2007) showed the dependency of derived mathematical parameters of compressibility from models like Heckel and Kawakita on particle size. Particle size influences the compact final porosity, tensile strength, and dissolution as well (Caraballo et al., 1996; Siepmann et al., 2000; Olsson and Nyström, 2001; Sadeghi et al., 2004). Studies on particle size in literature are mainly directed to the effect of tablet tensile strength and particle bonding (Sheikh-Salem and Fell, 1982; Nokhodchi et al., 1995; Adolfsson et al., 1997; Garekani et al., 2001). Particle shape also plays an important role in the interparticulate as well as particle–die wall interaction (Sun and Grant, 2001). Particle shape would determine the pattern of particle rearrangement in planes and consequently the type of bonding such as interlocking or solid bridges (Karehill et al., 1990). Particle shape and surface roughness could increase friction tendency and adhesion of the particles to the punch or die-wall leading to a well known tableting problem which is sticking (Jones et al., 2003, 2004). Moreover, surface roughness of common excipients such as microcrystalline cellulose, mannitol, lactose and dibasic calcium phosphate dihydrate was reported to influence the mechanical behavior of these excipients (Narayan and Hancock, 2003). It was even found that particle size and shape of powders control the efficiency of lubrication (Vromans and Lerk, 1988).

There is no previous work investigating the effect of particle size and shape on compaction through radial die-wall (RDW) pressure

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Fig. 1. An instrumented die.

monitoring. Using a compaction simulator with an instrumented die, Fig. 1, to match the compaction process in industrial presses is highly beneficial in early product development and scaling up (Abdel-Hamid and Betz, 2011). The aim of this study was to investigate the effect of particle size and shape on compactability of differently deformable powders and granules through monitoring RDW pressure using a compaction simulator.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (MCC) (Avicel® PH101, PH102, FMC Corporation, DE, USA), directly compressible mannitol (Parteck® M200, M300 Merck KGaA, Darmstadt, Germany), calcium hydrogen phosphate dihydrate (CHPD) (Emcompress®, JRS Pharma, Rosenberg, Germany), milled lactose monohydrate (SorboLac® 400, Meggle, Wasserburg, Germany), magnesium stearate (Mg-stearate, supplied by Sandoz AG, Basel, Switzerland), paracetamol (Rhodapap®, Rhodia S.A., France), Kollidon® 30 (Polyvinylpyrrolidone (PVP), BASF, Burgbenheim, Germany).

2.2. Granulation

Granulation was done for size enlargement and for forming many size ranges.

2.2.1. Granulation in fluidized bed granulator

The starting mixture for granulation was composed of paracetamol (64.8%), Avicel® PH101 (27.8%), and Kollidon® 30 (7.4%) as binder. All granulation experiments were carried out in a Glatt GPCG-2 (Glatt, Binzen, Germany) using top spray method. The binder solution (10%, w/w in aqueous solution) was sprayed onto the powder bed using a nozzle assembled with 0.8 mm liquid insert and a 2 mm air cap with controlled atomizing air pressure (0.1 MPa) and a spray rate of 20 g/min. A constant inlet air temperature was chosen at 22 °C. Batch size was 500 g.

2.2.2. Granulation in roller compactor

Dry granulation was done for Parteck® M200, and SorboLac® 400 with a Chilsonator IR220 and a FitzMill LA1 (Fitzpatrick, Belgium), applying a roll pressure of 0.35 MPa, roll speed of 2 rpm, milling speed of 600 rpm, and screen sieve size of 1 mm.

Table 1 summarizes all powders and granules used in this study.

Table 1
List of powders and granules used for compaction.

Material	Deformation behavior
Avicel® PH101, PH102 powders	Viscoelastic
Parteck® M200, M300 powders	Plastic
Emcompress® powder	Brittle
SorboLac® 400 granules	Brittle
Parteck® M200 granules	Plastic
Avicel® PH101/Paracetamol	Viscoelastic/brittle

2.3. Powder/granules characterization

2.3.1. True density

True density of powders was measured by AccuPyc 1330 helium pycnometer (Micrometrics, Norcross, GA, USA). A known weight of the samples was placed into the sample cell. Values were expressed as the mean of five parallel measurements.

2.3.2. Particle-size distribution

2.3.2.1. Powders. The average particle size was determined by laser diffraction with a Malvern Mastersizer X (Malvern Instruments, Worcestershire, UK). The measurements were carried out 3 times for each sample. Obscuration value between 10 and 30% was shown in all measurements. The function "polydisperse" was activated. Mean and median particle size, span, and specific surface area were recorded.

2.3.2.2. Granules. The size distribution was evaluated by the sieve analysis method using a sieve shaker (Vibro, Retsch, Haan, Germany) at level 40 for 25 min with 710, 500, 355, 250, 180, 125, and 90 μm ISO-norm sieves. The fraction remaining on each sieve was determined by weighing.

2.3.3. Morphological studies

Particle morphology was assessed by scanning electron microscopy (SEM) (Nova NanoSem 230, Eindhoven, Netherlands). Samples were mounted on aluminum stubs using double side adhesive carbon tape and sputter coated with gold 20 nm (BalTec MED 020 Coating System, Lichtenstein).

2.4. Powder/granules compaction

Powder compaction was carried out using a mechanical compaction simulator (Presster™, Metropolitan Computing Corp., NJ, USA) simulating the tablet press Korsch PH336 (36 stations). The compaction rolls used were 300 mm in diameter. Accordingly, a flat-faced B-tooling with a diameter of 10 mm was used to make tablets of 250 mg in weight. Powder feed was manually done. All formulations had 1% (w/w) Mg stearate as a lubricant. The machine was set to perform compaction pressures of 50, 150, and 300 MPa at the compaction speeds of 0.5, 1.5 and 2 m/s corresponding to the following dwell times (19, 6.4, and 4.8 ms), respectively. Six tablets were compressed at the same experimental conditions and the mean was calculated. Residual die-wall pressure (RDP), maximum die-wall pressure (MDP), work of compaction (WC), and ejection force (EF) were measured.

The die-wall pressure reaches a maximum value, MDP, just after the upper and lower punches show maximum compression values, and shows a constant residual value, RDP, after upper and lower punch forces become zero. Lubrication ratio (LR) (ratio of lower to upper compression force) and axial to radial stress ratio (SR) (MDP to the average of upper and lower compression pressures) were also calculated.

2.5. Compact characterization

2.5.1. Radial tensile strength (RTS)

Crushing strength of a compact was determined by pressing it diametrically on a Pharmatron tablet tester (model 8D, Dr Schleuniger Pharmatron Inc., Solothurn, Switzerland). Radial tensile strength σ [MPa] was calculated according to the following equation:

$$\sigma = \frac{2F}{\pi dh} \quad (1)$$

where F is the force required to cause failure in tension [N], d is the compact diameter [mm], h is the compact thickness [mm] and π is a constant which equals 3.1416. Compacts dimensions were measured using a micrometer with a precision of 0.01 mm (Mitutoyo, Japan).

2.5.2. Porosity

Compact porosity was calculated from compact apparent density and dimensions according to the following equation:

$$\varepsilon = 1 - \left[\frac{m/\pi r^2 h}{\rho_T}\right] \quad (2)$$

where ε is the in-die porosity, m is the compact mass, r is the compact radius (5 mm), h is the in-die compact height, and ρ_T is the true density of powders/granules.

2.5.3. Elastic recovery (% ER_0)

The % ER_0 for a compact was calculated from "zero pressure thickness" in-die that could be seen from the force vs. thickness plot, and "minimum punch gap" (thickness at maximum compression), features of Presster® software.

$$ER_0(\%) = \frac{T_i - T_m}{T_m} \times 100 \quad (3)$$

where T_i is the compact thickness at zero pressure just before ejection and T_m is the minimum compact thickness at maximum compression force.

2.6. Data interpretation

To study the effect of different compaction variables, runs for granules were generated according to an experimental design using STAVEX® 5.0 (Aicos, Switzerland) applying a vertex-centroid design quadratic, D-optimization mode (Table 2). Compaction pressure (3 levels), speed (3 levels), and granular particle size (6–8 levels) were the factors. RDP, MDP, SR, EF, LR, WC, RTS, and ER_0 were the responses. Least square analysis was applied for the fitted model of optimization. The model was evaluated in terms of statistical significance using analysis of variance (ANOVA) at a level of significance $p < 0.05$.

Table 2
Experimental design generated by STAVEX® 5.0 to study the impact of particle size on radial die-wall pressure and friction tendency.

Run	Compression pressure (MPa)	Compression speed (m/s)	Particle size		
			G1	G2	G3
1	50	0.5	1	2	1
2	50	2	1	2	1
3	50	0.5	2	3	3
4	50	2	2	3	3
5	50	0.5	3	4	4
6	50	0.5	4	4	4
7	50	2	4	5	5
8	50	0.5	5	5	5
9	50	2	5	6	6
10	50	0.5	6	6	6
11	50	2	6	7	7
12	50	1.5	3	7	7
13	150	2	3	1	8
14	150	1.5	4	1	2
15	300	0.5	1	1	2
16	300	2	1	7	2
17	300	0.5	2	2	8
18	300	2	2	2	1
19	300	0.5	3	3	1
20	300	0.5	4	3	3
21	300	2	4	4	3
22	300	0.5	5	4	4
23	300	2	5	5	4
24	300	0.5	6	5	5
25	300	2	6	6	5
26	300	1.5/2/0.5[a]	3	6	6
27	300	0.5/2[b]		7	6
28	300	2/0.5[b]		7	7
29	300	1.5/2[b]		1	7
30	300	0.5			8
31	300	2			8
32	300	1.5			2

G1 granules of mixture (paracetamol (64.82%), Avicel® PH101 (27.78%), Kollidon® 30 (7.4%)). G2 granules of SorboLac® 400, G3 granules of Parteck® M200. Particle size (μm): (1) <90, (2) 90, (3) 125, (4) 180, (5) 250, (6) 355, (7) 500 and (8) 710.
[a] G1/G2/G3.
[b] G2/G3.

3. Results and discussion

3.1. True density and particle size distribution

Table 3 shows the true density, median and mean diameters, as well as the span (particle size distribution), and the specific surface area of the investigated powders. Emcompress showed the highest density while Parteck M300 showed the lowest. MCC PH101 showed the lowest mean particle size (highest surface area) while Parteck M300 showed the largest particle size. However, Emcompress showed the lowest surface area due to the narrowest particle size distribution. MCC PH102 showed almost double the mean particle size of MCC PH101 and a narrower distribution as well. Parteck M300 showed greater particle size than Parteck M200 and wider particle size distribution, too. Particle size distribution was reported to be non critical for tablet porosity (Fichtner et al., 2005), so deeper investigation for size and shape was carried out in our study.

3.2. Particle shape

MCC PH101 and PH102 are elongated fibrous particles with rough surface while Parteck M200 and M300 are almost spherical particles with rug surface, and Emcompress particles show bumpy fibrous surface, Fig. 2. Regarding granules, MCC PH101/Paracetamol granules were fibrous in shape, while Parteck M200 and SorboLac 400 granules were irregular in shape; however, SorboLac 400 granules had a smooth surface compared to the rug surface of Parteck M200 granules, Fig. 3. Corrugated or rough particles have more surface area than smooth particles that occupy the same volume. This contributes to higher ability of bonding with other particles or to the die-wall. Surface roughness could lead to increased tendency of friction and sticking (Pesonen and Paronen, 1990; Nyström et al., 1993). Irregular particle shape and surface roughness help in powder interlocking and hence ease of bonding (Karehill et al., 1990). Fibrous materials have higher surface area and so more potential bonding points (Gustafsson et al., 1999). For plastically deforming materials, a large surface area and surface roughness generally give a greater bonding surface area and hence stronger compacts (Alderborn and Nyström, 1982).

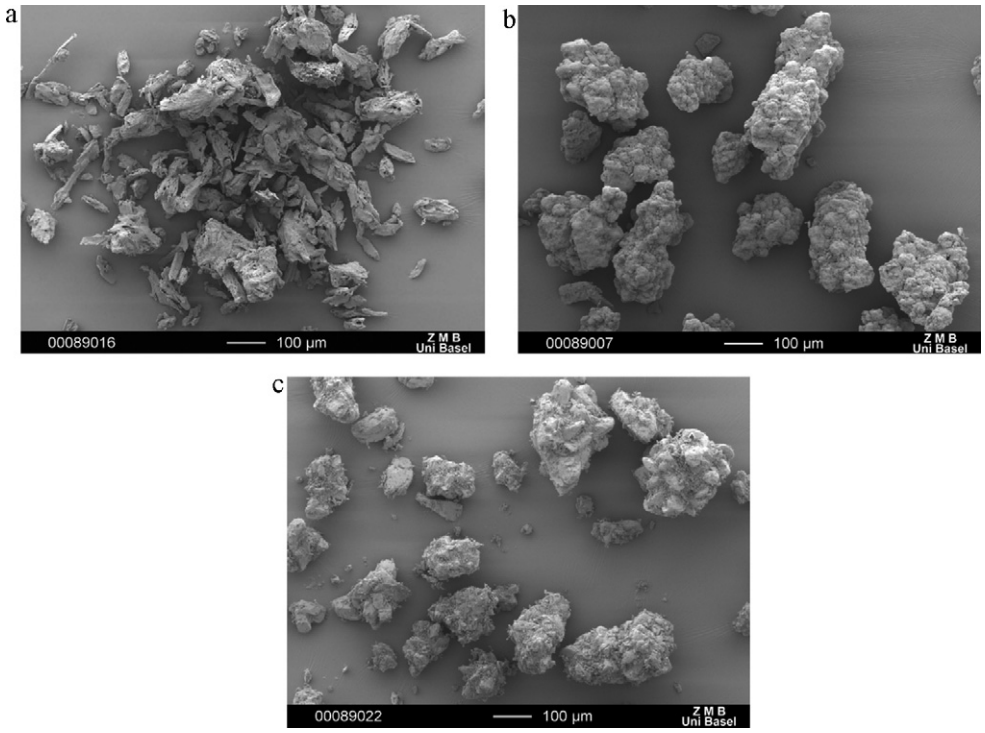

Fig. 2. SEM pictures of the particles of (a) MCC PH101, (b) Parteck M200 and (c) Emcompress.

3.3. *Effect of particle size and shape on radial die-wall pressure*

3.3.1. *Powders*

By increasing compaction pressure, there was no difference between the powders of MCC PH101 and PH102 regarding the effect of particle size on RDP and MDP, the same result was found also for Parteck M200 and M300 (Figs. 4 and 5). This is in accordance with what was reported that there was no difference in compressibility for two particle sizes of MCC (Patel et al., 1994).

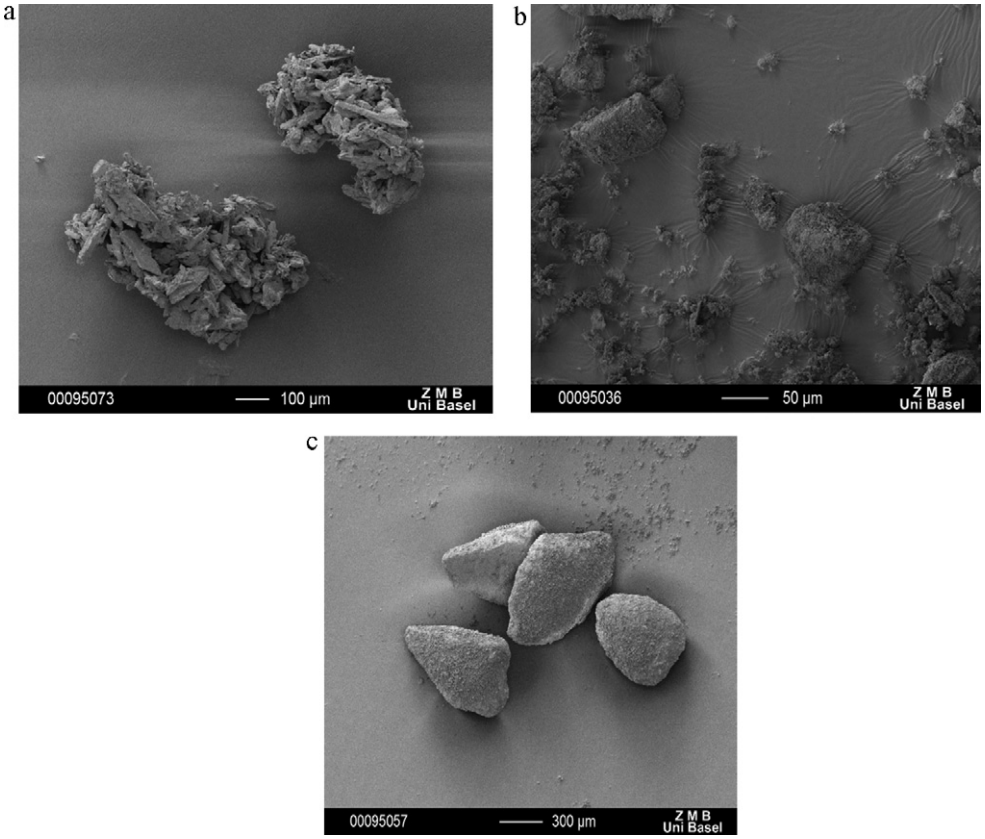

Fig. 3. SEM pictures of the granules of (a) MCC PH101/Paracetamol, (b) Parteck M200 and (c) SorboLac 400.

Table 3
Median, and mean diameters, span, specific surface area and true density of the investigated powders.

Powder	Median [μm] ± SD	Mean [μm] ± SD	Span[a] ± SD	Specific surface area [m^2/g] ± SD	True density [g/cm^3] ± SD
MCC PH101	44.37 ± 0.63	64.60 ± 2.31	2.87 ± 0.14	0.14 ± 0.00	1.44 ± 0.00
MCC PH102	124.63 ± 0.93	136.57 ± 0.94	1.68 ± 0.00	0.045 ± 0.00	1.59 ± 0.00
Parteck M200	131.15 ± 1.99	149.22 ± 2.55	1.73 ± 0.02	0.042 ± 0.00	1.52 ± 0.00
Parteck M300	179.04 ± 5.38	248.70 ± 5.49	2.24 ± 0.06	0.05 ± 0.00	1.39 ± 0.00
Emcompress	181.71 ± 3.02	188.02 ± 2.90	0.86 ± 0.01	0.0145 ± 0.00	2.48 ± 0.00

[a] Span is the measurement of the width of the distribution. The smaller the value, the narrower is the distribution. The width is calculated as: $d(0.9) - d(0.1)/d(0.5)$.

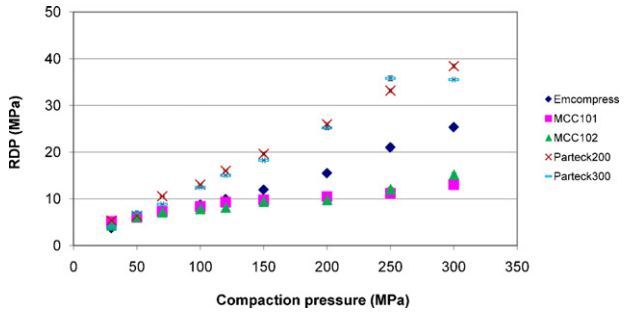

Fig. 4. Effect of powders with different mean particle sizes on residual die-wall pressure (RDP) by increasing compaction pressure.

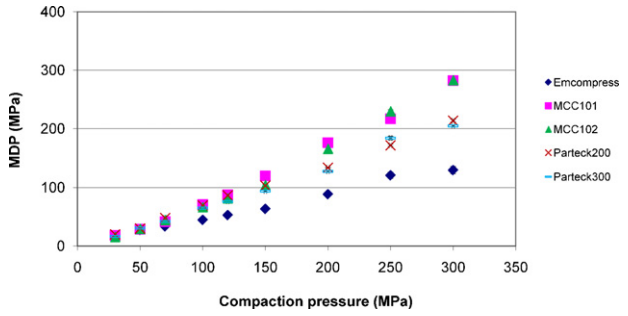

Fig. 5. Effect of powders with different mean particle sizes on maximum die-wall pressure (MDP) by increasing compaction pressure.

However, Parteck (mannitol) showed higher RDP values than MCC ($p < 0.05$), while Emcompress had values in between. This was due to the higher axial ER_0 for MCC, Fig. 6. Regarding MDP, there was no significant difference between powders until 150 MPa but by increasing compression pressure further, MCC showed higher values emphasizing their superiority in plasticity. Regarding shape, Parteck particles showed more surface rugosity than those of Avicel. This resulted in higher radial stress transmission, hence higher RDP values for Parteck and higher friction tendency. The elongated MCC particles aligned themselves parallel to the punch face, forming a layered structure that exhibited low radial stress and a higher axial one (i.e. higher elastic recovery).

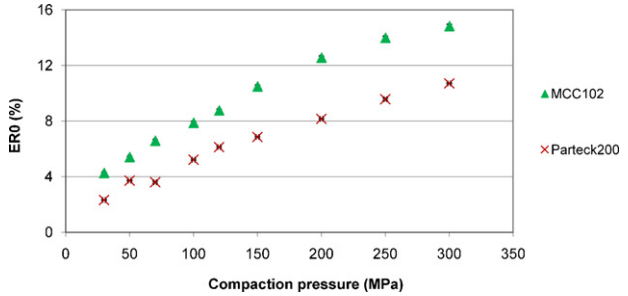

Fig. 6. Elastic recovery in-die (ER_0) for MCC PH102 and Parteck M200.

3.3.2. Granules

Regarding models' diagnostics, the fit for all models for the different responses was very good (0.9920–0.9999). There was no evidence for non-normality of model deviations (except for EF and ER_0, there was a weak evidence for non-normality of model deviations; for RDP and MDP in case of Parteck M200 granules, there was a strong evidence for non-normality of model deviations for the former and weak evidence for the latter). Means were independent on factor level.

3.3.2.1. Effect of size and shape on RDP and EF. Regarding granules, by increasing compression pressure, Parteck M200 granules less than 125 μm showed an increase in RDP while larger granules showed a decrease in RDP ($p < 0.05$), Fig. 7. This was further confirmed by high EF for the small granules and low EF for the large granules ($p < 0.0001$). This could be attributed to the higher interaction of small granules with the die-wall. It was also reported that larger particles exhibited higher degree of densification (Vromans et al., 1987; Patel et al., 2007), hence less particle–die interaction or friction. Small particles have higher tendency for friction, which results in higher capability of bonding due to surface activation (Hüttenrauch et al., 1985). On the other hand, MCC PH101/Paracetamol granules showed a decrease in RDP at high compaction pressure for granules below 125 μm, while larger granules showed an increase in RDP ($p < 0.05$). This effect was confirmed by lower friction (low EF and high LR) for small granules; and higher friction (high EF and low LR) for large granules ($p < 0.005$). This result could be explained by the presence of paracetamol as a major component in these granules, where for smaller granules; the effect of plastic MCC was more dominant over the elasticity of paracetamol, while in case of larger granules, the effect of paracetamol was more dominant due to high elastic recovery at high compression pressure. This is in accordance with Patel et al. (2007), who reported that large particles of paracetamol deformed mainly elastically while smaller particles deformed rather plastically. It was also reported that a change in particle size resulted in a different material deformation behavior (Alderborn et al., 1988). Particle size of SorboLac 400 granules did not have any effect on RDP. This is due to fragmentation behavior of lactose (Duberg and Nyström,

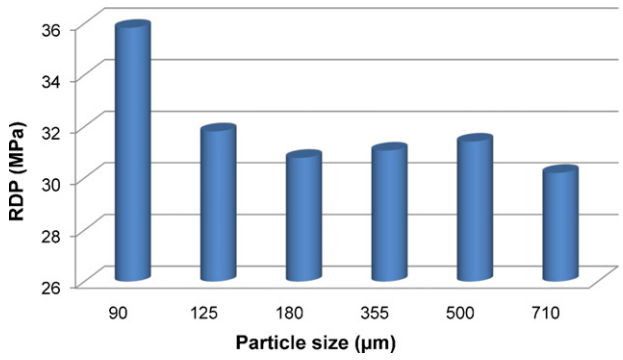

Fig. 7. Effect of particle size of Parteck M200 granules on residual die-wall pressure (RDP) at high compression pressure (300 MPa) and speed (2 m/s) (RSE = 0.4).

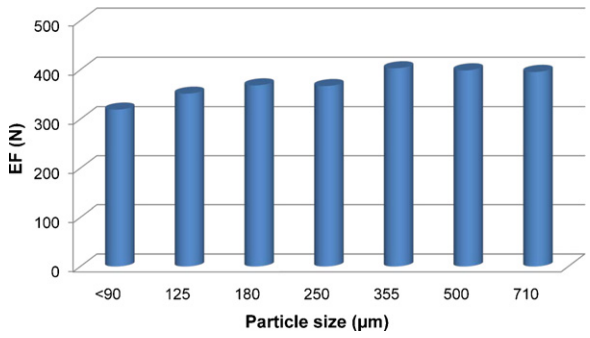

Fig. 8. Effect of particle size of SorboLac 400 granules on ejection force (EF) at high compression pressure (300 MPa) and speed (2 m/s) (RSE = 3.06).

1982; Riepma et al., 1991) where new contact points are continuously created by increasing compression, which leads to failure in bonding. Also, as shown previously lactose granules showed a smooth surface. Adolfsson et al. (1997) reported that particle size had no effect on the bonding structure of lactose. Materials deforming by fragmentation show less ER_0 due to formation of numerous contact points between particles (Nyström et al., 1993). However, granules of SorboLac 400 less than 180 μm, showed low EF, while larger granules showed high EF ($p < 0.002$), Fig. 8. This could be attributed to the decreased fragmentation propensity by increasing the particle size of lactose and due to the increase of irregularity by increasing particle size. This would lead to more friction for the large granules with the die-wall on ejection. This is in accordance with what was reported by Shotton and Obiorah (1975), Alderborn et al. (1985) and De Boer et al. (1986).

3.3.2.2. Effect of size and shape on MDP and SR. Small granules behave more plastic (Sun and Grant, 2001). That is why granules less than 125 μm of MCC PH101/Paracetamol, showed higher MDP ($p < 0.03$), Fig. 9. This could be also attributed to the dominant effect of MCC PH101 in case of small granules while in case of large granules; the effect of fragmenting paracetamol was more prominent. There was no difference between small and large granules of Parteck M200 and SorboLac 400 on MDP. However, the axial pressure transmission through granular bed SR was higher for granules less than 125 and 250 μm for Parteck M200 and SorboLac 400, respectively, than larger granules ($p < 0.03$). This result could be explained by the smaller void volume and close particle packing in case of small particles while in case of larger particles, some of the compression force is spent in particle rearrangement and packing. On the other hand regarding Parteck M200 granules, speed reduced SR for granules less than 355 μm ($p < 0.05$). Larger granules had better densification as mentioned before so the reduced dwell time was less influential on large than for smaller granules.

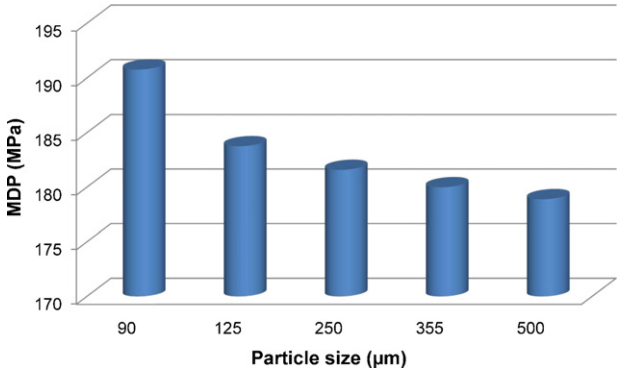

Fig. 9. Effect of particle size of MCC PH101/Paracetamol granules on maximum die-wall pressure (MDP) at high compression pressure (300 MPa) and speed (2 m/s) (RSE = 1.13).

3.4. Effect of particle size and shape on ER_0, WC, RTS and porosity

In our study, granule particle size had no effect on ER_0, although the literature was contradictory regarding this point where Patel et al. (2007) reported that higher elastic recovery was observed for large than for small particle size; however, Garekani et al. (2001) reported an opposite result.

Regarding the effect of particle size on WC, granules less than 180 and 125 μm for MCC PH101/Paracetamol and SorboLac 400, respectively, showed higher WC than larger granules ($p < 0.03$), which indicates more plastic behavior as mentioned before. This is attributed to the increased interparticulate interaction due to the numerous contact points per unit area for smaller particles. Similar results were reported by Garekani et al. (2001).

By increasing compaction pressure, granules less than 355 μm were more porous than large ones ($p < 0.005$), for MCC PH101/Paracetamol and SorboLac 400.This could be explained by the higher degree of densification for larger particles and the higher interparticulate friction between small particles which hinders densification (York, 1978; Roberts and Rowe, 1986). Moreover, larger particles undergo continuous fragmentation by increasing pressure so the smaller particles produced fill the voids (De Boer et al., 1986; Narayan and Hancock, 2003). Regarding RTS, granules less than 125 μm of MCC PH101/Paracetamol formed stronger tablets ($p < 0.05$). This effect was reported previously where the van der Waal's forces increase when particle size decreases (Vromans et al., 1985; Van der Watt, 1987; Adolfsson et al., 1997). This is due to the intimate contact as well as the friction and interaction between small granules, which make them more ready for bond formation. This effect was only prominent in MCC PH101/Paracetamol granules due to the rough irregular surface, which helped bonding (Sun and Grant, 2001).

4. Conclusion

Particle size and shape could completely change the compaction behavior of materials, which would finally affect the physical characters of the final compact. Particle size and shape play a crucial role in powder densification, cohesion and adhesion during compaction. Small/irregular particles acted more plastically at high compression pressure and speed, showed better axial pressure transmission, more porous and stronger compacts, and had higher tendency for friction and sticking. The application of RDW pressure monitoring was very useful to understand these phenomena and was well correlated with other compaction parameters, such as RDP was well correlated to EF and MDP to SR.

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