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A compressibility and compactibility study of real tableting mixtures: The impact of wet and dry granulation versus a direct tableting mixture

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ABSTRACT

The purpose of this study was to investigate the influence of various powder agglomeration processes on tableting mixture flow and compaction properties. Four different granulation methods of the same model placebo formulation were tested at a semi-industrial scale and their properties were compared to those of the directly compressed mixture. The wet granulated mixtures had superior flow properties compared to other mixtures and showed better compressibility, measured by the Heckel and Walker models. This was attributed to work hardening due to the double particle processing and also to shorter contact times due to higher initial densities of dry granulated mixtures, allowing a shorter time for deformation. A strong linear correlation was established between the Heckel and Walker coefficients, which was further confirmed by the net energy results of force–displacement measurements. It was shown that the Walker model had slightly better discriminative power to differentiate tableting mixtures according to compressibility. The compactibility was considerably lower for the slugged mixture; however, the roller-compacted mixture produced tablets with unexpectedly high tensile strength. In conclusion, it is important to emphasize that general assumptions like higher porosity ⇒ better compressibility or better compressibility ⇒ better compactibility cannot be established for complex tableting mixtures.

1. Introduction

Successful compaction and tableting of pharmaceutical powders requires a profound understanding of the fundamental properties of powders. These include physicochemical and mechanical properties, both of which dictate how formulations behave during tablet processing.

In the pharmaceutical industry, the preferred tablet production method is direct tableting. However, it is often necessary to improve the material's compaction and flow properties in order to obtain uniform die-filling and to produce tablets of adequate quality. These properties are commonly enhanced by converting fine powders into larger agglomerates by the process of wet or dry granulation. Wet granulation is traditionally used; this process consists of distributing the liquid binder in a powder blend followed by drying the agglomerates produced. This can be achieved using high-shear or fluid-bed technology. Alternatively, dry granulation (i.e., slugging or roller compaction) can be used to produce agglomerates. Dry granulation consists of a compaction step followed by a milling step. During slugging, the primary compaction step is performed using a conventional tablet press, whereas during roller compaction the powder mixture is passed between two rotating cylindrical rollers to form a compact ribbon that is further broken down into a product of granular size and then recompressed (Armstrong, 2007). Dry granulation has some advantages and disadvantages compared to wet granulation. It is a fairly simple technique, which should be more cost effective and can greatly improve the bulk density of voluminous materials. Dry granulation does not require water or organic solvents, thus making it an attractive method for moisture- and heat-sensitive drugs (Kleinebudde, 2004). However, it produces a relatively large amount of dust and fines (Herting and Kleinebudde, 2007; Inghelbrecht and Remon, 1998; Kleinebudde, 2004) and impairs the compaction properties of powders (Bacher et al., 2007; Freitag et al., 2004; Herting and Kleinebudde, 2007).

The compaction properties of pharmaceutical powders are characterized by their compressibility and compactibility. Compressibility is the powder's ability to deform under pressure, and compactibility is the ability to form mechanically strong compacts (Leuenberger, 1982; Sonnergaard, 2006). Three stages of this process can be distinguished during powder compaction: (i) rearrangement and powder densification due to increasing pressure; (ii) fragmentation of agglomerates; and (iii) fragmentation and deformation (both reversible elastic and irreversible plastic) of pri-

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mary particles with bond formation on contact surfaces (Duberg and Nyström, 1986). Compressibility is most often described by the change in the relationship between relative density, porosity, or volume and applied pressure represented by the Heckel (1961) and Walker (1923) models (Duberg and Nyström, 1986; Ilkka and Paronen, 1993; Paronen and Ilkka, 1996; Zupančič et al., 2008). In recent years the Walker model has received more attention in the study of pharmaceutical powder compressibility (Bacher et al., 2008; Ilić et al., 2009; Sonnergaard, 2000, 2006; Sovány et al., 2009).

Compactibility, on the other hand, can also be quantified in several different ways; most often it is expressed as the slope of the linear region of the tensile strength versus compression pressure (compactibility profile). The tensile strength of tablets defining powder compactibility can in some cases be correlated with the values K and w' of the Heckel and the Walker plot. Some studies have shown a relationship between the compressibility and compactibility of powders. Namely, well-compressible powders with high K or w' values are likely to generate many new contact points between the particles, which can lead to greater hardness and tensile strength of the compact (Sonnergaard, 2006).

There are many studies on the compression behavior of individual excipients and simple binary mixtures (Fichtner et al., 2007; Paronen, 1986; Patel et al., 2007, 2010; Roberts and Rowe, 1987; Sonnergaard, 1999, 2000; Yap et al., 2008) and the influence of preparation processes such as granulation on their compaction (Bacher et al., 2007, 2008; Freitag and Kleinebudde, 2003; Horisawa et al., 2000). According to the studies (Bacher et al., 2008) wet processed granules showed in general better compression properties. However, only a few published studies deal with the compression of complex but realistic mixtures that are produced for the market (Inghelbrecht and Remon, 1998; Zupančič et al., 2008). Especially interesting is the compression behavior of the same formulation produced using different technological procedures, such as wet and dry granulation or direct tableting on the production scale.

The purpose of this study was to investigate the effect of dry and wet granulation on particle size distribution and flow properties of the granules produced. It further aimed to evaluate compressibility and compactibility of dry granulated, wet granulated, and directly compressible mixtures and to compare the results. This was achieved using the Heckel and Walker models and analysis of compression energies in force–displacement curves; the results were compared. The quality of tablets produced was investigated with respect to friability and disintegration time in order to discover what the behavior of complex realistic mixtures used in tablet production is. Therefore, the same model placebo mixture was used throughout the study, either as a directly compressible mixture or by processing the powders using wet (high-shear and fluid-bed) or dry (roller compaction and slugging) granulation procedures.

2. Materials and methods

2.1. Materials

The model placebo mixture consisted of lactose monohydrate (filler, Pharmatose DCL15, DMV International GmbH), 65.42% (w/w); microcrystalline cellulose (filler/dry binder, MCC, Avicel PH 102, FMC International), 25.01% (w/w); sodium starch glycolate (disintegrating agent, Primojel, DMV International GmbH), 5.18% (w/w); polyvinylpyrrolidone (binder, Povidone K25, BASF SE), 3.31% (w/w); colloidal silica (lubricant, Aerosil 200, Evonik degussa GmbH), 0.36% (w/w); and magnesium stearate (antiadhesive agent, FACI SPA), 0.72% (w/w).

2.2. Preparation of tableting mixtures

Tableting mixtures were prepared according to the procedures enumerated and described below. Before preparation of the mixture, all materials were sieved manually through a sieve with a mesh size of 0.8 mm. The weighted amounts of powders were the same for all mixtures: lactose monohydrate (7.32 kg), microcrystalline cellulose (2.80 kg), Povidone K25 (370 g), and Primojel (580 g).

2.2.1. High-shear granulation (HSG)

Weighted powders were mixed with a high-shear mixer (Collette Ultima Gral TM 75, Collette, Wommelgem, Belgium) for 2 min at an impeller speed of 200 rpm. Purified water was sprayed with a spray rate of 0.7 kg/min at a constant impeller speed of 200 rpm until the motor power reached 1.1 kW. The total amount of granulation liquid used was 5.0 kg and the total spraying time was 410 s. After spraying, the granulate was kneaded for 120 s at an impeller speed of 305 rpm, without the chopper activated, until the motor power reached 2.3 kW. Wet granules were transferred to the fluid-bed dryer (Aeromatic TSG 2, GEA Aeromatic, Bubendorf, Switzerland) and dried at an inlet air T = 70–80 °C and air flow of 500 m^3/h. Drying lasted for 56 min until the exhaust air reached T = 41.5 °C. Dried granules were sieved (Quadro Comil U 10, Quadro Engineering, Waterloo, Ontario, Canada) using a sieve with a mesh size of 1.0 mm. The granules obtained were mixed with Aerosil 200 (37.2 g) in a 50 L biconical mixer (Iskra Pio, Šentjernej, Slovenia) at 20 rpm for 10 min. After the addition of Aerosil 200, magnesium stearate (74.4 g) was added and mixing was continued for 2 min at 10 rpm.

2.2.2. Fluid-bed granulation (FBG)

Weighted powders without Povidone were mixed in a fluid-bed granulator (Aeromatic TSG, 2 GEA Aeromatic, Bubendorf, Switzerland) at an inlet air T = 70 °C and air flow of 200 m^3/h. Mixing lasted 37 min until the exhaust air reached T = 37 °C. Then 5.37 kg of 6.89% (w/w) aqueous solution of Povidone K25 was sprayed at an inlet air T = 60 °C and the air flow was increased from a starting value of 250 m^3/h to 450 m^3/h by the end of the spray phase. The atomizing air pressure was 1.5 bar. Spraying of the granulation liquid lasted 14 min until the exhaust air reached T = 25.1 °C. Drying was performed for 52 min at an inlet air T = 60 °C; the air flow was decreased from a starting value of 450 m^3/h to 250 m^3/h at the end of drying phase, until an exhaust air T = 39.3 °C was reached. Dried granules were sieved and lubricated according to the procedure described in Section 2.2.1.

2.2.3. Dry granulation by roller compactor (DGRC)

Weighted powders were mixed in a 50 L biconical mixer (Iskra Pio, Šentjernej, Slovenia) at 20 rpm for 10 min. The powder mixture was compacted with a roller compactor (Chilsomator IR 220, Fitzpatrick, USA) using rolls 2 cm wide ($2R$ = 20 cm) using the following set parameters: roll pressure 20 bar, roll force 4.2 kN/cm, roll speed 4.0 rpm, gap width 1.8 mm, vertical precompression screw (VPS) speed 250 rpm, and horizontal feeding screw speed 21 rpm. The ribbons were crushed using an oscillating sieve with a 1.0 mm mesh size (Fitzmill L1A, Fitzpatrick, USA) at a mill speed of 1200 rpm. The obtained granules were sieved and lubricated according to the procedure described in Section 2.2.1.

2.2.4. Dry granulation by slugging (DGS)

Weighted powders with added Aerosil 200 (40 g) were mixed in a 50 L biconical mixer (Iskra Pio, Šentjernej, Slovenia) at 20 rpm for 10 min. Then magnesium stearate (80 g) was added and additional mixing was performed at 10 rpm for 2 min. Slugging was performed on a rotary tableting machine (Kilian T300/Vicon,

IMA, Köln, Germany) using round concave punches (⌀ = 13 mm, R = 26 mm) and the following set parameters: main compression force 11.5 kN and precompression force 1.3 kN. The tableting speed was 200,000 tbl/h. The slugs were crushed in a mill (Frewitt, Frewitt FMSA, Granges-Paccot, Switzerland) with a 1.0 mm sieve opening. The resulting granules were homogenized in the 50 L biconical mixer (Iskra Pio, Šentjernej, Slovenia) at 10 rpm for 2 min.

2.2.5. Mixture for direct tableting (DC)

Weighted powders with added Aerosil 200 (40 g) were mixed in the 50 L biconical mixer (Iskra Pio, Šentjernej, Slovenia) at 20 rpm for 10 min. Magnesium stearate (80 g) was then added and additional mixing at 10 rpm for 2 min was performed.

2.3. Characterization of tableting mixtures and tablets

2.3.1. Loss on drying

The loss on drying (%) of tableting mixtures (approx. 10 g sample; 85 °C; 20 min) was determined in triplicate using a Mettler HR73 halogen dryer (Mettler Toledo, Greifensee, Switzerland).

2.3.2. Particle size distribution

The particle size distribution for all mixtures (20 g sample) was determined in triplicate with an oscillating sieve analyzer (Alpine 200 LS-N, Hosokawa, Augsburg, Germany) using the following sieves: 0.071, 0.125, 0.250, 0.500, 0.710, and 1.25 mm. The sieving lasted for 3 min at 1300 Pa. Results are represented as particle size distribution and also as the particle size at which 50% (w/w) of particles are below the given size denoted as median particle diameter, or d_{50}.

2.3.3. True density of tableting mixtures

The true density of mixtures was determined in triplicate with a helium pycnometer (AccuPyc 1330, Micromeritics, Norcross, GA, USA) according to Ph. Eur. 6th Ed. (2.9.23. Gas pycnometric density of solids).

2.3.4. Bulk and tapped density of tableting mixtures

The bulk and tapped densities were determined in triplicate according to Ph. Eur. 6th Ed. (2.9.34. Bulk density and tapped density of powders, method 1) using a Stampfvolumeter STAV 2003 apparatus (J. Engelsmann AG, Ludwigshafen, Germany).

2.3.5. Flow properties of tableting mixtures

The tableting mixtures' flow properties were determined by measuring the angle of repose and the flow time according to Ph. Eur. 6th Ed. (2.9.16. Flowability and 2.9.36. Powder flow) using a flowability tester (Pharma PTG-S3, Pharma Test Apparatebau GmbH, Hainburg, Germany). In addition, flow properties were also determined using the Carr index and Hausner ratio according to Ph. Eur. 6th Ed. (2.9.36. Powder flow).

2.3.6. Tablet friability

Tablet friability (%) was determined according to Ph. Eur. 6th Ed. (2.9.7. Friability of uncoated tablets) using a friability apparatus (Erweka TAR200, Erweka, Heusenstamm, Germany).

2.3.7. Tablet disintegration

Tablet disintegration time was measured according to Ph. Eur. 6th Ed. (2.9.1. Disintegration of tablets and capsules) with a disintegration tester (Erweka ZT 72, Erweka, Heusenstamm, Germany). Disintegration time was determined for each type of tablet produced at each compression pressure.

2.4. Compressibility

The compressibility of mixtures was determined using the Heckel (Eq. (1); Heckel, 1961) and modified Walker (Eq. (2); Walker, 1923; Sonnergaard, 2006) compressibility models.

The Heckel model (Eq. (1)) is based on the assumption that the process of pore reduction during compression follows first-order kinetics:

$$-\ln\ \varepsilon = \ln\left(\frac{1}{1-D}\right) = K\,P + A \tag{1}$$

where D is the relative density of the compact, P is applied pressure, K (slope; Heckel coefficient) and A (y-intercept) are regression coefficients of the linear portion of the curve, and ε is porosity. Yield pressure (P_y), which is the reciprocal value of the slope (K) of the Heckel plot, is a measurement of the material's compressibility.

The Walker equation plots the specific volume of the powder compact against the logarithm of the axial pressure applied (Eq. (2)):

$$V' = w'\ \log\ P + V'_{sp} \tag{2}$$

where V' is the specific volume of a tablet and w' is the Walker coefficient expressing the volume reduction corresponding to one decade change in pressure P obtained by linear regression analysis, and V'_{sp} is the specific volume at pressure 1.

Each mixture was compressed at five different compression pressures (P: 50, 100, 150, 200, and 250 MPa) using an instrumented single-punch tablet press (Kilian SP300, IMA, Cologne, Germany) with round flat-faced punches (⌀ = 12 mm). Compression force was measured by strain gauges (full Wheatstone bridge) at lower and upper punch, which were coupled with linear displacement transducer mounted at upper punch. The raw data were transmitted on separate channels by individual amplifiers and recorded using 20-bit AD converter. Data was acquired at frequency of 2400 Hz using MS2000 (Kilian, IMA, Cologne, Germany) software. Forced-filling shoe was used to transfer the mixture from the hopper to the die with a carrousel speed of 100–150 rpm. The target tablet mass was 600 mg and the compression speed was 30 tbl/min. Tableting was performed at $T = 20 \pm 2$ °C and RH = 35 ± 5%. At each compression pressure 24 tablets were evaluated 24 h after compression. Compressibility was determined using the "out-of-die" Heckel (Eq. (1)) and Walker (Eq. (2)) models. The apparent density of the tablets was calculated from the volume and mass of tablets. Tablet thickness and diameter were measured using a slide caliper (MIB Messzeuge GmbH, Spangenberg, Germany) and mass was determined using an analytical balance AG245 (Mettler Toledo, Greifensee, Switzerland).

The Heckel (K) and Walker (w') coefficients (slopes) were estimated using a linear regression in which each point represents one tablet. The Heckel and Walker coefficients, standard errors (SEs), and two-sided 95% confidence interval (CI) of the slopes were calculated using Microsoft Office Excel 2007. The statistical significance between the slopes was calculated by means of the t-test using an OpenEpi (Dean et al., 2008) statistical calculator (two-independent samples t-test with either equal or unequal variance, depending on Hartley's test for equality of variance) such as that used in previous studies (Sonnergaard, 2006; Ilić et al., 2009).

2.5. Compression energies

Compression and decompression energies are based on a force–displacement diagram of the upper punch. The area under the decompression curve represents the reversible energy that is returned in the decompression stage and is related to the energy of the elastic relaxation of the material. The hysteresis between the compression (W_{in}) and decompression (W_{out}) energy repre-

sents irreversible energy (W_{net} = net energy, sometimes also termed effective work), which is not returned in the decompression stage. This energy can be related to processes that affect the compressibility of the material such as plastic deformation or fragmentation (Antikainen and Yliruusi, 2003; Horisawa et al., 2000; Ragnarsson, 1996). Specific net energy is reported as net energy divided by the average mass of a tablet (W_{net} in J/g).

2.6. Compactibility

The tablet crushing force (H) was evaluated using a hardness tester VK200 (Varian, USA). The radial tensile strength (σ_t) was calculated using Eq. (3) (Fell and Newton, 1970):

$$\sigma_t = \frac{2H}{\Pi dh} \quad (3)$$

where H is the tablet crushing force (N), d is the tablet diameter, and h is the tablet thickness. The compactibility slopes were estimated using the linear regression from the plot of tablet radial tensile strength versus compression pressure (MPa), in which each point represents one tablet. The SE, 95% CI, and statistical testing were performed as described in Section 2.4.

3. Results and discussion

Compressibility and compactibility studies were performed on tableting mixtures produced on a semi-industrial scale, which elucidates the reason for choosing excipients and production methods commonly used in the pharmaceutical industry, in order to thereby shorten the development of full-scale formulations. Although numerous data can be found on the compaction of lactose, MCC, and starch, very little is still known about the complexity of realistic mixtures' behavior during tableting. This is the reason for selecting excipients currently in common use in industrial tablet formulation development and production. The knowledge currently available in the scientific literature on the impact of pretreating the powder mixtures for compression was found to be insufficient, which was the main driving force behind our work. In our study, mixtures of the same composition were processed by means of four different technological methods that allowed examination of the impact of various granulation methods on the compressibility and compactibility of tableting mixtures and the characteristics of the tablets produced.

3.1. Characterization of mixtures

Tableting mixtures were processed into granules using either two different wet granulation processes: fluid-bed granulation (FBG) and high-shear granulation (HSG), or two different dry granulation processes: roller compaction (DGRC) and slugging (DGS). The tableting mixture was also directly compressed (DC) into tablets for comparison. The most important properties of all mixtures were extensively characterized.

3.1.1. Loss on drying

It is known that the moisture content in granules or powders can influence the hardness and therefore compactibility of the tablets produced (Badawy et al., 2000; Sebhatu et al., 1997; Sun, 2008). Therefore, all tableting mixtures produced were dried to an approximately equal moisture level. It was established that the loss on drying (LOD) values of the tableting mixtures produced were the following: HSG 1.74%, FBG 1.70%, DGRC 1.48%, DGS 1.62%, and DC 1.43%. All LOD values are within the range of 1.43–1.74% and may be considered comparable or approximately equal because it is known that moisture content is difficult to control during drying processes of pharmaceutical materials, especially when drying wet granules in narrow ranges such as ±0.1%. Similar batch-to-batch variability in LOD values are commonly observed for regular pharmaceutical intermediate products such as granulates and tableting mixtures.

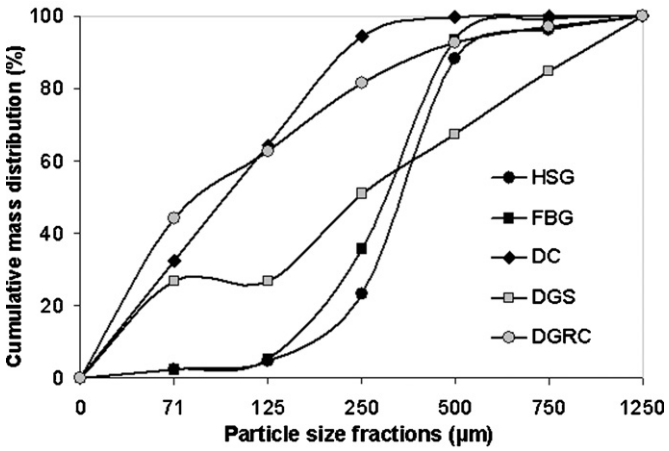

Fig. 1. Cumulative mass particle size distribution of compression mixtures studied. Tableting mixtures were prepared using different granulation methods: FBG = fluid-bed granulation, HSG = high-shear granulation, DGRC = roller compaction, DGS = slugging, DC = direct compression.

3.1.2. Particle size distribution

Processing particles with different agglomeration methods results in particles of different size and particle size distribution. Because the particle size can affect the compaction process, it is useful to evaluate these parameters. The results of the sieve analysis are shown in Fig. 1. When considering particle size distribution it is difficult to compare mixtures because this can only be done in a descriptive way. Thus, in order to compare the mixtures, a numerical particle size is given as the median particle diameter d_{50}. The HSG mixture has the largest particles, of approximately 353 μm, followed closely by particles of the FBG mixture at 314 μm and the DGS mixture at 245 μm. The particles of the DC and DGRC mixtures were considerably smaller, with d_{50} values of around 101 μm and 88 μm, respectively. It should also be noted that the DGRC and DGS mixtures have a wider size distribution than other mixtures. The DGS mixture has a bimodal distribution with one mode representing fines smaller than 71 μm and the other larger particles in the size range of 125–1250 μm (Fig. 2).

The larger particle size of agglomerates compared with the DC mixture is expected due to the granulation process, except for the d_{50} of DGRC, in which the particle size after roller compaction is smaller than the particle size of the input powders, which could be attributed to a suboptimal compaction procedure. This is also demonstrated by the higher percentage of fines (particles smaller than 71 μm) in DGRC compared to the DC mixture. A high fraction of fine particles is typically observed during roll compaction (Herting and Kleinebudde, 2007; Inghelbrecht and Remon, 1998). In our case this can be attributed to the fragmentation of lactose, which is the predominant component in the mixture. The lactose used in our study was an agglomerated type of lactose intended for direct compression. During roller compaction, fragmentation of brittle materials may occur at earlier stages and the fines produced are bonded together at higher roll pressure in a later stage of compaction to form agglomerates that are larger than the original particles. If the roller compaction conditions are suboptimal (i.e., too little roll pressure), partial fragmentation may occur without bonding in later stages, especially when brittle agglomerates of a material with a known tendency to fragment, such as lactose, are concerned.

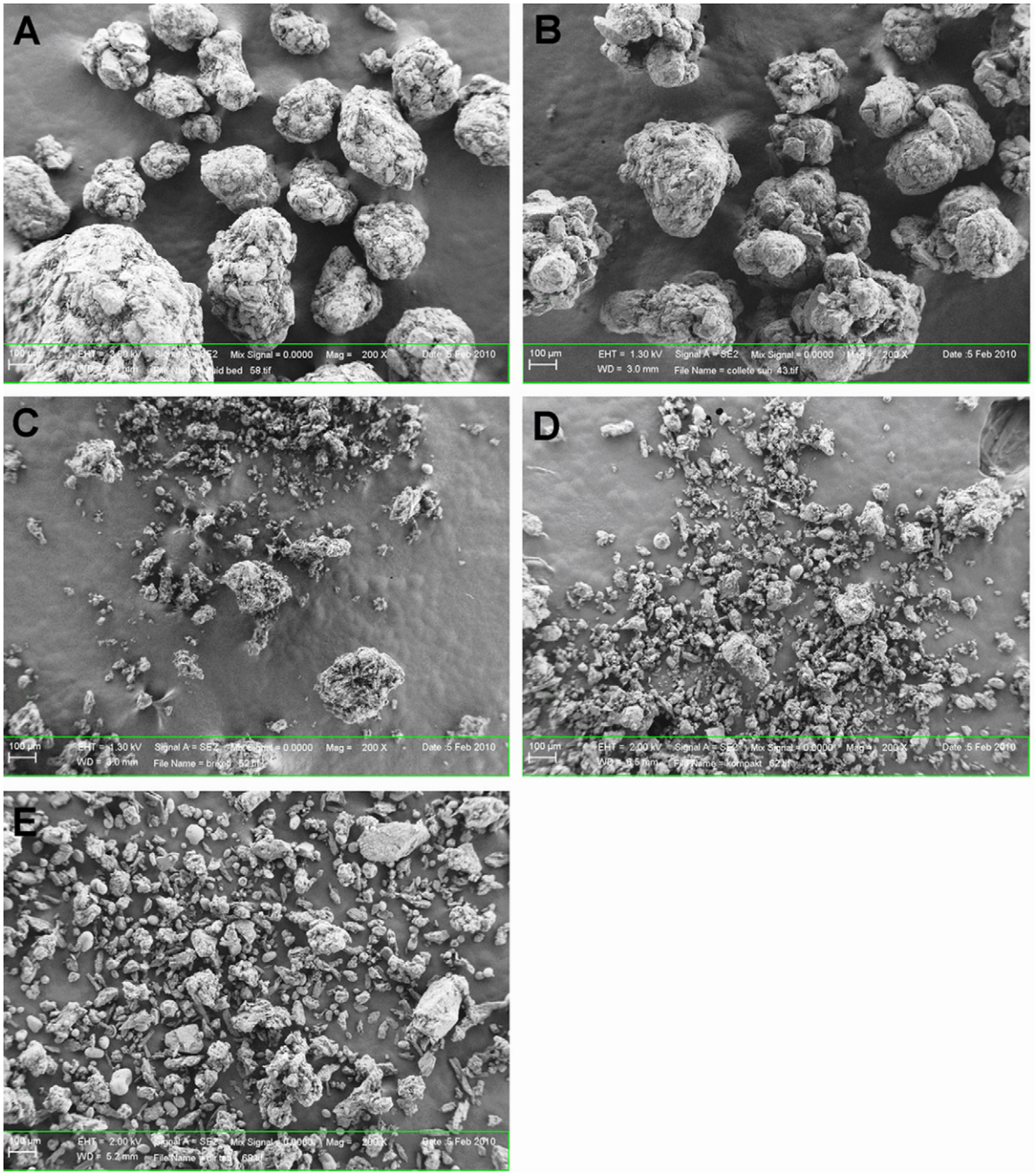

Fig. 2. SEM pictures of tableting mixtures: (A) FBG = fluid-bed granulation, (B) HSG = high-shear granulation, (C) DGS = slugging, (D) DGRC = roller compaction, and (E) DC = direct compression (magnification 200×).

3.1.3. Flow properties of tableting mixtures

The flow properties results are shown in Table 1. The flow properties as dictated by the Carr index, the Hausner ratio, and the flow time are entirely consistent with one other and also with the median particle diameter d_{50}: the larger the particles, the better the flowability (HSG > FBG > DGS > DC > DGRC). With decreasing particle size the specific surface area increases and thus produces more interaction between the particles and hinders flow properties. In general, flow properties of wet granulated mixtures are superior to other mixtures. DC mixture shows fair flow properties due to usage of directly compressible main component of the formulation. Worse flowability of dry granulated mixtures may be attributed to differences in the particle shape and morphology of produced particles (Bacher et al., 2007).

3.2. Friability and disintegration of tablets

It is interesting to know how various granulation methods of preparing tableting mixtures influence the friability and disintegration time of the tablets produced. Tablets were compressed at five different compression pressures. Our results show that the friability of tablets made from all mixtures decreases and the disintegration time becomes longer as compression pressure increases (Table 2). This is a well-known (Riippi et al., 1998) and frequently observed relationship in the pharmaceutical industry. To achieve tablet friability well below the pharmacopeially required 1.0%, DC and wet granulated mixtures should be compressed at 100 MPa, while dry granulated mixtures require pressures above 150 MPa.

Table 1
Comparison of the flow properties of tableting mixtures: FBG = fluid-bed granulation, HSG = high-shear granulation, DGS = slugging, DGRC = roller compaction, and DC = direct compression.

Tableting mixture	Carr index (%)	Hausner ratio	Flow time[a] (s)	Angle of repose (°)	Flow properties[b]
FBG	13.2 ± 0.3	1.15 ± 0.004	11.9 ± 0.2	29.5 ± 0.8	Good
HSG	12.8 ± 1.3	1.15 ± 0.017	11.2 ± 0.1	30.3 ± 0.8	Good
DGRC	21.8 ± 0.8	1.28 ± 0.014	43.3 ± 5.6	36.6 ± 0.1	Passable
DGS	18.2 ± 0.9	1.22 ± 0.014	24.8 ± 1.5	39.2 ± 1.0	Fair
DC	19.9 ± 0.2	1.25 ± 0.003	28.9 ± 0.7	30.9 ± 0.8	Fair

[a] Flow time reported is calculated on 100 g of sample.
[b] Flow properties are reported according to the Hausner (1967) ratio and classification in the European Pharmacopoeia 6th Edition, 2.9.36. Powder Flow (2008).

Table 2
Friability (F) and disintegration time (D) of tablets produced from different mixtures at different compression pressures. FBG = fluid-bed granulation, HSG = high-shear granulation, DGS = slugging, DGRC = roller compaction, and DC = direct compression.

Compression pressure (MPa)	F (%) D (min)[a]	Tableting mixture				
		FBG	HSG	DGRC	DGS	DC
50	F	2.21	36.61	26.38	57.95	2.50
	D	1.1 ± 0.1	0.6 ± 0.1	1.7 ± 0.1	1.5 ± 0.3	1.0 ± 0.2
100	F	0.06	0.26	1.90	1.59	0.05
	D	3.2 ± 0.8	2.1 ± 0.2	3.6 ± 0.7	2.8 ± 0.6	1.3 ± 0.1
150	F	0.03	0.05	0.39	0.31	0.02
	D	5.3 ± 0.6	5.4 ± 0.9	3.9 ± 0.6	3.1 ± 0.3	2.3 ± 0.1
200	F	0.02	0.03	0.07	0.15	0.02
	D	7.8 ± 0.3	8.8 ± 0.4	5.0 ± 1.3	4.0 ± 0.3	3.7 ± 0.2
250	F	0.02	0.03	0.04	0.05	0.01
	D	9.2 ± 0.5	10.5 ± 0.7	5.9 ± 1.1	6.1 ± 0.5	4.7 ± 0.4

[a] F: friability (%); D: disintegration time (min).

At the lowest compression pressure used in our study (50 MPa), the disintegration time of the tablets produced from dry granulated mixtures (DGS and DGRC) is the longest, but at compression pressures ≥150 MPa the disintegration time of the wet granulated mixtures (FBG and HSG) is much longer compared to the other mixtures (Table 2). Considering the change in disintegration time with compression pressure, the DGS, DGRC, and DC mixtures seem more robust than the FBG and HSG mixtures. Tablets produced from the DC mixture have the quickest disintegration at all compression pressures due to the optimal choice of excipients for direct compression in this tableting mixture.

3.3. Compressibility

For compressibility determination "in-die" and "out-of-die" methods can be applied. The "in-die" method is faster; however, it includes measured material's elastic part of the deformation, which we wanted to avoid. Therefore, "out-of-die" method was chosen.

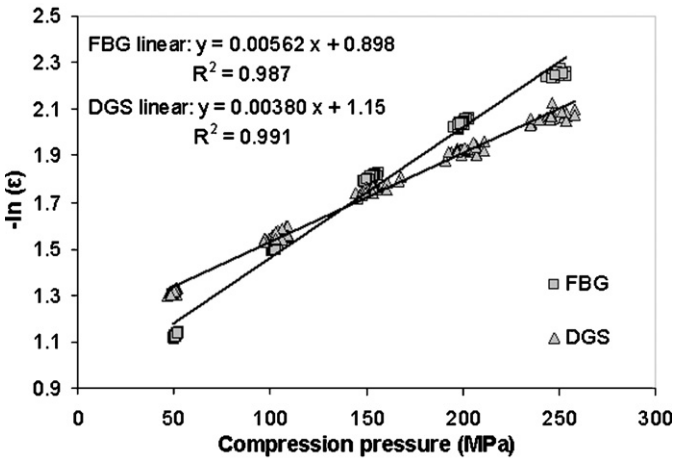

Fig. 3. A typical Heckel plot: the DGS mixture prepared by slugging and the FBG mixture prepared by fluid-bed granulation.

3.3.1. Heckel model

A Heckel plot enables measurement of the compressibility of materials that consolidate either by plastic deformation or fragmentation. A typical "out-of-die" Heckel plot is shown in Fig. 3. It is evident that the achieved linearity of the Heckel curves is satisfactory, as demonstrated by high values of $R^2 \geq 0.983$. The best linearity is observed in the DGS mixture, which is most probably the consequence of the double particle processing by means of slugging and recompressing the tablets. Particles are already fragmented to their maximum during the slugging process. In other words, the fragmented component is already used, which means that in the final tablet compression mostly plastic deformation of existing particles is possible.

The results of the Heckel analysis are summarized in Table 3. K represents the Heckel coefficient (slope of the Heckel plot) and P_y represents yield pressure as its inverse value. The FBG mixture is most compressible, with P_y of 178 MPa, followed by the HSG and DC mixtures (both have P_y around 195 MPa), whose 95% confidence intervals of K largely overlap; therefore it may be considered

Table 3
Compressibility of tableting mixtures studied using the Heckel model, where K represents the Heckel coefficient and P_y the yield pressure. RSE is the relative standard error of slope [RSE = (SE/K) × 100]. FBG = fluid-bed granulation, HSG = high-shear granulation, DGS = sluggeing DGRC = roller compaction, and DC = direct compression.

Tableting mixture	K (×10³ MPa⁻¹)[a]	P_y (MPa)	RSE (%)	R^2
FBG	5.62 [5.50–5.74]	178	1.07	0.987
HSG	5.14 [5.01–5.26]	195	1.22	0.983
DC	5.11 [4.99–5.24]	196	1.19	0.984
DGRC	4.25 [4.15–4.35]	235	1.15	0.985
DSG	3.80 [3.73–3.86]	264	0.88	0.991

[a] The two-sided 95% confidence interval is given in parentheses. For each tableting mixture 120 data points were included in the regression.

that the compressibility of these two mixtures is approximately the same ($p = 0.815$). These three mixtures are followed by the DGRC mixture with considerably lower compressibility and P_y of 235 MPa, and the DGS mixture as the least compressible tableting mixture studied, with P_y of 264 MPa. These results show the general trend that both dry granulated mixtures are noticeably less compressible than the two wet granulated mixtures and the DC mixture.

The reason for the direct mixture's excellent compressibility, which is comparable even with that of the wet granulated mixtures, most certainly lies in the choice of input raw materials that are themselves already suitable for direct tableting. Namely, DCL 15 lactose, a fragmentable substance that forms 65% of the entire mixture, is a pregranulated alpha-lactose known as an ideal filler for direct tableting. The compressibility of the direct compression mixture is also much better than that of both mixtures obtained by dry granulation. The lower compressibility of dry granulated mixtures may be partially attributed to double particle processing. In the compacting and slugging process, particles are compressed and milled during the dry granulation step and then recompressed during tableting. The reduction in the dry granulated mixtures' compressibility may be attributed to work hardening (Malkowska and Khan, 1983). These two mixtures' higher resistance to deformation and fragmentation is also demonstrated by the higher porosity of tablets compressed at 250 MPa compared to tablets made from tableting mixtures obtained via wet granulation or direct powder mixing. The porosities of DGS and DGRC tablets are 12.65% and 12.94%, respectively, compared to 10.55–11.30% for FBG, HSG, and DC tablets. Reduced compressibility due to this phenomenon has been previously observed for dry granulated materials (Bacher et al., 2007; Freitag and Kleinebudde, 2003).

Another reason for the dry granulated mixtures' lower compressibility is the increased density (both bulk and tapped) of the DGRC and especially the DGS mixtures. Consequently, the initial powder height is lower compared with lower-density mixtures and this shortens the contact time during tableting, which was 274–280 ms for the DC, FBD, and HSG mixtures, but only 242 ms for the DGRC and 224 ms for the DGS mixtures. Shorter contact time may influence rearrangement, deformation, and/or fragmentation in a negative way and therefore lower compressibility may be observed (Bacher et al., 2008). The tableting mixture density obviously plays an important role in powder compressibility. Usually, powders that are more porous are considered more compressible. For instance, if the porosity of two mixtures of the same material is equal, the mixture with lower bulk and/or tapped density is likely to be more compressible. This positive relationship was observed between the tapped densities and the Heckel coefficients of the mixtures studied (Fig. 4), which may be associated with the contact times mentioned above. A weaker relationship was found between bulk densities and compressibility parameters, probably due to various rearrangements of mixtures based on different particle size, morphology, and shape. It is important to emphasize that general assumptions (such as higher porosity ⇒ better compressibility) can sometimes be oversimplified.

3.3.2. Walker analysis

A typical Walker plot based on Eq. (2) is shown in Fig. 5. The Walker plots of compression for the respective mixtures showed even better linearity, expressed in higher R^2, compared to the Heckel plots (Table 4). This is also confirmed by the confidence intervals of the linear regression lines, which are narrower using the Walker model than they were with the Heckel model. The Walker model once again proved that the most compressible mixture is FBG, with w' of 35.0 (corresponding to 35.0% of specific volume reduction when compression pressure increases by one decade), followed by statistically equivalent ($p = 0.388$) compressibility of HSG and DC mixtures (w' of approximately 32). The considerably lower compressibility of DGRC was measured, with w' of 27.0, and the least compressible material is DGS with w' of only 21.0. These results demonstrate exactly the same order of compressibility as the Heckel model, and the positive correlation between these two methods that was already observed in one of our previous studies (Ilić et al., 2009) is thus confirmed (Fig. 6).

It is important to emphasize the Walker model's slightly better discriminative power over the Heckel model to differentiate tableting mixture compressibility. This is shown by the wider range between the most and least compressible materials.

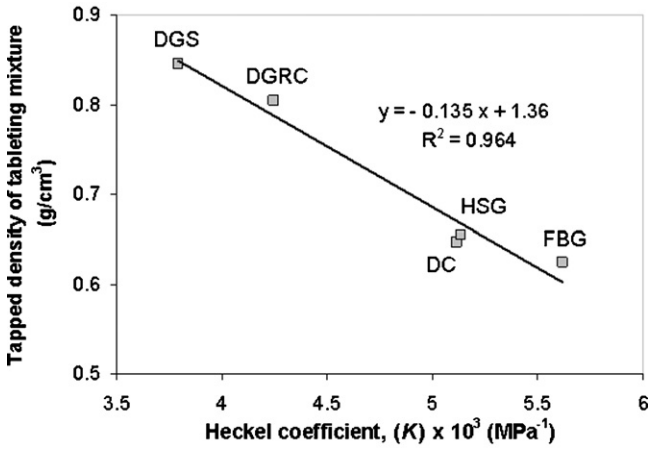

Fig. 4. A positive correlation between the tapped densities of tableting mixtures and their Heckel coefficients (K).

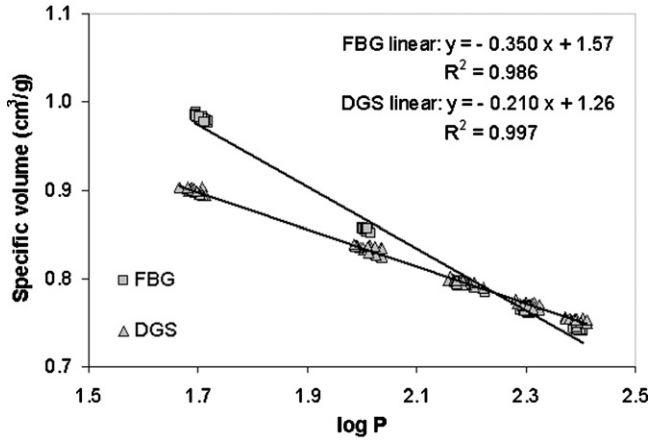

Fig. 5. A typical Walker plot: DGS mixture prepared by slugging and FBG mixture prepared by fluid-bed granulation.

Table 4
Compressibility of tableting mixtures studied according to the Walker model, where w' represents the Walker coefficient and RSE is the relative standard error of slope [RSE = (SE/K) × 100]. FBG = fluid-bed granulation, HSG = high-shear granulation, DGS = slugging, DGRC = roller compaction, and DC = direct compression.

Tableting mixture	$w' \times 100$ (%)[a]	RSE (%)	R^2
FBG	35.0 [34.3–35.8]	1.09	0.986
HSG	31.8 [31.2–32.4]	1.01	0.988
DC	32.2 [31.5–32.8]	1.03	0.988
DGRC	27.0 [26.7–27.4]	0.71	0.994
DGS	21.0 [20.8–21.2]	0.47	0.997

[a] The two-sided 95% confidence interval is given in parentheses. For each tableting mixture 120 data points were included in the regression.

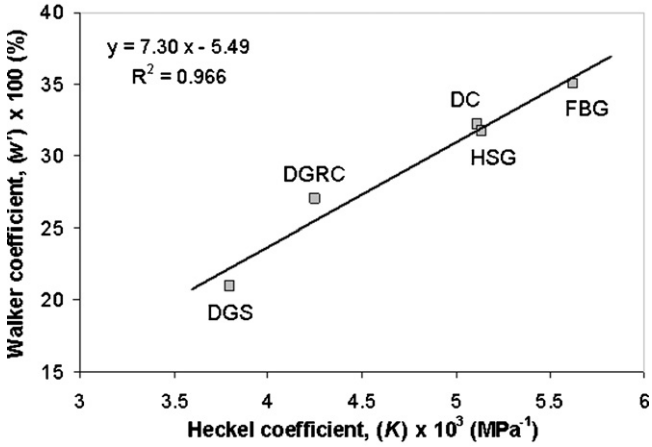

Fig. 6. Positive correlation between Heckel and Walker coefficients for the tableting mixtures studied.

3.3.3. Compression energies

Compressibility was also estimated using force–displacement measurements. The most informative part is the hysteresis between the compression and decompression curves, where the area under the curve was calculated. The area of hysteresis represents irreversible energy used during compression and may be related to the tableting mixture compressibility. This value is presented as specific net energy (W_{net}). W_{net} is reported at 250 MPa and the values are as follows: FBG 42.3 J/g, HSG 38.3 J/g, DC 35.0 J/g, DGRC 29.6 J/g, and DGS 21.6 J/g. The differences in W_{net} between tableting mixtures show that the FBG mixture uses the highest compression energy for irreversible processes such as plastic deformation and fragmentation, thus making the FBG mixture the most compressible material. In contrast, the least compressible material, which uses the lowest compression energy for irreversible processes, is the DGS mixture. This is in agreement with the Heckel and Walker results, presented as a relationship between the three parameters (Fig. 7). A strong linear correlation is established between both the Heckel and Walker coefficients and W_{net}. The results show that force–displacement measurements have a good potential for estimating materials' compressibility.

3.4. Compactibility

The measurement of a tableting mixture's compactibility is especially important with respect to tablet tensile strength and friability. Poorly compactible powders form weak bonds between the particles and extensive elastic relaxation may further decrease tablet tensile strength and induce or increase capping tendencies.

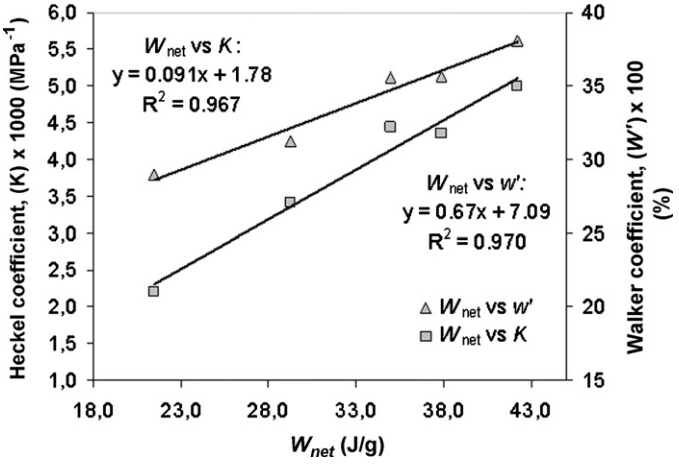

Fig. 7. A positive correlation between W_{net} at 250 MPa, Heckel coefficient (K) and Walker coefficient (w').

Table 5
The compactibility of the tableting mixtures studied, where C_p represents the compactibility of the tablets produced for the mixtures. RSE is the relative standard error of slope [RSE = (SE/C_p) × 100]. FBG = fluid-bed granulation, HSG = high-shear granulation, DGS = slugging, DGRC = roller compaction, and DC = direct compression.

Tableting mixture	C_p (×10²)[a]	RSE (%)	R^2
FBG	10.03 [9.91–10.15]	0.59	0.996
HSG	8.58 [8.47–8.69]	0.65	0.995
DC	8.87 [8.75–9.00]	0.70	0.994
DGRC	9.83 [9.59–10.07]	1.26	0.982
DGS	5.83 [5.68–5.99]	1.38	0.978

[a] The two-sided 95% confidence interval is given in parentheses. For each tableting mixture 120 data points were included in the regression.

The compactibility was determined from the tensile strength (σ_t) versus compression pressure plot, where the slope or C_p represents the compactibility of the tablets produced for each tableting mixture studied. The results are summarized in Table 5. The FBG mixture again proves to be a superior mixture; however, its compactibility does not significantly ($p = 0.148$) differ from the DGRC mixture, which surprisingly produces tablets with very high tensile strength, especially in light of the compressibility results. These two mixtures are followed by the DC mixture, the only slightly less compactible HSG mixture, and the least compactible DGS mixture.

The superior compactibility of the FBG mixture is somewhat expected. The tablets' tensile strength is likely to depend on the level of granule fragmentation during tableting, at least for fragmentable materials like agglomerated lactose. This can be facilitated by higher porosity of the granules, which can be more easily achieved during fluid-bed granulation compared to high-shear granulation due to reduced mechanical stress on the granules during production. Another important parameter is the binder distribution (Wikberg and Alderborn, 1990), which may be more uniform in the FBG mixture.

On the other hand, the dry granulated mixtures were expected to have lower compactibility due to the lower initial porosity of the granules. Some authors have shown that the tensile strength of tablets from dry granulated mixtures is lower compared to that of tablets made by direct tableting (Farber et al., 2008; Freitag and Kleinebudde, 2003; Herting and Kleinebudde, 2007). This is most commonly associated with work hardening, which was confirmed for the DGS mixture. However, contrary to our expectations, the DGRC mixture shows a high degree of compactibility. The high compactibility of DGRC is attributed mainly to the much smaller particle size and high amount of fines compared to other mixtures, such that the DGRC mixture is able to form more bonds during tablet production.

Some authors have shown a correlation between compressibility (K and w' of the Heckel and Walker plots, respectively) and compactibility expressed as tensile strength (Sonnergaard, 2006). They proved that well-compressible materials form tablets with higher tensile strength. The same correlation is not valid in our case because Sonnergaard studied these properties on pure single-component mixtures, whereas complex agglomerates produced by various granulation methods were used in our study. From previous discussions it is evident that various parameters have an impact on both properties studied—compressibility and compactibility—and that sometimes a single parameter has an opposite impact. Therefore, a simple correlation between compressibility and compactibility does not seem feasible for complex systems.

4. Conclusion

Various powder agglomeration processes have a great impact on the tablet compaction process. In order to investigate the compressibility and compactibility properties of these complex tableting mixtures, they were precisely characterized. Wet granulation processes resulted in the formation of larger granules with narrower particle size distribution compared to dry granulation, in which a higher amount of fines (<71 μm) was produced, something that is typically observed in dry granulation processes. The flow properties of wet granulated mixtures were superior; however, all tableting mixtures had acceptable flow properties for tablet production on a single-punch tableting press. Tablets produced from wet granulated mixtures had lower friability at all compression pressures, but longer disintegration times at pressures over 150 MPa. The results of compressibility studies using Walker and Heckel analyses show that the FBG mixture has the best compressibility, followed by the HSG and DC mixtures, which are comparable to each other. The compressibility of the two dry granulated mixtures was considerably smaller, but the DGRC mixture has better compressibility than the DGS mixture. This is explained by the work hardening phenomenon and the differences in contact time observed due to the tableting mixtures' varying initial densities. It must be emphasized that analysis of compression energies confirmed the Heckel and Walker model results, therefore an easier and faster estimation of compressibility using force–displacement curves is proposed for this type of investigation. It can also be concluded that it is impossible to lay down general rules (such as higher compressibility ⇒ better compactibility) for complex tableting mixtures, because different material's characteristics or process parameters may have an opposite impact.

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