The original size of granules is an important property, which can affect the compression and compaction properties of aggregates as well as the pharmaceutical quality of prepared tablets (1). Effects of the initial particle size on the compression behavior of tableting mixtures have been studied by many authors (2–14), but only a few published studies have specifically reported a relationship between granule/pellet size and compression behavior (1, 15–17). Based on these studies, it seems that there is no simple rule regarding the impact of granule size on tablet strength. It has been reported that a reduction in granule size corresponds to an increase in tablet strength (16, 17) but contrary to this, some studies have confirmed that tablet strength increases with an increase in gran-
ule size (1, 15). On the other hand, Rehula (18) and Bangudu et al. (19) have even reported that tablet strength is independent of granule size.

Particle size can also influence other compression properties in addition to tablet strength. For example, it has been shown that the fragmentation propensity of a substance under load increases with its particle size (3, 14). For this reason, a change in the mean particle size may alter the predominant consolidation mechanism.

Sun and Grant (12) have demonstrated that at low compression pressures larger initial particles are more compressible than smaller particles. The differences in compressibility between particle-size fractions decreased with increasing compaction pressure. At the same compaction pressure, smaller particles formed tablets of greater tensile strength than larger particles. However, fragmentation of larger particles tended to equalize the particle size and reduce its influence.

Some authors have categorized the effects of particle size on the basis of the mechanisms involved in compaction, which depend on the mechanical properties of materials. For materials with a high tendency to fragment, the original particle size is less important than for plastic materials, and so volume reduction of the powder bed and tablet strength are generally independent of particle size (2, 4, 20).

Various studies have been performed on the same model excipients, such as sodium chloride, microcrystalline cellulose, or various types of lactose (1, 2, 4–7, 9).

There is, however, a lack of studies performed on real tableting mixtures. In this study, a realistic placebo formulation was used to investigate the effect of granule size on the pharmaceutical technological properties of tablets. According to the results of our previous paper (21), the fluid-bed wet-granulated (FBG) and dry-granulated slugging (DGS) mixtures were the most and the least compressible/compactible mixtures, and they were therefore chosen for further experimental evaluation.

This study investigates the effect of granule particle size on the compression and compaction properties of FBG and DGS tableting mixture in terms of possible improvement of compressibility and compactibility of both tableting mixtures. It also examines the effect of particle size on the quality of tablets produced. The compression mixtures produced were sieved into two particle-size fractions chosen according to the particle-size distribution of both initial mixtures. These different particle-size fractions were evaluated (for flowability, compressibility, compactibility, tablet friability, tablet disintegration, elastic recovery) and the results were compared with the initial FBG and DGS mixtures. The Heckel and Walker models were used to evaluate the compressibility of the mixtures. Compactibility was determined by measuring tablet tensile strength at various compression pressures.

EXPERIMENTAL

Materials

The model placebo mixture consisted of lactose monohydrate (filler, Pharmatose DCL15, DMV International GMBH), 65.42 % (m/m); microcrystalline cellulose (filler/dry binder, MCC, Avicel PH 102, FMC International), 25.02 % (m/m); sodium starch glycolate
(disintegrating agent, Primojel, DMV International GMBH), 5.18 % (m/m); polyvinylpyrrolidone (binder, Povidone K25, BASF SE), 3.31 % (m/m); colloidal silica (lubricant, Aerosil 200, Evonik Degussa GMBH), 0.36 % (m/m); and magnesium stearate (antiadhesive agent, FACIS SPA), 0.71 % (m/m).

Preparation of tableting mixtures

Tableting mixtures were prepared according to the procedures listed and described below. Before preparing a mixture, all materials were sieved manually through a sieve with a mesh size of 0.8 mm. 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).

Fluid-bed granulation (FBG). – Weighted powders without Povidone were mixed in a fluid-bed granulator (Aeromatic TSG, 2 GEA Aeromatic, Switzerland) at an inlet air \( t = 70 \, ^\circC \) and airflow of 200 m\(^3\) h\(^{-1}\). Mixing lasted 37 min until the exhaust air reached \( t = 37 \, ^\circC \). Then, 5.37 kg of a 6.89 % (m/m) aqueous solution of Povidone K25 was sprayed at an inlet air \( t = 60 \, ^\circC \) and the airflow was increased from a starting value of 250 to 450 m\(^3\) h\(^{-1}\) by the end of the spray phase. The atomizing air pressure was 1.5 \times 10^5 \text{ Pa}. Spraying of the granulation liquid lasted 14 min until the exhaust air reached \( t = 25.1 \, ^\circC \). Drying was performed for 52 minutes at an inlet air \( t = 60 \, ^\circC \); the airflow was decreased from a starting value of 450 to 250 m\(^3\) h\(^{-1}\) at the end of the drying phase, until the exhaust air \( t = 39.3 \, ^\circC \) was reached. Dried granules were sieved (Quadro Comil U 10, Quadro Engineering, Canada) and mixed with Aerosil® 200 (37.2 g) in a 50-L biconical mixer (Iskra Plo, 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 minutes at 10 rpm.

Dry granulation by slugging (DGS). – Weighted powders with added Aerosil 200 (40 g) were mixed in a 50-L biconical mixer at 20 rpm for 10 min. After magnesium stearate was added (80 g), additional mixing was performed at 10 rpm for 2 min. Slugging was performed on a rotary tableting machine (Kilian T300/ Vicon,IMA, Germany) using round concave punches (\( \phi = 13 \text{ mm}, r = 26 \text{ mm} \)) 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\(^{-1}\). The slugs were crushed in a mill (Frewitt, Frewitt FMSA, Switzerland) with a 1.0 mm sieve opening. The resulting granules were homogenized in the 50-L biconical mixer at 10 rpm for 2 min.

Sieving of tableting mixtures

Two particle-size fractions of the FBG mixture (0.180–0.400 mm, 0.400–0.710 mm) and two particle-size fractions of the DGS mixture (0.180–0.400 mm, 0.400–0.710 mm) were obtained by sieving the materials through test sieves (Retsch GmbH) on a mechanical vibrating sieve (AS 200 Basic, Retsch GmbH, Germany).

Characterization of tableting mixtures and tablets

Particle-size distribution. – The particle-size distribution for both mixtures and their fractions (20 g sample) was determined in triplicate with an air-jet sieve analyzer (Al-
pine 200 LS-N, Hosokawa, Germany) using the following sieves: 0.071, 0.125, 0.250, 0.500, 0.710, and 1.25 mm. Sieving lasted for 3 minutes at 1300 Pa. Results are presented as particle-size distribution and as the particle size at which 50% (m/m) of particles were below the given size denoted as the median particle diameter, or $d_{50}$.

**True density of tableting mixtures.** – True density of both mixtures and their fractions was determined in triplicate with a helium pycnometer (AccuPyc 1330, Micromeritics, USA) according to European Pharmacopoeia. (22).

**Bulk and tapped density of tableting mixtures.** – Bulk and tapped densities were determined in triplicate according to European Pharmacopoeia (22) using a Stampvfolumeter STAV 2003 apparatus (J. Engelsmann AG, Germany).

**Flow properties of tableting mixtures.** – Flow properties of tableting mixtures were determined by measuring the angle of repose and the flow time according to European Pharmacopoeia (22) using a flowability tester (Pharma PTG-S3, Pharma Test Apparatebau GmbH, Germany). In addition, flow properties were also determined using the Carr index and Hausner ratio according to European Pharmacopoeia (22).

**Tablet friability.** – Tablet friability (%) was determined according to European Pharmacopoeia (22) using a friability apparatus (Erweka TAR200, Erweka, Germany).

**Tablet disintegration.** – Tablet disintegration time was measured according to European Pharmacopoeia (22) with a disintegration tester (Erweka ZT 72, Erweka, Germany). Disintegration time was determined for each type of tablet produced at each compression pressure.

**Compressibility**

The compressibility of mixtures was determined using the Heckel (equation 1; 23) and modified Walker (equation 2; 24, 25) compressibility models. The Heckel model (equation 1) is based on the assumption that the process of pore reduction during compression follows first-order kinetics:

$$-\ln \varepsilon = \ln \left( \frac{1}{1-D} \right) = K \cdot P + A$$  \hspace{1cm} (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 $\varepsilon$ 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 (equation 2):

$$V' = w' \cdot \log P + V_{sp}'$$  \hspace{1cm} (2)
where $V'$ is the specific volume of a tablet and $w'$ is the Walker coefficient expressing the volume reduction corresponding to a 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, 250 MPa) using an instrumented single-punch tablet press (Kilian SF300, IMA, Germany) with round flat-faced punches ($\phi = 12$ mm). The target tablet mass was 600 mg and the compression speed was 30 tbl min$^{-1}$. Tableting was performed at $20 \pm 2$ °C and RH = 35 ± 5 %. At each compression pressure, 24 tablets were evaluated 24 hours after compression. Compressibility was determined using the «out-of-die» Heckel (equation 1) and Walker (equation 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 micrometer (Mitutoyo, Japan) and mass was determined using an analytical balance AG245 (Mettler Toledo, Switzerland).

The Heckel ($K$) and Walker ($w'$) coefficients (slopes of the corresponding curves) were estimated using a linear regression in which each point represents one tablet. The Heckel and Walker coefficients, standard errors (SEs), and the two-sided 95 % confidence interval (CI) of the slopes were calculated using Microsoft Office Excel 2007. Statistical significance between the slopes was calculated by means of a $t$-test using an OpenEpi (26) statistical calculator (two-independent-sample $t$-test with either equal or unequal variance, depending on Hartley’s test for equality of variance) like the one used in previous studies (21, 25, 27).

**Elastic recovery**

The percentage axial elastic recovery (ER, %) (at 150 MPa) was calculated using the equation described by Armstrong and Haines-Nutt (28):

$$ER = \frac{H - H_p}{H_p} \cdot 100$$

(3)

where $H_p$ is the thickness of the tablet under maximum pressure and $H$ is the thickness of the tablet after the compression force was removed. In-die tablet thickness under maximum pressure ($H_p$) was calculated using data obtained from upper and lower punch displacement. Tablet thickness 24 hours upon compression ($H$) was measured using a micrometer.

**Compactibility**

The tablet crushing force ($H$) was evaluated using a hardness tester VK200 (Varian, USA). The radial tensile strength ($\sigma_t$) was calculated using equation 4 (29):

$$\sigma_t = \frac{2H}{\pi d \cdot h}$$

(4)
where $H$ is the tablet crushing force (N), $d$ is tablet diameter, and $h$ is tablet thickness. Compactibility slopes were estimated using linear regression from the plot of tablet radial tensile strength vs. compression pressure (MPa), in which each point represented one tablet. The SE, 95% CI, and statistical testing were performed as described above (2.5).

RESULTS AND DISCUSSION

Characterization of tableting mixtures and their size fractions

In our previous study (21), five different tableting mixtures of the same model placebo formulation were prepared. Tableting mixtures were prepared using a wet granulation process (fluid-bed (FBG) and high-shear granulation (HSG)), a dry granulation process (dry granulation by slugging (DGS), and by roller compacting (DGRC)) and direct mixing (DC). The results of compressibility studies using the out-die Walker and Heckel analyses showed that the FBG mixture had the highest compressibility and the DGS mixture had the lowest compressibility. Similar results were achieved in compactibility measurements and in determination of compression energies. According to these results, the most and least compressible/compactible tableting mixtures (out of five) were chosen to investigate the effect of granule particle size on a possible improvement of their compaction properties. Appropriate particle-size fractions of both mixtures were prepared and all mixtures were precisely analyzed.

The results of sieve analysis in Fig. 1 show that the DGS-sieved fraction (180–400 µm) has a somewhat smaller median particle size compared to the FBG fraction (180–400 µm). In contrast, particles of the FBG fraction (400–710 µm) are slightly larger than particles of the DGS fraction (400–710 µm).

Fig. 1. Cumulative mass particle size distribution of DGS and FBG mixtures and their fractions (180–400 µm, 400–710 µm).
Factor \( f \) in Table I is a measure of particle-size distribution width defined as the quotient between \( d_{90} \) and \( d_{20} \). The results for \( f \) indicate broader particle-size distribution for a smaller particle-size fraction (180–400 µm) compared to a larger particle-size fraction (400–710 µm), which is evident for both compression mixtures. Both initial tableting mixtures have a similar median particle size; however, the initial DGS mixture has a considerably broader particle-size distribution.

The results for particle-size distribution and bulk and tapped densities of mixtures are presented in Table I. The initial FBG mixture has a considerably lower bulk and tapped density compared to the initial DGS mixture. This trend was also observed for sieved fractions of both mixtures and was attributed to the higher intragranular porosity of FBG particles. It is evident that the density (bulk or tapped) increases with decreasing particle size independent of the mixture type (FBG or DGS).

Comparing the initial mixtures with their sieved fractions, it can be seen that both initial mixtures showed higher densities in comparison with their sieved fractions. This could be explained by the fact that wider particle-size distribution by initial mixtures contributed to denser packing of the particles. In a wide particle-size distribution, different particle rearrangement can be expected, in which smaller particles fill the gaps between larger particles, resulting in denser packing.

The results for the Carr index and angle of repose in Table II demonstrate that all FBG mixtures have better flowability compared to DGS mixtures. This is probably due to irregularly shaped DGS particles with a rough surface area, which could have a negative impact on flowability (Fig. 2). The results of flow time give a somewhat different picture of flowability, but at the same time these results are less reliable considering the low accuracy of flow-time measurements. It is evident that there is no good correlation between different types of flowability measurements. To find out which flow property is the most reliable, the standard deviation of tablet mass (compressed at 150 MPa) was plotted against each flow property. The best fit between both variables was obtained for the Carr index (CI) (data not shown). CI is entirely consistent with the median particle diameter \( d_{50} \): the larger the particles, the better the flowability (FBG > DGS).

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According to the most reliable results for CI, both FBG fractions have good flowability, even slightly
better than the initial FBG mixture. Flowability of the larger DGS fraction (400–710 µm) and flowability of the initial DGS mixture are better than the flowability of smaller DGS fractions (180–400 µm).

Friability and disintegration of tablets

Tablets from all tableting mixtures were compressed at five different pressures and friability (F) and disintegration (D) were determined (Table III). Friability decreased with increasing compression pressure. It is usually observed that an increase in compression pressure causes a reduction in friability (30). The friability of DGS tablets was much higher compared to FBG tablets, which was already observed in our previous work (21). The friability of tablets from the initial mixture (DGS/FBG) was slightly higher in comparison with the friability of tablets made from both size fractions of each mixture at all compression pressures.
If we compare friability of DGS mixtures, the lowest friability was achieved by tablets from the larger DGS fraction (400–710 \(\mu\)m). In contrast, the effect of particle size on the friability of tablets from FBG mixtures is negligible. To achieve tablet friability below the pharmacopoeia requirements of 1.0 %, all FBG mixtures should be compressed at a minimum of 100 MPa, whereas all DGS mixtures require pressures above 150 MPa.

Disintegration time of tablets increased with increasing the compression pressure used (Table III), which is in agreement with the finding of Rippip et al. (30). In general, the disintegration of DGS tablets was faster compared to FBG tablets. Disintegration times of FBG and DGS tablets from particle-size fractions 180–400 µm and 400–710 µm are comparable to the disintegration time of tablets from both initial mixtures, meaning that granule size has no impact on the disintegration time. However, when the disintegration time of the same granule size or fraction prepared using two different procedures is compared, the influence of the agglomeration process of granules (wet/dry granulation) is evident.

**Compressibility**

A typical »out-of-die« Heckel plot is shown in Fig. 3. Results of the Heckel analysis are summarized in Table IV. \(K\) represents the Heckel coefficient (slope of the Heckel plot) and \(P_y\) represents yield pressure as its inverse value. The results show that all FBG mixtures were much more compressible than DGS mixtures. For both mixtures, particle-size fractions were found to be significantly more compressible than the initial tableting mixtures \((p < 0.026)\). A difference in compressibility between granule size fractions was noticed only in the case of the DGS mixture, in which a bigger fraction showed statistically significant poorer compressibility \((P_{DGS(180–400)/DGS(400–710)} = 0.009)\). However, it should be stressed that the differences, even when statistically significant, are not pronounced. Based on our experience, a difference in \(P_y\) in the order

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**Table III. Friability and disintegration time of tablets**

<table>
<thead>
<tr>
<th>(P) (MPa)</th>
<th>(F) (%)</th>
<th>FBG (180–400)</th>
<th>FBG (400–710)</th>
<th>DGS (180–400)</th>
<th>DGS (400–710)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>F</td>
<td>3.17</td>
<td>2.38</td>
<td>2.51</td>
<td>28.44</td>
</tr>
<tr>
<td>100</td>
<td>D</td>
<td>1.3 ± 0.05</td>
<td>1.1 ± 0.05</td>
<td>1.0 ± 0.08</td>
<td>1.8 ± 0.07</td>
</tr>
<tr>
<td>150</td>
<td>D</td>
<td>3.7 ± 0.03</td>
<td>3.6 ± 0.10</td>
<td>2.7 ± 0.07</td>
<td>2.6 ± 0.18</td>
</tr>
<tr>
<td>200</td>
<td>D</td>
<td>5.3 ± 0.12</td>
<td>5.3 ± 0.14</td>
<td>5.1 ± 0.16</td>
<td>3.8 ± 0.19</td>
</tr>
<tr>
<td>250</td>
<td>D</td>
<td>8.4 ± 0.05</td>
<td>8.3 ± 0.08</td>
<td>7.1 ± 0.12</td>
<td>4.5 ± 0.09</td>
</tr>
</tbody>
</table>

\(a\) The size of particle fractions (\(\mu\)m) is given in parentheses.

\(b\) \(P\) – compression pressure; \(F\) – friability; \(D\) – disintegration time.
of 10 MPa does not essentially change the tableting behavior of the mixture. On the other hand, the influence of a difference in $P_y$ in the order of 50 MPa, such as in the case of FBG and DGS mixtures, can be clearly observed in the compression properties of the two mixtures.

A typical Walker plot is shown in Fig. 4. Walker plots of compression for various granule fractions (Table V) confirm that FBG mixtures are considerably more compressible compared to DGS mixtures. Both FBG sieved fractions exhibit equal and statistically insignificant differences in the Walker coefficient $w'$, both against each other as well as against initial tableting mixture. The small difference in compressibility between both particle-size fractions was statistically significant only for the DGS mixture ($P(DGS(180–400)/DGS(400–710)) = 0.000$), but the differences were too small to have a real impact on the compression behavior.

### Table IV. Compressibility of tableting mixtures studied using the Heckel model

<table>
<thead>
<tr>
<th>Tableting mixture*</th>
<th>$K \times 10^3$ (MPa$^{-1}$)</th>
<th>$P_y$ (MPa)</th>
<th>RSE (%)</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG</td>
<td>6.42 (6.30–6.54)</td>
<td>156</td>
<td>0.95</td>
<td>0.993</td>
</tr>
<tr>
<td>FBG (180–400)</td>
<td>6.70 (6.56–6.83)</td>
<td>149</td>
<td>1.02</td>
<td>0.992</td>
</tr>
<tr>
<td>FBG (400–710)</td>
<td>6.65 (6.53–6.76)</td>
<td>150</td>
<td>0.90</td>
<td>0.994</td>
</tr>
<tr>
<td>DGS</td>
<td>4.53 (4.42–4.65)</td>
<td>221</td>
<td>1.26</td>
<td>0.989</td>
</tr>
<tr>
<td>DGS (180–400)</td>
<td>4.93 (4.80–5.06)</td>
<td>203</td>
<td>1.29</td>
<td>0.988</td>
</tr>
<tr>
<td>DGS (400–710)</td>
<td>4.71 (4.60–4.82)</td>
<td>212</td>
<td>1.15</td>
<td>0.991</td>
</tr>
</tbody>
</table>

* The size of particle fractions (µm) is given in parantheses.

$K$ – Heckel coefficient. The two-sided 95 % confidence interval is given in parentheses. For each tableting mixture 120 data points were included in the regression.

RSE – relative standard error of slope [RSE = (SE/$K$) × 100].

![Fig. 3. A typical Heckel plot: the fraction (400–710 µm) of the DGS mixture and the fraction (400–10 µm) of the FBG mixture.](image)
of each tableting mixture. Contrary to the results obtained by the Heckel model, only the DGS fraction (180–400 µm) was observed as significantly more compressible than the initial DGS mixture ($p = 0.000$).

Considering slopes and their RSE values, it is difficult to conclude whether there are real differences in compressibility among the particle-size fractions within the FBG and DGS mixtures. Some authors (9, 20) categorized the effect of particle size on the basis of the deformation mechanism involved in compaction. They showed that for materials with a high tendency to fragment, the original particle size is less important than for plastic or low-fragmenting materials. The fact that our formulation consists of 65 % highly fragmenting material (lactose monohydrate) may explain the lack of differences in compressibility between different particle-size fractions. It is already known (2) that

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**Table V. Compressibility of tableting mixtures studied according to the Walker model**

<table>
<thead>
<tr>
<th>Tableting mixture</th>
<th>$w' \times 100$ (%)</th>
<th>RSE (%)</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG</td>
<td>34.8 (34.0–35.7)</td>
<td>1.24</td>
<td>0.989</td>
</tr>
<tr>
<td>FBG (180–400)</td>
<td>33.8 (32.9–34.8)</td>
<td>1.38</td>
<td>0.986</td>
</tr>
<tr>
<td>FBG (400–710)</td>
<td>33.8 (32.9–34.6)</td>
<td>1.28</td>
<td>0.988</td>
</tr>
<tr>
<td>DGS</td>
<td>22.5 (22.1–23.0)</td>
<td>0.99</td>
<td>0.993</td>
</tr>
<tr>
<td>DGS (180–400)</td>
<td>24.9 (24.3–25.5)</td>
<td>1.19</td>
<td>0.990</td>
</tr>
<tr>
<td>DGS (400–710)</td>
<td>22.8 (22.5–23.1)</td>
<td>0.65</td>
<td>0.997</td>
</tr>
</tbody>
</table>

---

$a$ The size of particle fractions (µm) is given in parentheses.

$b$ $w'$ – Walker coefficient; The two-sided 95 % confidence interval is given in parentheses. For each tableting mixture 120 data points were included in the regression.

$c$ RSE – relative standard error of slope [$RSE = (SE/K) \times 100$].
larger particles, especially granules, fragment to smaller particles at quite low compres-
sion pressures and extensive fragmentation at higher compression pressures nullifies the
effect of initial particle size on compressibility. Poor compressibility of the initial mix-
tures compared to size fractions is likely to be a consequence of higher bulk density.
Because of wider particle-size distribution of the initial mixture, small particles (at the
initial stage) serve a void-filling role between larger particles. The void-filling role in-
creases the relative density and consequently lowers the starting porosity/specific tablet
volume. This results in poorer compressibility of these mixtures determined by the He-
ckel and Walker models.

Compactibility and elastic recovery

Compactibility was measured using the approach of the compactibility profile (ten-
sile strength (σt) vs. compression pressure), where the slope or \( C_p \) represents the com-
patibility of tablets produced for each tableting mixture studied. The results are sum-
marized in Table VI.

The tablets compacted from the larger-sized fractions showed significantly higher com-
patibility than tablets made of finer size fractions in the case of both tableting mixtures.
Both initial tableting mixtures showed the poorest compactibility compared to their corre-
ponding size fractions. The FBG fraction (400–710 µm) showed the highest compactibility
and produced tablets with the lowest friability. An explanation of higher compactibility in
the case of larger particles could be the higher rate of fragmentation. Stronger bonding for
the larger particle-size fractions was already reported in some earlier studies (1, 7, 9, 16). In
the case of materials undergoing intensive particle fragmentation, particle size can have a
smaller effect on tablet strength compared to substances that fragment less intensively. In
the case of highly fragmentable particles, larger particles break into smaller particles and
when a certain particle-size level is reached, fragmentation propensity and also tablet
strength seem to be independent of particle size (2, 4). The granules in our complex formu-
lations mainly consist of high-fragmenting material (lactose monohydrate) and a sur-
prisingly strong effect of particle size on tablet strength was observed. The reason for in-

Table VI. The compactibility and elastic recovery of the tableting mixtures studied

<table>
<thead>
<tr>
<th>Tableting mixture(^a)</th>
<th>( C_p \times 10^2 ) (^b)</th>
<th>RSE (%)(^c)</th>
<th>( R^2 )</th>
<th>ER (%)(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG</td>
<td>11.1 (10.9–11.3)</td>
<td>0.84</td>
<td>0.995</td>
<td>7.35</td>
</tr>
<tr>
<td>FBG (180–400)</td>
<td>12.5 (12.2–12.8)</td>
<td>1.27</td>
<td>0.988</td>
<td>5.92</td>
</tr>
<tr>
<td>FBG (400–710)</td>
<td>13.2 (13.0–13.4)</td>
<td>0.82</td>
<td>0.995</td>
<td>5.28</td>
</tr>
<tr>
<td>DGS</td>
<td>7.03 (6.76–7.31)</td>
<td>1.98</td>
<td>0.972</td>
<td>6.65</td>
</tr>
<tr>
<td>DGS (180–400)</td>
<td>8.07 (7.81–8.34)</td>
<td>1.67</td>
<td>0.980</td>
<td>9.46</td>
</tr>
<tr>
<td>DGS (400–710)</td>
<td>8.83 (8.62–9.03)</td>
<td>1.15</td>
<td>0.991</td>
<td>5.70</td>
</tr>
</tbody>
</table>

\(^a\) The size of particle fractions (µm) is given in parentheses.

\(^b\) \( C_p \) – compactibility; The two-sided 95 % confidence interval is given in parentheses. For each tableting
mixture 120 data points were included in the regression.

\(^c\) RSE – relative standard error of slope \( [\text{RSE} = (\text{SE}/C_p) \times 100] \).

\(^d\) ER – elastic recovery for the mixtures at 150 MPa (%).
creased compactibility of larger granules is likely the higher propensity to create clean surfaces during compaction. These are less contaminated with lubricants such as magnesium stearate or Aerosil, which lower the crushing strength of the tablets produced. Similar results of higher interparticular bonding due to uncontaminated surfaces for fragmentable materials have already been reported (3, 9).

As seen in Table VI, all tablets compacted from particle-size fractions exhibited significantly higher compactibility (higher $C_p$) compared to the tablets compacted from the initial mixtures. As a result of wider particle-size distribution in the initial mixture, percolation of finer particles in the matrix of coarse particles may decrease the fragmentation potential of the tableting mixture. Consequently, compaction of these mixtures results in tablets with decreased crushing strength compared to the strength of tablets compressed from the particle-size fractions, as it was already proved by Riepma et al. (6). This may be an additional reason for poorer compactibility of the initial tableting mixtures compared to the corresponding size fractions.

Elastic recovery is the reversible part of deformation and is indicative of poor interparticulate bonding (14, 31). In this study, it was observed that the elastic recovery of each particle-size fraction increased with increasing compression pressure, which was already observed by Patel et al. (14). In this section, we report ER at 150 MPa. Higher elastic recovery was obtained by DGS mixtures. Particle size also had an influence on the elastic recovery of tableting mixtures. Our results show that higher elastic recovery was obtained for smaller-sized granules rather than larger-sized granules (Table VI). In general, tablets with higher compactibility showed lower elastic recovery (with the exception of the unexpectedly high ER of the DGS 180–400 fraction). This finding supports the idea of stronger bonding between larger particles. Increased elastic recovery in the case of smaller-sized particles indicates weaker attraction between them and could mean lower compactibility of the tableting mixture; a similar result was reported by van der Voort Maarschalk et al. (10).

Which parameter is more influenced by particle size: compressibility or compactibility?

Our results demonstrate that the compressibility of FBG and DGS tableting mixtures does not depend on particle size, which was attributed to the high fragmenting nature of the formulation used in this study. With increasing compression pressure, the extensive fragmentation of granules actually nullified the effect of initial particle size on compressibility. Both fractions of the FBG mixture and both fractions of the DGS mixture were more compressible than the initial unsieved mixtures. This is due to the broader particle-size distribution of the initial mixtures and consequently more densely packed rearrangement of particles at initial stages, which increased relative density and lowered the compressibility.

Despite the fact that fragmentation may also nullify the effect of particle size on compactibility, the significant effect of particle size on the compactibility profile was proved in this study. The tablets compacted from larger-sized fractions showed higher crushing strength than tablets from finer particle-size fractions. During the fragmentation of larger particles, many new, uncontaminated surface areas were created, which allowed stronger bonding between particles and formed tablets of higher crushing strength. In
addition, the compactibility of each sieved fraction was significantly higher than the compactibility of the corresponding initial mixture. Broader particle-size distribution in the initial mixture again enabled denser packing between particles and decreased the fragmentation potential of the tableting mixture. The higher compactibility of larger-sized granules was also confirmed through the lower friability and lower elastic recovery of tablets made of larger-sized granules. This confirms stronger interparticulate bonding of larger particle-size fractions.

CONCLUSIONS

Our results allow the most appropriate tableting mixture for industrial scale in terms of its compaction properties to be selected. The FBG mixture has better compaction properties (both compressibility and compactibility) compared to the DGS mixture, but both mixtures show poor or no dependence of compressibility on the particle size of granules (180–400 or 400–710 µm). From the compactibility point of view, the selection of a tableting mixture with larger granules may be preferred because it produces tablets with superior crushing strength compared to other mixtures. Regarding the fact that there are no significant differences between the compressibility of both particle-size fractions, a narrower particle-size range (400–710 µm) of both mixtures (FBG and DGS) should be selected to produce tablets with the lowest friability and elastic recovery and with the highest crushing strength.

REFERENCES


POVZETEK

Študij kompresibilnosti in kompaktibilnosti realne zmesi za tabletiranje: Vpliv velikosti granulata

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Ključne besede: velikost delcev, kompresibilnost, kompaktibilnost, Heckel, Walker

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