Deciphering the role of granule deformation and fragmentation for the tableting performance of some dry granulated powders

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HIGHLIGHTS

- The granule composition affects degree of granule fragmentation and deformation
- The absolute tablet tensile strength is governed by the degree of deformation
- The lubricant sensitivity is controlled by the degree of granule fragmentation
- The granule fragmentation affects the loss of tabletability by number of bonds
- The granule deformation affects the loss of tabletability by bonding force

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ABSTRACT

In this study, the question of how fragmentation and deformation of granules during compression can be linked to the tableting performance of dry granulated powders is addressed. Granulated powders of a systematically varied composition of a plastic and a brittle material were prepared by slugging and thereafter compacted into tablets. The tablet’s micro-structure, porosity, and tensile strength were assessed; moreover, the relationships between the Adams compression parameters $\tau_0$ and $\alpha$ and the tableting performance were studied.

The composition and the slugging pressure had a limited effect on the tablet porosity. However, they had a marked effect on the tablet micro-structure, which varied from tablets composed of deformed but otherwise preserved granules to tablets composed of small granule fragments. The tablet tensile strength, the loss of tabletability, and the lubricant sensitivity varied with the Adams compression parameters, indicating a complex effect of granule fragmentation and deformation on the tableting performance. The effect of the granule compression properties on the tableting performance is mediated by the number and average force of the intergranular bonds of the tablet.
1. Introduction

Dry granulation has become a common technique to produce a granular powder that subsequently is to be formed into tablets [1]. In a previous paper [2], we discussed the compression properties of some dry granulated powders prepared from microcrystalline cellulose and lactose in different proportions. Based on the character of the in situ strain-pressure curves, three compression stages were identified, which are proposed to be dominated or controlled by different compression mechanisms as follows: In the first stage, the granules became rearranged and fragmented which occurred over a range of relatively low compression pressure; in the second stage, fragmentation ceased and granule deformation dominated the rate of compression and finally, in the third stage, granule deformation ceased and a stiff body with high resistance to deformation was formed. In order to derive quantitative metrics of the compression properties, some compression parameters were derived using a global compression equation (the Kawakita eq. [3]) and a micro-mechanical compression equation (the Adams eq. [4]). The Adams parameter ($\alpha$) was shown to reflect a critical part of the compression process described as macroscopic stiffening, a part proposed to be controlled by the degree of granule deformation. Hence, this parameter can be hypothesized to indicate the degree of granule deformation and show some correlation to the single granule plastic stiffness.

The tableting performance of a powder typically refers to its flowability and tablet forming ability [5]. In this paper, the tablet forming ability of some dry granulated powders is reported regarding the following three aspects: the tabletability of un lubricated granules, the loss of tabletability caused by the dry granulation, and the lubricant sensitivity (the reduction in tablet tensile strength due to the admixing of a lubricant to the granulated powder). This is a continuation of the previous paper which focuses on the performance of the granules in the final tablet.

The term tabletability is used here to describe the ability of a powder held in a confined space to cohere into a tablet due to the application of pressure. Accordingly, the change in tabletability of a dry granulated powder compared to the ability of the starting fine powder is hereinafter referred to as the loss of tabletability (LoT), a term that is also denoted as a loss of reworkability or loss of compactibility [1]. The term indicates that the dry granulation will cause a reduction in the tablet strength, but the opposite effect has also been reported [6–8]. Several underlying causes for this LoT have been proposed in the literature, including the compression properties of the granules. In an earlier study [9], the compression and compaction properties of a series of dry granulated powders of microcrystalline cellulose were studied. It was concluded that granules of low compression strength, as assessed by the Adams parameter, collapsed more or less completely and lost its structure during compression but at a higher granule compression strength, tablets of a microstructure described as a cluster of cohered granules were formed. Moreover, the loss of tabletability increased with increased compression strength, associated with a change toward granules, with an increased resistance to collapsing or becoming fragmented during compression. Thus, the LoT was proposed to depend on the degree of fragmentation of the granules. Later, in an overview of material properties affecting the tensile strength of tablets formed of dry granulated powders, Sun and Kleinebudde [1] proposed that deformation of the granules is a critical compression mechanism for the tablet strength. Thus, granule deformation may also play an important role in the LoT.

The lubricant sensitivity of a powder, i.e., the change in tablet forming ability, typically a reduced ability, due to the admixing of a hydrophobic lubricant, such as magnesium stearate, is a common phenomenon. The underlying cause behind this loss is the prevention of bonding between particle surfaces within the tablet due to a surface localization of lubricant. Besides the type and amount of lubricant and the mixing process used, the lubricant sensitivity depends also on the properties of the substrate (the particles or granules), especially the fragmentation of the granules creating lubricant free surfaces [10,11]. Hence, granule fragmentation may be relevant for the tableting properties of dry granulated powders by affecting the tabletability, the loss tabletability, and the lubricant sensitivity. Thus, the question of how fragmentation and deformation of the granules during confined compression can be linked to and explain the tableting performance of dry granulated powders deserves to be further explored. Therefore, in this study, the relationships between the Adams compression parameters, on the one hand, and the tabletability, loss of tabletability, and lubricant sensitivity, on the other, were studied. It has previously been stated [1] that as a golden rule, a balance between brittle and plastic properties of the starting materials should be sought when a granulated powder is prepared by dry granulation. Accordingly, as model materials, granular powders prepared from five fine powders comprising a systematically varied excipient ratio of a plastic and a brittle material were used.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose, abbreviated MCC (Avicel PH 101, FMC Biopolymer, U.S.A.), and crystalline α-lactose monohydrate, abbreviated LAC (Pharmatose 200 mesh, DMV, Veghel, The Netherlands), were used as received. The two powders were selected to represent common pharmaceutical excipients but with different properties with regard to compression properties and its ability to compact into tablets. The specific excipient qualities used (Avicel PH 101 and Pharmatose 200 mesh) were selected as representatives of common fillers in tablet formulation.

Five powders were used in the experiments, i.e., the two single powders and three binary blends of the fine powders in the proportions 25:75, 50:50, and 75:25 of MCC:LAC (the concentration of MCC in the powders are henceforth abbreviated $\beta_{MCC}$). The binary mixtures were prepared by dry mixing for 5 min in a laboratory shear mixer (QMM-II, Donsmark Process Technology, Denmark) at an impeller speed of 500 rpm. Before starting any experiments, the five powders were
equilibrated for at least three days at a relative humidity (RH) of 40% in a desiccator containing a saturated solution of sodium iodide stored at room temperature. Magnesium stearate, abbreviated MgSt (Sigma-Aldrich, Sweden), was used as a lubricant.

Particle and compression characteristics of the fine powders have been reported in an earlier paper [2].

2.2. Dry granulation

Dry granulated powders were prepared of all five powders by slugging and milling, as described earlier [2]. In short, slugs were formed at two slugging pressures, 50 and 100 MPa, and thereafter milled into granules by hand. For each granulated powder, two sieve cuts were prepared by dry sieving by hand, using three precision sieves (Veco, Eerbeek-Holland) giving the following granule size fractions for all powders of different concentrations of magnesium stearate, i.e., 0.5% and 1% w/w, were prepared.

Table 1

<table>
<thead>
<tr>
<th>Powder</th>
<th>Slugging pressure (MPa)</th>
<th>σf (MPa)</th>
<th>a</th>
<th>a (%)</th>
<th>σt (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% fBCC</td>
<td>50</td>
<td>2.79</td>
<td>0.757</td>
<td>4.43</td>
<td>2.03</td>
</tr>
<tr>
<td></td>
<td>(2.35)</td>
<td>(0.02)</td>
<td>(0.28)</td>
<td>(1.32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>6.28</td>
<td>0.717</td>
<td>5.02</td>
<td>2.32</td>
</tr>
<tr>
<td></td>
<td>(5.94)</td>
<td>(0.03)</td>
<td>(0.35)</td>
<td>(1.49)</td>
<td></td>
</tr>
<tr>
<td>75% fBCC</td>
<td>50</td>
<td>1.72</td>
<td>0.750</td>
<td>4.79</td>
<td>1.49</td>
</tr>
<tr>
<td></td>
<td>(3.46)</td>
<td>(0.01)</td>
<td>(0.13)</td>
<td>(0.83)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>4.45</td>
<td>0.715</td>
<td>5.45</td>
<td>1.46</td>
</tr>
<tr>
<td></td>
<td>(2.18)</td>
<td>(0.04)</td>
<td>(0.19)</td>
<td>(1.21)</td>
<td></td>
</tr>
<tr>
<td>50% fBCC</td>
<td>50</td>
<td>0.99</td>
<td>0.731</td>
<td>5.64</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>(2.45)</td>
<td>(0.02)</td>
<td>(0.19)</td>
<td>(1.53)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>2.58</td>
<td>0.681</td>
<td>6.39</td>
<td>1.11</td>
</tr>
<tr>
<td></td>
<td>(7.05)</td>
<td>(0.04)</td>
<td>(0.31)</td>
<td>(2.06)</td>
<td></td>
</tr>
<tr>
<td>25% fBCC</td>
<td>50</td>
<td>0.51</td>
<td>0.669</td>
<td>7.98</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>(2.66)</td>
<td>(0.03)</td>
<td>(0.58)</td>
<td>(4.29)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>1.28</td>
<td>0.644</td>
<td>8.54</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>(4.10)</td>
<td>(0.04)</td>
<td>(0.81)</td>
<td>(5.99)</td>
<td></td>
</tr>
<tr>
<td>0% fBCC</td>
<td>50</td>
<td>0.30</td>
<td>0.589</td>
<td>12.93</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>(6.17)</td>
<td>(0.06)</td>
<td>(0.56)</td>
<td>(5.22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>0.64</td>
<td>0.564</td>
<td>12.60</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>(7.90)</td>
<td>(0.02)</td>
<td>(0.78)</td>
<td>(6.80)</td>
<td></td>
</tr>
</tbody>
</table>

determined using linear regression in the pressure range 10–50 MPa (R² > 0.999).

2.3. Lubrication of granules

One of the dry granulated powders, prepared at a slugging pressure of 100 MPa and of the size fraction 500–710 μm, was mixed with magnesium stearate using a Turbula mixer (Willy A. Bachofen AG, Basel, Switzerland) operating at 22 rpm for 5 min. Two lubricated granulated powders of different concentrations of magnesium stearate, i.e., 0.5% and 1% w/w, were prepared.

2.4. Tableting and tablet characterisation

The same compression set-up was used to prepare tablets as used in the earlier study investigating the compression properties of the powders. Approximately 400 mg of unlubricated or of lubricated dry granulated powders were manually filled into the die and compacted into tablets using a material testing instrument (Zwick Z100, Zwick/Roell GmbH & Co, Ulm, Germany) equipped with circular flat-faced punches with a diameter of 11.3 mm. Unlubricated and lubricated granulated powders were compacted at tabletting pressures of 100 and 300 MPa using a linear loading rate of 10 mm/min. Before compaction, the punches and the die were brushed with 1% w/v magnesium stearate suspension in ethanol, which was allowed to evaporate prior to the manual filling of the die before each compaction.

After compaction, the tablet was ejected from the die, and its weight (W), height (h), and diameter (D) were determined shortly after ejection using an analytical balance and a height gauge (Litematic VL 50A, Mitutoyo, Japan). From the weight and dimensions of the tablet, geometrical tablet density (ρt) was calculated as [12]:

\[ \rho_t = \frac{4W}{\pi D^2 h} \quad (3) \]

Thereafter, the geometrical tablet porosity (Eg) was calculated as [12,13]:

\[ E_g = 1 - \frac{\rho_f}{\rho_{app}} \quad (4) \]

where ρ_{app} is the helium pycnometry density, also referred to as the apparent and true particle density (AccuPyc II 1340, Micromeritics, U.S. A.).

The force needed to fracture the tablets while compressed diametrically (Ff) was determined using a tablet hardness tester (PharmaTest PTB 511E, ISO 9001, Hainburg, Germany) operated at a linear force increase rate of 20 N/s. The tablet tensile strength (σt) was subsequently calculated according to Fell and Newton [14], as follows:

\[ \sigma_t = \frac{2F_t}{\pi hD} \quad (5) \]

All reported tablet data are the average of five measurements. The loss of tabletability after roll compaction is typically represented by the difference in tensile strength of tablets compacted of the ungranulated and granulated powders (unworked and worked powders) at the same tabletting pressure [15–17]. Here, the loss of tabletability is calculated in an analogous way to the lubricant sensitivity ratio (eq. 7 below) by the following expression:

\[ \text{LoT} = 1 - \frac{\sigma_t \text{granulated}}{\sigma_t \text{ungranulated}} \quad (6) \]

For the tablets made of lubricated granules, a lubricant sensitivity ratio (LSR) was calculated as given by Bos and co-workers [18]:

\[ \text{LSR} = 1 - \frac{\sigma_t \text{lubricated granules}}{\sigma_t \text{unlubricated granules}} \quad (7) \]

In addition, a lubricant sensitivity difference (LSD) were calculated...
as follows:

$$\text{LSD} = \sigma_t^{\text{unlubricated granules}} - \sigma_t^{\text{lubricated granules}}$$  \hspace{1cm} (8)

2.5. Scanning electron microscopy imaging of tablets

Images of cross-sectional surfaces of tablets were obtained by scanning electron microscopy (SEM) using a Zeiss LEO 1530 microscope (Carl Zeiss, Germany) operating at an accelerating voltage of 2.0 kV. Images were taken at 100× magnification; furthermore, before imaging, the samples were sputtered with gold/palladium under argon gas in a sputter coater (Polaron SC7640, Quorum Technologies Ltd., U.K.).

Radial cross-sectional tablet surfaces were obtained by fracturing tablets formed of unlubricated and lubricated granulated powders in two halves perpendicular to the axes of tablet compaction by diametrical compression, as described above. Axial cross-sectional surfaces were obtained by splitting tablets formed from unlubricated granulated powders parallel to the axes of tablet compaction. In order to ensure splitting along the axial cross-section, a parchment paper was placed in the middle of the powder column in the die before compaction. This was accomplished by pouring the granules into the die in two steps; by firstly

![Microphotographs of axial fracture surfaces (on the left side) and radial fracture surfaces of cross-section of split tablets (on the right side). The tablets were compacted at 100 MPa using unlubricated granulated powders of size fraction 500–710 μm at a slugging pressure 100 MPa.](image-url)
pouring half of the measured granules and placing the paper on top of the first layer of granules and secondly adding the remaining half of the granules. The weight of all produced tablets were approximately 400 mg.

2.6. Statistical data analysis

All graphs and statistical calculations were done in GraphPad Prism 8 for Windows (GraphPad Software, San Diego, California, U.S.A.). All data are presented as mean and relative standard deviation in percent (RSD%).

Fig. 1. (continued).

Fig. 2. Microphotographs of MCC granule (on the left side) and LAC granule (on the right side) produced at a slugging pressure of 50 MPa and a size fraction of 500–710 μm.
3. Results

3.1. Tablet micro-structure

In Fig. 1 (left panel), examples of images of axial fracture surfaces of tablets formed at 100 MPa are shown, illustrating the effect of composition and slugging pressure on the tablet microstructure. Regarding the granule composition, tablets formed from granules consisting only of MCC (100% MCC) had an uneven cross-sectional surface with structural features that resemble the original granules (Fig. 2). A step-wise reduction of $f_{\text{MCC}}$ of the granular powders gave, for most compositions, a qualitatively similar tablet microstructure, i.e., tablets consisting of a cluster of bonded granules with discernible boundaries but with a gradually reduced topographical variation. However, tablets of 0% MCC had relatively flat surfaces with no clear boundaries between the original granules. For the slugging pressure, an increased slugging pressure gave a more uneven cross-sectional surface for all compositions (images not shown).

Examples of images of radial cross-sectional surfaces of fractured tablets formed at 100 MPa are also shown in Fig. 1 (right panel). The
Fig. 3. (continued).

Fig. 4. Effect of composition ($f_{MCC}$) on the porosity ($E_t$) of tablets compacted using all unlubricated fine and granulated powders at 100 MPa and 300 MPa. Filled bar = powders; a = granules 250–500 μm, slugging pressure 50 MPa; b = granules 250–500 μm, slugging pressure 100 MPa; c = granules 500–710 μm, slugging pressure 50 MPa; d = granules 500–710 μm, slugging pressure 100 MPa; pattern bar = 0.5% lubricant, unfilled bar = 1% lubricant; $P_t$ = tableting pressure.
radial cross-sectional surfaces were generally smoother than the axial fracture surfaces and structures that reflect the dimensions of the original granules, hence more difficult to discern. For tablets formed using f_MCC of 100%, 75%, and 50%, the topographical variation reflects the original granules. However, for tablets formed using 25% f_MCC and 0% f_MCC, no clear boundaries could be seen between the original granules. The tablets formed using both lubricated and granular powders gave the same qualitative information (Fig. 3).

3.2. Tablet porosity

For the unlubricated powders, an increased tableting pressure gave as expected a decreased tablet porosity (Fig. 4), i.e., E_t of 16–18% compared to E_t of 8–9%. For each composition and compaction pressure, the fine and the granulated powders gave practically the same tablet porosity. For tablets formed at a pressure of 100 MPa, the most deviating tablet porosity was obtained for tablets consisting only of LAC. For tablets prepared at 300 MPa, the composition of the powder had a negligible effect on the tablet porosity.

The porosities of tablets formed using the lubricated granulated powders were similar to or slightly higher than the porosities of the corresponding unlubricated granules (Fig. 4), i.e., a difference of 1–3% independent of the compaction pressure. The concentration of lubricant did not affect the tablet porosity.

3.3. Tabletability

A decreased f_MCC generally decreased the tablet tensile strength, i.e., MCC enhanced the tabletability of the powders which also is reported earlier [15]. An increased tableting pressure gave, as expected, an increased tablet tensile strength for each fine and granulated powder. The larger granules tended to give a lower tablet tensile strength than the smaller and the more pronounced difference was observed for granules consisting mainly of MCC. The effect of granule size was generally small (Table 2). A limited effect of granule size on the tablet tensile strength of tablets formed of spherical granules of a similar size difference as used here has also been reported earlier [19]. The limited effect of granule size may be due to the small size difference between the smaller and larger granules and thus, a larger size difference may give a larger difference in tabletability.

An increased slugging pressure generally reduced the tensile strength of the tablets. A perfect agreement was obtained between the tensile strength of slugs and tablets prepared at an applied pressure of 100 MPa (Tables 1 and 2).

3.4. Lubricant sensitivity

The lubricated granules, i.e., the larger sieve fraction of granules prepared at a slugging pressure of 100 MPa, gave tablets of similar or lower tensile strength than the corresponding unlubricated granules (Fig. 5). The degree of strength reduction, i.e., the lubricant sensitivity ratio (LSR), was dependent on both the lubricant concentration and the composition of the powders. For most granular powders, the higher concentration of lubricant (1%) gave a higher LSR. An increased f_MCC affected the strength reduction in a non-linear manner, i.e., the

![Fig. 5. Effect of composition (f_MCC) on the lubricant sensitivity ratio (LSR) due to admixing of magnesium stearate at two concentrations (0.5% and 1% w/w) of tablets compacted using granulated powders of size fraction 500–710 μm at 100 and 300 MPa. Filled bar = 0.5% lubricant; Pattern bar = 1% lubricant; P_t = tableting pressure.](image-url)

### Table 2

The tensile strength (σ_t) of tablets for all unlubricated powders and granules compacted at compaction pressures of 100 MPa and 300 MPa. Relative standard deviations are given in percent (%RSD) within brackets.

<table>
<thead>
<tr>
<th>Powder blend</th>
<th>Tableting pressure (MPa)</th>
<th>Slugging pressure (MPa)</th>
<th>Tableting pressure (MPa)</th>
<th>Slugging pressure (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100</td>
<td>300</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>100% f_MCC</td>
<td>6.39 (1.55)</td>
<td>12.8 (4.21)</td>
<td>50</td>
<td>4.09 (1.18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>3.28 (1.67)</td>
</tr>
<tr>
<td>75% f_MCC</td>
<td>4.44 (2.17)</td>
<td>9.57 (2.00)</td>
<td>50</td>
<td>3.13 (1.07)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>2.33 (1.75)</td>
</tr>
<tr>
<td>50% f_MCC</td>
<td>2.63 (1.86)</td>
<td>6.48 (0.88)</td>
<td>50</td>
<td>2.01 (2.51)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>1.53 (1.99)</td>
</tr>
<tr>
<td>25% f_MCC</td>
<td>1.31 (1.96)</td>
<td>3.83 (0.37)</td>
<td>50</td>
<td>1.02 (0.33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>0.85 (1.32)</td>
</tr>
<tr>
<td>0% f_MCC</td>
<td>0.69 (2.50)</td>
<td>2.40 (1.70)</td>
<td>50</td>
<td>0.55 (1.32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>0.57 (2.01)</td>
</tr>
</tbody>
</table>
granulated powder comprising up to 50% \( f_{\text{MCC}} \) gave no or a low strength reduction, but the granulated powder comprising predominantly MCC had a higher degree of strength reduction. The effect of compaction pressure was limited; furthermore, there was no general trend regarding the interplay between composition and compaction pressure.

### 3.5. Loss of tabletability

The un lubricated granulated powders generally gave tablets of lower tensile strength than the corresponding fine powders (Table 2). Thus, there was a general loss of tabletability (LoT) due to the dry granulation (Fig. 6), consistent with several other reports [1]. The LoT tended to increase with an increased \( f_{\text{MCC}} \), but the LoT was also dependent on the slugging pressure and the tableting pressure. For tablets prepared at 100 MPa, the LoT generally increased with an increased \( f_{\text{MCC}} \). However, for tablets prepared at 300 MPa, a different pattern was obtained, i.e., the addition of the lowest concentration of MCC (25% \( f_{\text{MCC}} \)) tended to decrease the LoT but thereafter, it generally increased with an increased \( f_{\text{MCC}} \).

### 4. Discussion

#### 4.1. Tablet porosity and micro-structure

It has previously been reported [2] that the dry granulation did not affect the yield pressure of the powders. Also, for the tablet porosities, an insignificant effect of the dry granulation step was obtained for the respective composition. Moreover, the tablet porosity showed only a small variation between the different compositions, albeit the tablet tensile strength varied markedly (Table 2). Thus, on the macroscopic level, the structure of the tablets showed a limited variation and could not explain the significant variations in tabletability between the powders. Hence, the differences in tabletability must be understood on a microstructural level, and the images of the tablet’s cross-sectional surfaces showed distinct structural differences. The fracturing of a tablet by diametrical compression may occur around the granules but also, as reported earlier [20,21], across the granules. Thus, the appearance of a tablet fracture surface may not be indicative of the degree of fragmentation. However, the surfaces obtained by splitting the tablets along a physical barrier consisting of a paper sheet, giving a fracture surface formed by a failure around the granule, showed a similar surface structure as the radial fracture surfaces. Moreover, the fracturing of tablets formed from lubricated granules will increase the probability of having a type of failure around the granule, which also resulted in tablet fracture surfaces showing a similar structural dependency on \( f_{\text{MCC}} \) (Fig. 3). It is concluded that a variation in the tablet’s micro-structure was obtained, ranging from tablets composed of deformed but otherwise preserved granules to tablets composed of small granule fragments. This micro-structural variation was primarily dependent on the powder composition but also on the slugging pressure. Granules consisting of LAC, a material typically considered as being brittle and prone to fragmentation, were markedly fragmented; consequently, the tablet consisted of cohered granule fragments and primary particles. The granules consisting of a high proportion of MCC, a material typically considered as ductile, fragmented to a limited degree, and the tablet consisted of granules with similar dimensions as the original granules. There was thus a direct relationship between the mechanical properties of the starting material and the granules formed thereof. For slugging pressure, the higher slugging pressure gave less porous and more robust granules less prone to fragmentation. It has earlier been reported [9] that highly porous granules of MCC collapse almost completely during compression, giving a tablet micro-structure that is similar to the tablets of the original fine powder. Thus, besides the composition, the granule porosity also affected the degree of granule fragmentation.

It is concluded that the physical micro-structure of the tablets, in terms of the distribution of the particles within the tablet, varied markedly. Specifically, for a tablet consisting of small nearly completely collapsed granules, a similar micro-structure to the tablets of the original fine powder will be obtained while for a tablet consisting of granules that were to a large degree preserved as coherent but deformed structures, the micro-structure will differ markedly compared to the tablets of the original fine powder. It can be assumed that such a variation in tablet micro-structure will subsequently affect the inter-granular bond structure of the tablet. In a simplified way, the bond structure can be viewed as consisting of two variables [22–24], i.e., number and the area of the bonds between the particles acting over a cross-sectional area of the tablet. This conception is used here in order to qualitatively discuss the differences in tableting performance between the granulated powders. Due to the complexity of the physical and bond structure of a tablet formed of granulated particles, no attempts have been made to derive quantitative indications of the number and areas of inter-granular bonds.

For tablets consisting of cohered granules, there were two types of pores, i.e., intragranular pores and voids (intergranular pores); moreover, the pore system can be described as a two compartment pore

![Fig. 6. Relationships between composition (\( f_{\text{MCC}} \)) and loss of tabletability (LoT) for tablets compacted using all granulated powders. Dark blue bar = granules 250–500 \( \mu \)m, slugging pressure 50 MPa; Light blue bar = granules 500–710 \( \mu \)m, slugging pressure 50 MPa; Orange bar = granules 250–500 \( \mu \)m, slugging pressure 100 MPa; Grey bar = granules 500–710 \( \mu \)m, slugging pressure 100 MPa; \( P_1 \) = tableting pressure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)](image-url)
system. Tablets formed from the fine powders consist of cohered fine particles, which were (excluding any small intraparticulate pores) separated by interparticular pores, i.e., a one compartment pore system. Hence, the granulation step, generally, changed the nature of the pore system from a monistic (i.e., a one compartment pore system) to a dualistic pore system (i.e., a two compartment pore system). However, for the LAC granules that were extensively fragmented, a similar monistic pore system, as for the tablets from the fine powder, was obtained.

4.2. Tabletability

As reported earlier [2], an increased $f_{\text{MCC}}$ gave an increased tensile strength of the slugs and also a general increase in the Adams $\tau_0$ parameter (Table 1). Since also the tablet tensile strength generally increased with $f_{\text{MCC}}$, positive correlations were obtained for all the $\sigma_t$ vs. $\tau_0$ relationships (Fig. 7). The positive relationships between $\sigma_t$ and $\tau_0$ may at least partly be explained by an increased bonding ability (increased bond strength) of the granules with an increased $f_{\text{MCC}}$. However, different $\sigma_t$ vs. $\tau_0$ relationships were obtained for the different types of granules, indicating that granule compression strength, and thus granule fragmentation, cannot explain the differences in tabletability between the un lubricated granules.

In contrast to the relationships between $\sigma_t$ vs. $\tau_0$, the $\sigma_t$ vs. $\alpha^{-1}$ relationships for each tableting pressure (Fig. 8), approached, coincided for all types of granular powders, i.e., a single relationship was obtained, independent of the granule composition, size, and porosity. However, there was a slight tendency for a higher tablet tensile strength for the smaller granules at the highest $\alpha^{-1}$. As reported earlier [2], the Adams $\alpha$ parameter represents a measure of the evolution of the macroscopic stiffening phase during the compression of the granular powders, proposed to be controlled by the degree of permanent deformation of the granules. It is thus concluded that granule deformation had a critical role in the development of tablet strength, i.e., granule deformation was a significant strength producing compression mechanism for the granulated powders. The difference in tensile strength of tablets formed at 300 MPa and 100 MPa increased with a decrease in the Adams $\alpha$ parameter, i.e., with a decreased plastic stiffness of the granules. Thus, the more deformable granules were more sensitive to compaction pressure with regard to the expressed degree of granule deformation.

The $\sigma_t$ vs. $\alpha^{-1}$ relationships were curved, and an extrapolation of the curves indicates that a value of $\alpha^{-1}$ of zero corresponds to a tablet tensile strength of zero. Thus, given that the $\alpha$ parameter is an indication of granule deformation, this means that a powder consisting of infinitely hard granules will not be able to form a tablet, which is physically reasonable.

The importance of granule deformation for the tablet strength can be explained by assuming that a granule cluster model of the tablet microstructure, i.e., the tablet consists of cohered granules, is applicable to the tablets formed from the granulated powders, irrespective of their composition. While subjected to an external force, the tablet will fail predominantly by an around type of failure mechanism (Fig. 1). An increased degree of granule deformation during compression will increase the area of contact; thus, the bonding forces between the “in tablet” granules holding the cluster together and the measured tablet strength will increase.

4.3. Lubricant sensitivity

The addition of a magnesium stearate to a powder will typically reduce the tablet strength. This effect of magnesium stearate can be understood by considering a tablet formed from a lubricated powder as consisting of bonding and non-bonding sites, where the non-bonding sites correspond to surfaces covered with the lubricant. Fragmentation of particles during compression will result in new lubricant free surfaces, and the proportion of bonding sites will increase. Thus, the relative reduction in tablet strength due to the addition of a hydrophobic lubricant, such as magnesium stearate, indicates the degree of granule fragmentation during tableting [10,11]. This lubricant sensitivity was markedly dependent on the composition of the granules (Fig. 5). The higher lubricant concentration gave a higher lubricant sensitivity ratio (LSR), possibly due to a better coverage of the enveloped granule surfaces with the lubricant, but the type of relationships was similar for the respective concentrations of the lubricant. The findings support that the degree of granule fragmentation decreased with an increased $f_{\text{MCC}}$, which is consistent with the reasoning above on the microstructural characteristics of the tablets.

The Adams parameter $\tau_0$, here denoted as the compression strength of the granules, is considered to indicate the stress, causing single granules to fail during powder compression by a crack opening mechanism [4]. In Fig. 9, $\tau_0$ is plotted as a function of the relative reduction (upper graph) and the difference (lower graph) in tensile strength due to the admixing of magnesium stearate. Generally, an increased $\tau_0$ corresponded to an increased susceptibility of the granulated powders to the presence of magnesium stearate, i.e., an increased lubricant sensitivity ratio (LSR) as well as an increased lubricant sensitivity difference (LSD). The relationships were markedly curved, with a strong sensitivity at the highest granule compression strength. The lubricant sensitivities vs. the $\tau_0$ relationships approached a LSR of unity and a LSD of zero. This type of relationships is physically justified, i.e., a granule of infinite low strength will fragment completely, causing a minute sensitivity to a
lubricant. Thus, the Adams Tofiq et al. M. Tofiq studied. the granulated powders, the LoT caused by the dry granulation was also area. Thus, in order to more broadly describe the tableting properties of position, the calculation of the loss of tabletability (LoT) will simplify the bonding strength can be assumed to be similar between tablets formed 

Fig. 8 indicates that the area of contact developed between the particles over the fracture area. Assuming a constant bond 

4.4. Loss of tabletability

The transformation of a powder into a coherent solid specimen is fundamentally a bond formation process. The strength of the bond network developed between the particles or granules of the tablet is often described as the product of two factors [25]: the area of the contact (bonding area) developed between the particles and the strength of the individual bonds. A change in the composition of a powder may affect both the bonding area and the bonding strength; for the granular powders used in this study, it can be assumed that the addition of microcrystalline cellulose to lactose will not only affect the granule mechanical properties [2] but also increase the mean strength of the bonds holding the tablet together. The impact of the composition on the tablet strength is thus difficult to resolve into these two fundamental factors. The importance of granule deformation for the absolute tablet tensile strength (Fig. 8) indicates that the area of contact developed between the granules during compression has a critical role for the differences in their tabletability. However, the evolution of the profiles may also be affected by an increased bond strength. Given that the mean bonding strength can be assumed to be similar between tablets formed from a fine powder and from a granulated powder of the same composition, the calculation of the loss of tabletability (LoT) will simplify the problem into a relationship between the composition and the bonding area. Thus, in order to more broadly describe the tableting properties of the granulated powders, the LoT caused by the dry granulation was also studied.

In all cases, there was a lower tablet strength for tablets formed using granulated powders than for those formed using fine powders (Fig. 6), i.e., a similar general finding as for the lubricant sensitivity ratio (Fig. 5). It seems thus that the degree of granule fragmentation also affected the LoT (Fig. 10). The general LoT is interpreted as a general shift in the microstructure of the tablets caused by the granulation step. This shift is characterized by a change from a tablet composed of cohered fine particles (a fine particle system) to a tablet composed of cohered granules (a granule system). Such a microstructural shift will also affect the bond distribution within the tablet. For a fine particle system tablet, the number of bonding sites will be high, and the bonding force at each site low. A change to a granule system tablet will reduce the number of bonding sites, depending on the degree of granule fragmentation and increase the bonding force, depending on the degree of granule deformation. It is proposed that the net-effect of the change in number and average force of the bonding sites per cross-sectional tablet area due to a microstructural shift will control the LoT.

For granular powders of both size fractions tableted at 100 MPa (Fig. 10, left panel), the more porous granules gave a nearly linear increase in LoT with \( \tau_0 \), illustrating the effect of gradually reduced number of bonding sites of the tablet for the tablet strength. However, it is noteworthy that a corresponding marked increase in LoT at high \( \tau_0 \), which was obtained for the LSR, was not obtained for the LoT. For the less porous granules (prepared at 100 MPa slugging pressure), a different LoT vs. \( \tau_0 \) relationship was obtained with an initial bended LoT, followed by a plateau in the LoT vs. \( \tau_0 \) relationship. The initial, more marked, LoT indicates that the degree of fragmentation was lower for the less porous and harder granules and the reduction in the number of bonding sites thus was higher. However, the leveling-off of the relationship at the highest \( f_{\text{MCC}} \) indicates that the reduction in the number of bonds is balanced by an increased bonding force due to an increased degree of granule deformation, causing an increased intergranular bonding area.

The relative importance of the number of and force of the bonding sites is illustrated also for the tablets compacted at 300 MPa (Fig. 10, right panel). For the LAC granules, the increased compaction pressure only had a limited effect on the LoT, indicating that the compaction pressure had a limited effect on the degree of granule fragmentation. For the granules prepared at 50 MPa slugging pressure, the LoT decreased initially due to the addition of MCC, but thereafter increased with an increased \( f_{\text{MCC}} \). It is likely that an increased compaction pressure from 100 MPa to 300 MPa increased the degree of plastic deformation of the granules that occurred during compression, which increased the bonding force between the granules. Thus, the reduction in LoT is explained by an increased average intergranular bonding force due to an increased degree of granule deformation, giving a limited loss of tabletability, i.e., the granule deformation over-compensated for the decreased number of bonding sites. Thereafter, the LoT decreased due to a reduction in the number of bonding sites.

The granular powders of the smaller granules generally tended to give lower values of LoT, i.e., the loss of tabletability was lower for the smaller granules explained by an increased number of intergranular bonding sites.

As stated above, the degree of deformation seems to be a critical process to explain the differences in the tablet strength between the lubricated and the un lubricated granulated powders. It seems thus that the area of the bonds developed between the granules during compression is decisive for the tablet strength, irrespective of any difference in granule fragmentation. However, the differences in the loss of tabletability seem to be a complex effect of three factors, i.e., the degree of granule fragmentation, the degree of granule deformation, and the original granule size.

In summary, the mechanistic explanation of the effect of \( f_{\text{MCC}} \) on the LoT is based on a simple bond summation concept, i.e., the tensile strength of the tablet equates the sum of the bonding forces acting between the particles over the fracture area. Assuming a constant bond
strength in the tablets composed of fine and granulated powders of the same composition, a difference in LoT between the different powders is accordingly dependent on a difference in tablet bond structure in terms of the number of bonding sites and the average bonding force over the tablet fracture area. A complete fragmentation of the granules will give a bond distribution similar to or equal to the bond structure of tablets formed from the ungranulated fine powder. Consequently, the tablet strength will be similar between the tablets of ungranulated and granulated powders and the LoT close to unity. When the strength of the granules increases, the degree of fragmentation that occurs during compression will decrease thus, reducing the number of bonds. However, if the granule plastic stiffness will decrease in parallel to a decreased granule fragmentation propensity, as for the mixtures used here, the reduction in the number of bonds is counteracted by an increased mean bonding force due to an increased degree of granule deformation, which will reduce the LoT.

The consequence of this reasoning is that the root cause for the phenomenon denoted LoT is the particle-to-granule size enlargement achieved during the dry granulation. This primary-to-secondary size enlargement process will result in different types of micro-structure of tablets, causing a change in the bond distribution controlling the tablet tensile strength. Such a micro-structural transition will occur unless the granules fragment completely into primary particles during compression, which probably is less likely for granules that should withstand handling during manufacturing.

5. Conclusions

It has previously been proposed [1] that one of the golden rules of roller compaction is that a balance between brittle and plastic properties of the starting materials is desirable when formulating a powder for dry granulation. In this study, granulated powders consisting of a brittle and a plastic material in different proportions were prepared and it is concluded that a change in powder composition will affect three properties of the granules related to their tableting performance, i.e., their fragmentation, deformation and their intrinsic bonding ability (bond strength). Fig. 11 represents an attempt to summarize the relationships between granule fragmentation, deformation and intergranular

![Fig. 10. Relationships between the Adams compression parameter $\tau_0$ and the loss of tabletability (LoT) for tablets compacted at 100 MPa and 300 MPa. Closed square = granules 250–500 $\mu$m, slugging pressure 50 MPa; Open square = granules 500–710 $\mu$m, slugging pressure 50 MPa; Closed triangle = granules 250–500 $\mu$m, slugging pressure 100 MPa; Open triangle = granules 500–710 $\mu$m, slugging pressure 100 MPa; $P_t =$ tableting pressure.](#)

![Fig. 11. Upper scheme: Overview of the proposed sequential relationship between formulation - processing - granule properties –granule tableting performance. Lower scheme: The role of three critical granule properties for the tensile strength and loss of tabletability of tablets compacted using unlubricated powders and for the lubricant sensitivity.](#)
bond strength for granulated powders without extragranular additives on the absolute tablet tensile strength (upper graph). Further, a deci-
phering of the role of the different compression mechanisms for the
tablet strength, the lubricant sensitivity, and the loss of tabletability are
summarized in the lower graph. These roles can be summarized as
follows:

1. **Granule deformation** will control the area and hence the bonding force of
   single granule-to-granule contacts in the tablet, which will be of
decisive importance for the differences in absolute tablet tensile strength between tablets formed from unlubricated dry granulated powders.

2. **Granule fragmentation** will decrease the lubricant sensitivity of a dry
   granulated powder by the formation of lubricant free surfaces that
   have a higher ability to bond, affecting the tablet tensile strength.

3. **Granule fragmentation** will affect the loss of tabletability by control-
   ling the number of granule fragments forming the tablet and thus the
   number of the inter-granular bonds in a tablet cross-section. The
   greater the similarity in the micro-structure between tablets of
   ungranulated and granulated powder, the lower the loss of
   tabletability.

4. **Granule deformation** will affect the loss of tabletability by increasing
   the area and hence the bonding force of single granule-to-granule contacts in the tablet and counteracts the adverse effects of a low
   degree of granule fragmentation.

The granule strength depends on the composition and the porosity of
the granules, and a certain mechanical strength of the granules is typi-
cally required to make them robust enough to withstand attrition during
the tabletting process. Thus, there will, in practice, be a window of
granule strength variation within which the compression properties and
subsequent tabletting performance can be controlled.

CRediT authorship contribution statement

Maryam Tofiq: Conceptualization, Methodology, Validation, Investigation, Writing – original draft. Josefina Nordström: Method-
ology, Writing – review & editing. Ann-Sofie Persson: Conceptualization, Methodology, Writing – review & editing. Göran Alderborn: Conceptualization, Methodology, Writing – original draft, Supervision, Resources, Funding acquisition, Project administration.

Declaration of Competing Interest

The authors report no competing interest.

Data availability

Data will be made available on request.

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