The effect of excipient particle size on the reduction of compactibility after roller compaction

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A B S T R A C T

Developing a robust roller compaction process can be challenging, due to the diversity in process parameters and material properties of the components in a formulation. A major challenge in dry granulation is the reduction of tablet strength as a result of re-compaction of the materials. The aim of this study is to investigate the impact of excipient type and particle size distribution on tablet tensile strength after roller compaction. Lactose mono-hydrate, anhydrous lactose and microcrystalline cellulose with different particle sizes are roller compacted at varying specific compaction forces. Granules obtained are compressed into tablets to evaluate the reduction in tablet strength upon increasing the specific compaction force. The impact of particle size of the starting material is shown to be vastly different for the three types of excipients investigated, due to the differences in mechanical deformation mechanisms. The presence of rough surfaces and a high degree of fragmentation for anhydrous lactose appears to be beneficial for compaction and re-compaction process. Additionally, the particle size of anhydrous lactose hardly affects the tensile strength of tablets, which can be beneficial for the robustness of a roller compaction process.

1. Introduction

Granulation is often a necessary step to improve powder properties for pharmaceutical processing. In most cases, granulation is performed prior to tableting to increase particle size, providing better flowability and reduced risk of segregation of components.(Parikh, 2016) Dry granulation refers to the controlled formation of granules by compaction and densification of powders. It is a popular granulation method, because of the fewer processing steps compared to wet granulation and the absence of water. It is especially attractive for drugs which are sensitive to moisture or solvent.(Jannat et al., 2016) Roller compaction is the preferred dry granulation technique, because of the greater production capacity, increased control over operating parameters and dwell time, and the minimal need for a powder lubricant.(Kleinebudde, 2004) Additionally, roller compaction is of particular interest for integration in a continuous manufacturing line, due to the inherently continuous nature of the process.(Rowe et al., 2017)

Despite the advantages of dry granulation, developing a robust roller compaction process can be challenging, due to the diversity in controlling factors and material properties.(Rogers et al., 2013) A major challenge in dry granulation is the reduction of tablet tensile strength as the result of recompression.(Bultmann, 2002) Compactibility of granules produced by roller compaction is impacted by many factors, like moisture content, lubrication, ribbon density, granule density, size, shape, surface roughness and deformation behavior of primary particles constituting the granules.(Sun and Kleinebudde, 2016; Wu and Sun, 2007) Several different mechanisms have been proposed to explain the loss of compactibility after dry granulation, with granule size enlargement and granule hardening as main mechanisms.(Sun and Kleinebudde, 2016) Granule size enlargement refers to a loss of compactibility as the result of a reduction in available bonding area between the granules during tableting.(Sun and Himmelspach, 2006) Granule hardening refers to a loss of compactibility as the result of densification of granules.(Patel et al., 2011)

For brittle materials that show extensive fragmentation upon compaction, granule hardening has been proposed as the main

mechanism for loss of compaction.(Skelbæk-Pedersen et al., 2021) Hardening of granules results in reduced porosity after roller compaction, thereby making the granules less prone to fragmentation. A lower degree of fragmentation results in lower tablet tensile strength by reducing the available bonding area upon compaction.(Skelbæk-Pedersen et al., 2021) The effect of granule hardening for brittle materials is even more pronounced for lubricated formulations, as for these formulations the bonding capability of the surface before fragmentation is limited by coverage of the lubricant. For the same reasons, the impact of reduced bonding area as a consequence of granule size enlargement is thought to be limited for lubricated brittle granules.(Wu and Sun, 2007)

Plastically deforming materials also show a reduction of compactibility upon roller compaction, which is explained by a combination of size enlargement and granule hardening. Size enlargement of granules results in significantly less available bonding area during tableting.(Sun and Himmelspach, 2006; Herting and Kleinebudde, 2008) Furthermore, the reduced surface area also increases the risk of a reduction of tablet strength by lubrication.(Skelbæk-Pedersen et al., 2021) Granule hardening is also a relevant mechanism for plastically deforming excipients, as a reduction of porosity reduces the deformability, resulting in lower bonding area.(Patel et al., 2011; Herting and Kleinebudde, 2008; Nordström and Alderborn, 2015) Typically, higher loss of compactibility upon roller compaction is observed for plastically deforming materials than for brittle materials.(Mosig and Kleinebudde, 2015)

The combination of multiple mechanisms that depend on both material properties and process parameters makes predicting the compactibility of pharmaceutical formulations after roller compaction a difficult task.(Kleinebudde, 2004; Pishnamazi et al., 2019) Currently, limited knowledge is available on the impact of raw material particle size on the tableting behavior of granules obtained after roller compaction. Research has mainly been performed on relating raw material particle size to the performance of the roller compaction process. (Yu et al., 2012; Miguélez-Morán et al., 2008; Von Eggelkraut-Gottanka et al., 2002) It was concluded that fine material may be less suitable for continuous roller compaction, due to potential fluctuation of fill levels in the roller compactor.(Von Eggelkraut-Gottanka et al., 2002) Additionally, powder feeding of very fine material might cause aeration during roller compaction, which could facilitate the formation of large voids in compacted ribbons and therefore limit the densification.(Yu et al., 2012; Miguélez-Morán et al., 2008) Using starting material with smaller particle size can however also be beneficial. Herting and Kleinebudde (Herting and Kleinebudde, 2007) for example, reported that a finer particle size of microcrystalline cellulose (MCC) and theophylline can be beneficial for the tensile strength of tablets produced after dry granulation.

So far, a direct comparison of the effect of excipient particle size on granule tableting behavior for excipients with different deformation mechanisms is lacking. This systematic, empirical study aims to expand the current knowledge on the difference in re-compactibility behavior of MCC, anhydrous lactose and lactose monohydrate by evaluation of the effect of raw material particle size on the re-compactibility behavior. A systematic approach is used for roller compaction of plastic and brittle deforming excipients at different specific compaction forces. Granules are lubricated before compaction into tablets, since pharmaceutical manufacturing processes typically require lubrication to reduce friction. In addition, a method is proposed to quantify the sensitivity of tablet tensile strength to specific compaction force applied during roller compaction.

2. Materials and methods

2.1. Materials

Anhydrous lactose (SuperTab® 21AN, SuperTab® 22AN, Lactopress® anhydrous fines), milled lactose monohydrate (Pharmatose® 150 M, Pharmatose® 200 M, Pharmatose® 350 M) and microcrystalline

cellulose (Pharmacel® 101, Pharmacel® 102) were obtained from DFE Pharma (Goch, Germany). Before roller compaction, materials were dry blended with 4% *w*/w croscarmellose sodium (Primellose®, DFE Pharma, Goch, Germany) in a PM 600 (L.B. Bohle, Ennigerloh, Germany) bin blender at 6 rpm for 15 min.

2.2. Roller compaction

Dry blends are granulated with a roller compactor (BRC 25, L.B. Bohle, Ennigerloh, Germany) using a gap width of 1.5 mm and a roll speed of 2 rpm. Specific compaction forces ranging from 3 to 16 kN/cm are applied automatically by adjustment of the feed rate. Feeding of the roller compactors was performed via auger screws; one horizontal screw was connected to the hopper followed by a vertical screw for tamping. Ribbon milling was performed by an integrated conical sieve (BTS 100) at 400 rpm applying a rasp sieve with 1.5 mm screen.

2.3. Raw material and granule characterization

Scanning electron microscopy (SEM) images were recorded using a Phenom Pro scanning electron microscope (Thermo Fischer Scientific, MA, USA) at an acceleration voltage of 10 kV. Prior to the measurements, samples were coated with a gold layer with a thickness of 4 nm. Particle size distributions were determined ($n = 3$) by dry laser diffraction (Helos/KR R7, Sympatec, Germany) using a dispersion unit with a feed rate of 75% and an air pressure of 1.5 bar. The R7 lens has a measurement range from 18 to 3500 μm. The measured particle size distributions are used to calculate the surface area (S_m) of the materials, assuming that particles are spherical. The specific surface area (SSA) was measured with multipoint krypton BET (TriStar, Micromeritics, UK). Bulk and tapped density were measured ($n = 2$) according to USP method <616>, method I. The Hausner ratio (HR) was calculated as the quotient of the tapped density (TD) and the bulk density (BD):

$$HR = TD/BD \qquad (1)$$

2.4. Granule tableting

Blends of 500 g are produced in a Turbula blender (Turbula T2F, Willy A. Bachofen, Basel, Switzerland) at 90 rpm for 2 min. Blends consist of 99.5% *w*/w of granules and 0.5% w/w magnesium stearate (Sigma Aldrich, Netherlands). Tablets were compressed using a rotary tableting press (Luxner RoTab T, Germany) with compression forces of 5 kN, 10 kN and 15 kN. Flat beveled punches (iHollland, United Kingdom) with diameter 9 mm are used to compact tablets of 250 mg with a rotating frequency of 25 rpm, resulting in a dwell time of 60 ms.

2.5. Tablet analyses

Tablets were analyzed on tablet crushing force, weight, diameter and thickness ($n = 20$) using an automated tablet tester (Sotax AT50, Switzerland). Force to break the tablet is measured at constant speed of 120 mm/min (2 mm/s), maximum force needed to break the tablets is used as tablet crushing force. The tablet tensile strength (TTS) is derived from the tablet crushing force (TCF), diameter (D) and tablet height (H) for flat beveled tablets(Pitt and Heasley, 2013):

$$TTS = \frac{2 \bullet TCF}{\pi \bullet D \bullet H} \qquad (2)$$

The sensitivity to specific compaction force (SSC) parameter is introduced to quantify the decrease in tablet tensile strength upon increasing specific compaction force. This parameter is a measure for the decay in tablet tensile strength and is defined by least square fitting. Two type of decays are characterized, being a linear and an exponential decay. When the improvement in R^2 for switching from a linear to an exponential model for a material was more than 0.05 for all three

compaction forces, the relationship was classified as exponential. For linear models, the SSC-L is defined as the slope of the linear fit of the tablet tensile strength as function of specific compaction force. The relative sensitivity to specific compaction force (rSSC-L) is subsequently calculated by scaling towards the tablet tensile strength that a tablet would have with starting material that has not been roller compacted. For exponential relationships, the relative sensitivity to specific compaction force decay factor (rSSC-E) is defined as the decay constant for the best exponential fit of the tablet tensile strength as a function of the specific compaction force.

3. Results and discussion

3.1. Raw material characterization

A range of physical properties of the materials that are evaluated in this study are shown in Table 1. Three grades with different particle sizes are evaluated for lactose monohydrate and anhydrous lactose. Two different particle sizes are evaluated for microcrystalline cellulose. A scanning electron microscopy (SEM) picture of each material is shown in Fig. 1.

The SEM picture in Fig. 1 shows that milled lactose monohydrate consists of tomahawk shaped particles with surrounding fines. The milled lactose monohydrate grades used for roller compaction cover a range of median particle sizes from 31 to 51 μm, with bulk densities from 0.53–0.65 g/L. Grades with smaller particle size show a lower bulk and tapped density. Lactose monohydrate is classified as quite brittle, but typically has a lower degree of fragmentation than anhydrous lactose. (Gamble et al., 2010)

The anhydrous lactose grades used for roller compaction cover a range of median particle sizes from 66 to 203 μm, which is higher than the evaluated range for the milled lactose monohydrate grades. Anhydrous lactose is produced by roller drying and has a rough surface structure with clusters of microcrystals and shard-shaped particles. Anhydrous lactose does not contain crystal water, and the isomeric purity is approximately 80% *w*/w β-lactose and 20% w/w anhydrous α-lactose.(Lara-Mota et al., 2021; López-Pablos et al., 2018) Anhydrous lactose demonstrates better compaction behavior than α-lactose monohydrate, due to the presence of rougher surfaces and a higher degree of fragmentation.(Gamble et al., 2010; Vromans et al., 1987)

Microcrystalline cellulose (MCC) is a partially depolymerized cellulose that occurs as crystalline powder composed of porous agglomerates. MCC1 and MCC2 have median particle sizes of 59 μm and 101 μm and the porous structure is reflected in the low bulk densities of 0.33 g/mL and 0.36 g/mL respectively. MCC is typically used for its ability to be compressed and compacted, due to the extended porous structure, surface roughness, and plastic deformation.(Fara et al., 2020; Thoorens et al., 2014) The high degree of plastic deformation of MCC is explained

by the presence of slip planes that facilitate MCC dislocation on a microscale.(Haware et al., 2009) The formation of hydrogen bonds between MCC aggregates results in strong bonding between particles. (Thoorens et al., 2014; Haware et al., 2009)

3.2. Granule characterization

For all materials, bi-modal particle size distributions were obtained after roller compaction at varying compaction forces and subsequent milling (Supplementary Fig. S1). The first peak of the particle size distribution represents the raw material and the second peak the coarser granules.(Perez-Gandarillas et al., 2016; Pérez Gago and Kleinebudde, 2017) The x10, x50 and x90 values are summarized in Supplementary Tables S1-S3. For most materials, the extend of granulation increases with increasing specific compaction force. Above 7 kN/cm, the increase in granule size upon increased specific compaction force however is marginal. This shows that at these high specific compaction forces, granule size is largely controlled by the milling step after roller compaction.

For milled lactose monohydrate, a smaller granule size after roller compaction at 7–16 kN/cm and subsequent milling is observed for formulation LM3 compared to LM1 and LM2. This observation is explained by the lower surface area available for bonding of formulation LM3 as a result of the larger particle size. Ribbons from this material break more easily upon milling, resulting in finer granules. This is in line with findings from Ingelbrecht et al.[30], who showed higher granule friability for granules produced from lactose monohydrate with larger particle size. The observed inverse relationship between the particle size of the starting material and the granule size for milled lactose monohydrate is not observed for anhydrous lactose and MCC. Anhydrous lactose has a rough structure consisting of aggregates of brittle microcrystals and the surface area is mainly determined by the surface of the microcrystals. It also has a high degree of fragmentation during roller compaction, which results in the creation of bonding surface during roller compaction. The particle size of anhydrous lactose therefore has little influence on bonding properties.(Hein et al., 2008) For MCC, bonding between particles is mainly the result of hydrogen bonds between aggregates,(Thoorens et al., 2014; Haware et al., 2009) which is not dependent on the primary particle size of the particles in the granule.

3.3. Sensitivity of tablet tensile strength to specific compaction force

Fig. 2 shows the tablet tensile strength for granules that are roller-compacted at different specific compaction forces for the milled lactose monohydrate grades, anhydrous lactose grades and microcrystalline cellulose grades. Separate graphs for tableting compaction forces 5 kN, 10 kN and 15 kN are provided. Data for direct compression of the powder is not available for formulations LM1, LM2, LM3 and MCC1, due

Table 1
Type, compaction behavior, formulation abbreviation, lactose grade, particle size distribution, specific surface area and density data for the excipient formulations used in this study.

| Type	Compaction behavior	Formulation abbreviation	Grade	x10 (μm)	x50 (μm)	x90 (μm)	S_m (m²/g)	SSA (m²/g)	Bulk density (g/L)	Tapped density (g/L)	Hausner ratio (−)
Milled lactose monohydrate	Brittle fragmentation	LM1	Pharmatose 350 M	4.2	31	85	0.33	0.98	0.53	0.83	1.56
		LM2	Pharmatose 200 M	4.5	38	103	0.30	0.78	0.58	0.87	1.51
		LM3	Pharmatose 150 M	5.8	51	149	0.24	0.39	0.65	0.92	1.42
Anhydrous lactose	Brittle with a high degree of fragmentation	AL1	70%w/w SuperTab 21AN + 30%w/w Lactopress anhydrous fines	9.5	66	328	0.13	*	0.68	0.89	1.32
		AL2	SuperTab 21AN	16	146	356	0.08	0.41	0.72	0.88	1.23
		AL3	SuperTab 22AN	36	203	414	0.06	0.30	0.66	0.77	1.17
Microcrystalline cellulose	Plastic deformation	MCC1	Pharmacel 101	25	59	125	0.08	1.03	0.33	0.45	1.37
		MCC2	Pharmacel 102	36	101	233	0.06	1.16	0.36	0.46	1.28

*Data is not available.
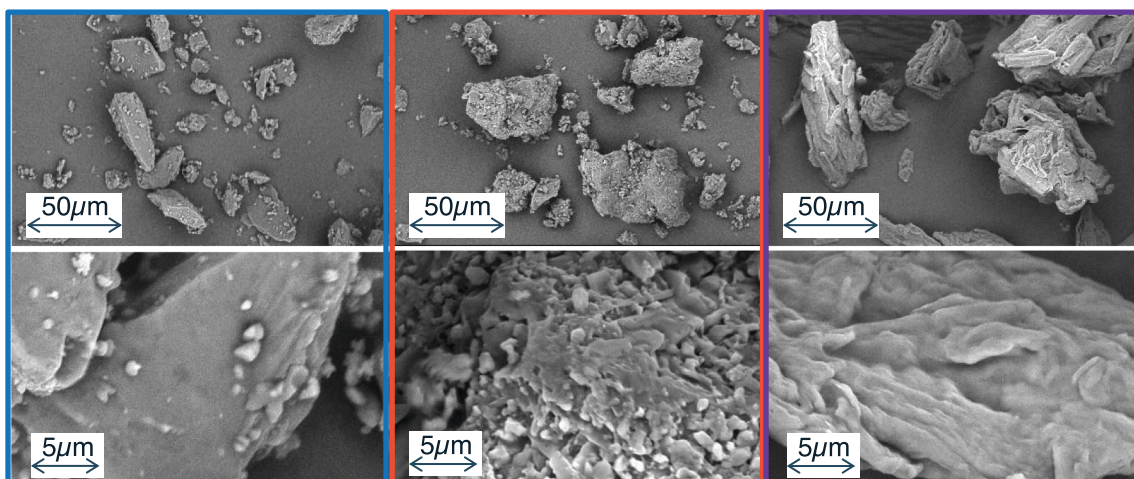
Fig. 1. SEM pictures of milled lactose monohydrate Pharmatose 200 M (as used in formulation LM2, left), anhydrous lactose SuperTab 21AN (as used in formulation AL2, middle), and microcrystalline cellulose Pharmacel 102 (as used in formulation MCC2, right).

to flow limitations of these formulations during tableting. All formulations show a decrease in tablet tensile strength upon increasing specific compaction force. This decrease is explained by a combination of size enlargement and granule hardening upon increased specific compaction force. The loss of compaction due to size enlargement is thought to be limited, as granules are lubricated before compaction. Lubricated granule surface has limited bonding capabilities, and contributes only minimally to the bonding for material with fragmentation during the compaction process.(Wu and Sun, 2007) With tablet compaction forces of 5 kN, a maximum tablet tensile strength of 0.5 MPa can be obtained for formulations with granules from milled lactose monohydrate. Approximately twice as high tablet tensile strength is obtained for formulations with anhydrous lactose. Compaction of MCC that is not roller compacted or roller compacted at 3 kN/cm results in significantly higher tensile strength than compaction of lactose monohydrate or anhydrous lactose. The tablet tensile strength of MCC however, decreases much more strongly upon increasing specific compaction force.

The relative sensitivity to specific compaction force (SSC) parameter is introduced to quantify the loss in tablet tensile strength of the different materials. This parameter is a measure for the decay in tablet tensile strength upon increasing the specific compaction force in the granulation process and is defined by least square fitting. R^2 values for the linear and exponential models are provided in Supplementary Table 4. For linear models, the SSC-L is defined as the slope of the linear fit of the tablet tensile strength as function of specific compaction force. The relative sensitivity to specific compaction force (rSSC-L) is subsequently calculated by scaling towards the tablet tensile strength that a tablet would have with ungranulated starting material. For exponential relationships, the relative sensitivity to specific compaction force decay factor (rSSC-E) is defined as the decay constant for the best exponential fit of the tablet tensile strength as a function of the specific compaction force. Parameters are calculated for each tableting compaction force and averaged to one number per material, as shown in Supplementary Tables 5–7. The model classification and average SSC per material is provided in Table 2.

For lactose monohydrate formulations, the highest tablet tensile strength at each specific compaction force is obtained for formulation LM1, which is explained by the higher surface area available for bonding for smaller crystals.(De Boer et al., 1986) All three milled lactose monohydrate grades show a linear decay in tablet tensile strength upon roller compaction with increased specific compaction force. Granule compactibility of formulations LM1 and LM2 also decreases upon increasing the specific compaction force from 7 to 16 kN/cm, whereas in this range the granule size distribution remains constant. Size

enlargement can therefore not fully explain the loss of compaction. Instead, the majority of the observed loss of compaction is explained by granule hardening, in line with previous research by for example Mosig et al.[14]. Granule hardening leads to more dense granules that are less prone to fragmentation during tableting, thereby decreasing the bonding area upon compaction. When milled lactose monohydrate is roller compacted at 16 kN/cm, error bars of the tablet tensile strength for all formulations start to overlap. The highest rSSC-L for milled lactose monohydrate is observed for the smallest starting material formulation LM1, followed by LM2 and LM3. These observations are in accordance with the strongest granule hardening effect that would be expected for formulation LM1. With more surface area available, harder ribbons are formed during roller compaction, resulting in granules with lower propensity to fracture.(Inghelbrecht and Remon, 1998) This is in contrast to the propensity for fracture of solid particles during roller compaction, which is expected to be the highest for larger particles. (Roberts and Rowe, 1987) The current results show that the increased amount of created surface does not compensate the higher initial bonding surface area available.

For anhydrous lactose, no significant effect of particle size on the tablet tensile strength is observed. This is the case for direct compression of the starting material, as well as for compression of the granulated materials. For all anhydrous lactose grades, a linear decrease in tablet strength with rSSC-L of 1.7–1.9% per kN/cm is observed. This is explained by the fragmentation behavior of anhydrous lactose combined with the structure of aggregates of microcrystals, which results in similar bonding properties for all sizes of anhydrous lactose.(Hein et al., 2008) The major factor for the loss of compaction for anhydrous lactose is granule hardening.(Skelbæk-Pedersen et al., 2021) The combination of the reduced fragmentation propensity and the coverage of the granule surface with magnesium stearate results in the observed decrease in tablet tensile strength with increasing specific compaction force. The rSSC-L of anhydrous lactose is similar to the rSSC-L of lactose monohydrate LM1, despite the higher compactibility and the higher particle size of the evaluated anhydrous lactose grades.

The tablet tensile strength of MCC decreases much more strongly upon increasing specific compaction force than the tablet tensile strength of lactose monohydrate or anhydrous lactose. In contrast to linear decays for lactose monohydrate and anhydrous lactose, MCC shows an exponential decay. At a specific compaction force of 16 kN/cm, tablet tensile strengths are decreased by 90% to values below 1 MPa, while the tablet tensile strength of lactose monohydrate and anhydrous lactose only decreased with 7–29%. The high loss of compaction for MCC relates to the plastic deformation behavior that makes MCC
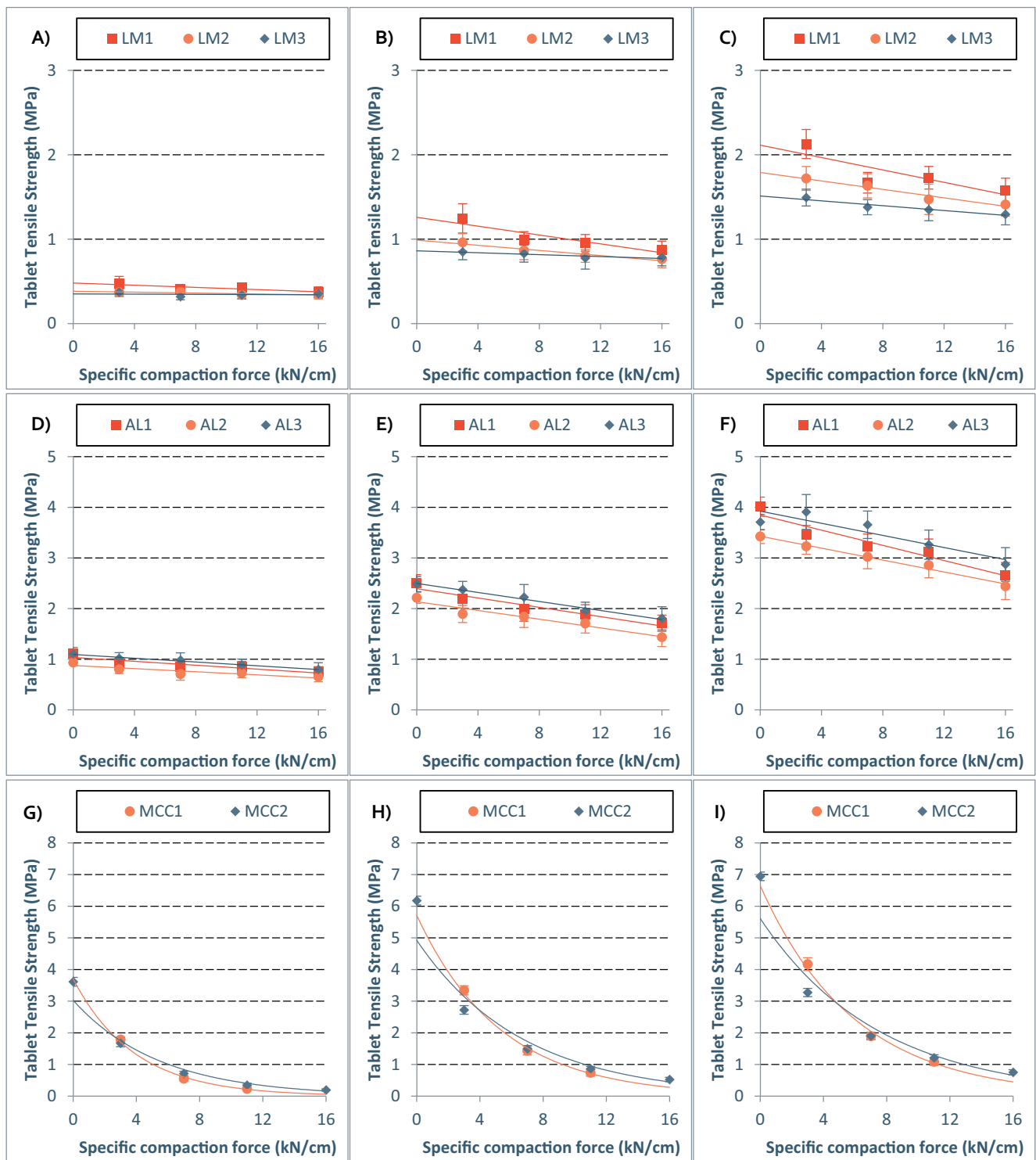
Fig. 2. Tablet tensile strength of granules from the three milled lactose monohydrate grades (A-C), three anhydrous lactose grades (D-F) and two microcrystalline cellulose grades (G-I) after roller compaction at different specific compaction forces. Tablet compression is performed at 5 kN (left), 10 kN (middle) and 15 kN (right). $N = 20$ tablets per datapoint were analyzed and error bars represent the standard deviation. Solid lines represent linear fits (A-F) and exponential fits (G-I) to quantify the decrease in tablet tensile strength upon increasing the specific compaction force.

sensitive to both size enlargement and granule hardening.(Mosig and Kleinebudde, 2015) Size enlargement results in less available bonding area during tableting, although this effect might be less relevant after lubrication of the granules. Moreover, roller compaction increases the powder density of MCC up to 80% (Supplementary Fig. S2). Higher powder density indicates lower particle porosity and therefore lower possible deformation. The densification observed for MCC is

significantly larger than for lactose monohydrate or anhydrous lactose and the correlation between density and compaction properties of MCC is well-described in literature.(Shah et al., 2017; Liao et al., 2012; Ahmat et al., 2012) No significant difference in compactibility is observed for granules prepared from the two MCC grades at specific compaction forces above 7 kN. This is explained by the hydrogen bond formation as compaction mechanism of MCC,(Thoorens et al., 2014; Haware et al.,

Table 2

Relative sensitivity to specific compaction forces (rSSC) for the tested formulations. Milled lactose monohydrate grades and anhydrous lactose grades show linear behavior. The rSSC-L of milled lactose monohydrate depends on the particle size of the starting material, whereas for anhydrous lactose the rSSC-L is independent of particle size. For MCC exponential decay behavior was observed, with no significant differences in rSSC-E for different particle sizes.

Material	Formulation	SSC type	rSSC-L $(\%\frac{cm}{kN})$	rSSC-E $(\frac{cm}{kN})$
Milled lactose monohydrate	LM1	linear	1.7	x
	LM2	linear	1.2	x
	LM3	linear	0.6	x
Anhydrous lactose	AL1	linear	1.9	x
	AL2	linear	1.8	x
	AL3	linear	1.7	x
MCC	MCC1	exponential	x	0.18
	MCC2	exponential	x	0.18

2009) which is merely dependent on the density and the specific surface area of the material. MCC101 and MCC102 have previously been shown to differ in the size and number of agglomerates rather than in primary particle size, hence the surface area is often identical for different grades of MCC.(Gamble et al., 2011)

Fig. 3 shows the relationship between relative bulk density and tablet tensile strength of lactose monohydrate, anhydrous lactose and MCC for roller compaction at 0–16 kN/cm. The bulk density of the starting material is taken here as reference. The relationship between the absolute bulk density and tablet tensile strength is provided in Supplementary Fig. S3. A change in bulk density can be the result of changes in various powder properties, including particle size distribution, shape, and granule density. The observed changes in density are however large compared to changes that would be expected from changes in size and shape only. Therefore, the increase in relative bulk density is likely related to granule densification. This is also in line with the increase in bulk density observed for roller compaction forces between 7 and 16 kN/cm, in which the change in particle size is only minor. All materials show a similar trend with lower tablet tensile strength for higher bulk density material, indicating the granule hardening effect. Lactose monohydrate shows the smallest increase in density upon increasing the specific compaction force. This is also in line with the relatively small loss of compactibility observed for this excipient. The largest densification is observed for MCC, corresponding to the largest loss of compactibility. The presented results highlight a general relationship

between the degree of densification and loss of compactibility for excipients with varying deformation mechanisms in a dry granulation process.

4. Conclusions

In this study, the relevance of excipient particle size for the reduced compactibility upon increasing specific compaction in a dry granulation process is investigated. The compactibility of milled lactose monohydrate granules with brittle fracture upon compaction depends on the raw material particle size, due to the difference in available bonding area. The relative sensitivity to specific compaction force is linear (rSSC-L) with values of 0.6–1.7% per kN/cm. This sensitivity is higher when the particle size of the raw material is lower, due to increased granule hardening when more surface is available for bonding.

In contrast to lactose monohydrate, the compactibility of brittle anhydrous lactose is independent of particle size. The sensitivity to specific compaction force in this case is also independent of raw material particle size with linear values of 1.7–1.9% cm/kN. This is explained by the fragmentation behavior of anhydrous lactose combined with the structure of aggregates of microcrystals, which results in similar bonding properties for all sizes of anhydrous lactose. The combination of good compactibility and low sensitivity to specific compaction results in 80% higher tablet tensile strength at a specific compaction force of 16 kN/cm compared to formulations with lactose monohydrate or microcrystalline cellulose (MCC).

The tablet tensile strength of MCC decreases much more strongly with increasing specific compaction force than the tablet tensile strength of lactose monohydrate or anhydrous lactose. At a specific compaction force of 16 kN/cm, tablet tensile strengths are decreased by 90% to values below 1 MPa, while the tablet tensile strength of lactose monohydrate and anhydrous lactose only decreased with 7–29%. In contrast to linear decays for lactose monohydrate and anhydrous lactose, MCC shows an exponential decay of tablet tensile strength upon increasing specific compaction force The exponential relationship is related to the high densification combined with the plastic deformation of MCC, which amplifies the impact of densification for this material.

CRediT authorship contribution statement

Pauline H.M. Janssen: Conceptualization, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Maarten Jaspers:** Conceptualization,
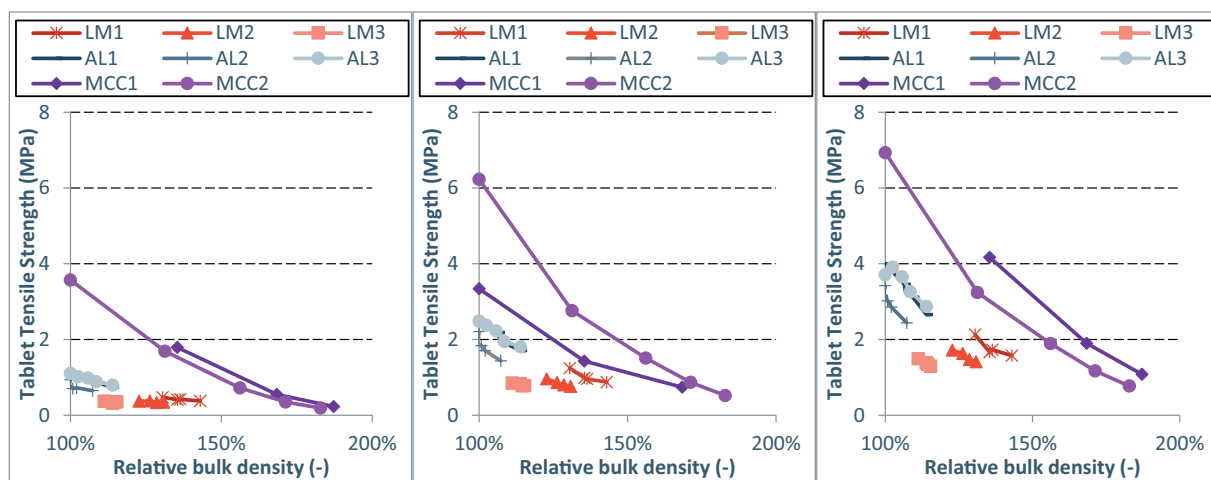

Fig. 3. Relationship between relative bulk density and tablet tensile strength for the roller compacted granules of lactose monohydrate (red), anhydrous lactose (blue) and microcrystalline cellulose (purple).Tablet compression is performed at 5 kN (left), 10 kN (middle) and 15 kN (right). $N = 2$ repeats for density measurements and $N = 20$ tablets per datapoint were analyzed. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing. **Robin Meier:** Conceptualization, Methodology, Resources, Writing – review & editing. **Timo P. Roelofs:** Methodology, Investigation, Resources, Writing – review & editing. **Bastiaan H.J. Dickhoff:** Conceptualization, Resources, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.ijpx.2022.100117.

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