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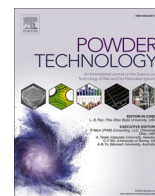
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The impact of material chemistry and morphology on attrition behavior of excipients during high shear blending

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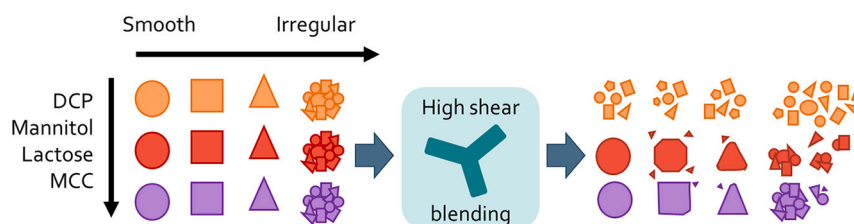
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HIGHLIGHTS

- Attrition during high shear blending depends on chemistry and morphology.
- Changes in particle size were quantified for different excipients after blending.
- Brittle deforming material shows more attrition than plastic deforming material.
- Smooth morphologies are more prone to attrition than irregular morphologies.
- Impact of attrition on functionality differs per material.

GRAPHICAL ABSTRACT



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ABSTRACT

Particle breakage by attrition is unavoidable in some unit operations and can lead to uncontrolled behavior of materials during processing. The aim of this study is to clarify the impact of material properties on attrition behavior. For the first time, an integral study with varying morphologies and chemistries is performed to identify the key drivers that impact attrition during high shear blending. Based upon the observed changes in particle size distribution, it was concluded that dicalcium phosphate (DCP) was the most prone to attrition, followed by mannitol, lactose and microcrystalline cellulose (MCC). Granular particles were more sensitive to attrition than sieved and spherical particles. Changes in bulk density, flow function coefficient and tablet tensile strength were observed as the result of attrition. The magnitude and direction of change in these parameters was not only dependent on the amount of attrition, but also on the morphology and the material deformation properties.

1. Introduction

Driven by the pharmaceutical industry's adoption of quality by design (QbD), a fundamental understanding of critical material attributes and their interaction with different unit operations is desired. This fundamental understanding can be used to guide the selection of relevant materials and process settings, which can accelerate product

development and reduce the risk of quality failures [1]. Consistent material properties are key, as they are required for predictable behavior in the different unit operations. However, achieving consistent and predictable behavior can be especially challenging if the material properties are sensitive to change during processing.

Attrition can be defined as the unintended breakdown of solids (powders) due to particle-particle and particle-process interactions. The

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breakdown of solids during attrition involves two distinct mechanisms, being surface abrasion and fragmentation [2–5]. Surface abrasion is described as the process of chipping and wearing. The size of particles is almost unaffected by surface abrasion, while some extremely small daughter particles are being formed [2]. During fragmentation, the initial particle is broken down into a number of fragments. Resulting particles are typically of intermediate size, but in extreme cases, fragmentation can lead to fines with a similar size as the fines from abrasion [2,3].

Particle breakage is unavoidable in some unit operations and can lead to uncontrolled behavior of materials [2,3,6,7]. For example an increased fines content can be a challenge, as fines are easily aerated, potentially causing dust hazards, loss of material and quality failures [3,7]. Additional steps such as filtration and recycling might be required to handle the fines, leading to an undesirable increase in operational costs [7]. Uncontrolled changes in particle size are also undesirable for predictable processing of a formulation into a tablet. Particle size changes can impact for example the flow and tabletability of the formulation, but also the final disintegration or dissolution of a tablet [8]. In next generation processes like continuous manufacturing, changes in properties can have an impact on downstream operation, process settings or desired locations for process analytical tools [9–13].

There are many different factors that can have an impact on the type and amount of attrition in a process. Process parameters that can have an impact include the humidity, the applied shear and the direction of forces [14,15]. Especially high shear processes, like high shear blending or powder feeding of a roller compactor system, can result in a substantial amount of attrition [16–18]. Material properties such as size, shape, morphology and deformation mechanism are reported to have a major effect on particle breakage as well. Larger particles are more likely to break than smaller particles, explained by the greater crack density of these particles [8,19,20]. Additionally, irregular shaped particles have higher risks for breakage than spherical particles, due to the high local stresses that can be present at the edges [19,21]. This also explains the impact of morphology on particle breakage, with more particle breakage for granular lactose than for spray dried or anhydrous lactose [18]. Plastically deforming materials, like MCC, are reported to be less sensitive for particle breakage than materials with brittle fracture behavior, like DCP [22,23]. The deformation mechanism of materials has mainly been characterized by Heckel analyses of tableting data [23–25]. Low yield strengths ($P_y < 80$ MPa), combined with high strain rate sensitivity ($SRS > 10\%$), indicate plastic deformation behavior. High yield strengths with lower SRS in contrast, indicate brittle fracture of materials [23,26,27].

The aim of the present study is to extend the current understanding of the impact of material properties on attrition behavior in high shear blending processes. Furthermore, it is also desired to understand the effect of attrition on functional properties such as density, flow and tablet tensile strength. High shear blending is one of the high energy operations in drug manufacturing that provides a risk for attrition, especially when short residence times with high shears are used in continuous processing. For the first time, an integral study with varying morphologies and chemistries is performed to identify the key material properties that impact attrition during high shear blending. Based upon observed changes in particle size, it was concluded that DCP was the most prone to attrition, followed by mannitol, lactose and MCC. Additionally, irregular particles were shown to be more sensitive to attrition than sieved and spherical particles. Attrition of materials was shown to result in changes in the bulk density, flow function coefficient and tablet tensile strength. The amount and direction of change was not only dependent on the amount of attrition, but also on the morphology and the deformation properties of the materials.

2. Materials and methods

2.1. Materials

Table 1 provides an overview of the twelve excipients with varying morphologies and chemistry that were tested. Materials are abbreviated by combining the abbreviated material chemistry in uppercase with the abbreviated morphology in lowercase.

2.2. Blending

High shear blending was performed in a Procept Form-8 (Zeel, Belgium) with three impeller blades of 17 cm diameter for two minutes at 30% fill volume. The impeller speed was set at 310 rpm, corresponding to Froude number 9. The effect of blending time and the Froude number was evaluated as part of the initial screening study. The results of screening study are provided in Supplementary Fig. 1 and Supplementary Fig. 2.

2.3. Powder characterization

Excipients were analyzed for particle size distribution, density, flow, and tablet compaction before and after blending. Particle size distributions were measured ($n = 3$) by dry laser diffraction (Helos/KR, Sympatec, Germany) at 100% feed rate. A dispersion pressure of 0.5 bar was used for granular products and 1 bar was used for the sieved and spray dried materials. Flow of powders was measured ($n = 2$) by a ring shear tester (RST-XS, Dietmar Schulze, Wolfenbuttel, Germany) to obtain the flow function coefficient (ffc). The ffc is the ratio of the consolidation stress and the unconfined yield strength. Flow was measured at pre-consolidation stress (σ_{pre}) of 4 kPa while normal stresses of 1, 2 and 3 kPa were used for shear to failure. Bulk density was measured ($n = 2$) according to Ph. Eur. method I. Approximately 100 g of powder was poured into a 250 mL graduated cylinder. The change in

Table 1

Overview of the twelve excipients used in this study. For each excipient, the chemistry, morphology, abbreviation (abbr.) and the supplier is indicated.

Name	Chemistry	Morphology	Abbr.	Supplier
SuperTab® 24AN	Lactose Anhydrous (LA)	Granular (g)	LAg	DFE Pharma (Goch, Germany)
SuperTab® 30GR	Lactose Monohydrate (LM)		LMg	
SuperTab® 40LL	Co-processed Lactose-Lactitol (LL)		LLg	
Mannogem® Granular	Mannitol (M)		Mg	SPI Pharma (Wilmington, USA)
Di-cafos A150	Dicalcium phosphate anhydrate (DA)		DAg	Budenheim KG (Budenheim, Germany)
Di-cafos D160	Dicalcium phosphate dihydrate (DD)		DDg	
SuperTab® 21AN	Lactose Anhydrous (LA)	Sieved (s)	LAs	DFE Pharma (Goch, Germany)
Pharmatose® 100 M	Lactose Monohydrate (LM)		LMs	
SuperTab® 11SD	Lactose Monohydrate (LM)	Spray dried (sd)	LMsd	DFE Pharma (Goch, Germany)
Pharmacel® 102	Microcrystalline cellulose (MCC)		MCCsd	
Pharmacel® sMCC 90	Co-spray dried Silicified microcrystalline cellulose (SMCC)		SMCCsd	
Mannogem® XL Opal	Mannitol (M)		Msd	SPI Pharma (Wilmington, USA)

particle size and bulk density was quantified by the percentage relative change. Scanning electron microscopy (SEM) images were recorded using a Phenom ProX scanning electron microscope (Thermo Fischer Scientific, MA, USA). Material was coated with a 6 nm gold and images were recorded at an acceleration voltage of 10 kV at magnifications of 450-500 \times . Aspect ratio (AR) was evaluated by imageJ software for individual particles using different SEM images ($n = 40$). The AR is the ratio of major axis to minor axis of an ellipse fit to each particle by the software based on the particle contour. Heckel analysis was performed ($n = 3$) at a compaction simulator (Merlin PC, Loughborough, United Kingdom) using flat faced punches with a diameter of 10 mm at punch speeds of 0.1 mm/s and 300 mm/s. Lubrication of the dies was performed with magnesium stearate in acetone. The yield pressure (P_y) of a material is calculated as the reciprocal of the slope over the linear region of a Heckel plot, using the relative density of the compact (D) and the applied compression pressure (P) [28]:

$$\ln\left(\frac{1}{1-D}\right) = \frac{1}{P_y}P + \text{Intercept} \quad (1)$$

The strain rate sensitivity (SRS) was calculated as the relative difference between the yield pressure at 300 mm/s (P_{y300}) and the yield pressure at 0.1 mm/s ($P_{y0.1}$) according to [27]:

$$\%SRS = \frac{P_{y300} - P_{y0.1}}{P_{y0.1}} \bullet 100\% \quad (2)$$

2.4. Tableting

Formulations were prepared in portions of 500 g by blending 95.5% w/w filler with 4% w/w croscarmellose sodium (Primellose®, DFE Pharma, Goch, Germany) in a Turbula blender (Turbula T2F, Willy A. Bachofen, Basel, Switzerland) for 8 min. Lubrication was performed by adding 0.5% w/w magnesium stearate (Sigma Aldrich, Netherlands) and blending for another 2 min in a Turbula blender. Blending speed was set to 90 rpm for blends containing lactose, mannitol or DCP. Blending speed was set to 67 rpm for blends containing MCC grades.

Tablets were compressed on a Rotab T rotary tablet press (Luxner, Berlin, Germany) with five punches rotating at 25 rpm with an optifiller speed of 13 rpm. Tableting was performed at a compaction force of 10 kN using flat beveled 9 mm punches (iHolland, Nottingham, UK). The filling depth of the die was set to achieve tablets of a weight of 250 mg \pm 2 mg and samples were taken 2 min after reaching equilibrium.

Tablets ($n = 20$) were analyzed on tablet crushing strength, weight, diameter, and thickness by using an automated tablet tester (Sotax AT50, Aesch, Switzerland). Force to break the tablet was measured at constant speed of 2 mm/s, maximum force needed to break the tablets was used as crushing force. The tablet tensile strength (TTS) is calculated from the tablet crushing strength (TCS), diameter (D) and tablet height

(H) for flat beveled tablets as [29]:

$$TTS = \frac{2 \bullet TCS}{\pi \bullet D \bullet H} \quad (3)$$

3. Results and discussion

3.1. Material characterization

The physical properties of the evaluated excipients are shown in Table 2. The median particle size (x50) for all the excipients was between 90 and 200 μ m, except for Mg that had a median particle size of 574 μ m. The bulk density of the tested materials varied between 0.35 and 0.90 g/mL. Microcrystalline cellulose (MCC) grades had the lowest bulk density, followed by the other spray dried and granular materials. Granular and spray dried morphologies typically have lower bulk density than sieved grades, due to the space between individual particles that are agglomerated together. MCC consist of spray dried fibrous microcrystals, which results in a porous structure with low density [30]. Dicalcium phosphate (DCP) grades showed the highest bulk density, which is related to the inherent high true density of DCP [31]. The flow of all excipients was classified as free flowing ($ffc > 10$), except for LMs, MCCsd and SMCCsd which were classified as easy flowing ($4 < ffc < 10$) [32]. Results were in line with previous knowledge on particle morphologies, as spray drying and granulation techniques are well-known to result in particles with good powder properties [33]. The morphology of spray dried grade materials is generally spherical and thereby results in a lower aspect ratio. Whereas granular and sieved morphologies are characterized by a higher aspect ratio due to their irregular and sharp edges. This effect is visualized by the SEM images in Fig. 1, where both spray dried lactose monohydrate and mannitol show a more spherical morphology and therefore have a lower aspect ratio compared to the sieved and granular grades. However, MCCsd and SMCCsd although produced by spray drying are characterized by a high aspect ratio. The lack of a spherical structure for MCC grades is explained by their non soluble nature. Lactose and mannitol are soluble in the spray dried suspension while, MCC retains the fibrous structure during spray drying and therefore doesn't result in a spherical morphology. (SEM images and aspect ratios of other materials are provided in Supplementary Fig. 3). The fibrous MCC grades were also expected to have lower flow than the other used excipients, due to the lower powder density of these materials, resulting in less gravitational forces that drive powder flow [34]. MCCsd and sMCCsd tablets showed the highest TTS (>5.5 MPa), attributed to the extended porous structure, surface roughness, and plastic deformation of MCC grades [34,35]. The high degree of plastic deformation of MCC was confirmed by Heckel testing, as a low yield pressure combined with high SRS was found. The high degree of plastic deformation for MCC results from the presence of slip planes that

Table 2

Particle size data, aspect ratio, density, flow function coefficient, tablet tensile strength (TTS) at 10 kN compaction force, yield pressures (P_y) and strain rate sensitivity (SRS) for the excipients used in this study.

Abbr.	Particle size (μ m)			Aspect ratio (-)	Bulk density (g/mL)	ffc (-)	TTS @10kN (MPa)	Py @0.1 mm/s (MPa)	Py @300 mm/s (MPa)	SRS (%)
	x10	x50	x90							
LAg	26	94	233	1.47	0.52	26	2.4	155	166	7
LMg	42	133	281	1.49	0.56	24	1.6	151	192	10
LLg	58	143	298	1.35	0.54	24	4.0	155	177	14
Mg	178	574	960	1.61	0.62	14	0.9	161	185	15
DAG	42	167	274	1.54	0.73	37	1.1	627	665	6
DDg	83	172	263	1.38	0.90	37	1.1	331	335	1
LAs	11	152	319	1.49	0.77	12	1.6	194	208	7
LMs	24	134	240	1.73	0.71	7	1.0	172*	172*	0*
LMsd	45	119	217	1.34	0.62	13	1.3	154	170	11
MCCsd	29	92	200	2.43	0.35	7	5.9	76	86	13
SMCCsd	30	97	216	2.48	0.35	9	6.7	85	100	17
Msd	74	153	247	1.23	0.47	56	2.5	187	191	2

* Data presented is taken from an equivalent product with slightly coarser particle size (Pharmatose® 80 M).

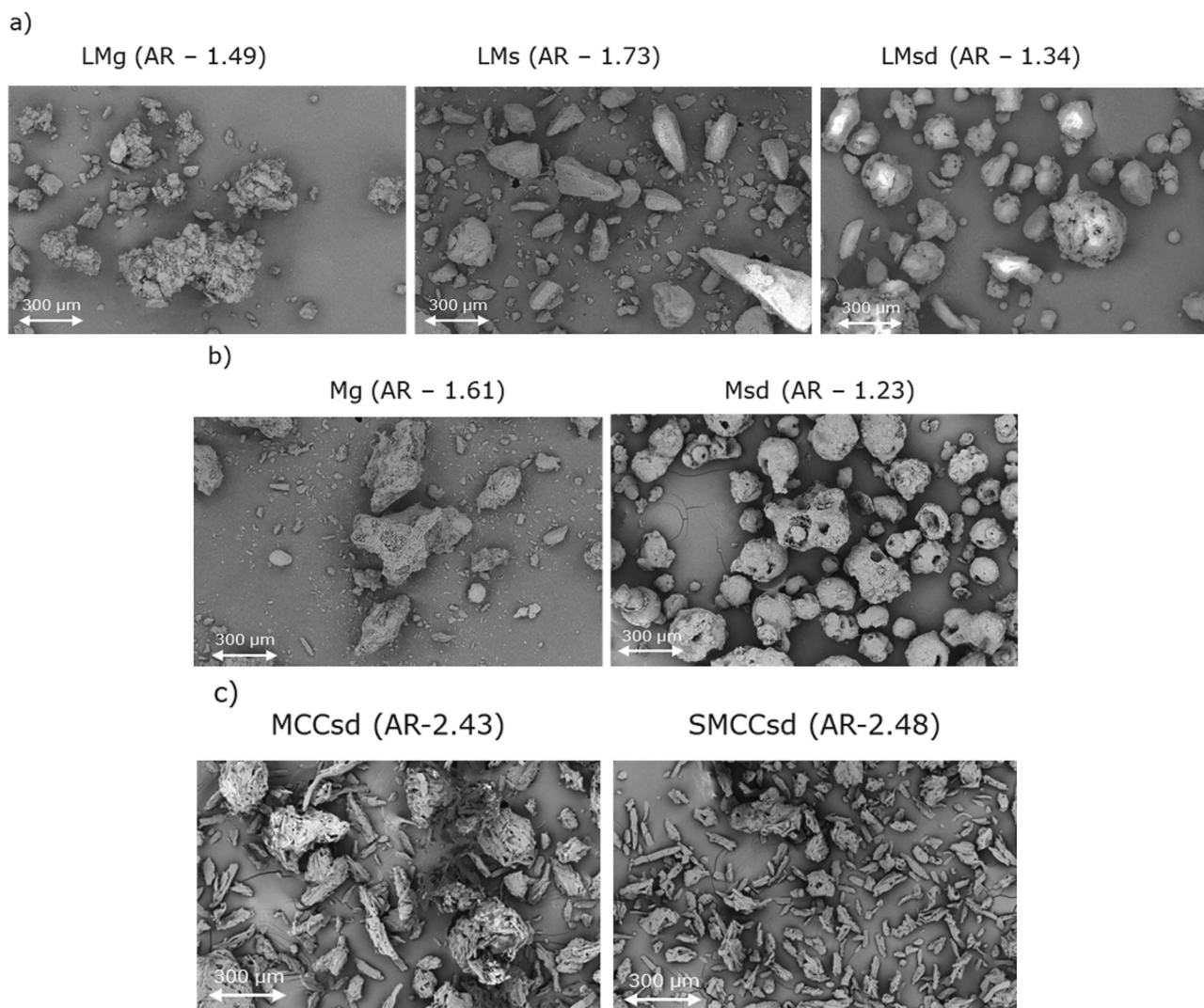


Fig. 1. SEM images and aspect ratios of starting material: Granular lactose monohydrate (LMg), sieved lactose monohydrate (LMs), spray-dried lactose monohydrate (LMsd) (a); granular mannitol (Mg), spray-dried mannitol (Msd) (b) and spray dried microcrystalline cellulose (MCCsd) and co-spray dried silicified microcrystalline cellulose (SMCCsd) (c). LMsd and Msd have a spherical morphology while LMg, LMs and Mg show an irregular surface morphology. MCC grades have a high aspect ratio due to their fibrous structure.

facilitate dislocation on a microscale, combined with the ability to form hydrogen bonds [34,35]. Tablets of DAg and DDg showed low TTS, combined with high yield pressures and low SRS. It is known that DCP has brittle fracture behavior during compaction, and therefore does not form strong compacts [36]. Tablets from Mg and LMs resulted in the lowest TTS (<1.1 MPa). Mg had a large particle size compared to the other used grades, reducing the available surface for bonding upon compaction. The material characterization of brittle and ductile (plastic) nature is also visualized in Supplementary Fig. 4 and is based on the work by Leane et al. and Roberts et al. [1,37]. MCC and DCP grades are the two extremes within the materials studied. Based on the classification, MCC grades are ductile and undergo plastic deformation while DCP grades are extremely brittle in nature. All the remaining lactose and mannitol grades exhibit moderate brittleness, with yield pressures relatively high compared to MCC grades. Previous work has also shown that DCP and lactose are both classified as brittle however, DCP having a much higher propensity to fragment [38].

3.2. The effect of high shear blending on particle size

Fig. 2 shows the effect of blending on particle size as quantified by

the relative change in particle size parameters x_{10} (solid fill), x_{50} (lined fill) and x_{90} (dotted fill). Almost all materials showed a reduction in particle size, which indicated the presence of attrition behavior. The more substantial changes in the fine region of a particle size distribution, represented by changes in the x_{10} , were expected. A reduction in x_{10} value represents an increase in fines content, resulting from surface abrasion or particle fragmentation. Changes in x_{50} and x_{90} are typically only substantial when particles are being fragmented, as surface abrasion hardly impacts the size of the initial particle.

All evaluated materials showed a decrease in particle size, except LMs and LMsd. No particle attrition was observed for these two grades, mainly explained by the smooth surface of sieved and spray dried materials. Particles of sieved materials typically are solid crystals, with strong lattice binding keeping the molecules together [39,40]. This also explains why sieved anhydrous lactose (LAs) had more attrition than sieved lactose monohydrate (LMs). Anhydrous lactose is produced by roller-drying, resulting in particles that are composed of multiple microcrystals. This is beneficial for compaction, but results in more weak points than in a solid monohydrate crystal [41]. Spray dried materials are spherical materials with strong interparticle bonding and low surface irregularities, reducing the likelihood for particle breakage [23,27].

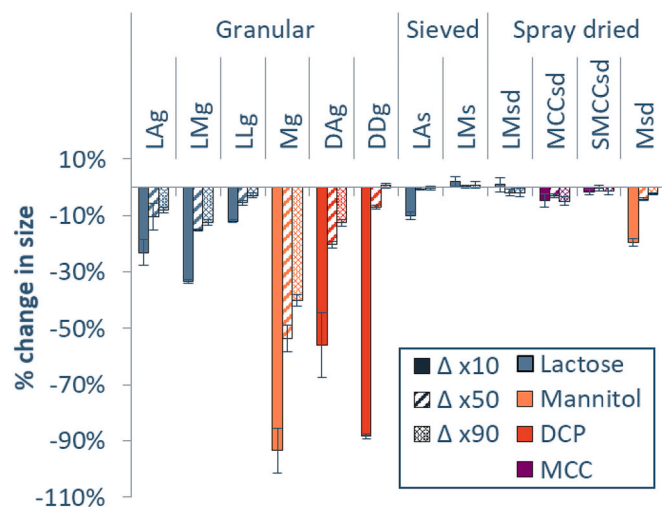


Fig. 2. Relative change in particle size distribution parameters x_{10} (solid bars), x_{50} (lined bars) and x_{90} (dotted bars) after blending lactose (blue), mannitol (orange), DCP (red), and MCC (purple) in a high shear blender. Error bars indicate the standard deviation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Differences between different spray dried grades were not expected to be the result of shape differences, as previous research has shown that attrition is independent of shape when the morphology is smooth [7]. Granular materials showed the largest changes in particle size among all morphologies, explained by the irregular surfaces (higher aspect ratio) with particles held together only by weak solid bridges [42]. The mean particle size (x_{50}) reduction for the granular materials was between 7 and 54%, while the sieved and spray-dried materials showed a reduction in mean particle size of 0–4%. This trend was also observed when comparing the different morphologies of mannitol or lactose monohydrate. Mg showed a reduction in x_{50} of 54%, compared to 4% for Msd. LMg showed a reduction in x_{50} of 15%, compared to 0% and 2% for LMs and LMsd respectively. The results highlight the effect of spherical morphology (low aspect ratio) on the degree of attrition. Results were also in agreement with previous reported work, where granular lactose showed a larger reduction in size than spray dried lactose and anhydrous lactose [18].

Besides differences in the amount of attrition, also differences in the type of attrition were observed for different morphologies. Fig. 3 shows the SEM images of a sieved material (LAs), spray dried material (Msd) and two granular materials (Mg and DAG) before and after blending.

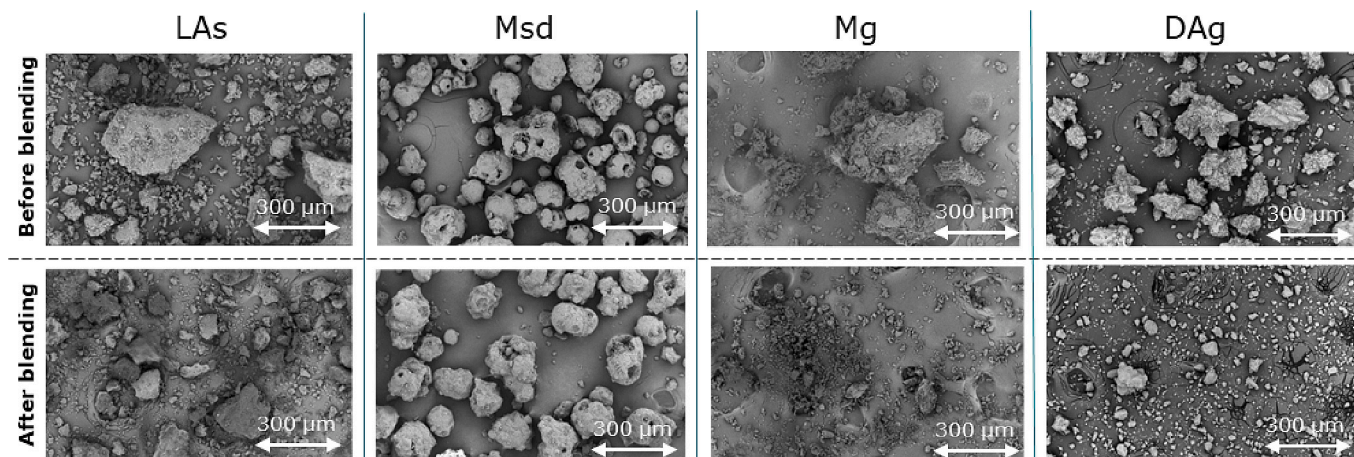


Fig. 3. SEM images of sieved lactose anhydrous (LAs), spray-dried mannitol (Msd), granular mannitol (Mg) and granular DCP anhydrate (DAG), before (top) and after (bottom) blending. LAs and Msd attrition is dominated by surface abrasion, while Mg and DAG attrition is dominated by fragmentation.

SEM images of the other materials are provided in Supplementary Fig. 5 and Supplementary Fig. 6. Fragmentation behavior was mainly observed for granular materials, indicated by a large number of intermediate and small sized daughter particles after blending. Fragmentation of the granular grades was also confirmed by the large change in x_{10} , combined with substantial changes in x_{50} and x_{90} . During high shear blending, granular materials can build up high localized stresses at the relatively weak solid contacts, leading to granule attrition via fragmentation. Materials with smooth surface particles, like sieved and spray dried materials, show a change in x_{10} with limited change in the x_{50} and x_{90} . Changes in particle size only in the fine region indicates the presence of surface abrasion over fragmentation. SEM pictures confirmed surface abrasion for LAs and Msd, showing the presence of small fines with the primary particles remaining unfragmented.

Differences in attrition behavior were also observed for different chemical compositions. Mg, DDg and DAG showed significantly higher amount of attrition than granular lactose grades. This was in line with the observations for spray dried materials, where Msd showed more attrition than LMsd, MCCsd or SMCCsd. The high amount of attrition for DCP grades was related to the brittle and highly fragmenting nature of this material and was in agreement with the material classification performed based on Heckel testing [23,26,27]. The high amount of attrition for mannitol was in contrast with the characterization by Heckel testing, which indicated moderate brittleness for this material. Heckel characterization might be misleading in this case however, as it has been reported that granules of mannitol show fragmentation behavior, while the primary crystals plastically deform [43]. Attrition was therefore expected to be dominated by the breakage of granules, which was also confirmed by the SEM pictures. The high amount of attrition for Mg was further explained by the large particle size of this material, leading to a high crack density [8,23–25]. Materials that were characterized as plastically deforming by Heckel testing, like MCC grades, showed very low amounts of attrition [23,26,27]. These materials were also expected to have a low amount of attrition, as these materials typically do not break upon the application of forces but deform instead. Although the MCC grades are characterized by higher aspect ratios, the ductile nature of MCC helps in minimizing attrition. Plastic deformation also explains why lower attrition is observed for LLg than for LAG or LMg. LLg contains 5% w/w plastically deforming lactitol monohydrate, resulting in lower brittle fracture, confirmed by the higher SRS while having the same yield pressure. The aspect ratio of LLg was also found to be the lowest among granular grades which also explains the reduced attrition.

3.3. The effect of high shear blending on bulk density

Fig. 4 shows the change in bulk density of the different materials upon blending. An increase in bulk density was observed for all materials, except for the sieved grades.

Granular grades showed the largest densification after high shear blending, in line with the highest amount of attrition that was observed for these grades. The large densification was related to improved packing efficiency, as the result of particle smoothing and an increased fines content [6]. Especially with a low to medium amount of fines, fine particles can occupy the spaces between the larger particles, increasing the bulk density.

Mg and DDg showed limited densification compared to other granular grades, while the change in particle size for these materials was substantially larger as the result of fragmentation. The limited densification in this case was explained by the increased cohesiveness as the result of the increased fines content. Fines are known to dominate the powder behavior when they compose the majority of the formulation [41]. In conclusion, an increase of fines content can increase the bulk density via improved packing efficiency, while larger quantities of fines can also reduce the bulk density by providing increased cohesion [41].

Sieved materials did hardly show any change in density, explained by the limited amount of attrition. Spray dried materials in contrast, did show a substantial densification after high shear blending, even though these materials showed limited changes in particle size. Densification for these materials was partly attributed to the minor increase in fines content that improved the packing efficiency. Additionally, densification for spray dried materials was hypothesized to be the result of an increase in interparticle bonding strength (e.g. van der Waals forces, hydrogen bonding) by press-on forces during high shear blending. This increased interparticle bonding can result in improved packing efficiency during bulk density measurements.

3.4. The effect of blending on flow properties

Fig. 5 shows the flow function coefficient of the materials before and after blending. Note that the vertical axis is plotted on a logarithmic scale, as the flow function coefficient (ffc) is not linearly related to powder flow. Mg was the only grade that changed in flow classification after high shear blending. Mg showed a substantial decrease in flow function coefficient, explained by the increased cohesion by the higher fines content of this material after high shear blending. These results are

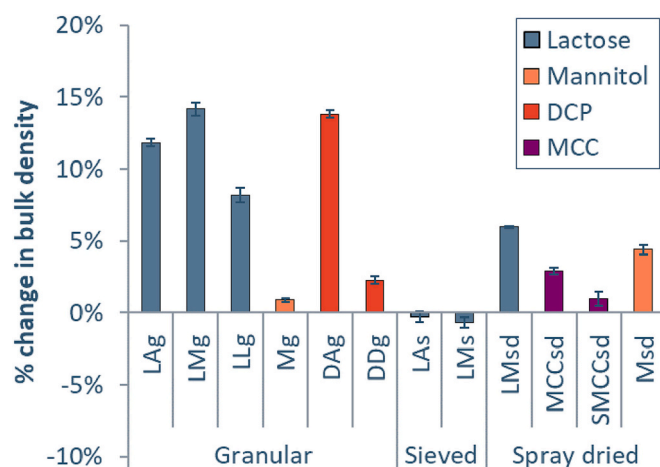


Fig. 4. Relative change in bulk density after blending different grades of lactose (blue), mannitol (orange), DCP (red), and MCC (purple) in a high shear blender. Error bars indicate the standard deviation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

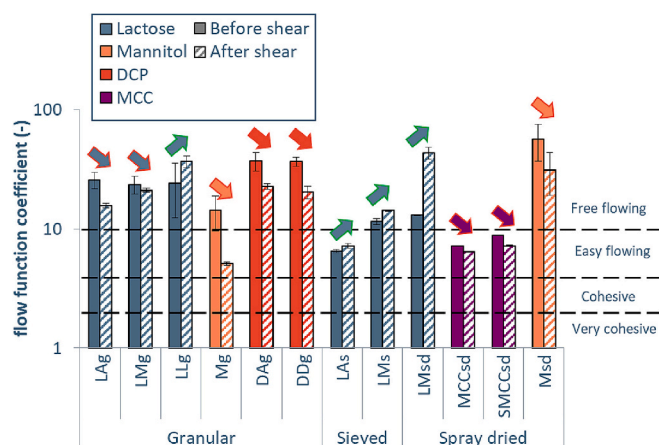


Fig. 5. Absolute change in flow function coefficient after blending different grades of lactose (blue), mannitol (orange), DCP (red), and MCC (purple) in a high shear blender. Error bars indicate the standard deviation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in line with the limited amount of densification that was observed, which was also explained by an increased cohesion of this material by the large amount of attrition.

Besides the change in flow classification for Mg, no substantial changes in ffc were observed after high shear blending. Only minor differences in ffc were observed, of which the direction of change differed per material. The variable direction was explained by the presence of two counteracting effects by the creation of fines. On one hand, an increased fines content results in increased cohesion by increasing the available surface area. On the other hand, fines can lubricate larger particles and thereby reduce the total interparticle forces [6]. Granular and spray dried materials generally showed a reduction in ffc after high shear blending. This was attributed mainly to the increased cohesion as the result of attrition. Granular and spherical particles have limited interparticle contact points [41], resulting in limited gains to be obtained by the lubrication effect. Sieved materials on the other hand have flat crystal surfaces with larger interparticle forces. Lubrication by fines creation was therefore observed to effectively reduce the interparticle forces, making this effect dominating. Due to the presence of two counteracting effects however, some individual grades behaved differently and no concluding statements on the direction of change in ffc as the result of attrition could be provided.

3.5. The effect of blending on tableting properties

Fig. 6 shows the relative change in tablet tensile strength (TTS) after high shear blending of the materials.

Most of the excipients showed an increase in TTS after high shear blending as the result of attrition, which was attributed to the increased surface area available for bonding. DCP grades did not show a significant change in TTS, despite the high amount of attrition that is observed for these grades. DCP is a material with extensive brittle fragmentation upon compaction. Reducing the particle size before the compaction step therefore only hardly affects the available bonding area [44]. The absence of an increase in the TTS of DDg was explained by the extensive fragmentation before the lubrication step. With a higher fraction of the bonding area being lubricated, the tableting ability of a material is lower [41].

Lactose is a moderately brittle material, with a relatively low propensity for particle breakage upon compaction [41,45]. Fragmentation therefore increases the bonding area substantially, resulting in higher TTS after attrition. MCCsd and SMCCsd showed an increase in tablet tensile strength of 9–22%, indicating that the impact of attrition on

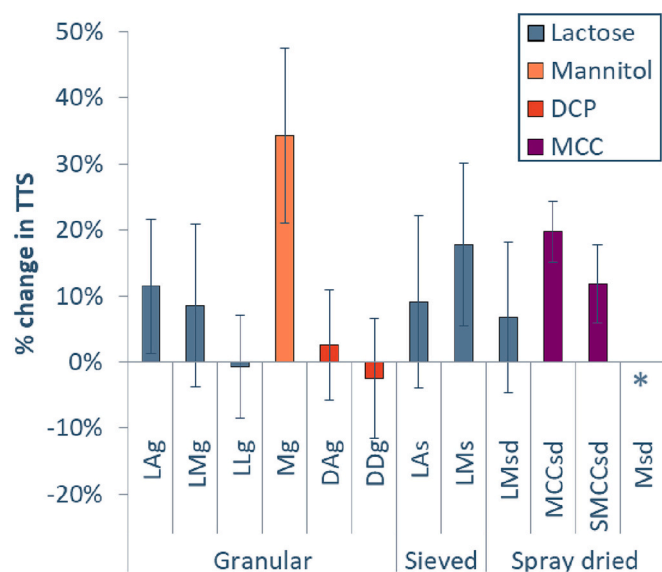


Fig. 6. Relative change in tablet tensile strength after blending lactose (blue), mannitol (orange), DCP (red), and MCC (purple) grades in a high shear blender. No data is available for Msd, due to punch sticking and capping of the tablets produced with this material. Error bars indicate the standard deviation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tablet tensile strength is larger for plastically deforming materials than for brittle fragmenting materials [25,46]. The large increase in TTS for the MCC grades was not expected, as only a minimal decrease in particle size (max. 3%) combined with an increase in bulk density was observed. Bulk density is well described to be a key driver for the tableability of MCC grades, with typically higher TTS for MCC with lower bulk density [47–49]. The minimal particle size decrease in this case however is thought to be responsible for the substantial improvement in TTS. As MCCsd and SMCCsd are both plastically deforming materials, a reduction in particle size results in a direct increase in available bonding area during tableting. Additionally, high shear blending of MCC might have resulted in dislocation of microcrystals on a microscale. This dislocation could have resulted in a higher amount of hydrogen groups at the surface, which are available for bonding during tableting [34]. Further research is recommended to confirm this hypothesis.

4. Conclusion

For the first time, an integral study to evaluate the impact of chemistry and morphology on the attrition behavior of excipients upon high shear blending was performed. The type and amount of attrition was shown to be dependent on both the morphology and the chemical composition of the material. Granular materials showed the most attrition, driven by fragmentation, due to the irregular surfaces with particles held together by weak solid bridges. Sieved materials showed the lowest amount of attrition, explained by the presence of strong crystal lattice bonds keeping the particles together. Spray dried materials also showed low amounts of attrition, due to strong interparticle bonding with low surface irregularities. The smooth surfaces of sieved and spray dried materials resulted in surface abrasion as main attrition mechanism. The amount of attrition was also shown to be dependent on the deformation mechanism of a material. Materials with brittle fracture upon compaction showed larger amounts of attrition than materials with plastic deformation behavior. DCP showed the largest amount of attrition, followed by mannitol, lactose and MCC respectively. Factors such as influence of humidity, batch to batch variability and formulation composition have not been evaluated during this study but are recommended as a follow up to the current work.

The attrition of materials by high shear blending resulted in changes in bulk density, flow function coefficient and tablet tensile strength. Granular grades generally increased in density, explained by improved packing efficiency by smoothening of particles and an increased fines content. The density of spray dried grades typically increased upon high shear blending, explained by an increased fines content combined with increased interparticle bonding. Sieved materials did not show densification, explained by the limited amount of attrition. An increase in fines content resulted in a reduced flow function coefficient for granular and spray dried materials, by having increased cohesiveness. For sieved materials, the minor increase in fines content lubricated the larger particles and thereby resulted in an increased flow function coefficient. Changes in the tablet tensile strength were more driven by the deformation properties than by the morphology. Even a large change in particle size hardly affects the tablet tensile strength of materials with extensive brittle fracture behavior, while a small change in particle size can have a major effect on tablet tensile strength for plastic deforming materials.

CRediT authorship contribution statement

Sri Sharath Kulkarni: Conceptualization, Data curation, Investigation, Methodology, Resources, Project administration, Writing – original draft, Writing – review & editing. **Pauline H.M. Janssen:** Conceptualization, Data curation, Methodology, Resources, Visualization, Writing – original draft, Writing – review & editing. **Bastiaan H.J. Dickhoff:** Conceptualization, Resources, Supervision, Writing – review & editing.

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.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.powtec.2023.118694>.

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