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Impact of alternative lubricants on process and tablet quality for direct compression

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ABSTRACT

Internal lubrication with magnesium stearate (MgSt) is associated with a reduced tensile strength and prolonged disintegration and dissolution times. In the current study, alternative lubricants to MgSt were compared with regard to lubrication efficacy and their impact on tablet properties. The lubricants were combined in different concentrations (0.5–5% w/w) with three fillers (lactose, mannitol and microcrystalline cellulose (MCC)). The high lubrication efficiency of MgSt was associated with the highest reduction of tensile strength. The micronized stearic acid (SA) grades proved good alternatives as they showed a good lubrication efficiency in combination with a limited negative effect on tensile strength. The hydrophobic lubricants (e.g., MgSt and SA) did not prolong disintegration. In contrast, delayed disintegration was observed for sucrose monopalmitate combined with all three fillers and for several other hydrophilic lubricants (sodium lauryl sulfate, poloxamers 188 and P407) combined with MCC. These unexpected findings were explained by the competition-for-water hypothesis. The potential of alternative lubricants to MgSt was demonstrated in this study. Nevertheless, the impact of lubricant addition on process and tablet quality depended on lubricant (type and concentration) and formulation (lubrication need, deformation mechanism and disintegration behavior) properties. Therefore, lubricant selection should be carefully considered in formulation development.

1. Introduction

Lubrication is an important aspect during the manufacturing process of tablets as excessive friction between die wall and tablet surface can impede tablet ejection (Abdel-Hamid et al., 2012; Hölzer and Sjögren, 1977; Puckhaber et al., 2022). The ejection force is defined as the force needed for the lower punch to push the tablet out of the die. High ejection forces can be correlated to tablets defects (chipping, capping and lamination) and tablet tooling wear (Abdel-Hamid et al., 2012; Bolhuis et al., 1985; Puckhaber et al., 2022; Sun, 2015). Therefore, a lubricant is used during tableting to reduce the friction between the die wall and tablet during ejection and subsequently, facilitate tablet ejection. Magnesium stearate (MgSt) is the most used lubricant in the pharmaceutical industry due to its excellent lubrication properties and low cost (Dun et al., 2020b). Traditionally, internal lubrication is applied where the lubricant is incorporated into the formulation prior to the tableting process via a blending step. Typical lubricant concentrations range between 0.5 and 5% (Li and Wu, 2014). Nevertheless, several negative effects (i.e., reduced tabletability, longer disintegration and dissolution times) can be associated with internal lubrication, especially for MgSt (Desai et al., 1993; Jarosz and Parrot, 1984; Vromans and Lerk, 1988; Zuurman et al., 1999). These effects are further enhanced by high lubricant concentration, long blending time, intensive blending and high paddle speed (PS) of the tablet press feed frame (Bolhuis et al., 1981; de Backere et al., 2022; Dun et al., 2020a; Lerk et al., 1982; Paul and Sun, 2018; Peeters et al., 2016). Furthermore, the

Abbreviations: CA, Contact angle; DBHG, Glyceryl dibehenate; HLB, Hydrophilic-lipophilic balance; MCC, Microcrystalline cellulose; MgSt, Magnesium stearate; PS, Paddle speed; rpm, Revolutions per minute; SA, Stearic acid; SE, Sucrose ester; SEM, Scanning electron microscope; SLS, Sodium lauryl sulfate; SpecWComp, Specific work of compaction; SSA, Specific surface area; SSF, Sodium stearyl fumarate; TBI, Tablet brittleness index.

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tensile strength of ductile materials is highly susceptible to the effect of internal lubrication as the lubricant-coated surfaces of ductile materials interferes with particle bonding. In contrast, brittle materials are less affected by lubricant addition as fragmentation creates new lubricant-free areas available for bonding (Bolhuis et al., 1975, 1985; de Backere et al., 2021; Mosig and Kleinebudde, 2014; Vromans et al., 1988; Wünsch et al., 2020; Mosig and Kleinebudde, 2015).

The use of alternative lubricants like sodium stearyl fumarate (SSF) (de Backere et al., 2022; Hölzer and Sjögren, 1979; Kapadia and Deshmukh, 2017; Paul and Sun, 2018; Shah et al., 1986), stearic acid (SA) (de Backere et al., 2022; Paul and Sun, 2018; Uğurlu and Halaçoğlu, 2014), poloxamers (Desai et al., 2007; Dun et al., 2020b), sodium lauryl sulfate (SLS) (Dun et al., 2018; Perrault et al., 2011), glyceryl dibehenate (DBHG) (N'Diaye et al., 2003; Shah et al., 1986; Uğurlu and Halaçoğlu, 2014), polyethylene glycol (Dinesh and Mutahar, 2009; Kapadia and Deshmukh, 2017; Uğurlu and Halaçoğlu, 2014) and sucrose fatty acid esters (Aoshima et al., 2005; Nakamura et al., 2017) for internal lubrication has been investigated by several authors.

A comparison of MgSt, SSF and SA regarding lubrication efficiency, tensile strength, tablet brittleness index (TBI), friability and disintegration was performed by Paul and Sun (2018). TBI is an important material property that quantifies brittle fracture behavior and can be determined from a force–displacement curve of a diametrical breaking test. A high TBI can be correlated to a higher friability and more tablet defects (Gong and Sun, 2015; Paul and Sun, 2017). Plastic (MCC/lactose 2:1) and brittle (lactose/MCC 1:3) formulations were blended with the lubricants (0–2% w/w). A higher lubrication efficiency was obtained with MgSt compared to SSF and SA, as the latter two needed a higher concentration (i.e., 1% w/w compared to 0.5% w/w for MgSt) to achieve comparable lubrication. MgSt induced the highest reduction in tensile strength as well as increase in TBI and friability followed by SSF and SA, while disintegration followed the order: SA > MgSt > SSF when comparing the lubricants at the same concentration level. Disintegration tests were only performed for the formulations containing 2% lubricant with addition of a disintegrant (2% w/w croscarmellose sodium).

The effectiveness of SLS, a surfactant, as lubricant was investigated by Dun et al. (2018). Higher lubricant concentrations were required for SLS to obtain a comparable lubrication efficiency as MgSt. Tensile strength was higher for SLS compared to MgSt at the same lubricant concentration. However, for the formulations with a higher lactose fraction, higher concentrations of SLS were needed which resulted in smaller differences in tensile strength between SLS and MgSt (Dun et al., 2018). Another study by the same authors investigated the suitability of two poloxamers grades (poloxamer 188 and poloxamer 407) as alternatives for MgSt (Dun et al., 2020b). For a ritonavir tablet formulation containing MCC and lactose in a 60/40 ratio, 2% of both poloxamers resulted in lower ejection forces, higher tabletability, and enhanced in vitro drug release compared to 1% MgSt. In both studies, disintegration tests were performed on a specific formulation with addition of disintegrant (5% w/w croscarmellose sodium), resulting in fast disintegration (<90 s). The effect of lubricant concentration on disintegration was not investigated (Dun et al., 2020b, 2018).

The lubricant performance of DBHG, SSF and MgSt were compared by Shah et al. (1986) for salicylic acid and lactose tablets. A higher concentration of DBHG (3% versus 1% w/w) was needed in comparison to MgSt and SSF for effective lubrication. Tablet hardness was similar for MgSt, SSF and DBHG at 1% concentration while DBHG and SSF showed superior compressibility at 3% compared to MgSt. Furthermore, the negative effect on the dissolution rate was less pronounced for DBHG and SSF in comparison with MgSt.

Different grades of sucrose esters (SEs) were compared to MgSt as tablet lubricants for a lactose-rich formulation (Nakamura et al., 2017). The tablets containing SEs were harder and less friable than those containing MgSt. Faster disintegration was seen for the SE-containing tablets compared to tablets formulated with MgSt. Additionally, differences in disintegration time between the SE grades were also observed based on their hydrophilic-lipophilic balance (HLB) value with faster disintegration for SE grades with lower HLB values. The lubricants could be easily processed on a rotary tablet press without tablet failures at lubricant concentrations of 0.5% or 1%, depending on the SE grade. Data of ejection forces were not monitored and tablets were only produced at a compression force of 10 kN.

The use of alternative lubricants to MgSt was highlighted in these previous papers, but such lubricants often require a higher concentration to achieve comparable lubrication efficiency. Furthermore, a negative impact on tensile strength was observed although often not to the same extent as MgSt, while disintegration might also be prolonged in case of hydrophobic lubricants. However, the comparison between lubricant types is hampered by the use of different formulations (e.g., filler and level of disintegrant). A systematic study of multiple lubricants and the effect of lubricant addition (type and concentration) on process (ejection force) and tablet quality (tensile strength, disintegration) is currently lacking. Therefore, a screening of 13 lubricants for a direct compression process was performed in the current study. The lubricants were combined with three commonly used fillers (lactose, mannitol and MCC) at different concentrations. The effect of lubricant type and lubricant concentration on ejection force, tensile strength and disintegration time was investigated. This study provides additional insights regarding the use of alternative lubricants in tablet manufacturing.

2. Materials and methods

2.1. Materials

Spray dried monohydrate lactose (SuperTab® 11SD, DFE Pharma, Goch, Germany), mannitol (Pearlitol® 200 SD, Roquette Frères, Lestrem, France) and microcrystalline cellulose (MCC, Avicel® PH102, DuPont Pharma, Wilmington, DE, USA) were used as fillers with different characteristics regarding lubrication need, deformation and disintegration mechanism. Ligamed® MF-2-V was purchased from Peter Greven (Bad Münstereifel, Germany) while the other investigated lubricants were kindly provided by Stéarinerie Dubois (Boulogne-Billancourt, France), JRS Pharma (Rosenberg, Germany) and BASF (Ludwigshafen, Germany). Table 1 provides an overview of the lubricants with their brand name, corresponding abbreviation used through

Table 1
Overview of used lubricants with corresponding supplier.

Material	Brand Name	Abbreviation	Supplier
Magnesium stearate	Ligamed® MF-2-V	MgSt	Peter Greven
Stearic acid 50	Stellipress 1200 poudre	SA50P	Stéarinerie Dubois
Stearic acid 50	Stellipress micro	SA50M	Stéarinerie Dubois
Stearic acid 95	Stellipress micro 95	SA95M	Stéarinerie Dubois
Glyceryl dibehenate	Stelliesters DBHG	DBHG	Stéarinerie Dubois
Sucrose monopalmitate	Stelliesters SE 15P	SE15P	Stéarinerie Dubois
Sucrose stearate (type II)	Stelliesters SE 5S	SE5S	Stéarinerie Dubois
/*	Dub Hydrolub	Hydrolub	Stéarinerie Dubois
Sodium stearyl fumarate	Pruv®	SSF	JRS Pharma
Hydrogenated vegetable oil	Lubritab®	Lubritab	JRS Pharma
Poloxamer 188	Kolliphor® P188 micro	P188	BASF
Poloxamer 407	Kolliphor® P407 micro	P407	BASF
Sodium lauryl sulfate	Kolliphor® SLS fine	SLS	BASF

* Mixture consisting of mannitol, sucrose palmitate (10–30% w/w), polysorbate 80 and simethicone.

the manuscript and supplier. Temperature (21.0 ± 2.0 °C) and relative humidity (45 ± 5%) were logged during material storage, blend preparation and tableting experiments.

2.2. Blend preparation

The lubricants were combined in different concentrations (0.5, 1, 2.5 and 5% w/w) with each filler. Filler and lubricant were blended for 5 min at 23 revolutions per minute (rpm) in a tumbling mixer (Turbula T2F mixer, WAB, Muttenz, Switzerland). The batch size was 350 g for all formulations. Prior to blending, the lubricants were sieved by hand through a 500 μm sieve to break up agglomerates. Fillers were used as received.

2.3. Preparation of tablets

Tablets were produced using a STYL'One Evolution compaction simulator (Medelpharm, Beynost, France) equipped with cylindrical flat-faced Euro B punches of 10 mm diameter (Natoli Engineering Company, Saint Charles, MO, USA). For each formulation, tablets were produced at 7 different main compaction pressures: 64, 127, 191, 255, 318, 382 and 509 MPa with a fixed pre-compaction pressure of 25 MPa. A compression profile simulating the MODUL P rotary tablet press (GEA Process Engineering, Halle, Belgium) at a turret speed of 50 rpm was used. This profile was executed in position control with an upper punch penetration depth of 3.25 mm. The distance between the punches for pre and main compression was adapted per formulation to obtain the predefined compaction pressures. The ejection force overload limit was set at 2500 N with higher ejection forces resulting in a safety stop of the machine. Tablet weight and overfill level were set at 350 mg and 2 mm, respectively. A single-paddle feeder with 6 fingers rotating clockwise at constant paddle speed (PS) of 60 rpm was used. The powder blend was poured into the feeder and the paddle of the feeder was rotated before starting the experiments and 150 tablets were produced to ensure the feeder was completely full and powder was conditioned before starting the experiments. Data was collected after reaching steady state conditions regarding the compaction pressure and tablet weight with a maximal allowed deviation from the setpoint of 5% and 3%, respectively. For each main compaction pressure, 50 tablets were collected when reaching steady state conditions.

2.4. Responses

The mean ejection force and corresponding standard deviation of each experiment were calculated for 50 tablets.

Tablets were stored for 24 h prior to analysis. Tablet diameter, thickness and breaking force (n = 10) were determined using a hardness tester (SmartTest 50, Sotax, Basel, Switzerland). Tablet diametrical tensile strength was calculated according to Equation (1) (Fell and Newton, 1970):

$$Tablet\ \ tensile\ \ strength\ \ (MPa) = \frac{2F}{\pi dt} \quad (1)$$

where F is the breaking force (N), d the tablet diameter (mm) and t the tablet thickness (mm).

Tablet disintegration time (n = 6) was determined using distilled water at 37 ± 2 °C as medium. The disintegration test (DIST-3, Pharma Test, Hainburg, Germany) was conducted as described in the European Pharmacopoeia (EDQM, 2020). Tablets compressed at 127 MPa were used for the tablet disintegration tests.

2.5. Material characterization

2.5.1. Particle size distribution

Particle size distributions (n = 3) were measured by laser diffraction (Mastersizer S long bench, Malvern Instruments, Worcestershire, UK). Measurements were performed using the dry dispersion unit in volumetric distribution mode, using a 300 RF lens combined with a dry dispersion unit at a feeding rate of 3.0 G and a jet pressure of 2.4 bar. The particle size was reported as a volume-equivalent sphere diameter. For each volumetric distribution, the 10%, 50% and 90% cumulative undersize fraction was reported as dv10, dv50 and dv90, respectively.

2.5.2. Specific surface area

Samples were degassed for 24 h using the vacuum mode of the VacPrep 061 (Micrometrics, Norcross, USA) and then purged with nitrogen for one hour. Subsequently, samples were subjected to nitrogen sorption measurements at −196 °C (TriStar 3000, Micrometrics). The specific surface area (SSA) of the samples was calculated making use of the Brunauer Emmett and Teller (BET) theory (Brunauer et al., 1938).

2.5.3. Particle morphology

The lubricants were examined by scanning electron microscopy (SEM) (FEI Quanta™ 200F, FEI, Hillsboro, USA) after sputtering with a gold coating (Emitech SC7620, Quorum Technologies, East Sussex, UK) to improve the electron conductivity of the samples. The electron accelerating voltage was 20 kV. The SEM images allowed visualization of the shape and morphology of the lubricants.

2.5.4. Compaction properties

Three phases can be distinguished in the compression cycle of a tablet as visualized in the pressure-displacement curve by plotting compaction pressure against punch separation (Fig. 1). The first step includes powder particle rearrangement and packing (A'-A) as the punches move towards each other. In the second phase (A-B), the compaction pressure increases until a maximal pressure (B) at minimal punch separation (D). During this phase, fragmentation and/or plastic deformation of the powder particles occur. The applied pressure is released in the third phase (B-C) called decompression or unloading, resulting in an elastic recovery of the compact (C-B-D) (Busignies et al., 2004; Grymonpré et al., 2017; Michaut et al., 2010; Pontier et al., 2002; Vachon and Chulia, 1999).

The energy of each phase can be calculated from the area under the curve. The work of compression or the total energy (ABD) can be determined from the integral calculus from A to D, while the work of elastic recovery (BCD) is calculated by integration from C to D (Fig. 1). The work of compaction or the net energy is calculated as the difference between the work of compression and work of elastic recovery, and expresses the energy needed to form a compact (Fig. 1). The specific work of compaction (SpecWComp) is calculated by dividing the work of compaction by the tablet weight (Equation (2)). The degree of elasticity was calculated using Equation (3) (Delacourte et al., 1993; Grymonpré

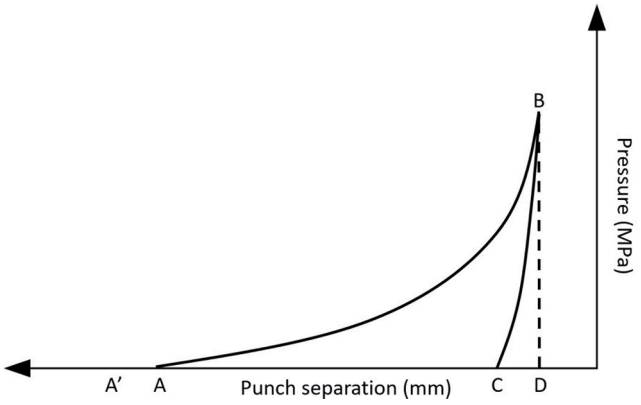

Fig. 1. Pressure-displacement curve illustrating the different phases during compression.

et al., 2017; Vachon and Chulia, 1999).

$$\text{SpecWComp}\left(\frac{J}{g}\right) = \frac{\text{Work of compaction}}{\text{Tablet weight}} \quad (2)$$

$$\text{Elasticity}\ (\%) = \frac{\text{Work of elastic recovery}}{\text{Work of compression}} x100 \quad (3)$$

The compaction properties were determined for the pure materials. Powders (n = 10) were individually weighed, manually filled into the die and compacted on the STYL'One Evolution compaction simulator. A main compaction pressure of 191 MPa was applied without a pre-compaction step at low tableting speed (punch speed of 13.5 mm/s). External lubrication with MgSt was applied to minimize confounding of the results due to friction. A spraying time of 500 ms and an atomizing pressure of 3 bar were used as settings for the automated external lubrication system (Medelpharm, Beynost, France) implemented in the compaction simulator.

2.5.5. Wettability

Sessile drop contact angle (CA) (°) measurements (n = 6) were performed using a Drop Shape Analyzer (DSA 30, KRÜSS, Hamburg, Germany). The powder-on-tape method was applied as tablets of pure lubricant could not be produced. A layer of double-sided tape was attached to a glass microscope slide and pressed into a smoothed powder bed. Subsequently, the excess powder was removed using compressed air. After a 5 μl drop of demineralized water was placed on top of the powder bed surface, the CA was measured immediately (CA_t0) and after 30 s (CA_t30).

2.6. Water uptake and force development

A system consisting of a texture analyser (TA.XT*Plus*, Stable Micro Systems Ltd., UK) and a balance (CP224S, Sartorius, Germany) was used to simultaneously quantify water uptake and force development of unlubricated and lubricated MCC tablets. This system was previously described by Quodbach and Kleinebudde (2014). A water-filled vessel was positioned below the measurement probe of the texture analyser. Next, a tablet holder with several holes to permit water flow was placed in the vessel in contact with the water surface and a round filter paper was placed on the holder. The water-filled beaker located on the balance was connected directly to the vessel under the texture analyser via a tube, allowing water to flow from one side to the other. The balance measured the water uptake, whereas the force development of the tablets was recorded by the texture analyser. The measurement time of each experiment was 300 s and the measurement frequency was set to 5 Hz in both cases. Tablets (n = 6) produced at a main compaction pressure of 127 MPa were used.

3. Results and discussion

3.1. Ejection forces

Unlubricated lactose and mannitol could not be tableted due to excessively high ejection forces (>2500 N). Therefore, these fillers were suitable for the evaluation of lubricants towards the ability to reduce the ejection forces (i.e., lubrication efficiency). Table S1 presents an overview of all performed experiments. An ejection force overload occurred for several lubricants in combination with lactose or mannitol, especially at lower lubricant concentrations. Ejection forces were plotted in function of main compaction pressure and the effective lubricant concentration for each lubricant was determined as the concentration yielding ejection forces below 600 N (Table 2). An additional increase in lubricant concentration, above the effective lubricant concentration, did not show a further relevant reduction of the ejection forces and thus did not improve lubrication efficiency (Figs. 2, 3 and S1). Furthermore, ejection forces were similar for the different lubricants once the effective lubricant concentration was obtained. Ejection forces increased at higher compaction pressures for lactose or mannitol formulations as friction intensified (Figs. 2, 3 and S1). As generally similar trends regarding the lubrication efficiency were observed in mannitol- and lactose-based formulations, both fillers will be discussed simultaneously. However, for some lubricants a shift towards higher effective concentrations was observed for mannitol indicating a higher lubrication need for this filler (Table 2). Ejection forces were lower for unlubricated and lubricated MCC, resulting in limited differences between the lubricant types and concentrations. Therefore, ejection force results of MCC were not taken into consideration for the lubrication efficiency of the investigated lubricants.

A high lubrication efficiency was observed for MgSt with effective lubricant concentrations of 0.5% and 1% for lactose and mannitol, respectively (Table 2). When lubricating mannitol with 0.5% MgSt, ejection forces were above the 600 N threshold at the highest main compaction pressure, but never exceeded 800 N (Figs. 2 and S1). The good lubrication performance of MgSt is well-known and can be attributed to its small particle size and high SSA (Table 3). The micronized SA grades (SA50M and SA95M) and SSF were good alternatives for MgSt as their effective concentration was 1% for lactose and mannitol (Table 2). Ejection forces were higher at the 0.5% level for SA50M, SA95M and SSF compared to MgSt. However, for the 1% lubricant concentration, comparable ejection forces were recorded for MgSt, SA95M and SSF with lactose and mannitol. Slightly higher ejection forces were observed for SA50M at lower compaction pressures (Figs. 3 and S1). Similar to MgSt, the small particle size and large SSA of SA95M, SA50M and SSF contributed to their good lubrication efficiency (Table 3).

Three SA grades were investigated: two micronized (SA50M and SA95M) and one powder form (SA50P). SA is a mixture that mainly consists of stearic acid and palmitic acid (EDQM, 2021). While the content of stearic acid ranges from 40.0 to 60.0% for SA50, it was minimum 90.0% for SA95. The effective lubricant concentration of SA50P was higher (5%) compared to the micronized grades (1%), SA50M and SA95M, which is linked to the larger particle size and lower SSA of the former (Tables 2 and 3). This indicated the importance of particle size and SSA towards lubrication effectiveness, while the impact of stearic acid/palmitic acid ratio is limited.

DBHG exhibited good lubrication properties when combined with lactose as the effective concentration was 1%. For mannitol, 2.5% was needed to allow production of tablets at all compaction pressures (Figure S1). Ejection forces up to 1000 N were recorded and as a result, the effective concentration of DBHG was 5% (Table 2). This indicated a

Table 2
Effective lubricant concentrations for lactose and mannitol, based on a reduction of the ejection forces below 600 N.

Lactose					Mannitol				
0.5%	1%	2.5%	5%	> 5%	0.5%	1%	2.5%	5%	> 5%
MgSt	SA50M SA95M DBHG SSF	SE5S Lubritab P188 P407	SA50P	SE15P Hydrolub SLS		MgSt SA50M SA95M SSF	SE5S	SA50P DBHG Lubritab P188 P407	SE15P Hydrolub SLS

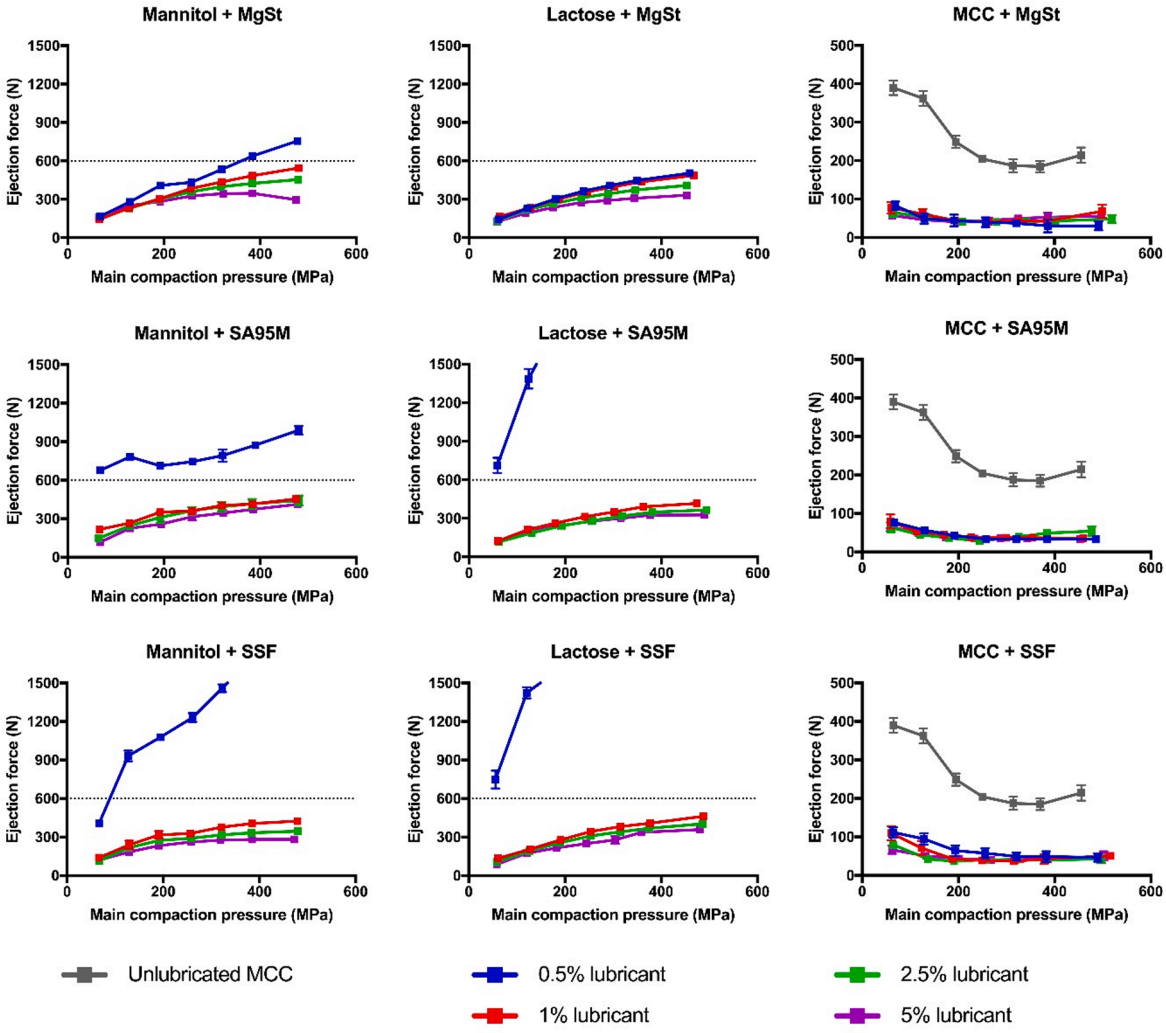

Fig. 2. Ejection forces of mannitol- (left), lactose- (middle) and MCC-based (right) formulations containing 0.5, 1, 2.5 and 5% MgSt (top), SA95M (middle) and SSF (bottom). The upper limit of the y-axis was set at 1500 N to improve the visualization.

lower lubrication potential of DBGH when combined with mannitol. Although Lubritab could already be processed at 1% for both fillers, the ejection forces at this lubricant concentration were too high (Figs. 3 and S1), and the effective lubricant concentration of Lubritab was set at 2.5 and 5% for lactose and mannitol, respectively (Table 2).

The lubrication performance of the poloxamer grades (P188 and P407) was similar as the same effective lubricant concentration was obtained, 2.5% for lactose and 5% for mannitol. This can be attributed to their similar particle size and SSA (Table 3). Two grades of SEs were evaluated: sucrose monopalmitate (SE15P) and sucrose stearate (SE5S). The effective concentration of SE5S was determined at 2.5% for both fillers (Table 2). On the other hand, even for 5% SE15P the ejection forces for lactose and mannitol were still above the threshold value of 600 N (Figs. 3 and S1). The better performance of SE5S as tablet lubricant compared to SE15P might be due to the smaller particle size and larger SSA of SE5S compared to SE15P (Table 3).

Poor lubrication properties were observed for SLS and Hydrolub (Table 2). For SLS, only formulations with the highest lubricant concentration (5%) could be processed at all compaction pressures for lactose and mannitol, recording ejection forces up to 1000 N (Fig. 3 and S1). Hydrolub could only be processed at the highest concentration (5%) in combination with lactose (Fig. 3). 5% Hydrolub combined with mannitol resulted in an ejection force overload. Hydrolub is a mixture consisting of mannitol, 10–30% w/w sucrose palmitate, polysorbate 80 and simethicone. Although the exact quantitative formula is not disclosed by the manufacturer, the presence of mannitol might partially explain the poor lubrication efficiency of Hydrolub. Furthermore, including 5% Hydrolub in a tablet formulation corresponds to only 0.5–1.5% sucrose palmitate which is – based on the SE15P data – a too low concentration to result in adequate lubrication.

For unlubricated MCC, ejection forces were already below 400 N. Although lubricant addition caused a further decrease in the ejection forces (Fig. 2 and S2), no relevant effect of lubricant type and lubricant concentration on the ejection forces of lubricated MCC was observed. Only for 0.5% SLS and 0.5 and 1% Hydrolub, slightly higher ejection forces were measured (Figure S2). The lower lubrication efficiency of SLS and Hydrolub is consistent with the results obtained for lactose and mannitol. In contrast to lactose and mannitol tablets, ejection forces of MCC tablets slightly decreased at higher compaction pressures for unlubricated and lubricated MCC (Fig. 2 and S2). This observation was previously linked to a reduction of tablet diameter in function of main compaction pressure (de Backere et al., 2020).

3.2. *Tensile strength*

The impact of lubricant type and concentration on tensile strength was most pronounced for MCC followed by lactose and mannitol (Fig. 4). The higher lubricant sensitivity of MCC can be attributed to its

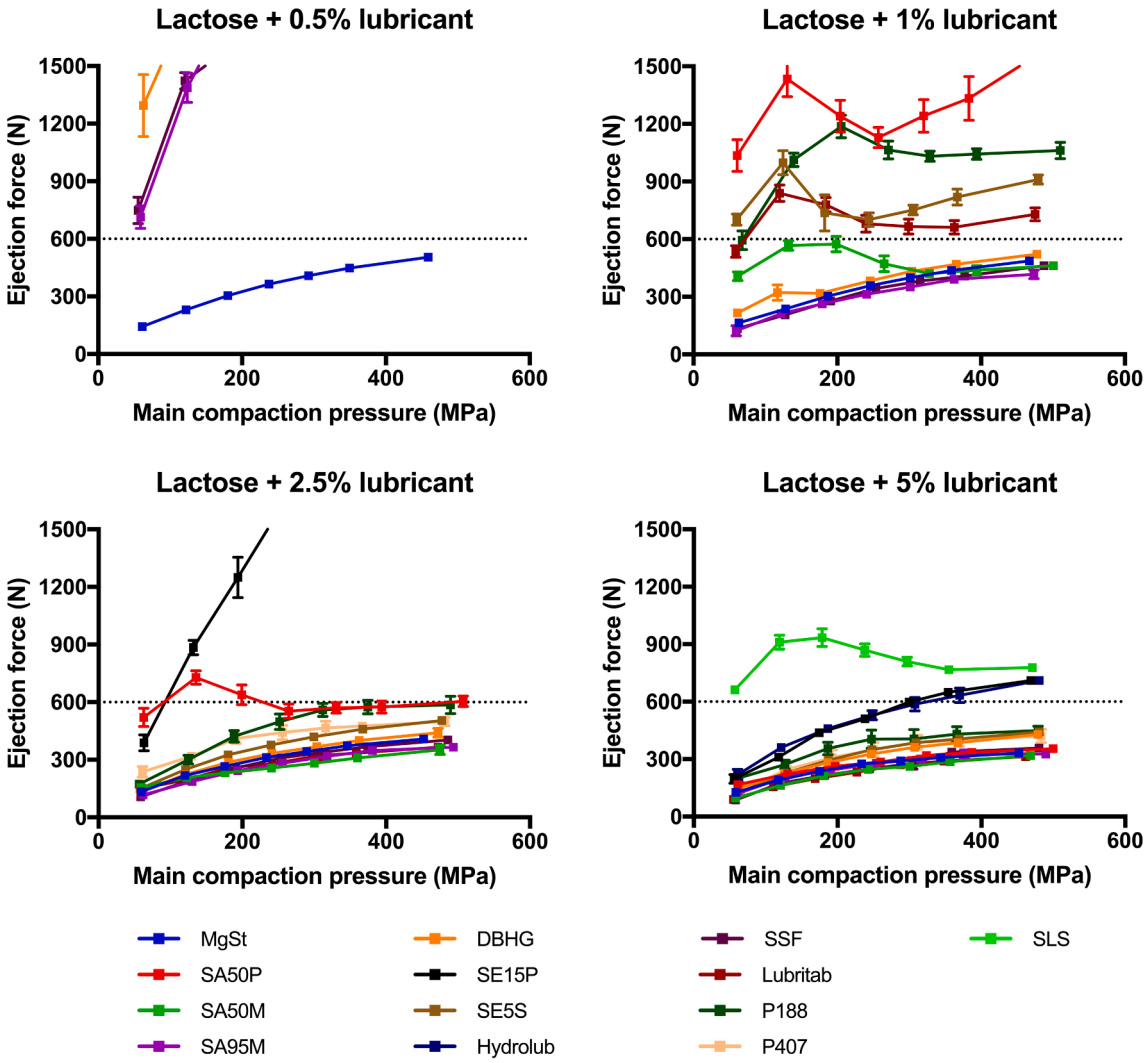

Fig. 3. Ejection forces of lactose containing 0.5, 1, 2.5 and 5% of lubricant. The upper limit of the y-axis was set at 1500 N to improve the visualization.

plastic deformation behavior, supported by the higher SpecWComp (33.5 ± 0.7 J/g) compared to lactose (23.4 ± 0.6 J/g) and mannitol (26.7 ± 0.2 J/g). For lactose and mannitol, the SpecWComp values were similar although lactose was slightly more susceptible to lubricant addition than mannitol. The lower lubricant sensitivity of mannitol is in agreement with previous research (de Backere et al., 2022; Tarlier et al., 2015) and can probably be attributed to its higher SSA (1.09 m^2/g) compared to lactose (0.13 m^2/g). The relative area covered by lubricant is smaller for a material with a larger SSA resulting in sufficient lubricant-free surface area available for bonding (Almaya and Aburub, 2008).

Ejection forces of unlubricated MCC were already low and therefore lubricant addition was not necessary. Nevertheless, MCC was used as model compound to study the effect of lubricants on tensile strength because of its plastic deforming behavior and thus high lubricant sensitivity. The addition of 0.5% lubricant to MCC already caused a significant decrease in tensile strength compared to unlubricated MCC (Fig. 4, 5 and S3). This effect was further enhanced by higher concentrations for all lubricants. Furthermore, differences in the extent of tensile strength reduction were observed between lubricant types, which will be discussed further in this section. The reduction of tensile strength can be attributed the small lubricant particles coating the MCC fibers, therefore limiting the formation of particle bonds during compaction.

Although all lubricants could be processed in combination with MCC on the compaction simulator given the low ejection forces, incomplete tabletability plots were obtained for several lubricants due to severe tablet defects like capping and lamination (Table S1 and Fig. 4, 5 and S3). Tablet defects were observed at concentrations starting from 1, 2.5 and 5% w/w for MgSt, SE5S and SSF, respectively. These tablets defects might indicate overlubrication of MCC due to its high susceptibility to internal lubrication. As the paddle movement of the forced feeder induced further mixing, a large fraction of the MCC particles will be covered with lubricant, reducing bonding strength and even resulting in tablet defects. This behavior, which is most noticeable for MgSt, SSF and SE5S, can be linked to their small particle size (dv10, dv50), high SSA (Table 3) and flake-like particle shape (Fig. 6) promoting coverage of the MCC particles. In contrast, the micronized SA grades had a less negative effect on tensile strength. While these grades also exhibited a small particle size and large SSA (Table 3), the spherically shaped particles of SA (Fig. 6) resulted in a less efficient coverage of the MCC particles.

Lactose- and mannitol-based formulations exhibited tabletability issues, especially at low lubricant concentrations (Section 3.1, Table S1). Additionally, no comparison with unlubricated lactose or mannitol could be made. For mannitol, the effect of lubricant type and concentration was limited, which indicated a low lubricant sensitivity. As a result, similar tabletability profiles were observed for the investigated lubricants and lubricant concentrations (Fig. 4 and S4). Only minor tablet defects were observed for tablets containing 5% MgSt compacted at the highest main compaction pressure (509 MPa), but these tablets showed a significant drop in tensile strength (Fig. 4). Differences in

Table 3
Raw material characteristics of the lubricants.

Lubricant	Particle size distribution			SSA (m^2/g)	Wettability	
	dv10 (μm)	dv50 (μm)	dv90 (μm)		CA_t0 (°)	CA_t30 (°)
MgSt	1.9 ± 0.0	5.5 ± 0.1	20.3 ± 1.2	9.97 ± 0.79	140 ± 2	140 ± 2
SA50P	82.8 ± 0.1	159.4 ± 0.5	261.0 ± 1.4	0.71 ± 0.00	129 ± 7	124 ± 2
SA50M	9.4 ± 0.1	54.1 ± 0.3	105.9 ± 0.5	1.26 ± 0.05	129 ± 4	132 ± 4
SA95M	8.0 ± 0.1	23.1 ± 0.4	88.7 ± 0.3	1.03 ± 0.01	140 ± 7	138 ± 5
DBHG	12.1 ± 0.2	55.6 ± 2.5	109.5 ± 0.6	0.52 ± 0.00	131 ± 3	132 ± 3
SE15P	3.2 ± 0.1	45.5 ± 3.5	190.1 ± 6.1	0.46 ± 0.01	93 ± 4	10 ± 4
SE5S	2.2 ± 0.1	15.2 ± 0.7	312.6 ± 9.6	0.80 ± 0.01	132 ± 4	120 ± 5
Hydrolub	13.2 ± 0.1	57.1 ± 1.9	170.9 ± 5.5	0.47 ± 0.06	87 ± 1	0 ± 0
SSF	2.7 ± 0.2	8.0 ± 0.3	20.9 ± 1.7	1.80 ± 0.28	144 ± 11	141 ± 5
Lubritab	16.6 ± 1.3	77.8 ± 3.4	136.2 ± 4.3	0.39 ± 0.01	134 ± 2	134 ± 2
P188	12.4 ± 0.1	53.0 ± 0.7	102.0 ± 0.3	0.35 ± 0.02	73 ± 2	48 ± 2
P407	11.5 ± 0.1	51.5 ± 0.5	109.3 ± 0.3	0.50 ± 0.01	79 ± 2	33 ± 6
SLS	4.5 ± 0.1	27.8 ± 3.6	358.7 ± 36.0	0.58 ± 0.03	52 ± 5	0 ± 0

tensile strength between the lubricant types and concentrations were more extensive for lactose due to its higher lubricant sensitivity compared to mannitol (Fig. 4). A higher lubricant concentration reduced the tensile strength although the extent was lubricant-dependent (Fig. 4 and S5).

Fig. 5 illustrates the tensile strength of MCC- and lactose-based tablets compressed at a main compaction pressure of 484 MPa in function of lubricant concentration. The reduction in tensile strength was highest for MgSt followed by SE5S and SSF, which was further enhanced at higher lubricant concentrations (Fig. 4, 5, S3 and S5). In contrast, the highest tensile strength was observed for the SA grades when comparing the lubricants at the same concentration level, where only a limited reduction of tensile strength in function of lubricant concentration was noticed.

The effect of SA and MgSt on tensile strength, respectively, on lactose and MCC formulations agree with previous studies (de Backere et al., 2022; Paul and Sun, 2018). This can be attributed to the spherical shape of SA which is a less favorable shape towards covering filler particles, hence affecting the tensile strength to a lesser extent. In contrast, the small particle size, high SSA and flake-like structure of MgSt will efficiently coat the surface of filler particles, reducing the tensile strength (Table 3, Fig. 6). Although MgSt displayed the highest reduction in tensile strength, SSF and SE5S also caused a significant reduction in tensile strength, attributed to their small particle size, high SSA and flake-like structure (Table 3, Fig. 6).

Between the SA grades small differences in their effect on tensile strength could be observed, especially for MCC (Fig. 5 and S3): SA50P yielded the highest tensile strength followed by SA95M and SA50M. Whereas a smaller particle size and higher SSA (Table 3) was correlated with a higher lubrication efficiency (i.e., lower effective lubricant concentration), the smaller particle size and higher SSA of SA95M and SA50M are associated with a higher reduction of tensile strength compared to SA50P.

Differences in tensile strength between SE-lubricated MCC tablets were also observed: SE5S had a larger effect on the tensile strength compared to SE15P (Fig. 5 and S3). The same trends could be observed for lactose to a smaller extent (Table S1). The smaller particle size and higher SSA of SE5S (Table 3) compared to SE15P contributed to the stronger deteriorating effect on tensile strength. These observations highlighted the different impact of lubricant type on the responses: SE5S was more effective towards reducing ejection forces but caused a larger reduction of tensile strength. The differences in tensile strength between poloxamer grades were smaller compared to the SE grades which is in agreement with the similar particle size and SSA of both poloxamers (Table 3).

Additionally, the tensile strength of the lubricants was also compared at their effective concentration level (Section 3.1, Table 2). This reflects a more realistic comparison as lubricant concentrations are typically kept as low as possible to avoid negative effects on tensile strength and disintegration time. While limited differences between the lubricant types were observed for mannitol (Figure S6), the tensile strength varied more for lubricated lactose tablets (Fig. 7). The highest tensile strength was observed for the micronized SA grades (1% SA50M and 1% SA95M), the lowest values were measured for 0.5% MgSt, 5% SE15P, 2.5% SE5S and 5% SLS, while the other lubricants showed an intermediate tensile strength (Fig. 7).

3.3. Disintegration time

Tablets prepared at a main compaction pressure of 127 MPa were subjected to disintegration testing. These tablets exhibited a similar tablet porosity for the different lubricants combined with a specific filler. Therefore, the effect of tablet porosity on disintegration could be excluded as a possible confounding factor. Additionally, differences in tensile strength in function of lubricant type and concentration were smaller compared to tablets produced at higher compaction pressures, minimizing the effect of tensile strength as a possible confounding factor for tablet disintegration.

Generally, a higher lubricant concentration yielded tablets with a longer disintegration time for lactose and mannitol (Fig. 8). Overall, disintegration times were slightly lower for mannitol compared to lactose which could be explained by the higher intrinsic dissolution rate of mannitol (Maclean et al., 2021). For mannitol, disintegration times below 200 s were recorded for all experiments, except for SE15P and both poloxamers. Longer disintegration times were recorded for 5% P188 (261 ± 10 s), 5% P407 (262 ± 8 s), 2.5% SE15P (383 ± 15 s) and 5% SE15P (541 ± 12 s). A similar effect was observed for using 5% SE15P to lubricate lactose: the disintegration time was 1901 ± 341 s, while disintegration times were below 600 s for all other lubricants and lubricant concentrations (Fig. 8).

Unlubricated MCC tablets showed a fast disintegration (44 ± 4 s) which was attributed to the fast water uptake and swelling capacity of MCC (Maclean et al., 2021). As a result, the effect of lubricant concentration on disintegration was limited for MCC as filler. However, prolonged disintegration was observed for several lubricants in combination with MCC: SE5S (5%), SE15P (1–5%), P188 (0.5–5%), P407 (5%) and SLS (1–5%) (Fig. 8). Disintegration times up to 1000 s were recorded for 5% SE15P, 5% P188 and 5% P407 (Fig. 8). The increase in disintegration was less pronounced for 5% SE5S (168 ± 9 s) and 5% SLS (374 ± 14 s). The fastest disintegration was observed with Hydrolub as disintegration times as low as 5 s were recorded at the highest concentration (i.e., 5%).

Disintegration times were longer using SE15P as lubricant in combination with all three fillers, especially at high concentrations whereas multiple other lubricants (P188, P407, SLS and SE5S) only yielded higher disintegration times when combined with MCC as filler. The different disintegration results with MCC compared to mannitol and lactose are probably linked to the different disintegration mechanism of the fillers. Mannitol and lactose are soluble fillers and disintegrate through dissolution, whereas MCC is a insoluble hydrophilic filler that disintegrates through water uptake and swelling (Maclean et al., 2021).

It was investigated whether the effect of the lubricants on the disintegration time was linked to the wettability of pure lubricants.

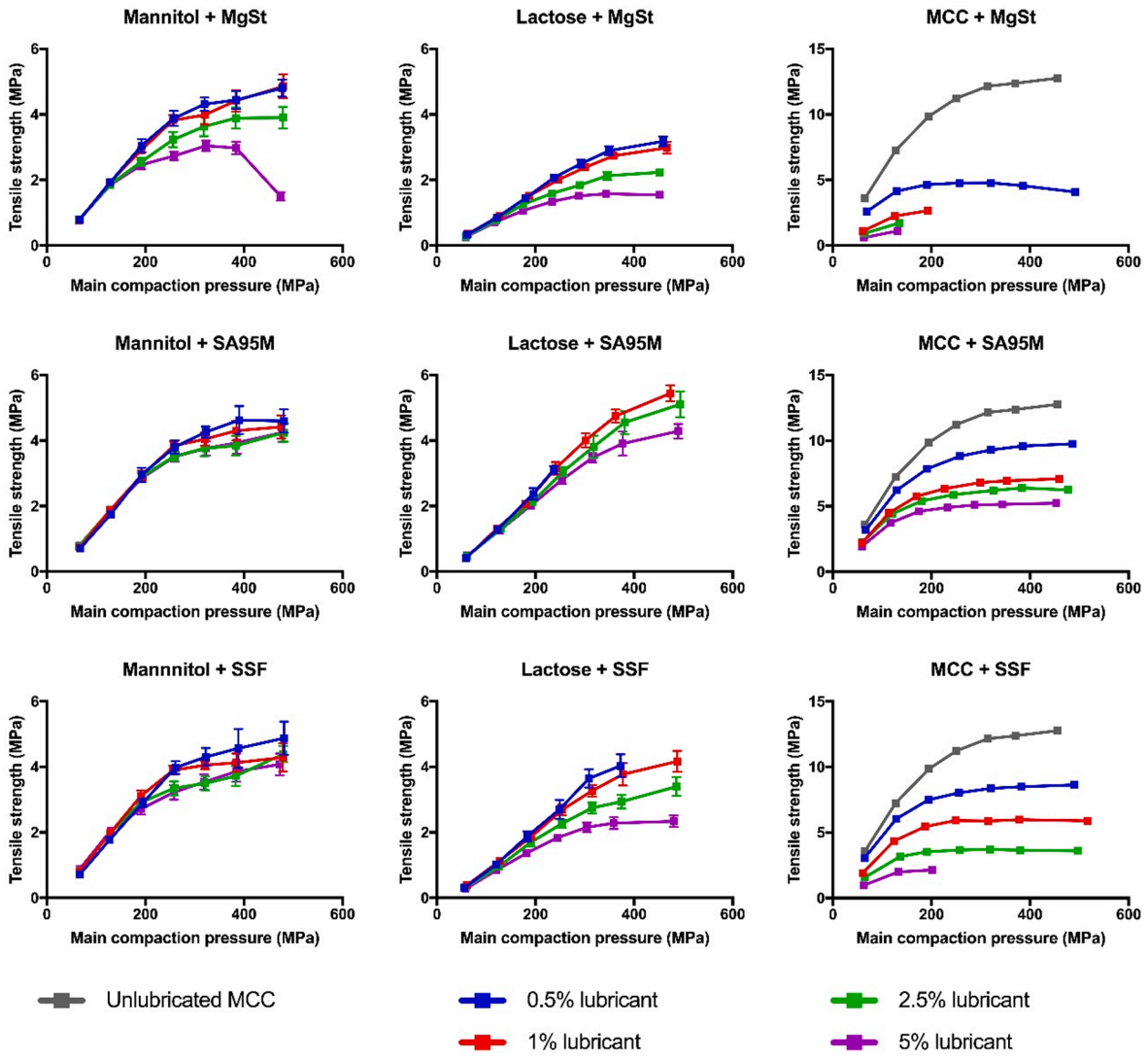

Fig. 4. Tensile strength of mannitol- (left), lactose- (middle) and MCC-based (right) formulations containing 0.5, 1, 2.5 and 5% MgSt (top), SA95M (middle) and SSF (bottom).

Wettability can be considered an important step to initiate tablet disintegration (Markl and Zeitler, 2017). Poor wetting was observed for MgSt, SA grades, DBHG, SE5S, SSF and Lubritab as high CAs (120-145°) were measured for these lubricants (Table 3). Additionally, no decrease in CA was observed over time as CA_t0 and CA_t30 were almost identical, confirming the poor wetting properties of these lubricants. CA values obtained with the other lubricants (Hydrolub, SE15P, P188, P407 and SLS) were lower with CA_t0 values between 50 and 100°. Furthermore, a significant decrease of CA over time was noted as CA_t30 values were below 50° for these lubricants, indicating good wetting properties (Table 3).

Lubricant wettability could not explain the disintegration data as the hydrophobic lubricants MgSt and SA exhibited poor wetting (i.e., high CA) but did not prolong disintegration. On the other hand, more hydrophilic lubricants (SE15P, poloxamers, SLS) showed good wetting properties (i.e., low CA) but prolonged the disintegration time. In contrast, Hydrolub, also a hydrophilic lubricant with good wetting properties showed the fastest disintegration behavior of all lubricants. Hydrolub is a multicomponent mixture consisting of mannitol, sucrose monopalmitate (10–30% w/w), polysorbate 80 and simethicone. The good disintegrating properties can probably be assigned to one or more compounds of Hydrolub, while the sucrose palmitate concentration in the tablets is too low to result in a delayed disintegration compared to pure sucrose palmitate (SE15P) as lubricant.

Significant differences in disintegration were also observed for tablets lubricated with the SE grades. Although SE15P is more hydrophilic compared to SE5S (i.e., lower CA for SE15P compared to SE5S and higher HLB value of SE15P compared to SE5S), higher disintegration times were seen for SE15P in comparison with SE5S. To investigate the slower disintegration of tablets formulated with lubricants with a higher hydrophilicity, force development and water uptake of a selection of rapidly and slowly disintegrating tablets was determined: unlubricated MCC and MCC combined with 1 and 5% SE15P, 1 and 5% P188, 1 and 5% SLS, 5% SA95M, 5% SE5S and 5% Hydrolub (Fig. 8). Tablets compacted at 127 MPa were selected for these tests, consistent with the disintegration tests. The force development as a function of time is illustrated in Fig. 9. The highest force development of all samples was recorded for unlubricated MCC tablets which is reflected by fast disintegration (44 ± 4 s). The addition of any lubricant reduced the force compared to unlubricated MCC, and significant differences between the lubricants, in terms of both type and concentration, could be observed. While the force was slightly reduced for 5% SA95M, a drastic decrease was observed for 5% SLS and 5% SE15P. In function of the SE15P, SLS and P188 level in the tablets (i.e., 1 vs. 5%), the force was also reduced. Furthermore, a delayed onset in the force development of 5% SA95M was observed in Fig. 9, linked to a reduced tablet wetting due to the

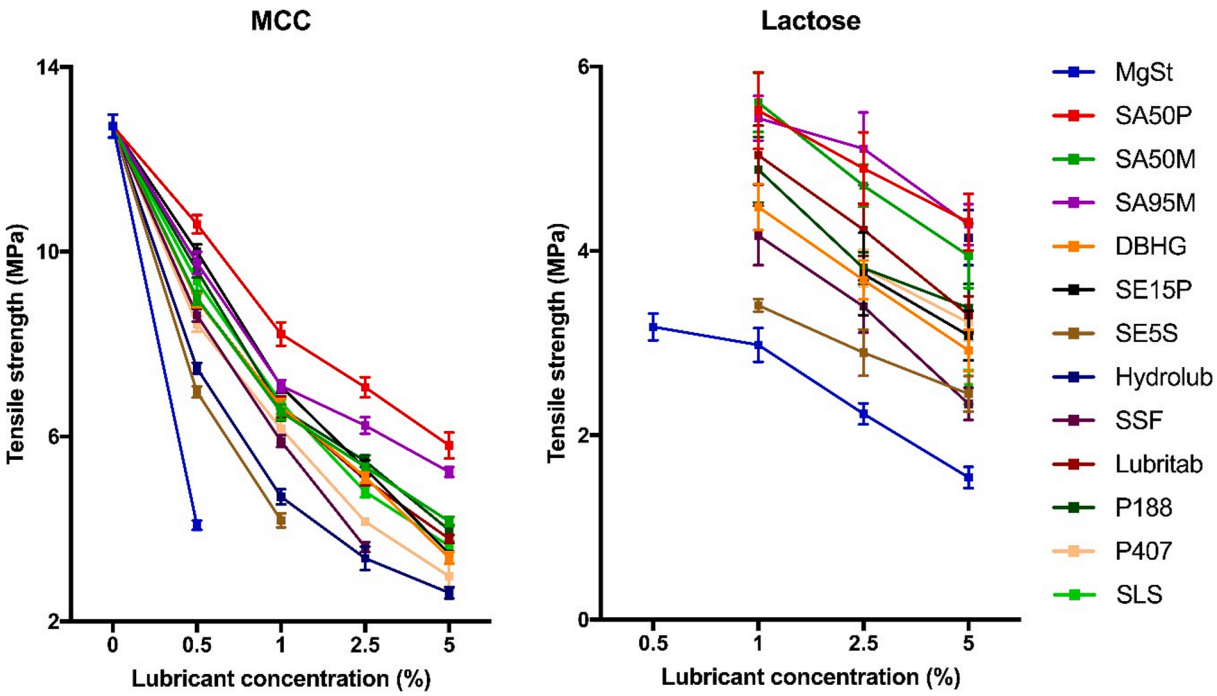

Fig. 5. Tensile strength of MCC (left) and lactose (right) in function of lubricant concentration for the different lubricants compressed at a main compaction pressure of 484 MPa.

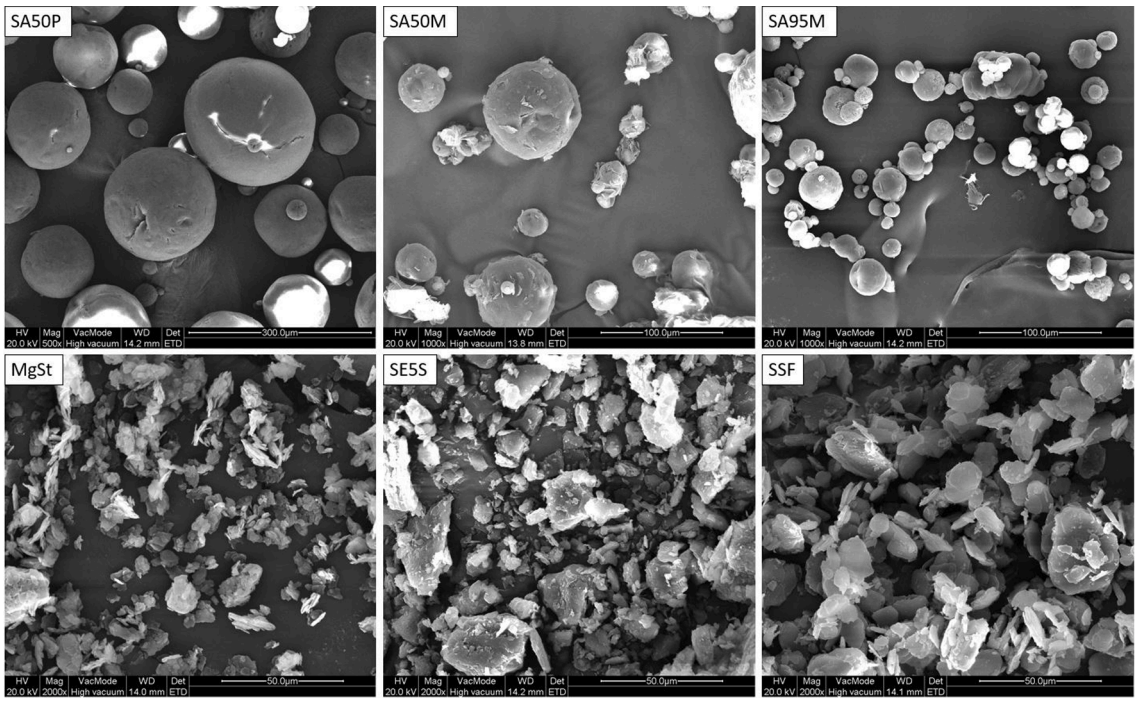

Fig. 6. SEM images for the SA grades, MgSt, SE5S and SSF.

presence of the hydrophobic SA. This caused a small delay in the first part of the force data but thereafter, the force rapidly increased to levels similar to unlubricated MCC at 300 s. This might indicate that a hydrophobic lubricant causes a delayed tablet wetting step, while it does not reduce the development of the disintegration force.

Scatter plots illustrate the force development or water uptake measured at 300 s in function of disintegration time (Fig. 10). A high force and intermediate water uptake were observed for unlubricated MCC, resulting in fast disintegration. For 5% SA95M, force and water uptake were only slightly reduced compared to unlubricated MCC, yielding fast disintegration as well. In contrast, while the water uptake of 5% SE15P and 5% P188 was relatively high, the force development was low resulting in disintegration times up to 1000 s (Fig. 10). This indicates that a high amount of water is absorbed in the tablet by SE15P and P188 while a low force development is generated causing prolonged disintegration. The force development was decreased at a higher lubricant level (1% versus 5%) as illustrated by Figs. 9 and 10. However, for the water uptake, correlations between lubricant concentration and

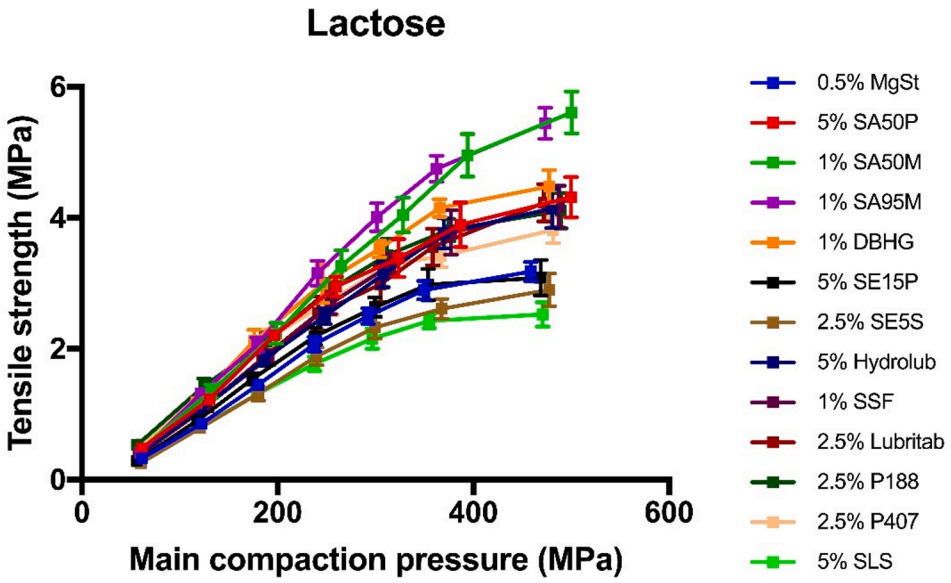

Fig. 7. Comparison of tensile strength of lactose-based formulations at the effective lubricant concentrations.

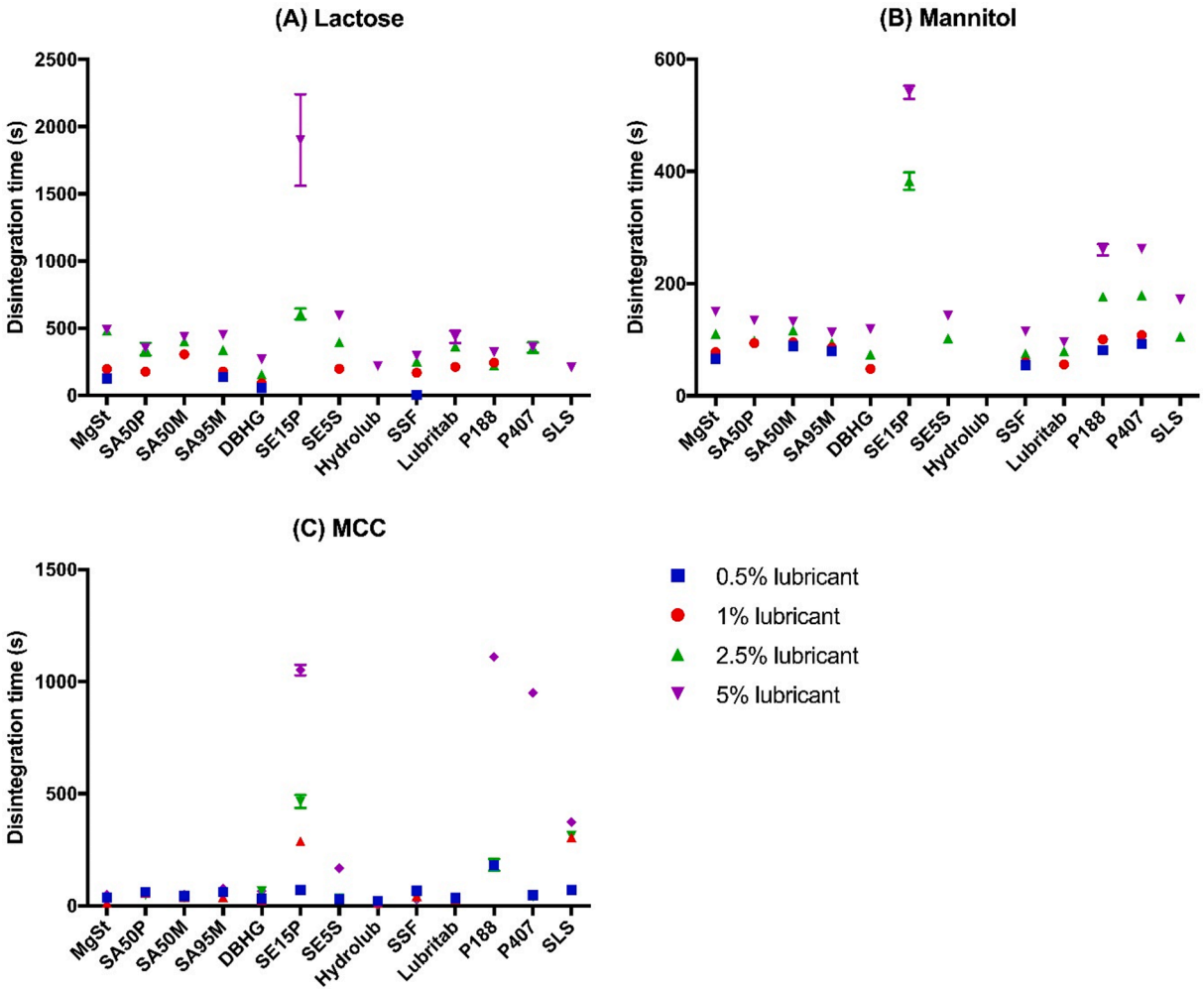

Fig. 8. Disintegration times of the different lubricants combined with lactose (A), mannitol (B) and MCC (C).

water uptake are less clear, which was attributed to the larger deviation on the measurements.

As illustrated in Fig. 10, the low force development combined with a high water uptake by hydrophilic lubricants cause a prolonged disintegration (i.e., SE15P and P188). This can be explained by the competition-for-water hypothesis (Ekmekciyan et al., 2018), which

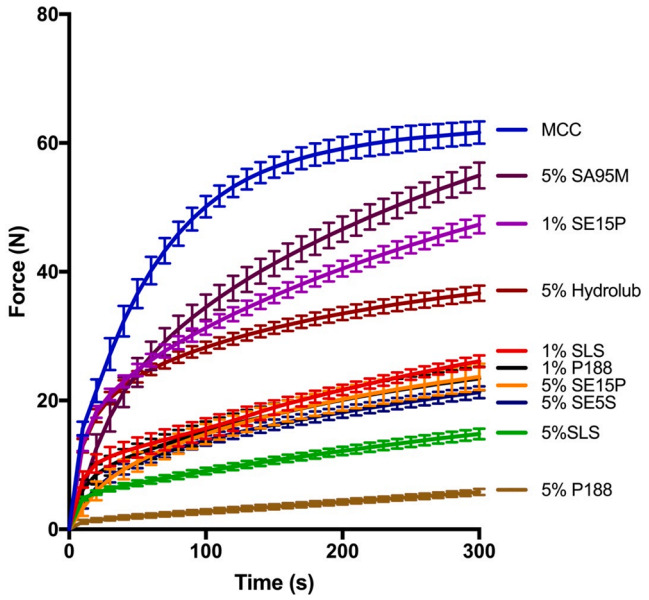

Fig. 9. Force development of unlubricated MCC and lubricated MCC tablets.

demonstrated that soluble fillers and binders required more water to dissolve. In contrast, only a limited amount of water was needed for wetting of the insoluble fillers, leaving more water available for disintegrant action (Ekmekciyan et al., 2018). Data from Maclean et al. (2021) supports this hypothesis. While these studies focused on filler-binder-disintegrant or filler-filler-disintegrant interactions, it is plausible that the hypothesis can be extended to filler-lubricant interactions. The hydrophilic lubricants competed with the filler for water due to their larger water affinity and, therefore, less water was available for the filler to disintegrate, resulting in delayed disintegration. This is supported by the high water uptake combined with low force development in the disintegrating tablets (Fig. 10). In contrast, hydrophobic lubricants (SA95M) might delay tablet wetting but will not interact with water, leaving all water available to the filler. This is reflected by a late onset of the force, yet, development of a high disintegration force and a small reduction of the water uptake, similar to pure MCC (Figs. 9 and 10).

In the current study, no disintegrant was included in order to investigate the impact of lubricant addition on disintegration without confounding of disintegrant addition. As distinct differences between the lubricant types were observed in terms of disintegration behavior, further research could focus on the impact of disintegrant addition on disintegration as this could potentially mask differences between the lubricant types. Furthermore, different types of superdisintegrants with each their dominant disintegration mechanism (e.g., swelling for sodium starch glycolate and sodium croscarmellose; shape recovery for crospovidone) could be evaluated in order to select the most suitable disintegrant for hydrophobic and hydrophilic lubricants (Quodbach and Kleinebudde, 2014).

3.4. Lubricant selection towards formulation development

A lubricant is incorporated in a tablet formulation to reduce the ejection forces. Nevertheless, lubricant addition can negatively impact other quality properties like tensile strength and tablet disintegration. Therefore, it is important to consider different aspects when selecting an appropriate lubricant for a formulation like the lubrication need and deformation mechanism of the formulation and required tablet quality attributes.

MgSt exhibited the highest lubrication efficiency as the effective lubricant concentration was the lowest of all lubricants. Nevertheless, the impact on tensile strength was the highest for MgSt, especially in combination with the plastically deforming material MCC. On the other hand, MCC inherently yielded lower ejection forces, requiring less lubrication (i.e., lower lubricant concentrations) and making the switch to alternative (and less efficient) lubricants easier for plastically deforming fillers. The negative effect on tensile strength was less for materials exhibiting (partially) brittle deformation, e.g., lactose and mannitol. For these fillers, more lubricant was required to achieve good processability. SSF and micronized SA grades (SA50M and SA95M) proved good alternatives for MgSt as lubricants. However, SSF also affected tensile strength to a certain extent, especially for MCC. For micronized SA, the impact on tensile strength was smaller and therefore these lubricants showed a high potential as they were effective at low concentrations without a severely deteriorating effect on tensile strength. The powdered SA grade had even less deteriorating effect on tensile strength due to its larger particle size and smaller SSA, but also resulted in less efficient lubrication. Additionally, MgSt, SSF and SA grades yielded similar disintegration times.

Other lubricants (DBHG, SE5S, Lubritab, P188 and P407) typically required a higher concentration (1–5%) to achieve the desired lubrication efficiency in lactose- or mannitol-based tablets. SE15P, Hydrolub and SLS even exhibited high ejection forces at 5% level (i.e., the highest tested lubricant level). The reduction in tensile strength of these lubricants was less pronounced compared to MgSt. Delayed disintegration was observed with several hydrophilic lubricants (SE15P, SE5S, P188, P407 and SLS), especially with MCC. SE15P yielded the longest disintegration times of all lubricants. This observation in combination with its poor lubrication properties makes SE15P less suitable as tablet lubricant. SE5S had a slightly better lubrication performance and

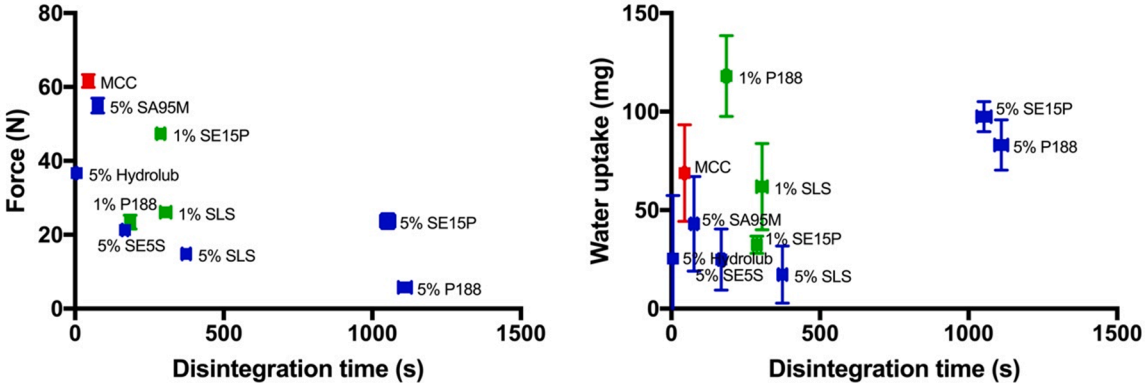

Fig. 10. Scatter plots of force development (left) and water uptake (right) at 300 s in function of the disintegration time. Unlubricated MCC tablets are highlighted in red while the lubricated MCC tablets with 1% and 5% lubricant are indicated in green and blue, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

resulted in shorter disintegration times compared to SE15P, but its negative effect on tensile strength was higher.

4. Conclusion

This study investigated the effect of multiple lubricant types and lubricant concentrations on the lubrication efficiency (i.e., ejection forces), tensile strength and disintegration time of 3 fillers (lactose, mannitol and MCC).

MgSt displayed the highest lubrication efficiency followed by SSF and micronized SA grades, while other investigated lubricants typically required a higher concentration to obtain comparable lubrication efficiency. The impact of lubricant addition on tensile strength was highest for MCC due to its ductile behavior followed by lactose and mannitol. Lubricant addition reduced the tensile strength in function of lubricant concentration, although the lubricants affected tensile strength differently. The high lubrication efficiency of MgSt and SSF was associated with a higher reduction of tensile strength. On the other hand, the highest tensile strength was observed for tablets lubricated with the SA grades. The smaller reduction of tensile strength and good lubrication properties indicated that the micronized SA grades are good alternatives to MgSt and SSF. In general, more lubricant addition prolonged the disintegration time. Delayed disintegration was observed for SE15P combined with all three fillers and for several other hydrophilic lubricants (SE5S, P188, P407 and SLS) combined with MCC. In contrast, hydrophobic lubricants like MgSt, SSF and SA, did not prolong disintegration of MCC tablets. These results were linked to the competition-for-water hypothesis which was previously introduced by Ekmekciyan et al. (2018) and was extended to filler-lubricants interactions in the current study.

The potential of alternative lubricants for MgSt was highlighted in this study. As the investigated lubricants affected the tablet properties differently, lubricant selection should not only focus on reducing the ejection forces, but should also take into account the effect on tensile strength and disintegration.

CRediT authorship contribution statement

Cedrine de Backere: Conceptualization, Formal analysis, Methodology, Validation, Data curation, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Julian Quodbach:** Formal analysis, Investigation, Writing – review & editing. **Thomas De Beer:** Writing – review & editing. **Chris Vervaet:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Valérie Vanhoorne:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2022.122012.

References

Abdel-Hamid, S., Koziolek, M., Betz, G., 2012. Study of radial die-wall pressure during high speed tableting: Effect of formulation variables. Drug Dev. Ind. Pharm. 38, 623–634. https://doi.org/10.3109/03639045.2011.621431.

Almaya, A., Aburub, A., 2008. Effect of particle size on compaction of materials with different deformation mechanisms with and without lubricants. AAPS PharmSciTech 9, 414–418. https://doi.org/10.1208/s12249-008-9059-3.

Aoshima, H., Miyagisnima, A., Nozawa, Y., Sadzuka, Y., Sonobe, T., 2005. Glycerin fatty acid esters as a new lubricant of tablets. Int. J. Ph. 293, 25–34. https://doi.org/10.1016/j.ijpharm.2004.12.007.

Bolhuis, G.K., Lerk, C.F., Zijlstra, H.T., De Boer, A.H., 1975. Film formation by magnesium stearate during mixing and its effect on tabletting. Pharm. Weekbl. 110, 317–325.

Bolhuis, G.K., Reichman, G., Lerk, C.F., Van Kamp, H.V., Zuurman, K., 1985. Evaluation of anhydrous α-lactose, a new excipient in direct compression. Drug Dev. Ind. Pharm. 11 (8), 1657–1681.

Bolhuis, G.K., Smallenbroek, A.J., Lerk, C.F., 1981. Interaction of Tablet Disintegrants and Magnesium Stearate during Mixing I: Effect on Tablet Disintegration. J. Pharm. Sci. 70, 1328–1330. https://doi.org/10.1002/JPS.2600701210.

Brunauer, S., Emmet, P.H., Teller, E., 1938. Adsorption of Gases in Multimolecular Layers. J. Am. Chem. Soc. 60, 309–319. https://doi.org/10.1021/ja01269a023.

Busignies, V., Tchoreloff, P., Leclerc, B., Besnard, M., Couarraze, G., 2004. Compaction of crystallographic forms of pharmaceutical granular lactoses. I. Compressibility. Eur. J. Pharm. Biopharm. 58, 569–576. https://doi.org/10.1016/j.ejpb.2004.04.007.

de Backere, C., De Beer, T., Vervaet, C., Vanhoorne, V., 2022. Effect of feed frame on lubricant sensitivity during upscaling from a compaction simulator to a rotary tablet press. Int. J. Pharm. 616, 121562. https://doi.org/10.1016/j.ijpharm.2022.121562.

de Backere, C., De Beer, T., Vervaet, C., Vanhoorne, V., 2021. Effect of binder type and lubrication method on the binder efficacy for direct compression. Int. J. Pharm. 607, 120968. https://doi.org/10.1016/j.ijpharm.2021.120968.

de Backere, C., De Beer, T., Vervaet, C., Vanhoorne, V., 2020. Evaluation of an external lubrication system implemented in a compaction simulator. Int. J. Pharm. 587, 119675. https://doi.org/10.1016/j.ijpharm.2020.119675.

Delacourte, A., Predella, P., Leterme, P., Provasi, D., Colombo, P., Conte, U., Catellani, P. L., Guyot, J.C., 1993. A method for quantitative evaluation of the effectiveness of tee lubricants used in tablet technology. Drug Dev. Ind. Pharm. 19, 1047–1060. https://doi.org/10.3109/03639049309063000.

Desai, D., Zia, H., Quadir, A., Desai, D., Zia, H., 2007. Evaluation of Selected Micronized Poloxamers as Tablet Lubricants. Drug Deliv. 14, 413–426. https://doi.org/10.1080/10717540701203042.

Desai, D.S., Rubitski, B.A., Varia, S.A., Newman, A.W., 1993. Physical interactions of magnesium stearate with starch-derived disintegrants and their effects on capsule and tablet dissolution. Int. J. Pharm. 91, 217–226. https://doi.org/10.1016/0378-5173(93)90341-C.

Dinesh, B.M., Mutahar, R.K.M., 2009. Compatibility studies of intrinsic lubricants for effervescent tablets: Formulation and in vitro evaluation. Biomed. Pharmacol. J. 2, 21–29.

Dun, J., Chen, H., Sun, C.C., 2020a. Profound tabletability deterioration of microcrystalline cellulose by magnesium stearate. Int. J. Pharm. 590, 119927. https://doi.org/10.1016/j.ijpharm.2020.119927.

Dun, J., Osei-Yeboah, F., Boulas, P., Lin, Y., Sun, C.C., 2020b. A systematic evaluation of poloxamers as tablet lubricants. Int. J. Pharm. 576, 118994. https://doi.org/10.1016/j.ijpharm.2019.118994.

Dun, J., Osei-Yeboah, F., Boulas, P., Lin, Y., Sun, C.C., 2018. A systematic evaluation of dual functionality of sodium lauryl sulfate as a tablet lubricant and wetting enhancer. Int. J. Pharm. 552, 139–147. https://doi.org/10.1016/j.ijpharm.2018.09.056.

EDQM, 2021. Stearic acid. Eur. Pharmacopoeia 10.4.

EDQM, 2020. 2.9.1. Disintegration of Tablets and Capsules. Eur. Pharmacopoeia 10.4.

Ekmekciyan, N., Tuglu, T., El-Saleh, F., Muehlenfeld, C., Stoyanov, E., Quodbach, J., 2018. Competing for water: A new approach to understand disintegrant performance. Int. J. Pharm. 548, 491–499. https://doi.org/10.1016/j.ijpharm.2018.07.025.

Fell, J.T., Newton, J.M., 1970. Determination of tablet strength by the diametral-compression test. J. Pharm. Sci. 59, 688–691. https://doi.org/10.1002/jps.2600590523.

Gong, X., Sun, C.C., 2015. A new tablet brittleness index. Eur. J. Pharm. Biopharm. 93, 260–266. https://doi.org/10.1016/j.ejpb.2015.04.007.

Grymonpré, W., Verstraete, G., Van Bockstal, P.J., Van Renterghem, J., Rombouts, P., De Beer, T., Remon, J.P., Vervaet, C., 2017. In-line monitoring of compaction properties on a rotary tablet press during tablet manufacturing of hot-melt extruded amorphous solid dispersions. Int. J. Pharm. 517, 348–358. https://doi.org/10.1016/j.ijpharm.2016.12.033.

Hölzer, A.W., Sjögren, J., 1979. Evaluation of sodium stearyl fumarate as tablet lubricant. Int. J. Pharm. 2, 145–153.

Hölzer, A.W., Sjögren, J., 1977. Comparison of methods for evaluation of friction during tableting. Drug Dev. Ind. Pharm. 3, 23–37. https://doi.org/10.3109/03639047709055603.

Jarosz, P.J., Parrot, E.L., 1984. Effects of Lubricants on Tensile Strengths of Tablets. Drug Dev. Ind. Pharm. 10, 259–273. https://doi.org/10.3109/03639048409064649.

Kapadia, C., Deshmukh, K., 2017. Comparative evaluation of Compritol® HD5 ATO with Sodium Stearyl Fumarate and PEG 6000 as amphiphilic, hydrodispersible pharmaceutical lubricants. J. Excipients Food Chem. 8, 5–18.

Lerk, C.F., Bolhuis, G.K., Smallenbroek, A.J., Zuurman, K., 1982. Interaction of tablet disintegrants and magnesium stearate during mixing. II. Effect on dissolution rate. Pharm. Acta Helv. 57, 282–286.

Li, J., Wu, Y., 2014. Lubricants in pharmaceutical solid dosage forms. Lubricants 2, 21–43. https://doi.org/10.3390/lubricants2010021.

Maclean, N., Walsh, E., Soundaranathan, M., Khadra, I., Mann, J., Williams, H., Markl, D., 2021. Exploring the performance-controlling tablet disintegration mechanisms for direct compression formulations. Int. J. Pharm. 599, 120221. https://doi.org/10.1016/j.ijpharm.2021.120221.

Markl, D., Zeitler, J.A., 2017. A Review of Disintegration Mechanisms and Measurement Techniques. Pharm. Res. 34, 890–917. https://doi.org/10.1007/s11095-017-2129-z.

Michaut, F., Busignies, V., Fouquereau, C., Huet De Barochez, B., Leclerc, B., Tchoreloff, P., 2010. Evaluation of a rotary tablet press simulator as a tool for the characterization of compaction properties of pharmaceutical products. J. Pharm. Sci. 99, 2874–2885. https://doi.org/10.1002/jps.22032.

Mosig, J., Kleinebudde, P., 2014. Evaluation of lubrication methods: How to generate a comparable lubrication for dry granules and powder material for tableting processes. Powder Technol. 266, 156–166. https://doi.org/10.1016/j.powtec.2014.06.022.

N'Diaye, A., Jannin, V., Bérard, V., Andrès, C., Pourcelot, Y., 2003. Comparative study of the lubricant performance of Compritol® HD5 ATO and Compritol® 888 ATO : effect of polyethylene glycol behenate on lubricant capacity. Int. J. Pharm. 254, 263–269. https://doi.org/10.1016/S0378-5173(03)00027-9.

Mosig, J., Kleinebudde, P., 2015. Critical Evaluation of Root Causes of the Reduced Compactability after Roll Compaction/Dry Granulation. J. Pharm. Sci. 104 (3), 1108–1118. https://doi.org/10.1002/jps.24321.

Nakamura, S., Ishii, N., Nakashima, N., Sakamoto, T., Yuasa, H., 2017. Evaluation of Sucrose Fatty Acid Esters as Lubricants in Tablet Manufacturing. Chem. Pharm. Bull. 65 (5), 432–441.

Paul, S., Sun, C.C., 2018. Systematic evaluation of common lubricants for optimal use in tablet formulation. Eur. J. Pharm. Sci. 117, 118–127. https://doi.org/10.1016/j.ejps.2018.02.013.

Paul, S., Sun, C.C., 2017. Lubrication with magnesium stearate increases tablet brittleness. Powder Technol. 309, 126–132. https://doi.org/10.1016/j.powtec.2016.12.012.

Peeters, E., Vanhoorne, V., Vervaet, C., Remon, J.P., 2016. Lubricant sensitivity in function of paddle movement in the forced feeder of a high-speed tablet press. Drug Dev. Ind. Pharm. 42, 2078–2085. https://doi.org/10.1080/03639045.2016.1200067.

Perrault, M., Bertrand, F., Chaouki, J., Perrault, M., Bertrand, F., Chaouki, J., 2011. An experimental investigation of the effect of the amount of lubricant on tablet properties. Drug Dev. Ind. Pharm. 37, 234–242. https://doi.org/10.3109/03639045.2010.505013.

Pontier, C., Champion, E., Viana, M., Chulia, D., Bernache-Assollant, D., 2002. Use of cycles of compression to characterize the behaviour of apatitic phosphate powders. J. Eur. Ceram. Soc. 22, 1205–1216. https://doi.org/10.1016/S0955-2219(01)00453-8.

Puckhaber, D., Finke, J.H., David, S., Serratoni, M., Zafar, U., John, E., Juhnke, M., Kwade, A., Puckhaber, D., Finke, J.H., David, S., Serratoni, M., Zafar, U., John, E., Juhnke, M., 2022. Prediction of the impact of lubrication on tablet compactibility. Int. J. Pharm. 617, 121557. https://doi.org/10.1016/J.IJPHARM.2022.121557.

Quodbach, J., Kleinebudde, P., 2014. Systematic classification of tablet disintegrants by water uptake and force development kinetics. J. Pharm. Pharmacol. 66, 1429–1438. https://doi.org/10.1111/jphp.12276.

Shah, N.H., Stiel, D., Weiss, M., Infeld, M.H., Malick, A.W., 1986. Evaluation of two new tablet lubricants - sodium stearyl fumarate and glyceryl behenate. Measurement of physical parameters (compaction, ejection and residual forces) in the tableting process and the effect on the dissolution rate. Drug Dev. Ind. Pharm. 12, 1329–1346. https://doi.org/10.3109/03639048609065862.

Sun, C.C., 2015. Dependence of ejection force on tableting speed-A compaction simulation study. Powder Technol. 279, 123–126. https://doi.org/10.1016/j.powtec.2015.04.004.

Tarlier, N., Soulairol, I., Bataille, B., Baylac, G., Ravel, P., Nofrerias, I., Lefèvre, P., Sharkawi, T., 2015. Compaction behavior and deformation mechanism of directly compressible textured mannitol in a rotary tablet press simulator. Int. J. Pharm. 495, 410–419. https://doi.org/10.1016/j.ijpharm.2015.09.007.

Uğurlu, T., Halaçoğlu, M., 2014. Effects of some lubricants and evaluation of compression parameters on directly compressible powders. Pharm. Dev. Technol. 19, 357–1354. https://doi.org/10.3109/10837450.2013.784443.

Vachon, M.G., Chulia, D., 1999. The use of energy indices in estimating powder compaction functionality of mixtures in pharmaceutical tableting. Int. J. Pharm. 177, 183–200. https://doi.org/10.1016/S0378-5173(98)00347-0.

Vromans, H., Bolhuis, G.K., Lerk, C.F., 1988. Magnesium stearate susceptibility of directly compressible materials as an indication of fragmentation properties. Powder Technol. 54, 39–44. https://doi.org/10.1016/0032-5910(88)80047-0.

Vromans, H., Lerk, C.F., 1988. Densification properties and compactibility of mixtures of pharmaceutical excipients with and without magnesium stearate. Int. J. Pharm. 46, 183–192. https://doi.org/10.1016/0378-5173(88)90076-2.

Wünsch, I., Friesen, I., Puckhaber, D., Schlegel, T., Finke, J.H., 2020. Scaling tableting processes from compaction simulator to rotary presses—mind the sub-processes. Pharmaceutics 12 (4), 310.

Zuurman, K., Van Der Voort Maarschalk, K., Bolhuis, G.K., 1999. Effect of magnesium stearate on bonding and porosity expansion of tablets produced from materials with different consolidation properties. Int. J. Pharm. 179, 107–115. https://doi.org/10.1016/S0378-5173(98)00389-5.