European Journal of Pharmaceutical Sciences 117 (2018) 118–127

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Systematic evaluation of common lubricants for optimal use in tablet formulation

Shubhajit Paul, Changquan Calvin Sun*

Pharmaceutical Materials Science and Engineering Laboratory, Department of Pharmaceutics, College of Pharmacy, University of Minnesota, 9-127B Weaver-Densford Hall, 308 Harvard Street S.E., Minneapolis, MN 55455, United States

ARTICLE INFO

Keywords:
Lubrication
Tablet compression
Mechanical property
Friability
Disintegration

ABSTRACT

As an essential formulation component for large-scale tablet manufacturing, the lubricant preserves tooling by reducing die-wall friction. Unfortunately, lubrication also often results in adverse effects on tablet characteristics, such as prolonged disintegration, slowed dissolution, and reduced mechanical strength. Therefore, the choice of lubricant and its optimal concentration in a tablet formulation is a critical decision in tablet formulation development to attain low die-wall friction while minimizing negative impact on other tablet properties. Three commercially available tablet lubricants, i.e., magnesium stearate, sodium stearyl fumerate, and stearic acid, were systematically investigated in both plastic and brittle matrices to elucidate their effects on reducing die-wall friction, tablet strength, tablet hardness, tablet friability, and tablet disintegration kinetics. Clear understanding of the lubrication efficiency of commonly used lubricants as well as their impact on tablet characteristics would help future tablet formulation efforts.

1. Introduction

More than 70% of the marketed drug products are tablets due to the advantages of cost-effectiveness, dose accuracy, patience convenience, and good stability of tablet dosage forms (Gupta et al. 2009). As an essential component of a pharmaceutical tablet formulation, lubricant facilitates tablet manufacturing by reducing friction at the interface between die-wall and tablet (Wang et al. 2010), reducing propensity to punch sticking (Roberts et al. 2004), and preserving tablet tooling. Lubrication efficiency of different materials can be very different (Nelson et al. 1954). Typical ranges of common lubricants in tablet formulation are suggested in the literature, such as the Handbook of Pharmaceutical Excipients (Rowe et al. 2009). However, the choice of type and amount of lubricant for optimal lubrication is not a simple matter. Firstly, ejection force tends to be higher at a higher tableting speed (Sun 2015). Thus, a decision on an optimal amount of a lubricant should be made by considering the lubrication efficiency at a high speed relevant to commercial tablet manufacturing. Secondly, ejection profiles can differ drastically for different materials (Sun 2015). Lastly, the incorporation of a lubricant usually leads to several notable adverse effects on tablet characteristics. For examples, the most commonly used lubricants, magnesium stearate or other metallic salts of fatty acid, reduce tablet strength (Leinonen et al. 1992; Wang et al. 2010; Zuurman et al. 1999) and delay tablet disintegration and dissolution (Bolhuis et al. 1981; Proost et al. 1983; Uzunovic and Vranic 2007). The incorporation of magnesium stearate was also found to increase tablet brittleness, which may lead to higher friability (Paul and Sun 2017c). Thus, identifying a suitable lubricant and its optimal concentration should not be based only on its ability to reduce die-wall friction but also other important criteria such as tablet strength, friability, disintegration, and dissolution. Unfortunately, to date, the choice of type and amount of lubricant is usually empirically made in tablet formulation development, depending on the formulator's personal experience and institutional memory. In this context, it should be pointed out that the tablet strength required for maintaining integrity of a tablet depends on tablet mechanical properties. For example, to have the same friability, a tablet of a more brittle formulation needs to be stronger (Osei-Yeboah and Sun 2015). However, overly strong tablets may exhibit too slow disintegration. Thus, where possible, friability should be used along with mechanical strength to guide the tablet formulation and process development for obtaining a tablet with optimum mechanical properties. Another important point to consider is that the die-wall friction depends on powder mechanical properties. For example, more plastic materials tend to exhibit lower ejection force partially because of the lower residual die wall pressure (Abdel-Hamid et al. 2012). Moreover, ejection force is influenced by particle size, shape, and asperity (Abdel-Hamid et al. 2011). Therefore, the optimum use of a lubricant depends on both its intrinsic lubrication efficiency and

* Corresponding author at: 9-127B Weaver-Densford Hall, 308 Harvard Street S.E., Minneapolis, MN 55455, United States.
E-mail address: sunx0053@umn.edu (C.C. Sun).

https://doi.org/10.1016/j.ejps.2018.02.013
Received 5 December 2017; Received in revised form 19 January 2018; Accepted 8 February 2018
Available online 10 February 2018
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properties of the compressed powder. An under-lubricated formulation leads to high ejection force, which subsequently causes chipped tablets and short life span of tooling. However, excessively lubricated formulations suffer low mechanical strength, high friability, or slow dissolution. Thus, the practice of arbitrarily choosing the type and level of a lubricant should be avoided in the era of quality by design. Extensive work has been done to better understand the effects of blender type, volume, mixing intensity and time on tablet properties of different formulations using magnesium stearate as a lubricant (Kushner and Moore 2010; Ragnarsson et al. 1979). Lubricants, such as magnesium stearate and sodium stearyl fumarate, were also used to improve flowability of cohesive powders without significantly affecting the tablet dissolution and strength (Qu et al. 2017; Qu et al. 2015; Wei et al. 2017). However, a study that systematically characterizes commonly used commercial lubricants on important tablet properties of powders exhibiting diverse mechanical properties is still lacking. The goal of the present work was, thus, to systematically assess lubrication effectiveness and their impact on important tablet characteristics of three commonly used lubricants, i.e., magnesium stearate, sodium stearyl fumerate, and stearic acid, as a function of lubricant concentration in two excipient matrices representing plastic and brittle formulations. Such insight facilitates the more scientific development of future tablet formulations.

2. Materials and Methods

2.1. Materials

Plastic microcrystalline cellulose (MCC; Avicel PH102, FMC Biopolymers, Philadelphia, PA) and brittle lactose monohydrate (LM; Fastflo®, Foremost Farms, Clayton, WI) were used as tablet binder and filler, respectively. Magnesium stearate (MgSt; HyQual™, Mallinckrodt, St Louis, MO), sodium stearyl fumerate (SSF; JRS Pharma LP, Patterson, NY) and stearic acid (SA; Sigma Aldrich, St. Louis, MO) were used as lubricants. Ac-Di-Sol (FMC Biopolymers, Philadelphia, PA) was used as a super disintegrant.

2.2. Methods

2.2.1. Powder Blending and Tableting

All ingredients were passed through a #30 sieve (USA standard sieves) before being used in a formulation. Mixtures containing MCC and LM at 2:1 and 1:3 ratios were placed in a blender (Turbula, Glen Mills, Clifton, NJ). Each of the lubricant at a predetermined concentration within 0–2% (w/w) was added. The mixture was blended at 100 rpm for 2.5 min. The batch size was kept at 20*g* for each formulation. The final formulations were equilibrated at 32% RH for 48 h prior to compaction. Formulations containing 3% of Ac-Di-Sol and 2% of respective lubricants were prepared for tablet disintegration test.

Tablets were prepared on a compaction simulator (Presster, Metropolitan Computing Corp., NJ) using flat-faced round punch with diameter 9.5 mm at a dwell time of 25 ms (corresponding to 49,300 tablets/h). To assess tabletability of a formulation, tablets were prepared over a compaction pressure range of 20–300 MPa, simulating a Korsch XL100, 10 station press. Tablets were relaxed overnight before further characterization.

2.2.2. Determination of Powder True Density

Because the conventional helium pycnometry is unfit for measuring true density (ρ_t) of water-containing powders, ρ_t of formulations with varying concentrations of lubricants was obtained by the Sun method, where nonlinear fitting of tablet density (ρ) vs. compaction pressure (P) data was performed according to Eq. (1) to obtain ρ_t (Sun 2004; Sun 2006).

$$P = \frac{1}{C}\left[(1-\varepsilon_c) - \frac{\rho}{\rho_t} - \varepsilon_c \ln\left(\frac{1-\frac{\rho}{\rho_t}}{\varepsilon_c}\right)\right] \quad (1)$$

where C and ε_c are constants. Eq. (1) was derived from the Kuentz-Leuenberger (KL) equation (Eq. 2)

$$P = \frac{1}{C}\left[\varepsilon - \varepsilon_c - \varepsilon_c \ln\left(\frac{\varepsilon}{\varepsilon_c}\right)\right] \quad (2)$$

Where ε is tablet porosity, which may be calculated from ρ and ρ_t using Eq. (3).

$$\varepsilon = 1 - \frac{\rho}{\rho_t} \quad (3)$$

The parameters 1/C is related to plasticity of the material where a higher 1/C value corresponds to lower plasticity. ε_c denotes the porosity at which a powder bed just starts to approach a state with mechanical rigidity (Kuentz and Leuenberger 1999). The Eq. (2) is superior to the Heckel equation in analyzing powder compressibility data (Paul and Sun 2017d).

2.2.3. Determination of Tablet Tensile Strength

Tablets were diametrically broken on a texture analyzer (Texture Technologies Corp., Surrey, UK) and radial tensile strength of tablets (σ) was obtained from Eq. (4) (Fell and Newton 1970).

$$\sigma = \frac{2F}{\pi.\ D.\ h} \quad (4)$$

where F, D, and h are the breaking force, tablet diameter, and thickness, respectively.

2.2.4. Powder Compactibility

Compactibility profile of each formulation was obtained from their corresponding tablet tensile strength - porosity data and analyzed using Eq. (5), which is known as the Ryshkewitch equation (Ryshkewitch 1953).

$$\sigma = \sigma_0 e^{-b.\varepsilon} \quad (5)$$

Where σ_0 is the tablet tensile strength at zero porosity and *b* is an empirical constant. A critical aspect of this analysis is the use of accurate powder true density to avoid gross errors in fitted parameters (Sun 2005).

2.2.5. Determination of Lubrication Efficiency

The lubrication efficiency during ejection was quantified based on friction coefficient, which was calculated according to Eq. (6) (Paul and Sun 2017b; Sun 2015).

$$\mu = \frac{EF}{\pi \bullet RDP \bullet D \bullet h'} \quad (6)$$

where D, RDP, and h′ are the tooling diameter, residual die wall stress, and in-die tablet thickness at the end of decompression phase, respectively.

2.2.6. Determination of Indentation Hardness

For indentation hardness measurement, separate sets of tablets were prepared over 50–300 MPa compaction pressure using the compaction simulator. Macroindentation hardness measurement was conducted on a texture analyzer fitted with a spherical indenter (3.175 mm diameter) (Patel and Sun 2016). The indenter approached with a speed of 0.05 mm/s and a constant force (F) of 40 N was applied on to the flat tablet surface and maintained for 3 min. The indented tablet surface was rubbed against a piece of carbon paper to facilitate the easy identification of indent circumference. An image was taken using a calibrated digital microscope (Dino-lite, AnMo electronic Corp., Hsinchu, Taiwan) at an appropriate magnification and the area of the

indent (A) was calculated by fitting the indent circumference with a circle. The average indentation hardness (H) was calculated using Eq. (7).

$$H = \frac{F}{A} \tag{7}$$

2.2.7. Determination of Tablet Brittleness Index (TBI)

Tablet brittleness was calculated using Eq. (8) according to the method described previously (Gong et al. 2015; Gong and Sun 2015).

$$TBI = \frac{\text{tablet diameter}}{\text{maximum elastic deformation}} \tag{8}$$

The maximum elastic deformation was extracted from the tablet breaking force - displacement profile using MATLAB (Mathworks, Natick, MA).

2.2.8. Expedited Friability Analysis

Tablet friability profile, i.e., weight loss of tablets due to impact and attrition as a function of compaction pressure, was obtained using an expedited method (Osei-Yeboah and Sun 2015; Paul and Sun 2017a). A separate set of tablets for each formulation containing 2% (w/w, the highest concentration in the series) of each lubricant was prepared on the compaction simulator over 20–300 MPa compaction pressure. Tablets were coded, weighed, and then loaded into a friabilator (Pharma Alliance Group Inc., Model F2, Santa Clarita, CA), which was run at 25 rpm for 4 min. The percentage weight loss for individual tablets was tracked and plotted against compaction pressure, from which compaction pressure corresponding to 1.0% friability was determined.

2.2.9. Tablet Disintegration Test

Tablets of different formulations containing 2% lubricant were compressed at 100 MPa and 150 MPa. Their disintegration times (DT) were measured using the USP disintegration test without a disc on a disintegration tester (Di200; Pharma Alliance Group, Valencia, CA) (Pharmacopeia, U.S., n.d.). For each formulation, DT was recorded for three tablets. Tablets were individually placed into each tube of a disintegration apparatus, which was immersed into a beaker containing 900 mL of phosphate buffer. The temperature of the unit was maintained at 37 °C.

3. Results and Discussion

Two mixtures of MCC and LM in different proportions were used to represent typical tablet formulations containing both plastic and brittle components. The MCC-LM (1:3) mixture was predominantly brittle while the 2:1 mixture was plastic. Tablets of predominantly brittle materials tend to be more friable, which leads to higher risk of batch rejection during quality check (Osei-Yeboah and Sun 2015). On the other hand, the presence of predominantly plastic excipients could lead to poor tabletability problem during granulation because of their resistance to brittle fracture during compression (Osei-Yeboah et al. 2014; Shi et al. 2010; Sun and Himmelspach 2006). MgSt was selected due to its widespread use as a lubricant for diverse pharmaceutical formulations (Wang et al. 2010), while SSF was employed to test its potential as alternative to MgSt. SA is a fatty acid that, although less effective than metallic stearates, has been reported to exhibit better efficacy than alcohols and hydrocarbons (Wang et al. 2010). Variables that may affect the lubricant performance, such as the mixing time and intensity, were kept constant to allow direct comparison of different lubricants. MgSt and SSF used in this work had particle sizes in the 10–50 μm range, while SA was slightly larger (50–100 μm) (Fig. S1). While particle size likely influences performance of these lubricants, we focused on assessing them as received to provide more practically useful information for selecting lubrication in future tablet formulation.

The X-ray diffraction pattern of MgSt matched with that of the monohydrate form (Fig. S2) (Delaney et al. 2017). TGA data showed a single step weight loss of 3.09% near 100 °C (Fig. S3), which matched well with the theoretical 2.95% water content of the monohydrate. It has been shown that hydrated MgSt shows greater lubrication efficiency than the anhydrate form (Wada and Matsubara 1994). MgSt and SSF are boundary lubricants that reduce friction by forming a lubricant film on the die wall. It was proposed that electropositive metal ion group interacts with the die-wall and the hydrophobic group is oriented outwards to form a lamellar structure in the lubricant film around the die to facilitate easier tablet ejection (Wang et al. 2010). The range of lubricant concentration of 0.5–2.0% (w/w) was employed for all three lubricants to compare their effectiveness in lubricating both brittle and plastic formulations. This range is also sufficiently wide for identifying the optimum concentration of each lubricant that satisfies all the criteria.

3.1. Lubrication Efficiency

The lubrication efficiency was then investigated for the two formulations with different concentrations of lubricant. We preferred coefficient of friction (μ) over EF for characterizing lubrication efficiency because μ is not affected by tablet diameter and thickness (Doelker and Massuelle 2004). For both formulations, μ decreased with increasing lubricant concentration (Fig. 1). However, the μ of unlubricated LM-rich powder was almost three times higher than the MCC-rich powder, which is consistent with the higher brittleness of LM compared to MCC (Abdel-Hamid et al. 2012). For the MCC-rich formulation, μ steadily decreased from 0.14 to 0.09 with increasing pressure. With increasing pressure, the decreasing trend in μ for MCC-rich formulation indicated more effective distribution of the lubricant film at the tablet - die wall interface (Sun 2015). In the case of LM-rich formulation, μ gradually increased from 0.25 to 0.39 in the compaction pressure range of 25–300 MPa. The higher μ in addition to the higher RDP of LM-rich formulation than MCC-rich formulation led to much higher EF of the LM-rich formulation (data not shown). For the MCC-rich formulation, all three lubricants exhibited similar performance in reducing μ over the concentration range investigated. Up to 2% of each of the three lubricants, μ was only slightly reduced. However, in the case of LM-rich formulation, notable decrease in μ from unlubricated profile was observed at 0.5% concentration for all lubricants. For each lubricant, a higher concentration led to lower μ. The concentration effect is most significant for MgSt. For SSF and SA, increasing concentration from 1% to 2% only marginally reduced μ. Overall, MgSt exhibited slightly better performance than SSF, which was better than SA. For lubricated LM-rich powder, EF and RDP varied almost proportionally and, therefore, μ did not change significantly with compaction pressure (Fig. 1d–f). Thus, for formulations exhibiting predominantly brittle properties similar to that of LM-rich powder in this study, approximately 1.0% of each of the three lubricants is likely sufficient in terms of reducing friction. A higher amount of lubricant does not noticeably improve lubrication efficiency but may lead to more negative impact on tablet properties.

3.2. Effect on Tablet Strength

The deteriorating effect of lubrication on tablet tensile strength is known (Jarosz and Parrott 1984; Leinonen et al. 1992; Wang et al. 2010; Zuurman et al. 1999). This effect by different lubricants is systematically examined here. Fig. 2 shows the tabletability plots of the two formulations containing the three lubricants at various concentrations. The tensile strength of the MCC-rich mixture exhibited sensitivity to lubrication, where a higher amount of lubrication by all three lubricants invariably led to noticeable decrease in tabletability (Fig. 2). Tabletability followed the descending order: SA > SSF > MgSt for MCC-rich formulation at the all lubricant concentrations. In contrast, much less deterioration in tabletability was observed for the LM-rich

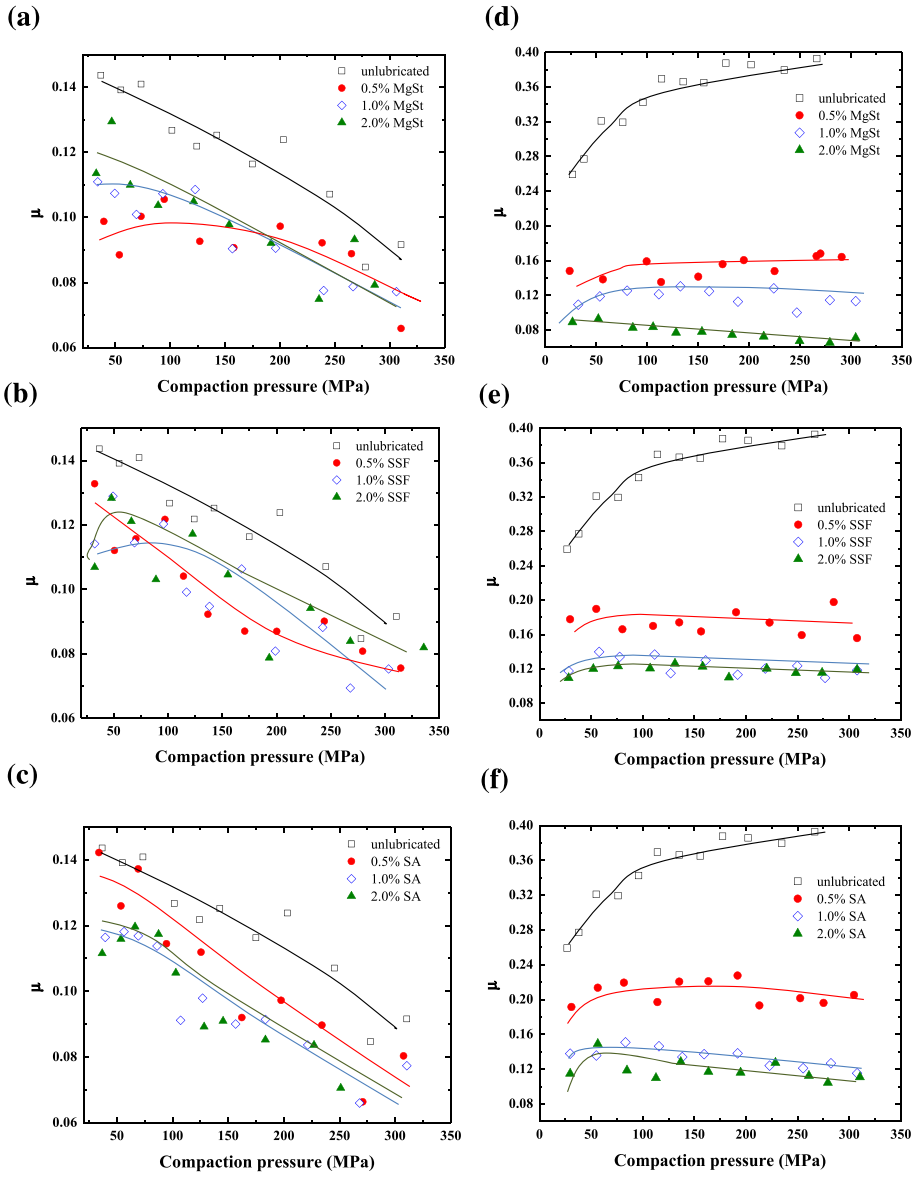

Fig. 1. Friction coefficient (μ) of binary mixtures, MCC-LM (2:1) (a–c) and MCC-LM (1:3) (d–f) containing 0–2% (w/w) of different lubricants (MgSt, SSF, and SA). Lines were drawn to assist the visual identification of trends in data points.

formulation when using up to 2.0% of the three lubricants. The impact by SSF and SA on tabletability was similar, which was less than that by MgSt. Therefore, although uncommon, the use of lubricant at a concentration as high as 2% for formulations similar to the LM-rich powder can be considered to overcome high ejection force without serious deterioration in tabletability. The greater sensitivity of tabletability of plastic materials to lubrication could be attributed to the weakening of the interparticulate bonding by deposition of the lubricant film. The lack of sensitivity by brittle materials may be attributed to the extensive fragmentation of particles during compaction, which generates lubricant-free surfaces to afford strong inter-particular bonding unaffected by the lubricant film formed before compression (Almaya and Aburub 2008; Zuurman et al. 1999).

The tensile strength - porosity relationship for all powders, regardless of lubrication type and level, well followed Eq. (5) (Fig. S4). The dependence of σ_0 on lubricant concentration for different lubricants is shown in Fig. 3. The σ_0 of the unlubricated MCC-rich formulation (Fig. 3a) was higher than that of the LM-rich formulation (Fig. 2b), which is consistent with the known superior tabletability of MCC over LM. The σ_0 of both powders decreased steadily with increasing amount of lubricant. This is expected because, for a given material, a higher lubricant concentration would lead to more complete coverage of particle surface or thicker lubricant layer, both of which reduce bonding strength. However, the rate of σ_0 reduction was faster for the MCC-rich formulation (Fig. 3a) than the LM-rich formulation (Fig. 3b), which is consistent with the lack of fragmentation of the plastic MCC in the powder. Among the three lubricants, MgSt exerted the most reduction in σ_0 at all concentrations, followed by SSF and then SA (Fig. 3). That is to say, the deterioration of σ_0 by lubrication followed the descending order of MgSt > SSF > SA. It should be noted that although tabletability of the LM-rich powder was relatively insensitive to lubrication (Fig. 2d-f), its σ_0 did reduce significantly when lubricated (Fig. 3b). This may be explained by the bonding area – bonding strength interplay model (Osei-Yeboah et al. 2016), where more efficient volume reduction of lubricated powder led to lower tablet porosity and larger bonding area when compressed at the same pressure. Consequently, the larger bonding area among particles compensated the reduction in bonding strength due to lubrication. To verify this, effects of lubrication on powder compressibility (porosity vs. compaction pressure) were examined (Fig. 4).

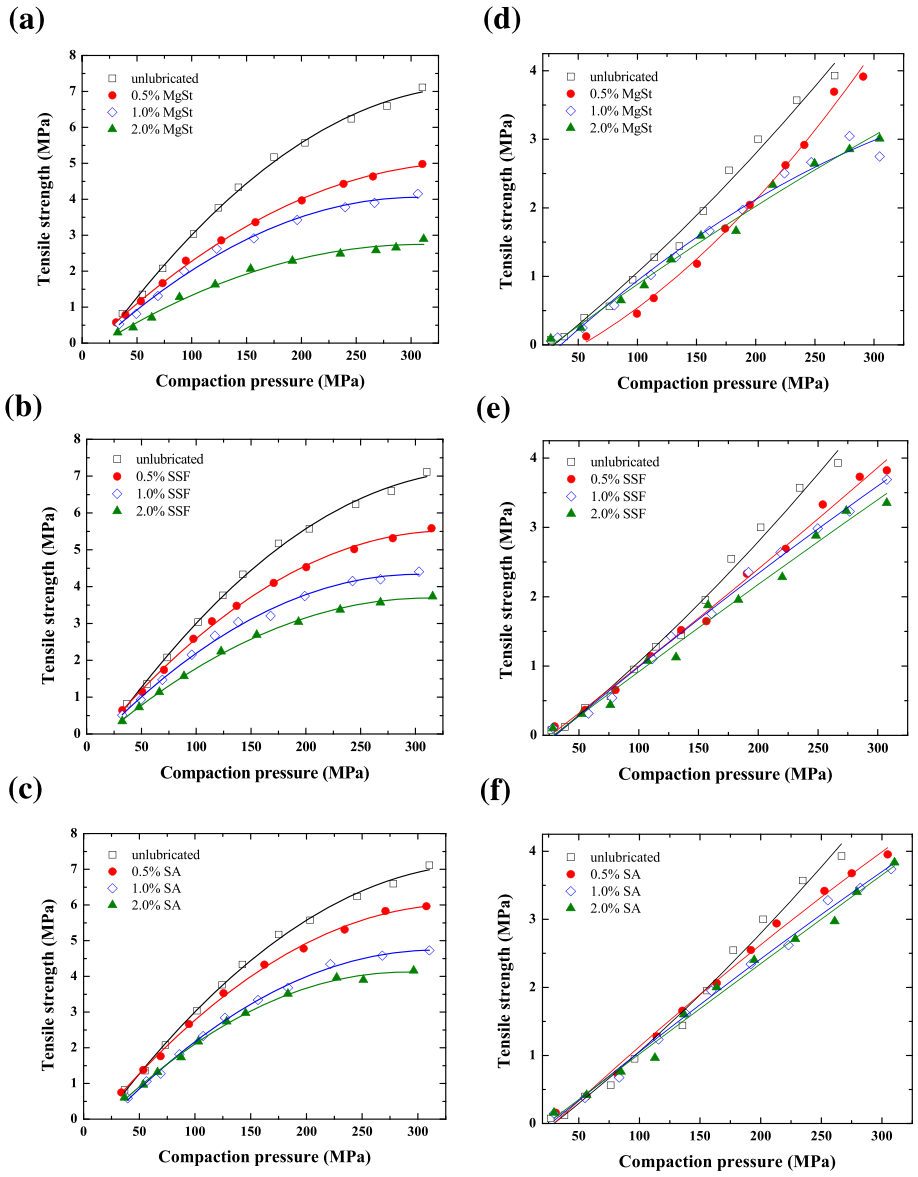

Fig. 2. Tabletability profiles of binary mixtures, MCC-LM = 2:1 (a–c) and MCC-LM = 1:3 (d–f) containing 0–2% (w/w) of different lubricants (MgSt, SSF, and SA). Lines were fitted to a quadratic function.

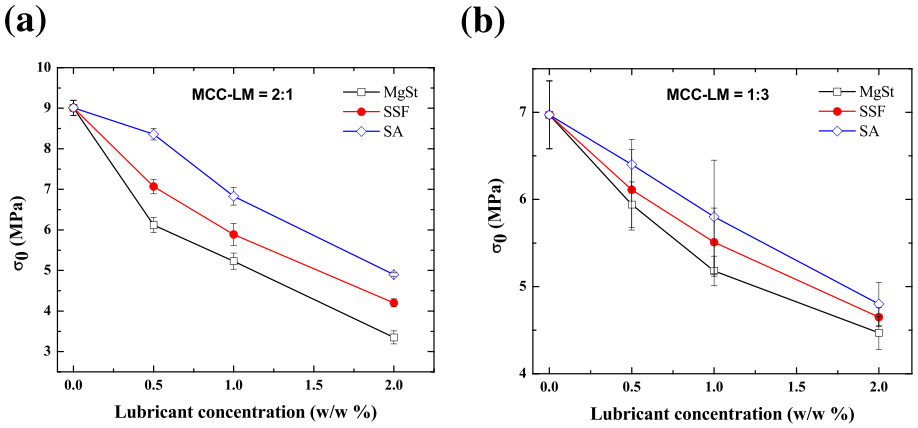

Fig. 3. Impact of lubrication on σ_0 of powders (a) MCC-LM (2:1) and (b) MCC-LM (1:3), containing 0–2% (w/w) of different lubricants (MgSt, SSF, and SA). Error bars indicate standard errors of fitting.

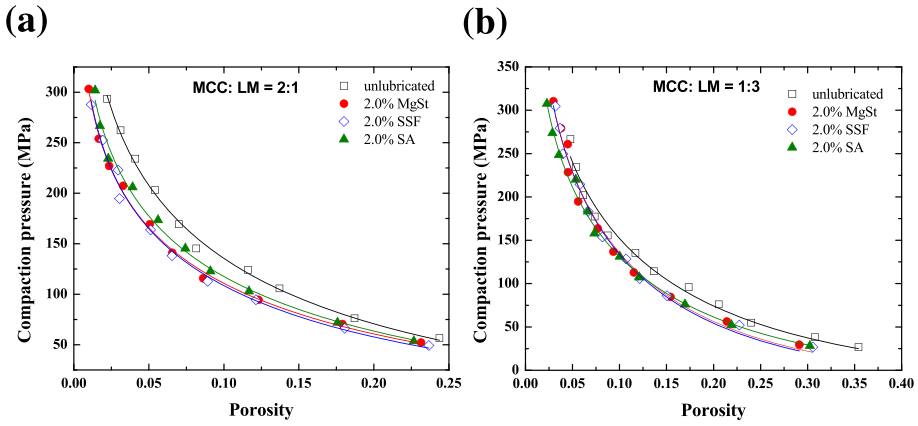

Fig. 4. Compressibility profiles of powders with and without 2% (w/w) of different lubricants (MgSt, SSF, and SA), (a) MCC-LM (2:1) and (b) MCC-LM (1:3). Lines were obtained by fitting data to Eq. (2).

3.3. Effect on Powder Consolidation

The compressibility data of powders containing 2% of lubricants (Fig. 4) were analyzed using Eq. (2). The unlubricated LM-rich formulation showed a greater 1/C than the MCC-rich formulation (Table 1), which is consistent with the presence of a higher percentage of the harder LM. The effect of lubrication on 1/C was formulation dependent. Under the same lubrication condition, 1/C changed to a greater extent for the MCC-rich powder than the LM-rich powder. The relatively lower impact of lubrication to a more brittle powder is consistent with the fact that brittle powders undergo volume reduction by not only particle slippage and rearrangement but also fragmentation, which is essentially absent in plastic powders. Since lubrication does not affect particle fragmentation, the relative impact of lubrication to volume reduction of brittle powders is less. For both powders, the effects of lubrication on plasticity as measured by 1/C followed the descending order of MgSt > SSF > SA (Table 1). This suggests that MgSt was the most effective and SA was the least effective in promoting more efficient powder packing during compression. This effect on consolidation was also reflected by the higher ε_c of lubricated powders than the unlubricated ones, implying that lubrication leads to the formation of a three dimensional particle bonding network at a higher porosity. The effect is more prominent for MgSt than SSF and SA (Table 1). The tabletability of MCC-rich powder was still significantly decreased by lubrication (Fig. 2a–c) despite its compressibility was improved more than the LM-rich powder (Fig. 4). This means the loss of bonding strength by the presence of lubricant film on particle surfaces dominates the bonding area – bonding strength interplay for the MCC-rich powder, where the particle fragmentation was absent.

3.4. Effect on Tablet Indentation Hardness

H is one of the powder mechanical properties that influence processes, such as milling and tableting (Cao et al. 2010; Meier et al. 2009). Potential effects of lubrication on H were evaluated using 2% lubricant concentration for both MCC and LM-rich formulations. The H decreased exponentially with increasing tablet porosity in all cases. Therefore, hardness at zero porosity (H_0) was obtained by non-linear regression using an exponential function ($R^2 > 0.98$). In all cases, lubrication led to lower H (Fig. 5) and H_0 (Table 1). The greater H_0 of LM-rich powder than the MCC-rich powder is consistent with the higher hardness of LM than MCC. The relative influence of lubrication on H was slightly greater for the MCC-rich powder (Fig. 5). When compared to the unlubricated powders, H_0 decreased by 15–21% for MCC-rich powder and 5–9% for LM-rich powder (Table 1). Thus, similar to the observed effect on 1/C, tablet H of the MCC-rich powder was more sensitive to lubrication. The observed effects on H suggest all three lubricants are more plastic than both MCC-rich and LM-rich powders. Among the three lubricants, MgSt is the most plastic as shown by its greatest reduction on H_0 compared to other lubricants (Table 1).

3.5. Effect on Tablet Brittleness

Lubrication by MgSt was shown to increase tablet brittleness in some materials (Paul and Sun 2017c). The broad applicability of this phenomenon was further examined in this work using three lubricants at 2% concentration. As observed before, (Paul and Sun 2017c) tablet brittleness (measured by TBI) generally decreased with increasing compaction pressure (Fig. 6). Since tablet porosity decreased with increasing pressure for all powders studied here (Fig. 4), this observation suggests that more porous tablets are more brittle. In fact, TBI

Table 1
Plasticity, hardness (H_0), tensile strength (σ_0), and disintegration time of MCC-rich and LM-rich formulations containing 2% of different lubricants (Values in parenthesis indicate standard error of fitting).

Formulation[a] (MCC:LM)	KL parameters		σ_0 (MPa)	H_0 (MPa)	Disintegration time (s), n = 3	
	1/C (MPa)	ε_c			100 MPa	150 MPa
2:1 (unlubricated)	147.3 (10)	0.74 (0.03)	9.0 (0.2)	140 (3)	25.3 ± 2.9	71.3 ± 5.0
2:1 (2% MgSt)	99.7 (7)	0.83 (0.04)	3.4 (0.2)	111 (3)	38.7 ± 1.5	93.3 ± 4.2
2:1 (2% SSF)	110.0 (13)	0.80 (0.06)	4.2 (0.1)	121 (3)	30.3 ± 3.5	83.0 ± 2.7
2:1 (2% SA)	122.1 (12)	0.80 (0.06)	4.9 (0.1)	120 (2)	35.3 ± 1.1	99.0 ± 2.6
1:3 (unlubricated)	304.5 (41)	0.52 (0.02)	7.0 (0.4)	196 (8)	30.7 ± 2.3	51.3 ± 1.5
1:3 (2% MgSt)	277.4 (22)	0.57 (0.03)	4.5 (0.2)	176 (6)	37.0 ± 3.6	68.0 ± 2.8
1:3 (2% SSF)	283.1 (18)	0.55 (0.03)	4.7 (0.1)	182 (6)	35.0 ± 2.7	63.7 ± 1.3
1:3 (2% SA)	290.7 (27)	0.53 (0.02)	4.8 (0.2)	186 (6)	38.6 ± 0.8	78.7 ± 0.8

[a] Formulations contain 3% of Ac-Di-Sol.

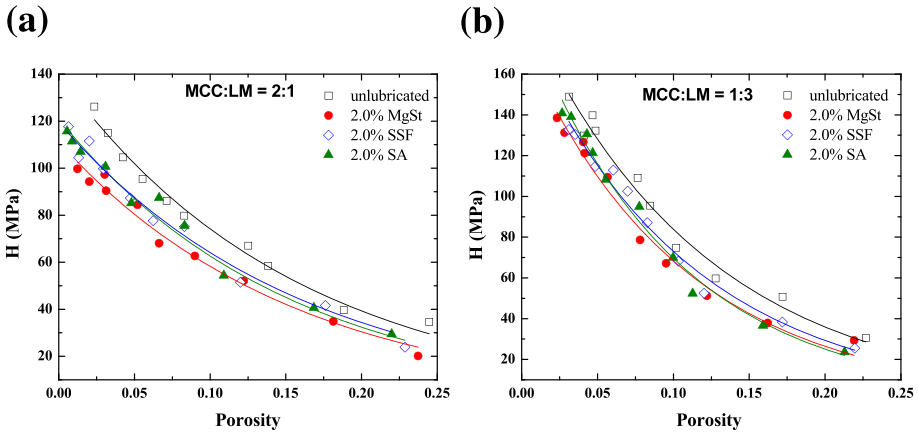

Fig. 5. Indentation hardness (H) as a function of porosity of powders containing 0% or 2% (w/w) of different lubricants (MgSt, SSF, and SA), (a) MCC-LM (2:1) and (b) MCC-LM (1:3). Lines were obtained by fitting points to an exponential function.

decreased exponentially with increasing porosity (Fig. S5), similar to the observations made in other materials (Gong et al. 2015). The TBI of the unlubricated MCC-rich powder was much lower than that of the LM-rich powder (Fig. 6). This is consistent with the greater plasticity and lower brittleness of MCC, and higher porosity of LM-rich powder under similar compaction pressure. Lubrication invariably led to higher TBI for both formulations (Fig. 6). The MCC-rich powder exhibited much more sensitivity, where 2% MgSt led to nearly doubled TBI than unlubricated powder (Fig. 6a). The extent of increase in TBI followed the descending order of MgSt > SSF > SA. This order is exactly opposite to that of tabletability (Fig. 2a–c) and σ_0 (Fig. 3a), which was the lowest when MgSt was used. This correlation and our recent observation that TBI decreased with increasing tensile strength when different lubrication processes were employed (Paul and Sun 2017c) suggest that TBI may be a useful quality attribute of tablet. The increase in TBI is attributed to the fact that lubrication leads to weakened interactions at the particle-particle bonding interface. Thus, the strain required to separate weaker bonding sites is smaller, which corresponds to higher TBI (Paul and Sun 2017c). For the LM-rich powder, differences among lubricants were much smaller. In fact, the effect by MgSt was only marginally greater than SSF and SA, which exhibited nearly identical effects (Fig. 6b). In summary, lubrication always made tablets more brittle while also reducing tensile strength. Greater reduction in tensile strength corresponded to larger increase in brittleness.

3.6. Effect on Tablet Friability

The influence of lubricant on tablet tensile strength and brittleness is expected to impact tablet friability, which is strongly influenced by the mechanical strength of the tablet and the deformability of the powder. The deteriorated tablet tensile strength and higher brittleness would likely make tablets more friable. The percent weight loss for all powders decreased with increasing compaction pressure, following the power law relationship as observed before (Osei-Yeboah and Sun 2015). The compaction pressure corresponding to 1% friability followed the ascending order of unlubricated < SA < SSF < MgSt for both powders (Fig. 7). Thus, lubrication led to increased friability for both formulations. Under identical lubrication conditions, the MCC-rich formulation exhibited lower friability than the LM-rich formulation. For example, at 30 MPa, the unlubricated MCC-rich powder did not reach 1% friability, while the friability of the unlubricated LM-rich formulation showed approximately 3% weight loss. This can be attributed to the lower tensile strength and higher TBI of the LM-rich formulation. The fitted lines of MCC-rich formulation showed different slopes for different lubricants but those of LM-rich formulation were nearly identical (Fig. 7). Thus, the choice of different lubricants in MCC-rich formulations impacts tablet friability more at the lower compaction pressure range where tablet porosity is high and tensile strength is low. A solution to counter this effect is to increase tablet tensile strength by applying a higher compaction pressure if a certain lubricant leads to increased friability. Results obtained here confirm the view that a predominantly plastic formulation usually requires lower tensile

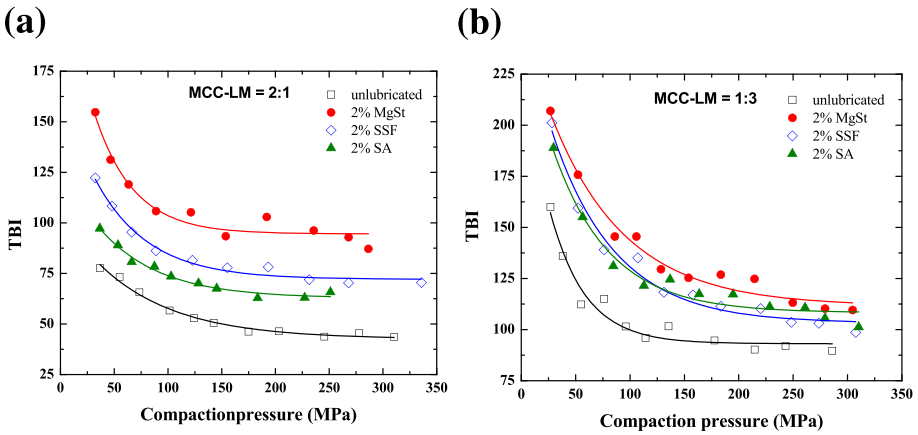

Fig. 6. TBI as a function of compaction pressure of powders containing 0% or 2% (w/w) of different lubricants (MgSt, SSF, and SA), (a) MCC-LM (2:1) and (b) MCC-LM (1:3). Lines were drawn to assist the visual identification of trends in data points.

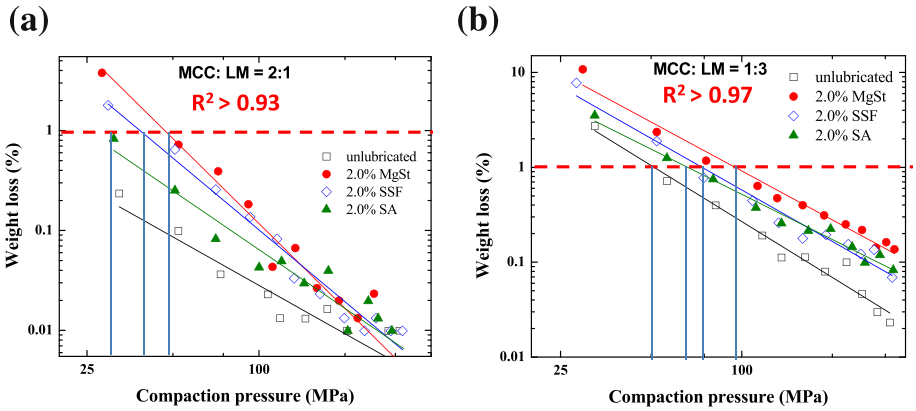

Fig. 7. Relationship between friability (% weight loss) vs. compaction pressure of powders containing 0% or 2% (w/w) of different lubricants (MgSt, SSF, and SA), (a) MCC-LM (2:1) and (b) MCC-LM (1:3), Lines were obtained by fitting points to a power law function.

strength to meet the friability requirement than a predominantly brittle formulation (Osei-Yeboah and Sun 2015).

3.7. Effect on Tablet Disintegration

Tablet disintegration time (DT) of the formulations containing 2% lubricant and 3% Ac-Di-Sol was tested in simulated intestinal media (pH 6.8) using the USP method (Table 1). The percent change in DT relative to the unlubricated formulations is shown in Fig. 8. Here, all tablets were compressed at 150 MPa because friability was much less than 1.0% for all the formulations (Fig. 7). Under this pressure, tablet porosity did not change significantly among the lubricated formulations (Fig. 4). However, lubricated formulations all exhibited lower tablet porosity than corresponding unlubricated powders. In order to compare lubricated and unlubricated formulations at the same porosity, an additional pressure of 100 MPa was used to obtain data that allowed comparison of DT to a common porosity for both lubricated and unlubricated formulations. Although a nonlinear relationship between DT and porosity is expected, linear interpolation is likely acceptable over a narrow porosity range of 0.08 to 0.15 (equivalent to pressure range of 100 and 150 MPa) as observed in this work. In all cases, lubrication led to an increase in DT for both MCC-LM (2:1) and MCC-LM (1:3) formulations (Table 1). At 100 MPa, the effect of MgSt and SA on DT was similar but DT was further prolonged at 150 MPa when SA was used. The effect by SSF was the least for both formulations, which corresponds to its hydrophilic nature (Wang et al. 2010). Although MCC is insoluble in water, it facilitates disintegration by swelling and capillary action that disrupts the particle-particle bond in the tablet (Lerk et al. 1979). The LM-rich formulation had lower DT than MCC-rich formulation particularly at 150 MPa. This, in part, may be attributed to the greater porosity of the LM-rich tablets (Fig. 4). Interestingly, the impact of pressure on DT was different for the two formulations (Fig. 7). In the case of the LM-rich formulation, percent change in DT increased with pressure for all the lubricants. This is expected since a higher pressure led to lower tablet porosity, hence, slower water penetration. However, the percent change in DT for MCC-rich formulation decreased with increasing pressure particularly for MgSt. This effect may have to do with the different disintegration mechanism of MCC-rich formulation, where water wicking into tablet through MCC fibers causes swelling and exerts disintegration force. A larger disintegration force is developed by swelling MCC fibers when tablets are denser. Regardless the actual mechanism to the effects of compaction pressure, the effect of lubrication on DT depends on lubricant type. At a porosity of 0.11, DT of the unlubricated MCC-rich formulation was 45 s while the formulation containing 2% MgSt, SSF, or SA were 54, 40 and 62 s, respectively. For the LM-rich formulation, the corresponding values were 47 s (unlubricated), 49 s (MgSt), 43 s (SSF) and 53 s (SA). Thus, the use of SSF did not lead to prolonged disintegration of tablet but MgSt and SA did. This may be explained by the more difficult penetration of water into more hydrophobic tablet matrix when a hydrophobic lubricant is used.

3.8. Considerations for Lubricant Selection

While the main purpose of incorporating a lubricant in a tablet formulation is to reduce friction during tablet ejection, significant effects of lubrication on several important tablet characteristics are also demonstrated for all three lubricants. The more plastic powder exhibited lower ejection force, which required less lubricant, but it was also more susceptible to lubrication in term of tablet tensile strength, friability, and disintegration. In contrast, the more brittle powder

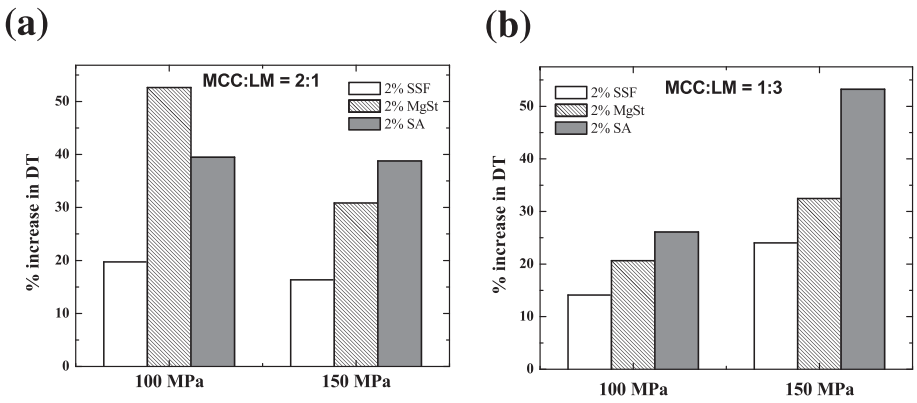

Fig. 8. Percent increase in disintegration time (DT) by different lubricants for formulations containing 2% lubricant and 3% of Ac-Di-Sol. (a) MCC-LM = 2:1 and (b) MCC-LM = 1:3.

exhibited greater ejection forces, thus, required more lubricant to reduce it. However, tablet properties of brittle materials were also less sensitive to lubrication. At 0.5% w/w lubricant level, MgSt exhibited greater lubrication efficiency than SSF and SA, which required roughly 1% loading to achieve lubricating effects comparable to 0.5% MgSt. However, the extent of tablet strength deterioration at a given concentration followed the order: MgSt > SSF > SA (Fig. 2). At 2% loading, effects of lubrication on TBI and friability followed the descending order: MgSt > SSF > SA (Figs. 6 & 7). Tablet DT followed the descending order of SA > MgSt > SSF. A comprehensive evaluation would suggest that SSF is a better choice over MgSt because, at the same lubrication efficiency, SSF does not negatively influence tablet disintegration and its detrimental effect on tabletability and friability is less than MgSt. If the lubricants are evaluated at the same concentration, SSF showed less effective die-wall friction reduction than MgSt but also much less deterioration on tablet strength, friability, and disintegration. Therefore, a higher concentration of SSF exhibiting comparable lubrication efficiency can be used without significantly deteriorating other tablet characteristics. The use of 2% of SA is as effective in reducing friction as 0.5% MgSt. However, SA is less favorable as it led to considerable increase in DT. In summary, while MgSt is the most effective in reducing friction among the three lubricants, it also exerted more profound negative impact on important tablet properties, such as tabletability, friability, and DT. Therefore, the development of a truly optimized tablet formulation must simultaneously consider all of these effects.

4. Conclusion

We have systematically quantified effects of three common commercial lubricants and their concentrations on lubrication efficiency and several key tablet characteristics of both plastic and brittle powders. Lubrication led to greater plasticity and lower hardness for either plastic or brittle formulations. MgSt was more plastic than SSF and SA and, hence, more effective in facilitating powder packing and consolidation. The lubrication efficiency of MgSt was also the highest. However, this advantage is shadowed by the much reduced bonding strength of MgSt, resulting in a more significant decrease in particle-particle bonding interactions and, therefore, more reduction in tablet strength than SSF and SA. Therefore, a slightly higher concentration of SSF is equally effective to MgSt but without overtly reducing other important tablet properties, including tablet strength, friability, and disintegration. In the era of quality-by-design, the choice of a lubricant and its optimum amount in a tablet formulation should be made based on systematic evaluation, as demonstrated in this work, instead of personal preference or empiricism.

Abbreviations

1/C	Plasticity parameter
ε_c	Critical porosity
μ	Friction during ejection
σ	Tablet tensile strength
σ_0	Tablet tensile strength at zero porosity
DT	Disintegration time
EF	Ejection force
H	Tablet indentation hardness
H_0	Tablet indentation hardness at zero porosity
KL	Kuentz and Leuenberger
LM	Lactose monohydrate
MCC	Microcrystalline cellulose (Avicel PH102)
MgSt	Magnesium stearate
RDP	Residual die-wall pressure
SA	Stearic acid
SSF	Sodium Stearyl Fumerate
TBI	Tablet brittleness index
TGA	Thermogravimetric analysis

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejps.2018.02.013.

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Pharmacopeia, U.S., USP Disintegration Test.

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