Lubrication in Pharmaceutical Tablet Manufacturing

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Jiangnan Dun

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Abstract

Appropriate compaction properties are critical to ensure a successful and robust tablet manufacture. According to Materials Science Tetrahedron (MST) theory, the quality of the tablet product is determined by the properties of pharmaceutical materials and the process conditions during manufacture.

Lubricant, as one of the most important tablet excipients, has great impacts on the flow and mechanical properties of formulation. This work is heavily focused on understanding of the effects of process parameters on the lubrication as well as development of new lubricants for tablet formulation. Magnesium stearate, the most commonly used tablet lubricant, though exhibits excellent lubrication efficiency, leads to deterioration in tablet strength and dissolution. Sodium lauryl sulfate (SLS), Poloxamer 188 and Poloxamer 407 were selected as MgSt-alternative lubricants to be tested in tablet formulations. We found that the lubrication efficiency of these three materials are comparable with MgSt. More importantly, no significant tablet strength reduction was observed. Given to the higher hydrophilicity, tablets containing either of SLS, P188 or P407 showed enhanced dissolution profiles compared with MgSt containing tablets. Furthermore, robustness of formulation was remarkably improved when P188 or P407 was used as lubricant.

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CHAPTER 1. INTRODUCTION

1.1 General introduction

The pharmaceutical tablet, one of the most preferred solid dosage forms for oral administration of drugs, contributes to more than 70% of the drug market. It possesses several advantages over other dosage forms: 1) high dose precision; 2) good content uniformity; 3) high manufacture efficiency and low manufacture cost; 4) ease of packaging and transportation; 5) outstanding chemical and physical stability and 6) ease of administration and great patient compliance [1]. In addition to the more traditional single layer tablet, different types of tablets were developed to meet certain clinical needs. For example, bilayer tablet could achieve both immediate and sustained releases by incorporating drugs in two separate layers [2]. Oral disintegrating tablet (ODT) with a rapid disintegration in mouth allows easy delivery of medicine for elder people [3, 4].

The manufacture of tablet in pharmaceutical industry involves three major methods: 1) direct compression; 2) dry granulation and 3) wet granulation [5]. Compared with granulation methods, direct compression is the most preferred choice because of its simplicity but high efficiency [6]. The process only involves blending and compression, with no further step required. Moreover, direct compression is also suitable for formulation that is sensitive to excess moisture or heat, which cannot be processed through granulation [7, 8]. This apparent simple process requires the drug formulation have satisfied properties including flowability and compaction properties [9-13]. Poor powder flowability often leads to material loss and segregation [14-16], which results in tablet weight variation [17, 18] and poor content uniformity [19]. Tablets with insufficient mechanical strength (< 2MPa) usually experience issues during down streaming processing such as coating and

packaging [20, 21]. However, many active pharmaceutical ingredients (API) do not meet these criteria, thus require additional excipients to compensate their deficiencies, which leads to a more complex tablet formulation [22, 23].

Instead of the more traditional "Trial and Error" that most pharmaceutical industries relied on during formulation development, which often leads to product failures during scale-up and commercialization, Materials Science Tetrahedron (MST), a science-based approach, provides a more optimized and reliable guidance for pharmaceutical research and product development [24]. MST depicts the relationship between structure, properties, performance and processing of a drug. The final performance of a drug product is determined by the properties (e.g., mechanical properties, flow properties) of both API and excipients in a formulation, which is determined by the structure of the chemical compounds. Additionally, by adjusting the processing used in manufacture, the performance of the drug product can be modified based on clinical purposes.

The purpose of this research is to facilitate the tablet formulation development based on the particle engineering to improve the flow and compaction properties of pharmaceutical materials, guided by the principle of MST. The main purpose of this research is to facilitate the tablet formulation development by powder engineering to improve the lubrication process, thus compaction properties in pharmaceutical relevant materials. The specific goals focus on 1) Understanding the variations in MCC tablet mechanical properties resulted from hand mixing by integrating the effects of lubrication intensity; 2)

Investigating the behaviors of new tablet lubricant candidates (SLS and Poloxamers) based on the systematic evaluations of flow, compression and dissolution performance in model excipients and drug formulations.

1.2 Literature review

1.2.1 The pharmaceutical tablet

The tablet, one of the most popular pharmaceutical oral solid dosage forms, is widespread in market. More than 70% of the over the counter (OTC) and medicines prescribed are in the form of tablet [1]. Compared with other dosage forms, tablet is relatively easier to administration, which results in high patient compliance. The size of tablet is usually small, which makes it more convenient to carry when travelling. Besides patients' preference, manufactures also prioritize developing drug into tablet because the production process is straightforward and efficient. Moreover, as one of the solid dosage forms, tablet has high stability in terms of both chemical and physical aspects, which make the transportation and storage simple and economic. Last but not the least, tablet has the highest accuracy and lowest variation of dose, which brings the delivery of expected biopharmaceutical performance more controllable.

Several types of tablet have been developed to meet different clinical goals. A majority of tablets prescribed are designated to swallow orally [25]. These tablets include: 1) Single layer and multilayer tablet; 2) film coated tablet; 3) controlled release tablet and 4)

sustained released tablet [26]. It is worth to mention that oral disintegrating tablet (ODT) has an relatively lower strength, and thus is intended to disintegrate in mouth before being swallowed [3, 27]. In addition, certain tablets are used in oral cavity only. These tablets are manufactured to disintegrate, dissolve and absorbed locally in oral cavity without ingestion [25]. Tablets under this category can provide the shortest onset of action and highest therapeutic concentration by avoiding the first-pass metabolism. Examples include: 1) buccal tablet [28]; 2) sublingual tablet [29]; 3) lozenges and troches [30] and 4) dental cones [31]. Moreover, tablets that are used to prepare solutions before administration, such as effervescent tablet [32], are also available in the market.

Regardless of the types of tablet, certain quality criteria must be satisfied before FDA approval. For example, immediate release tablet must exhibit sufficient tensile strength to overcome the downstream processing such as coating and packaging [33]. Insufficient tablet strength leads to products with low quality and potential recall. On the other hand, tablet strength cannot be too strong for ODT, otherwise, the rapid disintegration advantage will be diminished [27, 34].

With the high throughput screening (HTS) widely applied in drug discovery [35], many existing Active Pharmaceutical Ingredients (API) and drug substances under development belong to Biopharmaceutical Classification System (BCS) II or IV with low water solubility [36]. Additionally, the flow and compaction properties of API are usually not ideal either due to the small particle size [37] and many presented functional groups in the

molecule [38, 39]. These deficiencies of API require the corrections from excipients. Therefore, Most of the tablets are multi-component solid oral dosage forms that contain more than one component: API and excipients [40].

An active pharmaceutical ingredient (API) is any substance that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or function of the body [41]. It is possible that more than one APIs are presented in one tablet [42]. For example, multiple APIs can be formulated in one single tablet to decrease the pill burden and improve patient compliance [43]. API can be either crystalline or amorphous, depends on the molecule arrangements. Though chemically identical, crystalline and amorphous API could have significantly difference in terms of both physicochemical and mechanical properties [44, 45].

Crystalline API is usually obtained by crystallization, during which drug molecules are organized in a highly ordered way that the crystal lattices with infinite extension of three-dimensional networks are formed [46]. Crystalline particles exhibit highly-ordered molecular packing [47] and many of them are needle [48], tabular [49], prismatic [50] or columnar [51] shaped. Because of the strong intermolecular force between different layers, crystalline API usually exhibits lower free energy [52], thus higher stability [53], which makes it favorable to pharmaceutical industry.

Recently, the number of drug products approved by FDA that contains amorphous API is increasing [54, 55]. Compared with crystalline API, its amorphous form is usually prepared by spray drying (e.g., amorphous acetaminophen) [56] or quenching [57]. Due to the lack of repeated three-dimensional molecular packing, amorphous API does not have a defined geometric shape [58]. Because of the highest free energy, amorphous API usually exhibits better aqueous solubility advantage over crystalline form [59, 60]. This significantly improves the drug dissolution and thus became interest in pharmaceutical industry [61]. However, the drawback is that due to the intrinsic lower stability, recrystallization tends to occur which brings amorphous API back to its crystalline form [62, 63]. This unexpected form transformation diminishes the solubility advantage, causes issues in product quality, and potentially leads to product recall [64].

Excipients are inert substances other than the APIs that are included in the formulation to facilitate the manufacture and delivery of drug product [10]. The judiciously selection of correct types and amounts of excipient is a key to successful tablet formulation development [24]. Primary tablet excipients include diluent, binder, lubricant, glidant, and disintegrant [65]. In addition, sweetener (e.g., saccharine) is commonly used with drugs that exhibit bitter taste, especially in pediatric tablets and chewable tablets, to improve the flavor [66, 67].

Diluent is used to provide bulk, ensure accurate dose, and content uniformity [68]. Size is one of the quality attributes for pharmaceutical tablet, the amount of diluent used varies

based on the drug loading to ensure an optimal tablet size and patient compliance [69, 70]. For example, in low dose formulation, significantly more diluents are used compared to high dose formulation [71]. Commonly used tablet diluents include microcrystalline cellulous (MCC) and lactose [72, 73], which exhibits distinct mechanical properties. MCC is a plastic material, which is easily deformed under external pressure [74]. Lactose, however, is a brittle material, which undergoes fragmentations under external pressure [75]. The balance of plastic and brittleness is crucial for obtaining the formulation with optimal mechanical properties and robust manufacturability.

Binder is added into tablet formulation to bring the API and excipients together in a cohesive mix [20]. Compressible starch is the most commonly used binder in both direct compression and wet granulation [76]. For direct compression, starch promotes the formation of cohesive dry blends by its superior adhesive characteristics [77]. When used in wet granulation, starches dissolve in water and effectively form a wet mass with API and other excipients [8].

Lubricant is one of the most important excipients in tablet formulation. It is used to reduce the ejection force of tablet after compression by reducing the friction between tablet and die-wall [78]. Magnesium stearate (MgSt) is the most popular tablet lubricant that has been widely used for decades [79]. However, MgSt significantly deteriorates the tablet strength [80, 81] and reduce tablet dissolution [82, 83]. Recently, many MgSt alternatives have been investigated to have comparable lubrication performance but without sacrificing the

dissolution and compaction properties [78, 84]. MgSt can also be used to improve the powder flow property [85].

Glidant is specifically used to improve the flow property of formulation by reducing friction and adhesion between particles [86]. It can also be used as anti-caking agents. Colloidal silica is one of the most commonly used glidant [87, 88].

Disintegrant is used in tablet formulations to ensure a rapid break-down into primary particles, facilitating the dissolution or release of the drug [89]. It's an important excipient because a rapid disintegration is the prerequisite for fast dissolution. Croscarmellose sodium is the most commonly used tablet superdisintegrant, which is swelling up upon contact with water in GI track and breakup the tablet [90]. The word "superdisintegrant" refers to the disintegrant that requires a relatively smaller amount but achieves comparable or higher efficiency than traditional disintegrant (e.g., MCC) [91].

It is also worth to mention that not all of these excipients are required to be included in a formulation and the excipients (type, amount) used should be based on individual formulation (e.g., flow property, compaction properties). A judicious selection of excipients based on a systematic scientific approach is critical to provide the optimally balanced formulation, which leads to high manufacturability and quality of tablet.

1.2.2 Manufacture of pharmaceutical tablets

1.2.2.1 Processing methods

In pharmaceutical industry, manufacture of tablets is mainly through dry granulation, wet granulation, or direct compression, the choice of which depends on the properties of individual formulation [92]. Flow and compaction properties are two of the most influential factors to consider [93]. In addition, API stability (e.g., heat and moisture sensitivity) [94] and particle sizes [95] also play important roles in the manufacture of tablets.

Dry granulation is a size enlargement process that improve the flow and compaction properties of formulations. The process involves compaction of powders into solid compacts which are subsequently milled to produce granules that can be easily processed [96]. In pharmaceutical industry, dry granulation is commonly achieved by roller compaction because of the simplicity and high efficiency. It is a process where powder formulations are continuously passed through the middle of two counter-rotating rollers where ribbons are formed by densification and consolidation of powder. Then, the ribbons are further milled into optimal sizes, lubricated and compressed into tablets [97]. Another less commonly used technique is slugging. This process involves compression of powder formulation into large intermediate tablets by using a heavy-duty tablet press. The intermediate tablet is then milled for optimal sizing before lubrication and compaction [98]. The most critical drawback of dry granulation is the dust generation, which significantly affects the flow property of granules, leads to segregation and increases the content

variation in tablet, as well as increases cross contaminations [99]. Compared with slugging, roller compaction generates much less fines, therefore has less impacts on product quality. In addition, excessive fines generated during the dry granulation may lead to air pollution and upper respiratory tract infection in operators. While the purpose of the dry granulation is to increase the particle size, size enlargement can also have negative impacts on the tablet strength [100], which may become an issue in downstream processing, thus needs to be systematically evaluated when formulating a drug.

Compared with dry granulation, wet granulation is a process that involves forming agglomerate consisting of small primary particles by agitation in the presence of a liquid, which is removed in subsequent drying [94]. Thus, it is only used when the API and excipients are not heat or water sensitive. Powders granulated by wet granulation exhibit improved flow, reduced dust, and lower tendency to segregation during subsequent unit operations, which improve the manufacturability and content uniformity of the final product [101]. When properly formulated and processed, WG can be used for manufacturing tablets over a wider range of API loadings than dry granulation, while still maintaining good flowability, tabletability, and uniformity. Modern wet granulation is usually executed under high shear. During the high shear wet granulation (HSWG), a liquid is sprayed onto a powder bed as it is vigorously agitated under high shear in an appropriate equipment, such as a high shear mixer or twin-screw mixer, to produce agglomerates [102]. There are three major steps involved in HSWG: 1) wetting and nucleation; 2) growth and consolidation and 3) attrition and breakage [103]. The first step involves introducing liquid binder into contact with a dry powder bed and distributing it

evenly throughout the powder. The whole process is controlled by the drop penetration time and spray flux, which is described in a nucleation regime map [104]. The second step occurs when a granule is subject to external stress during collisions with another granule, granulator wall, or impeller. Depending on the deformability of granules, two granule growth mechanisms may result: steady growth and induction growth [105]. The last step involves granule breakage due to the external stress, the extent of which heavily depends on the both process parameters (e.g., impeller speed) and mechanical properties of material [106]. Granule breakage inside the high shear granulator is part of the granule growth processes and controls the final granule properties, therefore is not always unfavored. However, granule breakage during drying (e.g., fluid bed drying) process, if not properly controlled, can result in excessive of dust and lead to poor flowability and segregation during tablet manufacture [107].

Direct compression, unlike either dry granulation or wet granulation, does not lead to any particle size enlargement. The process only involves mixing of excipients and API, followed by compression, thus remains to be the simplest for making pharmaceutical tablets [108]. Whenever possible, direct compression is preferred by pharmaceutical industry mainly because of the lower manufacturing cost associated with the fewer unit operations [10]. However, successful direct compression demands the good tabletability, satisfying flowability, and acceptable content uniformity of the formulation. For high dose formulation, direct compression may not be possible if API exhibits extremely poor tabletability or flowability [109]. On the other hand, for low dose formulation, segregation and the poor content uniformity become the main challenges [110]. Therefore, designing

a robust formulation with good flow and compaction properties based on a clear scientific understanding of pharmaceutical materials is critical for successful direct compression.

1.2.2.2 High-speed tableting

In pharmaceutical industry, powder blends are compressed in the high-speed rotary press to produce tablets. The whole processes can be divided into three steps, which include die filling, compression and decompression, and ejection [111].

During the first step, powders flow from the hopper into the punch-die cavity by gravity, the volume of which depends on the position of the lower punch [112]. The position of the lower punch is controlled by a weight adjusting ramp attached in a weight control unit. This volume must be appropriately controlled as it determines the amount of powders in the die, which directly determines the tablet weight. To minimize the variation of tablet weight, powders are usually overfilled into the turret, followed by a removal of excessive powders from the die surface by a scraper [113].

The second step involves pre-compression, main compression and decompression of powders, which result in the formation of tablets. Pre-compression is an initial compression before the main compression take place. The compaction pressure used in pre-compression is much lower than the one used in main compression. The purpose of using pre-compression is to remove the dust and air trapped inside the powders, which

leads to capping or lamination in tablet [114]. During this process, powder particles undergo sliding and rearrangement within the die and powder porosity is decreased slightly. In this step, powder particles need to overcome the inter-particular friction in order to have effective volume reduction [115].

During the main compression, as the upper and lower punches move between the main compression rolls, maximum preset compaction pressure is applied to the powder to complete the consolidation and formation of tablet [116]. The gap between upper and lower punch determines the thickness and strength of tablets. In this step, as the powder particle rearrangement solely no longer provide effective volume reduction, particles undergo either plastic deformation, elastic deformation or fragmentation. Plastic deformation is a permanent deformation that leads to the formation of effective bonding area [115, 117]. On the other hand, elastic deformation is a temporary deformation, which will return to the original position upon removal of the compaction pressure [118].

During decompression process, the external compaction pressure gradually decreased from the maximum value to zero, in which tablet starts to expand due to the elastic recovery. The expansion of tablet stops when the external compaction pressure is completely removed [119]. The final deformation of materials depends on the relative magnitude of plastic deformation and elastic deformation (recovery). If elastic deformation dominates, loose powder or tablet with very low strength is obtained.

Fragmentation is another scenario other than plastic or elastic deformation. Brittle materials undergo fragmentation when an external compaction pressure is applied [120]. The fragments generated can either be plastic or elastic, which depends on the material's property. Fragments with plastic deformation dominated form greater effective bonding area than fragments with high elastic deformation.

Last but one of the most important steps is the tablet ejection, where tablets are pushed out from the die by the movements of lower punch. Ejection force is generated from the friction between tablet surface and die wall owing to the residual die wall stress [121]. Excessive ejection force leads to tablet quality issues such as low tensile strength, capping and lamination [122]. Moreover, tooling damage may occur with extremely high ejection force. In addition, high ejection force may lead to punch sticking [123]. In pharmaceutical industry, lubricant is added into the formulation to reduce the friction, thus ejection force, prevent sticking, and reserve tooling [124].

1.2.3 Lubrication in tablet formulation development

1.2.3.1 The physics of friction

Ejection force is originated from the friction between tablet side surface and die-wall. On novel compaction simulators, the value of ejection force can be directly obtained by using an instrumented die with built-in ejection sensors. Because surface asperities are commonly seen in pharmaceutical materials, e.g., active pharmaceutical ingredient (API), two approaching surfaces initially touch at their highest asperities. Upon being brought

closer, reversible elastic deformation occurs initially, followed by a permanent plastic deformation of the asperities, which promotes formation of real contact area [125]. Friction then occurs between the two solid surfaces when sliding [126].

In physics, friction can be characterized by Amontons's law, which emphasizes on the significant contributions of mechanical interlock of surface asperities without consideration of adhesion [127]. However, pharmaceutical materials, especially the APIs, are composed of very fine particles, in which high adhesion energy cannot be negligible. Therefore, friction force presented in pharmaceutical materials is given by Equation (1.1):

$$F_{\parallel} = \mu F_{\perp} + 2\varepsilon A \frac{\Delta_{\gamma}}{\delta} \qquad \text{Eq (1.1)}$$

Where $F_{\parallel}$ is the friction force, μ is the friction coefficient, $F_{\perp}$ is the applied normal force. The first part in this equation simply represents the Amonton's law. It is believed that, without adhesion, friction increases as the friction coefficient or applied normal stress increases. Amonton's law, however, does not consider the effects of the contact area and, therefore, adhesion between two irregular solid surfaces on friction force. This is accounted for by the second part in equation (1). A is the area of contact of two solid surfaces, ε is the fraction of kinetic energy transferred, $\Delta\gamma$ is the difference in surface energy between two contact surfaces and δ is the elemental distance [127]. Friction force is proportional to all parameters mentioned above except the elemental distance.

A few theories were developed to better understand the adhesion during powder compaction and tablet ejection. Among them, Johnson-Kendall-Roberts (JKR) model assumes that the adhesive force must be overcome during tablet ejection to push tablet out from the die by destroying the bonds formed between tablet and die wall. These adhesive interactions are referred as friction in tablet research [78].

1.2.3.2 Mechanisms of lubrication

To reduce the friction, therefore ejection force, between tablet and die wall, incorporating a lubricant in formulation is the most efficient way. There are two major types of lubricants currently used in pharmaceutical industry: fluid lubricant and boundary lubricant (more commonly used). In fluid lubrication, a layer of fluid (mineral oil, paraffin, etc. [128]) is placed in between the two solid surfaces and physically separate them from contacting with each other [129]. As the two solid surfaces are completely separated, lubrication performance is very good as indicated by the low friction coefficient (~0.001) and largely depends on the viscosity of the fluid [130]. Boundary lubricant, however, usually forms a very thin discontinued film on the solid surfaces, disrupts the interaction between two solid surfaces and decreases the friction in between. Since the two solid surfaces are not entirely separated, relatively high friction coefficient (~0.05-0.15) is expected [131-133]. Boundary lubricants usually have very low shear strength, which makes it extremely easy to slide upon shearing [134-136].

Unlike fluid lubrication, boundary lubrication is a surface phenomenon, which means that physical properties of the actual solid surfaces do have influence on the friction. The stress between two solid surfaces, upon contact, is supported by both lubricant film and junctions which are formed by the penetration of asperities. The total frictional force, F, equals to the sum of the force required to shear the lubricant film and the force required to shear the junctions (Equation 1.2):

$$F = A(\alpha Ss + (1 - \alpha)SL) \qquad \text{Eq (1.2)}$$

Where A represents the surface area over which asperities junctions formed, α is the fraction of the formed asperities junctions, Ss is the shear strength of solid surface and S_L is the shear strength of the lubricant film. By reducing the fraction of asperities junctions, along with the low shear strength itself, boundary lubricant reduces the friction force, therefore the ejection force of tablet when being pushed out from die.

Depending on the type and amount of lubricant used, the reduction of ejection force is varied. [137, 138] Lubrication efficiency is one of the most important criteria when selecting appropriate lubricant in tablet formulation development. Generally, lubrication efficiency can be characterized by either ejection force or coefficient of friction, where the higher of them, the worse the performance of lubricant. However, as ejection force is a function of tablet dimensions, change in tablet thickness will result in change of ejection

force. Therefore, inconsistent assessment of lubrication efficiency may occur. In contrast, the calculation of coefficient of friction is normalized by tablet dimensions (Equation 1.3):

$$\mu = \frac{EF}{\pi \cdot RDP \cdot D \cdot h\prime} \qquad \text{Eq (1.3)}$$

EF is the ejection force, RDP is the residual die wall stress at the end of decompression phase and before ejection, D is the tooling diameter and h' as the in-die tablet thickness at the end of the decompression. Figure 1.1 [139] shows the different forces/stresses presented during powder compression. Fa and Fb represent the applied compression force and the actual force transmitted to the lower punch. The loss (F_d) is due to the friction between upper punch and die-wall during compression. P_r stands for the residual die wall stress, which is resulted from the expansion of tablet during decompression cycle, when the external compression force is gradually removed. There are two different force transmissions involved during the compression and decompression processes: axial transmission and radial transmission. As the friction force is simply originated from applied force, die wall friction can be modelled by correlating the applied compression pressure P_a with actual pressure transmitted P_b by using the Equation 1.4: [140]

$$PaPb = e^{\frac{4\mu\eta L}{D}} \qquad \text{Eq (1.4)}$$

Where, μ represents the coefficient of friction, η is the ratio between the radial pressure and the applied pressure, L is the in-die tablet thickness and D is the in-die tablet diameter. In addition to characterizing lubrication efficiency, the value of μ along with η also provide a significant amount of information regarding to the stress and density distribution in compressed tablet [141].

The magnitude of radial stress transmitted from compression stress depends on the Poisson's ratio of materials [142]. The radial stress - axial stress relationship for both elastic and Mohr body have been investigated [143]. Viscoelastic constants obtained from decompression cycle provide insights into the mechanical properties of materials. Furthermore, studies of common excipients found that for viscoelastic material, whose deformation behavior depends on the time points during compression cycle, the elastic behavior of the tablet contributes significantly to the tablet deformation during decompression according to the large elastic constant under different compression pressures, while viscous does not affect much [144]. During decompression, with the removal of external compression force, tablets experience both the expansion in volume and the distortion in shape as its diameter is held constant by the rigid die. In this process, the in-die elastic recovery induces an increase in tablet porosity which tends to break the already formed interparticular bonds and releases the elastic energy stored to the die wall. As only plastic deformation contributes to the effective bonding area, for same material, larger bonding area leads to higher tablet strength [145], which tends to have less interparticular bonds broken during elastic recovery. In this situation, a positive elastic constant typically represents a material with ability to form strong interparticular bond. On

the other hand, materials with very weak interparticular bonds tends not to form intact tablet due to the internal structure disruption by elastic recovery. In this case, the radial die wall stress will increase as the compression force decreases, which is characterized by a negative elastic constant [146]. Therefore, carefully examining the viscoelastic constants can provide very important information for predicting the change of inner structure of tablet during compression and decompression.

1.2.3.3 Magnesium stearate

Magnesium stearate (MgSt) is the most widely used lubricant, due to its high lubrication efficiency [79, 80]. Depending on formulation, 0.25% to 1.0% (w/w) of MgSt can be sufficiently effective in reducing ejection force and punch sticking [147, 148].

However, incorporating MgSt, even at low concentrations, is known to cause undesirable problems, such as deteriorated tablet tensile strength [115, 149], increased tablet friability [150], delayed tablet dissolution performance [82, 151-153]. Also, lubrication efficiency of MgSt depends on crystal form [79, 154], chemical purity [155], and particle size of MgSt [78, 155]. The sensitivity of tabletability to lubrication depends on mechanical properties of the formulation. For example, plastic materials undergo significant reduction in tablet tensile strength when lubricated with MgSt but brittle materials do not [115]. This can be explained by the bonding area and bonding strength (BA-BS) interplay [145]. MgSt is a material with extremely low bonding strength. Thus, bonding between MgSt covered surfaces would be weak [115]. However, new surfaces created through extensive breakage

of brittle materials during compaction favors bonding between fresh particle surfaces free from MgSt. Moreover, the hydrophobic MgSt slows down wetting and, therefore, dissolution. Such unexpected dissolution slowdown may lead to undesired consequence in biopharmaceutical performance of poorly soluble drugs [156]. Owing to these problems, alternatives to MgSt have been continuously explored with varying degree of success [157-160].

1.2.3.4 Sodium lauryl sulfate

Sodium lauryl sulfate (SLS), also known as sodium dodecyl sulfate (SDS), is a synthetic alkaline anionic surfactant [161]. It is usually prepared by the sulfation of commercially available lauryl alcohol, followed by neutralization with sodium hydroxide. The chemical formula of SLS is $CH_3(CH_2)_{11}OSO_3Na$ and the molecular weight is 288.38 g/mol [162]. Besides the well-known solubilization function [163-167], SLS can also be used as emulsifying agent [168], penetration enhancer [169], as well as lubricant [84, 170]. It is commonly found in household products, but has also been approved by FDA as an excipient in varieties of dosage forms including tablets. Examples of marketed tablet products containing SLS are Brufen®, Janumet®, Nexavar®, Risperdal®, Sustiva®, and Tarceva® [161].

For SLS used in tablet, studies have confirmed the dissolution enhancement effects for poorly water-soluble drugs [165, 171-174]. Compared with the hydrophobic MgSt, SLS does not decrease the effective tablet-solvent interfacial area during dissolution, therefore,

does not negatively impact the dissolution rate. In addition, this dissolution enhancement is attributed by the improved penetration of water into tablets, which leads to more available API surfaces exposed to solvent, thus greater dissolution performance. In other words, the wettability of tablet is increased by incorporating SLS in the tablet [84]. However, as the amount of SLS used in a tablet as dissolution enhancer is small, change of pH in microenvironment around the tablet-solvent interface is less likely. Similarly, the solubility of API will not be increased by SLS before the concentration of SLS reach the CMC value and formation of micelles [175].

Due to the unfavored impacts of MgSt on tablet mechanical properties and dissolution performance, investigation of the lubrication effects of more hydrophilic SLS in tablet formulation received increased attentions over these years [84, 170, 176, 177]. Lubrication efficiency of SLS has been studied in common tablet excipients such as MCC and lactose. The mechanical properties of formulation are found to have great impacts on the lubrication property of SLS. For example, SLS is more effective at reducing ejection force in more plastic material. For extremely brittle material, SLS is not as effective as MgSt. However, increasing the amount of SLS in tablet formulation may increase the lubrication efficiency without significantly impacting tablet properties [84, 178]. In addition, studies show that SLS is effective at reducing ejection forces but not for reducing punch sticking. Therefore, people suggest using the combination of SLS and MgSt in formulation to simultaneously achieve optimized lubrication efficiency and dissolution enhancement without negatively impacting tablet properties [177].

One of the drawbacks of using SLS in tablet formulation is the incompatibility with API. Chemical reactions between ionized SLS and API at certain conditions leads to formation of insoluble salt, which significantly decreases the drug dissolution and therapeutic effects [179]. Studies also found that adding too much SLS in tablet formulations lead to failures in film coating [180].

Despite the previous studies on use of SLS in tablet formulation as lubricant or dissolution enhancer, the use of SLS in a DC tablet formulation remains empirical. Therefore, a systematic assessment of SLS for delivering both adequate lubrication and wetting without unduly deteriorating tableting performance is still required.

1.2.3.5 Poloxamers

Poloxamers are a group of nonionic triblock copolymers that consist of a central hydrophobic block of polypropylene glycol (PPG) flanked by two hydrophilic polyethylene glycol (PEG) [181]. The molecular formula and weight vary based on the length of PPG and PEG blocks. It is freely soluble in water and has a relatively high HLB value up to 30 [182]. Varying length of polymer blocks results in varieties of poloxamers with different properties. Nomination of poloxamer always starts with letter P, followed by a three-digit number, which is the fastest way to decode a poloxamer. The first two digits multiplied by 100 indicates the molecular weight of the PPG and the last digit multiplied by 10 represents the percentage of PEG content [183].

Among the commercially available poloxamers, P188 and P407 are two of the most commonly used tablet excipients [184-187]. They are white free flowing powder with great water solubility. While P188 or P407 does not significantly absorb water, they do become hygroscopic at RH higher than 80% [188]. Because of the coexistence of hydrophobic and hydrophilic chains, they are amphiphilic and thus used in pharmaceutical formulations as surfactants [189], solubilizing agents [190-192] and emulsifying agents [193, 194]. In addition, they can also be used as therapeutic agents. For example, P407 was used in contact lens liquid [195] and P188 was administered orally to treat constipation [196]. Recently, P188 and P407 were found to have certain lubrication properties, which can be potentially developed as a novel tablet lubricant to substitute the MgSt. The lubrication efficiency of P188 and P407 were analyzed in both pure excipients such as MCC or lactose, as well as in drug formulation [197-200]. Comparison with different tablet lubricants shows that both P188 and P407 has greater lubrication efficiency than other water-soluble lubricants, but lower than MgSt. However, the experimental conditions used such as compaction speed is not close to real manufacture and systematical evaluations of these two poloxamers on single component excipients are missing.

1.3 Thesis Organizations

Chapter 2

In chapter 2, we report surprisingly large deterioration in tabletability of microcrystalline cellulose by hand mixing, which indicates high mixing intensity of this process. To ensure reproducibility of future tabletability assessment of powders, hand-mixing should be avoided and mixing conditions need to be carefully controlled and reported.

Chapter 3

In chapter 3, we evaluated the effectiveness of sodium lauryl sulfate (SLS) as a tableting lubricant. Particle engineering was integrated to mitigate problems associated with hydrophobic lubricants. We showed that SLS exhibited comparable or higher lubrication efficiency than MgSt in all formulations except which containing large amounts of lactose. Dissolution of celecoxib tablets containing SLS is improved over MgSt-containing tablets due to the improved wetting. This strategy was further applied to chapter 4.

Chapter 4

In chapter 4, we systematically evaluated two poloxamers, P188 and P407, for their suitability as alternative tablet lubricants. We showed that both poloxamers exhibit acceptable lubrication efficiency without negatively impacting tabletability in both plastic MCC and brittle lactose. The performance of both poloxamers at a 2% level was also evaluated against 1% MgSt as lubricant in an experimental tablet formulation of ritonavir. The use of 2% poloxamer led to better lubrication, higher tabletability, and enhanced in vitro drug release.

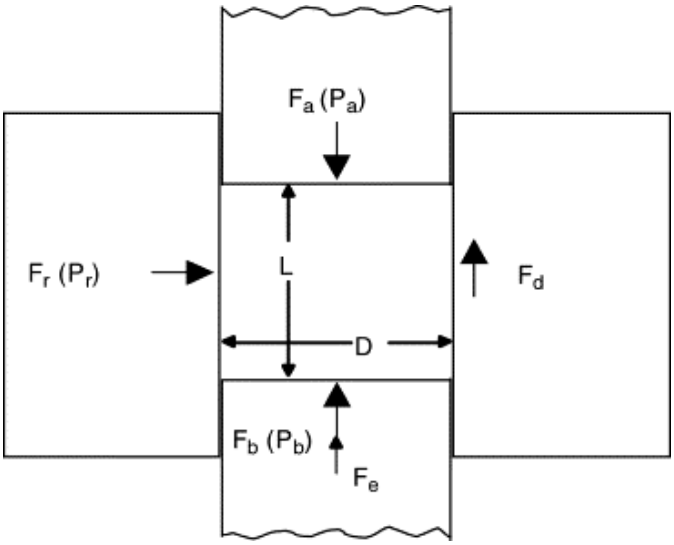

Figure 1.1 Forces and stresses during powder compression [139]

CHAPTER 2. PROFOUND TABLETABILITY DETERIORATION OF MICROCRYSTALLINE CELLULOSE BY "HAND MIXING" WITH MAGNESIUM STEARATE

2.1 Summary

Magnesium stearate (MgSt) is a common lubricant used in tablet formulations to facilitate tablet manufacturing by reducing ejection force. However, the use of MgSt in plastic powders may deteriorate tabletability and slow down drug dissolution. Here, we report surprisingly large deterioration in tabletability of microcrystalline cellulose by hand mixing, which indicates high mixing intensity of this process. To ensure reproducibility of future tabletability assessment of powders, hand-mixing should be avoided and mixing conditions need to be carefully controlled and reported.

2.2 Introduction

Ejection force (EF) is one of the important parameters that affect tablet manufacturing in pharmaceutical industry [1]. High EFs often correlate with tablet defects, such as tablet chipping, capping, and lamination [2-4]. EF is the external force required to overcome the frictional force between die-wall and tablet, a prerequisite for pushing the tablet out of die. EF positively depends on the residual die-wall stress, contact area, and friction coefficient [5]. To reduce the die-wall friction and EF, a lubricant is commonly used to lower the friction coefficient. Among the pharmaceutical lubricants, magnesium stearate (MgSt) is the most commonly used during tablet compaction [6]. MgSt is a boundary lubricant, which functions by reducing EF through forming a thin layer between the particle surface and die wall [3, 7, 8].

However, the use of MgSt can potentially deteriorate some tablet properties, including tabletability and dissolution [9-13]. Tabletability characterizes the relationship between tablet tensile strength and compaction pressure [14]; and it depends on both material properties and processing parameters [15]. A tensile strength of 2 MPa is sufficient for most pharmaceutical tablets to withstand stresses encountered during downstream processing, such as coating, packaging, and transportation [16]. Tablets with a low tensile strength corresponds to high friability, which should not exceed 1% of weight loss [17]. It is known that mixing with MgSt often reduces powder tabletability [9, 10, 18]. Therefore, the effect of lubrication with MgSt on tabletability of formulations is routinely assessed in tablet product development. [10, 13, 19-22]. Previous studies on the effects of lubrication

mainly focused on understanding the influence of lubricant type [23], lubricant amount [24], mixing time [21], and mixing intensity [25] on tableting performance and tablet quality.

The effects of mixing intensity are relevant to tablet manufacturing as tablet manufacturing is carried out using blenders with different sizes or designs, which inherently exert different mixing intensities, during the course of product development and scale up. If not properly accounted form, such difference can sometimes lead to issues with powder and tablet properties during commercial manufacturing [26-28]. Although the potential effects of mixing intensity are recognized, their magnitude is under-appreciated. Here, we report a case of surprisingly high sensitivity of powder tabletability to mixing intensity.

A grade of microcrystalline cellulose (MCC), after hand mixing with 0.25% MgSt for 2 min and equilibration at 60% relative humidity (RH), exhibited unexpectedly low tabletability (tensile strength < 3 MPa at 350 MPa, Figure 2.1), which was significantly ($p < 0.001$) lower than the tabletability of the same grade of MCC lubricated with 0.5% MgSt using a low intensity blender for 2 min at 22 rpm (~12 MPa tensile strength at 350 MPa) [29]. Such profoundly lower tabletability of the hand mixed sample, despite the low amount of MgSt, cannot be explained by possible variations in relative humidity [30], batch-to-batch variability in MgSt [31, 32] and batch-to-batch variability in MCC [33] among these studies. A logical explanation of this observation is that the intensity of hand mixing was much higher than that of low intensity blending, which magnified the

deteriorating effect of MgSt on tabletability. If this hypothesis is proven, hand-mixing during small scale studies of powders needs to be carefully controlled as the variations in mixing intensity can potentially introduce large variations in powder tableting performance. Consequently, surprises may be encountered during tableting studies and scale up of tablet manufacturing processes. We have designed this study to evaluate the impact of the variability of hand mixing intensity on tabletability, in comparison to mixing time and intensity using typical laboratory blenders.

2.3 Materials and methods

2.3.1 Materials

Microcrystalline cellulose (MCC, Avicel PH102, FMC Biopolymer, Philadelphia, PA) and magnesium stearate (MgSt, Covidien, Dublin, Ireland) were used as received.

2.3.2 Methods

2.3.2.1 Powder blending

Two commonly used laboratory scale blenders, a low intensity blender (V-shaped blender, Blender Master, Patterson Kelley, East Stroudsburg, PA) and a high intensity blender (Turbula, Glen Mills Inc., Clifton, NJ), were used to prepare mixtures of MCC with 0.25% (w/w) of MgSt. The V blender was run at 25 rpm, while the Turbula was run at 49 rpm, for 10, 20, 40, 60 min. The batch size was 40 g.

Given the popularity in laboratory research on powder compaction, hand mixing by a group of 10 people was also performed to evaluate variability of this blending technique. Each person was asked to hand mix a bottle of MCC with 0.25% (w/w) MgSt (added by the same operator) for 2 min without specific instructions on how to mix. All lubricated MCC powders were stored in a humidity chamber (~32% relative humidity) over a saturated magnesium chloride solution for at least 48 hours prior to use.

2.3.2.2 Powder compaction and tablet tensile strength

Powders were compressed on a Universal Materials Testing Machine (Model 1485, Zwick-Roell MaterialPrufung, Germany) using flat-faced round tooling with a diameter of 8 mm. Powder was manually filled into the die and compaction pressures ranging from 50 MPa to 350 MPa were applied with a punch velocity of 2 mm/min. All tablets were allowed to relax overnight before measuring their thickness (h) and diameter (d) using a digital caliper (Mitutoyo, Takatsu-ku, Kawasaki, Kanagawa Prefecture, Japan). Tablet flashing was carefully removed before measuring thickness [34]. Tablet weight was determined using an analytical balance (Mettler-Toledo, Columbus, OH). Tablet diametrical breaking force (F) was determined using a texture analyzer (TA-XT2i; Texture Technologies Corporation, Scarsdale, NY) at a speed of 0.01 mm/s with a 5 g trigger force. Tablet tensile strength was calculated using Eq. (2.1), following a standard procedure [35].

$$\sigma = \frac{2F}{\pi dh} \qquad \text{Eq. (2.1)}$$

Laboratory RH was maintained at approximately 32% by a humidifier during the entire period of this study.

2.3.2.3 Tabletability, compressibility, compactibility, and tablet brittleness

Tabletability describes the dependence of tablet tensile strength on compaction pressure of a powder [14]. Compressibility describes the dependence of tablet porosity on compaction pressure. Compactibility describes the dependence of tablet tensile strength on porosity [36]. Tablet porosity was calculated using Eq. (2.2).

$$\varepsilon = 1 - \frac{\rho}{\rho_t} \qquad \text{Eq. (2.2)}$$

where the true density (ρ_t) of 1.45 g/cm^3 for MCC was used [37] and tablet density was calculated from tablet weight and dimensions.

Tablet brittleness was obtained by using the tablet diameter and maximum elastic deformation according to Eq. (2.3). The maximum elastic deformation was obtained by extracting the force-displacement data using MATLAB according to a previously described method [38].

$$TBI = \frac{tablet\ diameter}{maximum\ elastic\ deformation} \qquad \text{Eq. (2.3)}$$

2.4 Results and discussion

2.4.1 Effects of mixing intensity and duration on the tabletability of MCC

The effect of mixing intensity on tabletability of MCC is shown in Figure 2.2a. After 10 min of mixing in the higher intensity Turbula, the tabletability of MCC is approximately 40% lower than that mixed in the lower intensity V blender. The significantly different tabletability can be explained by the different degrees of MgSt coverage on the surface of MCC. More intense mixing led to more efficient dispersion and spread of MgSt, which are prerequisites for coating MCC particles. A larger surface coverage leads to more reduction in tabletability due to the known low bonding strength of MgSt [9, 13]. This is supported by the significantly lower compactibility of MCC mixed in Turbula (Figure 2.2b)

For both V Blender and Turbula, a longer lubrication time led to lower tabletability (Figure 2.3). Such a large difference in tabletability cannot be attributed to different bonding area (BA) since the deformation of MCC particles is largely independent of surface coverage by MCC and permanent deformation of particles is expected to be similar. Therefore, according to the BABS interplay model [14, 39], the different tabletability likely resulted from their different bonding strength (BS). This is consistent with the common observation that the presence of MgSt on particle surface decreased the BS between MCC particles [40].

The rate of tablet tensile strength reduction by lubrication with MgSt was faster when the high intensity Turbula was used (Figures 2.3 and 2.4). This is also attributed to the fact

that the distribution of MgSt on to the surface of the MCC particle is more efficient under higher mixing intensity because of the higher shear stresses among particles during blending. Tablets with tensile strength higher than 2 MPa could be prepared at 50 MPa for MCC mixed for 60 min in V blender (low mixing intensity, Figure 2.3a). However, 100 MPa compaction pressure was needed to attain a tensile strength of 2 MPa when MCC was mixed for 40 min in Turbula (higher mixing intensity) (Figure 2.3b). This can be explained by the more coverage of MCC surface by MgSt in the higher intensity Turbula, which led to not only more inter-particular collision but also greater extent of shear during each collision. This is consistent with the observation that a large number of shear event between MgSt and host particles deteriorated tablet strength [41].

Results so far confirm that both the larger number of particle collisions (mixing time) and more extensive shear (mixing intensity) deteriorate tabletability of MCC because of the more efficient surface coating by MgSt. The same mechanism can explain the severely deteriorated tabletability of MCC in hand-mixed samples (Figure 2.1), provided the intensity is indeed high during hand-mixing.

2.4.2 Effects of hand mixing on the mechanical properties of MCC

The tabletability of ten batches of MCC powders hand mixed with 0.25% MgSt varied considerably (Figure 2.5), which followed the descending order of S9 ≈ S4 > S8 > S1 > S3 > S6 > S7 ≈ S2 > S5 > S10. The difference in tensile strength at the same pressure

between the highest and lowest samples was more than 50%. The magnitude of variations is larger if the tabletability data of the hand mixed MCC in Figure 2.1 is considered. However, that data was obtained using a different batch size and under a different environment RH.

To better understand the variations of tabletability, compressibility and compactibility of these samples were also compared (Figures 2.6a, b). The porosity of these tablets at the same pressure followed the descending order of: S4 > S9 > S1 > S3 > S6 > S8 > S5 > S2 > S7 > S10 (Figure 2.6a). Therefore, their compressibility followed the reverse order as a lower porosity corresponds to higher compressibility [36]. Lower tablet porosity corresponds to larger bonding area, which favors stronger tablet. The noticeable effect on compressibility is somehow surprising given the small amount (0.25%) of MgSt used as lubricant. This is possible only if the BS among MCC particles was significantly different, which allowed different degrees of elastic recovery during unloading and subsequent relaxation of tablets.

The compactibility of these MCC samples indeed significantly differed (Figure 2.6b). Correspondingly, tensile strength at zero porosity (TS_0), obtained by extrapolating tensile strength to zero porosity using exponential functions, are also significantly different, following the descending order of S9 ≈ S4 ≈ S8 > S1 > S3 > S6 > S7 ≈ S2 > S5 > S10 (Table 2.1). The order of TS_0 is closely similar to that of tabletability, suggesting that BS

dominates the BA-BS interplay in these samples despite BA also varied among these tablets (Figure 2.6a).

Lubrication with MgSt was shown to increase tablet brittleness (Paul and Sun, 2017). It is also expected that different distributions of MgSt in MCC tablets due to different mixing intensity and duration should also affect tablet brittleness. For each powder, tablets prepared under a higher compaction pressure are generally less brittle, as shown by lower TBI values (Figure 2.7a). In the entire compaction pressure range studied, none of the samples showed a TBI value higher than 150, which is a threshold value corresponding to unacceptably high friability [38]. This is consistent with the high plasticity of MCC. As observed before, tablet brittleness and tablet tensile strength data followed a power law relationship (Figure 2.7b) [42].

2.5 Conclusion

We have confirmed that both lubrication intensity and mixing duration are important process parameters that can potentially have a profound impact on tabletability of formulations. Hand mixing, which is generally more efficient than mixing using a laboratory V-blender or Turbula, leads to profound deterioration in tabletability of MCC. Given the widely variable mixing efficiency, the term “hand mixing” is not a rigorous description of mixing. For compaction studies to be reproducible, a standard operator-independent procedure for laboratory powder mixing is required. Mixing parameters, such

as batch size, mixing frequency, mixing duration, should be accurately recorded and reported.

Table 2.1. Tensile strength at zero porosity (TS_0) of MCC hand mixed for 2 min with 0.25% MgSt.

Sample	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
TS₀	8.33	6.75	7.41	8.77	6.08	7.19	6.63	8.73	8.83	5.74
(MPa)	(0.03)	(0.07)	(0.08)	(0.07)	(0.08)	(0.07)	(0.07)	(0.08)	(0.08)	(0.06)

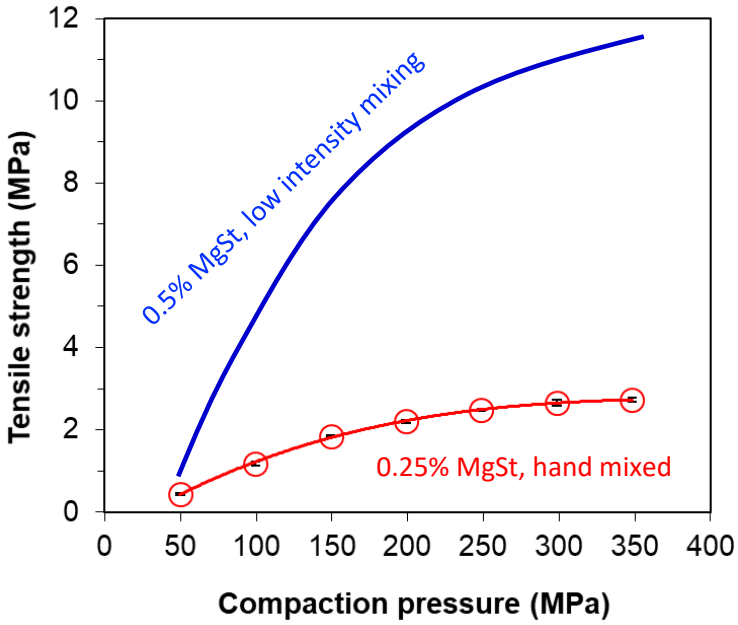

Figure 2.1. Tabletability of MCC lubricated with 0.25% MgSt (hand mixed in this study, n=3) and 0.5% MgSt (low intensity mixing, [29])

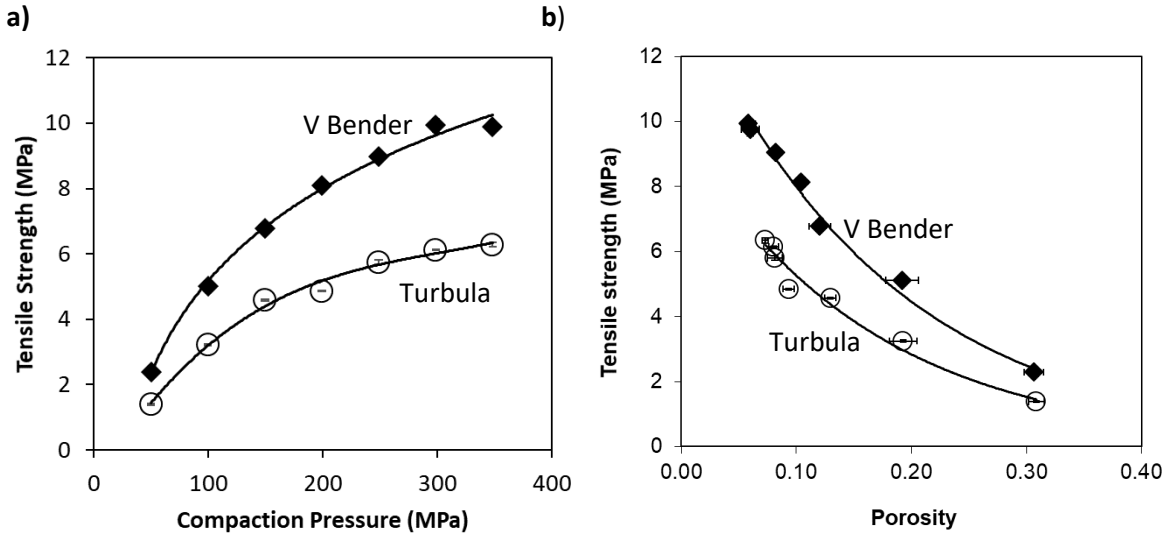

Figure 2.2 (a) Tabletability and (b) compactibility of MCC lubricated with 0.25% MgSt after mixing for 10 min in the V Blender and Turbula (n=3).

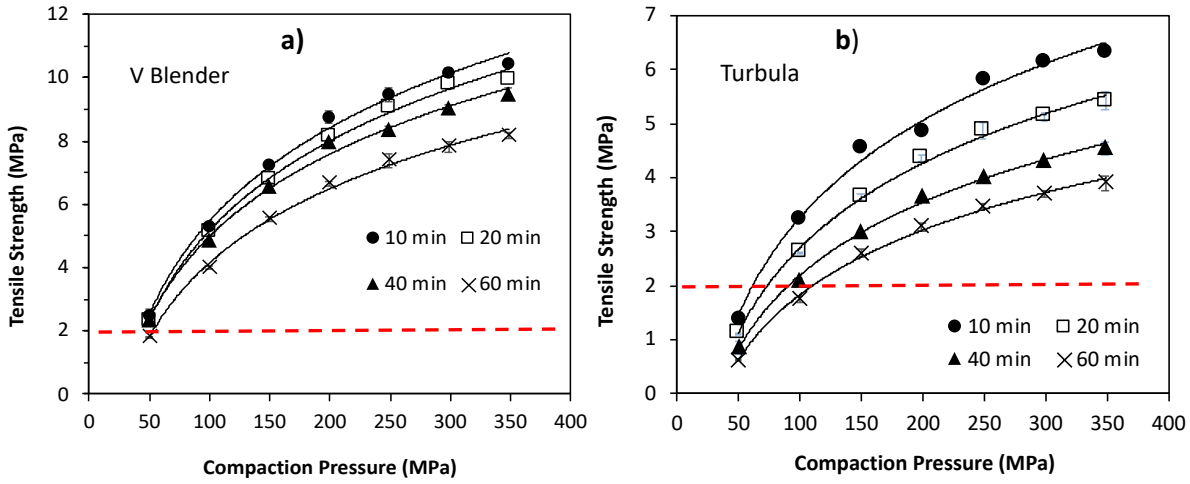

Figure 2.3 Effect of lubrication time on the tabletability of MCC mixed using (a) V-Blender; (b) Turbula (n=3).

Figure 42.3 Effect of lubrication time on the tabletability of MCC mixed using (a) V-Blender; (b) Turbula (n=3).

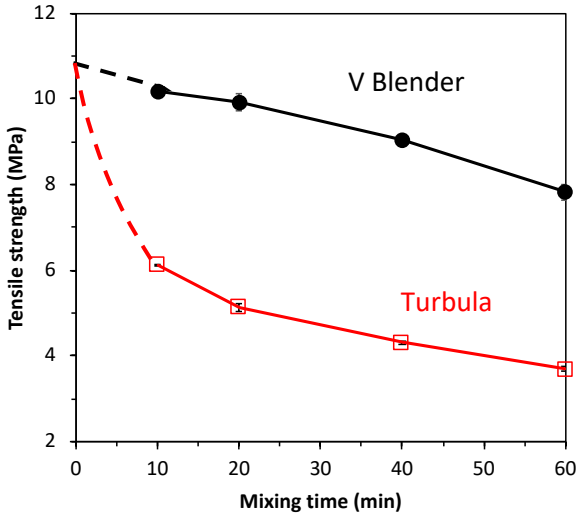

Figure 2.4 Effects of mixing time on the tensile strength of MCC at 300 MPa compaction pressure (n=3).

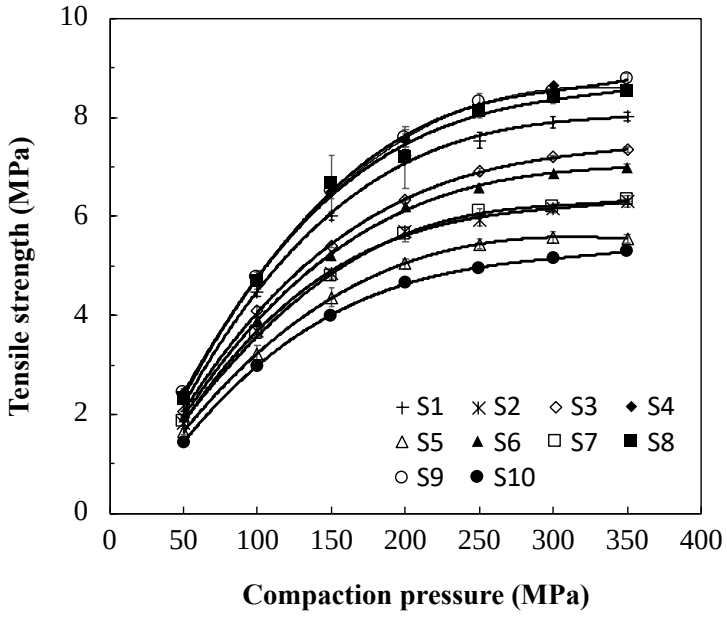

Figure 2.5 Tabletability of MCC with 0.25% MgSt hand mixed for 2 min by 10 different operators (n=3).

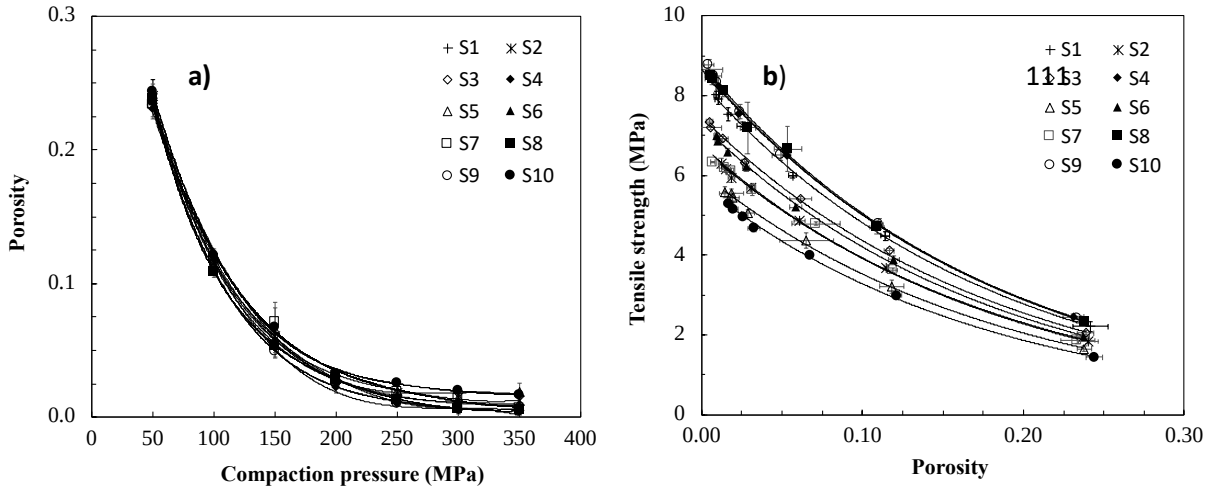

Figure 2.6 (a) Compressibility and (b) compactibility of MCC powders hand mixed for 2 min with 0.25% MgSt (n=3)

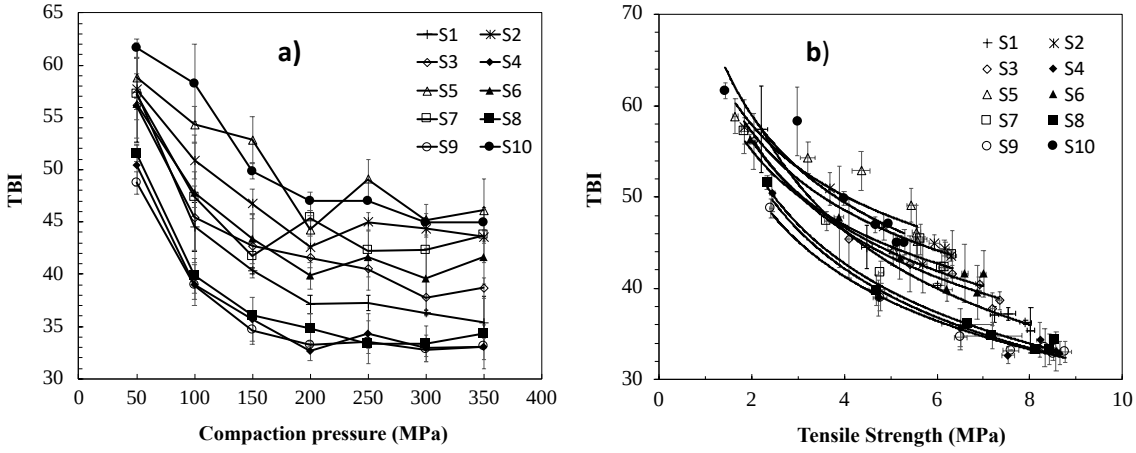

Figure 2.7 Relationships between TBI and (a) compaction pressure and (b) tensile strength (lines are power law functions obtained by non-linear regression). (n=3)

CHAPTER 3. A SYSTEMATIC EVALUATION OF DUAL FUNCTIONALITY OF SODIUM LAURYL SULFATE AS A TABLET LUBRICANT AND WETTING ENHANCER

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3.1 Summary

Appropriate lubrication is important in tablet manufacturing as it lowers punch sticking propensity and protects tooling by reducing friction between die wall and tablet during tablet manufacturing. Most commercial lubricants negatively impact tabletability and dissolution. A delicate balance is usually attained by trial and error to identify the optimal level of lubricant in a tablet formulation. In this work, we have evaluated the effectiveness of sodium lauryl sulfate (SLS), a surfactant, as a tableting lubricant. If adequate lubrication efficiency is achieved, the use of SLS may be suitable to mitigate problems associated with hydrophobic lubricants. Results show that SLS, when applied in the proper amount to typical pharmaceutical powder mixtures, achieved lubrication efficiency comparable to a grade of magnesium stearate (MgSt) without deteriorating tabletability. Moreover, SLS-containing tablets of celecoxib also exhibited improved *in vitro* dissolution compared to MgSt-containing tablets. The enhancement in dissolution properties was attributed to the improved wetting by the dissolution medium due to the presence of SLS.

3.2 Introduction

The tablet dosage form contributes to more than 70% of all marketed drug products [1]. Advantages of tablets include accurate dosing, good stability, low manufacture cost, and high patient compliance [1]. The manufacture of tablets primarily involves three common processes: direct compression (DC), dry granulation (DG), and wet granulation (WG). Among them, DC is the most desirable process for tablet manufacturing in pharmaceutical industry due to its simplicity and economy [2].

The successful development of high quality tablet products must overcome several potential pharmaceutical deficiencies presented by active pharmaceutical ingredients (API), such as poor mechanical property [3], bad taste [4], poor stability [5], and low solubility [6]. An acceptable tablet must be strong enough to withstand downstream processes, such as coating and transportation. On the other hand, overly strong tablets may cause problems, such as prolonged disintegration and slow drug release [7]. Therefore, optimal tablet strength must be determined based on comprehensive evaluation of pertinent performance expected of a tablet product. One process parameter that can impact the suitability of the tablet is the ejection force, which plays a distinct role in tablet manufacturing [8]. High ejection force should generally be avoided during a successful tablet manufacturing process to not only preserve the tooling but also maintain the integrity of tablet products [9]. Tablet ejection force, in turn, is affected by particle size, shape and roughness [10], API type, and API loading.

The most effective approach to reduce ejection force is by adding an external lubricant, which forms a thin film between the die wall and tablet to facilitate easy slippage at the contact points [11]. Lubrication efficiency is defined as the effectiveness of ejection force reduction by applying a lubricant. It depends on both the type and amount of lubricant in the formulation blend [12, 13] and tableting speed [14]. Magnesium stearate (MgSt) is the most widely used lubricant, due to its high lubrication efficiency [15, 16]. Depending on formulation, 0.25% to 1.0% (w/w) of MgSt is usually sufficient in reducing ejection force and punch sticking [17, 18].

However, incorporating MgSt, even at low concentrations, is known to cause undesirable problems, such as deteriorated tablet tensile strength [19, 20], increased tablet friability [21], and delayed tablet dissolution performance [22-25]. Also, lubrication efficiency of MgSt depends on crystal form [16, 26], chemical purity [27], and particle size of MgSt [11, 27]. The sensitivity of tabletability to lubrication depends on mechanical properties of the formulation. For example, plastic materials undergo significant reduction in tablet tensile strength when lubricated with MgSt but brittle materials do not [19]. This can be explained by the bonding area and bonding strength (BA-BS) interplay [28]. MgSt is a material with extremely low bonding strength. For plastic materials, this results in weak bonding between MgSt-covered surfaces [19]. For brittle materials, new surfaces created through extensive particle fracture during compaction favors bonding because fresh particle surfaces are free from MgSt. Moreover, the hydrophobic MgSt coat tends to slow down wetting and, therefore, dissolution of API. Such dissolution slowdown may lead to undesired consequence in biopharmaceutical performance of poorly soluble drugs [29].

Owing to these problems, many alternatives to MgSt have been continuously explored, including but not limited to other metallic salts of fatty acids, glycerin fatty acid esters, fatty acids, sucrose fatty acid esters, talc, PEG 6000, glycerin bibehenate, sodium stearyl fumarate, and magnesium lauryl sulfate. [30-37]. However, MgSt remains a first choice lubricant due to its superior lubrication efficiency.

The evaluation of sodium lauryl sulfate SLS as a possible dual functionality lubricant and wetting agent in this work is justified based on the following: a) SLS has been suggested to have lubricating function [38] and tested for its lubricating ability (Alexander, 1998; Michelucci et al., 1988; Wang et al., 2010), b) SLS is a surfactant commonly used in pharmaceutical formulations to improve drug dissolution [39-45], and c) SLS can be prepared with high chemical purity. SLS was found to be more effective in reducing ejection force than stearic acid in a DC formulation, [46] but less effective than MgSt. [47] (Perrault et al., 2011) Therefore, more SLS than MgSt would be needed to achieve equivalent lubrication efficiency. Fortunately, unlike MgSt, the use of a larger amount of SLS to achieve adequate reduction in ejection force does not deteriorate API dissolution. However, SLS was found to influence tableting performance and it can be adverse to safety when take in a large amount. [38, 48] Thus, the amount of SLS cannot exceed a certain level in a formulation. At present, despite the prior separate research on use of SLS in tablet formulation, the use of SLS in a DC tablet formulation remains empirical. there is still the need for a systematic assessment of SLS for delivering both adequate lubrication and wetting without unduly deteriorating tableting performance.

3.3 Materials and methods

3.3.1 Materials

3.3.1.1 Individual components

Two DC grade tablet excipients, microcrystalline cellulose (MCC; Pharmacel 102, DFE Pharma; Goch, Germany) and lactose monohydrate (SuperTab 11SD; DFE Pharma; Goch, Germany) were used in this study. MCC was intended as a dry binder while lactose was used as a filler. Croscarmellose sodium (CCS, Ac-Di-Sol, FMC Biopolymer, Philadelphia, PA) was used as a disintegrant. Magnesium stearate (MgSt; Covidien, Dublin, Ireland) or sodium lauryl sulfate (SLS; Ward's Science, Rochester, NY) was used as lubricant. Celecoxib, a BCS class II drug (weak acid with p*K*a of 11.1), was selected as a model drug because of its low solubility, about 3.3 μM in water at 25 °C [49]. Consequently, the marketed Celecoxib capsules contain SLS to improve its wetting and dissolution.

3.3.1.2 Placebo and Active Formulations

Binary mixtures between MCC and lactose were prepared in 20% increments to cover a wide range of mechanical properties that may be encountered during tablet formulation. They were mixed with 5% CCS and an appropriate amount of MgSt or SLS to prepare different placebo formulations for evaluation. A formulation (Table 3.1) containing Celecoxib was also prepared to allow an examination on the impact of SLS on dissolution of a hydrophobic drug in addition to its lubrication efficiency and impact on powder flowability and tabletability.

In all control formulations, 1% MgSt was used as a benchmark. This is at the high end of the range of MgSt used in tablet formulations. The intension was to present a more challenging test to evaluate lubrication efficiency of SLS. The amount of SLS needed to exhibit comparable lubrication performance to 1% MgSt is likely sufficient for most formulations.

3.3.2 Methods

3.3.2.1 Blending

Powder blends (both placebos and the celecoxib formulation) were prepared by placing accurately weighed individual components, other than the intended lubricant, in a glass bottle (250 mL). The powder filled bottle was blended on a mixer (Turbula, Glen Mills Inc., Clifton, NJ) at a frequency of 49 rpm for 2 min. Subsequently, an appropriate amount of chosen lubricant was added to the bottle and the mixture was further blended for 5 min. The batch size was 40 g in all cases. All powders were equilibrated in a 33% relative humidity (RH) chamber at room temperature, for at least 48 hours before further uses.

3.3.2.2 Powder flow property measurement

Flowability of the blends was determined using a ring shear tester (RST-XS, Dietmar Schulze, Wolfenbüttel, Germany) at room temperature and 33% RH. Accuracy of the shear cell was verified using a limestone powder standard. Shear cell data were collected at 1 kPa pre-shear normal stress. During each test, maximum shear stresses under five normal

loads (230, 400, 550, 700, and 850 Pa) were used to construct a yield locus. Major principal stress (σ_n) and unconfined yield strength (f_c) were obtained from the yield locus by Mohr stress analysis using RST-CONTROL software (RSV 95). The flowability index, $ff_c = \sigma_n/f_c$, was used to characterize powder flowability [50]. A higher ff_c suggests better flow property.

3.3.2.3 Determination of powder true density

Because helium pycnometry cannot be used to determine accurate true density, ρ_t, of powders containing volatile water, true density of all formulations containing hygroscopic MCC in this study were obtained by the Sun method, which involves model fitting of tablet density (ρ) vs. compaction pressure (P) using Eq. (3.1) [51]:

$$P = \frac{1}{C}\left[(1-\varepsilon_c) - \frac{\rho}{\rho_t} - \varepsilon_c \ln\left(\frac{1-\frac{\rho}{\rho_t}}{\varepsilon_c}\right)\right] \qquad \text{Eq. (3.1)}$$

Where, 1/C and ε_c represent the plasticity parameter and critical porosity, respectively. A lower 1/C value means higher plasticity of the powder. For lactose formulation (no MCC), true density was calculated from the literature values based on compositions [38, 52, 53].

3.3.2.4 Powder compaction

Powder compaction was conducted at room temperature and approximately 33% RH. Powder blends were compressed on a compaction simulator (Presster; Metropolitan Computing Company, East Hanover, NJ) to simulate a 29-station Korsch XL400 tablet press using round flat-faced tooling (9.5 mm diameter). The dwell time was set at 20 ms,

corresponding to a linear speed of 0.423m/s (52,000 tablets/h). No pre-compression was used. Compression force, in-die thickness, ejection force, and take-off force were recorded at the end of each compression cycle. Tablets with approximately 300 mg of weight were prepared separately at 150 MPa compaction pressure for *in vitro* tablet disintegration and dissolution tests.

Tablet dimensions (thickness and diameter) were measured immediately after ejection using a digital caliper. Tablet weight was determined using an analytical balance. Tablet diametrical breaking force was determined using a texture analyzer (TA-XT2i; Texture Technologies Corporation, Scarsdale, NY) at a speed of 0.01 mm/s and 5 g trigger force. Tablet tensile strength was calculated from the diametrical breaking force and tablet dimensions using Eq. (3.2) [54]:

$$\sigma = \frac{2F}{\pi dh} \qquad \text{Eq. (3.2)}$$

Tabletability is the capacity of a powder to be transformed into a tablet of specified strength under the effect of compaction pressure. It can be assessed by the plot of tensile strength as a function of compaction pressure [55, 56]. Ejection force as a function of compaction pressure was used to evaluate lubrication efficiency.

3.3.2.5 Contact angle measurement

Sessile drop contact angle measurements were performed using a contact angle analyzer (DMCE1, Kyowa Interface Science, Saitama, Japan) with attached FAMAS software to assess the wettability of tablets. Ultrapure distilled water (Milli-Q) was used as the wetting liquid. Drops with approximately 1μL of volume were generated with a micrometric syringe and placed on the tablet surface. The measurements were performed at room temperature (25°C). Immediately after stabilization, an image of the drop was captured every second over a period of 20 s. Three measurements were carried out each using a different tablet.

3.3.2.6 Tablet disintegration and dissolution

Disintegration time of the tablet was measured in de-ionized water at 37 ± 0.5 °C using a disintegration tester (Di-200, Pharma Alliance Group Inc., CA) with a frequency of 30 cycles/min. Disintegration time was recorded for each tablet as the time taken for all solid passing through the wired mesh (n = 6).

A USP Type II apparatus (Varian 705 DS, Varian, Palo Alto, CA) was used for dissolution test. The 900 mL dissolution medium (pH 1.2 HCl solution in water or 6.8 sodium phosphate buffer) was maintained at 37 ± 0.5°C and the paddle speed was set to 75 rpm. At each time point, 4 mL sample was withdrawn using a pipette from the dissolution medium, passed through a 0.45 μm membrane filter, and analyzed using a UV spectrometer (Beckman Coulter, Brea, CA) at 252 nm. The concentration of drug in the dissolution

medium was obtained from the UV absorption based on a previously constructed standard curve. The amount withdrawn for analysis was replaced with fresh dissolution medium immediately after each withdrawal to maintain a constant volume of the dissolution medium.

3.4. Results and discussion

3.4.1. Lubrication efficiency

Lubrication efficiency of SLS was compared to MgSt using placebo formulations of MCC, lactose, and their mixtures. MCC and lactose are common plastic and brittle tablet excipients, respectively. The use of these two excipients and their mixtures was intended to cover a wide range of mechanical properties for testing lubrication efficiency of SLS. Although MCC-lactose binary mixtures containing 20%, 40%, 60%, and 80% of MCC were studied (Figure. 3.S1), only the mixture containing 60% MCC is discussed here because of similarity in trend (Figure. 3.1).

For plastic MCC placebo formulation, lubrication efficiency of 1% SLS was comparable to that of 1% MgSt since they exhibited similar ejection force profiles (Figure. 3.1a). However, for the placebo formulation containing 60% MCC and 40% lactose mixture (Figure. 3.1b) and brittle lactose (Figure. 3.1c), 1% SLS was not as effective as 1% MgSt. Very high ejection force was observed when the lactose placebo formulation lubricated with 1% SLS was compressed at high pressures (data not shown). This was accompanied by powder adhering to the die inner surface (Figure. 3.S8). When the amount of SLS was

increased, lubrication efficiency improved. For the placebo formulation of the 60% MCC and 40% lactose mixture, 2% SLS exhibited better lubrication efficiency than 1% MgSt (Figure. 3.1b). Formulations containing 80% or 40% MCC showed a similar trend (Figure. 3.S1a and 3.S1b). For the placebo formulation of lactose, 2% SLS was still not as effective as 1% MgSt but 5% SLS was (Figure. 3.1c). The higher level of SLS required for the more brittle lactose placebo formulation, and likely other brittle formulations, is not an issue if it does not negatively impact performance of the tablet. At the same level of lubricant, higher amount of lactose in the formulation always corresponded to higher ejection force (Figure. 3.1 and 3.S1). Higher compaction pressure leads to either higher or lower ejection force, depending on the mechanical properties of the formulation and range of compaction pressure. For MCC placebo formulation lubricated with 1% MgSt, 1% SLS, or 2% SLS, ejection force decreased with increasing pressure after brief rise in the low pressure range (Fig. 3.1a). This is similar to the behavior of MCC [14]. For lactose placebo formulation lubricated with 1% MgSt or 5% SLS, ejection force continued to increase with increasing compaction pressure (Fig. 3.1c), which is similar to the behavior of compressible sugar [14] .

It should be mentioned that 1% MgSt is on the high end of its typical usage in a tablet formulation, corresponding to effective lubrication for most formulations. For a typical formulation with mechanical properties similar to the placebo formulation of the 60% MCC + 40% lactose mixture, 2% SLS exhibits lubrication efficiency similar to 1% MgSt.

Particle size was found to influence lubrication efficiency of MgSt [16]. Similarly, lubrication efficiency of smaller SLS was also higher. [57] Smaller SLS is more effective in reducing ejection force likely because they can more effectively coat particle surfaces. The grade of SLS used in this work had much larger particle size than MgSt (Figure. 3.2). Specific surface areas of SLS and MgSt by nitrogen adsorption using the BET method were 0.13 ± 0.01 and 6.42 ± 0.03 m^2/g ($n = 2$), respectively. Lubrication efficiency of SLS would have been better, had smaller SLS been available for this study. The effect of size of SLS on lubrication efficiency needs to be further examined in a future study to guide the optimal use of SLS in tablet formulations. More efficient lubrication by smaller SLS means sufficiently reduced ejection force can be attained using less SLS. This is important for avoiding possible toxicity by a high dose of SLS.

3.4.2 Effects on compression properties

The tabletability deteriorated with increasing lactose concentration in the placebo formulations (Figure. 3.3). This corroborates the fact that lactose exhibits significantly poorer tabletability than MCC [58]. For the placebo formulation of MCC, lubrication with 1% MgSt led to lower tablet tensile strength than 1% or 2% SLS. Increasing SLS concentration from 1% to 2% led to a lowering of the tablet tensile strength. However, the tabletability of the formulation containing 2% SLS is still significantly better than that containing 1% MgSt. Thus, for MCC, the use of 2% SLS is as effective as 1% MgSt in terms of simultaneously reducing ejection force and improving the tabletability.

For the placebo formulation of the 60% MCC + 40% lactose mixture, the rank order in tabletability is the same as that for MCC, 1% SLS > 2% SLS > 1% MgSt. Thus, 2% SLS for this powder is an acceptable alternative to 1% MgSt considering its slightly better lubrication efficiency than 1% MgSt (Figure. 3.1b) and the better tabletability (Figure. 3.3b). Formulations containing 80%, 40% and 20% MCC showed a similar trend (Figures. 3.S1 and 3.S2). However, for the placebo formulation of brittle lactose, tabletability did not differ significantly among the three lubricated powders containing 2% SLS, 5% SLS, or 1% MgSt except at very high pressures (Figure. 3.3c). This is consistent with the known insensitivity of tabletability of brittle materials to lubrication because of extensive fragmentation during compaction [59, 60].

In order to better understand the origin of the different tabletability, the compressibility and compactibility were analyzed (Figures. 3.S3 and 3.S4). Compressibility is the ability of a material to undergo a reduction in volume as a result of an applied pressure. It is usually evaluated by the plot of tablet porosity vs. compaction pressure. Compactibility is the ability of a powdered material to be transformed into tablets with strength during densification. It is usually evaluated by a plot of tablet tensile strength vs. tablet porosity. Therefore, for each formulation that contained MCC, true density was derived by model fitting. The plasticity parameter, 1/C, obtained from fitting tablet density vs. pressure data can be used to evaluate plasticity of the blends (Figures. 3.S5 - 3.S7). The results show that plasticity of mixtures decreased (increasing 1/C value) as the concentration of lactose increased (Tablet 3.S1). This is consistent with the higher plasticity of MCC than lactose.

The compressibility of placebo formulations containing MCC or 80% MCC + 20% lactose was insensitive to changes in lubricant type and amount as their compressibility profiles were essentially the same when 1% MgSt, 1% SLS, or 2% SLS was used to lubricate the formulation (Figure. 3.S3). As the concentration of lactose increases, lubrication by SLS resulted in better compressibility (i.e., lower porosity) than MgSt. For the placebo formulation containing the 60% MCC + 40% lactose mixture, 2% SLS led to slightly better compressibility, i.e., lower porosity at the same pressure, than 1% MgSt and 1% SLS (Figure. 3.4b). The compressibility of lactose placebo formulation followed the descending order of 5% SLS > 2% SLS ≈ 1% MgSt. The slightly lower compressibility of 1% MgSt formulation than 5% SLS formulation is attributed to the more efficient particle rearrangement and packing, which led to lower tablet porosity under pressure when SLS was used.

The lower tablet porosity indicates larger bonding area in lactose tablets containing 2% and 5% SLS compared to that containing 1% MgSt. However, the tabletability was insensitive to the type or amount of lubricant, except at pressures higher than 300 MPa (Figure. 3.3c). This means bonding strength must be lower for the tablets containing SLS according to the bonding area-bonding strength interplay [28, 61, 62]. Bonding strength can be quantified using compactibility where tablet tensile strength is normalized by porosity. The compactibility profiles show that tensile strength of 1% MgSt containing lactose tablets is much higher at the same porosity (Figure. 3.5). Tensile strengths at zero porosity, TS_0, for all formulations are summarized in Table 3.2.

It is interesting to note that, compared to 1% and 2% SLS, bonding strength of MCC placebo formulations is lower when 1% MgSt was used. Higher SLS level led to lower bonding strength (Figure. 3.5a). This is opposite to what was observed in the lactose placebo formulation (Figure. 3.5c). An explanation is that bonding in the MCC placebo formulation occurred mostly between MCC particles, which undergo plastic deformation rather than fracture during compression. Therefore, MCC surface coverage by lubricant deteriorated bonding strength. In this case, 1% MgSt was more effective in covering MCC surfaces than 1% SLS. Of course, 2% SLS covered more MCC surface area than 1% SLS. Therefore, compactibility followed the descending order of 1% SLS > 2% SLS > 1% MgSt (Figure. 3.5a). Thus, in the case of plastic MCC placebo formulation, lower tabletability by 1% MgSt was driven by lower bonding strength. The bonding area-bonding strength interplay for the placebo formulation of the 60% MCC + 40% lactose mixture falls between those of MCC and lactose placebo formulation.

3.4.3. Effects on Flowability

The flowability of various powder mixtures used in this study suggested that higher lactose concentration led to slightly better powder flowability (Table 3.3). This is reasonable because, in this work, the spray dried lactose grade had smoother surface and particles were less elongated than the grade of MCC [38, 63]. Additionally, the nearly 15% larger particle size of spray dried lactose (~125 μm) than MCC (~110 μm) [64] also contributed to the improved flowability [65]. For all powders, lubrication improved flowability but the extent of improvement depended on type and amount of lubricant. For the same mixture, the use of 1% MgSt led to more improvement in flowability than 1% SLS. Approximately 25%

increase in flowability index was observed when MCC was lubricated with 1% MgSt, while increase was insignificant (~6%) when lubricated with 1% SLS. The powders containing 2% SLS showed slightly lower or similar ff_c than those containing 1% SLS. The relative increase in ff_c is the largest for lactose, i.e., ~60% when 1% MgSt was used and ~32% when 1% SLS was used. In all cases, powder flowability is better than pure MCC (Avicel PH 102, $ff_c \approx 5.6$ at 33% RH under the 1kPa pre-shear normal stress) [66]. Therefore, all these powders are acceptable for processing on a high speed tablet press [67].

3.4.4. Assessing SLS in a realistic formulation

3.4.4.1 Lubrication efficiency and effect on tabletability

Figure 3.6a shows the effects of lubricant type on the lubrication efficiency of a tablet formulation containing 5% Celecoxib. It was found that 2% SLS was not as effective as 1% MgSt in terms of its ability to reduce die-wall friction (data not shown). However, by increasing the amount of SLS to 5%, ejection force was largely reduced to a level that is similar with 1% MgSt (Figure 3.6a). The tabletability of 5% SLS formulation is lower than that of 1% MgSt formulation (Figure 3.6b). However, tablet with tensile strength higher than 2 MPa can be easily attained in both cases. That means, despite the differences, 5% SLS and 1% MgSt did not have practical difference in lubrication efficiency and tabletability for this celecoxib formulation.

3.4.4.2 Effects on disintegration

Longer disintegration time may impact the dissolution of a drug from tablet and bioavailability, which then affects the clinical performance of the drug. Results show that all tablets, containing either 1% MgSt or 5% SLS, disintegrated within 90 s. This is much shorter than the disintegration time specified by USP [68] for most immediate release tablet products. Therefore, the use of 5% SLS is also unlikely to negatively impact tablet disintegration.

3.4.4.3 *In vitro* dissolution performance

Figure 3.7 shows the effects of different lubricants on the dissolution performance of Celecoxib formulation in both gastric and intestinal environments. The formulation containing 5% SLS has significantly better dissolution performance than that of the 1% MgSt. As previously discussed, the surfactant SLS improved the local wetting as shown by the lower contact angle (Fig. 3.8), which facilitated the dissolution of celecoxib. During the initial 20 min of dissolution, tablets containing 5% SLS have up to ~3 times faster dissolution rate compared with tablet containing 1% MgSt in simulated gastric and intestinal environments. At 30 min, the ratio of the amount of celecoxib released from 5% SLS tablet to that from 1% MgSt is 1.8 and 1.4 in the pH 6.8 and 1.2 media, respectively (Figure. 3.7). It is also worth to mention that non-sink condition was used in this experiment as incorporating additional surfactant in the dissolution medium to create a sink condition forfeits the goal of this study. This prevented celecoxib from fully releasing into the media even after 120 min (data not shown).

The initial lag in dissolution from MgSt-containing tablets may be attributed to the hydrophobic feature of MgSt. In comparison, tablets containing SLS show no significant lag during dissolution. The slower dissolution from tablets containing 1% MgSt may also be attributed to poor wettability of these tablets by water. This is shown by contact angle, which is significantly higher for the tablet containing 1% MgSt than that containing 5% SLS (Figure 3.8).

3.4.5 Effectiveness and safety

It appears that 5% of SLS can adequately lubricate even predominantly brittle powders. SLS is expected to be more effective for lubricating less brittle powders, such as most tablet formulations. For formulations that exhibit balanced plasticity and brittleness, the amount of SLS required for adequate lubrication will be lower than 5%, especially if SLS with smaller particle sizes is used. In comparison to 1% MgSt, the incorporation of SLS exhibiting comparable lubrication efficiency, up to 5% SLS, did not noticeably deteriorate tabletability and tablet disintegration for powders exhibiting a range of mechanical properties. For the model celecoxib formulation, the use of 5% SLS led to improved dissolution. This may be attributed to the better wetting of hydrophobic drugs in presence of SLS during dissolution.

For SLS, the proposed human lethal oral dose is 0.5–5.0 g/kg body weight [38]. In FDA approved tablet products that contain SLS, the amount of SLS ranges from 0.65 to 51.69 mg per dose [69]. For a 1 g oral tablet, 5% of SLS is equivalent to 50 mg per tablet. Thus,

the use of 5% SLS as a lubricant may be regarded acceptable from safety point of view. Overall, SLS can be considered as an acceptable alternative to existing lubricants. In the modern development of products, QbD principles will always be followed to understand the interactions between drug and excipients, impact of excipient content on product quality, level of excipient from both process and quality (dissolution) point of view. The inclusion of a wetting agent, such as SLS, in a formulation is justified if a drug is highly hydrophobic. The impact of SLS on drug product qualities, e.g., purity, chemical stability, and drug release, is evaluated during the usual course of development following the QbD approach. Thus, the risk of adverse effects by SLS to the product quality is minimal. An interesting formulation approach is to add SLS along with MgSt to take advantage of the more effective lubrication by MgSt while mitigating possible dissolution slow down. [70] [71] In this approach, the amount of SLS to attain adequate wetting is much lower than that to sufficiently reduce ejection force.

3.5. Conclusion

Our data suggests that SLS can be used as a lubricant. The lubrication efficiency of SLS is generally not as good as MgSt when used at the same weight percentage in a formulation. However, SLS can be used at higher amounts to attain desired level of lubrication without deteriorating tabletability and disintegration. For a celecoxib formulation, 5% SLS exhibited lubrication efficiency similar to 1% MgSt but better dissolution, due to the improved wetting of celecoxib in the presence of SLS. The results warrant further examination of the use of SLS as an excipient for the dual wetting and lubricating functionality in tablet formulation using other model drugs.

Table 3.1 Celecoxib tablet formulation

Material	**Amount (*w/w*)**	
Celecoxib	5%	5%
60% MCC + 40% Lactose	89%	85%
CCS	5%	5%
MgSt	1%	-
SLS	-	5%

Table 3.2. Effects of SLS and MgSt on the tensile strength at zero porosity (TS_0) of powders containing different amounts of MCC and lactose.

Mixture	Lubrication	TS_0 (MPa)
MCC	1% SLS	10.6 (0.07)
	2% SLS	8.8 (0.07)
	1% MgSt	7.2 (0.10)
80% MCC	1% SLS	8.9 (0.08)
	2% SLS	7.8 (0.04)
	1% MgSt	6.5 (0.07)
60% MCC	1% SLS	7.9 (0.07)
	2% SLS	7.0 (0.06)
	1% MgSt	5.6 (0.06)
40% MCC	1% SLS	6.7 (0.13)
	2% SLS	6.0 (0.08)
	1% MgSt	5.6 (0.09)
20% MCC	1% SLS	5.2 (0.11)
	2% SLS	6.0 (0.16)
	1% MgSt	5.4 (0.06)
Lactose	2% SLS	9.2 (0.57)
	5% SLS	6.8 (0.40)
	1% MgSt	9.3 (0.61)

Table 3.3. Flowability index, ff_c, of powder mixtures lubricated with MgSt or SLS (n = 3).

Materials	No Lubricant	1% MgSt	1% SLS	2% SLS
100% MCC	6.54 (0.48)	8.17 (0.28)	6.98 (0.34)	6.78 (0.14)
60% MCC and 40% Lactose	6.92 (0.13)	8.44 (0.91)	7.53 (0.56)	8.03 (0.59)
100% Lactose	7.19 (0.18)	11.39 (0.87)	9.52 (0.25)	9.38 (0.99)

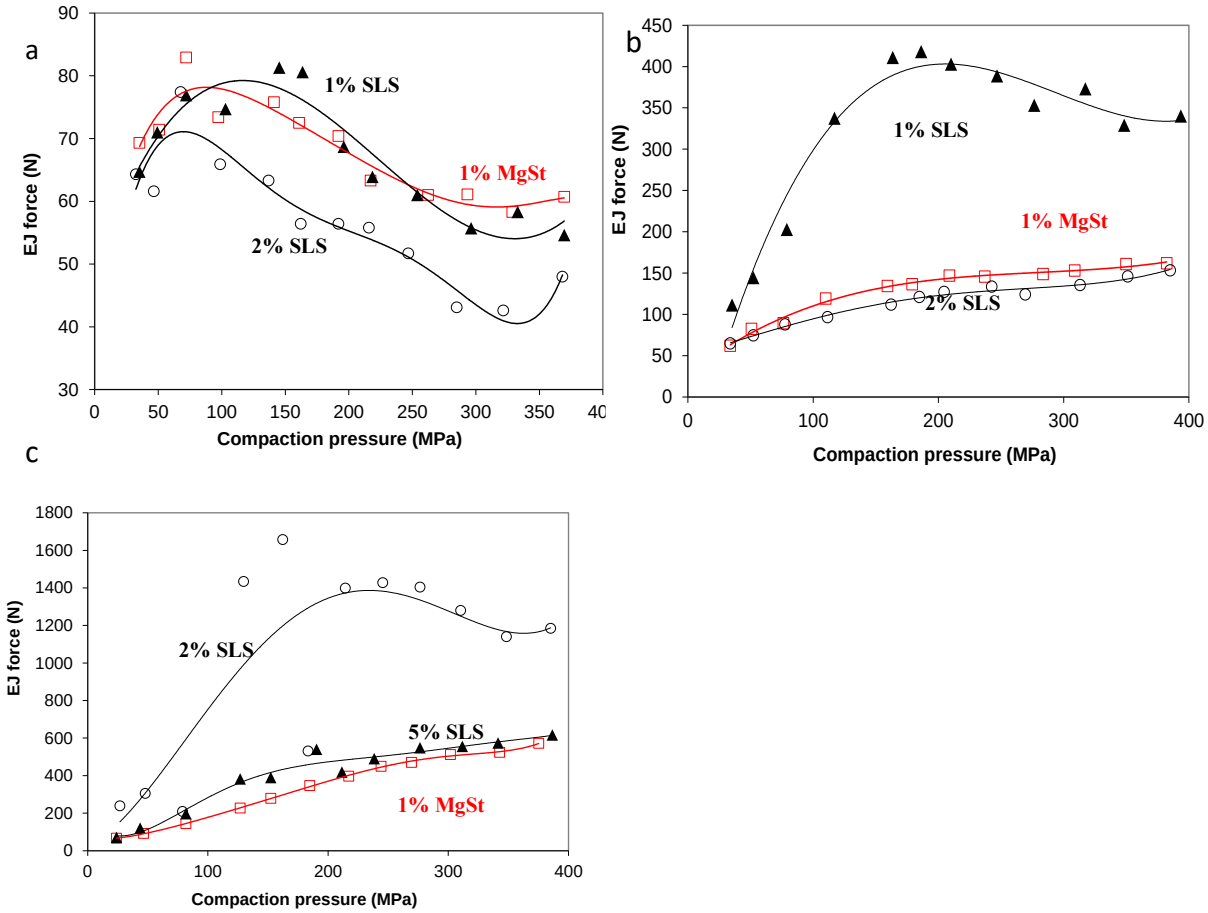

Figure 3.1. Lubrication efficiency of SLS and MgSt for a) MCC, b) 60% MCC + 40% lactose, and c) Lactose. Lines are best fit polynomial functions to the third order.

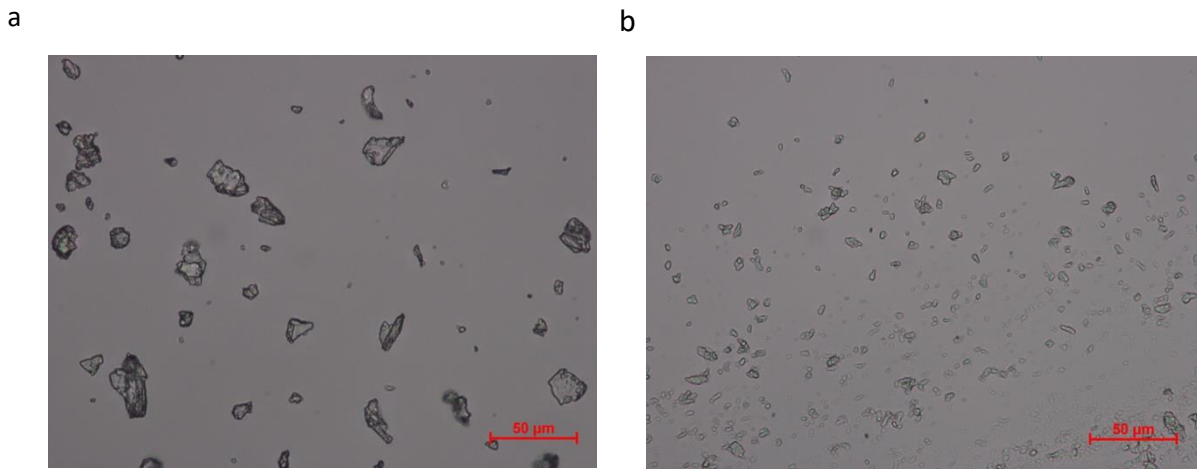

Figure 3.2. Polarized light microscopic images of lubricants used in this work, a) SLS, and b) MgSt. (magnification level: 40X)

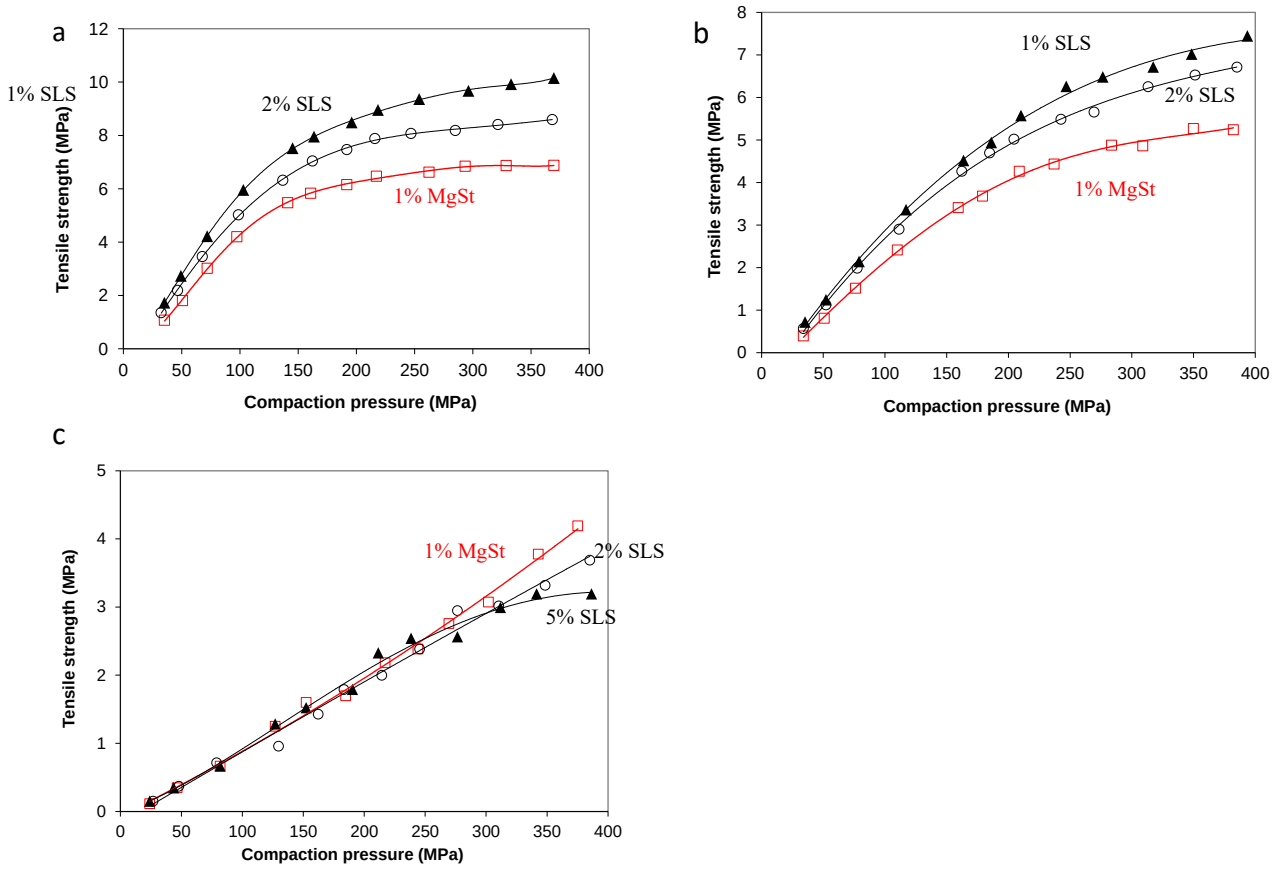

Figure 3.3. Effects of SLS and MgSt on tabletability. a) MCC, b) 60% MCC + 40% lactose, c) Lactose. Lines are best fit polynomial functions.

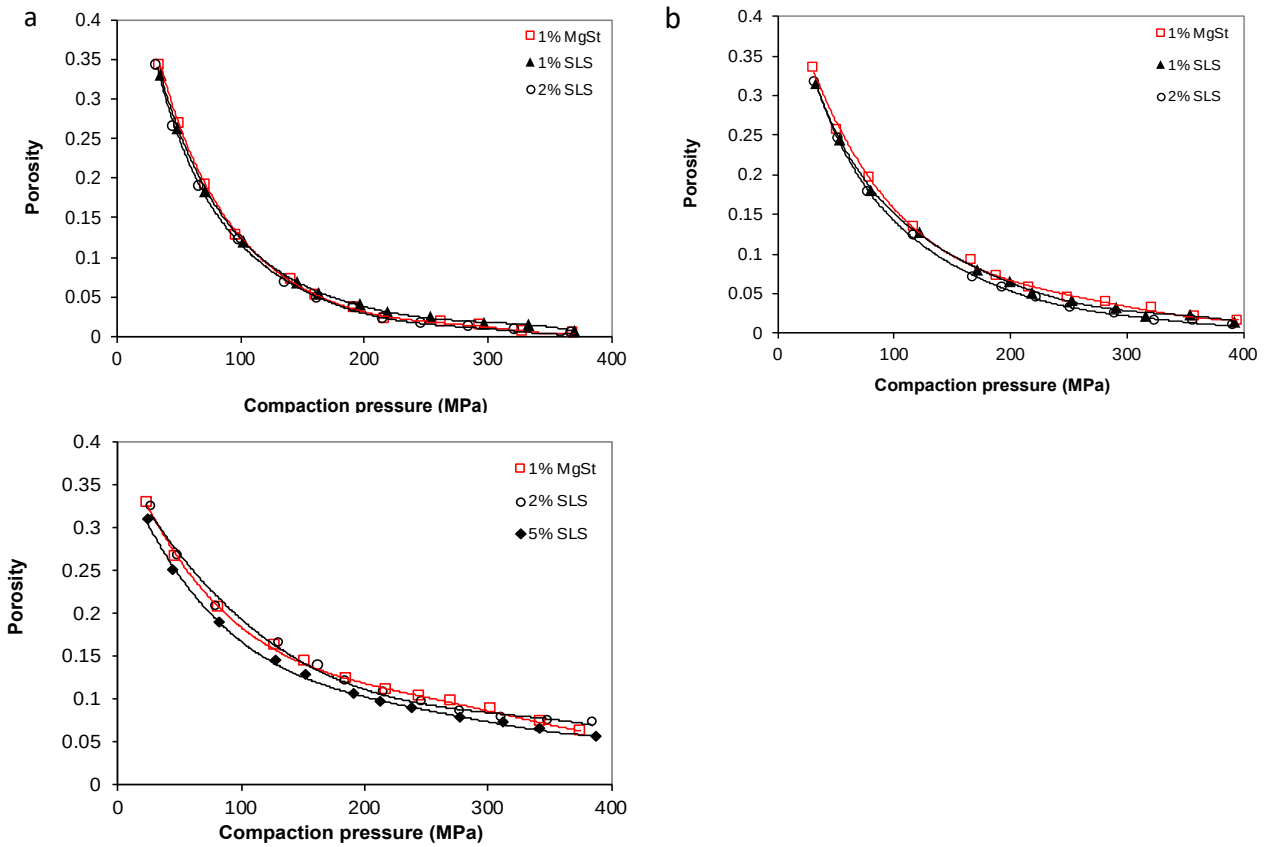

Figure 3.4. Effects of lubrication on compressibility profiles of various placebo formulations of a) MCC, b) 60% MCC + 40% lactose, and c) Lactose. Lines are fit polynomial functions to third or fourth order.

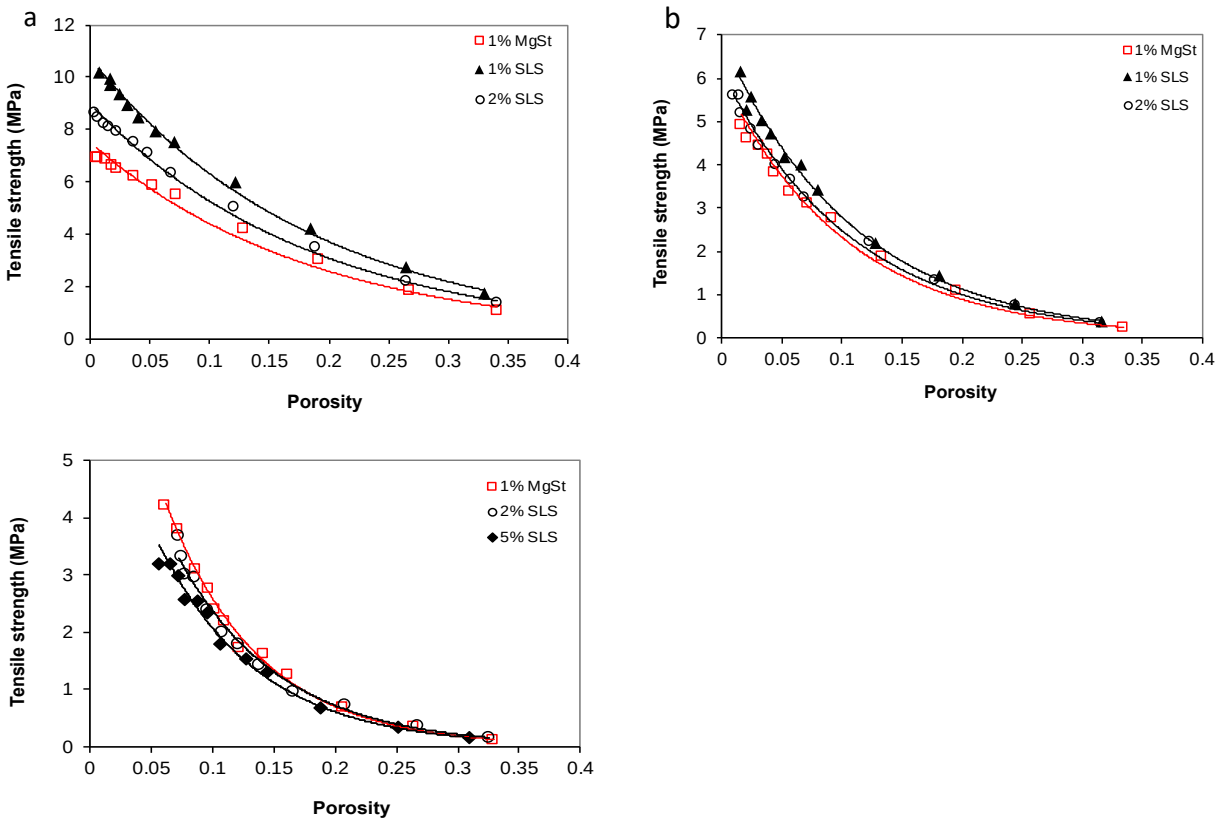

Figure 3.5. Effects of lubrication on compactibility profiles of various placebo formulations of a) MCC, b) 60% MCC + 40% lactose, and c) Lactose. Lines are fit exponential functions.

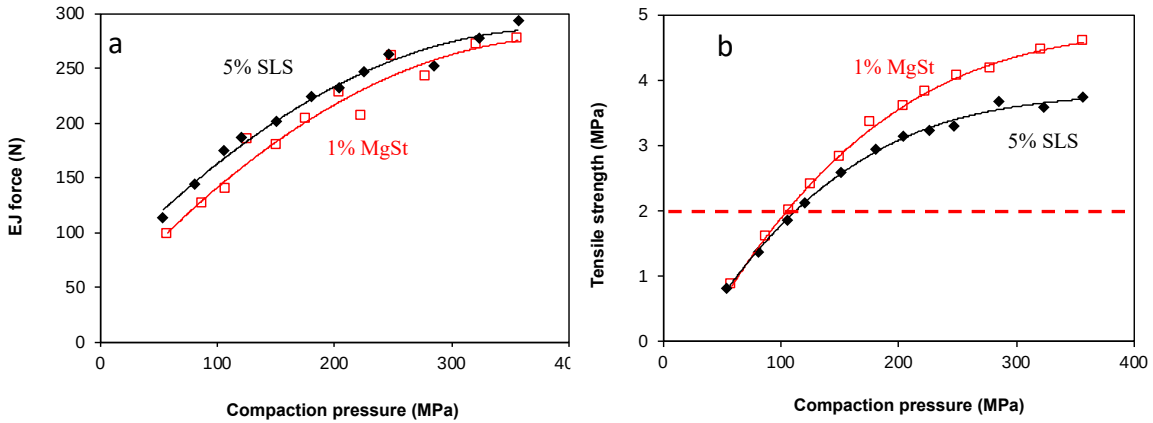

Figure 3.6. a) Lubrication efficiency and b) tabletability of the Celecoxib formulation containing 1% MgSt and 5% SLS. Lines are best fit polynomial functions to the third order.

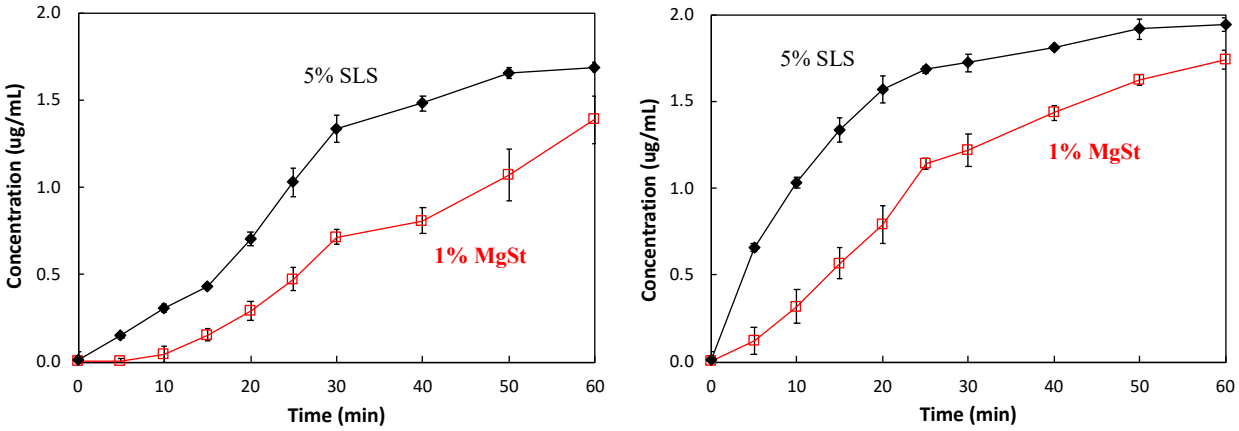

Figure 3.7. In vitro dissolution profiles of a celecoxib tablet formulation in (a) pH 6.8 sodium phosphate buffer, (b) pH 1.2 water

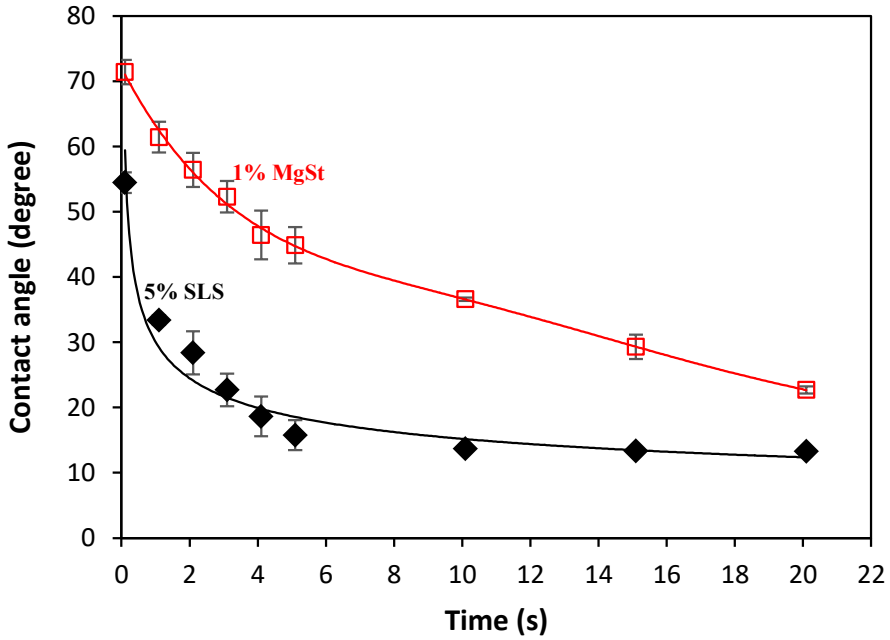

Figure 3.8. Contact angle of water on formulated celecoxib tablets containing 5% SLS or 1% MgSt.

Table 3.S1. Plasticity parameter and true density of formulations (standard errors of fitting are in parentheses)

Materials	Plasticity parameter (1/C) MPa
100% MCC 1%MgSt	84 (9.67)
80% MCC 1% MgSt	216 (40)
60% MCC 1% MgSt	320 (55)
40% MCC 1% MgSt	335 (35)
20% MCC 1% MgSt	**561 (66)**
0% MCC 1% MgSt	766 (61.21)
100% MCC 1% SLS	93 (3.91)
80% MCC 1% SLS	159 (18)
60% MCC 1% SLS	252 (31)
40% MCC 1% SLS	407 (68)
20% MCC 1% SLS	**664 (125)**
100% MCC 2% SLS	83 (5.21)
80% MCC 2% SLS	187 (26)
60% MCC 2% SLS	319 (54)
40% MCC 2% SLS	383 (59)
20% MCC 2% SLS	**527 (46)**
0% MCC 2% SLS	866 (149.00)
0% MCC 5% SLS	878 (85.9)

* Calculated from true density of individual components reported in the literature.

Table 3.S2. Effects of SLS and MgSt on the tensile strength at zero porosity (TS_0) of powders containing different amounts of MCC and lactose.

Mixture	Lubrication	TS_0 (MPa)
MCC	1% SLS	10.6 (0.07)
	2% SLS	8.8 (0.07)
	1% MgSt	7.2 (0.10)
80% MCC	1% SLS	9.2 (0.09)
	2% SLS	8.3 (0.05)
	1% MgSt	7.0 (0.08)
60% MCC	1% SLS	8.6 (0.09)
	2% SLS	8.1 (0.08)
	1% MgSt	6.6 (0.10)
40% MCC	1% SLS	8.2 (0.21)
	2% SLS	7.4 (0.15)
	1% MgSt	6.3 (0.12)
20% MCC	1% SLS	8.5 (0.38)
	2% SLS	7.3 (0.26)
	1% MgSt	7.1 (0.13)
Lactose	2% SLS	9.2 (0.57)
	5% SLS	6.8 (0.40)
	1% MgSt	9.3 (0.61)

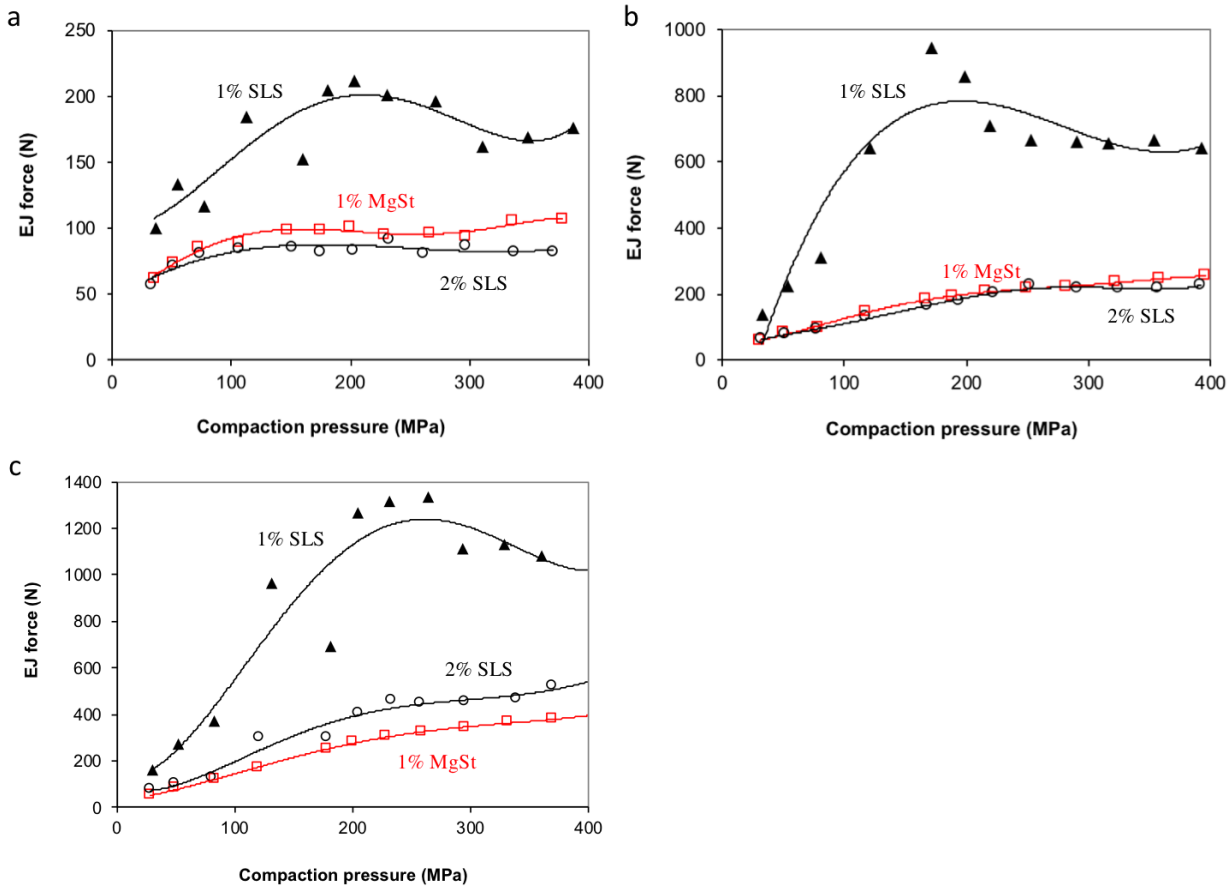

Figure 3.S1. Lubrication efficiency of SLS and MgSt for a) 80% MCC + 20% lactose, b) 40% MCC + 60% lactose, and c) 20% MCC + 80% lactose. Lines are fitted polynomial function.

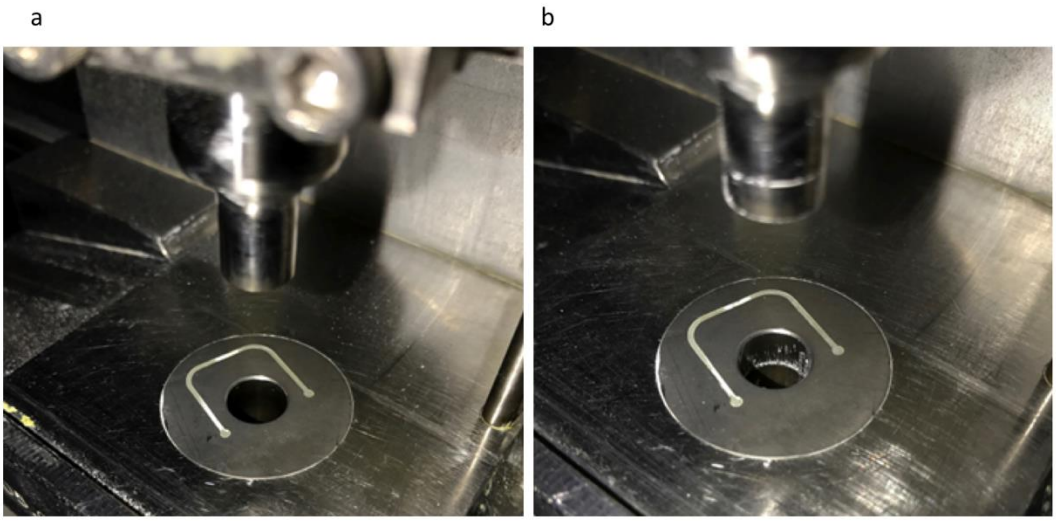

Figure 3.S2. Surface of die wall after tablet ejection. a) clean, b) with material sticking.

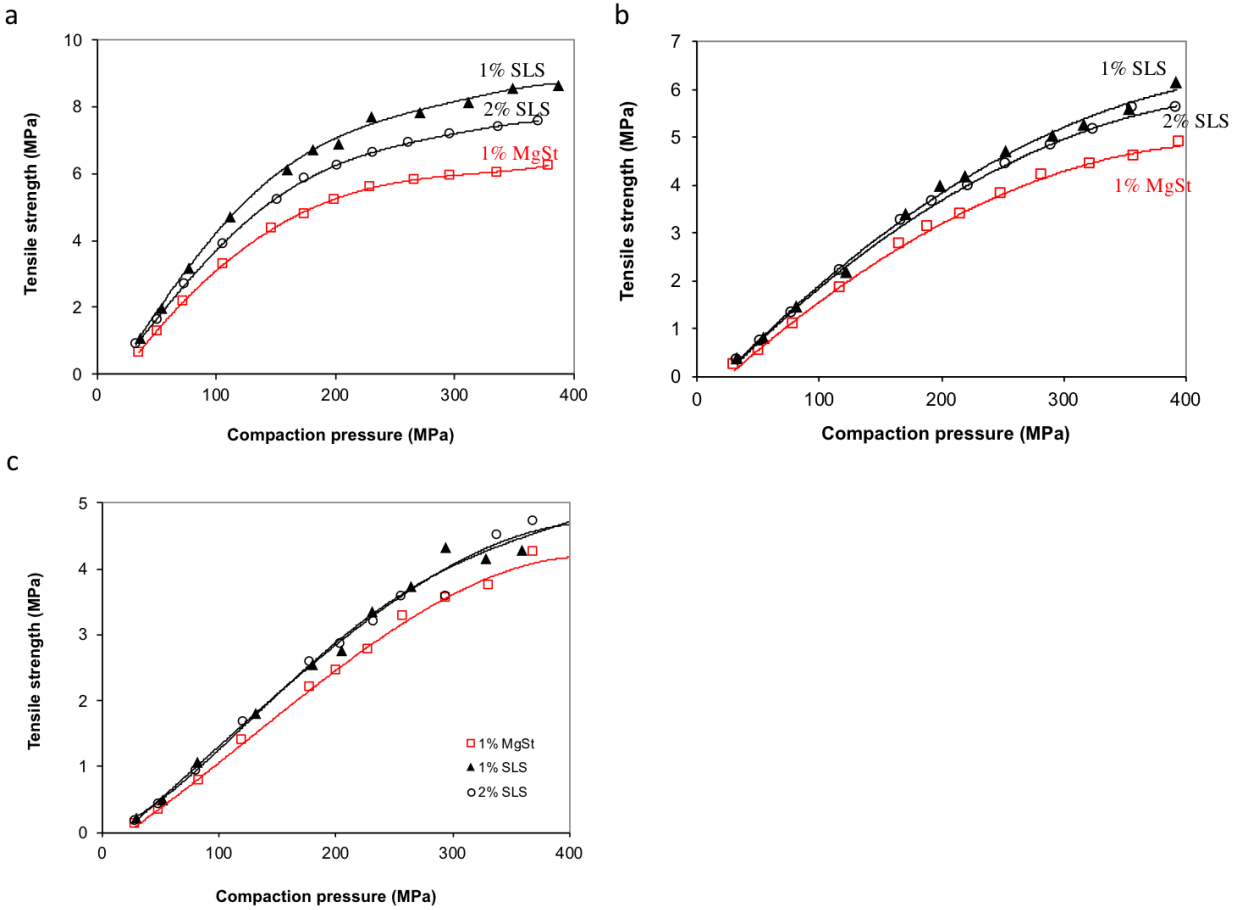

Figure 3.S3. Effects of SLS and MgSt on tabletability. a) 80% MCC + 20% lactose, b) 40% MCC + 60% lactose, and c) 20% MCC + 80% lactose. Lines are fitted polynomial functions.

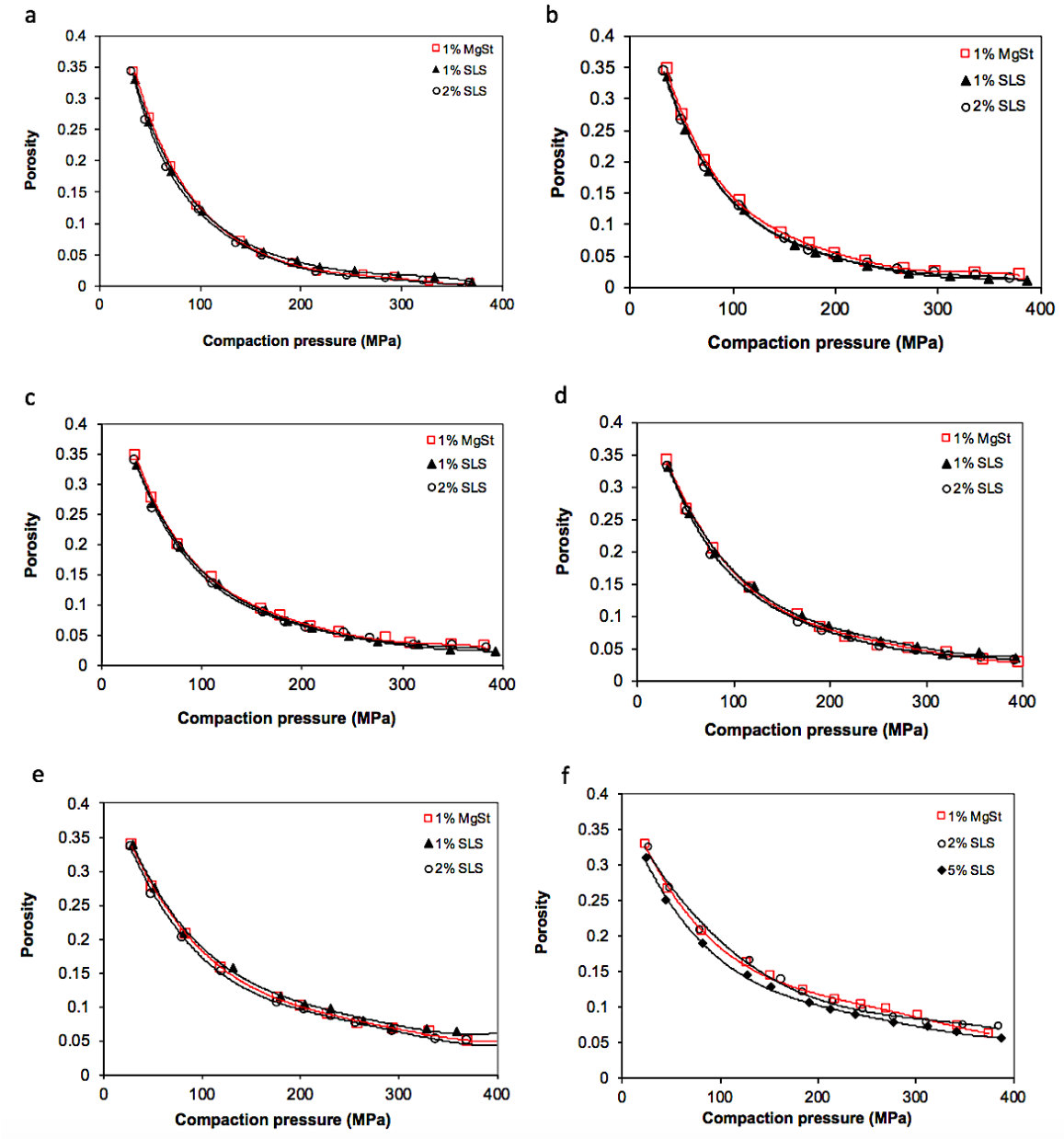

Figure 3.S4. Effects of SLS and MgSt on compressibility. a) MCC, b) 80% MCC + 20% lactose, c) 60% MCC + 40% lactose, d) 40% MCC + 60% lactose, e) 20% MCC + 80% lactose and f) Lactose. Lines are fitted polynomial functions.

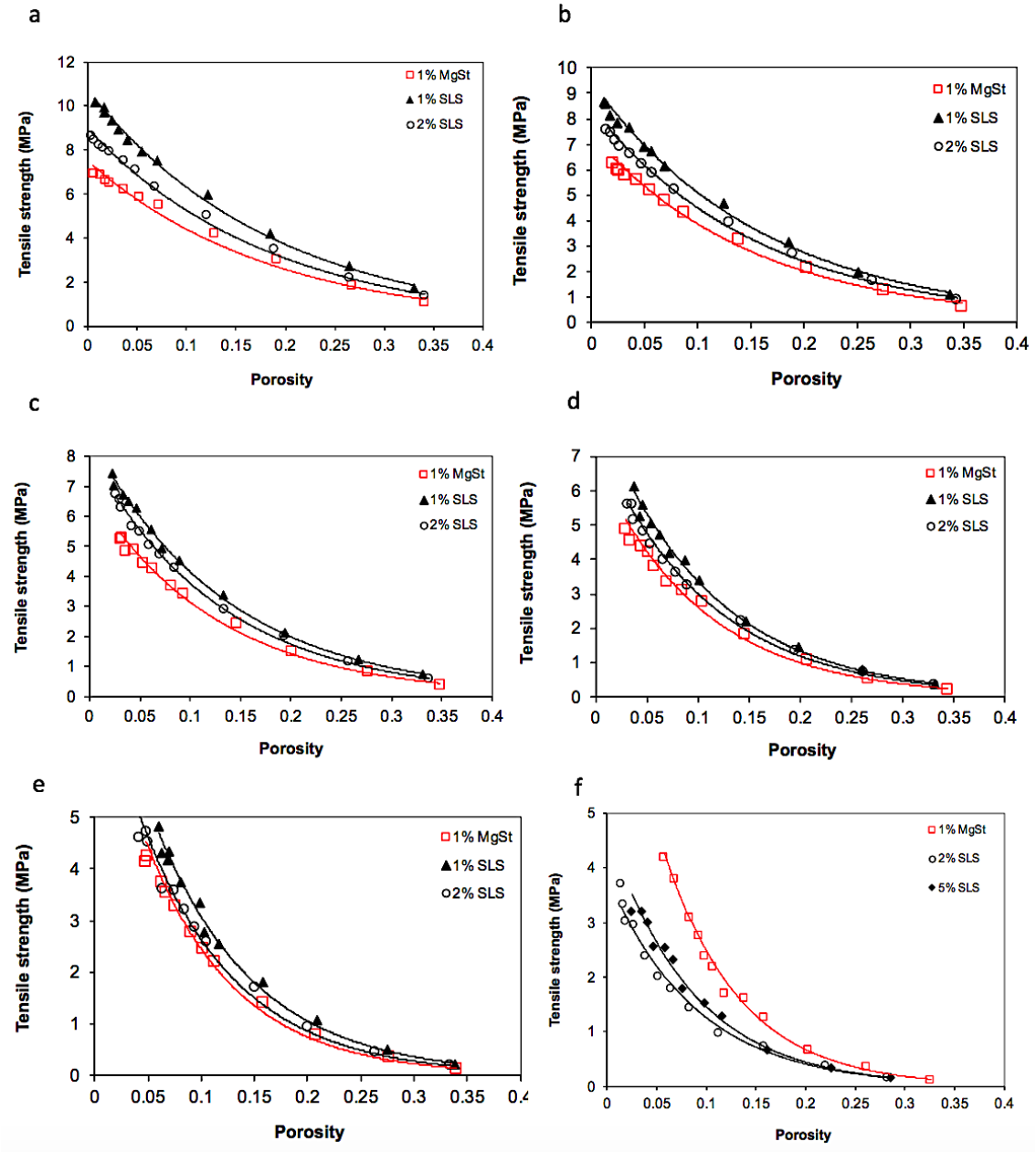

Figure 3.S5. Effects of SLS and MgSt on compactibility. a) MCC, b) 80% MCC + 20% lactose, c) 60% MCC + 40% lactose, d) 40% MCC + 60% lactose, e) 20% MCC + 80% lactose and f) Lactose. Lines are fitted exponential functions.

CHAPTER 4. A SYSTEMATIC EVALUATION OF POLOXAMERS AS TABLET LUBRICANTS

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4.1 Summary

Lubricants are important for both preserving the tooling of high-speed tablet presses and attaining quality tablets. Magnesium stearate (MgSt) is most commonly used due to its superior lubrication efficiency; however, it can lead to negative effects on tabletability and dissolution. In this study, we have systematically evaluated two poloxamers, P188 and P407, for their suitability as alternative tablet lubricants. For two excipients with different mechanical properties, i.e., microcrystalline cellulose and lactose, both poloxamers exhibit acceptable lubrication efficiency without negatively impacting tabletability. Compared to 1% MgSt, the performance of both poloxamers at 2% in an experimental tablet formulation of ritonavir led to better lubrication, higher tabletability, and enhanced *in vitro* drug release. Thus, the use of P188 and P407 as alternative tablet lubricants deserves further evaluations.

4.2 Introduction

Pharmaceutical tablet manufacturing requires three major steps: 1) powder die-filling, 2) powder compression, and 3) tablet ejection and detachment. The first step requires a robust control system to accurately and consistently deliver the correct amount of powder into the die [1, 2]. In the second step, a loose powder is compressed into intact tablet by applying a compaction pressure with the main compression roller [3], usually after applying pre-compression at a lower pressure [4, 5]. Tablets are typically produced using a high-speed tableting machine in pharmaceutical industry [6]. Modern high-speed tableting machine (e.g., Korsch XL800) can routinely have an hourly output of 1,026,000 single layer tablets, corresponding to 285 tablets every second, which makes each step even more crucial in such a fast-paced environment. Systematic understanding of powder filling, compression, and tablet ejection is thus critical to ensure tablets meeting desired quality [7]. In comparison to die filling and powder compression, the tablet ejection and detachment step has received far less attention. The tablet is ejected when the lower tablet punch is ramped up over the ejection cam as the upper punch is simultaneously lifted to avoid any further contact with the tablet [8]. The process is completed when the tablet is removed from the lower punch tip by a scraper.

Ejection forces originate from the friction between tablet and die wall due to the residual die wall stress post compaction [8, 9]. A high ejection force often leads to tablet quality issues, such as low tablet strength [10], lamination [11] and tooling damages [12]. It also correlates with punch sticking [13-15]. Hence, reducing ejection force is an important

consideration in tablet formulation development and manufacturing. Though external lubrication techniques have been developed [16, 17], the most cost-effective way to reduce ejection force during tablet manufacturing is to incorporate a lubricant into a formulation [18]. Boundary lubricants function by forming a thin film between tablet and die wall to reduce the friction coefficient [19, 20]. Lubrication efficiency, which may be defined as the extent of ejection force reduction of a lubricant, varies with type of lubricant [21, 22], amount of lubricant [23, 24] , mixing condition [20, 25-27] as well as compaction speed [28, 29].

Magnesium stearate (MgSt) is one of the most widely used lubricants in tablet manufacturing due to its high lubrication efficiency and low cost. Generally, 0.25% to 1.0% of MgSt can provide sufficient lubrication to most formulations [30, 31]. However, the coating of particle surfaces by MgSt may significantly reduce tablet mechanical strength [31-35], because of lower bonding strength among particles [35-37]. Highly plastic materials are more susceptible to tabletability deterioration than brittle materials because brittle materials undergo extensive fragmentation during compression to expose MgSt-free surfaces, which alleviates the deterioration of bonding strength by MgSt coating [38, 39]. Tableting performance of plastic materials lubricated with MgSt is affected by mixing time [26], mixing intensity [40], as well as compaction speed [29, 38]. Additionally, the use of MgSt may reduce dissolution of drugs [41-44], because the hydrophobic MgSt can significantly lower the wettability in an aqueous medium. Lastly, physical properties of MgSt are highly variable [45], depending on its origin [46], crystal form and impurities [47-49]. If not controlled, variable properties of MgSt may lead to product failure during

commercial tablet manufacturing of an MgSt containing formulation. There is the need for alternative lubricants that are effective in lubrication but without the negative issues brought about by MgSt [18, 50-56]. Along this line, recent work showed that sodium lauryl sulfate (SLS) exhibited adequate lubrication efficiency during compression and improved *in vitro* dissolution of celecoxib [57]. However, SLS may form poorly water-soluble complexes with alkaline drugs in solution at low pH, which reduces the dissolution performance [58]. Therefore, SLS may not be suitable for use in tablet formulations of alkaline drugs.

Poloxamers are nonionic triblock copolymers consisting of a central hydrophobic block of polypropylene glycol (PPG) flanked by two hydrophilic blocks of polyethylene glycol (PEG) (Figure 4.1) [59]. The properties and performance of poloxamers can be modified by altering their chain length, molecular weight of PPG block, as well as the PEG percentage. Poloxamer 188 (P188) and Poloxamer 407 (P407) are two commercial poloxamers commonly used in drug product as wetting agents and dissolution enhancers [60], especially for sparingly soluble drugs [61]. The maximum amount in FDA approved tablets is 66.9 mg for P188 and 110 mg for P407 [61]. P188 and P407 have also been suggested to have some lubrication properties [62], when tested with microcrystalline cellulose and lactose monohydrate. However, compaction was assessed in a highly abbreviated fashion, only using two forces for each material (4 and 5 KN for MCC and 12 and 17 KN for lactose). In addition, the work was carried out at a low speed of ~0.67 mm/s, a condition drastically different from the high-speed tableting process [63]. The applicability of the finding to high speed tableting is thus unknown. Moreover, materials

representative of real tablet formulations were not included. Thus, a more systematic evaluation of the two poloxamers as alternative lubricants with a focus on their impact on tabletability and dissolution under realistic tableting conditions was carried out.

4.3 Materials and methods

4.3.1 Materials

Microcrystalline cellulose (Pharmacel 102) and lactose monohydrate (SuperTab 11SD) were received from DFE Pharma, Goch, Germany. Magnesium stearate (MgSt) was received from Covidien (Dublin, Ireland). Poloxamer 188 (P188 micro) and Poloxamer 407 (P407 micro) were received from BASF (Ludwigshafen, Germany). Croscarmellose sodium (CCS, Ac-Di-Sol) was received from FMC Biopolymer, Philadelphia, PA. Ritonavir (RTV) was received from Wuhan Beier Biopharm Ltd. (Wuhan, China). All materials were used as received.

4.3.2 Methods

4.3.2.1 Preparation of powders mixtures

Powder mixtures containing MCC or lactose were prepared by mixing accurately weighed MCC or lactose with a targeted amount of lubricant of interest on a Turbula mixer (Glen Mills Inc., Clifton, NJ) at 49 rpm for 2 min.

Three direct compression tablet formulations of RTV (Table 4.1) were prepared by pre-blending accurately weighed individual components except the lubricant in a 250 mL glass bottle on a Turbula mixer (Glen Mills Inc., Clifton, NJ) for 2 min. After adding lubricant, the mixture was further blended at 49 rpm for additional 2 min. The batch size for all mixtures was 40 g. All mixtures were equilibrated in a 32% relative humidity (RH) chamber at room temperature for at least 2 days before use. CCS is a tablet disintegrant, which is normally used at 5% level in tablet formulation.

4.3.2.2 Powder compaction

Powder compaction was conducted at room temperature and approximately 32% RH unless stated otherwise. Round flat-faced tablets were made using 9.5 mm diameter tooling on a compaction simulator (Presster; Metropolitan Computing Company, East Hanover, NJ), simulating a 29-station Korsch XL 400 rotary tablet press. The dwell time was either 30 ms or 100 ms, corresponding to a linear speed of 0.423 m/s (52,000 tablets/h) and 0.127 m/s (15,600 tablets/h). No pre-compression was applied.

Immediately after ejection, tablet out-of-die thickness (h) and diameter (d) were measured by a digital caliper (Mitutoyo, Takatsu-ku, Kawasaki, Japan). Tablet weight was measured by an analytical balance (Mettler Toledo, Columbus, OH). Tablet porosity was calculated from true density obtained from literature (1.46 g/cm^3 for MCC and 1.531 g/cm^3 for lactose) [64] [65], tablet dimensions, and weight [66]. Tablet diametrical breaking force (F) was

determined using a texture analyzer (TA-XT2i; Texture Technologies Corporation, Scarsdale, NY) at a speed of 0.01 mm/s. Tablet tensile strength (σ) was calculated from using Eq. (4.1):

$$\sigma = \frac{2F}{\pi dh} \qquad \text{Eq. (4.1)}$$

Powder compaction properties are characterized by tabletability (dependence of tablet tensile strength on compaction pressure), compressibility (dependence of tablet porosity on compaction pressure), and compactibility (dependence of tablet tensile strength on porosity) [67, 68]. Lubrication efficiency was evaluated by plotting ejection force as a function of compaction pressure [57]. At a given compaction pressure, a lower ejection force indicates better lubrication efficiency.

4.3.2.3 Robustness of lubricant

To test the robustness of formulations containing different lubricants against variations in blending process, the plastic MCC was selected because it is more susceptible to variations in lubrication conditions. Powders were prepared and evaluated by mixing MCC with 1% MgSt, 2% P188, or 2% P407 under four combinations of blending time and compression speed (Table 4.2).

All powders were equilibrated in a 55% relative humidity (RH) chamber at room temperature for at least 2 days before further uses. The environment RH was ~55% during compaction.

4.3.2.4 Wettability

To assess the wettability of drug formulations containing different lubricants, sessile drop contact angle measurements were performed using an automatic contact angle analyzer (DMCE1, Kyowa Interface Science, Saitama, Japan) at room temperature. Milli-Q water was used as a wetting liquid. A water drop with a volume of approximately 2 μL was dispensed by a microsyringe onto the tablet surface. After stabilization, the high-speed camera captured an image of the water droplet on tablet surface every second for 30 s. Values of the contact angle as a function of time were derived from the images using the FAMAS software. All measurements were made in triplicate using a new tablet for each measurement.

4.3.2.5 In vitro tablet disintegration and dissolution

Tablets (approximately 300 mg) prepared at 100 MPa were used for *in vitro* tablet disintegration and dissolution tests. Tablet disintegration time was measured by a disintegration tester (Di-200, Pharma Alliance Group Inc., CA) at 37 ± 0.5 °C using DI water. Frequency of the disintegration tester was set to 30 cycles/min. Disintegration time was recorded for each tablet when all solid passed through the wired mesh. Six

measurements were carried out for each formulation. Dissolution tests were carried out in a 500 mL jacketed beaker at 37 °C. Degassed pH 1.2 HCl solution was chosen as the medium to simulate the gastric fluid. Under stirring with an overhead paddle stirrer at 100 rpm, drug release was monitored by a pre-calibrated fiber optic ultraviolet-visible probe for 30 min. Three measurements were carried out for each formulation.

4.3.2.6 Particle size, shape, and surface area

Powders were dispersed in a drop of silicone oil placed on a glass slide. Shape and size of particles were examined under a polarized light microscope (Nikon, Minato, Tokyo, Japan) at the magnification of 40X. The particle size distribution was measured by laser diffraction (Mastersizer M3000, Dry Aero S Module, Malvern Instruments Ltd, Malvern UK) using a dispersion pressure of 1.5 bar and a feed rate of 30 – 50%. The specific surface area of the materials was obtained using nitrogen gas adsorption over the partial pressure, P/Po, range of 0.05 – 2 and analyzed by the Brunauer, Emmet, and Teller (BET) method on Tristar II (Micromeritics, Norcross, GA)

4.4 Results and discussion

4.4.1 Particle size and specific surface area

All three lubricants consist of irregularly shaped particles, where P188 and P407 particles are much larger than those of MgSt by both microscopy (Figure 4.2) and particle size distributions (Figure 4.3 and Table 4.3). Specific surface areas of P188, P407 and MgSt

were 0.24 ± 0.003, 0.25 ± 0.007, and 6.42±0.03 m^2/g (n = 2), respectively. The significantly lower surface area of P188 and P407 is in agreement with their larger particle sizes than MgSt.

4.4.2 Lubrication efficiency

Lubrication efficiency of P188, P407, and MgSt was assessed using MCC and lactose. The use of 1% of MgSt, which is at the higher end of its typical range (0.25% - 1%) in tablet formulation, was intended to set a high bar for the lubrication efficiency of the two poloxamers. The use of the commonly used tablet excipients, MCC and lactose, is based on their very different mechanical properties. Tableting properties of the plastic MCC are more sensitive to lubrication than the brittle lactose [57]. The plastic MCC requires little or no lubrication, because of its low ejection force, while lactose and other brittle excipients demand more efficient lubrication because of their high ejection force [29].

The ejection force of MCC mixtures with 1% of P188, P407, and MgSt was less than 90 N for the compaction pressure range of 50 to 350 MPa (Figure 4.4a). With increasing compaction pressure, the ejection force of MCC initially increased then decreased as observed previously [29]. When compaction pressure was <75 MPa, 1% MgSt exhibited better lubrication efficiency than 1% P188 and 1% P407. However, at >75 MPa pressure, 1% P188 and 1% P407 exhibited better lubrication efficiency than 1% MgSt. At >200 MPa, 1% P407 exhibited slightly better lubrication efficiency than 1% P188. In the typical

pressure range of 150-250 MPa for pharmaceutical tableting, both P188 and P407 exhibit better lubrication efficiency for MCC than MgSt at 1% concentration.

Lactose exhibited considerably higher tablet ejection force than MCC. When 1% MgSt was used, the ejection force was 100 N at 50 MPa and continued to increase with increasing compaction pressure (Figure 4.4b). The use of 1% P188 or 1% P407 was significantly ($p < 0.05$) less effective in reducing ejection force than 1% MgSt. However, the use of more poloxamer corresponded to lower ejection force, and 5% P188 or P407 led to better lubrication efficiency than 1% MgSt. Although the use of more poloxamer is required to attain lubrication efficiency similar to MgSt, it is not expected to reduce dissolution, because poloxamer can promote wetting. Moreover, pure lactose represents an extreme challenge to lubrication efficiency. Lactose is typically used along with plastic excipients, such as MCC, in actual formulations. Their ejection forces are lower than that of pure lactose. Therefore, lubrication comparable to 1% MgSt is expected to be achieved using <5% P188 or P407 in pharmaceutically relevant formulations.

The lubrication efficiency of P188 and P407 is expected to be improved, if the particle size is reduced due to better surface coverage. To that end, it is interesting to point out that P407 exhibited slightly better lubrication efficiency than P188 at the same concentrations, despite the larger particle size of P407. Therefore, it is possible that smaller P407 can lead to even more efficient lubrication, i.e., P407 is likely a more efficient lubricant than P188.

Whole ejection force profiles of MCC - lubricant mixtures compressed at 160 MPa and lactose – lubricant mixtures compressed at 150 MPa are shown in Figures 4.4c, d. In each of the profiles, ejection force rose sharply to a peak value, which moved tablet relative to die wall. Once the tablet slides along the die wall, kinematic friction force was always lower. However, the kinematic ejection force generally trended with the peak static ejection force. Therefore, the ability of the two poloxamers in reducing kinematic ejection force is as effective as that for static ejection force. For this reason, only peak ejection force will be used to compare lubrication efficiency in the following sections.

4.4.3 Tableting performance

Tablet tensile strength of MCC initially increases nearly linearly with increasing compaction pressure up to about 150 MPa and then gradually levels off (Figure 4.5a). Tabletability follows the descending order of 1% P407 > 1% P188 > 1% MgSt. The tabletability of lactose is lower than that of MCC, as observed in previous studies [38, 69, 70]. Tablet tensile strength increases nearly linearly up to 350 MPa for all the lactose powders. Variations in P188 and P407 concentration up to 5% did not lead to any appreciable change in tabletability. All formulations containing poloxamer exhibited slightly better tabletability than that containing 1% MgSt. Therefore, for both MCC and lactose, the use of poloxamers is advantageous over MgSt in term of tabletability.

To further understand the effects of poloxamers on tabletability behaviors of MCC and lactose, compressibility and compactibility were analyzed (Figure 4.6). The compressibility of MCC containing 1% of P188 and P407 is similar, which is slightly better than that containing 1% MgSt (Figure. 4.6a). Thus, tablets containing 1% poloxamers had slightly larger bonding area compared to that containing 1% MgSt. From the compactibility plots (Figure. 4.6c) , the apparent bonding strength as evaluated by tablet tensile strength extrapolated to zero porosity (σ_0) [69] follows the descending order of 1% P407 (9.9 MPa) > 1% P188 (9.0 MPa) > 1% MgSt (7.4 MPa) (Table 4.4). The same rank order in tabletability and compactibility suggests the dominant role of bonding strength in the MCC formulations.

The compressibility of lactose containing 1% MgSt is less than those containing poloxamers (Figure 4.6b). For a given poloxamer, higher concentration corresponds to better compressibility (i.e., lower tablet porosity at the same pressure). Poloxamer type only slightly affects compressibility (Figure 4.6b). Compactibility indicates that tablet tensile strength decreases with increasing amount of P188 or P407 in the formulations. At 1% (w/w) concentration, formulations containing P188, P407 and MgSt had similar tablet tensile strength at a given porosity. Since lactose containing 1% MgSt exhibits the lowest compressibility (Figure 4.6b) and highest compactibility (Figure 4.6d), its lower tabletability (Figure 4.5b) is attributed to smaller bonding area. The insensitivity of tabletability to changes in poloxamer concentration is explained by the simultaneous increase in bonding area (Figure 4.6b) and decrease in bonding strength (Figure 4.6d), which have opposite effect on tablet tensile strength.

4.4.4 Robustness of formulation

When MgSt is used in a formulation, compression properties can be sensitive to process conditions, such as blending time [26] and mixing intensity [40]. This effect is more significant for materials that do not undergo extensive fragmentation during compression. A superior alternative to MgSt should ideally exhibit lower or no sensitivity to such process parameters. Therefore, both poloxamers at 2% were examined for this phenomenon using MCC, with 1% MgSt used as a control. The use of 2% poloxamers was intended to aggravate any existing sensitivity, so that it can be unambiguously identified.

With 1% MgSt, ejection force was higher when compaction speed increased (dwell time changed from 100 ms to 30 ms) (Figure 4.7a). Therefore, lubrication efficiency of 1% MgSt was lower at a higher compaction speed as observed before [28, 29]. This phenomenon was initially attributed to the compromised ability for MgSt to migrate to the tablet-die wall interface during the faster compression [29]. It was later shown that such speed dependency could be observed even for tablets compressed using only external lubrication with MgSt. [28]. Therefore, the differential migration of MgSt during compaction process is a sufficient but not necessary condition for observing the speed dependence of ejection force. However, changes in blending intensity (49 rpm vs. 101 rpm) or duration (5 min vs. 10 min) did not lead to noticeable change in lubrication efficiency. The MCC powder containing 2% P407 or P188 did not exhibit any dependence of ejection force on tableting speed, blending time or intensity (Figures 4.7b, 4.7c).

The MCC powder lubricated with 1% MgSt also showed significant ($p<0.05$) tensile strength reduction, when blended at a higher intensity (101 rpm), indicating more efficient coating of MCC particles by MgSt that reduced bonding strength. The maximum difference among the tabletability of the four MCC powders processed under different conditions is approximately 25% (Figure 4.8a). In contrast, MCC lubricated with either 2% P188 or 2% P407 showed negligible tensile strength variation when the same set of processing parameters were applied (Figure 4.8b, 4.8c). Thus, MCC lubricated with both poloxamers is more robust than that lubricated with 1% MgSt.

4.4.5 Characterization of an RTV formulation

4.4.5.1 Lubrication efficiency and tabletability

The use of 2% P188 or P407 led to significantly ($p<0.05$) lower ejection force than 1% MgSt for the RTV formulation used in this study (Table 4.1). For this formulation, 2% P407 exhibited better lubrication efficiency than 2% P188 (Figure 4.9a). The tabletability of the RTV formulations containing poloxamers was also better than that containing 1% MgSt (Figure 4.9b). This is likely due to the higher bonding strength than that of the formulation containing 1% MgSt, as shown by their comparable compressibility (Figure 4.9c) but higher compactibility (Figure 4.9d).

4.4.5.2 Disintegration and in vitro dissolution

Disintegration time is one of the Critical Quality Attributes (CQAs) for an immediate release pharmaceutical tablet. Slow disintegration often causes delay in tablet dissolution, which may affect the biopharmaceutical performance of the drug product. In this study, all tablets disintegrated very quickly (52±4 s for 1% MgSt, 60±4 s for 2% P188, and 57±3 s for 2% P407, n = 6).

The dissolution behaviors in pH 1.2 HCl solution among the three RTV tablets are similar, but the release of RTV from the tablets containing two poloxamers is slightly better (Figure 4.10a). The improvement can be explained by the improved wettability of tablets containing poloxamers. This is supported by the lower contact angles (both initially and after 1 s) of the tablets containing the poloxamers than that of the tablet containing 1% MgSt (Figure 4.10b).

RTV is a BCS class II drug and a weak base with two pK_as of 1.8 and 2.6 (solubility of 0.4 mg/mL in pH = 1.2 HCl solution and 0.001 mg/mL in pH 6.8 buffer) [71]. The use of SLS in a tablet formulation led to reduced dissolution due to the formation of an insoluble RTV-LS salt [58]. Hence, poloxamer may be used as a good alternative to MgSt for RTV or other similar basic drugs.

4.5 Future work

4.5.1 Justification of the work

The performance of tablet lubricant is evaluated based on its ability to reduce ejection force [19]. After consolidation during compression process, tablet is constrained inside the die with part of the applied compression force transmitted into radial stress, which is known as residual die wall stress (RDWS) [72]. Friction occurs in the interface of tablet edge and die wall and the magnitude of which depends on the contact area and coefficient of friction [8]. The axial force that is required to move the tablet out of this constraint is termed as ejection force (EJ Force). EF force is dependent on three parameters: (1) tablet thickness; (2) coefficient of friction at die-wall interface; and (3) residual die-wall stress (RDWS) [18]. Larger tablet thickness or coefficient of friction increases the contact area between tablet and die wall, thus increases the friction. Uzondu et al proposed that the ejection of tablet can be divided into two processes: static phase and kinetic phase. Static phase represents the ejection before tablet starts sliding on the die-wall, while kinetic phase represents the ejection process after sliding [73]. However, it is reported that the EJ force associated with the kinetic phase is negligible compared with the static phase (i.e., maximum EJ force is exhibited to make tablet slides). The relationship between EJ force and these three parameters can be represented in the following equation:

$$EJ\ force = tablet\ thickness * coefficient\ of\ friction * RDWS$$

Magnesium stearate (MgSt) has a laminate structure, which slides easily upon receiving external pressure. This provides a remarkable reduction of coefficient of friction, therefore effectively reduce the ejection force. Since MgSt works as a perfect boundary lubricant, which is a surface phenomenon, it has relatively satisfied performance in virtually any materials. However, based on the experimental data collected in chapter 3, poloxamers, compared with MgSt, does not always give satisfied lubrication performance. For example, poloxamers works better than MgSt at same concentration in MCC, but not in lactose. MCC is known to have self-lubrication function, which has a relatively smaller coefficient of friction. On the other hand, lactose as a hard material, exhibited larger coefficient of friction. Therefore, MgSt is able to reduce the ejection force in lactose more effectively through reducing the friction, which is not the case in poloxamer. If poloxamers are not able to effectively reduce the coefficient of friction, reduction in RDWS is the alternative way considering the tablet thickness remains fixed. Also, particle size of the two poloxamers studied in chapter 3 were similar with the model excipients, which make it hard to migrate from inside to the die-wall surface. This further diminish the surface phenomena of these compounds and promotes the consideration of RDWS reduction.

Previous studies showed that RDWS heavily relies on the maximum compression force, the ratio of force transmission (Janssen constant), as well as Poisson's ratio [73]. Higher Janssen constant leads to more transmission of compression force into RDWS. For materials with poor tabletability, higher maximum compression force is required to achieve a comparable tablet density, therefore leads to high RDWS. Data in chapter 3 indicates that the formulations containing poloxamer exhibit better tabletability and lubrication

efficiency, which partially supports this statement. In addition, the RDWS also depends on the elasticity of materials. High elastic material undergoes elastic deformation, which leads to high elastic recovery after withdrawal of compression force and low RDWS. Furthermore, lower Poisson's ratio leads to higher RDWS. However, since the EJ force depends on both friction and RDWS, interplay between these two parameters is crucial in understanding different lubrication behaviors. Literatures reported that coefficient of friction remains constant regardless of the lubrication conditions when MgSt was used as lubricant [74]. However, comparisons of coefficient of friction across different lubricants have not been clearly noted. Therefore, when investigating the possible mechanism of action for lubricants, both parameters need to be taken into control.

4.5.2 Hypothesis

Poloxamer 188 or poloxamer 407 reduces the ejection force through the reduction of RDWS.

4.5.3 Methods and Experimental Plan

4.5.3.1 Obtaining the shear strength of Poloxamers

4.5.3.2 Powder blending

4.5.3.3 Tablet compression

Tablet compression will be conducted in a compaction simulator with the capability of carrying instrumented die. Instrumented die provides useful in-die information such as

RDWS. Since RDWS varies based on tablet density, it is good to keep the maximum possible tablet density across the experiments, except for materials that are hard to reach same value as starch. In addition, to minimize the effects of tablet thickness on the friction, same in-die compaction thickness is kept for all materials. During compression, maximum compression force ($\sigma_{z,max}$) is determined by the instrument.

During the compression study, optimal tablet thickness needs to be determined prior to all experiments to ensure the tablets are perfectly positioned inside the die where die wall sensors are fully covered by tablets (Figure 4.11). This also determines the amount of materials used in each compression cycle. Fail to cover all three sensors may result in inaccurate determination of RDWS during ejection.

4.5.3.4 Determination of Janssen constant

Janssen constant can be determined by following the original methods [75] to explain the observed difference in RDWS to support the hypothesis. Poisson's ratio will also be determined from the maximum compression force and RDWS during unloading process.

4.5.3.5 Characterizations of lubrication efficiency and tabletability

4.5.3.6 Model fitting of RDWS and ejection force for different materials and experimental verification using other excipients.

4.5.3.7 Effects of the variations of particle size of Poloxamers on the RDWS and maximum compression force.

4.5.3.8 Effects of hydrophobicity of Poloxamers on the coefficient of friction and RDWS.

4.6 Conclusion

We have shown that P188 and P407 exhibit properties that support their use as alternative tablet lubricant. For MCC, either P188 or P407 at 1% level exhibits slightly better lubrication efficiency and tabletability than 1% MgSt. For lactose, more poloxamer is required to achieve a lubrication efficiency comparable to 1% MgSt; however, this does not deteriorate the tabletability. MCC mixed with either poloxamer is more robust against mixing intensity in terms of both lubrication and tableting performance. For a ritonavir formulation, the use of 2% P188 or P407 lowers the ejection force more effectively than 1% MgSt, while achieving better tabletability and dissolution. Overall, P407 slightly outperforms P188 as a possible alternative tablet lubricant.

Table 4.1. Ritonavir formulations tested in this work

Material	Amount (*w/w*)		
RTV	5%	5%	5%
60% MCC + 40% Lactose	89%	88%	88%
CCS	5%	5%	5%
MgSt	1%	-	-
P188 or P407	-	2%	2%

Table 4.2. Blending and compression conditions for robustness tests

Blending intensity (rpm)	Blending time (min)	Dwell time (ms)
49	5	30
101	5	30
49	10	30
49	5	100

Table 4.3. D10, D50 and D90 of P188, P407 and MgSt based on volume distribution (n = 3).

Material	D10 (μm)	D50 (μm)	D90 (μm)
P188	13.5 ± 0.9	44.1 ± 0.7	83.8 ± 2.2
P407	13.4 ± 0.1	46.3 ± 0.4	103.0 ± 1.0
MgSt	2.2 ± 0.0	8.0 ± 0.2	17.3 ± 0.4

Table 4.4. Effects of MgSt, P188, and P407 on the tensile strength at zero porosity (σ_0) of MCC and lactose.

Material	**Lubrication**	**σ_0 (MPa)**
MCC	1% MgSt	7.4 (0.12)
	1% P188	9.0 (0.17)
	1% P407	9.9 (0.09)
Lactose	1% MgSt	9.3 (0.61)
	1% P188	7.6 (0.28)
	2% P188	6.2 (0.29)
	5% P188	5.4 (0.13)
	1% P407	9.3 (0.46)
	2% P407	6.3 (0.21)
	5% P407	4.9 (0.11)

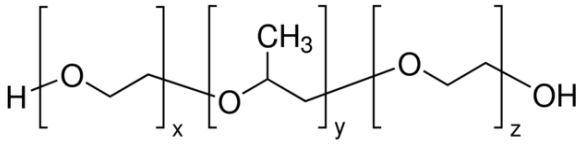

Figure 4.1. General structure formula of poloxamers

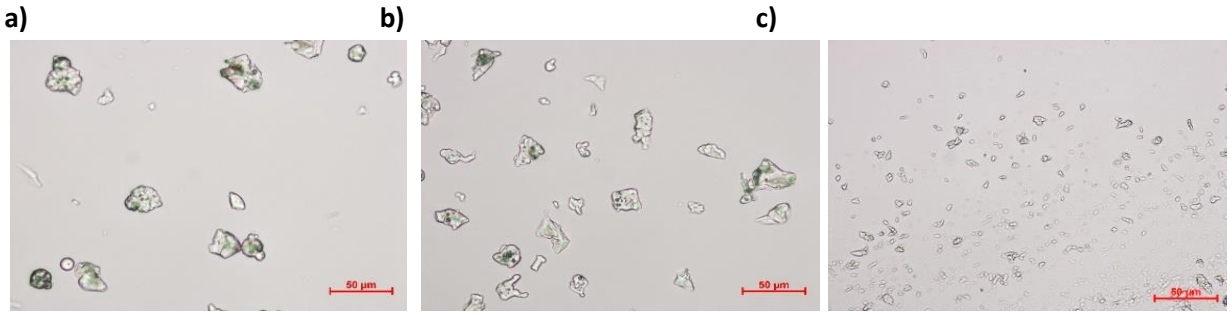

Figure 4.2. Polarized light microscope images of (a) Poloxamer 188, (b) Poloxamer 407, and (c) MgSt. The length of the scale bar is 50 µm.

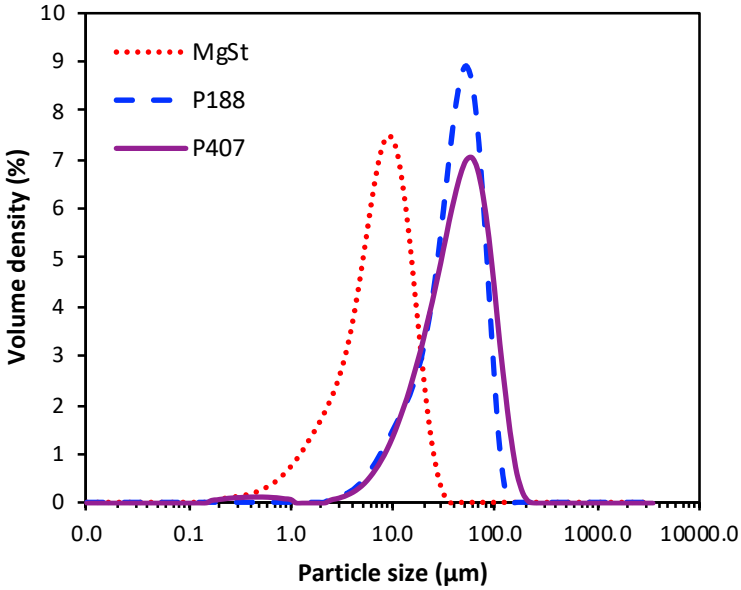

Figure 4.3. Particle size distributions of MgSt, P188, and P407.

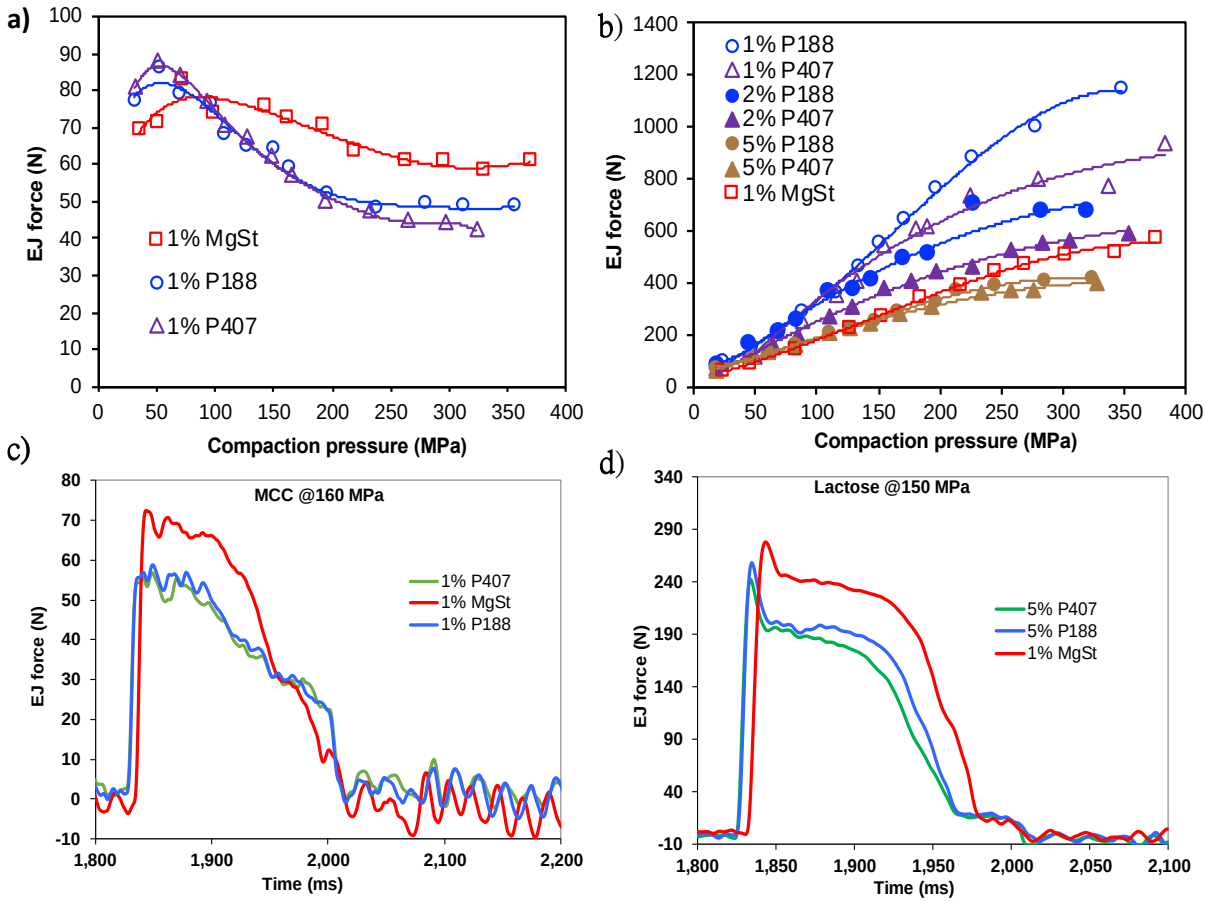

Figure 4.4 Lubrication efficiency of P188 or P407 on (a) MCC and (b) Lactose. Lines are fitted polynomial functions to the third order to show the trend. Full ejection force profiles of (c) MCC-lubricant mixtures, and (d) lactose-lubricant mixtures.

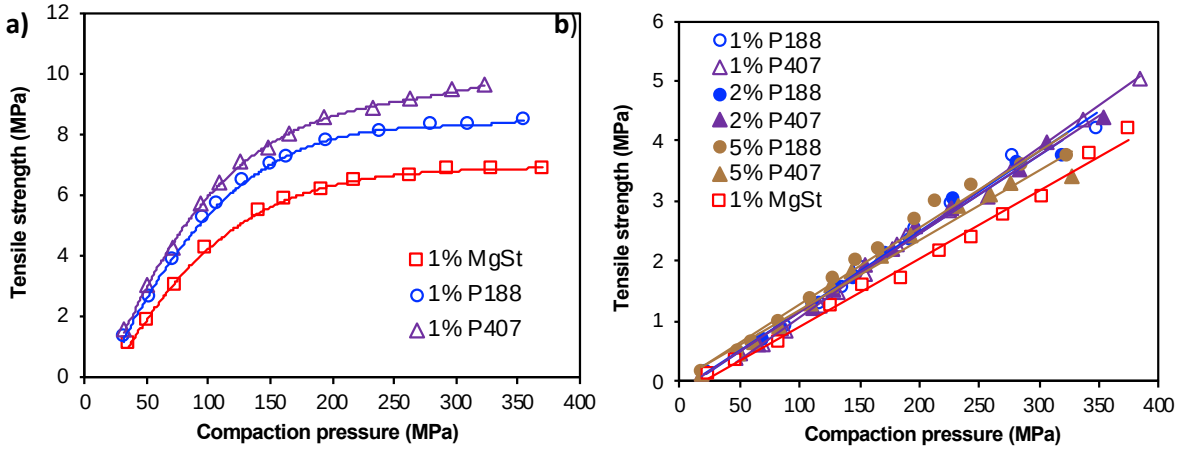

Figure 4.5 Effects of lubricants on tabletability. (a) MCC and (b) Lactose. To show the trend, lines are fitted with polynomial and linear functions for MCC and lactose, respectively.

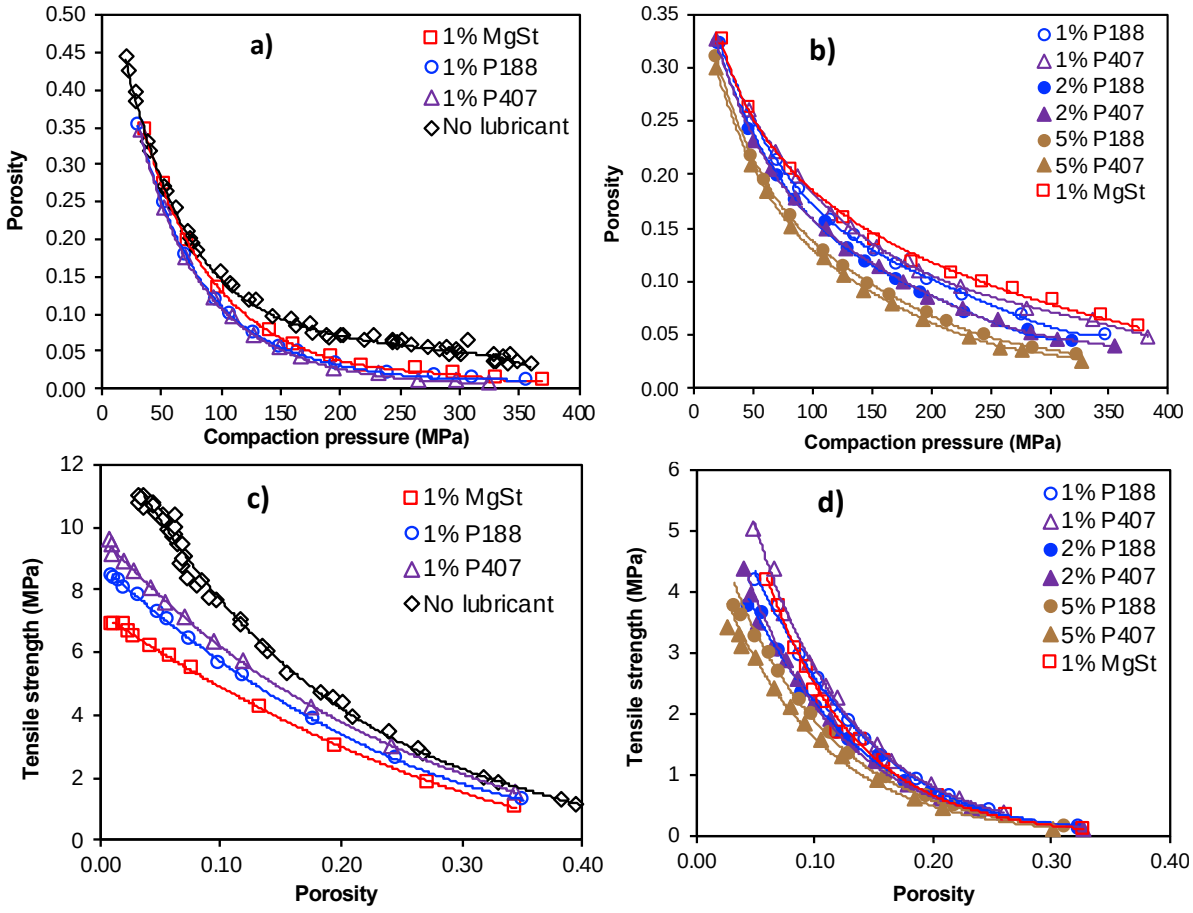

Figure 4.6. Effects of lubrication on compressibility of (a) MCC, (b) Lactose, and compactibility of (c) MCC, (d) Lactose. Lines are fitted with polynomial functions in a) and b) and exponential functions in c) and d).

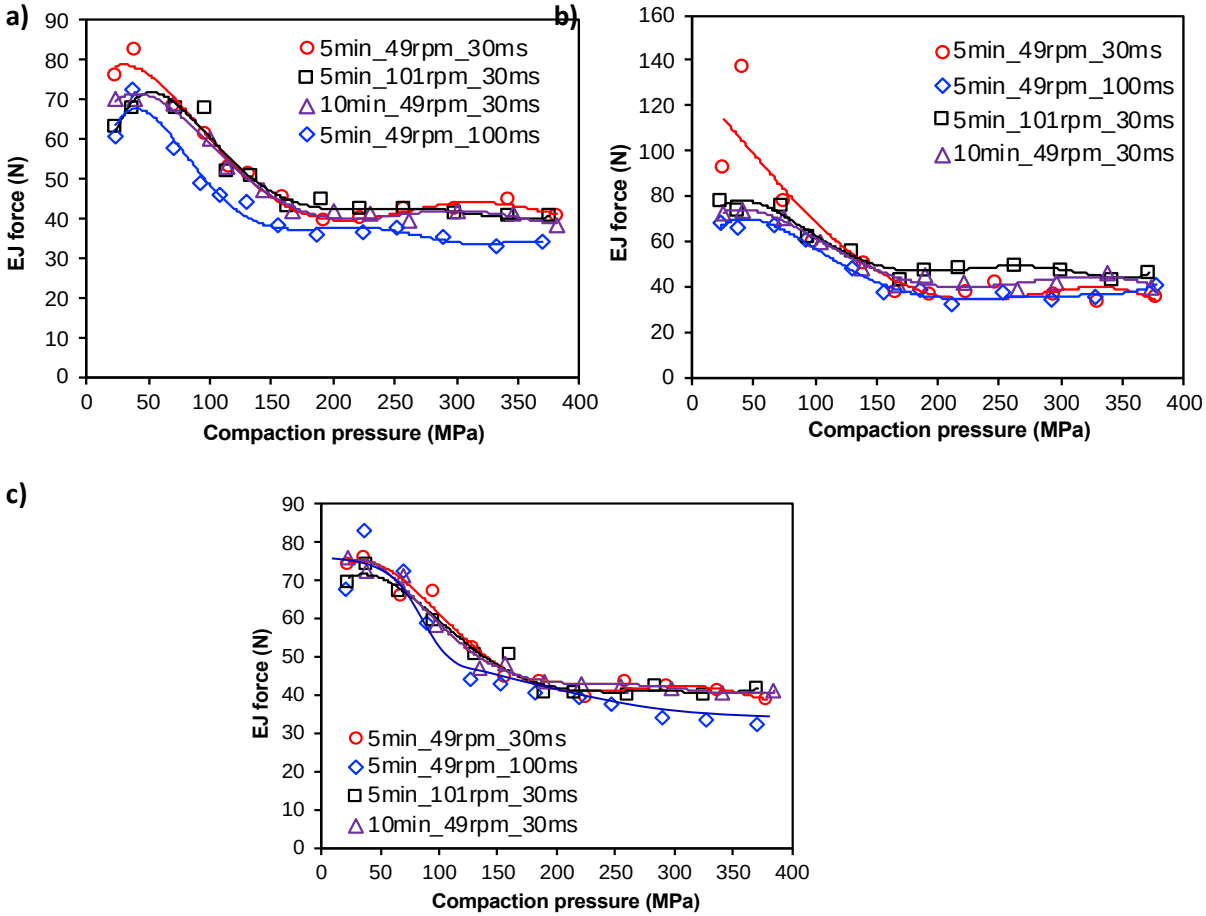

Figure 4.7. Effects of mixing time, mixing intensity and compaction speed on lubrication efficiency of MCC containing: (a) 1% MgSt, (b) 2% P188 and (c) 2% P407. Lines are manually drawn to show trend in data.

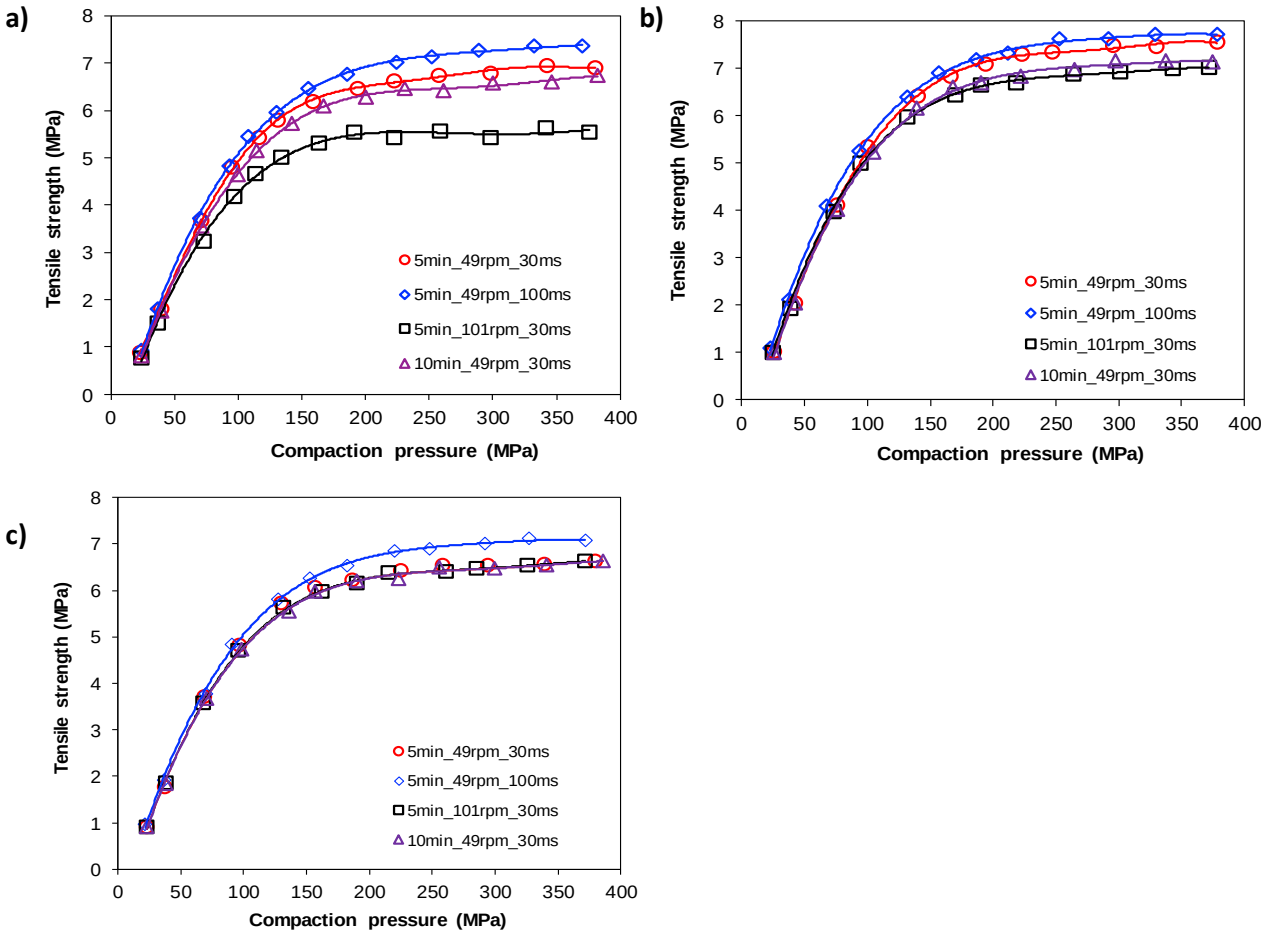

Figure 4.8. Effects of mixing time, mixing intensity and compaction speed on tabletability of MCC containing. (a) 1% MgSt, (b) 2% P188, and (c) 2% P407. Lines are fitted with polynomial functions to show trends

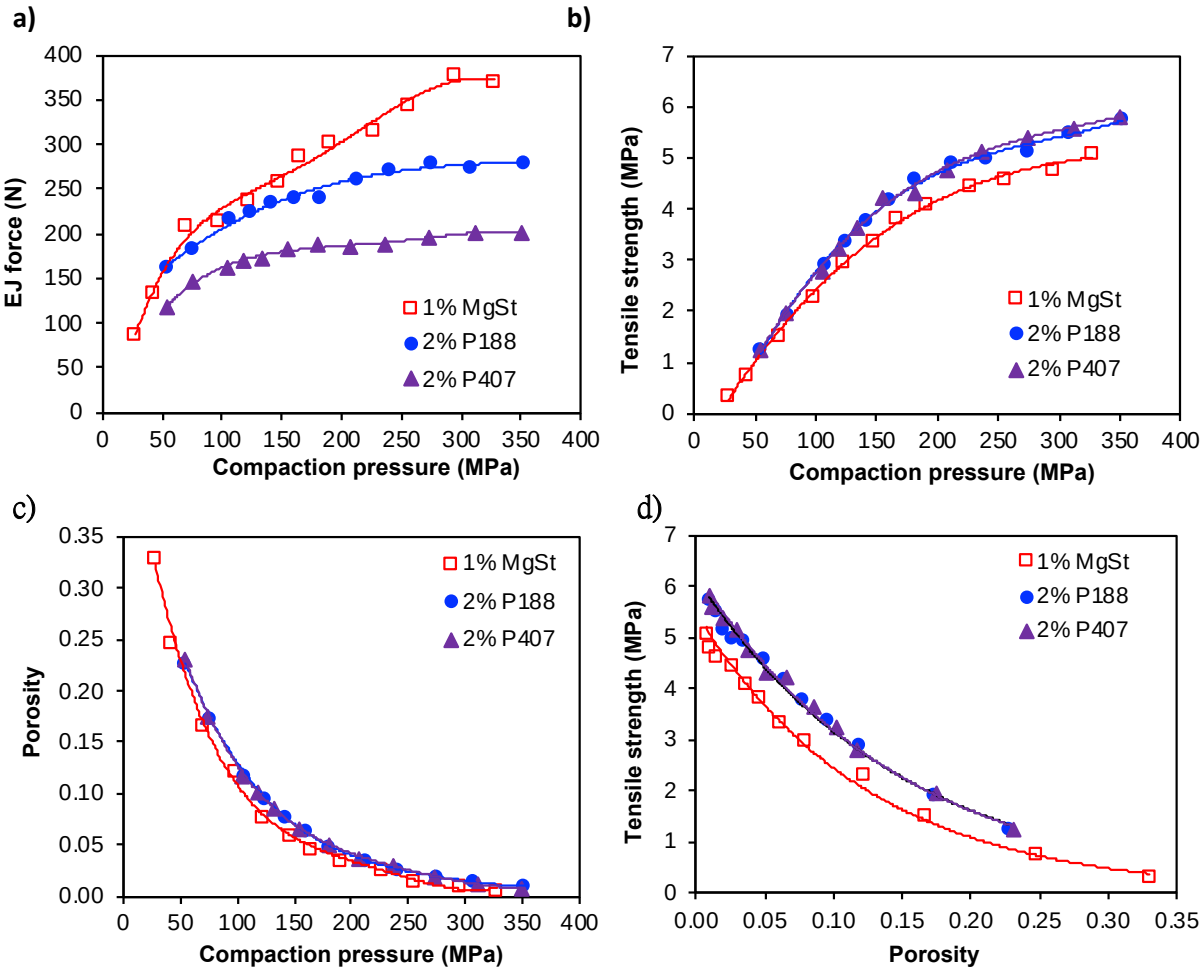

Figure 4.9. Effects of lubrications on the manufacturability of an RTV formulation. (a) lubrication efficiency, (b) tabletability, (c) compressibility, and (d) compactibility. Lines are fitted with polynomial functions in a) - c) and exponential functions in d).

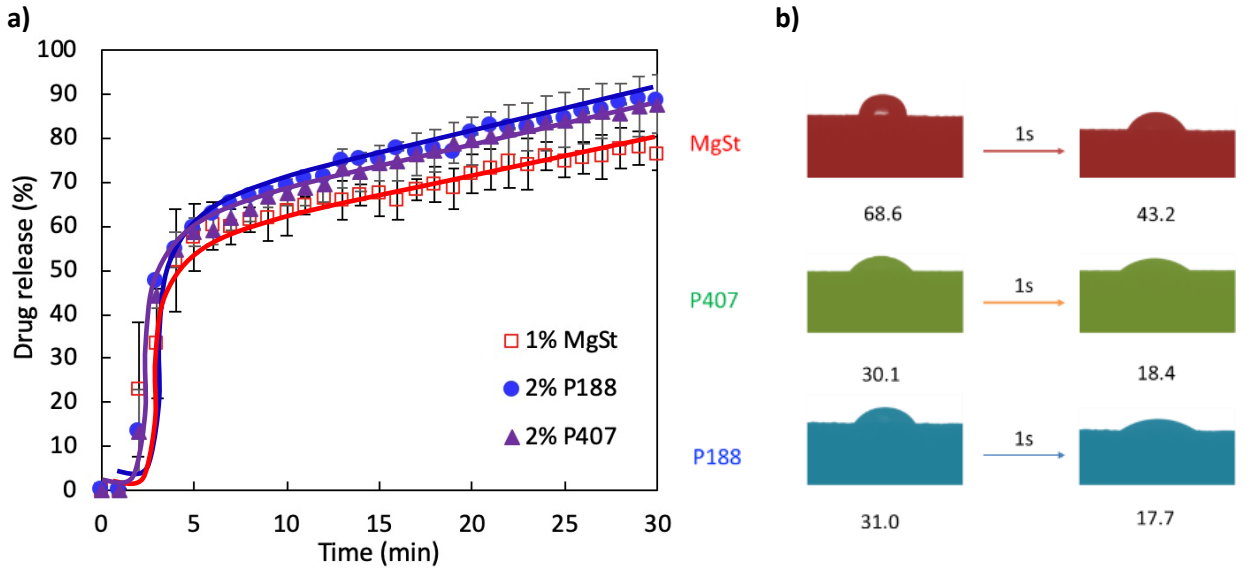

Figure 4.10 (a) In vitro dissolution of RTV tablets. (b) Wettability of RTV tablets. Lines are manually drawn show trend in data (n=3).

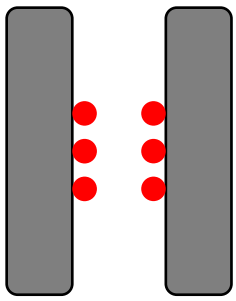

Figure 4.11 Die-wall sensors in an instrumented die

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Chapter 2.

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