

Review

## Lubricants in Pharmaceutical Solid Dosage Forms

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Received: 18 December 2013; in revised form: 21 January 2014 / Accepted: 24 January 2014 /  
Published: 25 February 2014

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**Abstract:** Lubrication plays a key role in successful manufacturing of pharmaceutical solid dosage forms; lubricants are essential ingredients in robust formulations to achieve this. Although many failures in pharmaceutical manufacturing operations are caused by issues related to lubrication, in general, lubricants do not gain adequate attention in the development of pharmaceutical formulations. In this paper, the fundamental background on lubrication is introduced, in which the relationships between lubrication and friction/adhesion forces are discussed. Then, the application of lubrication in the development of pharmaceutical products and manufacturing processes is discussed with an emphasis on magnesium stearate. In particular, the effect of its hydration state (anhydrate, monohydrate, dihydrate, and trihydrate) and its powder characteristics on lubrication efficiency, as well as product and process performance is summarized. In addition, the impact of lubrication on the dynamics of compaction/compression processes and on the mechanical properties of compacts/tablets is presented. Furthermore, the online monitoring of magnesium stearate in a blending process is briefly mentioned. Finally, the chemical compatibility of active pharmaceutical ingredient (API) with magnesium stearate and its reactive impurities is reviewed with examples from the literature illustrating the various reaction mechanisms involved.

**Keywords:** lubricants; boundary lubrication; magnesium stearate; friction; adhesion; the maximum compression pressure; ribbon and tablet density; chemical incompatibility

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## 1. Introduction

A lubricant, an additive to reduce friction, is an essential component of a drug formula since lubrication is often required to ensure the success of pharmaceutical manufacturing. Historically, use of animal fats as lubricants to reduce friction in transportation can be traced back to Egyptian time. However, the development of modern tribology, which is the study of friction and lubrication, did not gain ground until Frank P. Bowden established a research laboratory on friction, lubrication, and bearings in Melbourne, Australia during World War II [1]. Since then, a systematic study on friction and lubrication, termed “tribology”, was initiated. Lately, due to the development of instrumentations in surface and interfacial characterization, and force measurements as well as the improved understanding between friction and adhesion force, tribology has been developed into an active research field. In particular, in the pharmaceutical industry, the application of lubrication or tribology in drug development has become increasingly important for developing a successful manufacturing process [2].

For pharmaceutical operations such as blending, roller compaction, tablet manufacturing, and capsule-filling, lubrication is essential in order to reduce the friction between the surfaces of manufacturing equipment and that of organic solids as well as to ensure the continuation of an operation [3]. Pharmaceutical lubricants are the agents added to tablet and capsule formulations in a very small quantity (usually 0.25%–5.0%, w/w) to improve the powder processing properties of formulations. Albeit a fairly small amount, lubricants play important roles in manufacturing; they decrease friction at the interface between a tablet’s surface and the die wall during ejection so that the wear on punches and dies are reduced; they prevent sticking of tablets to punch faces as well as sticking of capsules to dosators and tamping pins. In terms of powder flow, lubricants can improve the flowability of blends and aid unit operations. For instance, for the blending of active pharmaceutical ingredients (APIs) of small particles with other excipients, the adhesion force between particles can significantly reduce the powder flowability by increasing inter-particle friction; poor flow can cause insufficient mixing of the blends (content uniformity) and rat-holing in the hopper of a tablet press (segregation issue), impacting both product quality and operation. To overcome these issues, lubricants are added (glidants) to enhance powder flow by reducing the inter-particle friction. Regarding lubrication agents, although magnesium stearate and stearic acid are the most frequently used lubricants in the pharmaceutical industry, there are other lubricants in use as well [4]. Moreover, because technologies for monitoring the dynamics of powder flow during manufacturing processes have been improved, the impact of lubricants on powder dynamics and compact properties are now better understood. All of this will be summarized in this paper.

In this review, we first present some fundamental principles on lubrication in terms of action mechanisms: friction reduction, friction and adhesion, and lubrication in pharmaceutical processes [5]. Then, a general overview on the use of lubricants in the pharmaceutical industry is provided. Specifically, magnesium stearate as a common lubricant will be examined in detail. Since there are many reviews on the lubricants of pharmaceutical uses, this review will concentrate on some new developments, including the pseudo-polymorphic aspect of magnesium stearate, the impact of magnesium stearate on compaction dynamics as well as the mechanical properties of compacts, and the technology development of online monitoring. Furthermore, we will review some potential chemical

interactions of magnesium stearate and its impurities with APIs in formulations. Finally, we conclude by presenting a general principle for selecting a lubricant for a pharmaceutical formulation.

## 2. Fundamentals of Lubrication

### 2.1. Friction

In general, lubrication is related to the reduction of friction. Contrary to the common belief, friction was actually first studied by Leonardo Da Vinci, but it was wrongly credited to Amontons, which is often referred to as Amontons's law [6]. The essential part of this law is expressed in Equation (1)

$$F_{\parallel} = \mu F_{\perp} \quad (1)$$

where  $F_{\parallel}$ ,  $\mu$ , and  $F_{\perp}$  are the force of friction proportional to the external load ( $F_{\perp}$ ), the coefficient of friction, and the normal force applied. In Equation (1), the following assumptions are made: The force of friction is proportional to the applied load; the frictional force is independent of the apparent contact area; the kinetics of friction is independent of the sliding velocity. Clearly, this is over-simplified. Since Amontons's law was derived from observing sliding wooden blocks, there is no consideration of adhesion. Amontons's law applies well to geometric or mechanic models that the interlock of surface asperities predominately contributes to the force of friction; the role of lubricants in reducing the frictional force is to fill these surface cavities. However, this model cannot account for adhesion forces involved which is ubiquitous for pharmaceutical operations due to the fine size of APIs and other excipients. Therefore, to understand the force of friction involved in pharmaceutical operations, a model with the incorporation of adhesion force is more suitable.

### 2.2. Friction and Adhesion

In general, friction is almost always associated with adhesion. By definition, the energy of adhesion is the energy required to break two dissimilar surfaces [6,7]. As expected, friction always increases with the adhesion between surfaces. The relationship between the force of friction and adhesion is shown in Equation (2)

$$F_{\parallel} = \mu F_{\perp} + 2\varepsilon A \frac{\Delta\gamma}{\delta} \quad (1)$$

The first term in Equation (2) represents a contact friction, where  $F_{\parallel}$ ,  $F_{\perp}$ , and  $\mu$ , are the force of friction, the applied normal force, and the coefficient of friction. The second term is the force involved in the adhesion hysteresis between two contacting materials, where  $A$ ,  $\varepsilon$ ,  $\Delta\gamma$ , and  $\delta$  are the area of contact, the transferred coefficient, the difference of surface energy, and the elemental distance [6]. As noted in Equation (2), the adhesion force involved in an adhesion hysteresis cycle strongly depends on the contact between two surfaces, which has been well investigated. Among the investigations are two notable theories, the Johnson-Kendall-Roberts (JKR) and Derjaguin-Muller-Toporov (DMP) models that have been reviewed by other authors [8]. Although each model has its own merits, they both assume a smooth surface contact with elastic deformation. Since, in practice, most of the surfaces of equipment used are rough rather than smooth, the effect of surface roughness on adhesion needs to be considered.

Recent experimental results suggest that adhesion force decreases exponentially with surface roughness as described in Equation (3).

$$F_{ad}(\sigma) = F_{ad}(0)e^{-\sigma/\sigma_0} \quad (2)$$

where  $F_{ad}(0)$  and  $\sigma$  represent the initial JKR adhesion force and the surface roughness parameter, respectively [5]. In addition, under compression, pharmaceutical powders may undergo a plastic deformation due to particle fracture or the deformation of excipients, or both. In this case, the adhesion force ( $F(\delta)$ ) for flat punch consists of forces from both plastic and elastic regimes as displayed in Equation (4).

$$F(\delta) = P_y A + C \quad (3)$$

where  $P_y$ ,  $A$ , and  $C$  are the force of adhesion per unit area, the area of contact, and an elastic component [6]. To reduce the frictional forces, (specifically the adhesion force), lubricants are incorporated into formulations to reduce the contact between powder particles and equipment surfaces [9]. In the next section, we will focus on the mechanisms of reducing these forces using lubricants.

### 2.3. Lubrication

In general, there are four lubrication mechanisms: hydrodynamic lubrication, elastohydrodynamic lubrication, mixed lubrication, and boundary lubrication [1,5]. As their names implies, the former three mechanisms are related to the usage of liquid lubricants to some extent. In the pharmaceutical industry, boundary lubrication is the most common mechanism functioning in unit operations [2]. For boundary lubrication, a lubricant typically forms layers/film between surfaces or at interfaces to reduce friction, where the penetration of the lubricant into surface asperities occurs. Structurally, the lubricants commonly used for boundary lubrication are long chain molecules with active end-groups such as stearic acid and its metallic salts. The typical end-groups include: (1)  $-\text{OH}$  (long chain alcohol); (2)  $-\text{NH}_2$  (long chain amine); (3)  $-\text{COOH}$  (long chain fatty acids); and (4) metal ions such as  $\text{Mg}^{2+}$ . The molecules with these end-groups can be readily adsorbed on the surfaces of metals or other particles to form an oriented monolayer or multilayers. The layers formed prevent further contact between the intended surfaces and powder particles. The efficiency of a boundary lubricant is measured by the extent to which these films can mask the field of force of the underlying surface [1]. In other words, a lubricant film such as the film of magnesium stearate needs to be sufficiently thick to cover the surface, typically a few layers. In addition, the breaking down of the lubricant film plays a significant role so that the motion of lubricated surface is facilitated. This will be illustrated by our discussion on the dihydrate of magnesium stearate, which in general gives the best lubrication efficiency due to its layered structure.

#### 2.3.1. Lubrication in Pharmaceutical Processes

To prepare solid dosage forms, many pharmaceutical operations, including blending, die-filling, compaction, capsule-filling, and compression, are utilized in the pharmaceutical industry. In these processes, friction occurs at either powder-tool interfaces or particle-particle interfaces. For the interaction between powder particles and the wall of equipment, it is commonly called wall friction; for the particle-particle interaction, it is termed as internal friction. In the following sections, we focus on the

fundamental aspects of friction reduction through lubrication for both wall friction and internal friction.

### 2.3.1.1. Wall Friction

Wall friction is the friction between a bulk solid and a solid surface such as between powder particles and the wall of a bin blender, where the bulk solid moves over the surface of the blender. To quantify wall friction, the wall friction angle,  $\phi_x$ , and the coefficient of wall friction,  $\mu$ , are often used. They are defined by the following Equations:

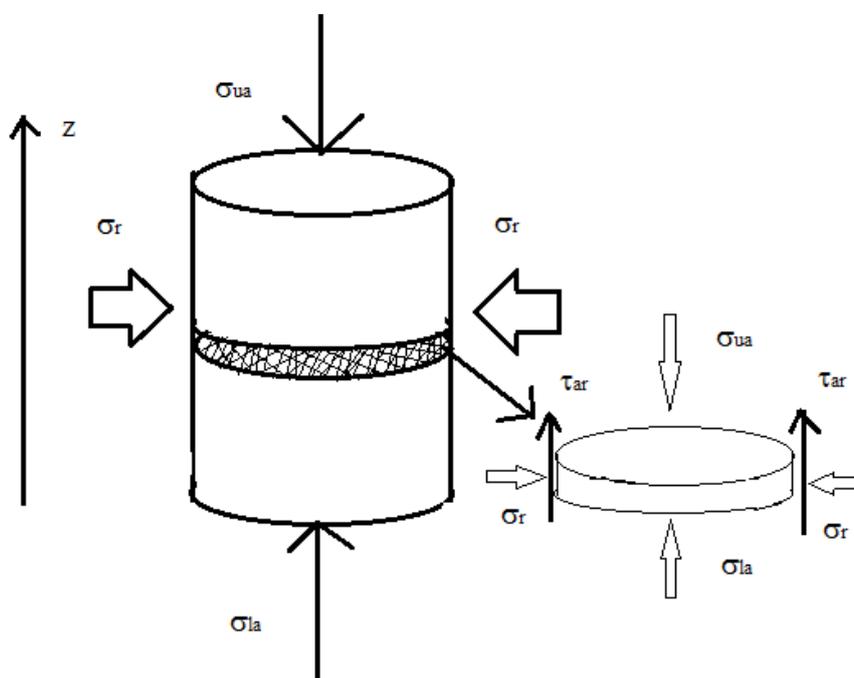
$$\mu = \frac{\tau_w}{\sigma_w} \text{ and } \phi_x = \arctan \frac{\tau_w}{\sigma_w} \tag{4}$$

where  $\tau_w$  and  $\sigma_w$  are the wall shear stress and the wall normal stress [10]. The larger the wall friction angle or the coefficient of wall friction, the greater is the wall friction. Although the wall friction angle is an important parameter to consider, in this paper, our discussion will focus on the coefficient of wall friction. In terms of boundary lubrication, the addition of a lubricant in formulations is to reduce the coefficient of wall friction by forming a boundary layer. For example, in a tableting process, the coefficient of friction is derived by the application of a force balance through integration (see Equation (6) and Figure 1) [11].

$$\mu = \frac{D}{4kL} (\ln \sigma_{zt} - \ln \sigma_{zb}) \tag{5}$$

where  $D$ ,  $L$ ,  $\sigma_{zt}$ , and  $\sigma_{zb}$  are the diameter of a powder compact, the length of the compact, the axial stress on the top, and the axial stress on the bottom, and  $k$  is the ratio of radial stress ( $\sigma_r$ ) over vertical stress ( $\sigma_z$ ).

**Figure 1.** Stress balance and the lubrication coefficient for powders in a tablet die:  $\sigma_{ua}$  and  $\sigma_{la}$  are stresses from top and bottom;  $\tau_{ar}$  is the shear stress.

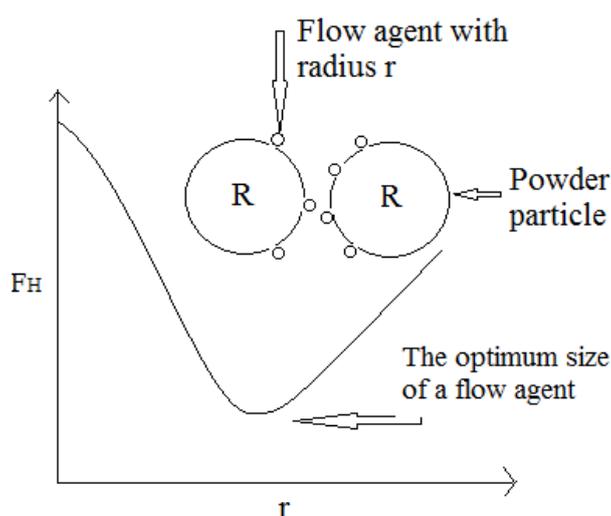


In this case, lubricants are used to reduce the shear stress required to move a tablet out of a die for a given normal stress. Similarly, lubricants can be used to decrease the internal friction among powder particles.

### 2.3.1.2. Powder Flow

Flowability of a bulk solid is characterized mainly by its unconfined yield strength,  $\sigma_c$ , as a function of the consolidation stress,  $\sigma_1$ . Usually, flow-function ( $ff_c$ ), which is the ratio of the consolidation stress,  $\sigma_1$ , to the unconfined yield strength,  $\sigma_c$ , is used to characterize the flowability of a blend numerically:  $ff_c < 1$ , not flowing;  $1 < ff_c < 2$ , very cohesive;  $2 < ff_c < 4$ , cohesive;  $4 < ff_c < 10$ , easy-flowing;  $10 < ff_c$ , free-flowing [10]. Poor flowability of powders in a hopper means that flow obstruction due to arching occurs or uneven flow causes ratholing. In addition, poor flowability can also cause content uniformity concern because of insufficient mixing. To improve the flowability of powders, flow aids or lubricants such as magnesium stearate are often incorporated in formulations. Flow agents are used to enhance the flow behavior of solids by reducing the inter-particle adhesion force. To achieve this, a flow agent should adhere to the surface of particles of solids as shown in Figure 2. More or less, the role of flow agent particles is similar to that of an increased surface roughness, in which the adhesion force is reduced due to the increased distance between particles. In addition, in the case of magnesium stearate, the hydrophobicity of the material surface also plays a role. As shown in Figure 2, the adhesion force of powders with flow agents first decreases with the radius of flow agent particles followed by a minimum. Then, it increases with the radius of particles. The optimal radius for reducing the inter-particle adhesion force is approximately in the range of 5–50 nm as calculated, depending on the particles size of powders [12].

**Figure 2.** Adhesive force ( $F_H$ ) as a function of the radius ( $r$ ) of a flow agent for powder particles with a radius of  $R$ .



## 3. Common Lubricants Used in Drug Development

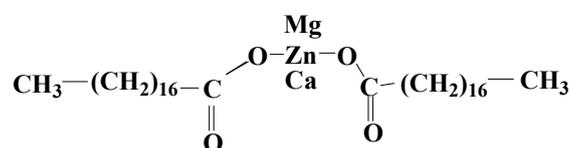
As described before, most of the lubricants used in the pharmaceutical processes are boundary lubricants; certainly, metallic salts of fatty acids such as magnesium stearate and stearic acid are the most

common ones. However, there are other lubricants, including fatty acid esters, inorganic materials, and polymers, which can be used in the cases when both magnesium stearate and stearic acid do not meet their performance expectation [13]. So, in the next section, various pharmaceutical lubricants other than magnesium stearate and stearic acid will be briefly discussed.

### 3.1. Metallic Salts of Fatty Acids

Use of the metallic salts of fatty acids as lubricants has a long history in the pharmaceutical industry and they are still the most dominant class of lubricants. Magnesium stearate, calcium stearate, and zinc stearate are the three common metallic salts of fatty acids used and their chemical structures are shown in Figure 3 [14]. Of these three lubricants, magnesium stearate is one of the most frequently used, and its application will be discussed in the following sections. In this section, we concentrate on the fundamental aspects of metallic salts of fatty acids in terms of friction reduction. Relative to fatty acids including lauric, myristic, palmitic, and stearic acids—they are typically melted at low temperatures (stearic acid has the highest melting point of about 69 °C), the metallic salts of fatty acids have much higher melting temperatures: zinc stearate (120 °C), magnesium stearate (140 °C), and calcium stearate (160 °C). In terms of the effect of chain length on friction reduction, typically friction decreases with increasing length of the hydrocarbon chains; approximately, the coefficient of friction can be reduced from about 0.5 to about 0.1. All in all, stearic acid has a chain length of the desired friction coefficient reduction. In addition, temperature has little effect on lubrication until it reaches the melting points of the lubricant. Furthermore, the structure of a lubricant layer at metal surfaces also plays a role in friction reduction; a thick layer can maintain and sustain a friction reduction with time. However, use of too much lubricant in tablet formulations can impact the product performance by decreasing tablet dissolution. In summary, most of the metallic salts of fatty acids can reduce the coefficient of friction to about 0.1. Nonetheless, other factors such as chemical compatibility will influence their use in the pharmaceutical industry. In the following sections, we will discuss a few classes of fatty acids/salts of fatty acids lubricants.

**Figure 3.** The chemical structures of metallic salts (calcium, magnesium, and zinc) of stearic acids.



### 3.2. Fatty Acids

Fatty acids are also common lubricants used in the pharmaceutical industry with stearic acid as the most popular one. Chemically, stearic acid is a straight-chain saturated monobasic acid found in animal fats and in varying degrees in cotton seed, corn, and coco [14]. The commercial material of stearic acid has other minor fatty acid constituents such as myristic acid and palmitic acid. Depending on the proportion of various acids present, the physical structure of commercial materials of stearic acid can range from macrocrystalline to microcrystalline. Correspondingly, its material properties can vary from

hard, to brittle, quite soft, and crumbly. For the macrocrystalline form of stearic acid, it has a ratio of stearic acid to palmitic acid of 45:55 (w/w); for the microcrystalline form, the ratio for stearic acid to palmitic acid is between 50:50 and 90:10. Table 1 shows the physical properties of these acids. As shown in Table 1, stearic acid has the highest melting and boiling points of the three. In addition, the lubrication property of stearic acid is listed in Table 2. Table 2 summarizes the friction coefficient, breakdown temperature-transition temperature from solid to liquid-of stearic acid at various metal surfaces. As shown in Table 2, the measured coefficient of friction varies with different metal surfaces (including steel), but their values are close to 0.1, similar to those reported for the metallic salts of fatty acids [1]. Therefore, it is expected that the lubrication performance of stearic acid should be similar to that of magnesium stearate at metal surfaces.

**Table 1.** Physical properties of pure solid fatty acids.

Fatty acid	Formula	Molecular weight	Melting point (°C)	Boiling point at 16 mm (°C)
Stearic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>16</sub> COOH	284	69.6	240
Palmitic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>14</sub> COOH	256	62.9	222
Myristic	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>12</sub> COOH	228	54.4	202

**Table 2.** Breakdown temperatures and friction coefficients at various metal surfaces.

Surfaces	Lubricant	Coefficient of friction at 20 °C	Breakdown temperature (°C)
Copper	1% stearic acid	0.08, smooth	90
	Smear copper stearate	0.08	94
Platinum & cadmium	1% stearic acid	0.05	130
	Cadmium stearate	0.04	140
Platinum & steel	Smear sodium stearate	0.1	280

### 3.3. Fatty Acid Esters

Fatty acid esters, including glyceride esters (glyceryl monostearate, glyceryl tribehenate, and glyceryl dibehenate) and sugar esters (sorbitan monostearate and sucrose monopalmitate), are often used as lubricants in the preparation of solid dosage forms [13,15,16]. Glyceryl dibehenate (Compritol<sup>®</sup> 888 ATO) is the one commonly used [17]. In particular, Compritol<sup>®</sup> 888 ATO is an effective lubricant to replace magnesium stearate when the latter causes delay of dissolution and other compatibility issues. Relative to magnesium stearate, Compritol<sup>®</sup> 888 ATO has similar lubrication efficiency with a higher optimal concentration (around 2%, w/w). In addition, the use of Compritol<sup>®</sup> 888 ATO does not affect compressibility. Furthermore, when a hot-melt coating process is used, the optimal concentration of Compritol<sup>®</sup> 888 ATO can be reduced to 0.5%–1% due to the reason that a uniformed coating is obtained [17].

### 3.4. Inorganic Materials and Polymers

Inorganic materials and polymers are also used as lubricants when magnesium stearate is not appropriate [2,13]. In terms of inorganic materials, talc (a hydrated magnesium silicate (Mg<sub>3</sub>Si<sub>4</sub>O<sub>10</sub>(OH)<sub>2</sub>)), is often used as a lubricant or a glidant in formulations [18]. Talc provides some essential lubricity for

pharmaceutical operations because of its hydrophobicity and weakly-bonded sheet structure. Compared with magnesium stearate, talc is less efficient in lubrication. However, when the formulation lubricated with magnesium stearate exhibits compatibility issues such as dissolution slow-down, talc can be used as a replacement or in combination with magnesium stearate. In many cases, the use of talc as a lubricant in formulations can improve tablet hardness, friability, and appearance. Similarly, polymers, such as PEG 4000, are occasionally used as lubricants in solid dosage forms when the use of magnesium stearate displays compression and chemical incompatibility issues [19]. Overall, as mentioned before, magnesium stearate is still the principal lubricant used in the pharmaceutical industry. In the following discussion, we will focus our attention on the effect of magnesium stearate on process and product performance, including the effect of its pseudo-polymorphic properties on lubrication, the impact of powder properties on blend flowability, and the influence of lubrication on compaction/compression dynamics and the mechanical properties of compacts and tablets, as well as its incompatibility with APIs and other formulation components.

#### 4. Magnesium Stearate

Magnesium stearate ( $\text{Mg}(\text{C}_{18}\text{H}_{35}\text{O}_2)_2$ ) is a solid and white powder at room temperature; it is a Food and Drug Administration (FDA)-approved inactive ingredient commonly used in the pharmaceutical industry. Magnesium stearate may be derived from plants as well as animal sources. It is prepared either by the chemical reaction of an aqueous solution of magnesium chloride with sodium stearate, or by the reaction of magnesium oxide, hydroxide or carbonate with stearic acid at elevated temperatures. The raw materials used in the manufacturing of magnesium stearate are refined fatty acids, a mixture of palmitic and stearic acid. Due to its manufacturing process, there are various impurities in magnesium stearate, often causing incompatibilities with APIs. So the chemical instability of APIs in the presence of magnesium stearate and their incompatibility, caused by either magnesium stearate or its impurities such as magnesium oxide, will be discussed in the chemical stability and incompatibility section. In the next few sections, our focus will center on the effect of magnesium stearate on the manufacturing process and product performance.

##### 4.1. Effect of Pseudo-Polymorph [20,21]

Magnesium stearate can form a variety of hydrates upon exposure to humidity. In addition to amorphous, magnesium stearate possesses four hydration states: anhydrate, monohydrate, dihydrate, and trihydrate. These hydration states can interchange reversibly, depending on temperature and relative humidity (RH). For instance, the trihydrate of magnesium stearate could be generated by exposing its anhydrate to a RH >70%. Therefore, depending on the environment in which materials have been exposed, magnesium stearate obtained from a vendor can be a mixture of anhydrate, hydrates, and amorphous. Consequently, most of the commercial supplies for this lubricant contain a mixture of various hydrates in unknown ratios. As reported, the lubrication efficiency of magnesium stearate as a lubricant varies from one hydration state to another; in general, the dihydrate is considered to be the most efficient lubricant of all, due to its crystal structure which is suitable for shearing. As a result, the flowability, permeability, porosity, and compressibility of a particular formulation lubricated with magnesium stearate depend on its moisture content or the RH of storage conditions. To further

investigate the impact of the hydration state of magnesium stearate on the performance of formulations, each hydrate was isolated and tested in formulations. For example, to test the lubrication efficiency of each hydrate and their mixtures, each hydrate or a combination of two (1%, w/w) was mixed with other formulation components: MCC (72%, w/w), lactose monohydrate (22%, w/w), and acetaminophen (5%, w/w). In general, different hydration states produce varied effects on the performance of formulations. For example, the formulation lubricated with the monohydrate of magnesium stearate showed the lowest permeability and porosity followed by the formulations lubricated with the dihydrate and the anhydrate of magnesium stearate, and finally the un-lubricated formulation. This suggests that the structure of the lubricant affects the inter-particle packing arrangement, and consequently the blends containing the monohydrate require a higher pressure to establish a flow relative to those with the dihydrate and the anhydrate. However, in terms of the crush strength of compacts, the un-lubricated formulation produced compacts with the highest crush strength (15.471 kg/cm<sup>2</sup>) followed by the formulations containing the dihydrate, the monohydrate, and the mixture of (50:50, w/w) the dihydrate and the monohydrate. Regarding lubrication, lubricity index—a measure of over-lubrication—can be expressed as:  $(\sigma_{\text{unlubricated}} - \sigma_{\text{lubricated}}) / \sigma_{\text{unlubricated}}$ , where  $\sigma_{\text{unlubricated}}$  and  $\sigma_{\text{lubricated}}$  are un-lubricated and lubricated crush strengths for compacts; the formulation containing the dihydrate showed the least tendency to cause over-lubrication. Thus, the lubricity index-ranking for the tendency to cause over-lubrication at a fixed concentration and lubrication time was: the dehydrate < the monohydrate < binary mixtures < the anhydrate. These results suggest that the level of water of hydration in the lubricant influences the tendency of over-lubrication. Furthermore, considering the effect of the hydration state on the compression process (pre-compression, main compression, ejection, and total forces), all blends containing the monohydrate yielded compression forces with less variability. In fact, the compression force profiles of the blends with the binary mixtures of the monohydrate and dihydrate or anhydrate were similar to those using the monohydrate alone, suggesting that the monolithic structure of the monohydrate of magnesium stearate appears to be the dominant influence in achieving a stable compression force. Further results indicated that the blends with either the anhydrate or the dihydrate required less total force for compression. Moreover, the blends containing the binary mixtures of the dihydrate with the anhydrate in various ratios seemed to require less total force than those with the dihydrate and the monohydrate, suggesting that the presence of the monohydrate in formulations requires more ejection force. In summary, when comparing the performance of three hydrates of magnesium stearate and their binary combinations (ratio varied from 25:75, 50:50 to 75:25), the formulations containing the monohydrate tend to have less permeability and porosity, and these formulations produce tableting forces with less variability during operation. However, they in general require more ejection force. In contrast, relatively, the formulations lubricated with the dihydrate appear to have less tendency for over-lubrication and require less total compression force. Overall, the performance of formulations having the dihydrate form of magnesium stearate is superior to others (see Table 3 for detailed ranking). Fundamentally, it is generally believed that the long spacing in the crystal structure of magnesium stearate dihydrate contributes to its lubrication efficiency although it has been suggested that the determination of the exact spacing for these forms is challenging due to the reversible exchange of water between forms. Finally, in addition to its pseudo-polymorphic effect on lubrication, the powder properties or the solid properties of magnesium stearate such as particle size, particle morphology, and

surface area also influence the lubrication performance of formulations with magnesium stearate, and this will be discussed in the following section.

**Table 3.** The overall performance ranking of three pseudo-polymorphs of magnesium stearate and their binary mixtures [20].

Formula	Magnesium stearate ratio	Pre-Compression force	Main compression force	Ejection force	Porosity	Overall ranking
1	A50:M50	F	F	P	P	12th
2	A25:M75	P	G	P	P	11th
3	A75:M25	P	G	F	F	5th
4	D50:A50	P	G	G	G	5th
5	D75:A25	F	G	G	G	3rd
6	D25:A75	F	P	G	G	4th
7	D50:M50	F	P	P	F	8th
8	D75:M25	F	F	F	P	8th
9	D25:M75	F	F	F	P	8th
10	Anhydrous	G	F	G	F	2nd
11	Monohydrate	F	P	P	P	7th
12	Dihydrate	G	F	G	F	1st

A, M, and D represent anhydrous, monohydrate, and dihydrate; P, F, and G stand for poor, fair and good.

#### 4.2. Effect of Powder Properties on Lubrication

In practice, the effect of the hydration state of magnesium stearate on lubrication cannot be separated from other factors such as surface areas and agglomeration [22]. The materials of magnesium stearate obtained from various vendors or different batches of the same vendor often have varied powder properties such as particle size, surface area, and particle shape [23]. Therefore, it is important to understand the impact of these properties on the performance of the lubricated formulations, including the mechanical properties of the compressed products, the dissolution of tablets, and the flowability of powder. Generally, it is expected that the lubrication efficiency of magnesium stearate improves with increasing its surface area or decreasing its particle size since the increase of surface area can provide more surface coverage [24]. Consequently, with more coverage of particle surfaces by magnesium stearate, the particle-particle bonding is weakened, resulting in weak tablets. In addition, because the surface of API particles is covered with the lubricant which is hydrophobic, it causes slow-down of dissolution. For instance, as reported by Dansereau and Peck [25], the tensile stress of MCC tablets lubricated with magnesium stearate decreased with increasing surface area of the lubricant. As a result, the friability of these tablets went up with increasing the surface area. Additionally, it was reported that the dissolution of dexamethasone-lactose tablets was enhanced by increasing the particle size of magnesium stearate, and the optimal size range for the lubricant was found to be from 350–500  $\mu\text{m}$  [26]. More recently, the impact of the variability of powder properties of magnesium stearate on the roller-compacted, immediate release tablets was investigated based on a quality-by-design study [27]; in addition to the lubricant, MCC, spray-dried lactose, and sodium starch glycolate were also included in the study. Particularly, the effect of the variability of the lubricant on formulation performance such as the flowability of blends, segregation propensity, hardness, and tensile strength was evaluated. It was

concluded that the ribbon tensile strength and tablet hardness significantly increased as the specific surface area of magnesium stearate decreased (particle size increased), which is consistent with the results reported previously.

The flowability of blends in pharmaceutical operations is critical for the success of manufacturing. Since the addition of magnesium stearate in a formulation generally improves the flowability of the formulation, it is often used as a flow agent. The flowability of a blend is typically assessed by measuring the following parameters: static angle of repose, Carr index, Hausner ratio, and the flow-function obtained from a shear-cell measurement. Of these parameters, the flow-function is the most useful parameter for assessing blend flowability, but other parameters are often used because of their simplicity. In general, the flowability of a blend is affected by many factors: the type of lubricant, the interaction of the lubricant with other materials, lubricant concentration, and mixing time. For example, relative to other lubricants including magnesium silicate, calcium stearate, and stearic acid, magnesium stearate is the most effective lubricant in improving the flowability of lactose even with a small amount [28]. This is because the particles of magnesium stearate preferentially interact with lactose particles and fill the surface cavities of these particles. The impact of magnesium stearate on the flowability of a blend also depends on the material nature of the blend. For instance, for a free-flow blend, the effect of the lubricant on the blend flowability is not significant. However, as the blend becomes more cohesive, the presence of lubricant greatly improves its flowability [29]. In addition, the flowability of the blends containing an API is also related to the API particle size and size distribution. As an example, the flowability of ibuprofen particles of various sizes was shown to be significantly improved by lubrication using magnesium stearate based on internal angle measurement [30]. This can be explained by the fact that small particles (fines) of APIs typically cause a flow issue, and the incorporation of the lubricant as a flow agent can coat the surface of particles to reduce inter-particle friction, which ultimately improves the powder flow. For a lubricant to be effective as a flow agent, it needs to adhere to the surface of particles. Thus, distribution of the lubricant throughout blends by mixing is critical. However, over-mixing often causes dissolution delay or other issues. As shown in a study, for a mixture of lactose and magnesium stearate, when it was mixed beyond the optimal time (a few minutes), the performance of tablets decreased; the hardness of tablets was reduced, and the disintegration time was prolonged. This is because once magnesium stearate delaminates and forms a film around substrate particles, it is very difficult to disrupt. Furthermore, the distribution of magnesium stearate among substrate particles and its film formation around the substrate particles is also dependent on the mixing speed and the equipment used as shown by the study [31]. Mechanistically, the mixing behavior of magnesium stearate is governed by shear, as well as dispersion and convective actions, and shear mixing has been proven to be the most important of the three [32]. Since magnesium stearate is fairly hydrophobic, its mixing behavior is similar to that of sodium dodecyl sulfate. Finally, magnesium stearate can be combined with other additives such as silicon dioxide to further improve the flowability of micronized APIs. In conclusion, magnesium stearate is an effective agent to improve the flowability of APIs and formulations.

#### 4.3. Effect on the Mechanical Properties of Compressed Products [33–35]

As discussed before, the presence of magnesium stearate in a blend can significantly affect the flowability of the blend, which consequently impacts on the dynamics of compaction/compression processes (such as roller compaction). Therefore, the mechanical properties of any compacts/tablets manufactured are lubricant dependent. For instance, during the roller compaction of the blends of microcrystalline cellulose (MCC) and dicalcium phosphate dihydrate (DCPD), the presence of magnesium stearate modified the compaction dynamics by influencing both the maximum compression pressure and the nip angle of the process. Specifically, comparing the blend of MCC lubricated with magnesium stearate with that without, both the maximum compression pressure and the nip angle were reduced with lubrication at roll speeds of 3 rpm as well 5 rpm. Additionally, the reduction of the maximum compression pressure and the nip angle increased with increasing lubricant concentration. In terms of the method of lubrication, it was found that mixing the lubricant with MCC powders (bulk-lubrication) was much more effective than just spraying the lubricant to press surfaces (roll-lubrication). Furthermore, since lubrication reduced the compression pressure and the nip angle, the mechanical properties of compacts such as density were also altered. In particular, relative to the MCC blend without lubricant, the relative density of the lubricated ribbon, compressed from the MCC blend containing magnesium stearate, was consistently lower. This is because the compression pressure for the lubricated blend is generally lower compared with the un-lubricated one, due to the improved flowability and the reduction of wall friction. As expected, the average relative density of the ribbons remained unaffected when just the press was lubricated by spraying; this is due to the fact that roll-lubrication only reduces the friction between powders and the surface of a compactor, not the inter-particle friction of powder particles. However, for DCPD blends, a brittle material, the maximum compression pressure and the nip angle were reduced by both roll-lubrication and bulk-lubrication; the values of reduction were comparable for both, reaching a constant value at 0.25% (w/w) lubricant concentration. The reason for the difference between MCC and DCPD blends is that DCPD powders are brittle (easy to fracture) and less cohesive relative to MCC powders. Therefore, the flowability of DCPD powders is dominated by new surfaces generated by particle fracture so that its effect on the compression pressure and the nip angle is about the same, whether roll-lubrication or bulk-lubrication.

Lubrication also affects the solid fraction of ribbons after compaction as well as the solid fraction and the tensile strength of tablets made. In this case, for the ribbons prepared with MCC blends, the reduction of the solid fraction increased with the lubricant concentration for both bulk-lubrication and roll-lubrication; relatively, bulk-lubrication yielded a larger reduction. In addition to the reduction of the solid fraction, the fracture energy for MCC ribbons was also reduced. Interestingly, a similar trend was observed for the ribbons made from DCPD blends although the solid fraction of DCPD ribbons was smaller than those made with MCC blends. Besides, the ribbons of DCPD were too fragile for measuring the fracture energies. Overall, the ribbon density is determined by how powder is fed into the compaction zone, which is influenced by the flowability of the powder. In terms of operating parameters including the nip angle and the maximum pressure in the nip region as well as the variation in density across a ribbon, they often increase with increasing friction, and therefore, these parameters would decrease if the powder were to be lubricated.

When a uniaxial compression process is used to make tablets, lubrication impacts the properties of tablets whether powders or granules are used as feeding materials. In the case of MCC, the solid fraction of MCC tablets was not affected by lubrication, but their tensile strength was reduced, in particular at 1% magnesium stearate concentration; this was true whether the powders of MCC or the granules of MCC were fed into the tablet press; however, relative to the tablets made from feeding MCC powders, tablets have a lower solid fraction and tensile strength when MCC granules are used. For DCPD tablets, the solid fraction and tensile strength were not affected with lubrication for both feeding materials. However, in general, the tablets made with DCPD granules have much lower tensile strength. This is because MCC is a deformable material whereas DCPD is a brittle material. Mechanistically, the reduction of tensile strength for MCC tablets is due to magnesium stearate, a boundary lubricant, which coats the particle surface to form a layer and reduces the tablet strength. Interestingly, for DCPD, it appears that lubrication with magnesium stearate has little effect on both the solid fraction and the tablet strength, primarily because the fractured-nature of DCPD creates fresh surfaces without lubricant attached, so that the tablet strength is not affected.

#### *4.4. Online Monitoring of Magnesium Stearate in Blending*

As discussed above, lubrication can significantly change the dynamics of blending and compaction/compression, as well as the mechanical properties (solid fraction and tensile strength) of compacts/tablets made. Therefore, monitoring of the change of magnesium stearate during manufacturing and storage becomes very critical. In particular, the hydration state of magnesium stearate changes with humidity and temperature, and its lubrication efficiency varies with its composition. To detect the composition change, near infrared spectroscopy (NIR) in conjunction with other thermal methods was used to monitor the variability of the hydration state during operation, in which the absorption wavelengths for monohydrate and dehydrate are 7045 and 5100  $\text{cm}^{-1}$ , respectively [36]. The results from NIR were in general consistent with those obtained using other methods such as thermal gravimetric analysis. However, the NIR method with partial least squares regression analysis is more sensitive to the presence of small quantities of hydrates. In addition, the distribution of magnesium stearate on tablet surfaces in a punch-face lubrication system was detected by Raman imaging technique using a wavelength of 1295  $\text{cm}^{-1}$ , allowing the determination of the domain size of magnesium stearate in one dimension [37]. In contrast, when the same approach was applied to lubricated formulations, Raman failed to detect the signal of magnesium stearate presumably due to interferences from other materials in the formulations. Furthermore, to determine the end-point of a blending process for a formulation with magnesium stearate, thermal effusivity sensors can be used to monitor the blend uniformity [38]. This was demonstrated for the blend of magnesium stearate and sugar sphere in a V-blender. Comparing the thermal effusivity data with the powder density, the former correlated well with the powder characteristics of the system for achieving optimal mixing. This is important since when various hydrates of magnesium stearate are used as lubricants, the time required to achieve a homogeneous blend varies. Hence, using thermal effusivity sensors to monitor a blending process can detect the end-point nondestructively without sampling the blend to avoid over-lubrication. Overall, the online monitoring of pharmaceutical processes becomes increasingly important for

achieving the optimum performance for a formulation and avoiding the detrimental effect due to over-lubrication and inhomogeneous distribution.

## 5. Chemical Stability and Compatibility

Chemical instability issues of APIs in the presence of lubricants have been widely reported, especially for magnesium stearate. Regarding the effect of magnesium stearate on the chemical instability of an API, there are several factors to consider, including the impurities (MgO), the effect of alkalinity caused by magnesium stearate, its catalytic effect, and other chemical reactions initiated and mediated by magnesium ions. These will be discussed in the following sections.

### 5.1. Potential Interactions with Impurities (MgO)

The commercial materials of magnesium stearate contain several impurities such as magnesium oxide (MgO) and palmitic acid; so, these impurities often react with APIs in the solid state causing stability issues. For instance, as reported by Kararli *et al.*, MgO reacts with ibuprofen at certain temperatures and humidity values in the solid state [39]. Specifically, when the mixture of MgO and ibuprofen was stressed at 40 °C and 75% RH, a significant amount of degradation was detected by differential scanning calorimeter (DSC), thermal gravimetric analysis (TGA), and multiple internal reflectance infrared (MIR). In fact, MgO reacted with ibuprofen to form the magnesium salt of ibuprofen. The reaction was accelerated with increasing temperature; it degraded at 40 °C after 1 day; but at 30 °C, no significant interaction was observed for up to 80 days. In another study, ketoprofen was found to form a eutectic mixture with magnesium stearate [40,41]. Besides, the magnesium stearate itself also reacts with APIs, and a few examples are given in the following passage.

### 5.2. Hydrolytic Degradation at Basic pH

The presence of magnesium stearate in a formulation can increase the micro-environmental pH of the formulation, creating an alkaline condition and consequently accelerating the hydrolysis of some drugs. For example, the degradation rate of acetylsalicylic acid (aspirin) in a blend increased with the addition of magnesium stearate; the hydrolysis rate depended on the concentration of magnesium stearate in the blend. This is because acetylsalicylic acid is a moisture-sensitive drug, and its degradation is often associated with the presence of water and/or an alkaline pH condition [42–44]. In addition, Kornblum and Zoglio [45] found that in the presence of magnesium stearate, the rate of degradation of acetylsalicylic acid in suspensions was associated with the high solubility of the magnesium salt of acetylsalicylic acid. Presumably, this is due to the fact that a buffer layer around the particles of acetylsalicylic acid was formed, creating an environment that was detrimental to the chemical stability of the compound [46]. Based on Miller and York's [13] description, the lowering of the melting point of acetylsalicylic acid may be facilitated by the formation of a surface film of magnesium stearate around the particles of acetylsalicylic acid, creating intimate contact between the two materials and leading to degradation. As a consequence of chemical incompatibility between aspirin and magnesium stearate, a number of potentially undesirable products, such as salicylic acid, salicyl salicylic acid and acetyl salicyl salicylic acid, are produced. Furthermore, the presence of MgO impurity in magnesium stearate may

also play a role since it could enhance the degradation by creating an alkaline pH environment. For example, Gordon *et al.* noticed that in the presence of magnesium stearate, ibuprofen forms a eutectic mixture which sublimates [47]. Additionally, quinapril (a tetrahydroisoquinoline carboxylic acid), an angiotensin-converting enzyme (ACE) inhibitor, was also found to be incompatible with magnesium stearate due to the basicity of the lubricant; the degradation of quinapril was mediated by the availability of moisture. However, on the positive side, as reported by Fouda *et al.*, although magnesium stearate accelerated the degradation of aspirin, stearic acid can protect drugs (aspirin) against degradation [44]. Therefore, for this reason, stearic acid is an alternative option in terms of lubricant selection. Finally, in addition to hydrolysis, oxidation is another reaction causing chemical instability issues associated with the presence of magnesium stearate, which is discussed in the next section.

### 5.3. Oxidation

The presence of magnesium stearate in a formulation can also induce an oxidation reaction. For instance, the decomposition of drotaverine HCl was accelerated when magnesium stearate and talc were present in a formulation [48]. In addition, the chemical instability of drotaverine hydrochloride was significantly influenced by the pH of the formulation, and the degradation rate was largely enhanced in the presence of magnesium stearate. Specifically, drotaverine HCl was degraded to drotaveraldine by an oxidative degradation pathway, which can be inhibited using an antioxidant or an acidic auxiliary material. A similar catalytic action of magnesium stearate was observed with the autoxidation of 2,6,10,14-tetramethylpentadecane, where magnesium stearate catalyzed the decomposition of hydroperoxide first to boost autoxidation of the compound [49]. Aside from its effect on oxidation, the metal ions from magnesium stearate also cause chemical instability.

### 5.4. Metal Ion-Mediated Degradation

Degradation of drugs is also mediated by the presence of magnesium ions. For example, upon an accelerated stress treatment, fosinopril sodium was degraded into a  $\beta$ -ketoamide (III) and a phosphoric acid (IV) in a prototype tablet formulation with magnesium stearate [50]. It was shown by further investigation that the degradation of fosinopril was mediated by magnesium metal ions, and thus a mechanism invoking metal chelation was postulated. Based on a kinetic study, it was established that the degradation was a second-order reaction between fosinopril and magnesium. Since many drugs are susceptible to ion-catalyzed degradation, it has been suggested that stearate salts should be avoided as tablet lubricants. However, by addition of malic acid, hexamic acid, and maleic acid in a formulation, the degradative effect of alkali stearates can be inhibited due to competition for the lubricant cation between the drug and an additive acid. The incompatibility of magnesium stearate with a drug also depends on the functional groups of the drug. For example, drugs with an amine group are often very reactive, which is discussed in the following section.

### 5.5. Reaction with Amines

Many drugs contain amine groups, and amines are typically prone to reactions with excipients and salt counter-ions. Specifically, the potential for a reaction with magnesium stearate or stearic acid is

particularly of concern when a drug has a primary amine group. In the case of norfloxacin, after a prolonged storage at 60 °C, the formation of a stearyl derivative was observed in the tablets containing magnesium stearate. Other drugs, found to be incompatible with magnesium stearate, include glimepiride, cephalexin, glipizide, ibuprofen, indomethacin, ketoprofen, moexipril, nalidixic acid, primaquine, promethazine hydrochloride, temazepam, glibenclamide, penicillin G, oxacillin, clopidogrel besylate and erythromycin [51]. In summary, drugs with a primary amine group are often very unstable in formulations containing magnesium stearate. Besides the reaction associated with a primary amine group, the incompatibility between magnesium stearate and drugs can be caused by other interactions as well, which is described in the following section.

### 5.6. Other Interactions between Magnesium Stearate and Drugs

There are other interactions between drugs and magnesium stearate causing incompatibility. Captopril (another ACE inhibitor) is a pyrrolidine carboxylic acid derivative used in the treatment of hypertension. During grinding (5 min at room temperature at 32% or 80% RH), it was shown that captopril interacted with a metallic stearate at surfaces, in which the mixtures of captopril and each metallic stearate gave different results, before and after grinding, as detected by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and Fourier transformed infrared spectroscopy (FTIR). It appeared that grinding accelerated the solid-state interaction of captopril with magnesium stearate. In addition, the solid-state interaction between captopril and magnesium stearate was also evidenced by the shifting of the IR spectral peak for the  $\text{-COOH}$  of the stearate moiety from  $1578\text{--}1541\text{ cm}^{-1}$ . This can be attributed to the interaction of the  $\text{-OH}$  group in the carboxylic acid of captopril with bridging coordination of the  $\text{-COO}$  group of magnesium stearate via hydrogen bonding involving water; the interaction between captopril and magnesium stearate was stopped at 60 °C due to evaporation of water from the ground mixture.

Other interactions between lubricants and drugs also affect the performance of drug products. For example, as described before, prolonged mixing of formulations with magnesium stearate can result in slow-down of dissolution due to the excessive coating of granules by magnesium stearate, which acts as a water repellent. The extent of slow-down in the dissolution of formulations may depend upon the aqueous solubility of the active ingredients. This phenomenon was also observed for other hydrophobic lubricants such as calcium stearate or zinc stearate. However, when replacing magnesium stearate with hydrophilic lubricants such as Stear-O-Wet<sup>®</sup> or sodium stearyl fumarate, the dissolution slow-down was not observed. Similarly, changing a disintegrant can also improve the dissolution of formulations. For instance, Desai *et al.* studied the effect of magnesium stearate on the content uniformity of three APIs in powder blends [52]. Among the hydrophobic lubricants, magnesium stearate caused the maximum slow-down in dissolution, followed by zinc stearate and calcium stearate, respectively. Replacement of pregelatinized starch by starch-derived superdisintegrants such as Explotab<sup>®</sup> or Primojel<sup>®</sup> resulted in no slow-down of the dissolution of capsules, even after over-mixing with 1% w/w magnesium stearate. Interestingly, although the granules over-mixed with 1% w/w, hydrophobic lubricants exhibited slow-down in dissolution when filled into capsules, tablets compressed from these granules dissolved rapidly, indicating the impact of dosage forms on dissolution. Besides magnesium stearate, stearic acid and sodium stearyl fumarate are two common alternative lubricants used in pharmaceutical

formulations. Their lubrication properties and interactions with APIs are briefly reviewed in the following sections.

### 5.7. Stearic Acid

Although stearic acid (12 out of 200 tablet formulations), in comparison with magnesium stearate (108 out of 200 tablet formulations), is a less frequently used lubricant, it provides an important alternative option when the use of magnesium stearate is not feasible. As reported by Desai *et al.*, the incompatibility of stearic acid with other formulation components is of concern [53]. For example, it was observed that two formulations in capsules, containing povidone as a binder and stearic acid as a lubricant, exhibited slow-down in dissolution, after 3–6 weeks of storage under elevated temperature and humidity conditions [53]. Once stearic acid was replaced with magnesium stearate, a rapid dissolution was obtained under similar storage conditions. On further investigation, it was shown that the mixture of povidone and stearic acid formed a transparent, hard, glass-like insoluble substance at 50 °C. Because the porosity of granules was reduced by the glassy material formed, the dissolution of the granules was slowed down. To further verify, powder X-ray diffraction was used to examine the mixture of stearic acid and povidone, showing that stearic acid lost its crystallinity. Based on this observation, it was suggested that a combination of stearic acid and povidone should be avoided for immediate release formulations. In addition, as reported by Wang *et al.*, stearic acid can also play a role in the polymorphic phase transformation of an API, which subsequently results in slow-down of the dissolution of its tablets [54]. Specifically, when formulations were subjected to high shear mixing or high temperature drying, the dissolution slow-down was more significant. Mechanistically, it was found the slow-down of tablet dissolution was due to the transformation of polymorphic forms (Form II to Form I), which was facilitated by stearic acid [54]. In summary, even though stearic acid has incompatibility issues with APIs or formulation components, it is still an important alternative lubricant to be used in solid dosage forms.

### 5.8. Sodium Stearyl Fumarate

In addition to stearic acid, sodium stearyl fumarate is another alternative lubricant to be used in solid dosage forms. Since sodium stearyl fumarate is often supplied in a purer form, it can provide an option when the less pure stearate-type lubricants (stearic acid and magnesium stearate) are unsuitable due to chemical incompatibility. Sodium stearyl fumarate has a usage rate of four out of 200 drugs as a lubricant in formulations. It is less hydrophobic and has a less retardant effect on tablet dissolution than magnesium stearate. As reported by Arne W. Hölzer, *et al.*, compared with magnesium stearate, sodium stearyl fumarate has the same lubrication efficiency, and about the same influence on tablet strength and disintegration [55]. However, due to the importance of the particle size of sodium stearyl fumarate, prolonged mixing improved its lubricating effect and had no effect on tablet disintegration. Therefore, sodium stearyl fumarate appears to be a good alternative to magnesium stearate in certain solid dosage formulations.

## 6. Considerations for Selecting a Lubricant

In summary, there are many factors to be considered for selecting an appropriate lubricant for preparing solid dosage forms including: low shear strength, being able to form a durable layer covering the surface/particles, non-toxic, chemically compatible with APIs and other components in the formulation, low batch to batch variability, and having minimum adverse effects on the performance of the finished dosage forms. In addition, the optimal concentration and mixing time are also needed to be taken into consideration when selecting a lubricant because both of these two parameters greatly impact the performance of pharmaceutical products and processes. Although low lubricant concentration and inadequate mixing cause inefficient lubrication issues such as sticking, capping, and binding in the die cavity, over-lubrication-high lubricant concentration and over-mixing-often results in an adverse effect on products as well as processes, including the reduction of tablet hardness, compression variability, the prolongation of disintegration time, and the decrease of the rate of dissolution. In Table 4, the recommended concentrations of typical lubricants used in solid dosage forms are listed. In terms of the process of adding a lubricant, the lubricant is often added at the end of the granulation process in the outer phase when other components have been mixed thoroughly. Furthermore, the mixing time for distributing a lubricant is typically 0.5–5 min for better results on compactability and the hardness of tablets. Finally, selecting a lubricant for a formulation requires a systematic approach with careful consideration of the performance of both product and process.

**Table 4.** The optimal concentration of commonly used lubricants for preparing solid dosage forms.

<b>Water soluble lubricant</b>	<b>Amount in formulation (%)</b>	<b>Water insoluble lubricant</b>	<b>Amount in formulation (%)</b>
<b>Boric acid</b>	1	<b>Metal (Mg, Ca, Na) stearate</b>	0.25–2
<b>Carbowax (PEG) 4000/6000</b>	1–5	<b>Stearic acid</b>	0.25–2
<b>Sodium oleate</b>	5	<b>Sterotex</b>	0.25–1
<b>Sodium benzoate</b>	5	<b>Talc</b>	1–5
<b>Sodium acetate</b>	5	<b>Waxes</b>	1–5
<b>Sodium lauryl sulfate</b>	1–5	<b>Stear-O-Wet</b>	1–5
<b>Mg-Lauryl sulfate</b>	1–2	<b>Glyceryl behenate (Compritol 888)</b>	0.5–3

## 7. Conclusions

In this paper, the fundamentals of lubrication and the action mechanisms of lubricants in typical pharmaceutical manufacturing processes have been reviewed; the role of lubricants in improving pharmaceutical operations by reducing the adhesion forces between powder/equipment as well as particle/particle in terms of wall friction and inter-particle friction has been summarized. In addition to other classes of lubricants used in the pharmaceutical industry, magnesium stearate as the most frequently used lubricant has been discussed in detail. Furthermore, the lubrication efficacy of hydrates of magnesium stearate and their effect on the performance of formulations in pharmaceutical operations were discussed. Overall, it was concluded that the dihydrate of magnesium stearate is the best hydration state for lubrication. In terms of the effect of lubricant particle size, magnesium stearate with a large

surface area and small particle size has the best lubrication efficiency, but it reduced the hardness of tablets and caused slow-down of dissolution. Moreover, the lubricant significantly affects the dynamic process of compaction/compression and the mechanical properties (solid fraction and tensile strength) of ribbons as well as tablets due to the improved flowability of the lubricated blends. For adequate lubrication, on-line monitoring can help to determine the end-point of a blending process, and the distribution of lubricant as well as its composition. Finally, magnesium stearate and its impurities often cause chemical instability of APIs. In selection of a lubricant for a formulation many factors including chemical instability, physical incompatibility, and lubrication efficiency should be considered.

### Acknowledgments

The authors would like to thank Jennifer Wang of Teva Pharmaceutical Industries Limited for suggestions.

### Conflicts of Interest

The authors declare no conflict of interest.

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