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Review article

Lubrication in tablet formulations

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ABSTRACT

Theoretical aspects and practical considerations of lubrication in tablet compression are reviewed in this paper. Properties of the materials that are often used as lubricants, such as magnesium stearate, in tablet dosage form are summarized. The manufacturing process factors that may affect tablet lubrication are discussed. As important as the lubricants in tablet formulations are, their presence can cause some changes to the tablet physical and chemical properties. Furthermore, a detailed review is provided on the methodologies used to characterize lubrication process during tablet compression with relevant process analytical technologies. Finally, the Quality-by-Design considerations for tablet formulation and process development in terms of lubrication are discussed.

1. Theoretical aspects of lubrication during tablet compression

Tablet compression leads to the consolidation of particles into a pellet of specific strength. Tablet compression normally results in particle rearrangement, deformation of particles, interparticulate bond formation, and elastic recovery upon ejection of the compact from the die [1]. The penultimate step in a tablet compression process is ejection. The ejection force is the force needed to push the tablet out of the die. Significant decrease in the overall ejection force is observed when the material and/or the die are properly lubricated. The extent of lubrication also becomes important in the last step during tablet compression when the tablet leaves the lower punch. The take-off force is the force required to scrape the formed tablet off the lower punch face after it is ejected from the die. Lubrication is most relevant to the tablet ejection and tablet take-off steps as the lubricant helps to reduce the friction between the tablet and the metal surface, making the overall tablet compression process much smoother.

The physical basis of either ejection force or take-off force during tablet compression is intermolecular interactions of the powder blend. Due to the thermodynamic nature of the intermolecular and interparticulate interactions, it is easier to understand them through energy terms. However, it is the interaction forces between macroscopic bodies that are often easier to measure experimentally. For example, interactions between the sides of the tablet and the die wall are determined by measuring the magnitude of the tablet ejection force, not the ejection energy. The same is true for the tablet take-off process. Both the tablet ejection and take-off forces are measures of the adhesive interactions between two surfaces.

A rigorous theoretical treatment of the adhesive interactions of elastic spheres was proposed by Johnson, Kendall and Roberts [2] based on the assumption that real particles (surfaces) are not completely rigid. Since then, the theoretical treatment, known as the "JKR theory", has formed the basis of much of the modern theories of adhesion mechanics. While different pharmaceutical powders may tend toward elastic, plastic deformation, or brittle fragmentation, most pharmaceutical ingredients, however, exhibit mixed behavior.

As indicated by the JKR model, the radius of the contact area, a, can be calculated by:

$$a = \left(\frac{R}{K}\left[F + 3\pi R W_{12} + \sqrt{6\pi R W_{12} F + (3\pi R W_{12})^2}\right]\right)^{1/3} \quad (1)$$

where K is the elastic constant, W_{12} is the interfacial surface energy, R is the radius of the sphere, and F is the external force. If zero external force is applied to the sphere, the contact radius, a_0, is given by:

$$a_0 = \left(\frac{6\pi R^2 W_{12}}{K}\right)^{1/3} \quad (2)$$

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Because of adhesion, the sphere cannot be separated from the surface until the pull-off force reaches a critical value, F_S, as given by the following equation (Fig. 1 [3]):

$$F_S = \frac{3}{2}\pi R W_{12} \quad (3)$$

In the case of tablet ejection, instead of breaking the adhesive interactions by a "pull-off" force for which a vertical force is exerted to pull one particle apart from another, it is assumed that the "bond" between the sides of the tablet and the die wall is broken up by pushing the tablet out of the die during tablet ejection. These adhesive interactions are often expressed in terms of "friction", which can be characterized by the "coefficient of friction". For the tablet take-off process, the adhesive interactions are broken up by the scraping action. So, if a material has the ability to reduce the adhesive interactions between the tablet and the die wall or lower punch surface, such a material has the potential of being a lubricant.

There are two basic mechanisms by which a lubricant affects tablet compression [4,5]. The first is by means of a continuous fluid thin layer in which the lubricant, such as mineral oil, separates the tablet surface and the metal surface. The coefficient of friction of such fluid lubricants can be as low as 0.001. The second mechanism is by means of "boundary lubrication". The lubricant particles form a continuous or non-continuous resistant layer or film on the tableting material or metal surfaces. The coefficient of friction of boundary lubricants can range from 0.15 to 0.5. The fluid lubricants need to be used in larger quantity than boundary lubricants, often making their use impractical in tablet formulations.

According to the JKR theory (see Eq. (3)), there are two main approaches to reducing adhesive interactions during tablet ejection or take-off with the boundary lubrication mechanism. They are as follows:

(1) reduction in the intrinsic adhesive interactions, i.e., the interfacial interactions, between the tableting powder material and the metal surface and
(2) reduction in the contact area between the tablet powder particles and the die wall surface or between the tablet face and punch surface.

The commonly used boundary lubricants usually have one or both functions. An effective "boundary" lubricant typically has such attributes as low shear stress, relatively high melting point, large specific area/small particle size, amphiphilic activity, and film-forming tendency. Hirai et al. [6] have also proposed that the junctions between the particles and the die wall grow in size during the course of sliding, and the lubricants prevent this growth resulting in a decrease in the friction and adhesion forces.

The aforementioned attributes of a lubricant are unique as they are not normally found with other excipients, such as fillers, binders, or disintegrants, in a tablet formulation. For example, the lubrication function of magnesium (Mg) stearate, a well-known lubricant used for tablet compression, arises from these characteristics. According to the United States Pharmacopeia (USP32-NF27) and European Pharmacopeia (6th Edition), Mg stearate is a mixture containing mainly magnesium stearate and magnesium palmitate with stearate content not less than 40% and the sum of the stearate and palmitate not less than 90% of the total of all fatty acid ester. Its physical properties are widely reported in the literature. First of all, Mg stearate has a remarkably low maximum shear stress of 85 kg/cm^2, which is determined by its coefficient of friction on the die wall surface [7,8]. The lower shear stress indicates that Mg stearate has little affinity for the metal surface. Water and/or gas molecules from the environment may also enter the long lattice of the Mg stearate crystal structure, spreading within spaces, and decreasing the interactive force of the crystal lattice. This reduces the shearing force required to cleave the crystalline particles of Mg stearate [9]. Secondly, Mg stearate has very small particle size and large surface area. A wide range of physical properties have been reported [10,11] for Mg stearate with most of the values falling in the ranges provided in parenthesis: melting point 94–150 °C (125–127 °C); specific surface area 1.3–10.5 m^2/g (4–6 m^2/g); particle size 2–15 μm and moisture content, by Karl Fischer, 4.8–5.2%. Thirdly, it has been reported [5] that, due to its amphiphilic property, Mg stearate adheres to metal surfaces with its polar head leaving the carbohydrate tail group to stick out to form boundary film lubrication. Convincing evidence that Mg stearate forms a film in order to be an effective lubricant was provided by Bolhuis et al. [12] in 1975. Mg stearate film in a sodium chloride solution is shown in Fig. 2. In this classic experiment, one crystalline particle of sodium chloride, out of a well-mixed blend of sodium chloride with 0.5% Mg stearate, was placed on a water surface saturated with Mg stearate. Once sodium chloride started to dissolve, the Mg stearate film unfolded as a film maintaining the shape of the salt crystal. It has also been shown by a flow-through dissolution technique [13,14] that Mg stearate forms a hydrophobic thin film on the surface of the carrier material.

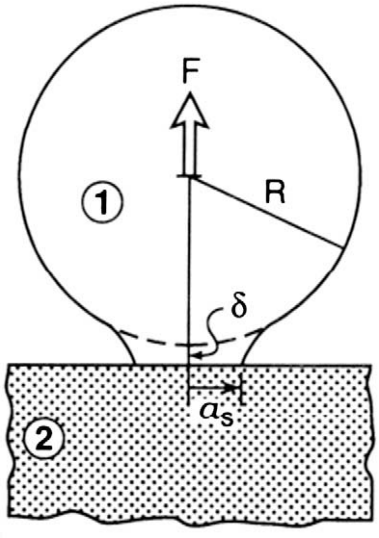

Fig. 1. Critical pull-off force due to adhesion of a sphere (1) on a flat surface (2).

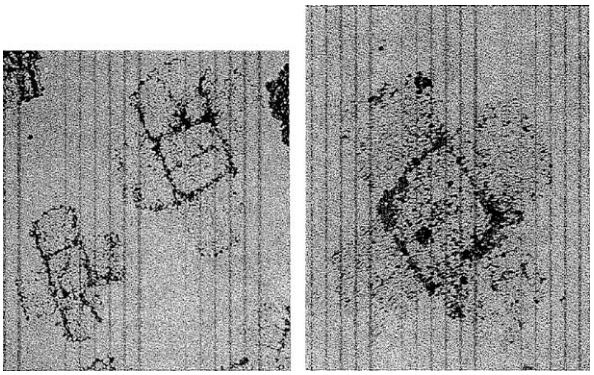

Fig. 2. Unfolded magnesium stearate envelopes on water, isolated from sodium chloride crystals, after mixing with magnesium stearate (approx. 30× and 60×).

2. Types of lubricants

Most of the lubricants used for pharmaceutical processes are boundary lubricants. They are chemically inert, odorless, and tasteless. Some commonly used lubricants for tablet compression are described in the following paragraphs.

2.1. Metallic salts of fatty acids

Mg stearate, aluminum stearate, calcium stearate, sodium stearate, and zinc stearate are a few examples in this group of lubricants. These lubricants are commonly used in the range of 0.25–1.0% (w/w) for tablet compression [15]. Mg stearate can be replaced with sodium stearate or calcium stearate if Mg stearate cannot be used in the formulation due to chemical stability concerns [16].

Mg stearate is very widely used for tablet compression [17], so it is not surprising that it has become the most studied lubricant. Stearic acid from food-grade crude oil is the key raw material to produce Mg stearate. The oil is initially hydrogenated and then thermally split into fatty acid and glycerin. The fatty acid and glycerin are separated by distillation. Mg stearate is then produced by using sodium hydroxide to saponify the fatty acid to the soluble sodium salt form, followed by the addition of Mg sulfate solution to precipitate the Mg stearate.

In terms of the source of Mg stearate, there has been increasing concerns about the potential risk of the transmissible spongiform encephalopathies (TSE) including the bovine form occurring in cows (BSE or mad-cow-disease), the scrapie disease in sheep, as well as the human form, the variant Creutzfeldt–Jakob disease. In order to minimize the risks, materials with a potential risk of BSE/TSE-infectivity must be eliminated from the human and animal food-chain. Therefore, the vegetable-derived, not animal-derived, Mg stearate has increasingly gained its popularity in the pharmaceutical industry. In addition, Mg stearate has been included in various compendia such as USP-NF, Eur.Ph., BP, and JP. While USP-NF has published General Chapters such as Good Manufacturing Practices for Bulk Pharmaceutical Excipients ⟨1078⟩ and Bulk Pharmaceutical Excipients-Certificate of Analysis ⟨1080⟩, the harmonization of the international excipient standards (e.g., the excipient master file guide by the International Pharmaceutical Excipients Council) is still an ongoing effort [18].

The particle size and specific surface area of Mg stearate may be the key factors influencing its lubrication efficiency. In practice, the particle size, instead of the surface area, is much more often used as a measure of the lubricant characteristics. It is mainly due to the fact that particle size measurement of a powder material is faster, easier, and less controversial. Three batches of Mg stearate differing in morphology, specific surface area, bulk density, and particle size were compared in the same formulation [10]. Although they were in the same amount, they gave rise to tablets differing in hardness, disintegration, and dissolution [10]. It was suggested that the specific surface area and not the amount of Mg stearate should be used to determine its usage since the difference between Mg stearate batches could be explained to a great extent by differences in surface areas [19]. For example, if the concentration of Mg stearate increases from zero to 0.2% in tablets, the coefficient of friction on die wall decreases by more than 50% [20]. When the lubricant concentration reaches a certain concentration, it did not make much difference whether the lubricant is in granular form or powder form in terms of how it performed its lubrication function [21].

Sadek et al. [13] deduced the minimum amount of glidant/lubricant in a formulation as follows:

$$\text{Minimum amount } (\%) = 6 \times \frac{d \cdot \rho_g}{D \cdot \rho_p} \times 100 \quad (4)$$

where d is the diameter of the glidant/lubricant particle, D is the diameter of the host particle, ρ_g is the true glidant density, and ρ_p is the bulk density of the powder. Their study suggested that the use of an excessive amount would hinder flowability because the forces of interparticulate adhesion would be greater than the interparticulate friction between the host particles. The crystalline structure of Mg stearate is also important. Monohydrate and dihydrate forms of neat Mg stearate have been shown by SEM, XRPD, NIR, DSC, and TGA techniques [22] to have distinct physicochemical properties. In general, the commercially available Mg stearate consists of the dihydrate or a mixture of monohydrate, dihydrate, and trihydrate, with the material from some vendors containing more amorphous components [23]. Tablet compaction studies showed that the blends lubricated with Mg stearate monohydrate required higher compression forces, ejection force, and take-off force than those with the dihydrate form. Another important point to note is that materials supplied by different vendors are unlikely to be of exactly the same physical properties but lot-to-lot variability of materials obtained from the same vendor is less likely to present a problem.

2.2. Fatty acids, hydrocarbons, and fatty alcohols

In general, fatty acids are more effective die lubricants than the corresponding alcohols, and the alcohols are better than the corresponding hydrocarbons. Among fatty acids with carbon atom content of C10 to C24; alcohols with carbon atom content of C12 to C22; and hydrocarbons with carbon atom content of C16 to C22, the lubrication effectiveness increases as the length of the molecular carbon chain increases to a certain point. For example, stearic acid (C18) offer greater lubrication than such shorter carbon chain compounds as decanoic (C10) and dodecanoic (C12) acids or longer carbon chain cousins such as eicosanoic (C20), docosanoic (C22), and tetracosanoic acids (C24) [24–27]. Similarly, octadecanol (C18) provides a more effective lubrication effect than alcohols with longer or shorter carbon chains. The lubrication effect of octadecanol, however, decreases when tablet compression run is prolonged. Hydrocarbons such as hexadecane (C16) and octadecane (C18) do not provide any better lubrication in formulations without lubricants confirming their lack of lubricating capability. Octacosane (C28), on the other hand, maintains its lubrication efficiency at the beginning and during extended periods of tablet compression. The lower melting point of the materials in this category is reported to be the reason for their less lubrication effectiveness compared to that of metal stearates [28].

Stearic acid (C18) is the most commonly used lubricant in this category, typically at levels of 2.5% (w/w). Physical properties reported for stearic acid include [11]:

- specific surface area 1.1–1.9 m^2/g,
- geometric mean diameter 43.8–56.8 μm,
- bulk density 0.38–0.46 g/mL,
- tapped density 0.48–0.54 g/mL, and
- melting point 52.2–54.7 °C.

Three polymorphs of stearic acid, Forms A, B, and C, have been made using different organic solvents under different crystallization conditions [29]. Form C is most stable. Form B has an irreversible endothermic phase transition to Form C at 54 °C, while Form A transforms to Form C at 64 °C. The DSC and TGA thermograms indicate that stearic acid from different vendors show very little batch-to-batch or manufacturer-to-manufacturer variability [29,30].

2.3. Fatty acid esters

A variety of fatty acid esters have been used as lubricants for tablet compression. Some examples are listed below [31–33]:

- sodium stearyl fumarate (Pruv®), 1–3% (w/w),
- sodium lauryl sulfate, 1.0% (w/w),
- magnesium lauryl sulfate,
- glyceryl behenate (Compritol® 888), 1.5–3% (w/w),
- dodecanoic triglyceride, 1% (w/w),
- glyceryl-palmito stearate (Precirol® ATO), 0.5% (w/w),
- sucrose monopalmitate,
- sucrose monolaurate, 0.12% (w/w),
- samarium stearate.

Sodium stearyl fumarate (Pruv®) and glyceryl behenate (Compritol® 888) are the most commonly used among the above-mentioned list of fatty acid esters. Compared to Mg stearate, these lubricants show less interference with tablet strength and have a less negative effect on tablet dissolution. About 0.5% of Pruv®, in combination with PEG 4000 or PEG 6000, acted as a successful lubricating system for some effervescent tablets [34]. Pruv® was also needed in lower concentration than talc for the optimal lubrication in pentobarbitol tablets [35]. An amount equal to 2% (w/w) of Compritol® 888 showed the same lubrication effectiveness as 0.75% (w/w) of Mg stearate in microcrystalline cellulose tablets [36]. Although Compritol® 888 was used in a greater amount, it did not negatively affect the tablet hardness or disintegration time. The rank order for anti-adherent (sticking and picking) effect of the three studied lubricants in salicylic acid tablets [37] was Mg stearate $\geqslant$ sodium stearyl fumarate > glyceryl behenate.

Some oils, such as hydrogenated vegetable oil (Lubritab®), hydrogenated castor oil (Cutina® HR), hydrogenated cottonseed oil (Sterotex® K), are also used as lubricants in amounts ranging from 0.5% to 2% (w/w). For example, the effectiveness of 2.5–3% (w/w) of Lubritab® was very close to that of 0.5% (w/w) Mg stearate [38]. Lacking the disadvantageous mixing time sensitivity of Mg stearate, formulations lubricated with Lubritab® exhibited much higher tablet strength and faster dissolution in prednisolone tablets [39].

2.4. Alkyl sulfate

Magnesium lauryl sulfate and sodium lauryl sulfate (mainly used as a surfactant) are both water-soluble lubricants. Magnesium lauryl sulfate is better than sodium lauryl sulfate and was an equally effective lubricant as Mg stearate in lithium carbonate tablets. It also possesses the lubricating properties of Mg stearate but without its waterproofing liability. However, the use of 0.5% (w/w) magnesium lauryl sulfate in the direct compression of a tablet containing an insoluble compound indicated that it has more retarding effect than 0.5% (w/w) of Mg stearate [40]. The disintegration time was also much higher, 75 s versus 25 s for Mg stearate, at certain tablet compression pressures.

2.5. Inorganic materials

If Mg stearate is not appropriate for a compound because of chemical instability, it may be replaced with talc as a glidant and lubricant. Talc is hydrous magnesium silicate, sometimes containing small amount of aluminum silicate [41]. The physical properties of talc from several vendors fall within the following ranges:

- specific surface area 3.5–10 m^2/g,
- geometric mean diameter 9.4–18.3 μm,
- bulk density 0.41–0.45 g/mL, and
- tap density 0.74–0.79 g/mL.

Most inorganic materials used as lubricants come in various mixture of sizes characterized as laminated flakes (2–5 μm) and aggregates of flakes (50–150 μm) [11]. Although there is only small batch-to-batch variability in the physical property of the material from the same manufacturer, the differences observed from different manufacturers can be large. In experiments with acetaminophen tablets [42], 1% (w/w) talc was found not to be significantly different from 0.25% (w/w) Mg stearate in terms of granulation flowability and ejection force, and the tablets were also harder and less fragile. On the other hand, talc was also found to be a very suitable lubricant at a concentration of 0.5–3% and up to 5% (w/w) for aspirin tablets [43,44].

2.6. Polymers

If Mg stearate cannot be used due to problems of compaction, lubrication, chemical instability, or for other biopharmaceutical reasons, some polymers may be used as the tablet lubricant of choice. PEG 4000, PEG 6000 (Carbowax® 6000), polyoxyethylene–polyoxyproprylene copolymer (Lutrol® F68), and polytetrafluoroethylene (Fluon® L 169), for example, have successfully been used in various tablets [43,45]. Fluon® L 169 has approximately the same lubricating properties as Mg stearate in acetylsalicylic acid tablet, but it did not eliminate the electrostatic charges of the formulation as was observed with small percentages of Mg stearate [46].

3. Processing factors that may affect lubrication

3.1. Internal lubrication

Lubricant(s) used for tablets are often incorporated into the formulation as the last step prior to tablet compression. It is usually blended with the mixture consisting of all of the other ingredients in granular or powder forms in a blender. This type of procedure is often called internal lubrication. The selection of lubricant(s) affect the type of mixing equipment and process to use and these, in turn, may affect the lubrication process and consequently the tablet properties. This is exemplified by the study [47] in which the dependence of tablet tensile strength on lubricant mixing time, pre-compression, and main compression forces were measured with microcrystalline cellulose containing 0.5% (w/w) Mg stearate. By measuring the adhesion of tablets on the lower punch surface using an instrumented rotary tablet press, the adhesion of microcrystalline cellulose tablets appeared to decrease with an increase in blending time or intensity of blending with Mg stearate at any given compression force [48]. The tablet ejection force also decreased with longer and more vigorous blending. Tablet hardness, however, decreased with the increase in blending time and intensity of blending. In another study [49], power consumption during mixing of a direct compression blend was measured. Fig. 3 shows the power consumption as a function of Mg stearate concentration. The change in power consumption also correlated well with the changes in tablet ejection force, tablet crushing strength, and tablet dissolution. Bolhuis et al. [50] also found that the effect of Mg stearate, when mixed with a lactose/microcrystalline cellulose formula, was strongly dependent on the type, size, and rotation speed of the mixer. The decrease in tablet crushing strength was much steeper for the large industrial type mixers than for small lab mixers when they are operated at the same rotation speed. In other words, at industrial scale, tablet crushing strength was more sensitive to the mixer rotation speed than the type, size, and the load of the mixer.

The adverse effects of over-mixing of Mg stearate on tablet ejection force, tablet hardness, and disintegration time have been shown by Kikuta et al. [51]. They also found that a semi-logarithmic plot of ejection force, hardness, or disintegration time versus mixing time all yielded two-phase straight lines with the early

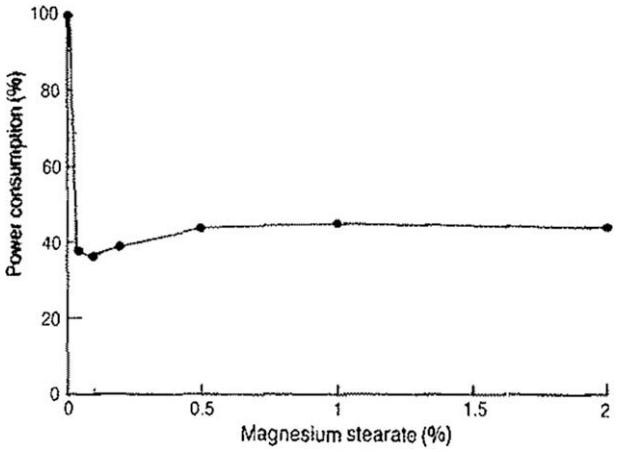

Fig. 3. Plot of power consumption versus magnesium stearate concentration.

phase having a larger first-order rate and continued to decrease, in the second phase, at a smaller first-order rate. As shown in Fig. 4, these results suggested that the mixing time in the second phase should be selected to optimize Mg stearate concentration such that the change in tablet hardness is less pronounced on the tablet properties. The effect of mixing time on lubrication and its negative impact on tablet crushing strength is not limited to Mg stearate [52]. Similar effects were observed on other lubricants, such as hydrogenated vegetable oil, glycerides, talc, and PTFE [52].

The effect of mixing on lubrication has also been studied with artificial neural network and the polynomial regression methods [53]. Using hydrochlorothiazide as a test compound, the models successfully showed that the mixing time was the dominant factor that decreased tablet crushing strength when mixing with Mg stearate longer than 10 min. The models also showed that the crushing strength of tablets containing glyceryl behenate (Compritol® 888) was not significantly affected by the mixing time.

3.2. External lubrication

As opposed to mixing lubricant with formulation ingredients, external lubrication often refers to a lubrication process in which only the lower punch and die, not the final blend material, are lubricated [54]. This type of lubrication procedure may be used when tablet properties are very sensitive to lubricants. As shown in Fig. 5, a suspension of 5% (w/w) Mg stearate in liquid petroleum was transferred through a tube to the foam rubber rings surrounding the lower punch. An effervescent tablet containing nicotinic acid and sodium bicarbonate was successfully compressed using this lubrication method. A similar technique was used to make an orally disintegrating tablet [55]. Using similar automated technique during rotary tablet compression, Yamamura et al. investigated the effects of external lubrication on tablet properties of the eprazinone hydrochloride tablets [56]. The amount of lubricant required to prevent sticking with external lubrication was only 0.08% of that with internal lubrication. In the meanwhile, external lubrication gave 40% higher tablet crushing strength without prolonging tablet disintegration time.

Trypsin tablets have been made with both internal and external lubrication [57]. Compared to tablets made with internal lubrication, tablets made with external lubrication needed lower compression energy but higher ejection energy. The tablets also showed higher hardness, less total pore volume, faster dissolution and higher trypsin activity.

When tablet tensile strength or dissolution are susceptible to the lubrication, it is perhaps more important to consider the option of external lubrication. As the adverse effects of lubrication on tablet properties are often exacerbated when the mixing operation is conducted at larger scale for internal lubrication, the usage of external lubrication should help avoid such problems.

Although not cost-effective, it is possible to treat the tooling surfaces of a tablet press with highly polished chromium coating in order to reduce their coefficient of friction. Additionally, the die is sometimes treated with Mg stearate powder or its solution in organic solvent to provide lubrication in tablet compaction research.

4. Characterization of the lubrication process

Trial-and-error methods have been used for a very long time to determine whether a lubricant should be used, and if so, what lubricant to use and how much would be the optimal amount. With recent advancements in analytical techniques, tablet press instrumentation, and other process analytical technologies, many researchers have made the effort to understand the fundamental workings of lubricants by characterizing the lubrication process.

4.1. Coefficient of friction during tablet ejection

During tablet compression, because a residual die wall force is generated, an ejection force is needed to overcome this force in order to push the tablet out of the die. Intuitively, the coefficient

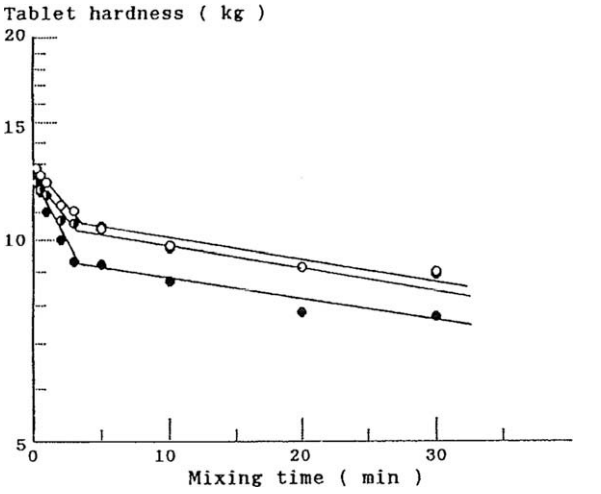

Fig. 4. Semi-logarithmic relationship of the tablet hardness and magnesium stearate concentration. Key: open circle – 0.1%, half-open circle – 0.3%, solid circle – 0.5%

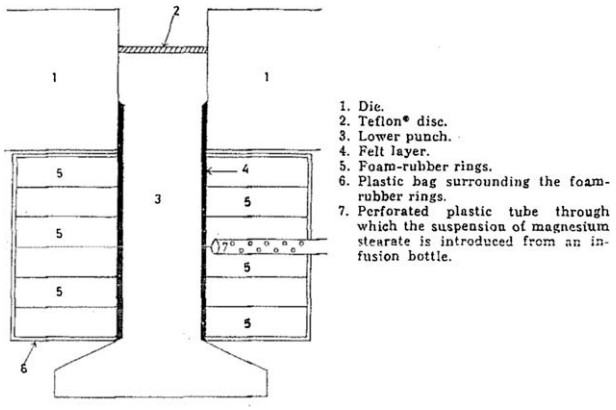

Fig. 5. Diagram of the arrangement for the lubrication of the lower punch and die (external lubrication).

of friction should be a good indicator of the effectiveness of lubrication. Hölzer and Sjogren [17] investigated the coefficient of friction among a few other parameters during tablet compression. By comparing several lubricants, they found that there was no correlation between the coefficient of friction of the lubricant itself and the lubricating effect in sodium chloride tablet compression. On the other hand, the negative effects on tablet strength and disintegration time correlated quite well with the lubricating ability. Although the study was quite comprehensive, there may be a serious flaw in attempting to obtain the coefficient of friction by simultaneously measuring both the axial and radial forces at different compression forces during tablet compression.

To overcome the shortfalls of this method, which operates on the assumption that varying compression forces may cause changes of the structure of the tablets, Kikuta and Kitamori [58] developed a method to estimate the coefficient of friction and the adhesive force at constant tablet compression force. The relationship between the tablet ejection force, radial force at given compression force is illustrated by Coulomb's equation:

$$F_e = \mu F_r + C \quad (5)$$

where F_e is the ejection force, F_r is the radial force, μ is the coefficient of friction between the tablet side and the die wall, and C is an indicator of adhesive force. Using lactose as a model material, the authors proved that the linear relationship held for the ejection force and radial force (Fig. 6). The ejection forces were determined under various radial forces produced by regular compression and the subsequent re-compression (without surpassing the regular compression force), or relaxation of the tablet in the die. Fig. 7 shows that, using this method, the coefficients of friction of Mg stearate and calcium stearate gave the lowest value (0.04) and talc the highest value (0.25), indicating better lubrication properties of Mg stearate and calcium stearate compared to talc [59]. The affinity of lubricants to the die wall was studied by conditioning the die wall with each lubricant followed by compressing lactose tablets. As shown in Fig. 8, the lubrication effect of talc and corn starch was lost after several tablets, while Mg stearate maintained its lubrication effect even after ten or more tablets. In authors' opinion, even though this method is time-consuming and requires custom-built equipment, it is the most convincing method for characterizing lubricants and their lubrication effects in tablet compression at macroscopic level. In another work [60], the coefficients of friction of some lubricants on a steel surface were measured with a modified annular shear cell to rank order their lubrication effectiveness. In all comparisons, Mg stearate had the lowest coefficient of friction. Divalent salts of stearic acid, such as calcium stearate, appeared to be better than the other lubricants, such as aluminum monostearate, glyceryl behenate, and PEG 8000.

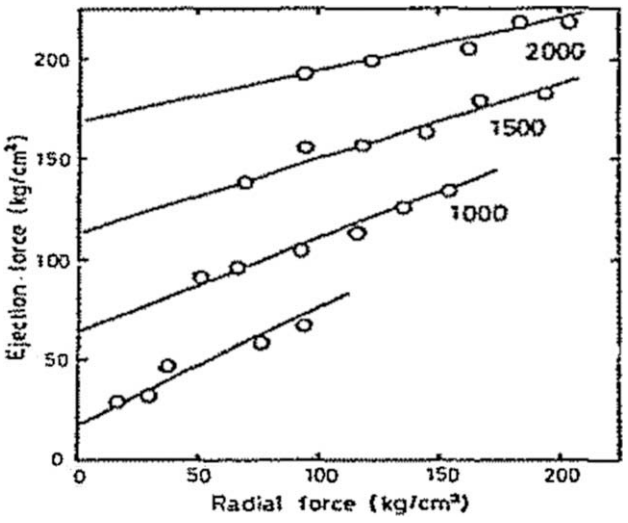

Fig. 6. Relationship between ejection and radial forces after sixth ejection.

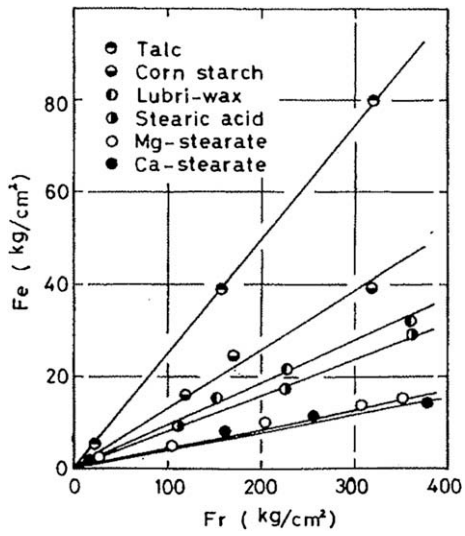

Fig. 7. Relationship between ejection and radial forces for the compacts of some lubricants.

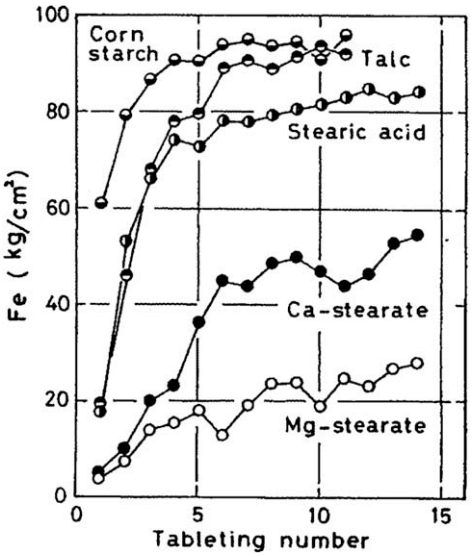

Fig. 8. Change in ejection force in serial tableting of un-lubricated lactose granulates after tableting of each lubricant.

4.2. Other parameters or indices during tablet compression

Compaction parameters, such as the ratio of the residual die wall pressure to maximum die wall pressure, or RDP/MDP, has been used to evaluate the effectiveness of lubrication [61]. Shown in Fig. 9 are the differences in RDP/MDP values for lactose and mannitol without Mg stearate versus the lubricant is added internally or externally. Potassium chloride (KCl), a well-known plastically deformable material, was studied to further demonstrate the usefulness of the RDP/MDP. As shown in Fig. 10, RDP/MDP values decreased with increasing Mg stearate concentration, suggesting reduced compactability. Tablet tensile strength, however, decreased as the lubricant amount exceeded 0.5%. The residual die

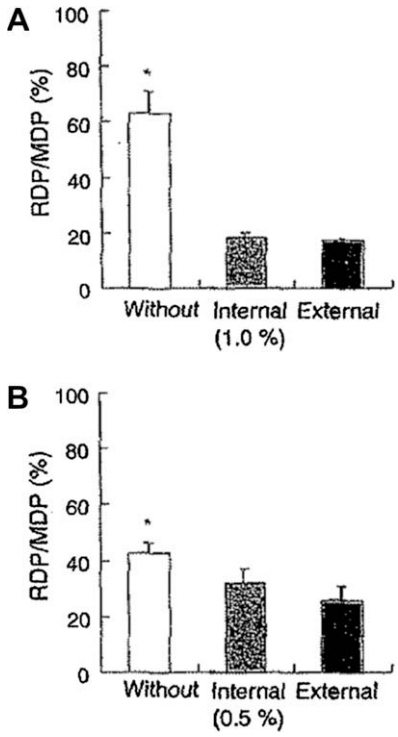

Fig. 9. The effect of external lubrication on the RDP/MDP of lactose or mannitol. Compression pressure is 100 MPa.

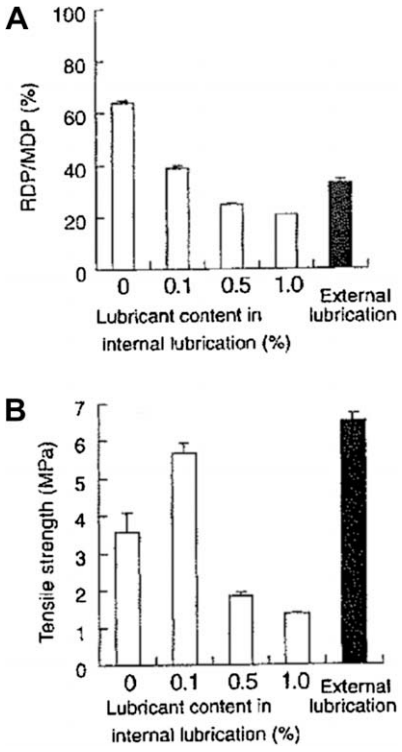

Fig. 10. The effects of lubricant content and lubrication method on the RDP/MDP and tensile strength of potassium chloride tablet.

wall pressure of microcrystalline cellulose–lactose tablets increased as the degree of curvature of the tablet face increased, in the order of flat < shallow curved < deeply curved < double radius curved [62]. Consequently, this had the effect of increasing friction between the tablet and die wall. The addition of 0.1% Mg stearate to the flat-faced tablets eliminated color distribution differences in the tablet, while 0.3% was needed for curve-faced tablets.

The compression force transmission *R* value, the ratio of the maximum lower punch force to the maximum upper punch force, is another often used parameter used to evaluate the effects of tablet lubricants. For example, Mollan and Çelik [63] found that the *R* values for the compacts made of three types of maltodextrin (spray drying, fluidized bed agglomeration, and roller compaction) reached a plateau when magnesium stearate concentration was 0.5% (w/w) or higher. The compacts of the maltodextrin generally experienced increased tablet porosity with an increase in lubrication concentration with the exception of one type of maltodextrin, which was processed by the roller compaction method. In addition, Hussain et al. reported [64] that changes of the R values for the unlubricated and lubricated tablets maybe one way of differentiating materials with different consolidation mechanism during compression (e.g., sodium chloride primarily by plastic deformation versus acetaminophen by fragmentation and plastic deformation).

Quantitative analysis of the tablet ejection curve and ejection force versus time was performed to evaluate lubricant effectiveness [65]. Both the ejection curve shape and ejection force peak value provided information on the total resistance exhibited by the tablet to the recovering movement of the lower punch. This method was used to optimize the selection of lubricant type and amount during formulation development. Similarly, the ejection energy of eleven lots of Mg stearate was measured and rank ordered using a Universal Testing Instrument (Instron 1122) [66]. The ejection energy rank order of a mixture containing 1% of the lubricant in lactose showed a completely different sequence from that of the lubricant alone. The results suggested that excipients played an important role in determining the practical efficiency of a lubricant. It showed that the interactions between the lubricant and excipient affected the lubrication process.

Some indices created for a tablet compression process, such as indentation hardness, bonding index, brittle fracture index, and strain index have been investigated with a modified Hiestand pendulum impact apparatus using mixtures with different levels of lubricants [67]. Tablet axial and radial work of failure for microcrystalline cellulose was obtained by analyzing the force–displacement curves during tensile strength measurements [68]. As the lubricant concentration increased for five different lubricants including Mg stearate, stearic acid, and PEG 4000, both axial and radial work of failure was reduced considerably. The reasons could be that the lubricant particles interfered with the interactive bonding between the microcrystalline cellulose particles themselves, leading to reduced tablet strength.

4.3. Tablet hardness/crushing strength and intrinsic dissolution

As described in other parts of this review, tablet hardness and crushing strength have been widely used to characterize lubricants and lubrication process. Lerk et al. [69] studied the effect of Mg stearate on the hardness of pre-gelatinized starch tablets and its interactions with colloidal silica. As shown in Fig. 11, the addition of 0.1–0.4% colloidal silica significantly suppressed the adverse effects of 0.1% Mg stearate on the hardness of pre-gelatinized starch tablets. Fig. 12 also shows that, while tablet strength decreased from 18 kg to 3.5 kg by mixing with 0.1% Mg stearate for 60 min, the addition of colloidal silica "reversed" the negative effect caused by Mg stearate. Fig. 13 shows that the highest pre-gelatinized starch tablet hardness was obtained by mixing first with colloidal silica and then with Mg stearate.

In another study, intrinsic dissolution rate has been used to evaluate how lubricants affected the surface area and porosity of compacts [70]. The effective surface areas coated by lubricant

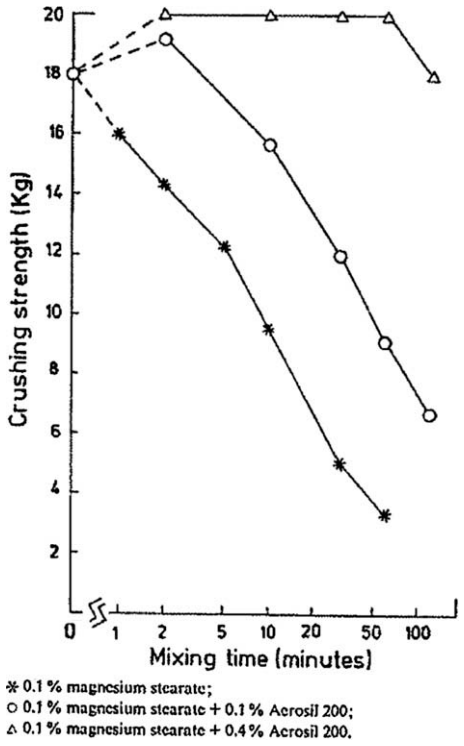

Fig. 11. The effect of mixing time on the crushing strength of tablets compressed from blenders of STA-Rx 1500 with magnesium stearate or with magnesium stearate and Aerosil 200.

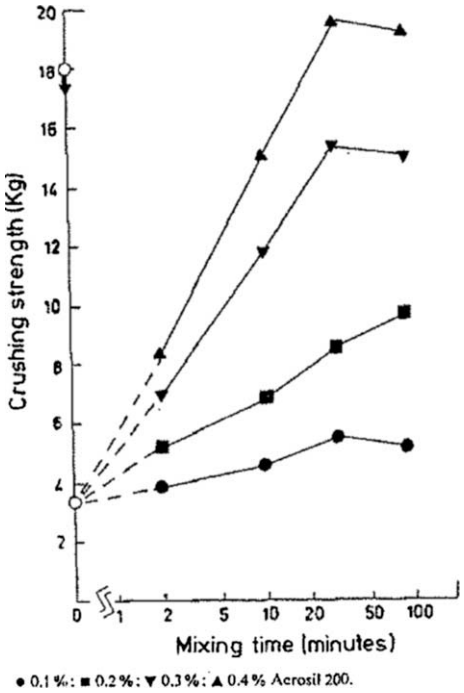

Fig. 12. The effect of mixing with Aerosil 200 on the crushing strength of tablets compressed from previously mixed (1 h) blends of STA-Rx 1500 and 0.1% magnesium stearate.

particles were determined by comparing the dissolution rates of acetylsalicylic acid and alaproclate hydrochloride tablets made with various lubricants (Fig. 14). At a given concentration of each lubricant, the ability to form a film on the particles seemed to correlate with the specific surface area of the lubricant [71]. As shown

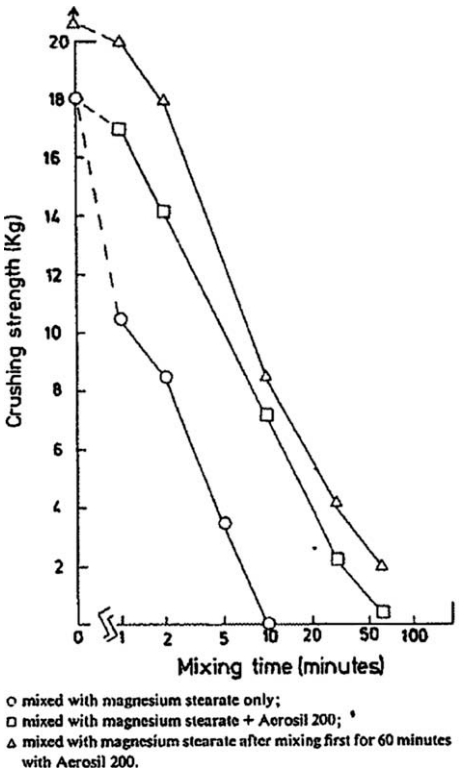

Fig. 13. The effects of mixing time and mixing sequence on the crushing strength of tablets compressed from blends of STA-Rx 1500 with 0.5% magnesium stearate and 0.2% Aerosil 200 when compared with STA-Rx 1500 containing 0.5% magnesium stearate only.

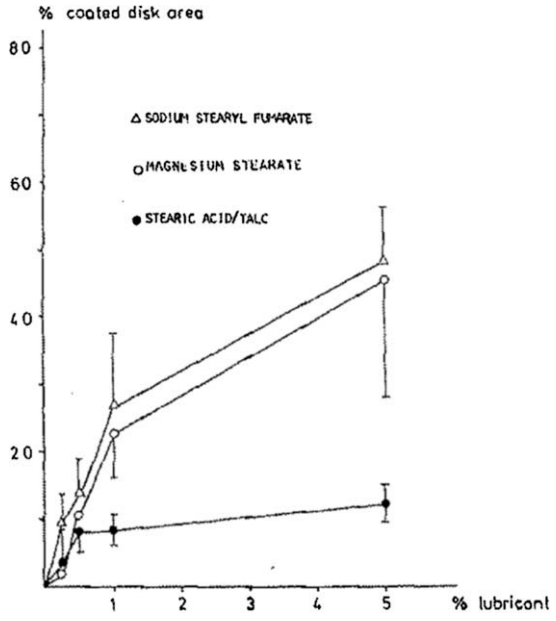

Fig. 14. Calculated coated disk area as a function of lubricant concentration for alaproclate hydrochloride (250–300 μm).

in Fig. 15, stearic acid and talc mixtures affected the surface area to a much lesser extent than Mg stearate or sodium stearyl fumarate.

4.4. Instruments used for the evaluation of tablet lubrication

Texture analyzer has been used to study the effect of different lubricants on the compression properties of granules [72]. In these

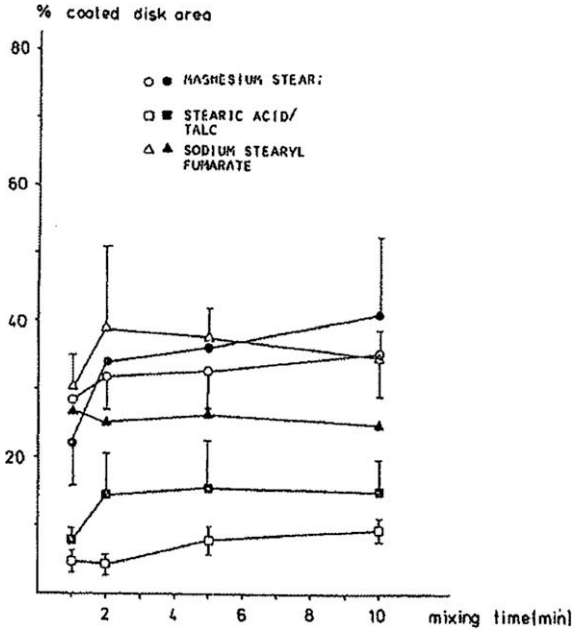

Fig. 15. Calculated coated disk area as a function of mixing time (with 1.0% lubricant). ○ – Aspirin (250–300 μm); ● – alaproclate hydrochloride (250–300 μm).

studies, consolidation mechanisms and stress relaxation behaviors were correlated by measuring the probe force decay and probe displacement change after the completion of a compaction cycle. The results suggested that Mg stearate demonstrated more plastic deformation with no evidence of fragmentation, while talc deformed mainly by fragmentation.

Infrared thermography has also been used to investigate the heat released during tablet compression [73]. High-resolution temperature image of a tablet at the take-off point was obtained in less than 1 s after compaction. As shown in Fig. 16, Mg stearate concentration levels had significant effect on the amount of heat released during a compaction run. Tablets lubricated with 1.0% Mg stearate had a surface temperature of 39–40 °C after 20 min of run time, as opposed to 50–51 °C for tablets with 0.5% Mg stearate. The impact on the stability of the product was not reported. It was also found that the extent of the temperature rise on a tablet's upper and lateral surfaces was different in the presence or absence of Mg stearate [74].

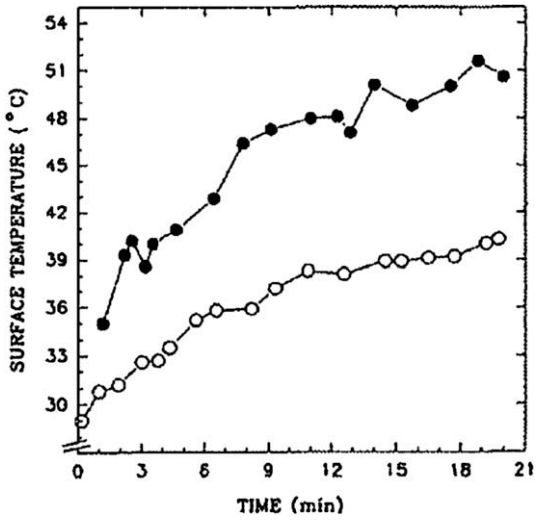

Fig. 16. Tablet surface temperatures as a function of run time for granulations lubricated with 0.5% (●) and 1.0% (○) magnesium stearate.

A friction meter has been used to measure the tangential and normal forces outside the die in order to determine the minimum effective lubricant concentrations [75]. As shown in Fig. 17, with either unsieved or 80/100 mesh cut, the coefficient of friction of dicalcium phosphate decreased with the applied tablet pressure in a more linear fashion at lower concentration (0.2%) of Mg stearate than at a higher concentration (2%). Fig. 18 shows the coefficient of friction of dicalcium phosphate as a function of Mg stearate concentration at given pressures. Mg stearate did not show any effect until its concentration reached 2%. The coefficient of friction decreased as a function of the lubricant level.

The Food and Drug Administration (FDA) of the United States released a draft guidance that introduced the Process Analytical Technology (PAT) to the pharmaceutical industry in 2004. PAT tools typically perform real-time, on-line or at-line measurements of evolving quality parameters to ensure the manufacturing process is properly monitored and controlled. A few on-line PAT tools, such as near-infrared (NIR) spectroscopy, laser-induced breakdown spectroscopy (LIBS), and effusivity measurements, are particularly suitable for the internal lubrication process that often requires that the mixing of the lubricant be uniform but without over-mixing [76–78]. In each of these methods, a mathematical model was developed to provide real-time predictions on whether and when the lubricant can uniformly reach the desired concentration level in the blending process. Ideally, the method should provide real-time response to the sudden spikes in lubricant concentration, changes in ingredient attributes, and perturbations to standard mixing procedures. A comparative study of the NIR

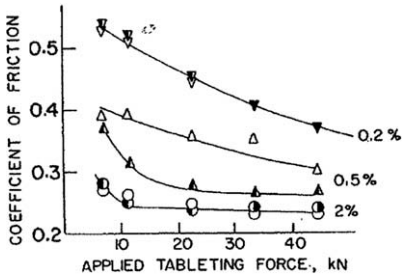

Fig. 17. Frictional coefficient as a function of applied compression force. Open circles represent unsieved (polydisperse) dicalcium phosphate and half-closed circles represent 80/100 mesh cut. (▼) 0.2% magnesium stearate, (△) 0.5% magnesium stearate, (○) 2% magnesium stearate.

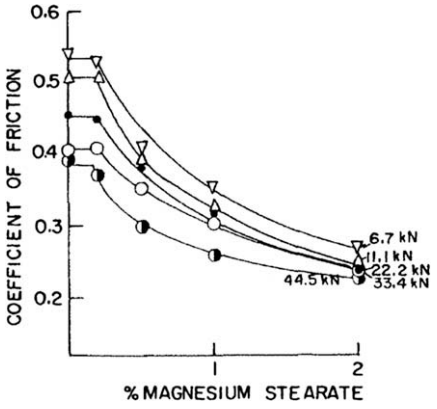

Fig. 18. Frictional coefficients of unsieved dicalcium phosphate plotted as a function of percent magnesium stearate. Compression pressure is shown for each curve.

and LIBS methods for this application showed that the NIR method provided better accuracy and precision than LIBS under certain experimental conditions, whereas LIBS showed superior selectivity [79]. Regarding the effusivity method, the accuracy in determining optimal blending times depended on the blend physical characteristics and was significantly affected by the blend density [78].

5. Effects of lubrication on tablet compression and tablet properties

Lubricant type, concentration, method of lubrication, and the manner of incorporating the lubricant into the process all affect tablet compression in terms of compactibility and tablet weight variation [80]. Lubricants may, therefore, impact tablet properties such as hardness, friability, disintegration/dissolution. They may also affect tablet surface roughness, polarity, and adhesion to coating materials [81]. The tablet's in vivo behaviors, such as bioavailability, may also be affected.

5.1. Effect of lubrication on tablet strength

Under certain compression force, tablet strength depends on the area of intimate contact between particles of the tableting materials and the attractive forces between the particles over the entire contacting area. The fine lubricant particles can interfere with the interactive bonding forces between the particles to be compressed thus interfering with the eventual strength of the resulting tablet. The impact of a lubricant on tablet mechanical strength is dependent on the material-bonding mechanism and concentration of the lubricant. Materials that have different compaction behavior (e.g., deformation versus fragmentation) are subject to different effects by the lubricants or the lubrication process.

It is generally accepted that Mg stearate has more negative effect on the hardness and tensile strength of tablets with more deformable materials than brittle ones. Brittle materials are more likely to fracture and fragment during compaction. As more fresh surfaces not covered by lubricant particles are generated, they tend to bond together. Film formation on deformable particles, on the other hand, weakens the bonding of the granules as there are less fresh surfaces formed during compaction. In a study conducted by Jarosz et al. [82], dibasic calcium phosphate was used as an example of a material that is susceptible to brittle fracture during compaction. As shown in Fig. 19, the tensile strength of the tablet did not change when up to 3% of Mg stearate was mixed into the formulation. Other lubricants, such as stearic acid, hydrogenated vegetable oil, and talc, did not markedly affect the tensile strength and bonding of dibasic calcium phosphate dihydrate tablets even at levels as high as 8%.

In contrast, when Mg stearate mixed with microcrystalline cellulose, a representative of plastic materials, the tablet tensile strength was weakened as the amount of lubricant increased (Fig. 20). Microcrystalline cellulose from seven different manufacturers showed vendor-to-vendor differences in lubrication sensitivity, while lot-to-lot variations were not similarly impacted [83]. Similar results were obtained when stearic acid, hydrogenated vegetable oil, talc, or PEG was mixed with microcrystalline cellulose. Adverse impact of Mg stearate on tablet tensile strength was also observed for other commonly used plastically deformable excipients such as lactose, pre-gelatinized starch, and spray-dried rice starch [84]. Thus, overall sensitivity of formulation to Mg stearate is dependent of what proportion of brittle and deformable material is used in the formulation.

It has been shown [85] that the hardness of sorbitol lozenge dosage form is significantly affected by the amount of Mg stearate and the length of the mixing time. As shown in Fig. 21, increased amount of Mg stearate resulted in decreased lozenge hardness and slower dissolution. The hardness of the lozenge, on the other hand, decreased linearly as mixing time increased. The mixing time, however, affected hardness to a lesser extent than changes in Mg stearate concentration. Also, the proportional decrease in lozenge hardness with increased mixing time was most pronounced at lower Mg stearate concentrations. At higher Mg stearate concentration, mixing time had little effect. Lordi et al. [86] studied changes in the hardness of aged tablets of chloride, bromide, and iodide salts of sodium, potassium, and ammonium stored at various relative humidity conditions. Tablet hardness increased with increasing moisture content and reached a maximum value in the region of deliquescence and then decreased drastically as the salt deliquesced. The effect of the relative humidity on tablet hardness was much less when a lubricant was added. It is postulated that lubricants coat the salt crystals and form an insulating layer thereby minimizing the inherent molecular forces of attraction. Similar deleterious effects of tablet tensile strength caused by Mg stearate were observed with crystalline sucrose, hexamine, aspirin, and sodium chloride granulations [87].

Various forms of Mg stearate, amorphous, anhydrous, monohydrate, dihydrate, and trihydrate, were characterized [23]. Among the inter-conversion of these forms, the dihydrate form cannot be converted to the monohydrate form directly, while it can be converted into the trihydrate form under certain temperature and relative humidity conditions. Not an intermediate in the formation of trihydrate from anhydrous form, the dihydrate was a stable form. Okoye and Wu [22] used thermal effusivity technology to study lubrication effects caused by different forms of Mg

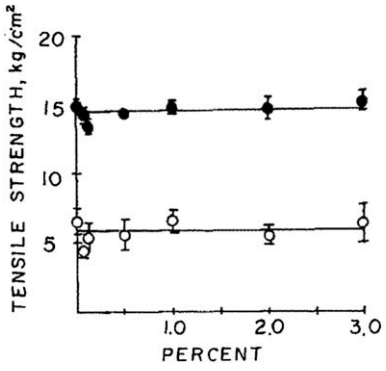

Fig. 19. Concentration effect of magnesium stearate on the tensile strength of dibasic calcium phosphate dehydrate tablets compressed at 2268 kg. ○, Axial; ●, radial.

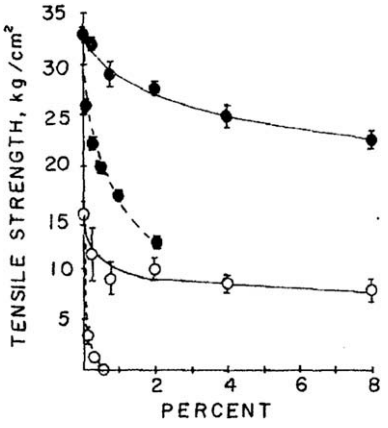

Fig. 20. Concentration effects of magnesium stearate and stearic acid on the tensile strength of microcrystalline cellulose tablets compressed at 454 kg. ○, Axial; ●, radial; —, stearic acid; - - - - -, magnesium stearate.

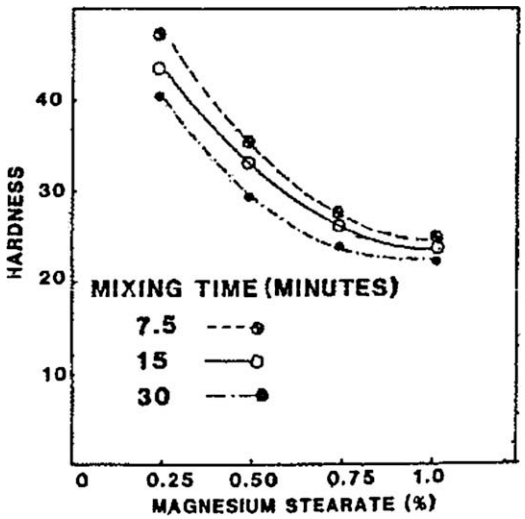

Fig. 21. The effect of magnesium stearate concentration and mixing time on a sorbitol lozenge hardness.

stearate. They found that the dihydrate form showed less degree of densification than the monohydrate form for both microcrystalline cellulose/lactose/lubricant and microcrystalline cellulose/dicalcium phosphate/lubricant systems. For the manufacture of identical tablets, the compression force and ejection force during tablet compression were lower for the dihydrate form than for the monohydrate form. The tablet dissolution profiles made with these two lubricants were, however, similar.

5.2. Effects of lubrication on tablet dissolution

In general, most of the studies on how Mg stearate affected tablet dissolution suggested that lubricants had some negative effects on the in vitro dissolution of immediate release tablets, with the more hydrophobic lubricants (e.g., Mg stearate) seemingly showing more pronounced deleterious effects. A number of experimental findings [88–90] have led to the theoretical conclusion that the observed deleterious effect of lubricants on dissolution is due to their large surface area which, in combination with their hydrophobicity, hinder water penetration to affect dissolution. It has been demonstrated that [21], compared to the granular form of Mg stearate, the powder form had more pronounced negative effects because of the larger surface area on sodium chloride tablet hardness and disintegration time.

In a tablet comprised mostly of calcium phosphate dibasic, with the other excipients maintained constant, a decrease in the Mg stearate level, from 1.7 mg to 0.85 mg, reduced the disintegration time from 10 min to 4.5 min [91]. The deleterious effect of Mg stearate and stearic acid on tablet disintegration and dissolution was quite evident in nitrofurantoin tablet formulations [88]. As shown in Figs. 22 and 23, tablet dissolution rates decreased when the concentration of the lubricants was increased. The time it took for 60% dissolution increased from 5.1 min to 75.4 min when the Mg stearate level increased from 0.5% to 3.0%.

Researchers have seen similar lubricant retarding effects in controlled release tablets. In an extended release theophylline tablet, Mg stearate modulated the erosion rate constants and acted as an effective release-controlling excipient [92]. As mentioned earlier, this effect has been attributed to the formation of hydrophobic film on the surface of the granulation particles. In these instances, the retarding effect of Mg stearate on drug release was especially dramatic over the range of 0–1%. In contrast to above-mentioned observations, the effects on the diphenhydramine HCl controlled release tablet containing mostly hydroxypropyl methylcellulose

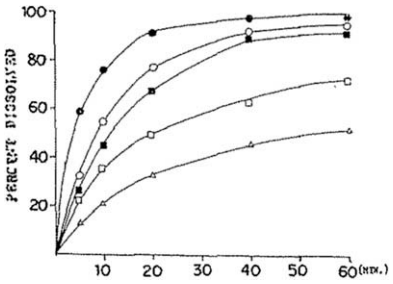

Fig. 22. The impact of Mg stearate concentration on the dissolution rate of nitrofurantoin tablets granulated with starch paste. ● – Magnesium stearate 0.5%; ○ – magnesium stearate 1.0%; ■ – magnesium stearate 1.5%; □ – magnesium stearate 2.0%; △ – magnesium stearate 3.0%.

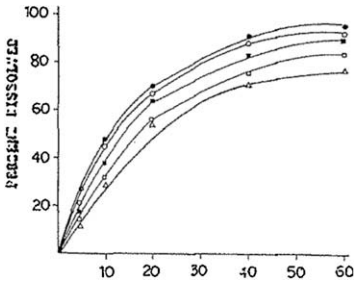

Fig. 23. The impact of stearic acid concentration on the dissolution rate of nitrofurantoin tablets granulated with starch paste. ● – Stearic acid 0.5%; ○ – stearic acid 1.0%; ■ – stearic acid 1.5%; □ – stearic acid 2.0%; △ – stearic acid 3.0%.

and lactose as well as the hydrochlorthiazide controlled release tablet containing hydroxypropyl methylcellulose and dibasic calcium phosphate were different. Both tablets that made with 0.2% Mg stearate had higher tablet hardness than those made with 2.0% Mg stearate. The drug release profiles from the matrix systems were rather insensitive to the hydrophobic effects of the lubricant [93].

5.3. Effect of lubrication on tablet bioavailability

There are not many studies conducted on the bioavailability of over-lubricated tablets, and this makes it difficult to fully understand the effect of lubrication on the in vivo behavior of such tablets. When the Mg stearate (0.8%) mixing time for sulfadiazine tablet was prolonged from 15 min to 60 min, the tablet dissolution increased from 27.8 min to 591.5 min for 50% of drug to dissolve. Although the difference in tablet dissolution was significant, the total excreted sulfadiazine in urine only decreased from 448.0 mg to 413.6 mg. This observation indicated that the length of lubricant mixing time had little impact on the in vivo behavior of the sulfadiazine tablets. In a similar study, when Mg stearate amount was increased from 0% to 0.5% for a sulfadiazine tablet, the disintegration time increased from 25 s to 117 min, while dissolution rate reduced from 3.94 to 0.70 μg/mL/h [94,95]. Such stark in vitro differences were not replicated in vivo. The differences were so much minimized in vivo that the C_{max} was 10.5 versus 8.3 μg/mL, and t_{max} was 4.0 h for both tablets. Only a decrease in the AUC from 47.7 to 33.2 μg/mL h correlated with what was observed for the in vitro dissolution of the tablets. On the other hand, the disintegration time of 40 mg furosemide tablets made with 0.5% or 2.0% (w/w) Mg stearate did not change very much, ranging only from 42 to 51 s [96]. Even though other in vitro tablet quality attributes were similar, there were significant differences in the bioavailability of the furosemide tablets. It was surprising to note that the tablets with 2.0% (w/w) Mg stearate had 25% higher bioavailability than those with 0.5% (w/w) of the same lubricant.

6. Drug and excipient interactions with lubricants and impact on tablet stability

Although the amount of lubricant in the tablet formula may be quite small, interactions between the lubricant and the active ingredient or other excipients may have some effect on the tablet's physical properties and chemical stability. The interactions often occur at the solid state level.

6.1. Physical interactions of lubricants with drug substances and other excipients in tablet formulations

The effect of a lubricant on tablet tensile strength and dissolution is not only determined by the physicochemical nature of the lubricant itself, but also made more complicated by the presence of the drug substances and other excipients in the formulation. For example, the addition of a super-disintegrant is a good remedy for overcoming the retarding effects of lubricants in immediate release tablet dosage forms. The effect of Mg stearate on dicalcium phosphate dihydrate tablet dissolution slowdown was minimized when a strongly swelling disintegrant croscarmellose sodium was incorporated in the tablets [97]. The same study showed that the high water penetration rate and volumetric water uptake of tablets with 4% sodium starch glycolate appear to be independent of the presence of Mg stearate.

Lactose is a very commonly used excipient in formulation development. It comes in different grades, such as α-lactose monohydrate, anhydrous α-lactose, and roller-dried β-lactose (which includes 20% of anhydrous α-lactose). Tablets compressed from either α-lactose monohydrate or β-lactose disintegrated very rapidly in water, while tablets with anhydrous α-lactose did not disintegrate but dissolved in water by slow erosion [98]. The decrease in tablet hardness was found to be more significant when 0.5% Mg stearate was mixed with α-lactose monohydrate or anhydrous β-lactose than with roller-dried β-lactose [98].

The effect of capsule dissolution slowdown caused by over-mixing of Mg stearate with granules of three drug substance granules in the hopper of a capsule-filling machine were investigated [99]. The solubilities of these three compounds, hydrochlorothiazide, sorivudine, and aztreonam, in the dissolution medium of 0.1 N hydrochloric acid were 0.6, 5.0, and 12 mg/mL, respectively. It was found that the extent of dissolution slowdown was maximum for the drug substance with the lowest solubility in the dissolution medium, hydrochlorothiazide, followed by sorivudine and aztreonam. For the sorivudine capsule, replacement of Mg stearate in the formulation with other hydrophobic lubricants such as calcium or zinc stearate gave similar results of dissolution slowdown, while the replacement with hydrophilic lubricants such as Stear-O-Wet® (wettable Mg stearate) or sodium stearyl fumarate did not result in dissolution slowdown. In addition, replacement of pre-gelatinized starch by starch-derived super-disintegrants such as sodium starch glycolate resulted in no slowdown of capsule dissolution even after over-mixing with 1% (w/w) of Mg stearate.

6.2. Chemical interactions of lubricants and impact on stability

The effect of lubricants on the chemical stability of prednisone tablets [100] is shown in Fig. 24. Tablets made with Mg stearate underwent more degradation than those made with talc or stearic acid. Oxidation was found to be the means by which prednisone degraded. The alkalinity imparted by Mg stearate catalyzed oxidation of prednisone. In situations like this, talc and stearic acid are preferred to Mg stearate as tablet lubricants from the standpoint of prednisone stability. In a different situation, Mg stearate was preferred as lubricant over talc in tablets containing cyanocobalamin [101]. The reason was talc adsorbed cyanocobalamin and consequently interfered with its intestinal absorption.

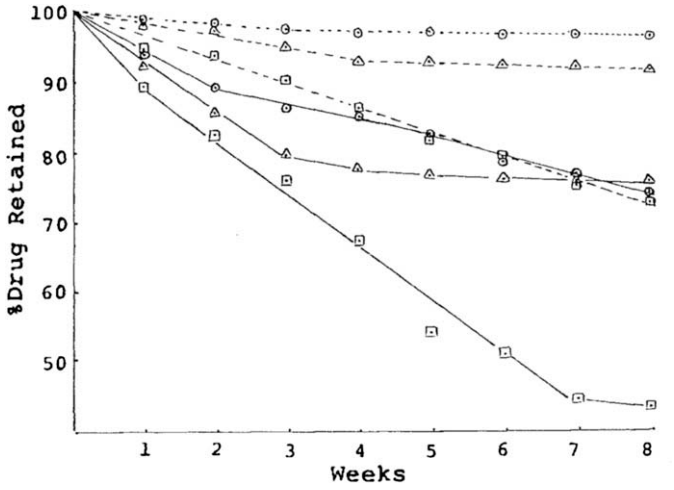

Fig. 24. The impact of lubricants on the chemical stability of prednisone tablets stored at 50 °C and 83% RH (———) and at 70 °C and 96% RH (—). □ – Magnesium stearate; △ – talc; ○ – stearic acid.

Thakur et al. reported that fosinopril sodium transformed into a β-ketoamide by and a phosphonic acid, mediated through metal ion participation [102]. The results of the study helped rationalize the degradation of fosinopril sodium in the tablet formulation lubricated with Mg stearate by identifying two distinct pathways of degradation, i.e., Mg stearate mediated and hydrolysis. During the storage of the tablets at 50 °C and 100% relative humidity, the formation of magnesium ion-mediated product leveled off whereas the formation of hydrolysis product continued with time.

Desai et al. [103] found that there existed solid state interactions between stearic acid and povidone, leading to dissolution slowdown upon storage. They found this to be true for at least two drug capsule formulations. It was observed that the mixtures of stearic acid and povidone formed a transparent, hard, and glass-like insoluble substance after storing for one week at 40 °C/75% and 50 °C. Examined by powder X-ray diffraction, the crystallinity of stearic acid was lost upon storage. There was also a slight broadening of the povidone carbonyl band when examined by IR spectroscopy. Differential scanning calorimetry (DSC) curves showed that recrystallization of stearic acid was inhibited by the mere presence of povidone. In comparison, no such interactions were seen between povidone and Mg stearate.

DSC has been used to study the compatibility between ampicillin and a number of lubricants [104]. Fig. 25 shows the thermograms of ampicillin, stearic acid and their mixture. While the peak positions remained the same, the enthalpy change of the mixture was found to be quantitatively identical to the predicted values. Fig. 26 shows the thermograms of ampicillin, Mg stearate and their mixture. The shifts in the Mg stearate and the ampicillin peaks demonstrated the possibility of incompatibility of the mixture. It can be deduced from these results that stearic acid can be used while Mg stearate cannot be used as the lubricant for ampicillin tablets.

7. Quality-by-Design aspects of lubricants

7.1. Formulation ruggedness studies

Like any other formulation excipients, the selected lubricant must be compatible with the active pharmaceutical ingredient (API) in the formulation. The chemical compatibility of excipients

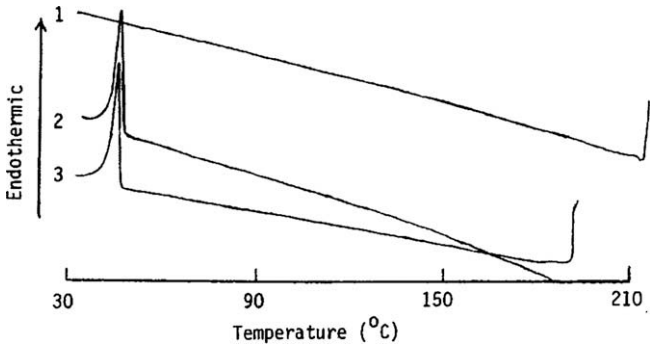

Fig. 25. DSC thermograms of ampicillin (1), stearic acid (2) and 1:1 ampicillin–stearic acid mixture (3).

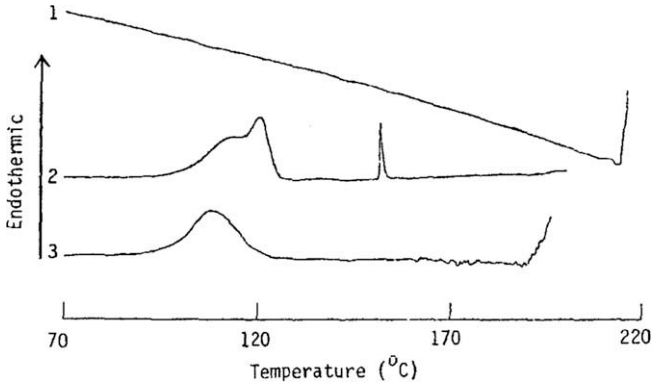

Fig. 26. DSC thermograms of ampicillin (1), magnesium stearate (2) and 1:1 ampicillin–magnesium stearate mixture (3).

with the API is established in the drug excipient compatibility study to select the excipients for the formulations [105]. Once the formulation excipients and the dosage form are decided, it is vital to identify if any excipients including lubricant has the ability to influence the finished product critical quality attributes (CQAs) [106]. As reported in this article, magnesium stearate can influence dissolution of capsules and tablets. It can also influence tablet hardness, friability, and disintegration. For many drug products, dissolution is a rate-limiting step for drug absorption. For these products, dissolution is considered as a CQA. For some film coated tablets, core tablet hardness and friability are considered CQAs since they need to be rugged enough to withstand the rigor of the coating process.

Formulation ruggedness studies are conducted to establish the range of each excipient in which the dosage form can be manufactured without influencing the final product CQAs. The normal range for magnesium stearate in the tablet or capsule formulations is 0.1–2% (w/w), with most of the commercial products containing 0.1–1% (w/w). Similarly, the range for another commonly used lubricant stearic acid is 1–3% (w/w). A statistically designed factorial studies are often conducted in order to determine the impact of excipient variations on the product CQAs. The experiments may also help to determine the interaction between various excipients in the formulations and its impact on the product CQAs. The ruggedness studies are often conducted at pilot scale (typically 1–5 kg) in order to conserve the drug substance in the early stages of product development. The statistically designed studies should establish the range of each excipient, especially the lubricants since they may adversely impact the final product CQAs.

For the lubricants, additional factors such as the blender rotation speed and mixing time need to be studied as well. The mixing time is referred to the time when lubricant is mixed with the final formulation blend prior to tablet compression or encapsulation. For example, the formulation ruggedness studies establish 1% (w/w) as the highest concentration of magnesium stearate, the mixing studies need to be conducted at this concentration to study the adverse impact of over lubrication with extended mixing time on tablet dissolution, hardness, friability, etc. The lubricant is typically mixed with the final blend for several minutes (e.g., 3 min). It is useful to generate information on the extended mixing time of 10–15 min, if not any longer. If the extended mixing time adversely impacts the product CQAs, the study should be repeated with the lower lubricant concentration such as 0.75% (w/w), 0.50% (w/w), or 0.25% (w/w). Additional mixing also takes place in the feed frame or hopper for many automatic tablet presses and capsule-filling machines [99]. It is worthwhile to subject the final blend to such mixing conditions to ensure that during the large scale manufacturing, the product CQAs will not be adversely impacted by inadvertent mixing during the manufacturing process. As described in this article, many PAT tools such as NIR or Raman spectroscopy can be used to develop further process understanding.

7.2. Quality-by-Design expectations

The expectation under Quality-by-Design paradigm is that all possible sources of excipient variability should be studied and if needed, mitigation strategies should be identified. Once the acceptable range of the lubricant in the formulation is established, it is prudent to evaluate performance of the lubricant from multiple sources. The idea here is to ascertain that the lubricant range identified using the material from one vendor will work when the lubricant is sourced from different vendors. If the lubricant from other vendors do not give satisfactory results, then the existing lubricant specifications may not be adequate. Such outcome may lead to an opportunity to add tests and specifications for the lubricant in order to avoid any future surprises. Although many excipient monographs are undergoing international harmonization process, it is unrealistic to expect that the excipient meeting harmonized monograph will meet all of the functionality requirements in a particular dosage form. Therefore, it is highly recommended that formulators do their own evaluation of the lubricant sourced from multiple vendors in the dosage form. Many pharmaceutical companies routinely use three separate lots of excipients in the registrational stability batch manufacture. Three lots are used to capture lot-to-lot variability and its impact on product CQAs including stability profiles. While the registrational stability studies are conducted to establish finished product shelf-life, the knowledge base created during the development will not only meet the Quality-by-Design expectations from the regulatory authorities but will also help to manufacture robust dosage form products.

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