An Executive Summary

Best Practices for Effective Tablet Lubrication

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Internal lubricants facilitate the ejection of tablets from dies by reducing the friction at the interface between the tablet's surface and the die wall.

Overview

One of the most challenging steps in tablet manufacturing is identifying the correct lubricant level for producing defect-free tablets within a specific hardness range. As lubricant level and lubricant blending time increases, developers have a window in which they can produce in-specification tablets. Outside that window, where lubricant level is too high or low and/or mixing time may be too high or low, the process, product integrity, and product performance can be affected. Formulators must therefore search for the middle-ground between under- and over-lubrication, and keep in mind that the size and relative placement of this window is formulation-specific.

Under-lubricated tablets can exhibit picking and sticking and even capping, in which a portion of the tablet is missing. In extreme cases, under-lubricated tablets can actually break up upon ejection from the die.

On the other end of the spectrum, over-lubrication impairs cohesion of the particles in the formulation during compression, resulting in soft tablets with high friability (see **Figure 1**). A dangerous situation can occur when tablets are slightly over-lubricated. The challenges of compacting the blend in this scenario may be overcome with adjustments to the tablet press, which will produce tablets that appear defect-free with the correct hardness and friability, but do not disintegrate and dissolve according to specifications. This wastes both production time and the resulting finished product (since the problem is not discovered until finished product testing is conducted) and incurs further loss in batch, quality investigations, and follow-up.

Until recently, many formulators did not take the time to understand the effects of lubrication on the tableting process or the drug product's physical integrity and performance. Some formulators simply choose magnesium stearate because they feel it is their only option, and then are forced to modify their formulation and/or process to accommodate the lubricant. This issue has come to the forefront with the widespread requirement of quality-by-design (QbD) and quality risk management approaches, which emphasize product and process understanding and process control.

A tablet's proper lubrication level is not only determined by the formulation ingredients, but also by factors such as tablet shape and size, manufacturing batch scale, and the time spent blending the lubricant with the active pharmaceutical ingredient (API) and excipients.

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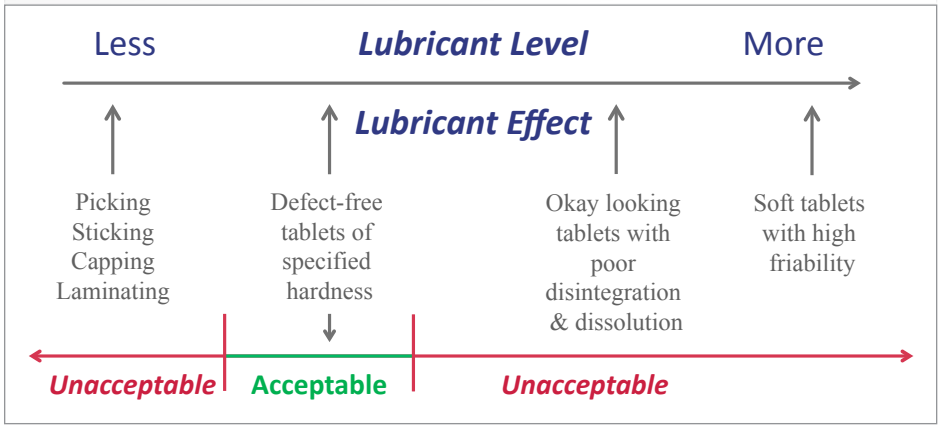
Figure 1: Manufacturing concerns. Quality concerns.



Lubrication 101: Why Lubricate?

There are two approaches to lubrication: internal, in which the lubricant is incorporated into the formulation, and external, in which the lubricant is lightly dusted on the die wall and punch faces before adding the formulation to the die. Several tablet press manufacturers offer die lubrication systems.

Internal lubrication, the focus of this article, facilitates the ejection of tablets from dies by reducing friction at the interface between the tablet's surface and the die walls and punch faces.

Die wall lubrication. During the manufacturing process, the forces of the upper and lower punches, acting on the blend in the die, compress the material into a hard tablet. The opposing forces of the material against the die wall and punch faces can cause adherence of the resulting tablet to these surfaces. The lubricant provides an interface between the tablet formulation and the die wall that will shear despite the force against the die wall, thus allowing the tablet to be easily ejected. A note about tooling here: If the die-walls are smooth, and the blend is properly lubricated, the tablets will be easily ejected. But, if the die-walls are worn, some of the tablet material could adhere to the walls, complicating matters and possibly causing further damage to the tooling.

Although not as crucial as its action at the die-walls, the lubricant also facilitates the separation of the upper and lower punches from the tablet faces.

Anti-adherence. To prevent sticking of the tablet blend on the upper and lower punchfaces, an anti-adherent—not additional lubricant—should be used. The most common anti-adherent is colloidal silicon dioxide. Although now used less frequently than colloidal silicon dioxide, talc also is an effective anti-adherent.

Additional effects of lubrication. Lubrication also reduces the friction between the particulates that make up a formulation. This may slightly enhance the formulation's flow through the hopper and feed frame and into the die. Because the presence of lubricant also reduces the inter-particulate cohesion, lubricants should not be used to improve flowability. A flow aid, or glidant—not additional lubricant—should be used. Reducing inter-particulate friction also decreases the heat that is generated by the motion of the formulation as it flows through the feed frame into the die.

Lubrication Types and Mechanisms of Action

Liquid film and boundary are the two major types of lubricants, each representing a different mechanism of action.

Liquid film lubricants. Liquid film lubricants include stearic acid and hydrogenated oils, many of which are used to manufacture nutraceutical products. The melting point of liquid film lubricants are generally low, ranging from about 50 °C to 70 °C. The heat produced during compaction partially or fully melts the lubricant and squeezes it to the outer tablet surface, thereby creating a film interface between the edges of the tablet and the die-wall as well as at the punch faces.

With some formulations, a liquid film lubricant can actually cause more picking and sticking. If this occurs, an anti-adherent should be incorporated into the formulation. Another possible downside of liquid film lubrication: it can impair the disintegration and dissolution of the finished product.

Liquid film lubricants are used at levels of 2–4%. Even higher amounts have been employed without negative effects, and in some cases much higher levels are used to create a hydrophobic matrix for modified-release applications.

Boundary lubricants. Boundary lubricants include magnesium stearate and other stearic acid salts as well as sodium stearyl fumarate. Boundary lubricants typically lubricate particles by coating them and providing a non-contiguous layer that can be sheared from the surface of the tablet during ejection. This coating of the particles of the blend can be a potential negative in downstream processing because it can reduce tablet hardness, increase friability, and impair disintegration and dissolution.

By coating the particles of the formulation, boundary lubricants reduce the friction between the sides of the tablet and the die-wall. Since punch faces also are exposed to the boundary lubricant, when proper levels are used, sufficient lubrication is achieved.

Boundary lubricants are typically used at levels of 0.25–2%. When used in excess, these lubricants can adversely affect compaction, disintegration, and dissolution as well as result in batch failures.

Soluble versus insoluble and hydrophobic versus hydrophilic. In addition to being categorized as either a liquid film or boundary agent, lubricants are generally classified as either soluble or insoluble. Most of the insoluble lubricants are not only insoluble, but are also hydrophobic (i.e., water repellent). A few insoluble lubricants may have a small degree of water solubility and therefore a degree of hydrophilicity, though none of them are strongly hydrophilic. In general, they are just less hydrophobic than most insoluble-type lubricants.

Hydrophilic lubricants include sodium stearyl fumarate, which is partially soluble in water, and the polyethylene glycols (PEGs) 4000 and 6000, which are fully soluble. Among hydrophobic lubricants, the most common are magnesium stearate and the stearic salts, both of which are insoluble.

Critical parameters. Several critical parameters affect tablet lubrication and blending. The following factors can affect mass shear:

- Blender size and geometry
- Particle morphology
- Formulation components
- Total surface area of the final blend
- Blending time

The degree of lubrication required is also a function of the tablet's size and shape. Ejection forces typically are higher for large tablets, which have more surface contact area in the die than smaller tablets.

In addition, when compressing tablets with concave tooling, there is less compaction force applied at the center of the tablet face than at the edges, and as a result, the lubrication effect can vary across the tablet face. If the lubricant effect is less in the center, picking in the center can occur, especially if debossed tooling is used. In many cases, picking can be prevented or reduced by "pre-picking" the area that will be debossed. This pertains to the tablet tooling design. Areas of the logo embossed on the face of the punch that are prone to picking, such as the areas inside the number "8" or the letter "B," are gently radiused and made shallower than the rest of the logo. This makes the punch less prone to remove material from the tablet upon compression (picking). This design modification is known in the industry as pre-picking.

Determining Lubrication Level and Timing

Ejection force measurement is the best way to determine the optimal level of lubrication. According to published studies, the optimal level ranges from 100 to 300 N, depending on tablet size. However, the optimal level can be substantially higher with larger tablets containing challenging materials such as supplement tablets, where tablet sizes of 2,000 mg and up are not uncommon. The measurement varies according to applied forces, the die wall contact area, radial die wall pressure, and formulation composition.

In determining the optimal lubrication level, formulators also should consider tablet hardness and friability and the disintegration and dissolution test results. The composition of the formulation directly impacts the resulting ejection force.

Of course, the larger the tablet, the greater the die-wall contact surface and the ejection force required. The higher the ejection force, the greater the wear on the tooling, requiring frequent replacement intervals for re-tooling.

Although the formulator determines when lubrication will occur, lubricants are customarily added close to or at the end of the blending process. Although not a common practice, in a study conducted at JRS Pharma, the addition of the lubricant sodium stearyl fumarate at the beginning of the blending process with the other ingredients was demonstrated not to affect tablet disintegration or dissolution.

Just as the formulation blending process plays a role in determining the level of lubrication that should be used, so do the factors of manufacturing scale and batch size. Due to the differences in shear forces and the length of mixing time, the dynamics of mixing differ between small-scale feasibility batches and production-scale batches. As a result, the lubrication level and mixing time required for a formulation can change substantially as the batch size increases. The take-home message: blending and lubricant level studies should be conducted at the scale of manufacture.

Choosing a Lubricant

As previously stated, magnesium stearate is the "gold standard" and most widely used lubricant in tablet manufacturing (see **Figure 2**).

Because it is reactive with some acidic APIs and is insoluble and very hydrophobic, magnesium stearate must be used carefully. Even when used at the recommended level and blended into a formulation, magnesium stearate can affect tablet disintegration and dissolution. When employed to manufacture effervescent tablets, magnesium stearate forms a film on the surface of liquids during dissolution. The film starts to form when bubbles of carbon dioxide carry magnesium stearate particles to the surface of the liquid.

Magnesium stearate also affects tablet tensile strength. Because there are five different polymorphs of the lubricant (anhydrous, monohydrate, disordered monohydrate, dihydrate, and trihydrate), the particle size grades and morphologies of magnesium stearate can vary from one manufacturer to the next and even within a single source. The variability of particle size between grades and sources can produce variability in performance (e.g., hardness, friability, disintegration and dissolution) in tablets manufactured with magnesium stearate from varying sources.

Generic companies should be very careful if they change magnesium stearate suppliers in an effort to save money. Lower cost magnesium stearate may not necessarily be lower quality magnesium stearate, but just due to its possible difference from what was previously used to formulate

the product, may be a lubricant that results in costly batch failures.

In contrast to magnesium stearate, sodium stearyl fumarate is hydrophilic (with some water solubility). It also has a melting point nearly 100 degrees higher than that of magnesium stearate. A scientific study published in 2005[1] showed that sodium stearyl fumarate did not affect the dissolution of tablets after over-blending and did not reduce tablet strength to the same extent as did magnesium stearate when used in the same process.

The study compared the effects of sodium stearyl fumarate and magnesium stearate on tablet hardness when compressed and measured after 2, 5, 10, 25, and 50 minutes of blending the lubricant into the formulation. Three different levels (0.25, 0.5, and 1%) of each lubricant were evaluated. The compaction force used for all tablets in the study was 12 kilonewtons.

At sodium stearyl fumarate's lowest level of 0.25%, with two minutes of blending, tablet hardness was 11.3 kiloponds (kp) (see **Figure 3**). When compared to tablets made from the highest level of 1%, and 50 minutes of blending, the reduction in tablet hardness was about 1 kp.

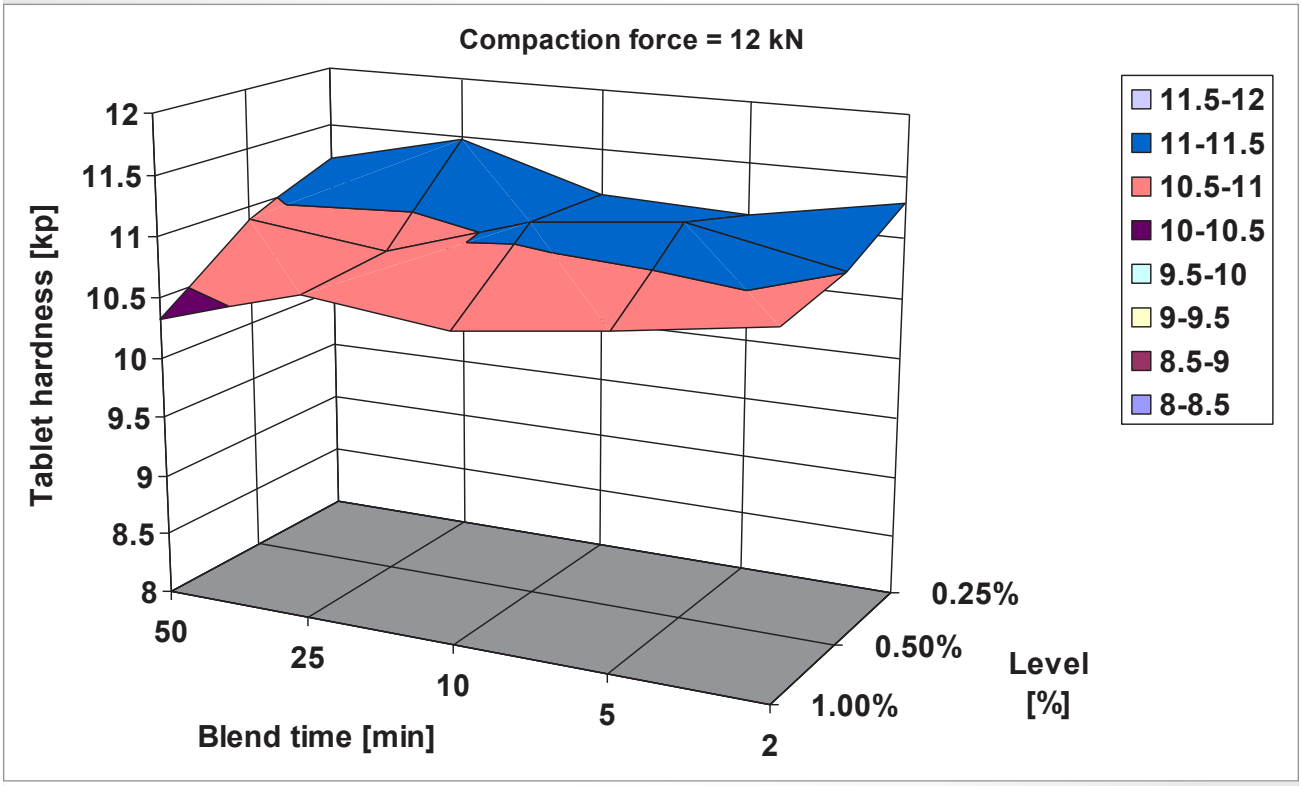
But when magnesium stearate was used as the lubricant, the reduction in tablet hardness from the 0.25% level with 2 minutes of blending versus the 1% level and 50 minutes of

Figure 2: Magnesium Stearate.

The most widely used tablet (and capsule) lubricant

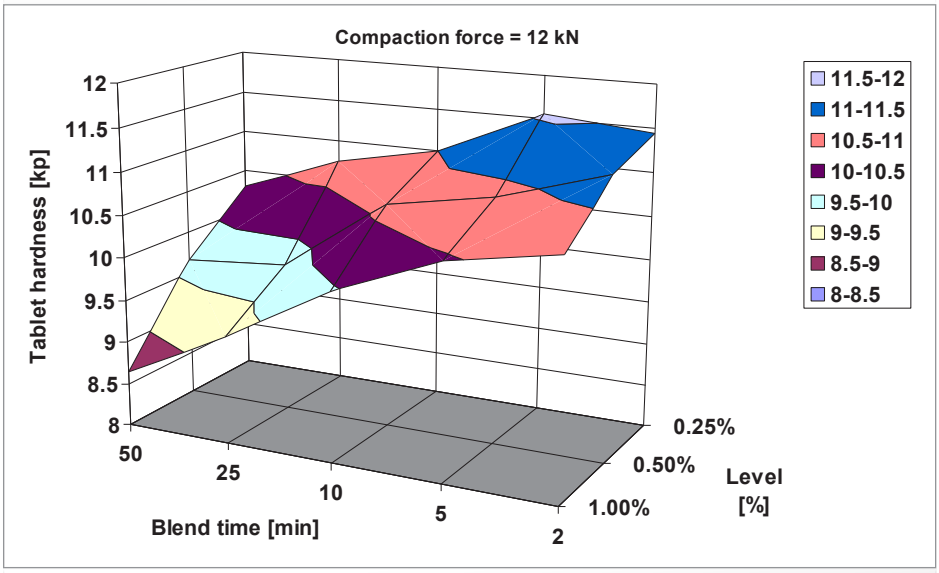
Advantages	Disadvantages
• Effectiveness (typical usage 0.5-1%) • Good combination of the main lubricant actions	• Reactivity with some APIs • Hydrophobicity • Effects of disintegration and dissolution • Forms film in effervescents • Effects on tablet tensile strength • Variability of key parameters both between manufacturers and from the same manufacturer • BSE/TSE risk

Figure 3: Tablet hardness as a function of lubrication level & blend time lubricated with Sodium Stearyl Fumarate.



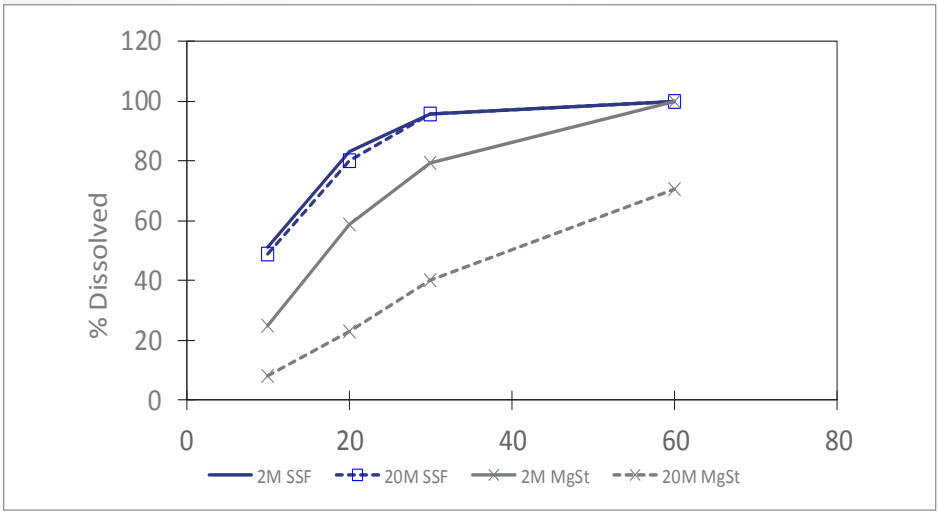
Schindler, Zeleznik, & Renak – 2005.

Figure 4: Tablet hardness as a function of lubrication level & blend time lubricated with Magnesium Stearate.



Schindler, Zeleznik, & Renak – 2005.

Figure 5: 2% Lubricant level, mixing time effect on Felodipine dissoluon rate.



blending was nearly 3 kp. (see **Figure 4**). This clearly shows that magnesium stearate reduces the cohesion of the particles in the formulation to a greater degree than does sodium stearyl fumarate.

The effects of the two lubricants on tablet dissolution also were examined using the poorly soluble cardiac drug, felodipine (see **Figure 5**). The lubricant level of magnesium stearate and sodium stearyl fumarate in both formulations was 2%. Tablets from both formulations were compressed after two minutes of lubricant blending and after 20 minutes of lubricant blending. Dissolution testing was carried out on tablets made under each condition.

When sodium stearyl fumarate was used, dissolution was unchanged. There was no impact on drug dissolution regardless of blending time. In contrast, the dissolution profiles for tablets containing magnesium stearate showed reduced drug dissolution for both the two-minute blending and the 20-minute blending conditions. The two-minute blending alone was enough to noticeably hinder dissolution, and the 20-minute blending significantly reduced the dissolution of the drug.

An added benefit to sodium stearyl fumarate, because of its partial solubility, is that it forms little or no film when used in effervescent tablets. In addition, unlike magnesium stearate, sodium stearyl fumarate does not react with acidic APIs and it does not produce a metallic taste.

Despite these differences, the typical usage levels of sodium stearyl fumare and magnesium stearate are much the same.

Most sodium stearyl fumarate that is produced today comes from a vegetable source. In the past, stearate from an animals source was primarily used. As a result, the sodium stearyl fumarate manufactured by JRS Pharma is not at risk of transmitting bovine spongiform encephalitis (BSE, i.e., mad cow disease) or the transmissible spongiform encephalopathies (TSEs).

Sodium stearyl fumarate is also less likely to exhibit lubrication changes in scale up.

Summary

A little lubricant can go a long way. Thus, do your homework. Do your lubricant level and blending time studies at or near scale and a good rule of thumb is to use, less not more lubricant, particularly if it is a boundary lubricant such as magnesium stearate and blend it longer.

Reference

1. Schindler B, Zeleznik J., Renak J. Sodium Stearyl Fumarate: An Effective Tablet Lubricant To Avoid Slippery Situations. JRS Pharma. http://www.aapsj.org/abstracts/AM_2005/AAPS2005-001769.pdf