dx.doi.org/10.14227/DT310324P122

Magnesium Stearate – Its Importance and Potential Impact on Dissolution of Oral Solid Dosage Forms

R. Christian Moreton[1]
[1]*FinnBrit Consulting, Waltham, MA, USA.*

e-mail: consulting@finnbrit.com

ABSTRACT

Magnesium stearate is the most commonly used lubricant in the formulation and manufacture of oral solid dosage forms (compressed tablets and powder-filled capsules). However, its chemical and physical properties can adversely impact the final dosage form by reducing the hardness of tablets and reducing dissolution of the active drug from both tablets and powder-filled capsules if used incorrectly. In addition, the potential for these negative aspects to occur in the formulation and manufacture of oral solid dosage forms is increased during scale up. This review article describes the advantages and disadvantages of magnesium stearate and explains how the properties of magnesium stearate can impact the manufacture and performance of the finished dosage form. A brief review of alternative lubricants for oral solid dosage forms is provided.

KEYWORDS: Magnesium stearate, excipients, dissolution, lubricants

INTRODUCTION

Chemically, magnesium stearate is the magnesium salt of stearic acid: $(C_{17}H_{35}COO)_2Mg$. Typically, magnesium stearate is far from such a straightforward chemical. It may be possible to produce a pure form of magnesium stearate, and it would likely work as a lubricant, but the material that is commercially available for pharmaceutical use typically contains a mixture of saturated long-chain fatty acids, notably including palmitic acid.

The range of fatty acids contained in a sample of magnesium stearate will reflect the source of the fatty acids used to manufacture the magnesium stearate: animal, vegetable, or synthetic. Vegetable source fatty acids are preferred for a variety of reasons, including the risk of transmissible spongiform encephalopathies (TSE) when using animal-sourced fatty acids. The detailed composition of magnesium stearate and other fatty acid magnesium salts in a particular sample is often unknown. In addition, magnesium stearate can exist as the anhydrous form or mono-, di-, or trihydrate forms. There may also be polymorphic or pseudo-polymorphic forms and different particle morphologies, all of which can impact its performance in a given formulation. For example, Koglin examined samples from different commercial sources and identified up to seven different forms of magnesium stearate (*1*).

The disadvantages of magnesium stearate became important after the introduction of dissolution testing in the early 1970s (the first dissolution specifications appeared in the *USP* in 1971). Before that, disintegration testing was the only in vitro performance test, and specification limits were typically quite broad. The potential impact of magnesium stearate on the compactibility of tablet blends was also known by that time.

WHY IS MAGNESIUM STEARATE SO POPULAR?

Given uncertainties as to the precise form of magnesium stearate, and its disadvantageous properties, why is it so popular? The reason is that magnesium stearate is arguably the best lubricant for tablets and powder-filled capsules. It is generally effective at low concentrations (typically 0.5–1.0%), and it has a good balance of the main lubricant functions, i.e., reduction in interparticle friction during consolidation and compaction, flow enhancement, lowering ejection force, and prevention of sticking to punches, capsule filling dosator pistons, or tamping pins. It also has a long history of use, certainly going back to the 19th century.

HOW MAGNESIUM STEARATE WORKS IN ORAL SOLID DOSAGE FORMS

Magnesium stearate is a boundary lubricant; it has a polar head (the magnesium ion) and a fatty acid tail. It achieves its effects by being adsorbed onto the other particles of the final powder blend to be tableted or filled into capsules, in effect forming a partial film around the blend of particles (*2*). Adsorption onto powder particles reduces cohesiveness and helps promote powder flow. This adsorption may also reduce the tendency of some materials to stick to the tablet punch or capsule dosing change parts. It may also adsorb onto metal surfaces and reduce the friction when powder moves across a metal surface, as in tablet ejection or capsule plug ejection. It may also lubricate moving metal surfaces. However, magnesium stearate can interfere with the compaction of materials if too much is included in the formulation or when mixed with other components for too long. This is due to the magnesium stearate forming a more complete film around the powder particles, which interferes with particle-particle bonding.

To work effectively as a lubricant in the formulation and manufacture of tablets and powder-filled capsules, magnesium stearate is prepared in very finely divided form; typically micronized. According to Allen and Luner, the particle size of magnesium stearate is typically < 20 µm (*3*). While this property may account, in part, for its advantageous performance in the formulation and manufacture of tablets and powder-filled hard gel capsules, it also gives rise to its disadvantages in reducing dissolution of active drugs under certain circumstances. In addition, its fine particle size and morphology (most often agglomerated lamellae) compounds its hydrophobicity because such particles can deagglomerate during pharmaceutical processing and spread over a greater surface area, such as during blending.

The agglomeration of fine particles is a well-known phenomenon in pharmaceutical processing. In general terms, for typical pharmaceutical powders, agglomeration becomes an increasing issue as the particle size of the powder particles is reduced below 50 µm. With such small particles, the van der Waals forces of attraction become larger than the gravitational forces that would cause the particles to separate. During processing, such as powder blending, there may be sufficient energy to cause the agglomerates of magnesium stearate to break up. The more energy that is input (longer blending times or more intense blending), the more the agglomerates will be broken up, and the resulting particles will adsorb onto the other particles of the blend, thereby partially coating the particles with hydrophobic magnesium stearate particles. At a certain point, the extent of magnesium stearate coverage of the other particles of the blend will be such that the penetration of water into the tablet matrix or capsule plug will be retarded, potentially impacting compaction of the tablet and dissolution of the active drug. This is shown in Figure 1.

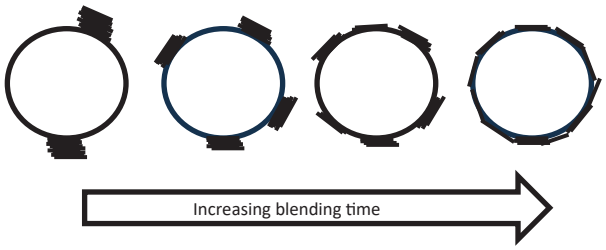

Figure 1. Diagram represents the effects of increased blending time on the formation of a magnesium stearate film on powder particles. The magnesium stearate is represented as the stacked lamellae.

In addition, if the amount of magnesium stearate is too great, even with shorter blending times, it will spread over the surface of the other components of the blend to such an extent that it can reduce the ability of water to penetrate into the tablet or capsule fill, and also into the granules contained in that fill, thereby reducing the rate of dissolution of the active ingredient (*4*). It will also reduce the compactibility of the tablet blend. The form of magnesium stearate (state of hydration, etc.) will also affect the formation of the hydrophobic film (*5*).

The formation of the magnesium stearate film is also the reason that over-lubrication with magnesium stearate causes reduced compactibility of tablet blends, resulting in softer tablets that are prone to capping and chipping during subsequent handling. The layer of adsorbed magnesium stearate interferes with the bonding between the other particles in the blend.

EFFECTS OF SCALE OF MANUFACTURE OF TABLETS AND POWDER-FILLED CAPSULES

When considering the impact of magnesium stearate on the dissolution of tablets and powder-filled capsules, the scale and intensity of mixing are important considerations. For example, Gunning reported that a reduction in dissolution, which occurred within minutes at large scale, required 30 hours blending to achieve a comparable reduction in dissolution at laboratory scale (*6*). From the author's experience in the late 1970s, working at the 2000-kg scale with an immediate-release capsule blend, and using a double cone tumbling blender, 5 minutes of final lubricant blend time gave acceptable dissolution, whereas 7 minutes gave dissolution results very close to

the lower limit, and potential failure. These results agree with those reported by Mehrotra et al., who found that high total shear impacted tablet hardness (*7*). However, for conditions of constant total shear, the shear intensity (intensity of mixing) only had a slight effect. This indicates that the total shear rather than the intensity of shear is important.

THE ANALYTICAL IMPACT OF MAGNESIUM STEARATE

The major impact of magnesium stearate in analytical terms is on the dissolution of drugs from the dosage form. Under certain circumstances, magnesium stearate can have a deleterious effect on the disintegration of dosage forms and the dissolution of drugs in vitro and possibly in vivo. This phenomenon has been known for many years, certainly in the 1970s for dissolution, and even earlier for disintegration testing. The adverse effect of magnesium stearate on dissolution from oral solid dosage forms is due to its propensity to adsorb onto the other components of the formulation during blending, as discussed above. Thus, it can create a hydrophobic 'coating' that retards the penetration of the dissolution medium into the formulation. The mechanism of this adsorption is due to electrostatic interactions owing to the small size of the magnesium stearate particle. Calahan et al. investigated the impact of different forms and sources of magnesium stearate on tablet manufacturing parameters and dissolution using a direct compression tablet formation (*8*). The authors reported differences in the optimum form that were related to the different parameters. Thus, the choice of magnesium stearate form and process parameters necessitates a compromise between the required tablet compaction or capsule filling process and the required dissolution from the finished dosage form.

INCOMPATIBILITY OF MAGNESIUM STEARATE AND DRUG MOLECULES

Chemical Incompatibility

Magnesium stearate is not chemically inert. When considering its chemical compatibility with drug molecules, it has the typical properties of a magnesium salt (and other salts of alkaline earth elements). Magnesium stearate is incompatible with esters, e.g., aspirin and enalapril, as it causes hydrolysis of the ester linkage. It may also facilitate certain other chemical interactions. It may facilitate the Maillard reaction between a primary amine and a reducing sugar. For example, again from the author's experience, during an excipient compatibility study of a primary amine drug, the Maillard reaction between the drug and lactose monohydrate was enhanced in the presence of magnesium stearate.

In addition, if the magnesium stearate contains unsaturated fatty acids, there is the possibility of the formation of an adduct with a primary amine; analogous to a Michaels addition. Thus, it is important to understand the chemical composition of the magnesium stearate, particularly the minor components.

Physical Incompatibility

Because magnesium stearate is an ionic salt, it can induce disproportionation of hydrochloride salts by exchange of ions, thus forming magnesium chloride, which is deliquescent. For example, John et al. reported on disproportionation of a drug hydrochloride salt occurring due to interaction with excipients including magnesium and sodium salts (e.g., magnesium stearate, sodium stearyl fumarate, and croscarmellose sodium) (*9*). However, the effects with magnesium stearate were greater than with the sodium salt excipients. The same authors also reported that disproportionation did not occur with neutral excipients or stearic acid. This disproportionation can impact susceptibility of the finished tablets to moisture uptake when stored at high humidity. This has implications for packaging, stability, and shelf-life of the finished product. In addition, the increased uptake of moisture by the finished tablets may cause premature activation of disintegrants, leading to soft tablets on storage and loss of disintegrant activity in use, which could cause a reduction in dissolution.

ALTERNATIVES TO MAGNESIUM STEARATE

Are there alternatives to magnesium stearate? The short answer is yes! However, they all have issues. Zinc stearate and calcium stearate have both been used as tablet and capsule lubricants, but have similar disadvantageous properties to, and show no clear advantages over, magnesium stearate. Many, but not all, alternatives to the stearate salts are also hydrophobic, and they all have other issues such as chemical incompatibilities and effectiveness as lubricants. For example, sodium stearyl fumarate is also an effective boundary lubricant and not hydrophobic (although not water-soluble at room temperature); however, it has the incompatibilities of a sodium salt. In addition, primary amines can interact with the olefinic double bond in the fumarate moiety to form an addition compound.

The so-called fluid film lubricants, such as stearic acid, hydrogenated castor oil, and hydrogenated vegetable oil type I work differently than boundary lubricants.

During compaction they melt, and the resultant oily film provides the lubricant effect. They also require higher concentration to achieve their lubricant effect. On removal of the compaction pressure, these lubricants re-solidify which is why they are prone to sticking, thus requiring the inclusion of an anti-adherent such as talc or fumed silica. There are other materials that have been used as lubricants, particularly for effervescent tablets, such as leucine and isoleucine, but they are not considered particularly effective, and have not been widely adopted.

POSSIBLE FUTURE DEVELOPMENTS

The ideal lubricant for the manufacture of tablets and powder-filled capsules would have all the beneficial properties of magnesium stearate but none of its drawbacks, such as hydrophobicity. Salpekar and Augsburger investigated the use of magnesium lauryl sulfate, which is water soluble, as a tablet lubricant (*10*). It was not as effective as magnesium stearate in that a higher concentration was required in the blend. Magnesium lauryl sulfate did not have the disadvantages of magnesium stearate (impacting dissolution or compressibility); however, it has not been commercialized. This may partly be due to its lachrymatory properties; it is highly irritant to the eyes and mucus membranes. Given its finely divided form, use of magnesium lauryl sulfate in pharmaceutical manufacturing areas would require significant personal protection measures. There is always the possibility of a new lubricant, but given the understanding surrounding magnesium stearate, it seems unlikely that any new lubricants will be introduced in the immediate future.

CONCLUSION

There is no ideal lubricant. Provided that there are no chemical compatibility issues, magnesium stearate is still arguably the best compromise for a lubricant from a tablet and capsule manufacturing perspective, despite some physical compatibility issues. Magnesium stearate will likely continue to be the most common lubricant for use in oral solid dosage forms for the foreseeable future. Despite its well-known disadvantages, the alternatives have their own drawbacks, and magnesium stearate is often the best compromise. However, when using it, it is necessary to understand its properties and limitations to produce robust formulations and consistent finished medicinal products. This understanding includes the balance between the level of incorporation, the scale of manufacture, and the extent of mixing to achieve sufficient lubrication to allow the tablet press or capsule filling machine to operate efficiently while avoiding any reduction in dissolution of the active drug, and the requirements for finished product packaging and shelf-life.

DISCLOSURES

The author received no financial support for this work and has no conflicts of interest.

REFERENCES

1. Koglin, J. Investigations into the pharmacuetiocal-technological quality of magnesium stearate [Dissertation; in German]. Department of Pharmacy and Food Chemistry, Philipps University, Marburg/Lahn, 1992.
2. Bolhuis, G. K.; Lerk, C. F.; Zijlstra, H. T.; De Boer, A. H. Film formation by magnesium stearate during mixing and its effect on tabletting. *Pharm. Weekbl.* **1975**, *110* (16), 317–325.
3. Allen, L. V.; Luner, P. E. Magnesium stearate. In *Handbook of Pharmaceutical Excipients*, 9th ed. Sheskey, P. J.; Hancock, B. C.; Moss, G. P.; Goldfarb, D. J., Eds.; Pharmaceutical Press and American Pharmacists Association, 2022; pp. 621–626.
4. Johansson, M. E.; Nicklasson, M. Investigation of the film formation of magnesium stearate by applying a flow-through dissolution technique. *J. Pharm. Pharmacol.* **1986**, *38* (1), 51–54. DOI: 10.1111/j.2042-7158.1986.tb04466.x.
5. Zarmpi, P.; Flanagan, T.; Meehan, E.; Mann, J.; Fotaki, N. Impact of magnesium stearate presence and variability on drug apparent solubility based on drug physicochemical properties. *AAPS J.* **2020**, *22* (4), 75. DOI: 10.1208/s12248-020-00449-w.
6. Gunning, S. R. Personal communication, 1977.
7. Mehrotra, A.; Llusa, M.; Faqih, A.; Levin, M.; Muzzio, F. J. Influence of shear intensity and total shear on properties of blends and tablets of lactose and cellulose lubricated with magnesium stearate. *Int. J. Pharm.* **2007**, *336* (2), 284–291. DOI: 10.1016/j.ijpharm.2006.12.013.
8. Calahan, J. L.; Paul, S.; Yanez, E. G.; DeNeve, D.; Sun, C. C.; Munson, E. J. The impact of solid-state form, water content and surface area of magnesium stearate on lubrication efficiency, tabletability, and dissolution. *Pharm. Dev. Technol.* **2021**, *26* (2), 150–156. DOI: 10.1080/10837450.2020.1839763.
9. John, C. T.; Xu, W.; Lupton, L. K.; Harmon, P. A. Formulating weakly basic HCl salts: relative ability of common excipients to induce disproportionation and the unique deleterious effects of magnesium stearate. *Pharm. Res.* **2013**, *30* (6), 1628–1641. DOI: 10.1007/s11095-013-1002-y.
10. Salpekar, A. M.; Augsburger, L. L. Magnesium lauryl sulfate in tableting: effect on ejection force and compressibility. *J. Pharm. Sci.* **1974**, *63* (2), 289–293. DOI: 10.1002/jps.2600630226.