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LUBRICANTS IN PHARMACEUTICAL SOLID DOSAGE FORMS WITH SPECIAL EMPHASIS ON MAGNESIUM STEARATE

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ABSTRACT

Lubrication plays a key role in successful manufacturing of pharmaceutical solid dosage form; lubricants are essential ingredients in robust formulation to achieve this. Although many failures in pharmaceutical manufacturing operations are caused by issues related to lubrication, in general, lubricants do not gain adequate attention in the development of pharmaceutical formulations. The addition of lubricants also affect tablet properties and can affect the behaviour of the powder mixture. In this review, the fundamental background on lubrication is introduced, in which the relationships between lubrication and friction/adhesion forces are discussed. The application of lubrication in the development of pharmaceutical products and manufacturing processes is discussed with an emphasis on magnesium stearate. In particular, the effect of hydration state (anhydrate, monohydrate, dihydrate, and trihydrate) of a lubricant like Magnesium stearate and its powder characteristics on lubricant efficiency, as well as product and process performance is summarized.

KEYWORD: lubricant, magnesium stearate, efeect of lubricant on tablet properties.

INTRODUCTION

The most important drug delivery route is undoubtedly the oral route. Despite the phenomenal advances in the inhalable, injectable, transdermal, nasal and other routes of administration the unavoidable truth is that oral drug delivery remains well ahead of the pack as the preferred delivery route.[1] Oral drug delivery is the most desirable and preferred

method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration and cost effective manufacturing process.[2]

Tablets are oral solid dosage form of medicaments with or without suitable diluents and prepared either by molding or compression. They are solid, flat and biconvex disc in shape. They vary greatly in shape, size, weight which depend upon amount of medicament used and mode of administration. They also vary in hardness, thickness, disintegration and dissolution characteristics and in other aspects depending upon their intended used and method of manufacture. Tablets are most widely used solid dosage form of medicament. Because their advantages their popularity is continuously increasing day by day.[3]

Advantages of tablet

- Tablets are easy to use, handle and carry by patient.
- Tablets provide prolong stability to medicament.
- Tablets are attractive and elegant in appearance.
- Tablets provide a sealed covering which protect the tablet from atmospheric condition like air, moisture and light etc.
- The manufacturing cost of tablets is low as compare to other dosage form.
- The unpleasant taste and odour of medicament can be easily masked by sugar coating.
- Whenever fraction at dose is required tablets are divided into halves and quarter by drawing line of tablets.
- Tablets provide administration of even minute dose of drug in as accurate amount.
- Tablets are formulated as special release of products such as enteric or delayed release products.

Disadvantages of tablet

- Difficult to swallow in case of children and unconscious patients.
- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.

- Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost.[3,4]

General properties of Tablet dosage forms[5]

1. A tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.
2. Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
3. Should have the chemical and physical stability to maintain its physical attributes over time
4. The tablet must be able to release the medicinal agents in a predictable and reproducible manner.
5. Must have a chemical stability over time so as not to follow alteration of the medicinal agents.

Excipients for tablet[6,7]

In addition to active ingredients, tablet contains a number of inert materials known as additives or excipients. Different excipients are:

1. Fillers and Diluents.
2. Binders.
3. Glidants.
4. Lubricants.
5. Antiadherents.
6. Disintegrants.

1. Fillers and diluents

Fillers fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. By increasing the bulk volume, the fillers make it possible for the final product to have the proper volume for patient handling. A good filler must be inert, compatible with the other components of the formulation, non-hygroscopic, soluble, relatively cheap, compactable and preferably tasteless or pleasant tasting. Plant cellulose (pure plant filler) is a popular filler in tablets or hard gelatin capsules. Dibasic calcium phosphate is another popular tablet filler. A range of vegetable fats and oils can be used in

soft gelatin capsules. Other examples of fillers include: lactose, sucrose, glucose, mannitol, sorbitol, calcium carbonate, and magnesium stearate.

2. Binders

Binders hold the ingredients in a tablet together. Binders ensure that tablets and granules can be formed with required mechanical strength, and give volume to low active dose is tablets. Binders are usually starches, sugars, cellulose or modified cellulose such as microcrystalline cellulose, hydroxypropyl cellulose, lactose, or sugar alcohols like xylitol, sorbitol or maltitol. Binders are classified according to their application:

- Solution binders are dissolved in a solvent (for example water or alcohol and used in wet granulation processes. Examples include gelatin, cellulose, cellulose derivatives, polyvinylpyrrolidone, starch, sucrose and polyethylene glycol.
- Dry binders are added to the powder blend, either after a wet granulation step, or as part of a direct powder compression (DC) formula. Examples include cellulose, methyl cellulose, polyvinylpyrrolidone and polyethylene glycol.

3. Glidants

Glidants are used to promote powder flow by reducing interparticle friction and cohesion. These are used in combination with lubricants as they have no ability to reduce die wall friction. Examples include colloidal silicon dioxide, talc and etc.

4. Lubricants

Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine. Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall. Common minerals like talc or silica, and fats, e.g. vegetable stearin, magnesium stearate or stearic acid are the most frequently used lubricants in tablets or hard gelatine capsules.

5. Antiadherents

Antiadherents are used to reduce the adhesion between the powder (granules) and the punch faces and thus prevent sticking to tablet punches.

6. Disintegrants

Disintegrants expand and dissolve when wet causing the active ingredients for absorption.

Disintegrant types include

- Water uptake facilitators.
- Tablet rupture promoters.

They ensure that when the tablet is in contact with water, it rapidly breaks down into smaller fragments, thereby facilitating dissolution.

Examples of disintegrants include: cross linked polyvinyl pyrrolidone, sodium starch glycolate, cross linked sodium carboxymethyl cellulose (crosscarmellose).

Method of Tablet Compression

1. Dry Method.

a. Direct Compression.

2. Wet Method.

b. Wet granulation.

LUBRICANTS

A lubricant, an additive to reduce friction, is an essential component of a drug formula since lubrication is often required to ensure the success of pharmaceutical manufacturing. Historically, use of animal fats as lubricants to reduce friction in transportation can be traced back to Egyptian time. However, the development of modern tribology, which is the study of friction and lubrication, did not gain ground until Frank P. Bowden established a research laboratory on friction, lubrication, and bearings in Melbourne, Australia during World War II.[8] Since then, a systematic study on friction and lubrication, termed "tribology", was initiated. Lately, due to the development of instrumentations in surface and interfacial characterization, and force measurements as well as the improved understanding between friction and adhesion force, tribology has been developed into an active research field. In particular, in the pharmaceutical industry, the application of lubrication or tribology in drug development has become increasingly important for developing a successful manufacturing process.[9]

For pharmaceutical operations such as blending, roller compaction, tablet manufacturing, and capsule-filling, lubrication is essential in order to reduce the friction between the surfaces of manufacturing equipment and that of organic solids as well as to ensure the continuation of an operation.[10] Pharmaceutical lubricants are the agents added to tablet and capsule

formulations in a very small quantity (usually 0.25%–5.0%, w/w) to improve the powder processing properties of formulations. Albeit a fairly small amount, lubricants play important roles in manufacturing; they decrease friction at the interface between a tablet's surface and the die wall during ejection so that the wear on punches and dies are reduced; they prevent sticking of tablets to punch faces as well as sticking of capsules to dosators and tamping pins. In terms of powder flow, lubricants can improve the flowability of blends and aid unit operations. For instance, for the blending of active pharmaceutical ingredients (APIs) of small particles with other excipients, the adhesion force between particles can significantly reduce the powder flowability by increasing inter-particle friction; poor flow can cause insufficient mixing of the blends (content uniformity) and rat-holing in the hopper of a tablet press (segregation issue), impacting both product quality and operation. To overcome these issues, lubricants are added (glidants) to enhance powder flow by reducing the inter-particle friction. Regarding lubrication agents, although magnesium stearate and stearic acid are the most frequently used lubricants in the pharmaceutical industry, there are other lubricants in use as well.[11]

Role of Lubricants[12]

There are three roles identified with lubricants as follows:

1. **True Lubricant Role**

To decrease friction at the interface between a tablet's surface and the die wall during ejection and reduce wear on punches & dies.

2. **Anti-adherent Role**

Prevent sticking to punch faces or in the case of encapsulation, lubricants prevent sticking to machine dosators, tamping pins, etc.

3. **Glidant Role**

Enhance product flow by reducing interparticulate friction.

Properties of a Good Lubricant[12]

1. Low Shear Strength- Want the lubricant to hear during blending, not the granules or other excipients in the formulation.
2. Able to form a "durable layer" over the surface covered.
3. Non-Toxic.
4. Chemically Inert.

5. Unaffected by Process Variables.
6. Posses Minimal Adverse Effects on the Finished Dosage Form.

Types of Lubricants.[13,14,1516]

Lubricants may be classified according to their water solubility (as water-soluble or water-insoluble). The choice of a lubricant may depend upon.

- The mode of administration and the type of tablet being produced,
- The disintegration and dissolution properties desired,
- The lubrication and flow problems and requirements of the formulation,
- Physical properties of the powder system being compressed,
- Drug compatibility considerations, and
- Cost.

(i) Water soluble lubricants

They are generally poor lubricants having no glidant or anti- adherent properties.

Table 1: Water soluble lubricants along with their concentration ranges

Water-soluble lubricants	Usual range (% w/w)
Boric acid	1
Sodium benzoate + sodium acetate	1-5
Sodium chloride	5
Dl-leucine	1-5
Carbowax 4000® (peg)	1-5
Carbowax 6000® (peg)	1-5
Sodium oleate	5
Sodium benzoate	5
Sodium acetate	5
Sodium lauryl sulphate	1-5
Magnesium lauryl sulphate	1-2

(ii) Water insoluble lubricants

Most widely used lubricants in use today are of the hydrophobic category. Water insoluble lubricants are generally good lubricants and are usually effective at relatively low concentrations. Many also have both anti-adherent and glidant properties. For these reasons, hydrophobic lubricants are used much more frequently than hydrophilic compounds.

Table 2: Water insoluble lubricants along with their concentration ranges.

Water- insoluble lubricants	Usual range (% w/w)
Stearates (magnesium, calcium, sodium)	0.25-2
Stearic acid	0.25-2
Sterotex®	0.25-2
Talc	1-5
Waxes	1-5
Stearowet®	1-5

Methods of Addition

Lubricants are generally added dry at a point where the other components are in a homogeneous state. Thus, the lubricant is added and mixed for a period of only 2 to 5 minutes rather than the 10 to 30 minutes necessary for thorough mixing of a granulation. Overmixing may lead to diminished disintegration-dissolution characteristics and loss of bonding in the tablet matrix. Lubricants have also been added to granulations as alcoholic solutions (e.g., Carbowaxes) and as suspensions and emulsions of the lubricant material. In one study[17] various lubricants were added, without significant loss of lubricating properties, to the initial powder mixture prior to wet granulation. However, as a rule, powdered lubricants should not be added prior to wet granulation since they will then be distributed throughout the granulation particles rather than concentrated on the granule surface where they operate. In addition, powder lubricants added in this manner will reduce granulating agent and binder efficiency.

Mechanism of Action[14,15,16]

Lubrication is accomplished via.

(i) Hydrodynamic lubrication

In this case of lubrication, lubricating oils (liquids) separate two surfaces with a viscous film, thereby enabling the surfaces to slide across one another.

(ii) Boundary lubrication

Unlike hydrodynamic lubrication, boundary lubrication is concerned with solids and is accomplished by shear gliding mechanisms. The lubricant, once partitioned between the two solid faces, resists high radial pressure due to its strong redial cohesive strength and shares easily in the axial plane because of low shear strength.

Magnesium Stearate

Magnesium stearate ($Mg(C_{18}H_{35}O_2)_2$) is a solid and white powder at room temperature; it is a Food and Drug Administration (FDA)-approved inactive ingredient commonly used in the pharmaceutical industry. Magnesium stearate may be derived from plants as well as animal sources. It is prepared either by the chemical reaction of an aqueous solution of magnesium chloride with sodium stearate, or by the reaction of magnesium oxide, hydroxide or carbonate with stearic acid at elevated temperatures. The raw materials used in the manufacturing of magnesium stearate are refined fatty acids, a mixture of palmitic and stearic acid.[17]

Magnesium stearate is widely used as a lubricant in pharmaceutical tablet formulations. The main reason for its good lubricating properties is its hydrophobic nature and an ability to reduce friction between tablets and die wall during the ejection process[18] Commonly used concentrations range between 0.25-5%.[19] It appears in different crystal forms, shows different particle size and shape, and occurs in several hydrate forms.[20,21,22]

Magnesium Stearate exists as “Plate-like” crystals (or lamellae) stacked together like a deck of cards. As the blending process proceeds, plates continue to shear off and coat adjacent particles of granules, drug or other excipients. The higher the concentration of Magnesium Stearate used or the longer this blending continues, the more complete this coating of the adjacent particles will become.

It has low friction coefficient and high covering potential. The lubricant efficiency and extent of surface coverage depend on the mixing time of the tablet mass with Magnesium Stearate because of its laminar structure.[23]

Introduction of the high-speed tableting machine requires the use of higher concentrations of Magnesium Stearate, but increasing concentration of Magnesium Stearate can adversely affect the flow properties of the tableting mass and the quality properties of tablets.[24,25,26]

In the next few sections, our focus will center on the effect of magnesium stearate on the manufacturing process and product performance.

1. Effect of Pseudo-Polymorph[27,28]

Magnesium stearate can form a variety of hydrates upon exposure to humidity. In addition to amorphous, magnesium stearate possesses four hydration states: anhydrate, monohydrate, dihydrate, and trihydrate. These hydration states can interchange reversibly, depending on

temperature and relative humidity (RH). For instance, the trihydrate of magnesium stearate could be generated by exposing its anhydrate to a RH >70%. Therefore, depending on the environment in which materials have been exposed, magnesium stearate obtained from a vendor can be a mixture of anhydrate, hydrates, and amorphous. Consequently, most of the commercial supplies for this lubricant contain a mixture of various hydrates in unknown ratios. As reported, the lubrication efficiency of magnesium stearate as a lubricant varies from one hydration state to another; in general, the dihydrate is considered to be the most efficient lubricant of all, due to its crystal structure which is suitable for shearing. As a result, the flowability, permeability, porosity, and compressibility of a particular formulation lubricated with magnesium stearate depend on its moisture content or the RH of storage conditions. To further investigate the impact of the hydration state of magnesium stearate on the performance of formulations, each hydrate was isolated and tested in formulations. For example, to test the lubrication efficiency of each hydrate and their mixtures, each hydrate or a combination of two (1%, w/w) was mixed with other formulation components: MCC (72%, w/w), lactose monohydrate (22%, w/w), and acetaminophen (5%, w/w). In general, different hydration states produce varied effects on the performance of formulations. For example, the formulation lubricated with the monohydrate of magnesium stearate showed the lowest permeability and porosity followed by the formulations lubricated with the dihydrate and the anhydrate of magnesium stearate, and finally the un-lubricated formulation. This suggests that the structure of the lubricant affects the inter-particle packing arrangement, and consequently the blends containing the monohydrate require a higher pressure to establish a flow relative to those with the dihydrate and the anhydrate. However, in terms of the crush strength of compacts, the un-lubricated formulation produced compacts with the highest crush strength (15.471 kg/cm2) followed by the formulations containing the dihydrate, the monohydrate, and the mixture of (50:50, w/w) the dihydrate and the monohydrate.

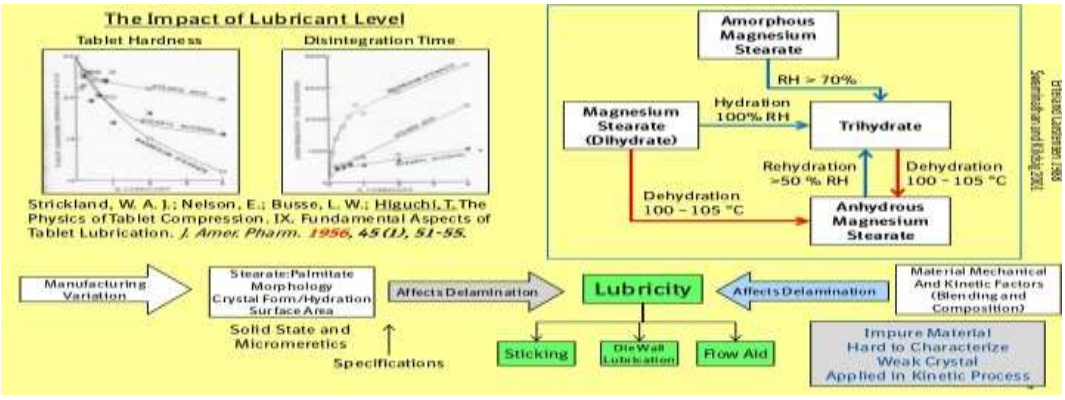

Figure 1: Effect of Pseudo-Polymorph.

2. Effect of Powder Properties on Lubrication

In practice, the effect of the hydration state of magnesium stearate on lubrication cannot be separated from other factors such as surface areas and agglomeration.[29] The materials of magnesium stearate obtained from various vendors or different batches of the same vendor often have varied powder properties such as particle size, surface area, and particle shape.[30] Therefore, it is important to understand the impact of these properties on the performance of the lubricated formulations, including the mechanical properties of the compressed products, the dissolution of tablets, and the flowability of powder. Generally, it is expected that the lubrication efficiency of magnesium stearate improves with increasing its surface area or decreasing its particle size since the increase of surface area can provide more surface coverage.[31] Consequently, with more coverage of particle surfaces by magnesium stearate, the particle-particle bonding is weakened, resulting in weak tablets. In addition, because the surface of API particles is covered with the lubricant which is hydrophobic, it causes slow-down of dissolution.

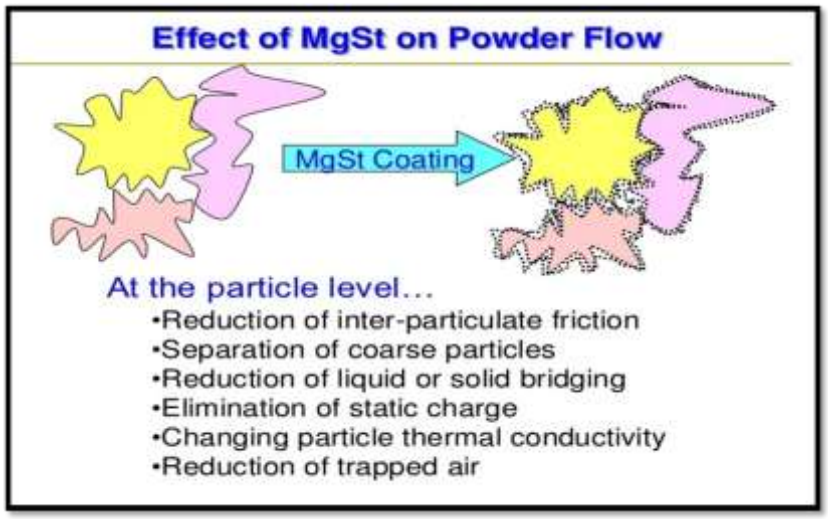

Figure 2: Effect of Powder Properties on Lubrication.

3. Effect on the Mechanical Properties of Compressed Products[32-34]

As discussed before, the presence of magnesium stearate in a blend can significantly affect the flowability of the blend, which consequently impacts on the dynamics of compaction/compression processes (such as roller compaction). Therefore, the mechanical properties of any compacts/tablets manufactured are lubricant dependent.

4. Online Monitoring of Magnesium Stearate in Blending

As discussed above, lubrication can significantly change the dynamics of blending and compaction/compression, as well as the mechanical properties (solid fraction and tensile strength) of compacts/tablets made. Therefore, monitoring of the change of magnesium stearate during manufacturing and storage becomes very critical. In particular, the hydration state of magnesium stearate changes with humidity and temperature, and its lubrication efficiency varies with its composition. To detect the composition change, near infrared spectroscopy (NIR) in conjunction with other thermal methods was used to monitor the variability of the hydration state during operation, in which the absorption wavelengths for monohydrate and dehydrate are 7045 and 5100 cm−1, respectively.[35] The results from NIR were in general consistent with those obtained using other methods such as thermal gravimetric analysis. However, the NIR method with partial least squares regression analysis is more sensitive to the presence of small quantities of hydrates. In addition, the distribution of magnesium stearate on tablet surfaces in a punch-face lubrication system was detected by Raman imaging technique using a wavelength of 1295 cm−1, allowing the determination of the domain size of magnesium stearate in one dimension.[36] In contrast, when the same approach was applied to lubricated formulations, Raman failed to detect the signal of magnesium stearate presumably due to interferences from other materials in the formulations. Furthermore, to determine the end-point of a blending process for a formulation with magnesium stearate, thermal effusivity sensors can be used to monitor the blend uniformity.[37] This was demonstrated for the blend of magnesium stearate and sugar sphere in a V-blender. Comparing the thermal effusivity data with the powder density, the former correlated well with the powder characteristics of the system for achieving optimal mixing. This is important since when various hydrates of magnesium stearate are used as lubricants, the time required to achieve a homogeneous blend varies. Hence, using thermal effusivity sensors to monitor a blending process can detect the end-point nondestructively without sampling the blend to avoid over-lubrication. Overall, the online monitoring of pharmaceutical processes becomes increasingly important for achieving the optimum performance for a formulation and avoiding the detrimental effect due to over-lubrication and inhomogeneous distribution.[38]

Considerations for Selecting a Lubricant

In summary, there are many factors to be considered for selecting an appropriate lubricant for preparing solid dosage forms including: low shear strength, being able to form a durable layer

covering the surface/particles, non-toxic, chemically compatible with APIs and other components in the formulation, low batch to batch variability and having minimum adverse effects on the performance of the finished dosage forms. In addition, the optimal concentration and mixing time are also needed to be taken into consideration when selecting a lubricant because both of these two parameters greatly impact the performance of pharmaceutical products and processes. Although low lubricant concentration and inadequate mixing cause inefficient lubrication issues such as sticking, capping, and binding in the die cavity, over-lubrication-high lubricant concentration and over-mixing-often results in an adverse effect on products as well as processes, including the reduction of tablet hardness, compression variability, the prolongation of disintegration time and the decrease of the rate of dissolution. In Table 1,2, the recommended concentrations of typical lubricants used in solid dosage forms are listed. In terms of the process of adding a lubricant, the lubricant is often added at the end of the granulation process in the outer phase when other components have been mixed thoroughly. Furthermore, the mixing time for distributing a lubricant is typically 0.5–5 min for better results on compactability and the hardness of tablets. Finally, selecting a lubricant for a formulation requires a systematic approach with careful consideration of the performance of both product and process.

CONCLUSION

In this paper, tablet and their properties have been discussed. In addition to other classes of lubricants used in the pharmaceutical industry, magnesium stearate as the most frequently used lubricant has been discussed in detail. In terms of the effect of lubricant particle size, magnesium stearate with a large surface area and small particle size has the best lubrication efficiency, but it reduced the hardness of tablets and caused slow-down of dissolution.

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