MAZEN MORTAGI
AL-MOHAYA

EFFECT OF SYNTHESIS CONDITIONS OF
MAGNESIUM STEARATE ON ITS
LUBRICATION PROPERTIES

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A THESIS SUBMITTED TO THE GRADUATE SCHOOL OF HEALTH SCIENCES OF NEAR EAST UNIVERSITY

By
MAZEN MORTAGI AL-MOHAYA

In Partial Fulfillment of the Requirements for The Degree of Master of Science in Pharmaceutical Technology

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ABSTRACT

Magnesium Stearate is a commonly used lubricant for preventing tablet compression issues, since it prevents the adherence of tablets in the dies, reduces friction at all interfaces, and improves granule flow properties. It is well known that the powder characteristics of magnesium stearate differ among magnesium stearates manufactured by different methods and conditions. It has multiple crystalline forms and, potentially, an amorphous form. Lubricating ability of magnesium stearate is directly impacted by its moisture content, which has been in turn regarding the ability of this compound to form species of differing hydration states. The aim of the current work is to evaluate the lubrication properties of magnesium stearate that have been impacted by its synthesis conditions and to compare with a commercial form. Evaluation of magnesium stearate used in this study have been made by using thermal analysis including (melting point, differential scanning calorimeter (DSC), and thermogravimetric Analysis (TGA)), structural characterization study including (x-ray powder diffraction (XRPD), and fourier transform infrared spectroscopy (FTIR)), microscopy study (scanning electron microscope (SEM)). In addition, comparison of the performance of both synthesis and commercial magnesium stearate in a modal in various concentrations (0.5%, 1.0%, 1.5%, and 2.0%), have been achieved by performing compaction study including (minimal thickness, rearrangement energy, compression energy, plastic energy, ejection energy, ejection force, ejection time, tensile strength, and lubrication effectiveness), and flowability study including (rheometry (flowability energy (BFE), stability index (SI), flow rate index (FRI) and specific energy (SE)), and avalanche behavior (avalanche energy, break energy absolute, avalanche time, avalanche angle, and surface fractal)). The results showed that both synthesis and commercial magnesium stearate have given different values at thermal, structural characterization, and microscopy study. Synthesis of magnesium stearate offers better properties as well as at compaction and flowability studies. Finally, synthesis magnesium stearate provides good lubrication effectiveness.

***Keywords*:** Magnesium stearate; lubricant; tableting; avalanche behavior; rheometry; compaction; thermal analysis; structural characterization; scanning electron microscope

ÖZET

Magnezyum Stearat, tablet sıkıştırma sorunlarını önlemek için yaygın olarak kullanılan bir yağlayıcıdır, çünkü tabletlerin kalıplara yapışmasını önler, tüm arayüzlerde sürtünmeyi azaltır ve granül akış özelliklerini geliştirir. Magnezyum stearatın toz karakteristiğinin, farklı yöntemler ve koşullar ile üretilen magnezyum stearatlar arasında farklı olduğu bilinmektedir. Çok sayıda kristalin formuna ve potansiyel olarak amorf bir forma sahiptir. Magnezyum stearat yağlama kabiliyeti, nem içeriğiyle doğrudan etkilenir; bu da, bu bileşiğin, farklı hidrasyon durumlarına sahip türler oluşturma kabiliyetine ilişkin olmuştur. Mevcut çalışmanın amacı, magnezyum stearatın lubirkasyon özelliklerinin sentez koşulları ile etkilendiğini gøsterilmesi ve ticari formla karşılaştırılmasının değerlendirilmesidir. Bu çalışmanın değerlendirilmesi, (erime noktası, diferansiyel taramalı kalorimetre (DSC) ve termogravimetrik Analiz (TGA)), (x-ışını toz difraksiyonu (XRPD) ve fourier transform infrared spektroskopisi ve yapısal karakterizasyon çalışması dahil olmak üzere termal analiz çalışması kullanılarak yapılmıştır. (FTIR)), mikroskopi çalışması (taramalı elektron mikroskobu (SEM)). Ek olarak, (minimal kalınlık, yeniden düzenleme enerjisi, kompresyon enerjisi, plastik enerji dahil) sıkıştırma çalışması kullanılarak çeşitli konsantrasyonlarda (% 0.5,% 1.0,% 1.5 ve% 2.0) bir modalda hem sentezin hem de ticari magnezyum stearatın performansının karşılaştırılması (ejeksiyon enerjisi, ejeksiyon kuvveti, ejeksiyon süresi, çekme kuvveti ve yağlama etkinliği) ve akışkanlık çalışması (reometri (akışkanlık enerjisi (BFE), kararlılık endeksi (SI), akış oranı indeksi (FRI) ve spesifik enerji (SE)) ve çığ davranışları (çığ enerjisi, kırılma enerjisi mutlak, çığ zamanı, çığ açısı ve yüzey fraktal)). Sonuçlar, hem sentez hem de ticari magnezyum stearatın termal, yapısal karakterizasyon ve mikroskopi çalışmasında farklı değerler verdiğini göstermiştir. Bununla birlikte, sentez magnezyum stearat, sıkıştırma ve akışkanlık çalışmasında olduğu gibi daha iyi özellikler sunar. Son olarak, sentez magnezyum stearat, iyi bir lubrikasyon verimi sağlar.

***Anahtar Kelimeler*:** Magnezyum stearat; yağlayıcı; tablet; çığ davranışları; reometre; sıkıştırma; ısı analizi; yapısal karakterizasyon; taramalı elektron mikroskobu

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LIST OF ABBREVIATIONS

FII:	Force of Friction
μ:	Coefficient of Friction
Ḟ:	External Load
A:	The Area of Contact
ε:	Transferred Coefficient
Δγ:	Difference of Surface Energy
δ:	Elemental Distance
JKR:	The Johnson-Kendall-Roberts
DMP:	Derjaguin-Muller-Toporov
Py:	Force of Adhesion per Unit Area
A:	Area of Contact
C:	Elastic Component
PEG:	Polyethylene Glycol
φx:	Angle of Wall Friction
τw:	Wall Shear Stress
σw:	Wall Ordinary Stress
D:	Diameter of a Powder Compact
L:	Length of the Compact
σzt:	The Axial Stress on the Top
σzb:	The Axial Stress on the Bottom
k:	The Ratio of Radial Stress
σr:	Over Vertical Stress
σc:	Unconfined Yield Strength
σl:	Function of the Consolidation Stress
FH:	Adhesive Force
r:	The Radius
W/W:	Weight Concentration
°C:	Degrees Celsius

Kg:	Kilogram
cm:	Centimeter
g:	Gram
ml:	Milliliters
Ω:	Lubricity Index
m:	Meter
µm:	Micrometer
MgO:	Magnesium Oxide
cm−1:	Reciprocal Centimeter
rpm:	Revolutions per Minute
MgC1:	Magnesium Chloride
IR:	Infrared Radiation
RH:	Relative Humidity
NaOH:	Sodium Hydroxide
h:	Hour
XRPD:	X-Ray Powder Diffraction
mm:	Millimeter
kV:	Kilovolt
mA:	Milliamperage
IR:	Infrared Radiation
Å:	Angstrom (Unit of Length**)**
θ:	Theta
SEM:	Scanning Electron Microscope
SE:	Secondary Electron
x:	Magnify
DSC:	Differential Scanning Calorimeter
TGA:	Thermogravimetric Analysis
λ:	Wavelength
FTIR:	Fourier Transform Infrared Spectroscopy
KBr:	Potassium Bromide

F:	Breaking Force
M:	Tablet Diameter
T:	Tablet Thickness
BFE:	Basic Flowability Energy
SI:	Stability Index
FRI:	Flow Rate Index
SE:	Specific Energy
kcps:	Kilo Counts per Second
mJ:	Megajoule
kJ:	KiloJoule
N:	Newton
J:	Joule
ms:	Millisecon

CHAPTER ONE

INTRODUCTION

1.1 Introduction

For pharmaceutical operations such as blending, roller compaction, tablet manufacturing, and capsule-filling, lubrication is primarily so as to decrease the friction between the surface of manufacturing equipment and powder material as well as to ensure the permanence of the operation (Bolhuis & Hölzer, 1996). Append pharmaceutical lubricants agent to tablet and capsule formulation in a quite small quantity (usually 0.25%-5.0% w/w) to make the powder materials better in processing properties of formulation. Furthermore, lubricants play important roles in manufacturing because:

a) They reduce friction at the interface between tablet's surface and the die wall pending ejection, so that the wear on punches and dies are minimized.

b) They blocked cement of tablet to punch face as well as cement of capsule to dosators and tamping pins.

Another key point, lubricants can enhance the flowability of blend and help unit operation. An illustration of the mixing of active ingredients of small particles with other excipients, the adhesion force between particles can safely diminish the powder flowability by raise inter particles friction, thus poor flow can bring about inadequate blending of the blend (content uniformity) and rat-holing in the hopper of the tablet press (segregation problem); influence both operation and product quality. In order to overcome these problems, lubricants are added as a glidant to improve powder flow by lessening the inter-particle friction (Goldberg & Klein, 2012).

1.2 Friction

On the whole it can be said that Friction is really minimized by lubrication. Opposite to the popular opinion, friction was truly first investigated by Leonardo Da Vinci. However it was mistakenly believed to Amontons, which is often mentioned to as Amontons's law. The basic part of this law is expressed in Equation (1.1).

$$FII = \mu F \qquad (1.1)$$

Where FII is the force of friction, μ is the coefficient of friction, and F is the external load. The friction force is proportional to the external load, the coefficient of friction, and the normal force applied. In Equation (1.1), there are some assumptions are made as follow:

1) The force of friction is proportional to the applied load.

2) The frictional force is not dependent on the obvious contact area.

3) The kinetics of friction is not dependent on the sliding velocity.

Apparently, this is oversimplified. Seeing as Amontons's law applies correctly to geometric or mechanic models that the interlock of surface harshness chiefly contributes to the force of friction; the function of lubricants in diminishing the frictional force is to replenish the cavities of surface. On the top of that, Amontons's law was derived from perceive sliding wooden blocks, there is no regarding of adhesion. Nevertheless, this model cannot consider adhesion forces contributory which is presented everywhere for pharmaceutical operations owing to the fine size of active ingredients and other excipients. As a result of understanding the force of friction involved in pharmaceutical operations, a model with combination of adhesion force is more suitable (Israelachvili & Jacob, 2011).

1.3 Friction and Adhesion

All in all, friction and adhesion are almost always related to each other as well as expected; friction always increases with the adhesion between surfaces. To put it in another way by definition, the energy of adhesion is the energy needed to break two disparate surfaces (Israelachvili & Jacob, 2011) (Pietsch, 1997). In Equation (1.2) is shown the relationship between the force of friction and adhesion.

$$FII = \mu \underset{\cdot}{F} + 2\varepsilon A \frac{\Delta\gamma}{\delta} \qquad (1.2)$$

There are two terms in Equation (1.2), the first symbolizes a contact friction, where FII is the force of friction, μ is the coefficient of friction, and $\underset{\cdot}{F}$ is the external load. The second symbolizes the force contributory in the adhesion hysteresis between two contacting materials, where A is the area of contact, ε is the transferred coefficient, Δγ is difference of surface energy, and δ is the elemental distance (Israelachvili & Jacob, 2011). As illustrious earlier in Equation (1.2), the adhesion force involved in an adhesion hysteresis cycle strongly depends on the contact between two surfaces, which has been well investigated. Mechanically, under compression, due to particle fracture or the deformation of excipients or both, so pharmaceutical powders may undergo a plastic deformation. In this case, the adhesion force (F (δ)) for flat punch contains of forces from both plastic and elastic regimes as exhibited in Equation (1.3).

$$F(\delta) = PyA + C \qquad (1.3)$$

Where Py is the force of adhesion per unit area, A is the area of contact, and C is the elastic component (Israelachvili & Jacob, 2011). Incorporated into formulations, lubricants reduce the fiction force, (specifically the adhesion force), in other words, reducing the contact between powder particles and equipment surfaces (Bowden & Tabor, 1973).

1.4 Lubricants

Lubricants have a really multifunction in tablet manufacture as following:

1) Preventing the adhesion of tablet materials on the wall of die.

2) Preventing the adhesion of tablet materials on the surfaces of punches.

3) Reducing the friction between particles.

4) Facilitating ejection of the tablet from the cavity of die.

5) Improving the tablet granulation flowability rate.

Frequently, talc, magnesium stearate, calcium stearate, stearic acid, glyceryl behanate, hydrogenated vegetable oils, and polyethylene glycol (PEG) used as lubricants. Inadequate selection and excessive amount can cause water proof tablets. In that case, tablets will have low disintegration and /or delayed dissolution of drug substance. Material that is going to stick to the punches and dies through tableting, hence the addition of appropriate lubricants is extremely desirable. Also most of tablets after compression directly tend to expand, then will bind and stick to the side of die, so selecting the proper lubricant in order to overcome that effectively (Sakr et al., 2013).

1.4.1 Lubrication Mechanism

Die-wall lubricants are chiefly accomplished by two mechanisms. First, fluid lubricant (hydrodynamic), fluid lubricants are rarely used in tablet formulation. Second, boundary lubricants are very small particulate solid, and the commonly use in tablet formulation (Alderborn, 2013).

a) Fluid lubricants

Fluid lubricants (hydrodynamic) are worked by making a layer of lubricant according separating moving surface. For instance, mineral oils or vegetable oils, and they may be either applied immediately to the die wall by means of wicked punches or added to the mix. Owing to uneven distribution of oily lubricant that contains, tablet may have a mottled appearance. Have been reported adding to the mix leads to affect oppositely on reducing tablet strength and on powder flow due to their tacky nature. Heat produced at the die wall, therefore low melting point lipophilic solid can sufficiently melt and form a fluid layer which solidifies on ejection, and it refers to act as fluid lubricants. On the other hand, low melting point lubricants should be used with care taken in tablets, which are to be film coated because lubricants can melt on the tablet surface during the film coating process, resulting in tablets with a pitted appearance. Fluid lubricants such as stearic acid, mineral oils, hydrogenated vegetable oils, glyceryl behenate, paraffins and waxes. Their using tends to be restricted to applications where a suitable boundary lubricant cannot be identified (Davies, 2004).

b) Boundary lubricants

Metallic stearates are considered to be one of the most utilized boundary lubricants, were they function by forming a thin solid film that is mainly presented at the interface of the die and the tablet. Usually, this mechanism is attained due to the adherence of polar molecular portions on their surface to the surfaces of one particle species and of non-polar surface components to the other species surface. Lubricants of such category usually have low shear strength implemented and tend to make inter-particulate films that are intended to resist wear and decrease surface wear. A list of lubricants with typical ranges for their usage is given in (Table 1.1) (Davies, 2004). The most ubiquitous functional mechanism in the pharmaceutical industry exactly in the unit operation is boundary lubricant (Wang et al., 2010). In other word, boundary lubricant forms layers in order to prevent the contact between the intended surfaces and powder particles. Furthermore, measuring its activity by concern the extent to which these films can cover the field of force of the underlying surface (Bowden & Tabor, 2001).

Table 1.1: Lubricants and their usage (After (Davies, 2004)).

Lubricant	Level Required (%)	Comments
Boundary Lubricants		
Magnesium stearate	0.2 – 2	Hydrophobic, variable properties between suppliers.
Calcium stearate	0.5 – 4	Hydrophobic.
Sodium stearyl fumarate	0.5 – 2	Less hydrophobic than metallic stearates, partially soluble.
Polyethylene glycol 4000 and 6000	2 – 10	Soluble, poorer lubricant activity than fatty acid ester salts.
Sodium lauryl sulphate	1 – 3	Soluble, also acts as wetting agent.
Magnesium lauryl sulphate	1 – 3	Acts as wetting agent.
Sodium benzoate	2 – 5	Soluble.
Fluid Lubricants		
Light mineral oil	1 – 3	Hydrophobic, can be applied to either formulation or tooling.
Hydrogenated vegetable oils	1 – 5	Hydrophobic, used at higher concentrations as controlled release agents.
Stearic acid	0.25 – 2	Hydrophobic.
Glyceryl behenate	0.5% – 4	Hydrophobic also used as controlled release agent.

1.4.2 Type of lubricants

Water solubility usually classifies lubricants either being water soluble or water-insoluble. There are several factors that implement the choice of lubricant being used. Such factors include the mode of administration, the type of tablet being manufactured, the disintegration and dissolution properties desired, the lubrication and flow problems and requirements of the formulation, various physical properties of the compressed granulation or powder system and finally drug compatibility issues and cost.

1.4.2.1 Water-insoluble lubricants

In general, water-insoluble lubricants are considered more efficient than water soluble lubricants and applied only in small concentration. In (Table 1.2) summarizes some of the typical insoluble lubricants and their applied levels. Regardless of the type of lubricant, it should be 200 meshes or finer and before its addition to granulation, also should be passed through a 100 mesh screen. As aforementioned, since lubricants function by coating; therefore, their efficiency is mainly contributed to both their surface area and to the degree of reduced particle size applied. The following features are considered to have a noticeable effect on the effectiveness of the lubricant and the disintegration-dissolution characteristics of the final tablet. These include the specific lubricant, its surface area, the time (point) and procedure of addition, and the length of mixing (Peck et al., 1989).

1.4.2.2 Water-soluble lubricants

Mainly, the using of water-soluble lubricants is restricted to certain situations. For instance, using them in tablets that are intended to be completely water-soluble such as effervescent tablets, or when unique disintegration, or more commonly dissolution characteristics are desired. In (Table 1.3) represents potential choices of water-soluble lubricants. A doubtful, member of the list includes boric acid which is due to the predictable toxicity of boron. A review is proposed that includes some newer water-soluble lubricants that have been combined

with talc and calcium stearate. Some of the suggested water-soluble lubricants include polyethylene glycols and 20 low melting point surfactants (Peck et al., 1989).

Table 1.2: Water-Insoluble Lubricants (After (Peck et al., 1989)).

Material	**Usual Range (%)**
Stearate (magnesium, calcium, sodium)	0.25 – 2
Stearic acid	0.25 – 2
Sterotex	0.25 – 2
Talc	1 – 5
Waxes	1 – 5
Stearowet	1 – 5

Table 1.3: Water-Soluble Lubricants (After (Peck et al., 1989)).

Material	**Usual Range (%)**
Boric acid	1
Sodium benzoate + sodium acetate	1 – 5
Sodium chloride	5
DL-Leucine	1 – 5
Carbowax 4000	1 – 5
Carbowax 6000	1 – 5
Sodium benzoate	5
Sodium acetate	5
Sodium oleate	5
Sodium lauryl sulfate	1 – 5
Magnesium lauryl sulfate	1 – 5

1.4.3 Function of lubrication

In pharmaceutical industry, there are many process used in pharmaceutical operation so as to prepare solid dosage. For example, blending, die filling, compaction, capsule-filling, and compression. Friction occurs at either powder interfaces or particle-particle interfaces. As revealed wall friction always refers to the interaction between powder particles and the wall of tool, in the same way internal friction means the particle-particle interaction. In the next parts, will be certainly clarified the most important aspects of friction lessening through lubrication for both wall friction and internal friction (Wang et al., 2010).

1.4.3.1 Wall Friction

Friction between a bulk solid and a solid surface just as between powder particles and the wall of a bin mixer (the bulk solid moves over the surface of the mixer); it is commonly called wall friction. They are often utilized the angle of wall friction φx, and the coefficient of wall friction μ to evaluate the amount of wall friction. They are realized by the subsequent Equations (1.4):

$$\mu = \frac{\tau w}{\sigma w} \text{ and } \varphi x = \arctan \frac{\tau w}{\sigma w} \qquad (1.4)$$

Where τw and σw are the wall shear stress and the wall ordinary stress respectively (Schulze, 2008). The increasing in the wall friction is a resulting of increasing in the wall friction angle or the coefficient of wall friction. In contrast, it is significantly considered the wall friction angle parameter. By the same we have observed in boundary lubrication, forming a boundary layer to decrease the coefficient of wall friction by adding lubricant in formulation. As evidence, in the tablet operation, the coefficient of friction is acquired by the application of a force balance through integration (Seen in Equation (1.5) and Figure 1.1) (Gethin et al., 2008).

$$\mu = \frac{D}{4KL} (\text{In } \sigma zt - \ln \sigma zb) \qquad (1.5)$$

Where D is the diameter of a powder compact, L is the length of the compact, σzt is the axial stress on the top, σzb is the axial stress on the bottom, and k is the ratio of radial stress (σr)

over vertical stress (σz). Under this circumstance, shear stress is minimized by utilizing lubricants to move a tablet out of a die for producing an ordinary stress. Likewise, lubricants can be used to reduce the internal friction among powder particles.

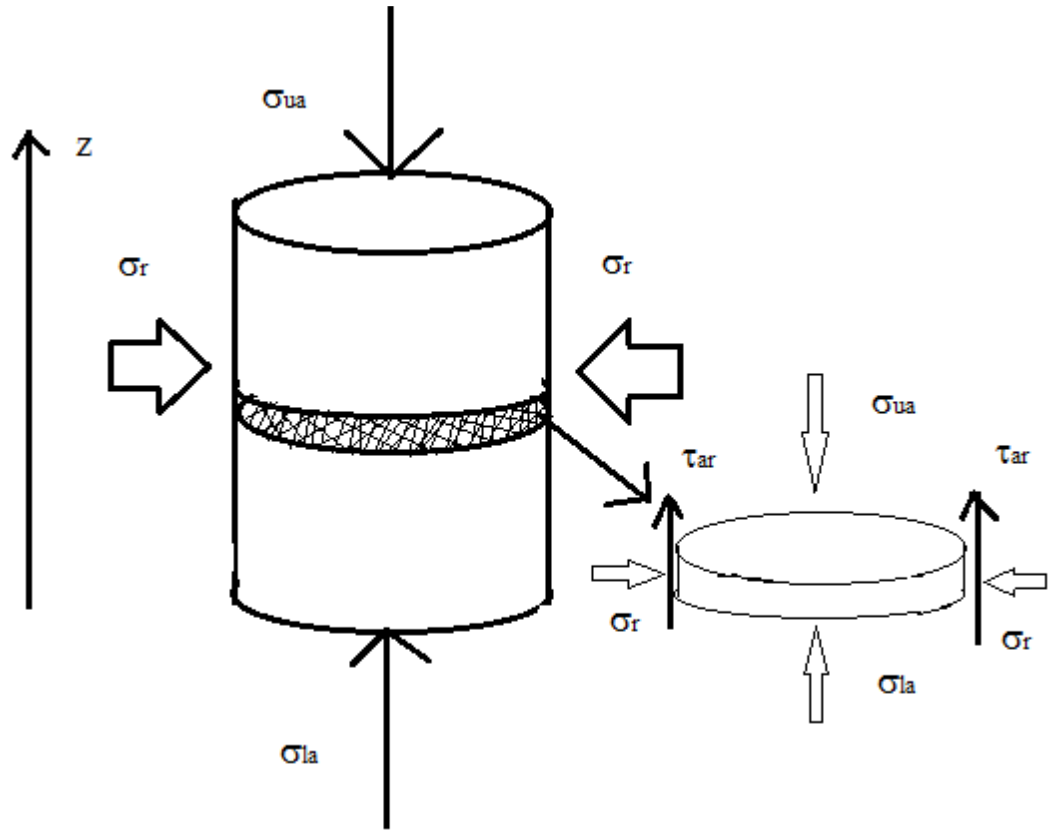


Figure 1.1: Stress balance and the lubrication coefficient for powders in a tablet die: σua and σla are stresses from top and bottom; τar is the shear stress.

1.4.3.2 Powder Flow

The unconfined yield strength σc, which is a function of the consolidation stress σl is considered as a way to characterize the flowability of a bulk solid. Now, the term flow function usually represents the ratio of consolidation stress to the unconfined yield strength, which in turn used to illustrate the flowability of the blend numerically. The following are represented as follows (Schulze, 2008):

- ffc<1 (not flowing)
- 1<ffc<2 (very cohesive)
- 2<ffc<4 (cohesive)
- 4<ffc<10 (easy flowing)
- 10<ffc(free-flowing)

Poor flowability is of a major concern due to its consequences. For instance, when the powder is poorly flowable in the hopper, this is due to arching or ratholing results due to uneven flow occurring. Another essential point, content uniformity due to insufficient mixing is another consequence resulting from flowability problems. In order to enhance the powders flowability, certain agents will be included in the formulation, which are known as flow aids or lubricants such as magnesium stearate. These agents mainly function by reducing the inter-particle adhesion force, which is achieved by the flow agent adhering to the surface of the solid particles as represented in (Figure 1.2). In other words, such agents usually aim to increase surface roughness by reducing the adhesion force as the distance between the particles increases. Not to mention that, magnesium stearate hydrophobicity of the material plays a crucial role. As declared in (Figure 1.2), the adhesion force of the powders with flow agents firstly decrease with the radius of the flow agent particles which then will be followed by an increase with the radius of the particles. Depending on the particle size of the powders, the calculated optimum radius considered to reduce the inter-particle adhesion force is approximately in the range of 5-50 nm (Zimmermann et al., 2004).

1.4.3.3 Punches adherence

By the same taken lubricant also serves as anti-adherent. During compression some materials can adhere to the punch surfaces since they have adhesive properties. This will primarily appear itself as sticking, with a film forming on the surfaces of the tablets, and leading to dull tablet surfaces. This may be resulted when punches are not properly cleaned or polished or when tablets are compressed in a high humidity, as well as when lubrication is inadequate. When tablet's solid particles stick to the punch surface, it is called "picking" the more extreme

version of sticking. This will often be obvious in the intagliations on the tablet surface, as a result of poor definition of the surface markings. Moreover, it can be inferred that picking usually results from improperly dried granulations, from punches with imperfectly designed logos, and from insufficient glidant utilize, practically when oily or sticky ingredients are compressed. Attempts evaluation of picking tendencies have been made by using instrumented tablet machines. Load cells have been placed appropriately to the edge of feed frames of rotary machines, then supervise the force required to knock tablets off the lower punch following ejection. Shah et al. (1986) claimed that the amount of the residual force still existing on the lower punch of a single punch machine after that removing of the upper punch was inversely related to the degree of adherence to the upper punch. Obviously, in practice sticking should be observed during tableting. It is not required to add a specific anti adherent caused most of die wall lubricants and many formulations have anti adherent action (Davies, 2004).

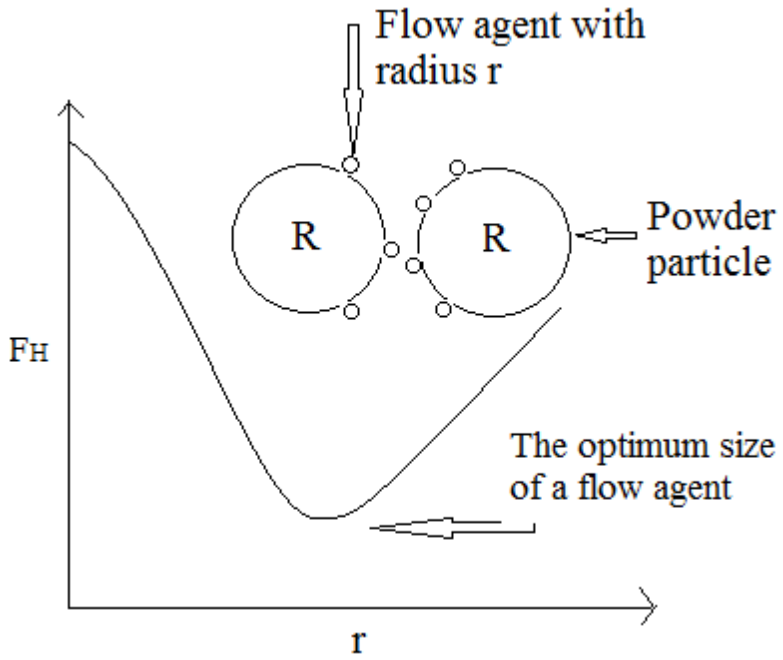


Figure 1.2: Adhesive force (FH) as a function of the radius (r) of a flow agent for powder particles with a radius of R.

1.4.3.4 Ejection force

In general, tablet compression produces a consolidation of the particles into a pellet of specific strength. Additionally, particle rearrangement, deformation of particles, interparticulate bond formation, and elastic recovery upon ejection of the compact from the die are resulted of tablet compression. Tablet compression processes include compression and consolidation, decompression, ejection and scrape off (take off). Ejection is the next to last step of tablet compression. Therefore, the required force to push the tablet out of the die is termed the ejection force. Notably, lubricating the material and/or the die significantly decrease the overall ejection force as well as when the tablet leaves the lower punch, the extent of lubrication also becomes important in the last step during tablet compression. After the tablet is ejected from the die, the needed force to scrape the formed tablet off the lower punch face is termed the scrape off force (take off). In fact, Lubrication is most relevant to the tablet ejection and tablet take-off steps which in turn aid to minimize the friction between the tablet and the metal surface. Hence, according to that, lubricant makes the overall tablet compression process much smoother. Physically, ejection force or scrape off force during tablet compression is intermolecular interactions of the powder blend. In other words, owing to the thermodynamic nature of the intermolecular and inter-particulate interactions, it is easier to understand them through energy terms. Nonetheless, many times it is easier to measure experimentally the interaction forces between macroscopic. For instance, this can be determined by measuring the amount of the tablet ejection force, not the ejection energy of the interactions between the sides of the tablet and the die wall. To put it on another way, the same is correct for the tablet scrape off process. The adhesive interactions between two surfaces for both the tablet ejection and scrape off forces are measured (Çelik, 1994). Johnson, Kendall and Roberts have depended on the hypothesis of real particles (surfaces) are not totally hard, so they suggested a rigorous theoretical treatment of the adhesive interactions of elastic spheres. From that time onward, it is called ‘‘JKR theory”, has highly established the modern theories of adhesion mechanics. At the same time, different pharmaceutical powders may characterize as elastic, plastic deformation, or brittle fragmentation materials (beside on its behavior). In contrast, most pharmaceutical ingredients exhibit mixed behavior (Johnson, 1971). Moreover, In termed of tablet ejection, rather than pulling-off force (vertical force is exerted to pull one particle

apart from another) in order to break the adhesive interaction, pushing the tablet out of the die during tablet ejection, it is assumed to break the bond between the sides of the tablet and the die wall. To demonstrate, friction expresses the adhesive interactions, which can be described by the ‘‘coefficient of friction”. In related to tablet scrape off process, the adhesive interactions are broken up by the scraping action. Thus, lubricant has the potential ability to reduce the adhesive interactions between the tablet and the die wall or lower punch surface (Israelachvili & Jacob, 1992).

1.4.4 Methods of Addition Lubricants

1.4.4.1 Internal lubrication

Internal lubrication operation is usually termed for lubricants that utilized as a part of the formulation for preparing tablets by blending the lubricants with the mixture containing granular or powder (has all the other ingredients) forms in a mixer previous tablet compression as the last step. Type of blending equipment and using process has been impacted by choosing the lubricants, and then all these may impact the lubrication process and consequently the tablet properties. This is can be observed by using microcrystalline cellulose including (0.5%, w/w) magnesium stearate, and they have been depended of measuring tablet tensile strength on lubricant mixing time, pre-compression, and main compression forces (Vezin et al., 1983). By use rotary tablet press instrument in order to measure the adhesion of the tablet on the lower punch surface, as a result of increasing either blending time or intensity of blending with magnesium stearate at any given compression force, the adhesion of microcrystalline cellulose tablets is decreased (Mitrevej & Augsburger, 1982). Furthermore, diminish the tablet ejection force with longer and more vigorous blending. Nevertheless, increasing in blending time and intensity of blending can cause reducing in tablet hardness. In another research, the power consumption has measured during blending of a direct compression mix. The power consumption represents the magnesium stearate concentration as shown in (Figure 1.3). Thus, changing such tablet ejection force, tablet crushing strength, and tablet dissolution depend on changing in power consumption (Schrank-Junghaeni et al., 1983). Additionally, have also noted the effectiveness of mixing magnesium stearate with a lactose/microcrystalline

cellulose, and how highly dependent on the type, size, and rotation speed of the mixer. Practically, in rotation speed procedure, the tablet crushing strength is decreased in large industrial type mixers much sharper than small lab mixers. To put it differently, tablet crushing strength is strongly affected by mixer rotation speed than the type, size, and the load of the mixer at industrial scale (Bolhuis et al., 1987). Has been found that the over mixing of magnesium stearate can cause counter effects on tablet ejection force, tablet hardness, and disintegration time (Kikuta & Kitamori, 1994).

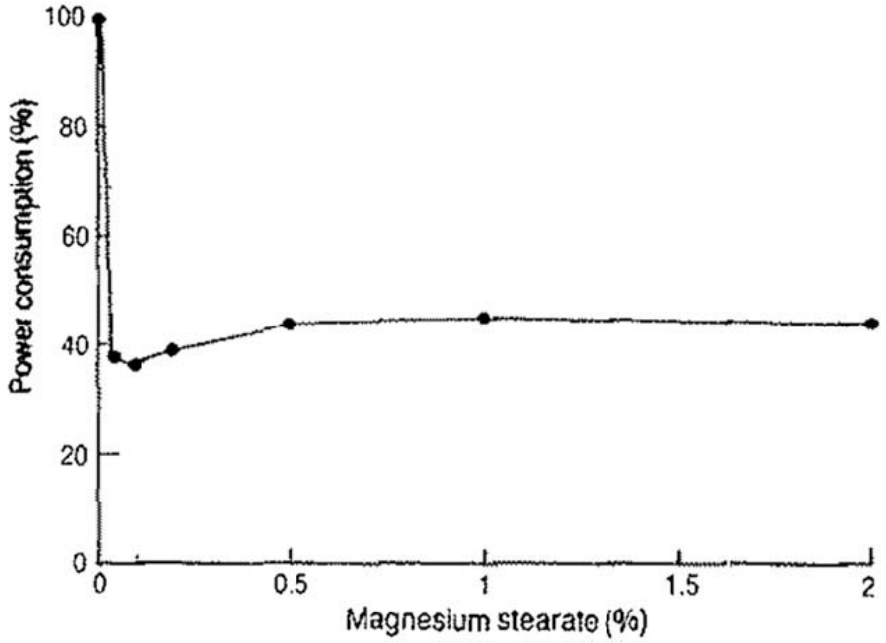


Figure 1.3: Plot of power consumption versus magnesium stearate concentration.

1.4.4.2 External lubrication

External lubrication operation may be utilized for very sensitive tablet properties from internal lubricants because external lubricants apply directly onto the punches and dies in industrial-scale tableting compression, not onto the final mixing material. Also, it can be called as apposed operation to mixing (internal) lubrication with formulation ingredients (Lindberg, 1970). Magnesium stearate is prepared as a suspension in liquid petroleum was transferred during a tube to the foam rubber rings that surrounding the lower punch as described in (Figure 1.4). Nicotinic acid and sodium bicarbonate is a content of effervescent tablet that successfully compressed by using external lubrication as well as the same lubrication method applied to manufacturer an orally disintegrating tablet (Hayakawa et al., 1998). Similar automated technique as formerly, Yamamura et al., have been studied how the external lubrication influence on tablet properties of eprazinone hydrochloride tablets according rotary tablet compression. Additionally, the required quantity of external lubrication with internal lubrication to prevent sticking was only 0.08%. As the matter of fact, external lubrication produced 40% greater tablet crushing strength with absence the adverse effect such extending tablet disintegration time (Yamamura et al., 2009). Lubricants have been studied by using both internal and external lubrication in making Trypsin tablets. In a comparative manner, external lubrication tablets required lower compression energy, but higher ejection energy, higher hardness, less total pore volume, faster dissolution and higher trypsin activity than internal lubrication (Otsuka et al., 2001). It should possibly pay attention the external lubrication option, while tablet tensile strength or dissolution is susceptible to the lubrication. Using the external lubrication helps avoiding such problems. For instance, in larger scale for internal lubrication, mixing operation often exacerbates the counter effects of lubrication on tablet properties. Even though not cost-effective, it is possible to treat the tooling surfaces of a tablet press with greatly polished chromium coating to reduce their coefficient of friction. Also, the die is sometimes treated with magnesium stearate powder or its solution in organic solvent to provide lubrication in tablet compaction research.

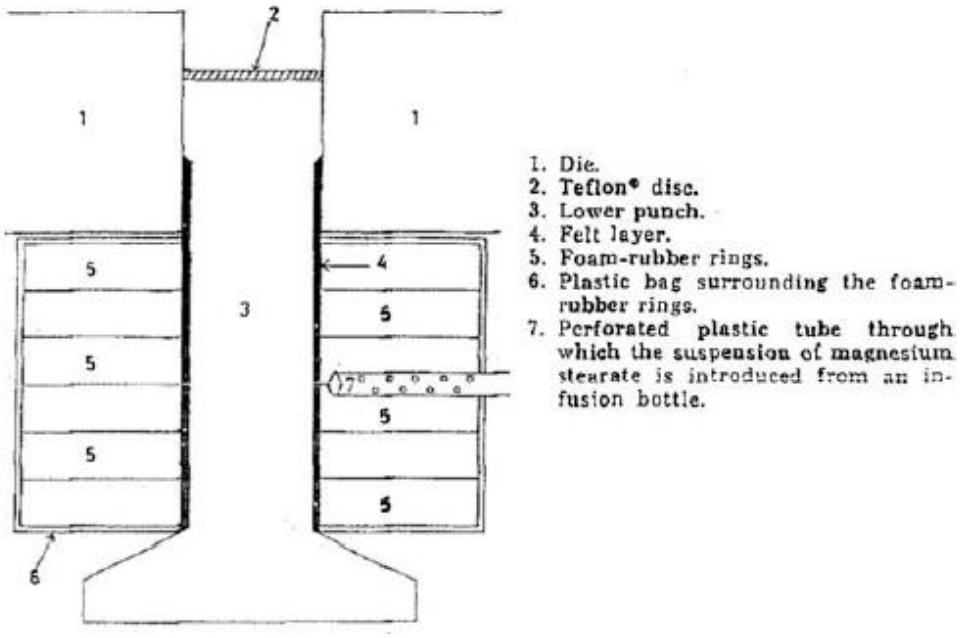


Figure 1.4: Diagram of the arrangement for the lubrication of the lower punch and die (external lubrication).

1.4.5 Common Lubricants Used in Drug Development

As has been noted before, boundary lubricants are the most lubricants utilized in pharmaceutical processes, and are chemically inert, odourless, and tasteless (Wang et al., 2010). Undoubtedly, magnesium stearate and stearic acid are the most widespread ones in metallic salts of fatty acid. Nevertheless, there are other lubricants, which can be used rather than magnesium stearate and stearic acid when do not meet their performance expectation (Miller & York, 1988), as instance of this fatty acid, inorganic materials, and polymers. Thus, some commonly lubricants will be described in the next sections.

1.4.5.1 Metallic Salts of Fatty Acids

Metallic salts of fatty acid are the most commanding lubricant type, resulting of having an extended history in pharmaceutical industry such as magnesium stearate, calcium stearate, and zinc stearate as well as their chemical structures is shown in (Figure 1.5) (O'Rourke & Morris, 1998). They are the three common metallic salts of fatty acids that used, but magnesium stearate is the most regularly utilized of the three lubricants. Equally important, in the following sections its application will be discussed. In this section is paid attention to the fundamental aspects of metallic salts of fatty acids in terms of friction reduction. In the light of fatty acids, lauric, myristic, palmitic, and stearic acids, in general, they are melted at low temperatures, even though stearic acid has the highest melting point about (69°C). The metallic salts of fatty acids have much higher melting temperatures. For example, zinc stearate (120°C), magnesium stearate (140°C), and calcium stearate (160°C). Important to realize, friction reduction is impacted by the length of the carbon chain (Wang et al., 2010). In like manner, the efficiency of lubrication increases as the length of the molecular carbon chain increases to a certain point. This can be seen in stearic acid (C18) present 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) (Juslin & Krogerus, 1970) (Juslin & Erkkila, 1972). Furthermore, stearic acid can reduced the coefficient of friction to the required friction coefficient from about 0.5 to about 0.1. Related to the melting point of the lubricant, temperature can little influence on lubrication until which reaches the melting points of the lubricant; comparatively the materials with lower melting point in this type is less lubrication effectiveness than metal stearate. Additionally, decreasing the friction also depends on the structure of a lubricant layer at metal surfaces, so thick layer can preserve and sustain a friction reduction with time. Conversely, the product performance specifically decreasing tablet dissolution can be affected by using too much of lubricant in tablet formulation. In brief, the majority of the metallic salts of fatty acids can diminish the coefficient of friction to about 0.1. However, other factors will impact their use in the pharmaceutical industry just as chemical compatibility (Li & Wu, 2014).

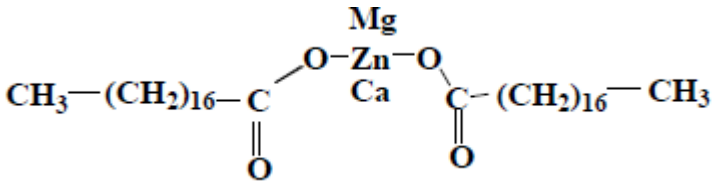


Figure 1.5: The chemical structures of metallic salts (calcium, magnesium, and zinc) of Stearic acid.

1.4.5.2 Fatty Acids

In pharmaceutical industry fatty acids are commonly used as lubricants. Specifically, stearic acid is the most popular one. Chemically, stearic acid is found as straight-chain saturated monobasic acid in both animal fats and different grads of plants such as cotton, seed, corn, and coco (O'Rourke & Morris, 1998). Stearic acid commercial material consists of other minor fatty acid, namely myristic acid and palmitic acid. The physical structure of stearic acid commercial material can be extended from macrocrystalline to microcrystalline by depending on the ratio of several acids present. Equivalently, its material ratio can differ from hard, to brittle, quite soft, and crumbly. Furthermore, the form of stearic acid in macrocrystalline, it proportionally consists of stearic acid to palmitic acid of 45:55 (w/w), also in the form of microcrystalline proportionally consists of stearic acid to palmitic acid is between 50:50 and 90:10. The physical properties of these acids exhibit in (Table 1.4). Comparatively between the three forms, stearic acid has the highest melting and boiling points as shown in (Table 1.4). In the same fashion, the stearic acid lubrication characteristic is listed in (Table 1.5). Also in (Table 1.5) epitomizes the friction coefficient, breakdown temperature-transition temperature from solid to liquid-of stearic acid at various metal surfaces. with different metal surfaces as steel, it causes varying in the measured coefficient of friction as exhibit (Table 1.5), yet their values are thereabout 0.1, like to those reported for the metallic salts of fatty acids (Bowden & Tabor, 2001). For that reason, at the metal surfaces, it is expected that both of stearic acid and magnesium stearate have the same lubrication performance.

Table 1.4: Physical properties of pure solid fatty acids (After (Bowden & Tabor, 2001)).

Fatty acid	Formula	Molecular Weight	Melting Point (°C)	Boiling Point at 16 mm (°C)
Stearic	CH3(CH2)16COOH	284	69.6	240
Palmitic	CH3(CH2)14COOH	256	62.9	222
Myristic	CH3(CH2)12COOH	228	54.4	202

Table 1.5: Breakdown temperatures and friction coefficients at various metal surfaces (After (Bowden & Tabor, 2001)).

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

1.4.5.3 Fatty Acid Esters

A variety of fatty acid esters have been utilized as lubricants for preparing tablet compression like glyceride esters (glyceryl monostearate, glyceryl tribehenate, and glyceryl dibehenate) and sugar esters (sorbitan monostearate and sucrose monopalmitate) (Miller & York, 1988) (Abramovici et al., 1985) (Aoshima et al., 2005). Glyceryl dibehenate (Compritol® 888) is the most frequently utilized among the above mentioned of fatty acid esters. Particularly, Compritol® 888 can be used as alternative of magnesium stearate in case delay of dissolution and other compatibility issues. Another point related to magnesium stearate, at higher

optimum concentration approximately 2% w/w Compritol® 888 has as lubrication effective as magnesium stearate, and uses without impacting the compressibility. Otherwise, using Compritol® 888 through the hot melt coating process, the optimum concentration of Compritol® 888 can be minimized to 0.5%–1% in order to obtain a uniformed coating (Jannin, Berard et al., 2003).

1.4.5.4 Alkyl sulfate

Magnesium lauryl sulfate and sodium lauryl sulfate are chiefly used as a surfactant, and at the same time both of them water soluble lubricants. Magnesium lauryl sulfate is better than sodium lauryl sulfate, also was an equally effective lubricant as magnesium stearate in lithium carbonate tablets. Even it owns the lubricating properties of magnesium stearate. However, magnesium lauryl sulfate has not the waterproof liability. In contrast, in direct compression tablet that contain insoluble compound, practically using (0.5%, w/w) magnesium lauryl sulfate has more retarding effect than (0.5%, w/w) of magnesium stearate as well as the disintegration time was much higher, 75 seconds in opposition to 25 seconds for magnesium stearate, at specific tablet compression pressures (Osseekey & Rhodes, 1976).

1.4.5.5 Inorganic Materials

An appropriate option to consider when magnesium stearate is not suitable as a lubricant is the use of inorganic materials and polymers (Wang et al., 2010) (Miller & York, 1988). The majority of inorganic materials that are utilized as lubricants, usually come in a variety of sizes characterized as laminated flakes (2–5 μm) and aggregates of flakes (50–150 μm) being mixed (Phadke & Collier, 1994). It has claimed that when having the material from the same manufacturer, a small batch-to-batch variability in the physical property of the material has been reported. On the other hand, when changing the manufacturer, the differences observed are much higher. Talc (a hydrated magnesium silicate ($Mg_3Si_4O_{10}$ $(OH)_2$)), is an inorganic material that sometimes may contain small amount of aluminum silicate (Gadalla et al., 1988), usually functions as a lubricant or as a glidant when added in formulations. Due to the

hydrophobicity and weakly-bonded sheet structure, talc is intended to provide the essential lubricity for pharmaceutical operations. When comparing talc with magnesium stearate from an efficacy perspective, talc is considered to be less efficient in lubrication than magnesium stearate. On the other hand, when using magnesium stearate, compatibility issues such as dissolution slow down are presented, which could be due to chemical instability and therefore, talc can be used as either a replacement or in combination with magnesium stearate. A remarkable progress has been showed in tablet hardness, friability, and appearance when talc has been used as a lubricant. In terms of granulation flowability and ejection force, experiments with acetaminophen tablets (Dawoodbhai et al., 1987), using (1%, w/w) talc or (0.25%, w/w) magnesium stearate was conducted and found that there is no significant difference and indeed the tablets were also harder and less fragile. Alternatively, the most appropriate concentration proposed for talc is 0.5–3% and up to (5%, w/w) for aspirin tablets (Delacourte et al., 1993) (Hajare & Pishawikar, 2006).

1.4.5.6 Polymers

Polymers are of quite importance in the pharmaceutical field, there use have been implemented in solid dosage forms as lubricants, when using magnesium stearate displays issues in compression, chemical incompatibility or other biopharmaceutical reasons (Lapeyre et al., 1988). Such polymers include, PEG 4000, PEG 6000 (Carbowax_ 6000), polyoxyethylene–polyoxyproprylene copolymer (Lutrol_ F68), and polytetrafluoroethylene (Fluon_ L 169). The latter has been considered to approximately have the same lubricating properties as magnesium stearate in acetylsalicylic acid tablet, although the electrostatic charges of the formulation was not eliminated as was observed with small percentages of magnesium stearate (Conte et al., 1972). Although, as previously mentioned, the principal lubricant used in the pharmaceutical industry is the magnesium stearate. In the upcoming discussion, the main spotlight will be on the effect of magnesium stearate upon the process and product performance, including the effect of its pseudo-polymorphic properties on lubrication, the impact of powder properties on blend flowability, and the influence of lubrication on

compaction/compression dynamics and the mechanical properties of compacts and tablets, as well as its incompatibility with pharmaceutical ingredients and other formulation components.

1.5 Considerations for Selecting a Lubricant

In conclusion, in order to select an appropriate lubricant for preparing solid dosage forms, it affects with many factors that should consider. For example, low shear strength, being able to form a durable layer coating the surface/particles, non-toxic, chemically compatible with active ingredients and other components in the formulation, low batch to batch variability, and having minimum adverse effects on the performance of the finished dosage forms. Besides that, there are two parameters highly influence on the performance of pharmaceutical products and operations, and needs to be taken into the count when selecting a lubricant including the optimal concentration and mixing time. Nonetheless, low lubricant concentration and inappropriate mixing cause inefficient lubrication issues such as sticking, capping, and binding in the die cavity. At the same time, over lubrication, high lubricant concentration and over-mixing-often produce an adverse effect on both products and processes. For instance, reduction tablets hardness, compression variability, prolongation of disintegration time, and decreasing rate of dissolution. There are some recommended concentrations of representative lubricants utilized in solid dosage form as mentioned previously. Related to add a lubricant during the manufacturing, lubricant is often added at the end of the granulation operations in the outer phase when other components have been mixed thoroughly. In addition, on compactability and the hardness of tablets, for the purpose of better resulting for the blending time for distributing a lubricant is typically 0.5–5 min. Lastly, we have to noted that selecting a lubricant for a formulation needs a systematic approach with careful consideration of the performance of both product and operations (Li & Wu, 2014).

CHAPTER TWO

MAGNESIUM STEARATE

2.1 Introduction

Magnesium stearate ($C_{36}H_{70}MgO_4$) is the most widely used lubricant in tablet manufacturing, and is a solid and white powder at room temperature. The United States Pharmacopeia (USP32- NF27) and European Pharmacopeia (6th Edition) describe magnesium stearate is a mixture compound containing chiefly of variable proportions of 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. In additionally, the physical properties of magnesium stearate are vastly reported in this literature. Overall, magnesium stearate has lower shear stress of 85 kg/cm2, and it can be considered by its coefficient of friction on the surface of die wall (Fukuda at al., 1980) (Ennis & Mort, 2006). As a result of that, the lower shear stress shows that magnesium stearate has little affinity for the metal surface. The interactive force of the magnesium stearate crystal lattice is reduced by water and/or gas molecules from the environment because it may get into the long lattice of crystal structure and spread within spaces, hence decreasing the shearing force needed to cleave the crystalline particles of magnesium stearate (Wada & Matsubara, 1994). Magnesium stearate has very small particle size and large surface area. The typical physical properties of magnesium stearate have been mentioned as follows (Phadke & Collier, 1994):

- ***Melting point:*** 94–150°C (125–127°C).
- ***Specific surface area:*** 1.3–10.5 m2/g (4–6 m2/g).
- ***Particle size:*** 2–15 μm.
- ***Moisture content by Karl Fischer:*** 4.8–5.2%.

Furthermore, it has been illustrated that, owing to its amphiphilic feature, magnesium stearate adheres to metal surfaces with its polar head leaving the carbohydrate tail group to stick out to form boundary film lubrication. In other words, magnesium stearate effectively lubricates with forming a film (Staniforth et al., 1989).

2.2 Effect of Pseudo-Polymorph on Lubrication

Magnesium stearate has four hydration states: anhydrate, monohydrate, dihydrate, and trihydrate due to exposure to humidity (moisture content), that means it can form a variety of different hydrates in addition to amorphous form. Moreover, Depending on temperature and relative humidity the hydration states can interchange reversibly. This is illustrated, anhydrate form of magnesium stearate can produce trihydrate form with exposing to a relative humidity >70%, and the anhydrate form can be produced by drying the dihydrate form at 105°C until constant weight was attained. Chemically, the anhydrate, dihydrate, and trihydrate forms have been prepared by using both pure magnesium stearate and magnesium palmitate, also given that all the three forms are characterized according to their structural characteristics at the same time. Comparative morphological studies was developed by using both electron and polarizing optical microscopies, it was observed that magnesium palmitate materials were significantly larger crystals than magnesium stearate materials, and the crystals of the dihydrate form for both materials were found to be most fully developed. In addition, through the polarizing optical microscopic investigation, the dihydrate form of magnesium palmitate was observed as an oblique extinction, which was used to conclude that dihydrate form belonged to the triclinic crystal system. By using X-ray powder diffraction, it was noted that the crystal structures of all materials were judged to be very similar to each other, varying mainly in the magnitude of the long (001) crystal spacing. The thermal analysis of the materials was primarily established by using thermogravimetry and differential scanning calorimetry, which in turn detected that the dihydrate form of either magnesium stearate or magnesium palmitate was more tightly bound to the water of hydration than the identical trihydrate form. In other words, all the result that are mentioned in this study for supporting the structural picture where the water contained in these lattice structures is exists between the

intermolecular planes, and is not an integral part of the crystal lattice (Sharpe et al., 1997). As we mentioned, materials have been exposed depending on the environment, so magnesium stearate obtained from a vendor can be a mixture of anhydrate, hydrates, and amorphous. In that case, most of the lubricant (the commercial supplies) can include a mixture of various hydrates in unknown ratios. By the same token, the magnesium stearate effectiveness like a lubricant differs from one hydration state to another. In fact, the most effective lubricant to be considered is the dihydrate because of its crystal structure which is suitable for shearing. Consequently, the flowability, permeability, porosity, and compressibility of a particular formulation lubricated with magnesium stearate depend on its moisture content or the relative humidity of storage conditions. It has been examined how the hydration state of magnesium stearate effect on the performance of formulations by isolating each hydrate then testing in formulations. This can be seen by testing the effectiveness of each lubricant hydrate and their mixtures. In practical, each hydrate or a combination of two (1%, w/w) was mixed with other formulation component (microcrystalline cellulose (72%, w/w), lactose monohydrate (22%, w/w), and acetaminophen (5%, w/w)). Equally important, varied effects on the performance of formulations are produced by different hydration states. For instance, the formulations lubricated with the dihydrate and the anhydrate of magnesium stearate is better than the formulation lubricated with monohydrate (the lowest) in permeability and porosity, and the un-lubricated formulation is highest permeability and porosity. This has been observed that the inter-particle packing arrangement is impacted by the structure of the lubricant. Thus, in comparative, the mixtures containing the monohydrate need a higher pressure to establish a flow relative to those with the dihydrate and the anhydrate. In contrast, related to the crush strength of compacts, the un-lubricated mixture has produced the highest crush strength (15.471 kg/cm2), then the mixture that include the dihydrate, the monohydrate, and the mixture of (50:50, w/w) the dihydrate and the monohydrate (un-lubricated Compacts > dihydrate> the monohydrate>dihydrate50/monohydrate50 >others). In the light of lubrication, Lubricity index (Ω) is a measure of the tendency of mixture to over-lubricate, and it represents the ratio of the difference between un-lubricated and lubricated material and the un-lubricated material, where the un-lubricated and the lubricated of the compact strengths. The dihydrate magnesium stearate mixture produced the least tendency to cause over-lubrication. Depending

on fixed concentration and lubrication time, the lubricity index ranking for lowest tendency to cause blend over-lubrication (dihydrate < monohydrate < binary mixtures < anhydrate < others). As showed in the ranking the level of water of hydration in the lubricant influences the tendency for over lubrication. Additionally, in terms of tablet compression (pre-compression, main compression, ejection, and total forces) and the influence of the hydration state, noted that all mixture that including the monohydrate and dihydrate produced tableting compression forces with less variability. Actually, the mixture ratios of the monohydrate and dihydrate in the tablet compression force profile resulted comparatively well to the form of monohydrate alone, suggesting that the monolithic structure of the monohydrate could have dominant influence on achieving stable tablet compression forces. Further suggestions reported that the mixture with either the anhydrate or the dihydrate required less total force for tablet compression. Moreover, the results of the mixture that containing the dihydrate with the anhydrate tended to need less total forces than those with the dihydrate and the monohydrate. Mentioned that suggestion, the presence of the monohydrate in any mixture require more ejection force, and likewise, seems to have adverse effect on the tableting performance. To sum up, in comparative, the performance of three hydrates of magnesium stearate and their varied mixture ratio: 25:75, 50:50 and 75:25, the tablets that consist of the monohydrate seemed to have less permeability and porosity, also these yield tablet forces with less variability during procedure. Even though, they commonly require more ejection force. However, the tablets with the dihydrate lubricant relatively show to have a less tendency for over-lubrication and require less total compression force. With taking everything in the account, the dihydrate form of magnesium stearate lubricated tablets has the higher rank as seen in (Table 2.1). More importantly, in most case, it is considered that the long spacing in the dihydrate crystal structure of magnesium stearate participates to its lubrication efficiency. However, it can be inferred that owing to the reversible exchange of water between forms; challenging to determine of the exact spacing for these forms. After all, additionally regarding to its pseudo-polymorphic effect, the properties either powder or solid of magnesium stearate included as particle size, particle morphology, and surface area impact the lubrication performance of tablet formulations with magnesium stearate, and this will be discussed in the following section (Okoye et al., 2012) (Bracconi et al., 2003).

Table 2.1: The overall performance ranking of three pseudo-polymorphs of magnesium stearate (After (Okoye, Wu, & Dave, 2012)).

Formula	MgSt Ratio	LI	Porosity	Permeability	Stability Index	Precompression Force	Main compression Force	Ejection Force	Total Ranking			
									Goo(G)	Fair (F)	Poor(p)	Overall ranking
D1	A50/M50	P	P	P	G	F	F	P	1	2	4	12th
D2	A25/M75	F	P	P	G	P	G	P	2	1	4	11th
D3	A75/M25	F	F	P	G	P	G	F	2	3	2	5th
D4	D50/A50	P	G	P	G	P	G	G	4	0	3	5th
D5	D75/A25	P	G	F	G	F	G	G	4	2	1	3th
D6	D25/A75	F	G	F	G	F	P	G	3	3	1	4th
D7	D50/M50	F	F	P	G	F	P	P	1	3	3	8th
D8	D75/M25	P	P	P	G	F	F	F	1	3	3	8th
D9	D25/M75	P	P	P	G	F	F	F	1	3	3	8th
DA01	MgSt-A	F	F	G	G	G	F	G	4	3	0	2nd
DM01	MgSt-M	G	P	P	G	F	P	P	3	1	4	7th
DD01	MgSt-D	G	F	G	G	G	F	G	5	2	0	1st

A, M, and D represent anhydrous, monohydrate, and dihydrate; P, F, and G stand for poor, fair and good.*Overall ranking ≥ 20 appears to suggest desirable performance (a factor of 5 was assigned to G; factor of 3 to F; and factor of 1 to P). LI = lubricity index.

2.3 Effect of solid state on Lubrication

Practically, the effect of the hydration state of magnesium stearate usually has effects on the lubrication but this cannot be separated from other factors such as surface areas and agglomeration (Rao et al., 2005). Varied powder properties such as particle size, surface area, and particle shape will often be obtained regardless the materials of magnesium stearate are

from either various vendors or different batches of the same vendor (Ertel & Carstensen, 1988). As a result, 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 are crucially needed to be understood. Mainly, by increasing the surface area or decreasing the particle size of the magnesium stearate, since the increase of surface area can provide more surface coverage it is expected that the lubrication efficiency of magnesium stearate will improve (Barra & Somma, 1996). Furthermore, the particle-particle bonding will be weakened which in turn results in weak tablets will be achieved by enhancing the coverage of the particle surfaces by magnesium stearate. Additionally, slowdown of dissolution will be caused due to the surface of active ingredient particles will be covered with the lubricant which is hydrophobic. For instance, as Dansereau and Peck reported that (Dansereau & Peck, 1987), by increasing the surface area of the lubricant, the tensile stress of microcrystalline cellulose tablets lubricated with magnesium stearate decreased. Therefore, by increasing the surface area the tablets friability showed an increase. Moreover, by increasing the particle size of magnesium stearate in an optimal size range of 350–500 μm reported an enhancement it in the dissolution of dexamethasone-lactose tablets (Soebagyo, 1994). Lately, based on a quality-by-design study, an investigation was implied on the impact of the variability of powder properties of magnesium stearate on the roller-compacted, immediate release tablets (Kushner et al., 2011); in addition to the lubricant, microcrystalline cellulose, spray-dried lactose, and sodium starch glycolate were also included in the study. Particularly, an evaluation on the effect of the variability of the lubricant on formulation performance such as the flowability of blends, segregation propensity, hardness, and tensile strength was conducted. The conclusion showed a consistency with the results reported previously which included that as the specific surface area of magnesium stearate decreased (particle size increased), the ribbon tensile strength and tablet hardness notably increased.

2.4 Effect of Lubricant on Powder Flowability

In terms the flowability of mixture in pharmaceutical procedures, it highly effects for the success of manufacturing. In general, improving the flowability of the formulation can be added of magnesium stearate in a formulation, so it usually uses as a glident (following agent). Practically, evaluation the flowability of a blend by using parameters related to the flowability such as static angle of repose, Carr index, Hausner ratio, and the flow-function obtained from a shear-cell measurement. As reported, all the previous parameters are often utilized because of their simplicity although the flow function is commonly used parameter for evaluating blend flowability. Typically, there are many factors impact the flowability of powder. For example, type of lubricant, the interaction of the lubricant with other materials, lubricant concentration, and mixing time. This is demonstrated that magnesium stearate is the most effective lubricant in comparatively to other lubricant (magnesium silicate, calcium stearate, and stearic acid) in improving the flowability of lactose even with a small amount (Morin & Briens, 2013); happening that, due to magnesium stearate particles preferentially interact with lactose particles and fill empty spaces within the surface of these particles. The material nature of the powder is an Influential factor in the effecting of magnesium stearate on the flowability of a powder. Presence the lubricant in the formulation does not represent any significant impact for free-flowing powders. In contrast, as the blending powder more cohesive, the lubricants largely improved flowability of powders (Faqih et al., 2007). Furthermore, in related to the particle size and size distribution of active pharmaceutical ingredients impact on the flowability of powder. For instance, magnesium stearate lubricant improves expressively the flowability of ibuprofen particles of various sizes depending on internal angle measurement (Liu et al., 2008). In fact, this can be illustrated by that one of causes of flow issues is small particles of active pharmaceutical ingredients, so lubricants as a glident diminish inter-particle friction with coating the surface of particles. Thus, improve powder flowability. The lubricant requires adhering surface of powder particles in order to be functional as glident (flow agent). Hence, critically, it needs to distribute throughout powder by blending. Although, mixing intensively (over-mixing) causes dissolution delay or other issues. Related to the over-mixing can be observed that mixing both of lactose and magnesium stearate more than the optimum time in a few mints cause some issues such as the performance of tablets decreased; the

hardness of tablets was reduced, and the disintegration time was prolonged. In other words, magnesium stearate delaminates and forms a film around powder particles, and at the same time it is really tough to disrupt. In addition, as noted by the same study magnesium stearate distribution among powder particles and its film formation around the powder particles is also relying on the mixing speed and the equipment used. Not to mention, shearing, dispersion, and convective actions are rule the mixing of cohesiveness of magnesium stearate particles (Kikuta & Kitamori, 1994). Likewise, Blending speed and filling volume have expressed to be the greatest two parameters that effect mixing performance, so it mentions that shear mixing is the most important (Perrault et al., 2010). Dynamically, related to the mixing, magnesium stearate and Sodium Lauryl Sulfate have similar mixing behavior. In detail, Sodium Lauryl Sulfate molecule includes a sodium atom, it can be made radioactive in the same approach as magnesium stearate, and the same methodology utilized to examine magnesium stearate mixing can be applied to Sodium Lauryl Sulfate. Lastly, improving the flowability of micronized ingredients can be achieved by using magnesium stearate in combination with other additives such as silicon dioxide. To put it briefly, magnesium stearate is a successful agent to progress the flowability of active ingredients and formulations.

2.5 Effect of Lubricant on the Mechanical Properties of Compressed Products

As a matter of fact, it was noted adding of magnesium stearate in powder can markedly influence the flowability of the powder. Accordingly, also affecting on the compaction/compression processes such as roller compaction. Thereafter, it has observed that the blending properties of any compacts or /and tablets produced are depended on lubricant. This exemplified during the roller compaction, magnesium stearate can impact the maximum pressure and the nip angle parameters of roll compaction, so it adjusted in the compaction properties. To put it comparatively, microcrystalline cellulose with lubricant (magnesium stearate) and without lubricant (as received), lubricated powder reduces both the maximum compression pressure and the nip angle at two roll speeds 3 then 5 rpm. Moreover, it showed that the more increasing lubricant concentration, the more decreasing the maximum pressure and the nip angle. In terms of the method of lubrication, they have seen that adding the

magnesium stearate lubricant with microcrystalline cellulose as internal lubricant was vastly greater efficient than suspension lubricant onto press surface as external lubricant. In addition, regarding to the properties of compacts, density was altered by lubrication because of minimizing the compression pressure and the nip angle. In detail, the relative density of microcrystalline cellulose powder without lubricant is almost 0.6, but with magnesium stearate lubricant is almost 0.43. That mean, powder without lubricant to produce ribbon larger than powder with lubricant owing to the improving in the flowability of the powder and thus the intense reducing in compression pressure. Undoubtedly, surface press lubricated (external lubrication) does not affect the average relative density of the ribbons as yet because of its mechanism included that external lubricant only decreases the friction between the powder particles and the surface of the compactor (wall friction), not the friction between the powder particle itself (inter-particle/internal friction). However, in another study, in comparison between microcrystalline cellulose and dicalcium phosphate dihydrate lubricated. The brittle material dicalcium phosphate dihydrate when it is lubricated by both roll-lubrication (external lubrication) and bulk lubrication (internal lubrication) yielded to diminish in the maximum compression pressure and the nip angle, reaching a constant value at 0.25% (w/w) lubricant concentration. In the light of the microcrystalline cellulose and dicalcium phosphate dihydrate, the main difference between them is that dicalcium phosphate dihydrate is simple to fracture and also less cohesive because of its brittle material in comparative to microcrystalline cellulose material. As a result of that, whether roll-lubrication or bulk-lubrication possess the same influence on the compression pressure and the nipple angle due to in the fact dicalcium phosphate dihydrate flowability is governed by new surfaces created by particle fracture. In the same study, they also noted the effect of the lubrication on the solid fraction of ribbons after compaction as well as the solid fraction and the tensile strength of tablets manufacture. Under this circumstances, for preparing ribbons of microcrystalline cellulose powder in both bulk-lubrication and roll-lubrication, it cause reduction in the solid fraction as the concentration of the lubricant increased, but bulk-lubrication resulted a larger reduction. Furthermore, related to decrease the solid fraction, microcrystalline cellulose (ribbons) fracture energy was also lessened. In the same manner was noted that the ribbons (bulk and roll lubricated) of dicalcium phosphate dihydrate powders were expressively smaller than ribbons

of microcrystalline cellulose powders. At the same time the dicalcium phosphate dihydrate ribbons were overly fragile for measuring the fracture energies. In general, feeding the powder into the compaction region is impacted by the flowability of the powder, and as well as define the ribbon density. As reported the nip angle and the maximum pressure in the nip region and then the differences in the density of the ribbon are roll compaction operating parameters, they often become greater with increasing friction, and of course, if the powder were to be lubricated, these defiantly parameters would minimize. Another point, when powders or granules materials are utilized in feeding during uniaxial compression process for the purpose of making tablets, lubrication affects the properties of tablets. Two cases are had first with microcrystalline cellulose; lubrication did not impact on the solid fraction of microcrystalline cellulose. However, practically, at 1% magnesium stearate concentration for either the powders of microcrystalline cellulose or the granules of microcrystalline cellulose were fed into the tablet press their tensile strength was reduced. Nevertheless, when tablets made from microcrystalline cellulose granules are used, they have a lower solid fraction and tensile strength comparatively with tablets made from feeding microcrystalline cellulose powders. Second with dicalcium phosphate dihydrate, also the solid fraction and tensile strength were not affected with lubrication for both granules and powders feeding materials. Conversely, because of microcrystalline cellulose is a deformable material (plastic) whereas dicalcium phosphate dihydrate is a brittle material, the tablets made with dicalcium phosphate dihydrate granules have much lower tensile strength. An important point, mechanistically, decreasing in the tensile strength of microcrystalline cellulose tablets because of magnesium stearate, a boundary lubricant, which coats the particle surface to form a layer and lessens the tablet strength. Related to dicalcium phosphate dihydrate, in an Interesting way, lubrication with magnesium stearate has little effect on both the solid fraction and the tablet strength, mainly for the reason that the fractured-nature of dicalcium phosphate dihydrate makes fresh particle surfaces (without lubricant attached) (He et al., 2007) (Yu et al., 2013) (Miguelez-Moran et al., 2008).

2.6 Online Monitoring of Magnesium Stearate in Blending

As previously mentioned, the dynamics of blending and compaction/compression can notably be affected by the lubrication, in addition to the mechanical properties (solid fraction and tensile strength) of compacts/tablets made. Thus, during manufacturing and storage, it's considered critical to monitor the change of magnesium stearate. Particularly, humidity and temperature usually affect the hydration state of magnesium stearate and according to its composition the lubrication efficiency will vary. In an operation, where the absorption wavelengths for the monohydrate and dihydrate where 7045 and 5100 cm−1, respectively, a near infrared spectroscopy in combination with further thermal methods was used to monitor the variability of the hydration state which is done to detect the composition change in the first place (Terashita, 2012). Generally, the results obtained from the near infrared spectroscopy when compared to those obtained using other methods such as thermal gravimetric analysis, consistency was established. Nevertheless, more sensitivity to the presence of small quantities of hydrates was established when using the near infrared spectroscopy method accompanied with partial least squares regression. Additionally, of 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−1that is detected by Using the Raman imaging technique at a wavelength of 1295 cm−1 enabled the detection of the distribution of magnesium stearate on tablet surfaces in a punch-face lubrication system, which in turn lead to the determination of the domain size of magnesium stearate in one dimension (Šašić et al., 2013). On the contrary, due to interferences from other materials in the formulations resulted in the failure of the Raman technique to detect the signal of magnesium stearate in the lubricated formulations. Moreover, to determine the end point of a blending process for a formulation consisting of magnesium stearate, the end point of a blending process is determined by using thermal effectively sensors in order to monitor the blend uniformity (Yoshihashi et al., 2013). This was seen in a V-blender consisting of a blend of magnesium stearate and sugar. As the thermal effectively data is compared with the powder density, the optimal mixing is attained as the former is correlated well with the powder characteristics of the system. This is vital since the time required to complete a homogeneous blend will vary with various hydrates of magnesium stearate when used as lubricants.

Therefore, to avoid over-lubrication, the end-point can be detected without sampling the blend by using the thermal effectively sensors in order to monitor the blending process. All in all, achieving the optimum performance for a formulation and avoiding the detrimental effects due to over-lubrication and inhomogeneous distribution is achieved by online monitoring of pharmaceutical processes.

2.7 Chemical Stability and Compatibility

Widely reported, presence of lubricants such as magnesium stearate has some chemical instability issues with active ingredients. The impurities (Magnesium oxide), the effect of alkalinity caused by magnesium stearate, its catalytic effect, and other chemical reactions initiated and mediated by magnesium ions these factors should be taken in the count because they effect on magnesium stearate on the chemical instability of active ingredients. They will be discussed in the next parts.

2.7.1 Interactions with Impurities (Magnesium oxide)

Magnesium oxide (MgO) and palmitic acid are impurities that presence in the commercial materials of magnesium stearate; hence, impurities often interact with active ingredients in the solid state causing stability issues. As exemplified by Kararli et al, Magnesium oxide impurities react with ibuprofen at certain temperatures and humidity values in the solid state (Kararli et al., 1989). Differential scanning calorimeter, thermal gravimetric analysis, and multiple internal reflectance infrared are used to detect the degradation of materials, thus when the mixture of Magnesium oxide and ibuprofen was stressed at 40°C and 75% RH, they used to detect a significant amount of degradation. In reality, the result of reacting of Magnesium oxide with ibuprofen is magnesium salt of ibuprofen. Increasing the temperature allows the reaction to accelerated. Accordingly, it degraded at 40°C after 1 day; yet at 30°C, no significant interaction was shown for up to 80 days. As reported in another study, eutectic mixture was formed by ketoprofen with magnesium stearate (Botha & Lötter, 1990) (Mura et al., 1995).

2.7.2 Hydrolytic Degradation at Basic pH

In practical, increasing the micro environmental pH of the formulation, creating an alkaline condition and then accelerating the hydrolysis of some drugs, due to the existence of magnesium stearate in a formulation. For instance, as mentioned, acetylsalicylic acid (aspirin) is often degradation by presence of water and/or an alkaline pH condition, at the same time a moisture-sensitive drug, so the addition of magnesium stearate in the blending which in turn increasing the degradation rate of acetylsalicylic acid, and also the hydrolysis rate depended on the concentration of magnesium stearate in the blend (Marcotegui & Sanchez Monge, 1981) (Ahlneck et al., 1987) (Fouda et al., 1998). Another illustration, as reported by Kornblum and Zoglio observed that relate to the presence of magnesium stearate with acetylsalicylic acid in suspensions (Kornblum & Zoglio, 1967), the rate of degradation of acetylsalicylic acid was associated with the high solubility of the magnesium salt of acetylsalicylic acid. Likely, making a medium that was tended to cause harm to the chemical stability of the compound. This is a result of forming a buffer layer around the particles of acetylsalicylic acid (Nelson et al., 1974). As depicted by Miller and York, formation of layer of magnesium stearate around the particles of acetylsalicylic acid, and also creation close contact between the two materials as well as leading to degradation, so it may facilitate causing in lowering of the melting point of acetylsalicylic acid. In the case that chemical incompatibility between aspirin and magnesium stearate, there are some potential undesirable products. For example, salicylic acid, salicyl salicylic acid and acetyl salicyl salicylic acid are produced. Moreover, making an alkaline pH medium due to in fact that magnesium stearate has Magnesium oxide impurity; it may also play a role in increasing the degradation (Miller & York, 1988). As seen by Gordon et al., related to existence of magnesium stearate with ibuprofen in the formulation form a eutectic mixture which sublimates. Another point, owing to the basic property of the lubricant, quinapril (an angiotensin-converting enzyme inhibitor) was also found to be incompatible with magnesium stearate, thus the degradation of quinapril was mediated by the availability of moisture. Even though, on affirmative idea, as illustrative by Fouda et al., stearic acid can protect drugs (aspirin) against degradation. However, magnesium stearate accelerated the degradation of aspirin. At the same time, for that reason, stearic acid is another choice as lubricant (Gordon et al., 1984).

2.7.3 Oxidation

In practical, oxidation reaction is induced by existence of magnesium stearate in blending. For example, presence of magnesium stearate and talc in the drotaverine HCl formulation can accelerate the decomposition of drotaverine HCl (Pawełczyk & Opielewicz, 1978). Furthermore, as mentioned already; the pH of the formulation significantly impacted the chemical instability of drotaverine HCL, and also magnesium stearate greatly increasing the degradation rate. Such as oxidative degradation pathway which in turn degraded drotaverine HCl to drotaveraldine, which can be inhibited using an antioxidant or an acidic auxiliary material (Osawa & Ishizuka, 1973).

2.7.4 Metal Ion-Mediated Degradation

In addition, relate to the Degradation of drugs, magnesium ions can be as mediated for degradation drugs. For instance, fosinopril sodium was degraded into a β-ketoamide (III) and a phosphoric acid (IV) in a prototype tablet formulation with magnesium stearate in upon an accelerated stress treatment (Thakur et al., 1993). It has been postulated a mechanism of metal chelation, which the degradation of fosinopril was mediated by magnesium metal ions. Based on a kinetic study, it was shown that the degradation that happens between fosinopril and magnesium was a second-order reaction. It has been proposed that stearate salts should be avoided as tablet lubricants. Many drugs are displayed to ion-catalyzed degradation. Regardless of adding malic acid, hexamic acid, and maleic acid in a formulation, the derivative impact of alkali stearates can be inhibited owing to competition for the lubricant action between the drug and an additive acid.

2.7.5 Reaction with Amines

In general, many drugs that have amine group are tented to react with excipients and salt counter-ions. For example, in practical, pay attention for the potential reaction of magnesium stearate or stearic acid when drug contains a primary amine group. Specifically, after a prolonged storage of norfloxacin at 60 °C, which in turn the tablets containing magnesium

stearate form a stearoyl derivative. Equally important, other drugs found to be incompatible with magnesium stearate, includeglimepiride, cephalexin, glipizide, ibuproxam, indomethacin, ketoprofen, moexipril, nalidixic acid, primaquine, promethazine hydrochloride, temazepam, glibenclamide, penicillin G, oxacillin, clopidogrelbesylate and erythromycin (Kumar et al., 2011). Briefly, drugs with a primary amine group and at the same time containing magnesium stearate are often very unstable in formulations.

2.7.6 Stearic Acid

Stearic acid can be used as an important alternative option when magnesium stearate is not convenient. In comparative between stearic acid (12 out of 200 tablet formulations), and magnesium stearate (108 out of 200 tablet formulations), stearic acid is not frequently used as lubricant. As observed by Desai et al., care of the incompatibility of stearic acid with other formulation components. For instance, capsules formulation consists of povidone as a binder and stearic acid as a lubricant, so after 3–6 weeks of storage under high temperature and humidity conditions, it appears slowdown in dissolution (Desai et al., 2008). In practical, stearic acid was replaced with magnesium stearate; hence a rapid dissolution was obtained under the same storage circumstances. On further investigation, at 50 °C, this illustrated that the mixture of povidone and stearic acid formed a transparent, hard, glass like insoluble substance. Due to the fact that the porosity of granules was lessened by the glassy material formed, also the dissolution of the granules was slowed down. In order to verify they utilized powder X-ray diffraction to examine the mixture of stearic acid and povidone, noted that its crystallinity is missed. According of that, proposing that in immediate release formulations stearic acid and povidone combination should be avoided. Another essential point, as invoked by Wang et al., in term of decreasing dissolution of stearic acid tablets, because of playing a role in the polymorphic phase transformation of an active ingredient. For example, in case of high shear mixing or high temperature drying of blend, the dissolution decreased was more significant. In detail, mechanistically, it was seen that stearic acid facilitated transformation of polymorphic forms (Form II to Form I) (Wang et al., 2010). Therefore, decreasing tablet

dissolution. All in all, stearic acid is still an important alternative lubricant to be used in solid dosage forms.

2.7.7 Sodium Stearyl Fumarate

Additionally, in term solid dosage forms, sodium stearyl fumarate is used as another alternative lubricant. Furthermore, provide sodium stearyl fumarate as purer form. In other hand, it can supply an option when the less pure stearate-type lubricants (stearic acid and magnesium stearate) are unsuitable because of no chemical compatibility. Relatively, as a lubricant in formulations, sodium stearyl fumarate has used in rate of four out of 200 drugs. It has a less retardant effect on tablet dissolution than magnesium stearate, due to its less hydrophobicity. In comparatively with magnesium stearate, this is illustrated by Arne W. Hölzer, et al., sodium stearyl fumarate and magnesium stearate have the same lubrication efficiency, and about the same influence on tablet strength and disintegration. On the contrary, particle size of sodium stearyl fumarate significantly effects on its efficiency, mixing for long time improved its lubricating effect and had ineffective on tablet disintegration. Consequently, as a good alternative to magnesium stearate, sodium stearyl fumarate is used in specific solid dosage formulations (Hölzer & Sjögren, 1979).

2.7.8 Other Interactions between Magnesium Stearate and Drugs

Incompatibility issues have evolved due to other interactions between drugs and magnesium stearate. Captopril is a pyrrolidine carboxylic acid derivative indicated for hypertension. As detected by differential scanning calorimetry, thermogravimetric analysis, and Fourier transformed infrared spectroscopy, captopril interacted with metallic stearate at surfaces during grinding (5 min at room temperature at 32% or 80% RH), given that the mixtures of captopril and each metallic stearate gave different results, before and after grinding. The solid state interaction of captopril with magnesium stearate was accelerated through grinding. As well, by the shifting of the IR spectral peak for the –COOH of the stearate moiety from 1578–1541 cm−, the solid-state interaction between captopril and magnesium stearate was

established. This can be endorsed to the water interaction, where the interaction of the –OH group in the carboxylic acid of captopril bridging with the –COO group of magnesium stearate through hydrogen bonding. Due to evaporation of water from the ground mixture, the interaction between captopril and magnesium stearate was stopped at 60 °C. The performance of drug products can also be affected by other interactions between lubricants and drugs. For instance, as previously mentioned, slow-down of dissolution due to the excessive coating is considered to be as a result of having prolonged mixing of formulations with magnesium stearate, which in turn acts as a water repellant. Depending upon the aqueous solubility of the active ingredients, this will usually determine the extent of the of slowdown mechanism in the dissolution of the formulations. This incident was also examined for other hydrophobic lubricants such as calcium stearate or zinc stearate. On the other hand, the dissolution slowdown did not occur when magnesium stearate was replaced with hydrophilic lubricants such as Stear-O-Wet® or sodium stearyl fumarate (Li & Wu, 2014). Likewise, the formulations dissolution can be advanced by changing the disintegrant. For example, the magnesium stearate effect on the content uniformity of three active ingredients in powder blends was studied by Desai et al., Amongst the hydrophobic lubricants, the maximum slowdown in dissolution was owed to magnesium stearate, followed by zinc stearate and calcium stearate, respectively. No slowdown of the dissolution of capsules, even after over-mixing with 1% w/w magnesium stearate was as a result of replacing pregelatinized starch by starch-derived superdisintegrants such as Explotab® or Primojel®. Amusingly, the hydrophobic lubricants showed slowdown in dissolution when filled into capsules despite the granules being over-mixed with 1% w/w, tablets compressed from these granules dissolved rapidly, demonstrating the impact of dosage forms on dissolution (Desai et al., 1993).

CHAPTER THREE

MATERIALS and METHODS

3.1 Materials

The following materials were used in the study:

Stearic acid (Lot # 39/07), sodium hydroxide pellets (puriss, used for adjusting the pH of the reaction media), magnesium chloride (≥ 98.0%), and acetone (99%) were obtained from DoğaİlaÇ, Sigma-Aldrich, FlukaI, Riedel-de Haen company, respectively as seen in (Figure 3.1). Water was used as distilled. Also, a commercial magnesium stearate (M125, Product's Metalast, Spain) was used in the experiments for the purpose of comparing with the magnesium stearate synthesized in this study.

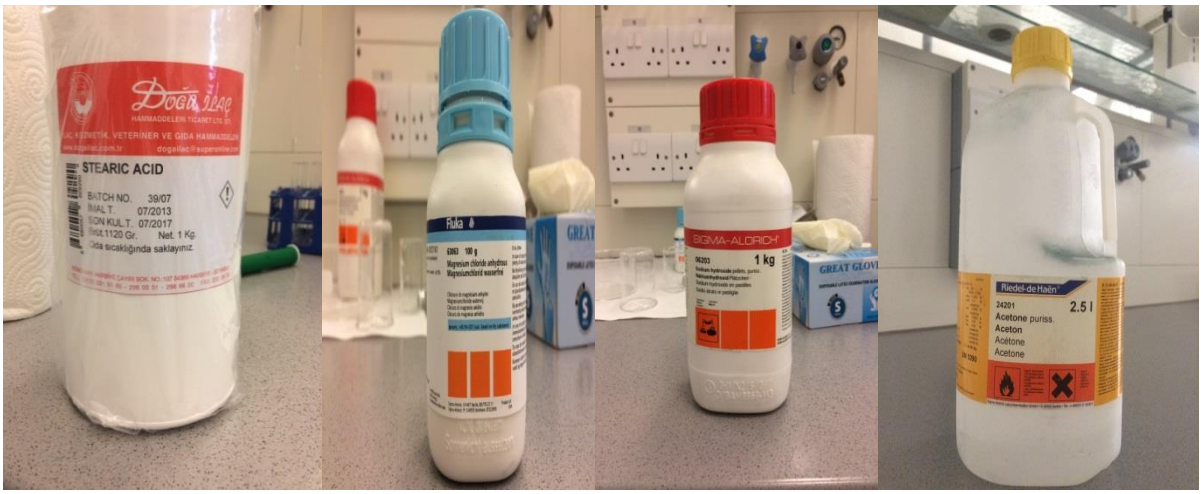


Figure 3.1: Raw Materials.

3.2 Method

3.2.1 Synthesis process of magnesium stearate

In this study, magnesium stearate was synthesized by following steps given below:

a. Precipitation

Chemically, pure samples of stearic acid were prepared by precipitation from aqueous solution. Four sub-batch samples (A, B, C, and D) were prepared to yield approximately 20g of magnesium stearate. Each sample was included 5.0g of stearic acid which was dispersed in 1000 ml of distilled water, and the suspension was heated to 75℃ on oil bath (silica oil) to fix the temperature, but the heater was 125℃. At the same time, the suspension was stirred at a rate of 500 rpm by a mechanical stirrer until it dissolved as shown in (Figure 3.2). Samples (A, B, C, and D) dissolved at different temperatures (50, 55, 54, and 51℃), and different time (90, 115, 90, and 100) minutes respectively as shown in (Table 3.1). Neutralization was made by adding sodium hydroxide (NaOH) pallet (0.704g) for each sample and stirring for 10 minutes to form sodium salts of the acids (i.e., metal soaps). Magnesium chloride (MgC12) (0.837g), in slight excess of that required for the stoichiometric reaction, was dissolved in 250 ml of distilled water and added drop wise to the metallic soap solution. The product was cooled at room temperature to the next day.

- **Calculations**

Number of moles of stearic acid: 5g/284.48a.m.u = 0.0176mols
Mass of NaOH= 0.0176mols*40a.m.u = 0.704g
Mass of MgCl2= 0.0176mols*95a.m.u = 1.672g/2=0.837g

b. Filtration of Magnesium stearate precipitate

Buchner funnel and flask were utilized to obtain white and clear filtrate (precipitate material) in a wet form (every sample filtrate separately). The filtrate was dried at room temperature for 24 hours and weighted after drying as seen in (Table 3.1) and (Figure 3.3).

Table 3.1: Differences between the synthesis conditions of four sub-batches (A, B, C, D).

No of samples	Amount of Stearic acid	Amount of MgCl2	Amount of NaOH	Temperature of heater	Temperature	Dissolving Temperature	Time (minutes)	Amount of MgSt	
								After Filtration	After Washing
Sample A	5.0gr	0.837gr	0.704gr	125°C	75°C	57°C	90	5.57gr	5.46gr
Sample B	5.0gr	0.837gr	0.704gr	125°C	75°C	55°C	115	5.53gr	5.48gr
Sample C	5.0gr	0.837gr	0.704gr	125°C	75°C	55°C	90	5.77gr	5.54gr
Sample D	5.0gr	0.837gr	0.699gr	125°C	75°C	52°C	100	5.71gr	5.13gr

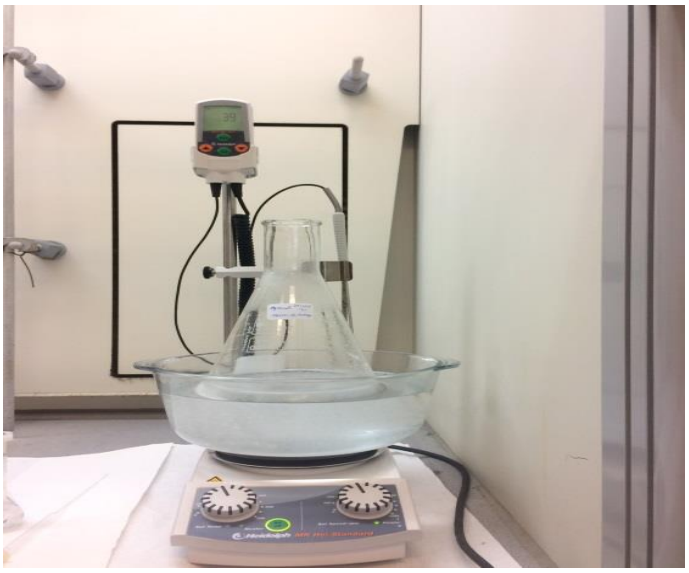


Figure 3.2: Precipitation in Oil Bath.

Figure 3.3: Filtration by Buchner funnel and flask.

c. Washing of Magnesium Stearate Filtrate

The filtrate was washed in Buchner funnel by distilled water and acetone to remove the impurity and unreacted materials. Then, the filtrate was dried at room temperature for 24 hours

and weighted after drying to see the difference before and after washing as determine in (Table 3.1) and (Figure 3.4).

d. Purification

Five filtrate samples were poured inside the Soxhlet thimble and washed again with water and acetone over 2 days for each solvent by Soxhlet extractor in order to remove any unreacted fatty acids, magnesium chloride, or sodium hydroxide, and obtain purity product as demonstrate in (Figure 3.5). The powder was dried at room temperature for 48 hours.

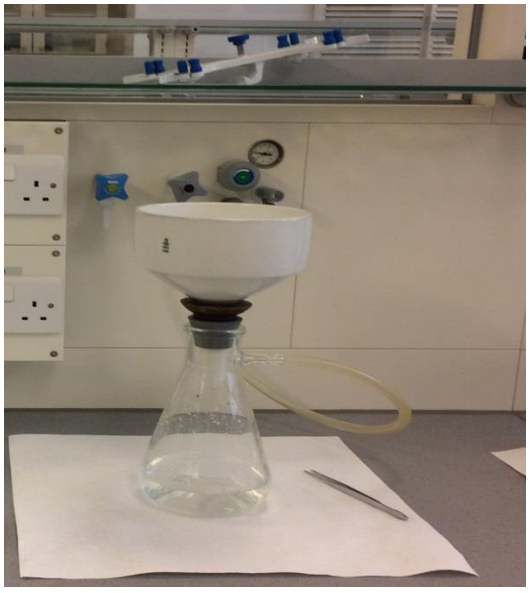


Figure 3.4: Washing by Buchner funnel and flask.

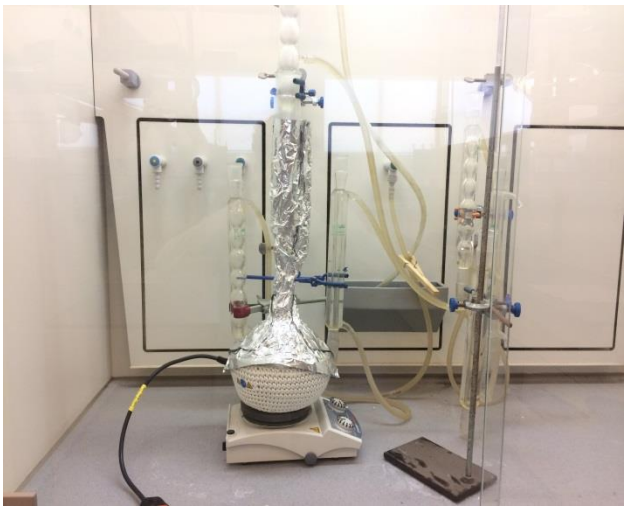


Figure 3.5: Soxhlet extractor.

e. Drying

Drying is one of the important steps in synthesis of magnesium stearate. The powder was dried by Autoclave at 55°C. Also, the powder was weighted every so often in order to obtain a constant weight, as demonstrate in (Table 3.2).

Table 3.2: Weights of powder at different times.

Period inside the Autoclave (Minutes)	**Weight of powder (g)**
—	27.72g
35	24.82g
90	22.87g
150	20.58g

f. Micronization

The average particle size of the synthesized magnesium stearate was much higher than that of commercially available ones. Therefore, in this study, the synthesized magnesium stearate was micronized using a jet mill.

3.3 Tests Performed

The following tests were applied to the synthesized magnesium stearate: for analysis:

A. Thermal analysis:

Melting point:

In order to ensure that the purity of magnesium stearate, melting points of magnesium stearate and stearic acid at a temperature increase rate of 1°C/min and 2°C/min. were measured using a Mettler Toledo melting point apparatus. For this purpose, the samples were loaded in the capillary by 2mm and expressed steric acid and magnesium stearate as X sample and Y sample, respectively.

Differential scanning calorimeter (DSC):

Differential scanning calorimetry (DSC-60, Shimadzu, Japan) was conducted between temperatures 25°C to 200°C at a heating rate of 2°C/min and nitrogen purge of 30 mL/min. Samples of weight 1.1 mg for milled magnesium stearate and 2.9 mg for commercial magnesium stearate (M125), were tested in aluminum pans and an empty pan was used as a reference.

Thermogravimetric Analysis (TGA):

(DTG 60H, Shimadzu, Kyoto, Japan) was used for investigation of the water content, that is, hydration state, of the magnesium stearate samples. In addition, nitrogen was utilized as the purge gas at a flow rate of 50 mL/min. Approximately 0.169 mg of milled magnesium stearate and 1.188 mg for commercial magnesium stearate (M125) were placed on an aluminum pan

and heated at 10°C/min from room temperature to 151°C. The total weight loss from room temperature to 151°C was analyzed for water content.

B. Structural Characterization:

X-ray powder diffraction (XRPD):

Powder x-ray diffraction patterns were (XRD 6000, Shimadzu, Japan) operated at 40 kV and 30 mA, using Cu Kα radiation (λ = 1.5406 Å) as the radiation source. Data were collected in a continuous scan mode with a sweep of 2°/min over an angular range of 10.0000 to 80.0000° 2θ and in step size 0.0200° 2θ.

Fourier transform infrared spectroscopy (FTIR):

A Fourier transform infrared (FTIR) spectra was recorded on a PerkinElmer Model 1600 apparatus. Samples were prepared in KBr disks by means of a hydrostatic press. The scanning range was 400 to 4000 cm–1 and the resolution was 4 cm–1. The spectra were recorded with the use of version (10.03.07). FTIR analysis has been performed using sample of magnesium stearate.

C. Microscopy:

Scanning electron microscope (SEM):

Images of magnesium stearate were examined using a scanning electron microscope (JSM-6010 LV, JEOL, Japan). The image resolutions were obtain using a Secondary electrons detector with 5kv. Various images were taken in magnification x500 and x1.000. The images allowed the shape and morphology of the powders to be examined.

D. Flowability:

Rheometry

FT4 Powder Rheometer (FT4, Freeman Technology, UK) was used to evaluate the flow properties (dynamic, shear and bulk properties in one system) of the powders in terms of energy required to make them flow by using a range of attachments while axial and rotational forces are measured. A number of control/measurement modes are available including position, velocity, force and torque (Freeman, 2007). FT4 Rheometer used in this study to evaluate Basic Flowability Energy (BFE), Stability Index (SI), Flow Rate Index (FRI) and Specific Energy (SE) of milled magnesium stearate and commercial magnesium stearate (M125) at different concentration. Dynamic test is a standard procedure was utilized to assess the flow properties of the powders under free surface conditions. A cylindrical vessel with a dimension of 50×160mL was filled with the materials and set on platform of the rheometer and prepared for testing. The torque exerted on the blade was analyzed using the computer software (data analysis V4, Freeman Technology, UK).

Avalanche Behavior

A revolution powder analyzer (Revolution®, Mercury Scientific Inc., USA) determines the cohesivity of a powder from its avalanching behavior. The equipment contains a rotating drum, a video camera that captures the resulting of avalanche behavior. Computer software monitored the avalanche behavior and calculated different avalanche characteristics including Avalanche Energy, Break Energy Absolute, Avalanche Time, Avalanche Angle and Surface Fractal. The plastic drum (10 cm diameter) was loaded with a sample and rotated at 0.3 rpm continuously until 150 avalanches had occurred. As the drum rotated, the powder moved up the side of the drum until the powder surface collapsed downward in an avalanche and a digital camera connected to a computer was used to monitor the flow.

E. Compaction:

A model formulation containing paracetamol was compressed using a compaction simulator and the thickness of the tablets was measured using a digital micrometer (Mitutoyo, Japan). The effect of tablet thickness variation was eliminated by calculating the tensile strength of tablets. The tablet breaking force was determined via diametrical compression between two platens using a tablet hardness tester (TBF 1000, Copley Scientific, UK). Tensile strength for each tablet was calculated using Equation (3.1), where F is the breaking force, M and T are tablet diameter and thickness in mm, respectively.

$$\text{Tensile strength} = \frac{2F}{\pi MT} \qquad (3.1)$$

CHAPTER FOUR

RESULTS and DISCUSSION

4.1 Thermal analysis:

Melting point:

As shown in (Table 4.1), steric acid has a different melting point range in different temperature range than magnesium stearate, even though; steric acid is the raw materials of synthesizing and as mentioned previously. Also, stearic acid has a different melting point range at 1°C/min and 2°C/min, also magnesium stearate has the same.

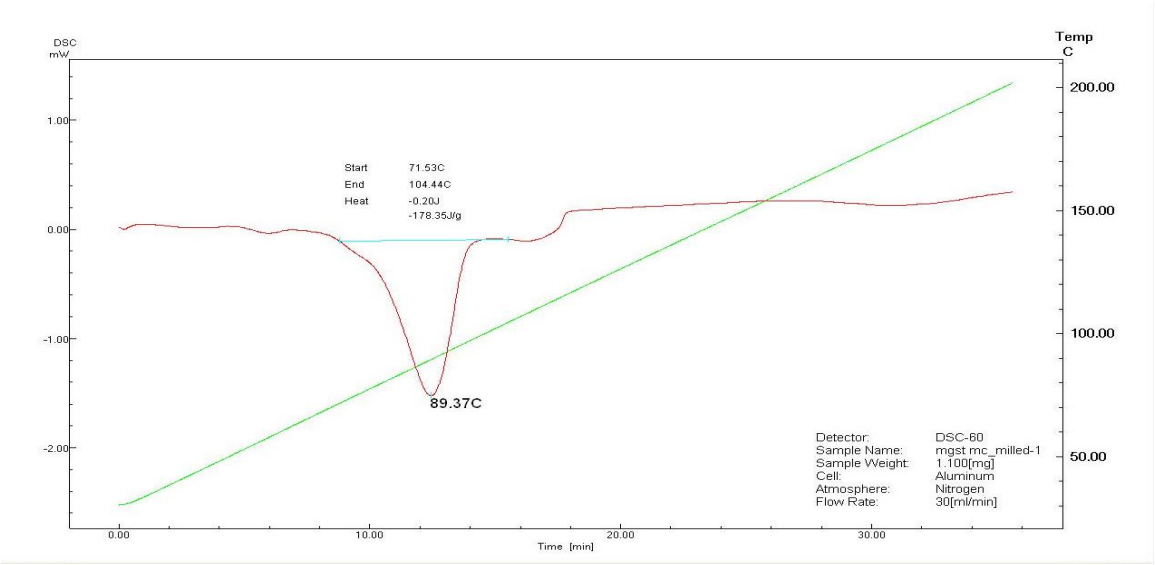
Table 4.1: Melting point ranges at different rates.

Sample	Temperature range	
	(1°C/min)	**(2°C/min)**
X= Steric acid	55°C—58°C	54.8°C—57.7°C
Y= Magnesium stearate	105.7°C—107.5°C	107.9°C—109.6°C

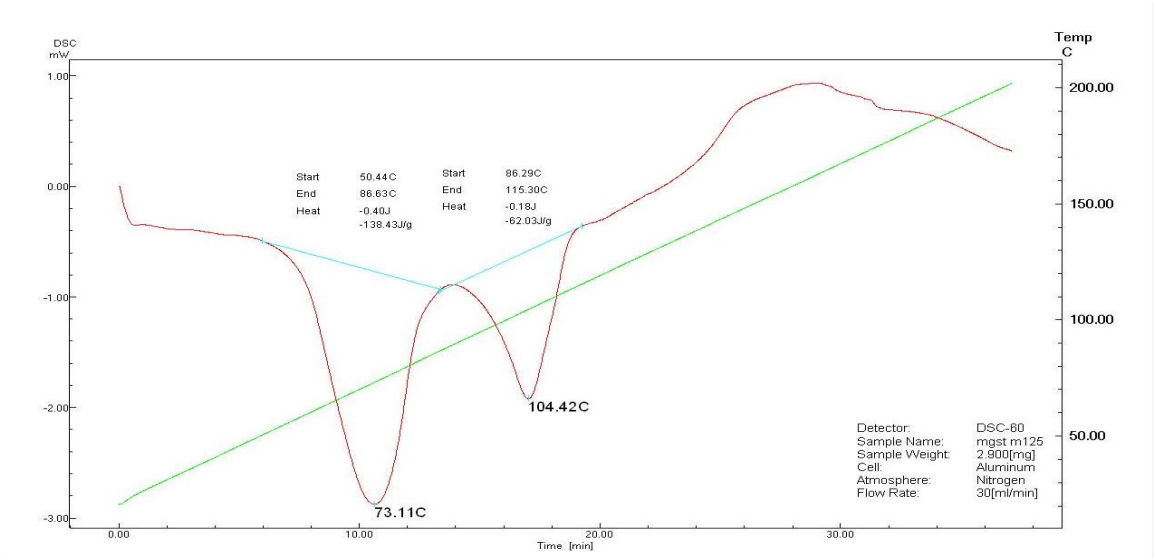
Differential scanning calorimeter (DSC):

As depicted in (Figure 4.1a) the Differential scanning calorimeter thermogram of milled magnesium stearate was found to contain one thermal event. The endotherm exhibited a maximum of 89.37°C (started at 71.53°C and ended at 104.44°C). As observed in (Figure 4.1b) the thermogram of commercial magnesium stearate (M125) exhibited two thermal events. The first endotherm exhibited a maximum of 73.11 °C (started at 50.44°C and ended at 86.63°C) and the second event transition was noted at 104.42°C (started at 86.29°C and ended at 115.30°C). The results suggest disagreement with the previous studies by (Sharpe, Celik,

Newman, & Brittain, 1997) and (Delaney, et al., 2016). Furthermore, both the milled and commercial offers different thermal events.



(a)

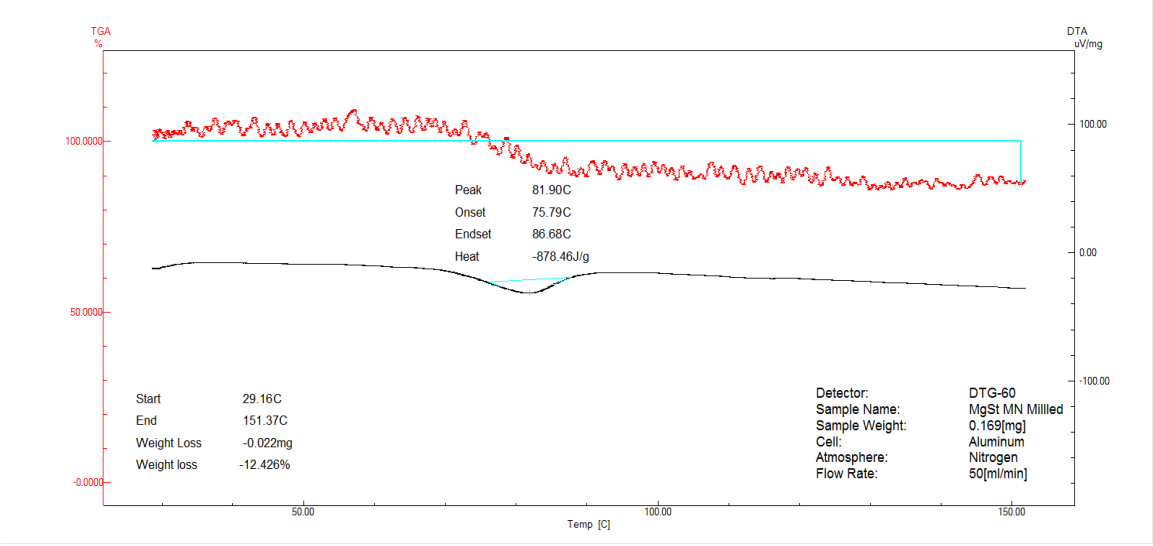


(b)

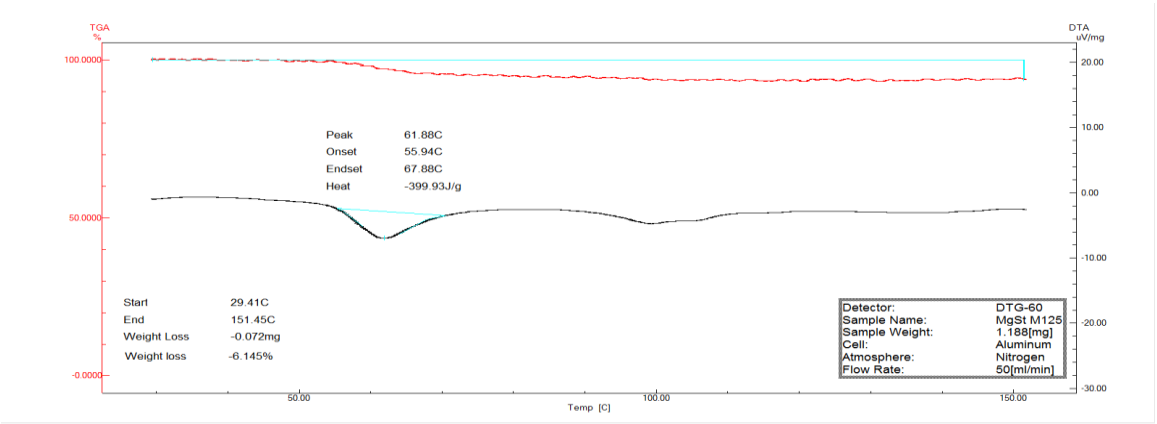
Figure 4.1: Differential scanning calorimeter: (a) Milled magnesium stearate; (b) Commercial magnesium stearate (M125).

Thermogravimetric Analysis (TGA):

As shown in (Figure 4.2) and (Figure 4.3), the Thermogravimetric thermogram indicates that a weight loss of milled magnesium stearate at approximately 12% (the scan started at 29.16°C and ended at 151.37°C). The weight loss of commercial magnesium stearate (M125) is approximately 6% (the scan started at 29.41°C and ended at 151.45°C). This result indicates the water molecule concentration of milled magnesium stearate is greater than commercial magnesium stearate (M125). In addition, previous studies of the TGA patterns of the forms of magnesium stearate are inconsistent with the TGA patterns of milled magnesium stearate shown in this study. For example, studies by (Okoye, Wu, & Dave, 2012), (Sharpe, Celik, Newman, & Brittain, 1997) and (Delaney, et al., 2016) have reported different weight loss according the hydrate states.

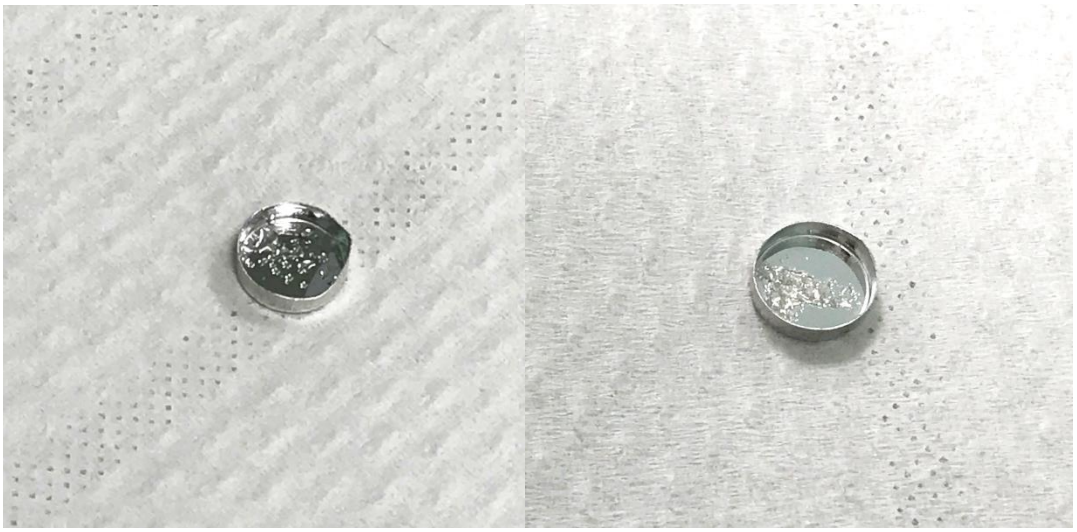


(a)



(b)

Figure 4.2: Thermogravimetric curve: (a) Milled magnesium stearate; (b) Commercial magnesium stearate (M125).



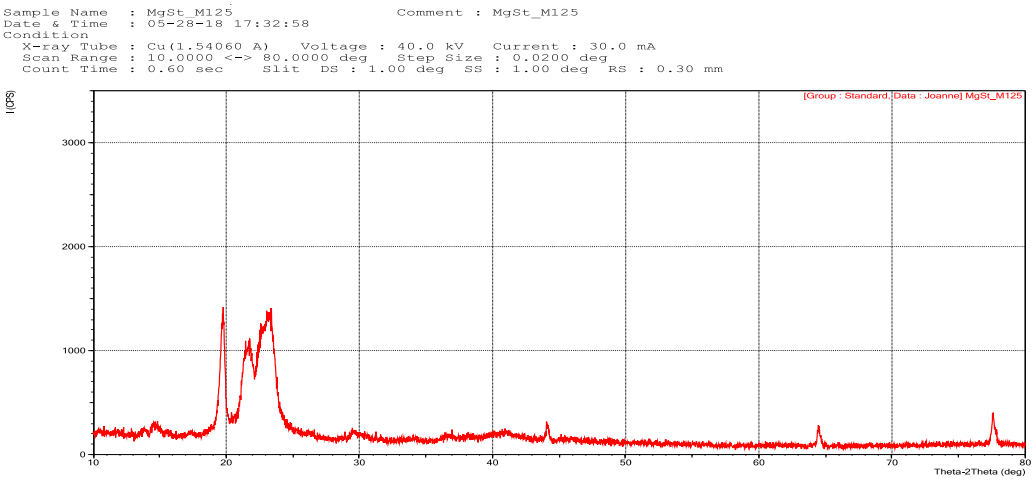
(a) (b)

Figure 4.3: Thermogravimetric Analysis: (a) Milled magnesium stearate; (b) Commercial magnesium stearate (M125).

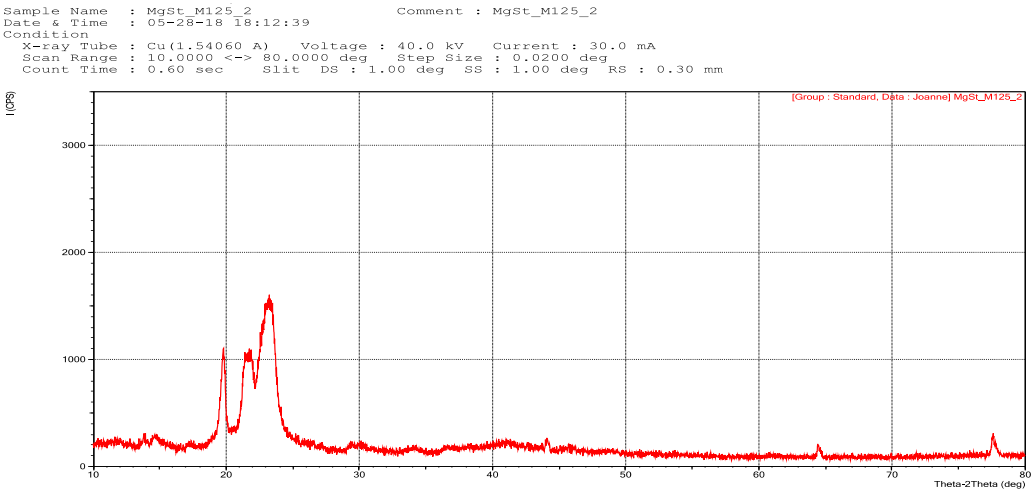
4.2 Structural Characterization:

X-ray powder diffraction (XRPD):

As summarized in (Table 4.2), commercial magnesium stearate (M125), unmilled magnesium stearate and milled magnesium stearate contain both crystal and amorphous form in different results. Also, variation results were found at every measurement of materials. However, milled magnesium stearate was found to be more crystalline than the other materials. Furthermore, as illustrated in (Figure 4.4, 4.5 and 4.6) all materials pattern was found to contain clustered peaks between 20° and 25° 2θ position, but milled magnesium stearate has sharper peaks (high intensity). The result of milled magnesium stearate is harmonious with the XRPD pattern (sample I and IV) of (Rao, Chawla, Kaushal, & Bansal, 2005) study, which have report Samples I and IV indicated a crystal structure as a mixture of dihydrate and other hydrates. Nevertheless, DSC and TGA patter of milled magnesium stearate did not agree with the previous studies of hydrate form.

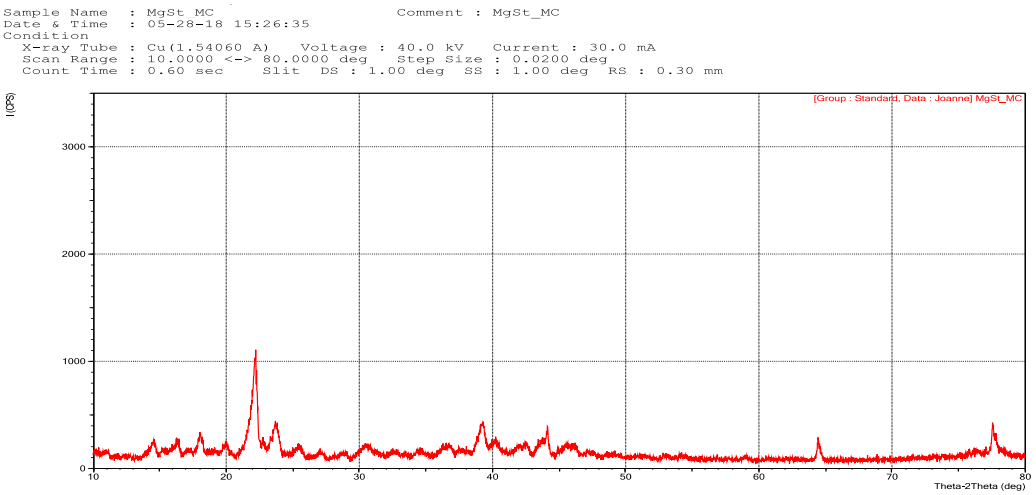


(a)

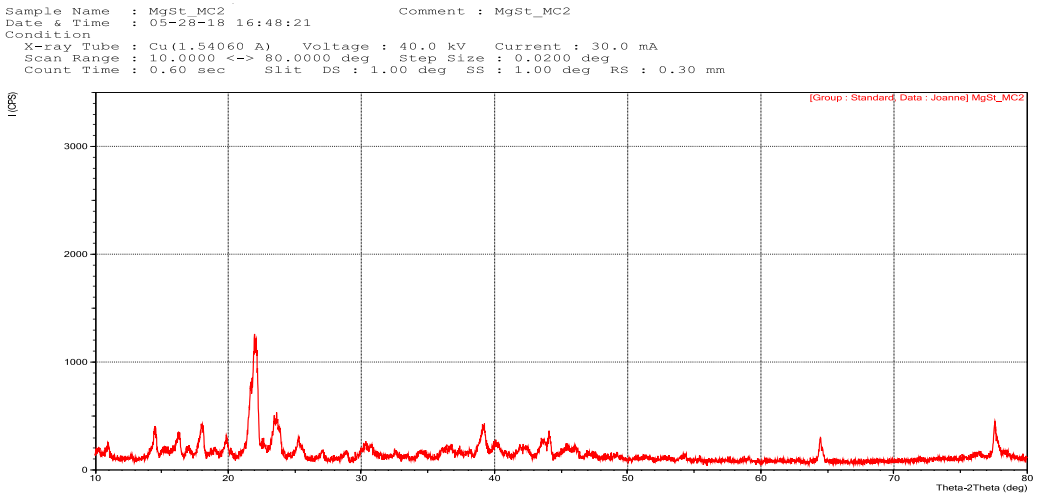


(b)

Figure 4.4: X-ray powder diffraction pattern of commercial magnesium stearate (M125): (a) Measurement 1; (b) Measurement 2.

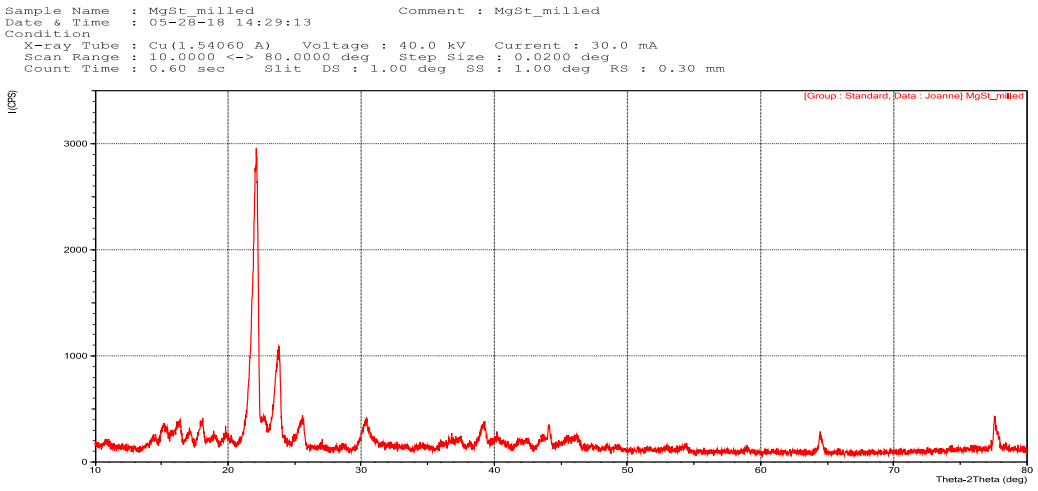


(a)

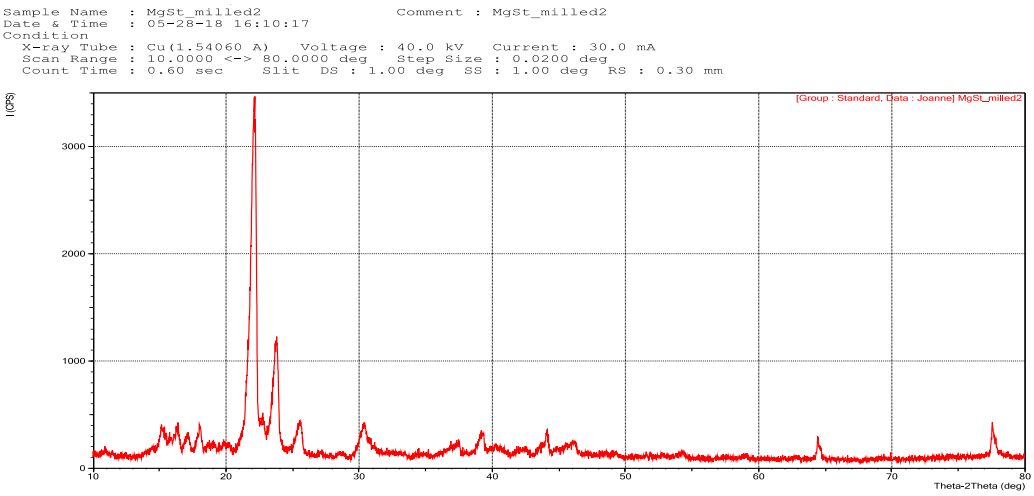


(b)

Figure 4.5: X-ray powder diffraction pattern of unmilled magnesium stearate: (a) Measurement 1; (b) Measurement 2.



(a)



(b)

Figure 4.6: X-ray powder diffraction pattern of milled magnesium stearate: (a) Measurement 1; (b) Measurement 2.

Table 4.2: X-ray powder diffraction data of unmilled magnesium stearate, milled magnesium stearate and commercial magnesium stearate.

Samples	Crystallinity (%)	Parameter K	Crystal lcr (kcps*deg)	Amorphous la (kcps*deg)
MgSt M125(1)	42.5547	1	1.8223	2.46
MgSt M125(2)	41.3164	1	1.9045	2.705
MgSt (1)	70.00031	1	1.7969	0.77
MgSt (2)	75.2268	1	2.0953	0.69
MgSt milled (1)	64.936	1	2.9291	1.5817
MgSt milled (2)	62.9515	1	3.246	1.9103

Fourier transform infrared spectroscopy (FTIR):

The mode of binding of carboxylate groups to metal ions has been investigated by Fourier transform infrared spectroscopy. The mode of binding of the carboxylate groups to metal ions can be elucidated from the Fourier transform infrared spectra of the unmilled magnesium stearate. As reported in (Table 4.3) and (Figure 4.7), the asymmetric and symmetric carboxylate vibrations for unmilled magnesium stearate are at 1.536.5 and 1.466.8 cm-1 respectively. This result indicates that it is in a bridging bidendate form. The FTIR spectrum of unmilled magnesium stearate exhibited absorbance at 2.917 cm-1 owing vibration CH3 stretching as well as the CH2 symmetric vibrations were reported to be at 2.850 cm-1. The unmilled magnesium stearate sample contains water molecules as the OH groups can be seen at 3300-3400 cm-1. The results show unmilled magnesium stearate presented in a hydrate form.

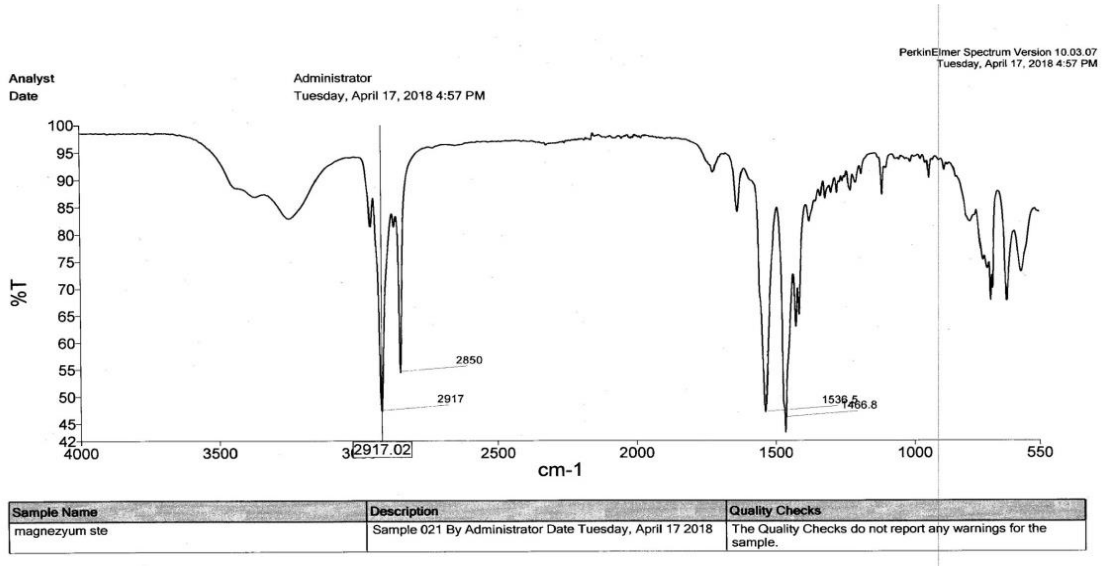


Figure 4.7: Fourier transform infrared spectra of unmilled magnesium stearate.

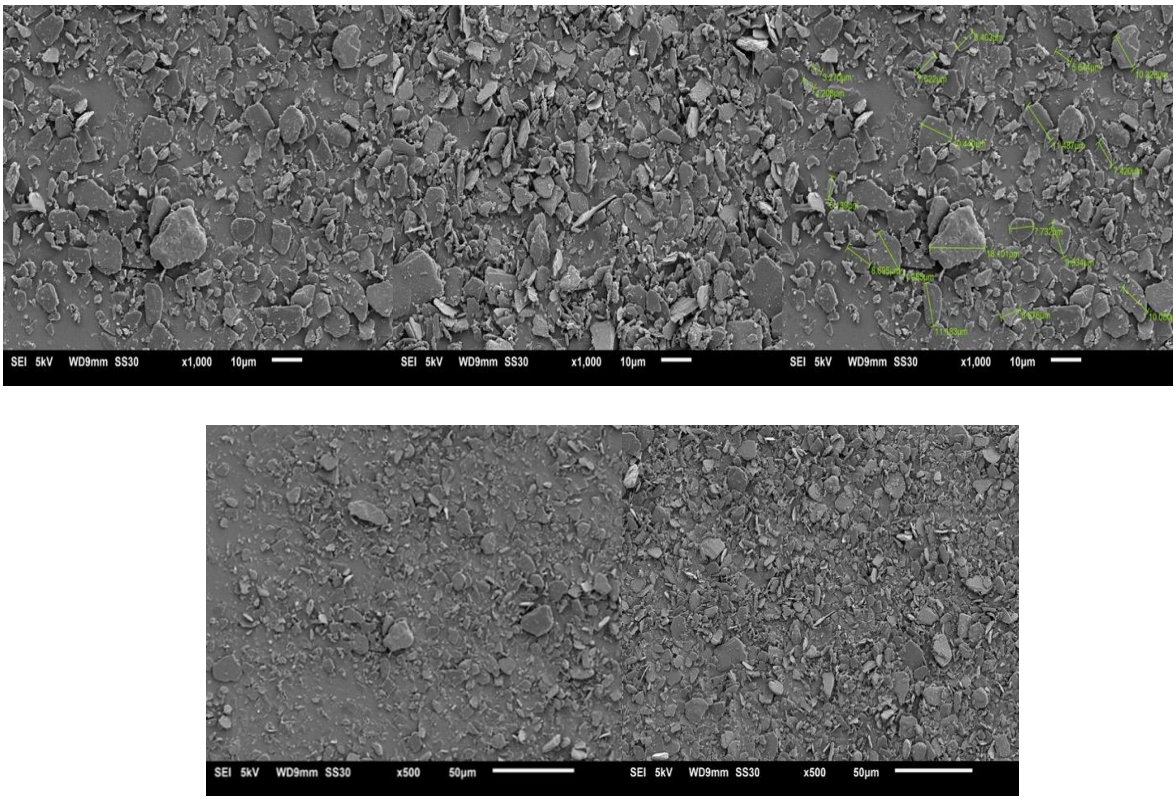
Table 4.3: Vibrations and waves numbers for unmilled magnesium stearate.

Vibration	**Wave number (cm-1) of unmilled magnesium stearate**
CH3 stretching	2.917
CH2 symmetric stretching	2.850
COO^- asymmetric stretching	1.536.5
COO^-symmetric stretching	1.466.8

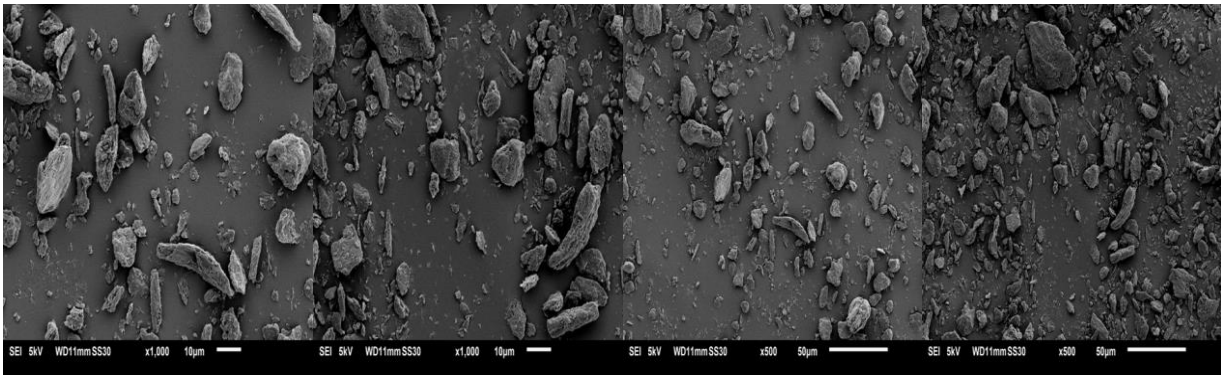
4.3 Microscopy:

Scanning electron microscope (SEM):

The surface morphology of the samples was investigated by Scanning electron microscopy. The milled magnesium stearate was compared to the commercial magnesium stearate (M125). As shown in the images in (Figure 4.8a), milled magnesium stearate was found to consist irregular small flakes. Also, in (Figure 4.8b), commercial magnesium stearate (M125) was approximately irregularly angular and acicular shaped materials. It is clearly milled magnesium stearate are more homogeneously dispersed (having homogeneous particle sizes) through the matrix. The average size and standard deviation of milled magnesium stearate are less than of commercial magnesium stearate (M125) as presented in (Table 4.4). The morphology of milled magnesium stearate is consistent with the previous studies.



(a)



(b)

Figure 4.8: Scanning electron microscope images: (a) Milled magnesium stearate; (b) Commercial magnesium stearate (M125).

Table 4.4: Sizing of magnesium stearate.

Samples	Average Size (µm)	Standard Deviation
MgSt M125	11.54	7.34
Milled MgSt	8.69	3.83

4.4 Flowability:

Rheometry

As report in (Table 4.5), the main parameters that obtained Basic Flowability Energy (BFE), Stability Index (SI), Flow Rate Index (FRI) and Specific Energy (SE).

The results of SI showed increasing in the stability of blending with increasing in the milled magnesium stearate, so there is decreasing a possibility of the change of particle size of the blending through agglomeration, degradation or segregation. However, the commercial magnesium stearate (M125) blending gave different values at different concentrations, but at (1.5% and 2.0%) gave the highest value. BFE results showed milled and commercial magnesium stearates (M125) blending have energy increasing with increasing of them concentrations, but the commercial magnesium stearate (M125) has higher energy, which generally means a higher flowability. FRI is the energy required to displace the powder decreased with increased the concentrations of both milled and commercial magnesium stearates (M125) blending, but the commercial magnesium stearate (M125) has lower energy, which generally means a better flowability (less cohesiveness). SE showed milled magnesium stearate blending has lesser values than commercial magnesium stearate (M125) blending, that's indicate of significantly improvement of flowability. Considering all the samples indicated a significantly improvement the dynamic flow properties but increasing in concentrations do not result in further enhancement.

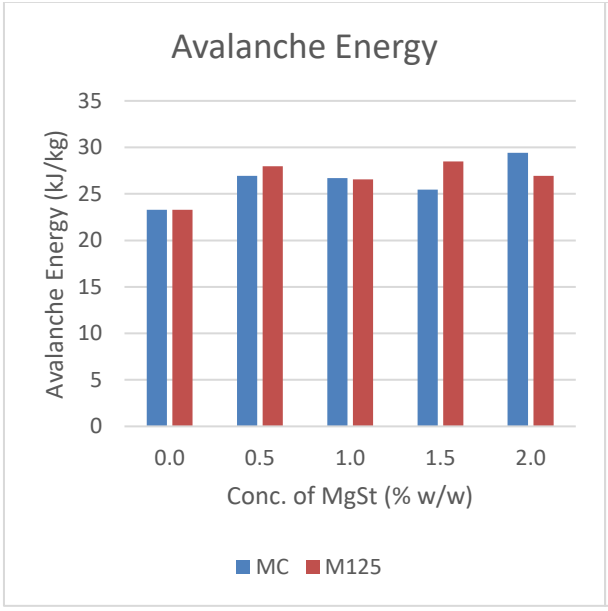
Table 4.5: Some rheological properties of milled magnesium stearate and commercial magnesium stearate (M125) at different concentrations.

Formula	BFE (mJ)	SI	FRI	SE (mJ/g)
Blank	226.8284	1.464102	1.191757	4.569856
0.5% Milled MgSt	74.21763	0.808167	1.01611	2.501497
1.0% Milled MgSt	86.64093	0.808053	1.044149	2.623659
1.5%Milled MgSt	90.10072	0.829193	1.023307	2.671744
2.0% Milled MgSt	95.01942	0.844139	1.018737	2.646238
0.5% MgSt M125	85.28577	0.810783	1.065797	2.753993
1.0% MgSt M125	103.1122	0.760955	1.037703	2.759177
1.5% MgSt M125	121.4777	0.897667	1.005641	2.954315
2.0% MgSt M125	128.0936	0.856077	0.999631	2.907084

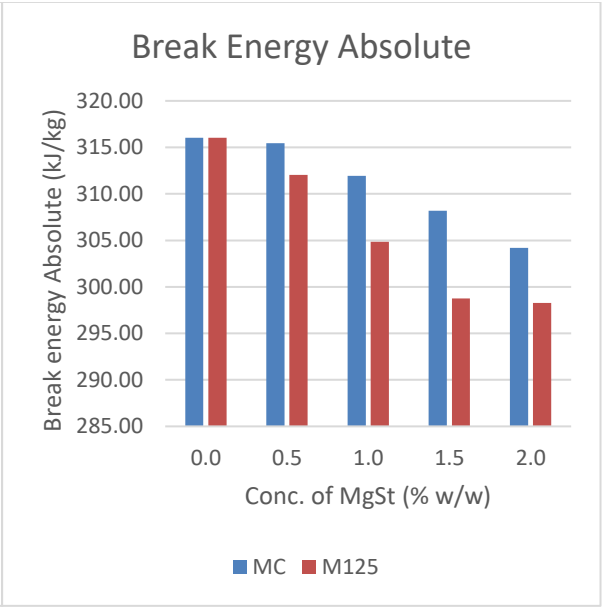
Avalanche Behavior

As reported in (Table 4.6), the avalanche behavior is a flowability indicator measured by the Mercury Scientific Revolution Powder Analyzer. As seen in (Figure 4.9a), the avalanche energy is the amount of energy released in an avalanche, at (1.5% and 1.0%) of both milled and commercial magnesium stearates (M125) blending have low energy (25.46 and 26.57 kJ/kg) respectively, which generally indicative of better powder flow. As expose in (Figure 4.9b), the results of break energy absolute for the commercial magnesium stearates (M125) blending less than milled magnesium stearate with increasing them concentrations. Thus, lower break energy is indicative of better flow and lower cohesion. As exhibit in (Figure 4.9c), the avalanche angle is the angle of the powder right before it avalanches and a smaller value indicates that the powder has better flowability. The results showed low angles with commercial magnesium stearates (M125) blending with increasing the concentrations. As demonstrated in (Figure 4.9d), the avalanche time for the blending with milled magnesium stearate and commercial magnesium stearates (M125) provided different avalanche time. Nevertheless, at 1.5% of milled magnesium stearate gave the lowest avalanche time. As revealed in (Figure 4.9e), the surface fractal measures the surface roughness of the powder and

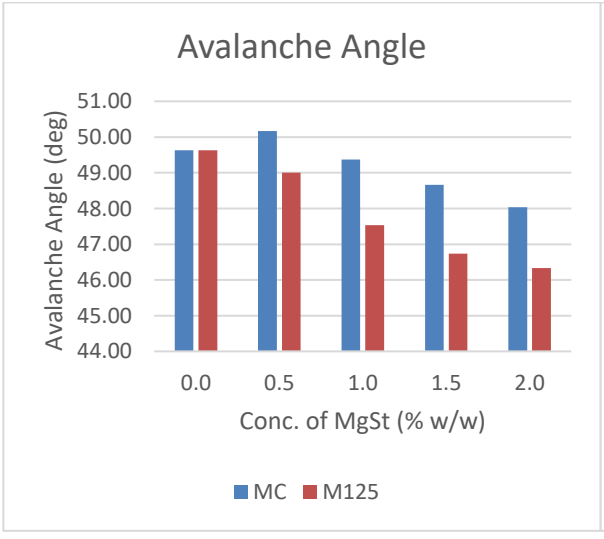
normalized values to give a range from 1 to 11. Milled magnesium stearate blend showed increasing in the surface fractal with increasing at the concentrations. In contrast, with increasing at the concentrations of the commercial magnesium stearates (M125) blending the surface fractal values decreased. At the same time both of them in the normalized range.



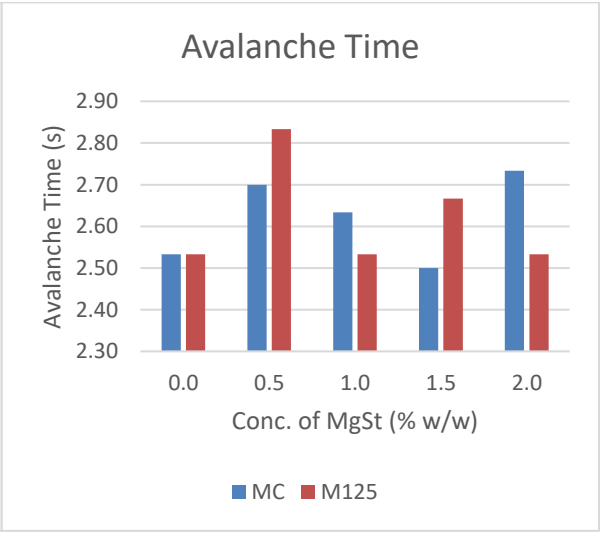
(a)



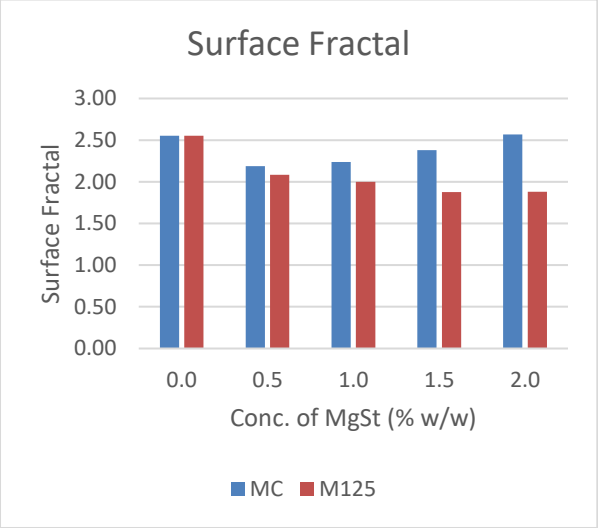
(b)



(c)



(d)



(e)

Figure 4.9: Avalanche Behavior study for milled magnesium stearate and commercial magnesium stearate (M125) at different concentration: (a) Avalanche Energy (kJ/kg); (b) Break Energy Absolute (kJ/kg); (c) Avalanche Angle (deg); (d) Avalanche Time (sec); (e) Surface Fractal

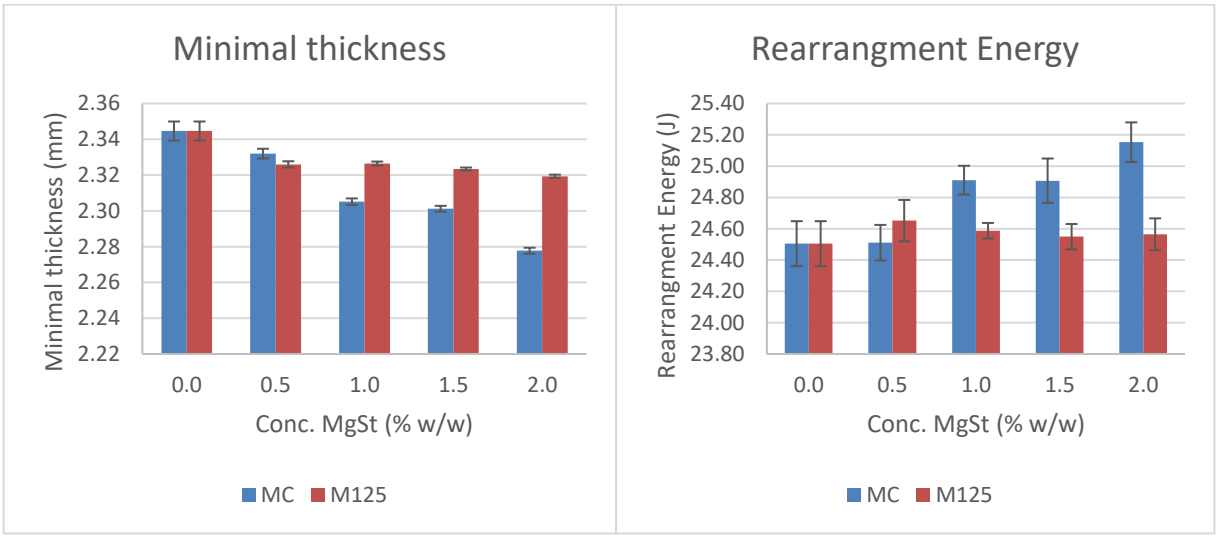
Table 4.6: Avalanche Behavior for milled magnesium stearate and commercial magnesium stearate (M125) at different concentrations.

Sample ID	Avalanche Energy (kJ/kg)	Break Energy Abs (kJ/kg)	Avalanche Time (sec)	Avalanche Angle (deg)	Surface Fractal
Blank	23.28	316.05	2.53	49.63	2.553
0.5% Milled MgSt	26.93	315.44	2.70	50.17	2.187
1.0% Milled MgSt	26.69	311.95	2.63	49.37	2.237
1.5% Milled MgSt	25.46	308.20	2.50	48.67	2.380
2.0% Milled MgSt	29.43	304.19	2.73	48.03	2.567
0.5% MgSt M125	27.98	312.03	2.83	49.00	2.083
1.0% MgSt M125	26.57	304.85	2.53	47.53	2.000
1.5% MgSt M125	28.48	298.75	2.67	46.73	1.877
2.0% MgSt M125	26.93	298.28	2.53	46.33	1.880

4.5 Compaction:

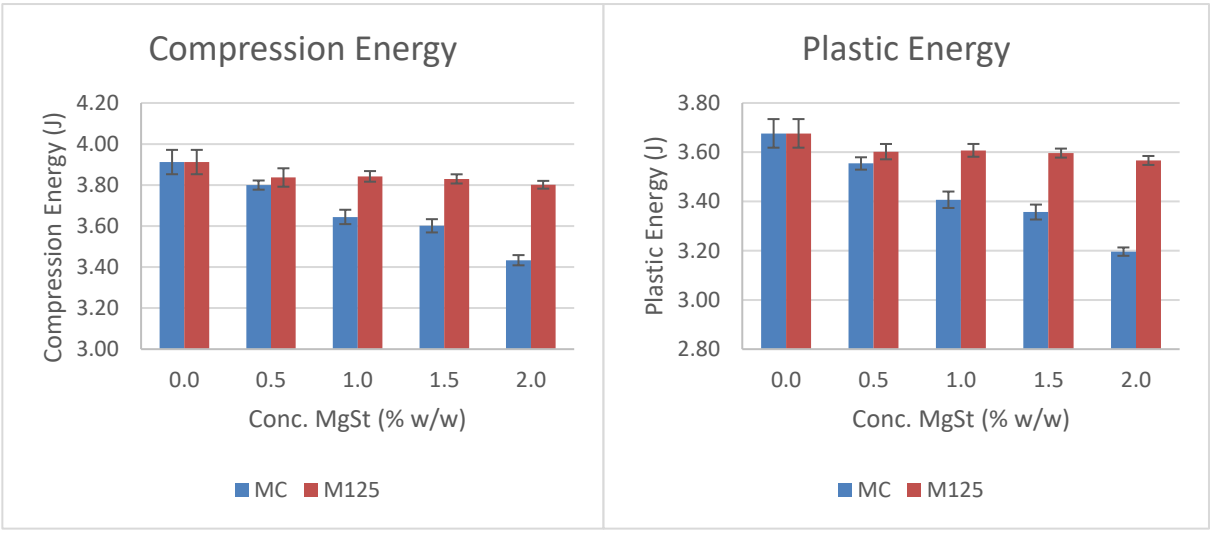
The data given in (Table 4.7) present a summary of data obtained from the compaction study performed using synthesized and milled magnesium stearate (synthesized in this study) and a commercially available magnesium stearate product (M125) containing model formulation with the active ingredient of paracetamol. The results given in (Table 4.7 and Figures 4.10a to 4.10i) show that the strength of the compacts was highest when there is no lubricant. However, the high ejection force (approximately 600N) of these tablets was not acceptable. The strength of tablets containing the milled magnesium stearate decreased as the concentration of the lubricant increased. The strength of the tablets containing commercial magnesium stearate were comparable at the lowest concentration of 0.5%. However, as the amount of magnesium stearate increase, the strength of the tablets containing milled product decreased further

whereas the commercial magnesium stearate resulted in tablet with approximately same hardness of about 0.60 N/mm^2. While the tablets containing synthesized/milled magnesium stearate produced lower strength, lower, lower ejection force, compression energy, plastic energy, and minimal thickness as the concentration of magnesium stearate increased, no trend was observed in case of the tablets containing commercially available magnesium stearate. Overall results of the compaction study indicate that milled magnesium stearate have better lubricant properties than that of the commercial one.



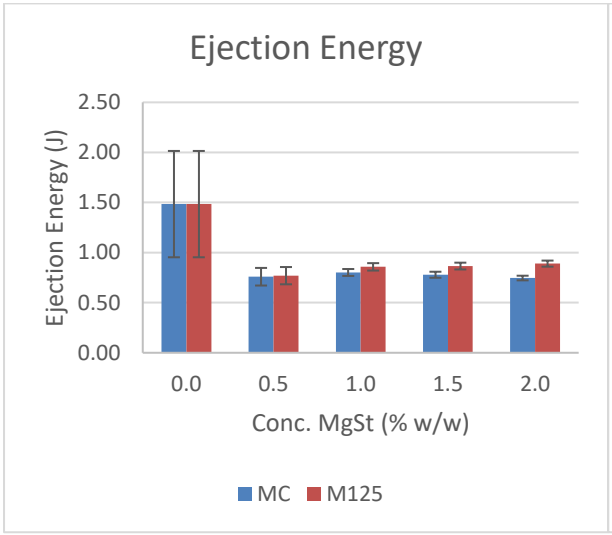
(a)

(b)

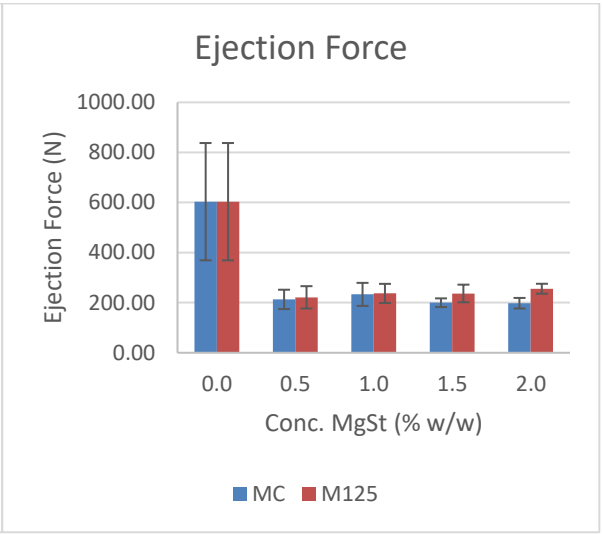


(c)

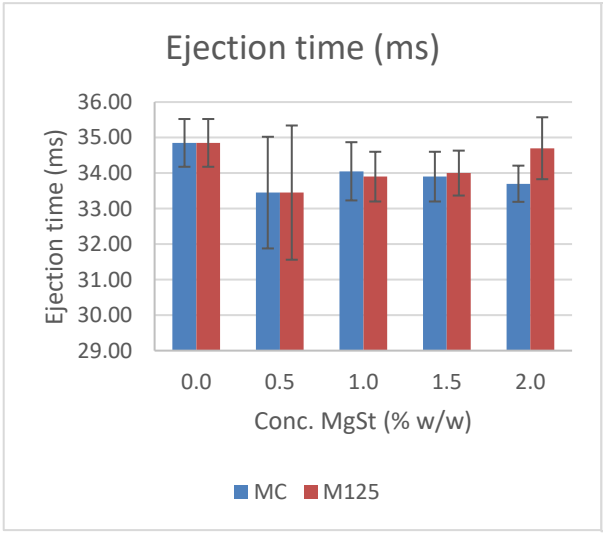
(d)


Ejection Energy
Ejection Energy (J)
2.50
2.00
1.50
1.00
0.50
0.00
0.0
0.5
1.0
1.5
2.0
Conc. MgSt (% w/w)
MC
M125

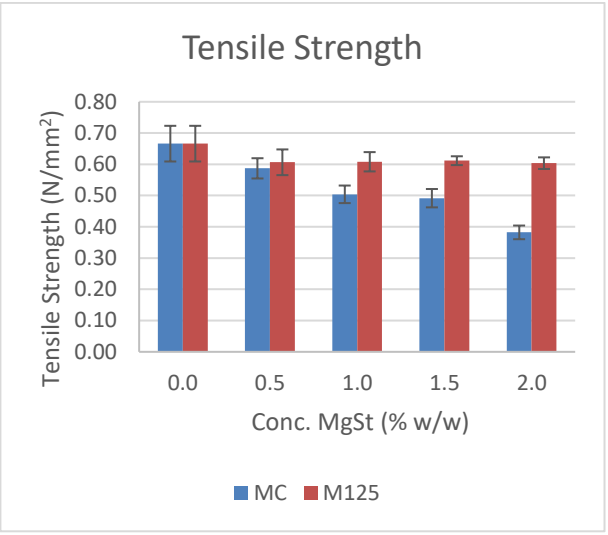
(e)


Ejection Force
Ejection Force (N)
1000.00
800.00
600.00
400.00
200.00
0.00
0.0
0.5
1.0
1.5
2.0
Conc. MgSt (% w/w)
MC
M125

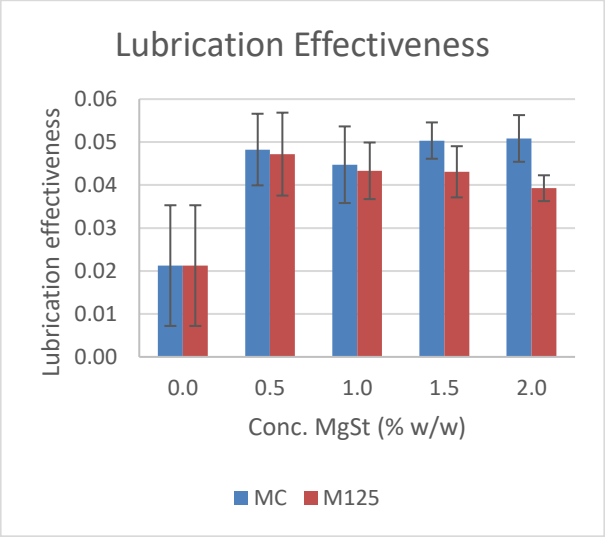
(f)


Ejection time (ms)
Ejection time (ms)
36.00
35.00
34.00
33.00
32.00
31.00
30.00
29.00
0.0
0.5
1.0
1.5
2.0
Conc. MgSt (% w/w)
MC
M125

(g)


Tensile Strength
Tensile Strength (N/mm²)
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0.0
0.5
1.0
1.5
2.0
Conc. MgSt (% w/w)
MC
M125

(h)



(i)

Figure 4.10: Compaction study of milled magnesium stearate and commercial magnesium stearate (M125) at different concentration: (a) Minimal Thickness (mm); (b) Rearrangement Energy (J); (c) Compression Energy (J); (d) Plastic Energy (J); (e) Ejection Energy (J); (f) Ejection Force (N); (g) Ejection Time (ms); (h) Tensile Strength (N/mm2); (i) Lubrication Effectiveness.

Table 4.7: Compaction study of milled magnesium stearate and commercial magnesium stearate (M125) at different concentrations.

Formula	Minimal Thickness (mm)	Rearrangement Energy (J)	Compression Energy (J)	Plastic Energy (J)	Ejection Energy (J)	Ejection Force (N)	Ejection Time (ms)	Tensile Strength (N/mm2)	Lubrication Effectiveness
Blank	2.34	24.50	3.91	3.68	1.48	603.35	34.85	0.67	0.02
0.5% Milled MgSt	2.33	24.51	3.80	3.55	0.76	213.20	33.45	0.59	0.05
1.0% Milled MgSt	2.31	24.91	3.64	3.41	0.80	233.14	34.05	0.50	0.04
1.5% Milled MgSt	2.30	24.91	3.60	3.36	0.78	199.87	33.90	0.49	0.05
2.0% Milled MgSt	2.28	25.15	3.43	3.20	0.75	197.86	33.70	0.38	0.05
0.5% MgSt M125	2.33	24.65	3.84	3.60	0.77	221.37	33.45	0.61	0.05
1.0% MgSt M125	2.33	24.59	3.84	3.61	0.86	237.00	33.90	0.61	0.04
1.5% MgSt M125	2.32	24.55	3.83	3.60	0.87	236.78	34.00	0.61	0.04
2.0% MgSt M125	2.32	24.56	3.80	3.57	0.89	255.68	34.70	0.60	0.04

CHAPTER FIVE

CONCLUSION

Magnesium stearate is the most commonly used tableting excipient after water. However, frequently encountered problems such as batch to batch and/or manufacturer to manufacturer variations of this material can result product failure. Variations in the particle size, shape, moisture content and polymorphic structure of magnesium stearate from one batch to another are the main causes of such problems as it has been shown in this study. Based on the outcome of the work described here, we do recommend the pharmaceutical scientists to do comprehensive physico-chemical characterization of magnesium stearate especially for lubrication sensitive formulations. Also, it is recommended to determine a design space for magnesium stearate by including polymorphic structure, particle size and shape factors.

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