Mathis
Blend Technology

www.MathisInstruments.com

PATHEON

www.Patheon.com

EFFECT OF MAGNESIUM STEARATE ON A PHARMACEUTICAL BLEND USING THERMAL EFFUSIVITY

Stephen Closs[1], Yves Roy[2], Jason Boodram[1], Sanjay Samudre[1], Murray Adams[1], Colin Minchom[1], and Nancy Mathis[2]

[1]Patheon, TRO, Mississauga, Ontario, Canada.
[2]Mathis Instruments, Fredericton, New Brunswick, Canada

Introduction

Powders are blended together to produce pharmaceutical products and the consistency of those powders is critical to the quality of the product. Typically a blender is charged with four or more individual components and they are blended for a fixed period of time and speed. A fixed blending process does not take into account the variability of the components and this can lead to variation in the product. Despite the fact that a lot of effort has been committed to reduce the lot to lot variability of the components, the industry is still facing the problem that slight variations in the chemical or physical properties of these components can potentially have a huge impact on the final product. Variation of the components could be due to several factors, some of these include: environmental temperature, humidity, feedstock grade, and particle size distribution. To add to the complexity, almost all tabletting materials require lubrication to some degree. Magnesium Stearate is the most widely used lubricant. It is typically added to the blend a few minutes (2-5 minutes) prior to the conclusion of the blending period. Even if it is used in low concentrations (0.2%-1.5%), it is often the cause of many issues experienced with solid oral dosage forms.

What are the most frequent problems?

Determining the amount of lubricant to use and the manner in which it is to be incorporated into a batch is critical. If the concentration is too low, or distribution and mixing time is inadequate, the compression of granules may exhibit punch filming; picking; sticking; capping or binding in the die cavity. If the concentration is too high, or distribution and mixing times are too great, other issues are often encountered including: a decrease in tablet hardness; reduced compressibility of the blend; an increase in tablet disintegration times and/or a decrease in the rate of dissolution may occur.

How does Magnesium Stearate work?

Magnesium Stearate is used primarily as a lubricant and to a lesser extent as an anti-adherent and glidant. Magnesium Stearate occurs as “plate-like” crystals stacked together like a deck of cards. As the blending process proceeds, plates continue to shear off the stack and coat adjacent particles or granules. The higher the concentration of Magnesium Stearate that is used, or the longer the blending continues, the more complete this coating of the adjacent particles will become.

For effective lubrication, you do not need and, in fact, you do not want to coat everything too completely with the lubricant or the aforementioned problems are likely to occur.

What causes these problems?

Magnesium Stearate creates a hydrophobic coating on the particles in the blend. This hydrophobic coating interferes with "wetting" thereby leading to an increase in the time required for the tablet to disintegrate and/or the drug to become dissolved. Additionally, a complete coating of the lubricant may affect tablet hardness by interfering with the inter-particle bonding required by formulations when tablets are formed with components that bond by plastic deformation. Tablets formed by brittle fracture are less affected because this mechanism produces clean "un-lubricated" sites where bonding can occur during compression. Similarly, the impact on wet granulation formulations is less pronounced relative to direct compression formulations because clean surfaces are formed during compression as the granules deform with shear to provide bonding sites.

The use of Magnesium Stearate is further complicated by significant batch to batch variation of lubrication properties. Three factors have been determined to be mainly responsible for this variation:

1. **Differences in chemical composition**: Commercial Magnesium Stearate actually consists of a mixture of several different fatty acids.
2. **Differences in specific surface area**: Since the lubricating properties of Magnesium Stearate are related to its ability to coat other particles in a formulation during mixing, samples of a greater surface area should be able to do this more effectively. There is some argument about this however, since it is known that the surface area of Magnesium Stearate continually changes during blending as a result of delamination.
3. **Differences in crystal structure**: Different crystalline structures have different strengths of attraction between adjacent lamella thereby affecting its relative ability to delaminate and subsequently coat the adjacent material.

How can Thermal effusivity measurements help?

A slight variation of particle size distribution, density or chemical composition of a powder blend can significantly change the properties of the product and impact dissolution profiles. This study introduces thermal effusivity as a means to assess the behaviour of Magnesium Stearate in a blend in order to improve the ability to monitor lubrication processes. The technique is non-invasive, quick and easy to use. Furthermore, no method development is needed.

Basic Principles of Thermal Effusivity Measurements of a Powder

$$Effusivity = \sqrt{k\rho c_p}$$

$Where:$

$k = thermal\ conductivity\ (W/m \cdot K)$

$\rho = density\ (kg/m^3)$

$c_p = heat\ capacity\ (J/kg \cdot K)$

Thermal effusivity of samples is measured using a Mathis Instruments BT™ unit. This instrument is an interfacial device which is in direct contact with the sample and is used to measure heat flow. The rate of heat transfer from the instrument's heating element is a function of the thermal effusivity of the sample material. Each material has its own thermal effusivity which is determined by the properties of the sample described in the sidebar.

The thermal effusivity of a powder sample will be driven by the properties of the sample composition and the properties of the inter-particle material (typically air). The thermal effusivity of air is very low with a value of 5 $Ws^{½}/m^2K$ whereas the thermal effusivity of solid pharmaceutical powders typically vary between 150 and 800 $Ws^{½}/m^2K$. For this reason, powder samples with small particles will show higher effusivity values than samples of the same material with comparable density and larger particles. It is hypothesized that Magnesium Stearate increases the thermal conductivity of the coated particles and reduces the inter-particle distances thus increasing the density and thermal effusivity of the lubricated material. Low levels of Magnesium Stearate particle coating result in small increases in thermal effusivity of the blend while higher degrees of particle coating will result in a greater increase in thermal effusivity. Consequently, greater variation in degree of coating throughout the blend will result in a proportionally larger relative standard deviation (RSD) in the associated thermal effusivity measurements, while samples with a low RSD would be indicative of a uniformly lubricated blend.

Thermal Effusivity versus Magnesium Stearate addition to a blend

The ability of the Mathis Instruments BT™ unit to measure the uniformity of tablet granules and lubricated blends was evaluated by testing a granule blend before and after addition of Magnesium Stearate. The initial excipient blend was composed of a fluid bed dried granulation (intra-granular composition: Microcrystalline Cellulose, Sodium Croscarmellose and Povidone K30), and extra-granular components (Sodium Croscarmellose and Talc) at circa 90%, 5%, and 5% (w/w) respectively. A 2 cubic ft V-shell blender was charged with 14.3 kg of the mixture resulting in a load of 70% of total blender working capacity. The initial excipient mixture was blended at 26 rpm for 5 minutes and thermal effusivity measurements were taken at 1 minute intervals. A total 118.4 g of Magnesium Stearate was added to the uniform blend which is equivalent to a formula % of 0.8% (w/w). Effusivity measurements were taken at 4 locations (Top Left – Sensor 1, Top Middle - Sensor 2, Top Right – Sensor 3 and at the bottom of the blender - Sensor 4) after an additional 1, 2, 3 and 4 minutes of blending.

The individual components were measured for thermal effusivity and results are presented in table 1. The effusivitiy measurements of the blend from individual sensors are presented in table 2 and figure 1. These data show a blending pattern typical of an unlubricated powder blend as well as the subsequent influence of Magnesium Stearate on the effusivity measurements as the powder is further mixed with the lubricant. The average effusivity measurement at each interval and the corresponding increase in thermal effusivity of the blend after the addition of Magnesium Stearate is presented. It is evident that the unlubricated blend achieves homogeneity after 5 minutes of mixing as well as the expected immediate decrease in homogeneity after the addition of Magnesium Stearate. These preliminary results indicate that thermal effusivity could potentially be very useful in monitoring the progress of lubrication of a pharmaceutical blend using Magnesium Stearate.

Table 1 – Thermal effusivity values of the individual components

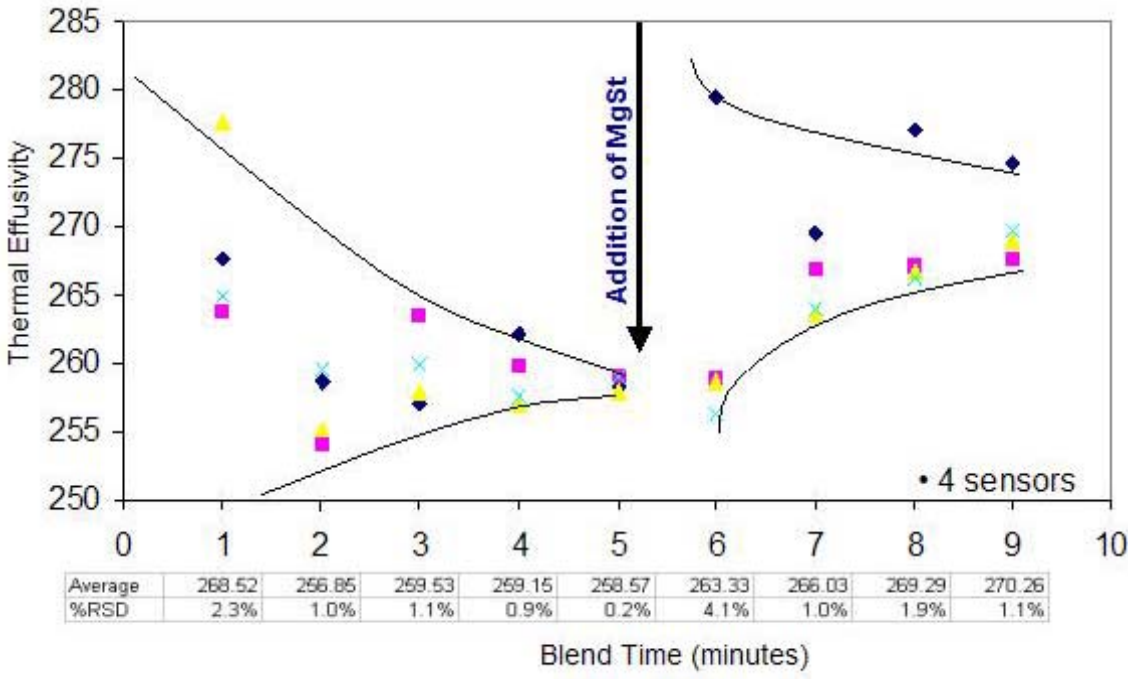
Components	Thermal Effusivity ($Ws^{1/2}/m^2K$)
Crosscarmelose	266.18
Talc	284.81
Dried Granulation	257.50
Mg Stearate	159.81

Table 2 – Thermal effusivity values of a pharmaceutical powder blend at different stage of blending; before and after of the addition of Magnesium Stearate.

	Blend Time (Minutes)								
Sensor	1.0	2.0	3.0	4.0	5.0	Addition of Magnesium Stearate	6.0	7.0	8.0	9.0
1	267.66	258.58	256.94	262.20	258.35		279.54	269.45	277.09	274.71
2	263.89	254.01	263.40	259.74	259.08		258.84	266.94	267.17	267.75
3	277.59	255.18	257.88	257.05	257.83		258.68	263.70	266.71	268.91
4	264.95	259.61	259.88	257.62	259.02		256.24	264.04	266.20	269.65
Average	268.52	256.85	259.53	259.15	258.57		263.33	266.03	269.29	270.26
%RSD	2.3%	1.0%	1.1%	0.9%	0.2%		4.1%	1.0%	1.9%	1.1%

(Data courtesy of Patheon Inc. – for further information on Patheon visit www.Patheon.com)

Figure 1 - Influence of the addition of Magnesium Stearate in a pharmaceutical blend using thermal effusivity: the blend is complete at 5 min at 0.2% RSD. MgSt addition causes an initial level of variation before uniformity again at 9 minutes (1.1% RSD).



Average	268.52	256.85	259.53	259.15	258.57	263.33	266.03	269.29	270.26
%RSD	2.3%	1.0%	1.1%	0.9%	0.2%	4.1%	1.0%	1.9%	1.1%