


Mallinckrodt  COVIDIEN


The Story of Magnesium Stearate as a Powder and a Tablet Lubricant

Presented by

Doug Lugge
Director, API Development
and Engineering
Mallinckrodt

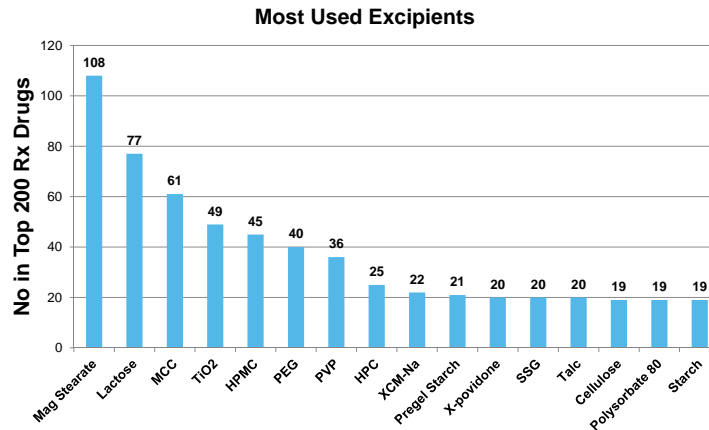
What Are Customers Looking for in Selecting Pharmaceutical Lubricants?

- Meet USP/NF *monograph* definition
- Demonstrate manufacturing *process control*
- Demonstrate measurable *benefits*, e.g.:
 - Powder flowability
 - Blend uniformity
 - Tableting ease
 - Tablet quality
- Provide product quality attributes for regulatory filing needs (*QbD*)
- Provide *application data* and *technical support*
- Made with suitable *vegetable source* materials

Mallinckrodt  COVIDIEN

Most Used Excipients

- Magnesium Stearate (MgSt) is used in >2,500 pharmaceutical products
- The most used excipient in top 200 Rx drugs



Mallinckrodt



Mallinckrodt's Pharmaceutical Lubricants

Products

- Magnesium Stearate Monohydrate
- Magnesium Stearate Dihydrate
- Stear-O-Wet™ (SOW)

Unique Attributes

- Purity
- Consistency
- Functionality

Mallinckrodt



Mallinckrodt's Magnesium Stearate

- Monohydrate MgSt Codes 2257, 5712 and 1726 are vegetable source lubricants produced by a precipitation process with tight control over particle physical properties. Certified to meet NF/EP/JP and FCC specifications.
- Dihydrate MgSt Code 1729 is produced through a proprietary process (U.S. Pat 7,385,068) and will meet NF/EP/JP specifications. The dihydrate crystalline structure is thought to contribute to better lubricity during tableting.
- Stear-O-Wet™ Code 8277 is a finely divided, uniform, spray-dried homogeneous mixture of Magnesium Stearate (NF/EP/JP) and Sodium Lauryl Sulfate (SLS) (NF/EP). This SLS-treated lubricant exhibits improved wetting characteristics, facilitating disintegration and dissolution of drug substances in tablets.

Mallinckrodt



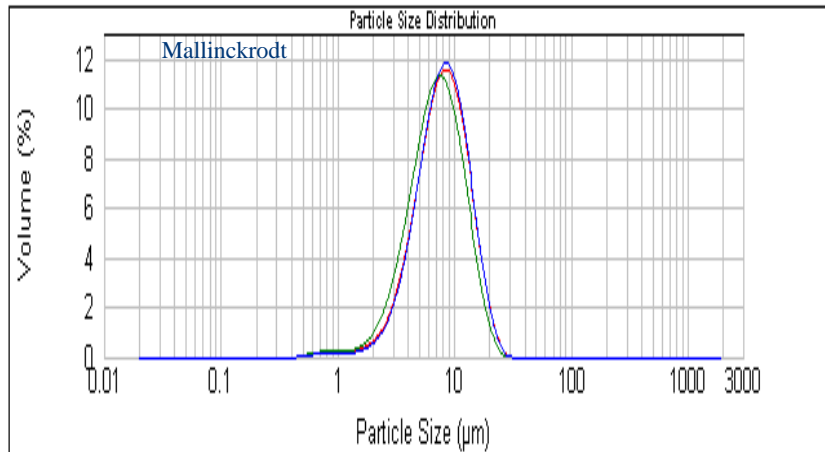
Mallinckrodt's Magnesium Stearate Monohydrate

- High purity
 - Well-defined crystalline state
- Consistent physical properties
 - Particle size distribution
 - Surface area
 - Morphology
- Minimum lot-to-lot variability
- Consistent performance

Mallinckrodt



Typical Monohydrate Particle Size Distribution



Mallinckrodt



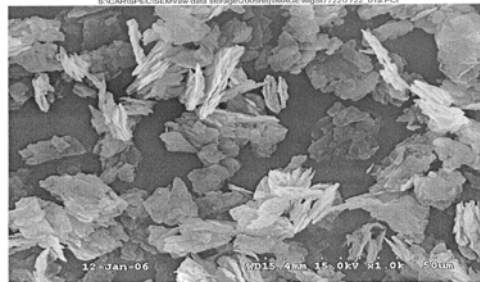
Typical Mallinckrodt Monohydrate Physical Properties

Code	SSA, m ² /g	Particle Size Distribution		Density, g/cc	
		d50, µm	d90, µm	Apparent	Tapped
2257	6.0-8.0	10.6-13.6	20-24	0.11-0.13	0.21-0.31
5712	6.5-9.0	8.6-11.0	17-24	0.11-0.13	0.21-0.29
1726	6.1-6.7	21-24	37-41	0.12-0.14	0.27-0.34

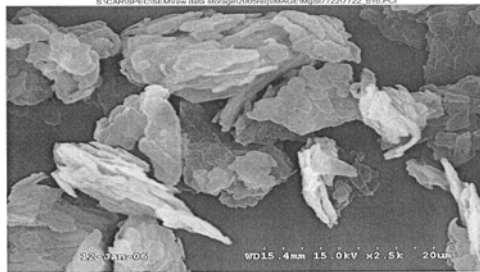
Mallinckrodt



SEM of Mallinckrodt MgSt Monohydrate



1000x



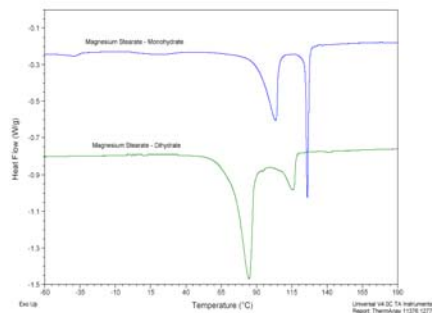
2500 x

Mallinckrodt

Mg Stearate 2207 H07978 Monohydrate

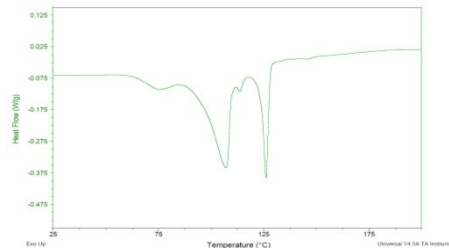


Thermal Analysis (DSC)



Common on the market are mixtures of variable ratios of mono- and dihydrate and other crystalline forms.

Mallinckrodt highly pure magnesium stearate monohydrate and dihydrate materials



Mallinckrodt



Major Customers' Experiences and University Research

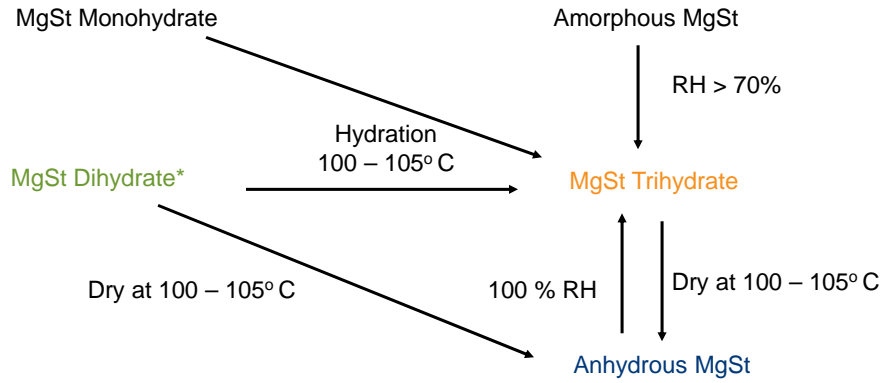
- Inconsistent hydrate forms of MgSt were linked to variable sticking properties of the tablets.
- Specifying the hydration state should be part of MgSt specifications.
- Capping issues were observed in making tablets when MgSt contained a mixture of hydration states. Tablets with no sticking issues used monohydrate and MgSt was better distributed in the tablet matrix.
- Sticking blends in roller compaction was linked to MgSt hydration state and vendor sources. Mallinckrodt MgSt monohydrate had no sticking issues.
- A study at Long Island University showed that pure MgSt monohydrate or dihydrate exhibited lower lubricity index and thus lower tendency to over-lubrication than a mixture of hydration forms.

Mallinckrodt



Magnesium Stearate Dihydrate

MgSt Dihydrate is a Stable Pseudopolymorph



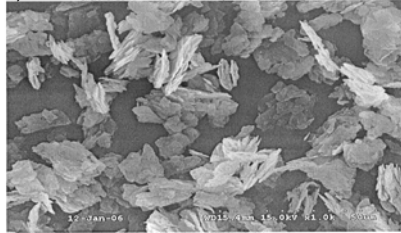
• The dihydrate is not an intermediate in the formation of trihydrate from anhydrous form. [V. Swaminathan and D. Kilsig AAPS PharmSciTech 2001; 2 (4) article 28.]

Mallinckrodt

COVIDIEN

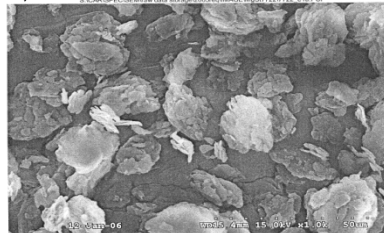
SEM of Mallinckrodt MgSt

1,000x



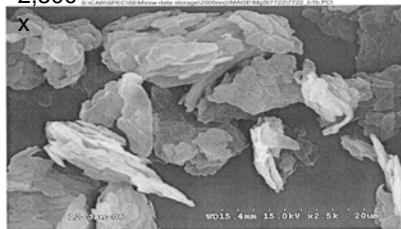
MgSt monohydrate

1,000x



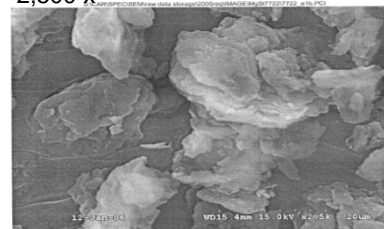
MgSt dihydrate

2,500 x



Mallinckrodt

2,500 x



COVIDIEN

Attributes of MgSt Dihydrate

- Stable crystalline form
- High purity
- Made from vegetable source of fatty acids and under validated well-controlled GMP process conditions
- Meets NF/EP/JP definition for magnesium stearate
- Beneficial functional attributes

Mallinckrodt



MgSt Dihydrate Functional Attributes

- More effective in lowering cohesive energy of a powder blend
- Disperses faster and more evenly into the powder bed during the blending step
- Less sensitive to blending time
- Induces less powder densification at the lubrication step
- Compression force more evenly distributed through the powder
- Lower ejection and take-off forces during the process for making tablets (better lubricity)
- Reduces sticking tendency when making smaller tablets with constrained geometry

Mallinckrodt



MgSt Dihydrate Offers New Possibilities

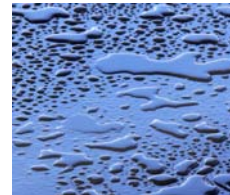
- Improved powder flow
- Consistent blending and blend uniformity
- Lower ejection force in tableting
- Less sticking at the press
- Fewer capping problems
- Reduced tooling wear
- Faster production rates

Mallinckrodt



Stear-O-Wet™

A co-processed material of MgSt and sodium lauryl sulfate (94/6)



Mallinckrodt



Stear-O-Wet™ – A Wettable Magnesium Stearate Lubricant

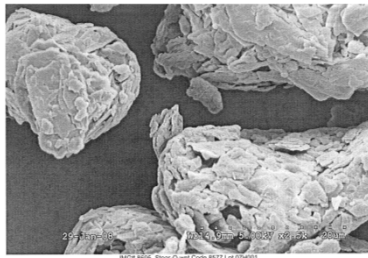
Stear-O-Wet™ is a finely divided, uniform, spray-dried homogeneous mixture of Magnesium Stearate (MgSt) and Sodium Lauryl Sulfate (SLS) manufactured by Mallinckrodt.

Because the surfaces of MgSt particles are modified with SLS, Stear-O-Wet™ exhibits enhanced wettability.

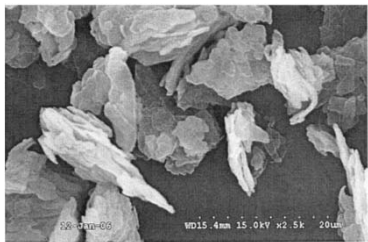
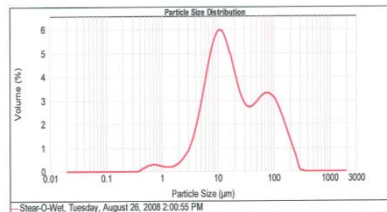
Mallinckrodt



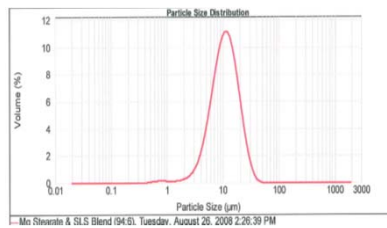
SEM and Particle Size/Size Distribution of Lubricants



Stear-O-Wet™



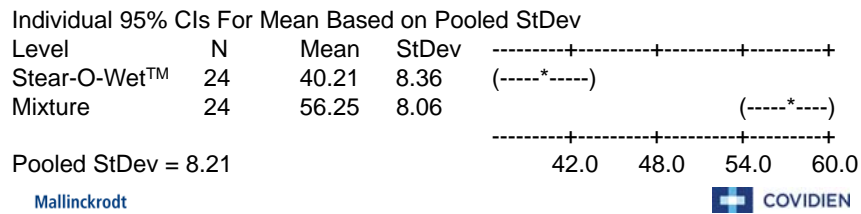
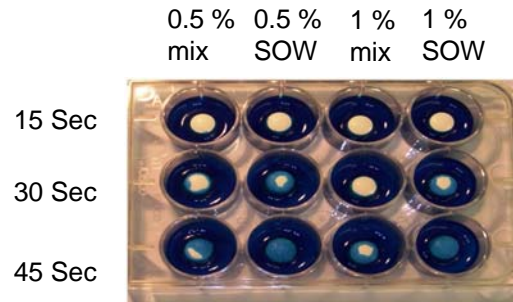
Mixture of MgSt/SLS (94/6)



Mallinckrodt



Stear-O-Wet™ provides better wetting than a mixture of MgSt and SLS



Comparison of Stear-O-Wet™ with MgSt/SLS Mixture

Comparison of Powder Flow and Compression Characteristics of MCC/Lactose (1:1)/APAP (5 %) at lubricant level of 0.5, 1.0 and 2.0 % and blending times of 2, 5, and 10 minutes.

	Stear-O-Wet®	Mixture of MgSt/SLS (94/6)
Powder densification	Lower	Higher
Powder cohesiveness	Lower	Higher
Lubricity	Higher	Lower
Powder compressibility at low pressure	Higher	Lower
Compactability	Higher	Lower
Tablet Wettability	Higher	Lower
Dissolution	Not distinguishable	Not distinguishable

Conclusion

- Stear-O-Wet™ consists of loosely agglomerated, spray-dried powder particles. The presence of SLS provides enhanced wettability, but the lubricity of MgSt remains when fresh MgSt surfaces are generated during the blending.
- Results from basic flow energy, wall friction angle, compression/ejection force measurement suggest Stear-O-Wet™ exhibits better lubricity than a mixture of MgSt/SLS. The wettable nature of Stear-O-Wet™ can overcome the hydrophobic effect of MgSt when used as a lubricant.

Mallinckrodt



Solid State Characterization and Tableting Performance of Magnesium Stearate Monohydrate, Dihydrate and Stear-O-Wet™

Jun Yang, Dan Ramlose, Gary Nichols and Stephen H. Wu

Mallinckrodt, the Pharmaceuticals Business of Covidien
385 Marshall Avenue, Webster Groves, MO 63119

Objective

- MgSt is commonly used as lubricant for solid dosage forms. The lubrication efficiency of magnesium stearate is closely related to its particle size, crystal structure, specific area and chemical composition.
- In this study, five Mallinckrodt pharmaceutical grade magnesium stearates were characterized and evaluated for their performance as tablet lubricants.

MgSt	Manufacturer	Product Code	Lot #
Mono-hydrate	Covidien	2257	0812000908
Mono-hydrate	Covidien	5712	P09245
Di-hydrate	Covidien	1729	J04688
Stear-O-Wet™ M	Covidien	8108	8108806E029
Stear-O-Wet™ D	Covidien	N/A	Drum#2, 170°F

Mallinckrodt



Solid State Characterization

- **Particle Size Analysis** – Malvern Mastersizer 2000 – Hydro 2000S Module
 - A 200-250mg portion of each sample was added to 40mL of dispersant (Isopropyl Alcohol) in a 50mL beaker.
 - The slurry was then stirred and sonicated before testing.
- **Powder X-ray Diffraction**
 - Used a Siemens D500 X-ray Diffractometer.
 - Each sample was crushed with a spatula and placed on a quartz, zero-background holder.
 - The following parameters were utilized: scan range – 2.0 to 40.0 deg 2-theta; step size – 0.02 deg 2-theta; scan time per step – 1.0 seconds; radiation source – copper K α (1.5406 Å); X-ray tube power – 40kV/30mA.

Mallinckrodt



Solid State Characterization

➤ Thermal Gravimetric Analysis

- Used TA Instruments Q500 TGA.
- A sample was weighed into an aluminum pan.
- The sample was heated from room temperature to 225° C at a rate of 5° C per minute, with a total nitrogen flow rate of 50mL/min.

➤ Differential Scanning Calorimeter

- Used TA Instruments Q200 DSC.
- Weighed a sample into an aluminum hermetic pan, and sealed with a lid containing a single pinhole.
- The sample was equilibrated at 15° C and then heated to 220° C at 2° C/min.

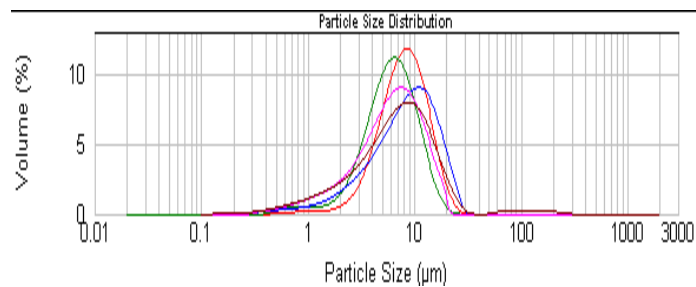
➤ Scanning Electron Microscope

- Used a Hitachi S3500N scanning electron microscope to obtain SEM images.
- Evenly distributed a powder sample onto a carbon adhesive tab on a Al SEM stub.
- Each specimen was coated with Au/Pd to reduce charging.

Mallinckrodt



Particle Size Distribution of MgSt



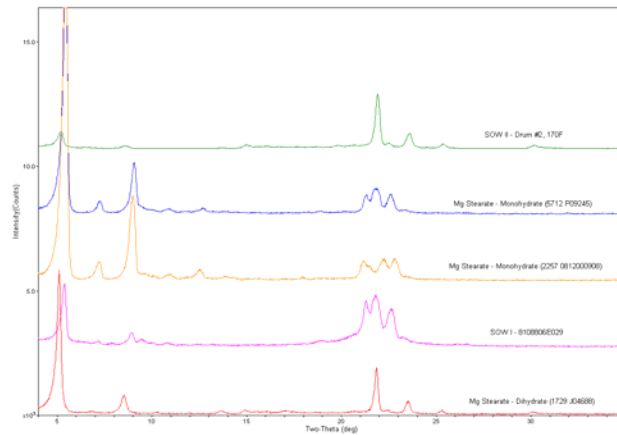
Green – Mg Stearate – Monohydrate (5712 P09245)
 Orange – Mg Stearate – Monohydrate (2257 0812000908)
 Blue – Mg Stearate – Dihydrate (1729 J04688)
 Pink – SOW M (8108806E029)
 Maroon – SOW DI (Drum #2, 170F)

The particle size of precipitated MgSt is narrowly distributed due to its tight process control. The size differences among different grades were finely tuned to satisfy the specific requirements of lubrication. Stear-O-Wet™ will de-agglomerate to smaller particles with vigorous stirring and sonication.

Mallinckrodt



Powder X-ray Diffraction

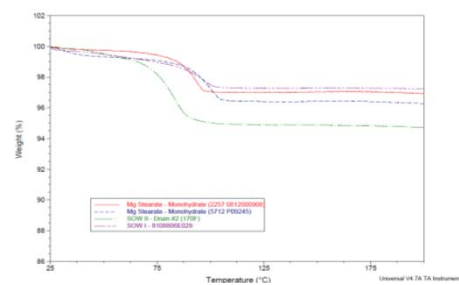


Predominant monohydrate crystalline structures were observed with MgSt 2257, 5712 and SOW-M, while as dihydrate crystalline structure were observed for MgSt 1729 and SOW-D.

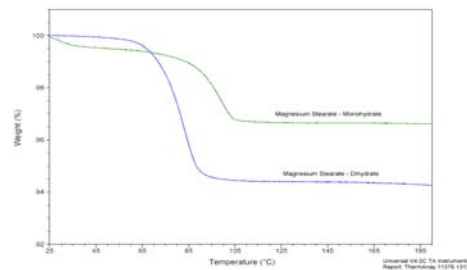
Mallinckrodt

COVIDIEN

Thermal Gravimetric Analysis



TGA traces of monohydrate MgSt 2257, 5712 and SOW-M exhibit a small loss of water of 0.2 - 0.5% below 50° C and followed by a 2.8 to 2.9% loss of water in 80 - 100° C which is consistent with the theoretical loss of water for monohydrate crystalline form (2.95%).

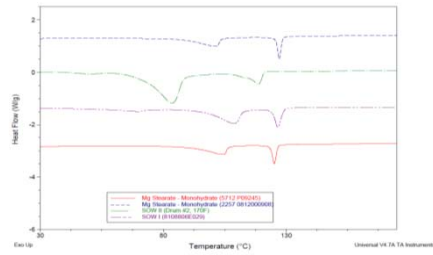


TGA traces of dihydrate MgSt 1729 and SOW-D show a weight loss of 5.6-5.7% from 70-90°C which is close to the theoretical loss of water from dihydrate crystalline form. (5.74 wt.%).

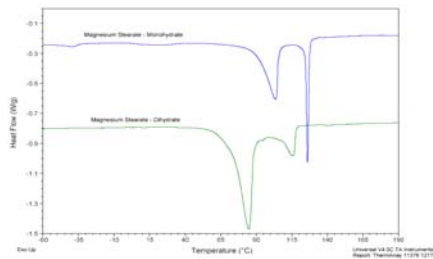
Mallinckrodt

COVIDIEN

Differential Scanning Calorimeter



DSC curves of monohydrate MgSt 2257, 5712 and SOW-M reveal two endothermic transitions at ~100-110° C and 126° C. The first peak is related to the loss of residual water (as indicated by TGA results). The 2nd peak is related to melting of samples.

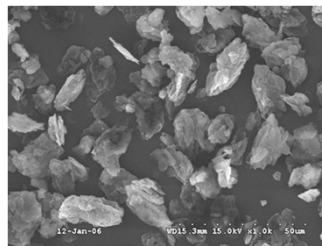


DSC traces of dihydrate MgSt 1729 and SOW-D shown two endothermic transitions at 85-100° C and 116° C respectively. The 1st peak is associated to loss of water (as indicated by TGA) and the 2nd relates to its melting temperature.

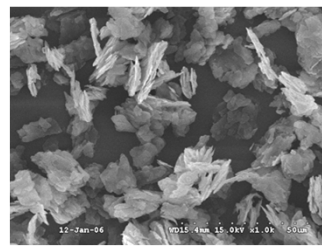
Mallinckrodt

COVIDIEN

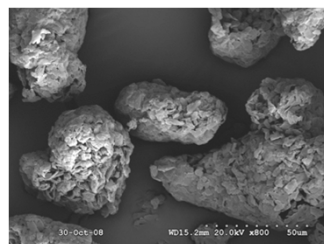
SEM of MgSt



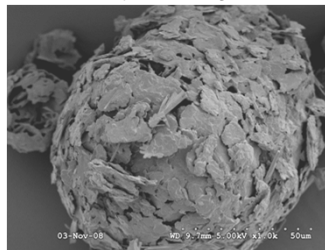
Monohydrate MgSt



Dihydrate MgSt



SOW-M



SOW-D

Mallinckrodt

COVIDIEN

Summary for Solid State Characterizations

- The PSD results show the precipitated magnesium stearate in finely divided particles with narrow size distribution.
- SEM images indicate monohydrate and dihydrate MgSt exhibit plate-like morphology. Spray-dried Stear-O-Wet™ were larger agglomerates (~50 µm) based on their SEM images.
- The PXRD results illustrate two distinct crystalline structures for magnesium stearate.
- TGA traces indicate that MgSt 2257, 5712 and Stear-O-Wet™ M are predominantly monohydrate crystalline structures while MgSt 1729 and Stear-O-Wet™ D contain predominately dihydrate forms.
- The DSC curves indicate two endothermic transitions for monohydrate MgSt at ~100-110° C and 126° C, while as dihydrate MgSt, the respective thermal transitions are at ~85-100° C and 116° C.

Mallinckrodt



Tablet Formulations

Sample No.	MgSt Grade	MgSt (g)	Compap 0090 (g)	Blending Time
1	1729	2.5	497.5	5
2	1729	10.0	490.0	10
3	2257	2.5	497.5	5
4	2257	10.0	490.0	10
5	5712	2.5	497.5	5
6	5712	10.0	490.0	10
7	SOW-M	2.5	497.5	5
8	SOW-M	10.0	490.0	10
9	SOW-D	2.5	497.5	5
10	SOW-D	10.0	490.0	10

Mallinckrodt



Tableting Parameters

➤ Formulation

- Used Compap 0090 (Lot# 009007E094) to evaluate the tableting performance of MgSt. Compap 0090 is spray dried APAP without internal lubricant.
- PK V-blender is utilized to blend all experimental blends.

➤ Equipment

- SMI single station tablet press (minipress) equipped with 10mm flat surface round die.

Mallinckrodt



Tableting Parameters

➤ Tableting Parameters

- Target weight: ~350mg
- Tablet speed: 55 rpm
- Compression force: 7.0, 14.0, 21.0, 28.0 and 35.0 kN

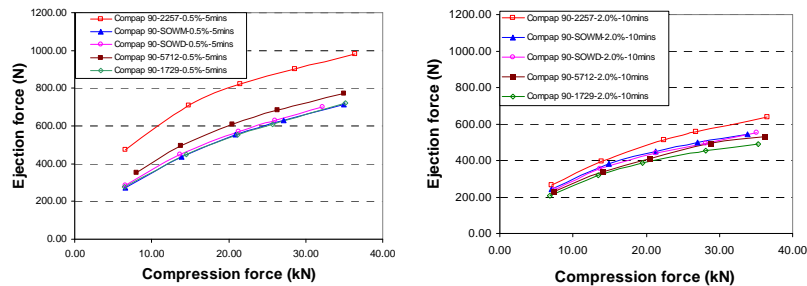
➤ Characterization of tablets

- Compaction – ejection profile
- Tablet weight, thickness, hardness, friability
- Disintegration time
- Dissolution profile

Mallinckrodt



Compression and Ejection Profiles for Tablet Formulations (1 – 10)

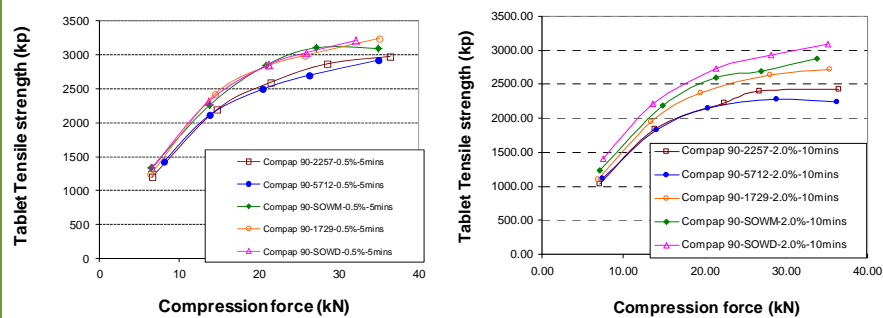


Tablets with dihydrate magnesium stearate as lubricant are shown to have the lowest ejection forces. The results suggest that dihydrate magnesium stearate exhibit better lubricity and can be used to minimize sticking issues during tableting.

Mallinckrodt



Tablet Tensile Strength

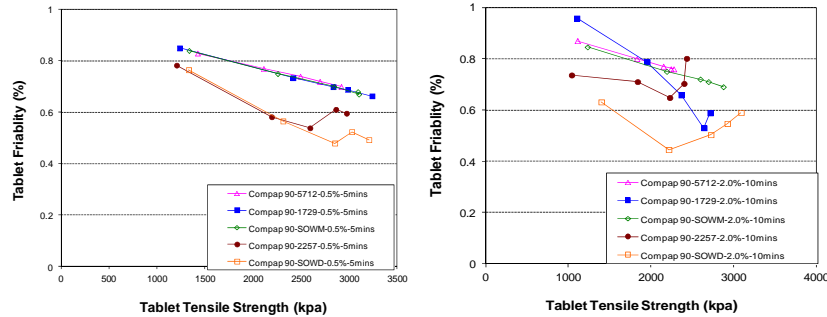


Tablets lubricated with SOWs exhibit higher tensile strengths than other formulations. Tablets with MgSt 5712 as lubricant are the lowest in tensile strength due to its higher surface area and hydrophobic nature.

Mallinckrodt



Tablet Friability

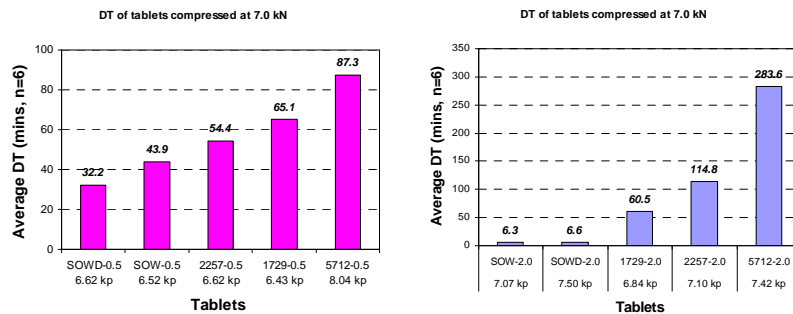


In general, tablets lubricated with SOWs have lower friability than others even at the same level of tablet tensile strength. The results suggest that hydrophilic lubricant is better for reducing the friability of APAP tablets.

Mallinckrodt

COVIDIEN

Tablet Disintegration Time

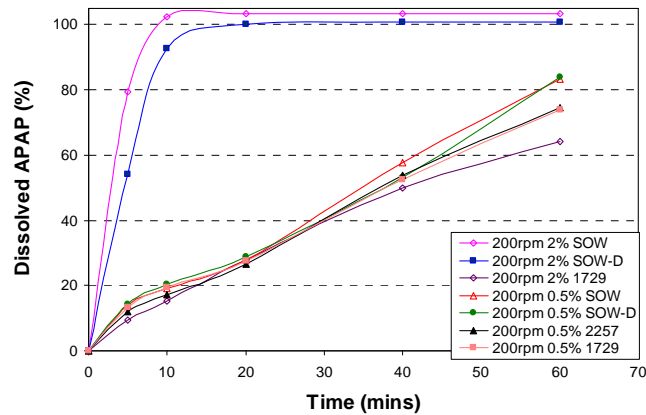


Tablets lubricated with SOWs result in much shorter disintegration time than others. Increasing the lubricant level of SOWs from 0.5 to 2.0%, a faster disintegration of the Compap 0090 tablets was observed. Tablets with MgSt 5712 as lubricant are the slowest in disintegration.

Mallinckrodt

COVIDIEN

Tablet Dissolution Profiles



Similar to disintegration, tablets lubricated with 2.0% of SOWs also shown quick release profiles in water.

Mallinckrodt

COVIDIEN

Summary for Tableting Performance

- Dihydrate magnesium stearate is shown to be the most effective lubricant for reducing ejection force in tableting.
- Small size magnesium stearate 5712 appears to be more efficient in transferring the compression force.
- Tablets lubricated with Stear-O-Wet™ M and Stear-O-Wet™ D have higher tablet strength than other magnesium stearates.
- Tablet friability seems to be lower when the lubricant is more hydrophilic.
- Stear-O-Wet™ M and Stear-O-Wet™ D are shown to have faster disintegration and release profiles than regular magnesium stearates.

Mallinckrodt

COVIDIEN

Key Message

- Using **consistent** and **high quality** lubricant in making tablets is critically important to tablet quality.
- Lubricant material properties – **particle size/size distribution, specific surface area and crystalline state** – are critical quality parameters influencing powder flow and compaction, and QbD consideration.
- The **lubricity** of MgSt depends on its **crystalline states**.
- Mg stearate **dihydrate is a stable crystalline state**, and pure MgSt dihydrate can be made consistently by Mallinckrodt.
- MgSt dihydrate has **better lubricity, disperses quickly** into the powder bed, and exhibits other value-added functionalities.
- **Stear-O-Wet™ is a wettable co-processed lubricant** containing MgSt monohydrate and sodium lauryl sulfate (94/6 by wt.). It is particularly suitable for overcoming disintegration and dissolution issues caused by tablet lubricants.

Mallinckrodt

