What Are Customers Looking for in Selecting Pharmaceutical Lubricants?

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

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

![Most Used Excipients Diagram]

Mallinckrodt’s Pharmaceutical Lubricants

- Products
  - Magnesium Stearate Monohydrate
  - Magnesium Stearate Dihydrate (not currently available)
  - Stear-O-Wet™ (SOW)
- Unique Attributes
  - Purity
  - Consistency
  - Functionality
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 can be 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. Not Commercially Available.

- Stear-O-Wet Code 8577 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’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
### Typical Monohydrate Particle Size Distribution

![Typical Monohydrate Particle Size Distribution](image)

### Typical Mallinckrodt Monohydrate Physical Properties

<table>
<thead>
<tr>
<th>Code</th>
<th>SSA, m²/gm</th>
<th>d50, um</th>
<th>d90, um</th>
<th>Apparent</th>
<th>Tapped</th>
</tr>
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<tbody>
<tr>
<td>2257</td>
<td>6.0 – 8.0</td>
<td>10.6 – 13.6</td>
<td>20 – 24</td>
<td>0.11 – 0.13</td>
<td>0.21 – 0.31</td>
</tr>
<tr>
<td>5712</td>
<td>6.5 – 9.0</td>
<td>8.6 – 11.0</td>
<td>17 – 24</td>
<td>0.11 – 0.13</td>
<td>0.21 – 0.29</td>
</tr>
<tr>
<td>1726</td>
<td>6.1 – 6.7</td>
<td>21 – 24</td>
<td>37 – 41</td>
<td>0.12 – 0.14</td>
<td>0.27 – 0.34</td>
</tr>
</tbody>
</table>
Magnesium Stearate Monohydrate and Dihydrate are Stable Pseudopolymorphs

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

Mallinckrodt highly pure magnesium stearate monohydrate and dihydrate materials

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

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.
Stear-O-Wet

A Stearate that will wet

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

SEM and Particle Size/Size Distribution of Lubricants

Stear-O-Wet

Mixture of MgSt/SLS (94/6)
Stear-O-Wet provides better wetting than a mixture of MgSt and SLS

<table>
<thead>
<tr>
<th>Level</th>
<th>N</th>
<th>Mean</th>
<th>StDev</th>
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</thead>
<tbody>
<tr>
<td>Stear-O-Wet</td>
<td>24</td>
<td>40.21</td>
<td>8.36</td>
</tr>
<tr>
<td>Mixture</td>
<td>24</td>
<td>56.25</td>
<td>8.06</td>
</tr>
</tbody>
</table>

Pooled StDev = 8.21 42.0 48.0 54.0 60.0

Individual 95% CIs For Mean Based on Pooled StDev
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.

<table>
<thead>
<tr>
<th></th>
<th>Stear-O-Wet</th>
<th>Mixture of MgSt/SLS (94/6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder Densification</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Powder Cohesiveness</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Lubricity</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Powder Compressibility at Low Pressure</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Compatibility</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Total Wettability</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Dissolution</td>
<td>Not Distinguishable</td>
<td>Not Distinguishable</td>
</tr>
</tbody>
</table>

Conclusion

► Stear-O-Wet consists of 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.
Stear-O-Wet Tableting Studies

Magnesium Stearate vs. Stear-O-Wet Study

- Acetaminophen blend, 500 mg tablets
- Lubricants:
  - Magnesium Stearate 0.25% and 1.0%
  - Stear-O-Wet 0.25% and 1.0%
  - Standard and 3x blend times
- Riva Mini-press
- Target 15 KN compression force
- Standard Dissolution Testing
Dissolution w/ Low Levels of Lubricant

Mg Stearate vs Stear-O-Wet (0.25%)
Typical Blend Times

Dissolution w/ Higher Levels of Lubricant

Mg Stearate vs Stear-O-Wet (1.0%)
Typical Blend Times
Level of Lubricant Effect on Dissolution

**Mg Stearate vs Stear-O-Wet (0.25% vs 1.0%) Typical Blend Times**

Results With Normal Blend Times

- At 1% lubrication level Stear-O-Wet dissolution is twice as fast in the first 11 minutes than Magnesium Stearate.
- 1% Stear-O-Wet had comparable dissolution times to 0.25% Magnesium Stearate, all else being identical.
- 0.25% Stear-O-Wet improved early dissolution compared to 0.25% Magnesium Stearate.
- Stear-O-Wet can help under lubricated formulations with less impact on dissolution time than Magnesium Stearate.
Dissolution w/ Low Level Lubricant, 3x Blend Time

Mg Stearate vs Stear-O-Wet (0.25%)
Extended Blend Times (3x)

![Graph showing dissolution with low level lubricant and extended blend times.]

Dissolution w/ Higher Lubrication, 3x Blend Time

Mg Stearate vs Stear-O-Wet (1.0%)
Extended Blend Times (3x)

![Graph showing dissolution with higher lubrication and extended blend times.]

Mallinckrodt Pharmaceuticals
Results with Extended Blend Times

► At 1% Stear-O-Wet had significantly faster dissolution compared to Magnesium Stearate.
► At 0.25% Stear-O-Wet had similar dissolution to Magnesium Stearate.
► Dissolution with SOW is less impacted by blend time.
► Stear-O-Wet can help under lubricated formulations with less impact on dissolution than Magnesium Stearate since it is more readily wetted.

Simulated Gastric Fluid Scenario

Mg Stearate vs Stear-O-Wet Extended Blend Time
(at 1%) in Simulated Gastric Fluid
Simulated Gastric Fluid Scenario Results

- Stear-O-Wet facilitated a much faster initial dissolution due to wettability of the tablet.
- High levels of Magnesium Stearate can slow dissolution even in Simulated Gastric Fluid case.

Some Tableting Definitions

- Applied Pressure: the pressure the top punch "applies" to make a tablet
- Transmitted Pressure: the pressure measured by the bottom punch
- Transmitted Pressure/Applied Pressure = a measure of Lubricity or "T/A"
- The closer the T/A value is to one, the better the Lubricity of the formulation.
- Ejection force: the force as measured to eject the tablet out of the die.
Modest Differences for Ejection Forces

Lubricant vs. Ejection Force

Stear-O-Wet Is a Better Lubricant

Lubricant vs. T/A Ratio
Tablet Press Measurement Results

- Tablet ejection force is modestly higher for Stear-O-Wet at 0.25% and about equal at 1.0% content.
- Blend time has little impact on Stear-O-Wet for press ejection forces.
- T/A Ratio for Stear-O-Wet indicates it is a better lubricant regardless of amount of lubricant added or blend time.

Tablet Wetting Study

- 0.25% Magnesium Stearate vs 0.25% Stear-O-Wet
- Blend Compap L and lubricant and tablet at 15 KN
- 35 microliters of 0.28% methylene blue indicator in water via pipette
- Watch for:
  - Wicking of water across tablet
  - Absorption of water into the tablet
Watch Carefully!

Stear-O-Wet vs. Magnesium Stearate in Water...

- Half a vial of deionized water
- Stear-O-Wet added to one vial
- Magnesium Stearate added to second vial
- Vials inverted twice and gently shaken.
Lubricant in Water Results

- Stear-O-Wet wets quickly and completely – slurry is created!!
- Magnesium Stearate for most part stays on top of the water – very little is wetted
Lubricant in Water Results

- 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 attributes influencing powder flow and compaction, and QbD consideration.

- The lubricity of Mg-stearate depends on its crystalline states and hydration matters.

- Mg stearate monohydrate is a stable crystalline state, and pure MgSt monohydrate is made consistently by Mallinckrodt.

- 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.