“Optimization of Feeding and Conveying Technologies for Difficult Flowing Pharmaceutical Powders”

Coperion K-Tron
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Food and Pharma
Process Equipment Group

- Feeding, pneumatic conveying and material handling systems and components
- Extrusion, compounding and pelletizing systems and components
Coperion K-Tron’s Patented Weigh System

- Improved Load cell Technology
- **Patented Digital Load cell** Design featuring:
  - Vibrating wire technology
  - Applied load is transmitted to the wire causing a change in its resonant frequency
- Fully digital processing of the weight signal
- 4,000,000 to 1 Resolution
- Higher Sampling Rate (140x’s per sec)
- Temperature Compensation
- Vibration Compensation due to short measuring distance of vibrating wire technology
Typical Dry Powder Feeder Applications in Pharmaceutical Tabletting Operations

**Batch Applications**
- Batch Dispensing
  - LIW and GIW
- Milling and Micronization (Batch)
- Tablet Press Lubrication

**Continuous Operations**
- Wet Granulation
- Hot Melt Extrusion
- Micronization/Milling (semi-batch)
- Continuous Coating
- **Continuous Direct Compression**
- **Continuous Dry Granulation**
Why are Feeders Necessary in a Continuous Process?

- To set the precise throughput to a downstream process
- Continuous processes such as mixing or extrusion become “slaves” to the feeders
- Provide an accurate blend of bulk solids and liquids for a formulation
- Eliminate pre-mixing of solids/segregation
- Using individual feeders for each component of the blend
- Feeders are used to set the flowrates of both liquids and bulk solids.
- Feeding performance (evaluated by setpoint (MF) deviation) can largely affect the performance of subsequent unit operations
Continuous Mixing Skid - FAT
What are key issues to consider for feeder accuracy improvement on short term basis in a continuous process?

- Feeder **type and configuration chosen** in accordance with material characteristics
  - Single screw versus Twin screw
  - Screw configuration
- Hopper configurations
  - Agitation versus vibration
- Controls and Weight Measurement
  - Load Cell Resolution
  - Reaction Time of Controller
  - Signal Clarity
    - Goal of filtering is to eliminate external true weight signal
- Method of refill
- Environmental influences and upstream/downstream connections
- Flexible Connections
- Proper Venting
- Drafts/Air currents
- Excessive Plant Vibration
Material Characteristics which affect Feeder Selection and Performance

- Bulk Density - Loose and Packed /Tapped
- Particle Size- Shape - Aspect Ratio
- Moisture and Temperature Sensitivity
- Angle of Repose
- Kinematic Angle of Surface Friction
- Gas Permeability
- Particle friability
- Compressibility/Springback
Material Characteristics which contribute to poor flowability

- Long AR
- Compressibility and Cohesiveness
- Wide PS & PSD
Typical Feeders Used in Pharma Processing

• Rotary Valves
• Vibratory Tray
  ✓ Volumetric
  ✓ Gravimetric/Loss in Weight
• Screw Types – Twin and Single Screw
  ✓ Volumetric
  ✓ Gravimetric/Loss in Weight
• Pneumatic Vacuum Receivers
Vibratory Feeders

• **Operation:**
  - Material is conveyed by vibration
  - Can be volumetric or gravimetric

• **Advantages:**
  - Simple design – good for free flowing materials
  - Can also be good for difficult flow materials - high aspect ratio
  - Gentle on products where attrition may be an issue

• **Disadvantages:**
  - Not ideal for packing/cohesive materials
  - No good control on product delivery, ie LUMPS IN TRAY
  - Limited turndown capabilities
  - May be only option for some API’s which can not be fed in screw feeders
Most common feeders for pharmaceutical processes: **Screw Feeders**

- **Operation:**
  - Material conveyed by either single or double screw
  - Can be volumetric or gravimetric

- **Advantages:**
  - Twin screws can be good for cohesive materials
  - Accurate delivery of product

- **Disadvantages:**
  - Design options are critical with regards to overall cleanability
  - Evaluate LIW versus volumetric for continuous operation
Single Screw vs. Twin Screw

• Single Screw ideal for free flowing materials, high volumes
• Twin Screw **ideal for more cohesive materials**
• Twin screws have a “self wiping” effect
• Twin screws can also **provide more even flow** to the process
Single Screw Feeder Running Lactose
Twin Screw Feeder Running Pigment
Volumetric vs. Gravimetric Screw Feeder Principles

Rate is done by speed adjustment of the feed screws

LIW controller adjusts feeder speed to produce a rate of weight loss equal to the desired feed rate setpoint
Loss in Weight Refill – Principle of Operation
Important Refill Considerations

- Choosing the Proper Refill Device
  - Reaction Time of the Device
  - Device must be LEAK FREE
  - Material characteristics
- Choosing the Proper Hopper Size for Refill
- Choosing the Refill Times
- Defining importance of accuracy during refill, particularly when low rate feeding
Optimization of Feeder Configurations

• Improper Selection of components can affect resultant RSD and flow rates
• Lower Rates are highly influenced by component selection
  In Microfeeding EVERYTHING matters
• Addition of screen at outlet of feeder helps with back pressure and resultant screw fill for some products
• For poor flowing products – screw fill is affected
• Requires Proper screw type configuration
• FDA Coatings available
• Sometimes blend of flow aids will help
Low rate lubricant or API addition to the continuous mixing, extrusion or granulation process

20 gm/hr – 2 kg/hr

New Coperion K-Tron
MT12/MT16/S12/S16 Microfeeder
Tablet Press Lubrication
Options in Lubrication: Magnesium Stearate Addition

- Addition during mixing process
- Can cause formulation to produce softer tablet
- Stearate addition to formulation may affect dissolution e.g. with effervescents - repels water
- Requires high proportion of the lubricating agent
- Direct addition to tablet press
- Press tooling is lubricated
- Formulation is unaffected
- Smaller amount of lubricant needed
Attachment of venturi line to press

- Each tablet press design is different so connection designed by press manufacturer
- The connections usually include direct connect of feeder line and a vacuum hose for excess dust
Gravimetric Design – KT20
Low Rate Lubricant Addition – MT12

50 g/hr to 2 kg/hr
Operational Benefits of Press Lubrication

- Constant feed rate (twin screw feeder)
- Volumetric or gravimetric
- Typical feed rates of Magnesium Stearate 0.2 – 2 kg/hour with standard twin screw feeder
- MT12 Microfeeder allows for rates as low as 50g/hr
- Uniform powdering of the tablet tools
- No sticking problems
- Tablet press tooling is coated
- Prevents adhesion of the powder to the surface of the punches and subsequent tablet ejection damage
- Automated, continuous process
- Lower investment and operation costs
- Less stearate consumption – as high as 97% reduction
CONSISTENCY OF MAGNESIUM STEARATE CONTENT USING EXTERNAL LUBRICATION IN TABLET COMPRESSION

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OBJECTIVE
To characterize the consistency and uniformity of magnesium stearate application to tablets compressed using external lubrication technology

INTRODUCTION
• Lubricant is typically blended with other components in order to prevent tablet sticking and sticking, and to ease tablet ejection from the die
• New technology has been developed to spray lubricant typically magnesium stearate directly on the punch and die wall surfaces
• External lubrication technology provides many potential benefits to the manufacture of tablet dosage forms – both traditional immediate release and the more sophisticated controlled release platforms
• System requires further characterization to determine consistency of lubricant content

METHODS
Materials
• Magnesium stearate
• Placebo blend with 1% internal magnesium stearate
• Placebo blend with no internal magnesium stearate
• Active blend with no internal magnesium stearate

Tablet Press
• Korsch XL400 (35 station)
• 34° DRO plan tooling
• 3/4” PPBE debossed tooling

Figures
1. Schematic of external lubrication and relative position on rotary tablet press
2. Compression profile of placebo tablets with internal (I) and external (O) magnesium stearate
3. SEM elemental analysis of placebo tablet surface
4. SEM elemental analysis of placebo tablet interior

RESULTS
• Comparison of tablets compressed with internal magnesium stearate and externally applied magnesium stearate.

Table 1. Weight percent of magnesium stearate on placebo tablets compressed using external lubrication technology.

<table>
<thead>
<tr>
<th>Portion of tablet mix</th>
<th>Weight % Mg Stearate</th>
<th>Average weight % Mg Stearate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beginning</td>
<td>0.0194</td>
<td>0.0194</td>
</tr>
<tr>
<td>Middle</td>
<td>0.0095</td>
<td>0.0095</td>
</tr>
<tr>
<td>End</td>
<td>0.0019</td>
<td>0.0019</td>
</tr>
<tr>
<td>Overall</td>
<td>0.0205</td>
<td>0.0205</td>
</tr>
</tbody>
</table>

Table 2. Weight at compressed using external lubrication.

<table>
<thead>
<tr>
<th>Portion of tablet mix</th>
<th>Weight % Mg Stearate</th>
<th>Average weight % Mg Stearate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beginning</td>
<td>0.095</td>
<td>0.095</td>
</tr>
<tr>
<td>Middle</td>
<td>0.075</td>
<td>0.075</td>
</tr>
<tr>
<td>End</td>
<td>0.075</td>
<td>0.075</td>
</tr>
<tr>
<td>Overall</td>
<td>0.095</td>
<td>0.095</td>
</tr>
</tbody>
</table>

• Quantification of magnesium stearate on placebo and active tablets using ICP-MS.
• Stacked sampling to show consistency within and across time points.

Table 3. Normalization of magnesium stearate content to surface area of tooling.

<table>
<thead>
<tr>
<th>Portion of tablet mix</th>
<th>Mg Stearate (mg)</th>
<th>Surface area (sq ft)</th>
<th>Normalized mass per surface area (mg/sq ft)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beginning</td>
<td>0.0019</td>
<td>0.0019</td>
<td>0.0019</td>
</tr>
<tr>
<td>Middle</td>
<td>0.0019</td>
<td>0.0019</td>
<td>0.0019</td>
</tr>
<tr>
<td>End</td>
<td>0.0019</td>
<td>0.0019</td>
<td>0.0019</td>
</tr>
<tr>
<td>Overall</td>
<td>0.0019</td>
<td>0.0019</td>
<td>0.0019</td>
</tr>
</tbody>
</table>

Table 4. Consistency of magnesium stearate on the tablet surface via SEM elemental analysis.

<table>
<thead>
<tr>
<th>Analysis Post</th>
<th>Mg Stearate (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.15</td>
</tr>
<tr>
<td>2</td>
<td>0.14</td>
</tr>
<tr>
<td>3</td>
<td>0.11</td>
</tr>
<tr>
<td>4</td>
<td>0.13</td>
</tr>
<tr>
<td>5</td>
<td>0.15</td>
</tr>
<tr>
<td>Average (5% 50)</td>
<td>0.14 (0.017)</td>
</tr>
</tbody>
</table>

CONCLUSIONS
• Magnesium stearate was applied at a constant rate for both placebo and active tablets.
• Mass of magnesium stearate on both placebo and active tablets was normalized against surface area of tooling.
• Magnesium stearate content was consistent at multiple points of analysis.

ACKNOWLEDGMENTS/REFERENCES
The authors wish to acknowledge the assistance of Korsch America for assistance in setup and operation of the equipment.

Percent of Mag stearate:
Standard Lubrication: .5-2.0%
External Lubrication: .005 -0.01 %
Summary: Key Design Considerations when choosing Feeders and Material Handling for Continuous Processing in the Pharmaceutical Industry

- Review of material characteristics and flow properties also critical to ensure constant flow without interruption of the continuous process
- Consult with feeder manufacturer – proper configuration of components is important to improved accuracy and performance
- Short term accuracy and repeatability are critical
- **Gravimetric devices versus volumetric**
  - High accuracy weigh cells – high resolution
  - Quick response control systems necessary for second to second accuracy
  - Refill Arrays to ensure constant feeding
  - Microfeeding devices for low rate feeding
- Refill of the feeders must also be evaluated to ensure constant and consistent supply of ingredients to the process
- Design of overall system, refill plus feed plus integration of controls and instrumentation must be carefully considered to ensure accurate and safe ingredient delivery and process quality
- Evaluate containment issues, cleanability, validatability of the overall process
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Thank you very much for your attention.