How HPMC Physicochemical Properties Impact Matrix Tablet Performance

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Slides courtesy of True Rogers, R.Ph., Ph.D.
Quality by Design (QbD)

The drug product must be safe and efficacious for the patient.
  • I.e., Ensure the dosage form performs as expected.

How robust is dosage form performance?

How robust is the process to make the dosage form?

How robust are the methods to characterize the dosage form?

What is the impact of raw material variability? (API? Excipients?)
  • Multiple suppliers?
  • Lot-to-lot variability?
Properties vs. Performance

Raw material properties
- Physical
- Chemical

Process
- Processability
  - E.g. Flowability
- Process steps and parameters which are critical to quality.

Performance
- Dosage form physical properties
- Achieving desired performance
  - API release
- Is desired performance reproducible (e.g. from lot-to-lot, day-to-day)?
**HPMC Matrix Tablets for Modified-Release**

Hydrophilic matrix tablets are the most commonly utilized MR dosage form.
- Simplest.
- Fastest to develop.
- Least expensive to manufacture.

Hypromellose 2208 is the most common rate-modifying excipient used in hydrophilic matrices.
How HPMC Physicochemical Properties Impact Matrix Tablet Performance
### METHOCEL MC and HPMC

**Table 15. Dow Wolff Cellulosics’ commercially available methylcellulose and hypromellose grades.**

<table>
<thead>
<tr>
<th>Commercial name</th>
<th>Mfr.</th>
<th>Chemistry type</th>
<th>MO (%)</th>
<th>HPO (%)</th>
<th>Viscosity range</th>
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</thead>
<tbody>
<tr>
<td>METHOCEL™ A15PLV</td>
<td>DWC*</td>
<td>MC</td>
<td>27.5-31.5</td>
<td>0</td>
<td>12-18*</td>
</tr>
<tr>
<td>METHOCEL™ A4CP</td>
<td>DWC*</td>
<td>MC</td>
<td>27.5-31.5</td>
<td>0</td>
<td>300-560*</td>
</tr>
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<td>DWC*</td>
<td>MC</td>
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</tr>
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<td>MC</td>
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<td>4.8-7.2*</td>
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<td>28-30</td>
<td>7-12</td>
<td>2663-4970*</td>
</tr>
<tr>
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<td>HPMC 2910</td>
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<td>7-12</td>
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<td>2663-4970*</td>
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<td>METHOCEL™ K15MP</td>
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<td>7-12</td>
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<td>HPMC 2208</td>
<td>19-24</td>
<td>7-12</td>
<td>75,000-140,000*</td>
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</tbody>
</table>

Critical-to-Quality Attributes of Hydrogel-Forming Matrix Polymer

- **X-Factor** (like % - HP content) - Adjusting HP content within HPMC chemistry adjusts hydrogel formation for unique performance.
- **Viscosity / Molecular mass** - Viscosity is an indicator of molecular weight and impacts chain disentanglement at the matrix tablet hydrogel erosion front.
- **Cellulose ether Chemistry** (like Methocel™ A, E, F or K) - Cellulose ether (CE) chemistry impacts solubility hydrogel formation temperature.
- **Particle size** - Sufficiently fine particle size needed for particles to uniformly distribute throughout matrix tablet.

**Foundational**
- **Selection for Matrix Tablets**
- **Basic MR Mechanism from Matrix Tablet**

[Dry Tablet](#)  
[Partially Hydrated Tablet](#)  
[Increasing Duration of Exposure to Aqueous Media](#)
HPMC Matrix Tablets for Modified-Release Oral Drug Delivery

HPMC 2208 is the predominant matrix tablet excipient

Chemical Structure of HPMC

Increasing 2% Viscosity

5% theophylline, 20% HPMC
74.5% lactose, 0.5% mag stearate

Time lapse images of tablets swelling over 24 h
Property → Performance Relationships

- PDT (°C)
  - Commercial Methocel™ K4M
  - Prototypes

- % paracetamol release at 1320 min (avg, n=6)

- HPO (%)
- 2% viscosity (mPa-s)
- PDT (°C)
Substitution Levels *Within HPMC 2208 Chemistry Can Impact Modified-Release*

50% acetaminophen, 30% K15M
19% lactose, 1% mag stearate

50% diclofenac sodium, 40% K15M
9.5% lactose, 0.5% mag stearate

40% salicylic acid, 30% K15M
29% lactose, 1% mag stearate

**Acknowledgements**
Tim Cabelka, Shawn Mitchell

Specification range for %OMe = 19-24%
Specification range for %HP = 7-12%
Comparison of Pilot Plant HPMC with varying HP contents to commercial Methocel™
### Paracetamol Model Example

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>% w/w</th>
<th>Weight per tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol*</td>
<td>50</td>
<td>250</td>
</tr>
<tr>
<td>METHOCEL™ K4M or Pilot Plant HPMC</td>
<td>30</td>
<td>150</td>
</tr>
<tr>
<td>Lactose</td>
<td>18</td>
<td>90</td>
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<tr>
<td>Magnesium stearate</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Talc</td>
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<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100</strong></td>
<td><strong>500</strong></td>
</tr>
</tbody>
</table>

Actual tablet weight: 502 ± 3 mg  
Hardness: 94 ± 8 N  

* Paracetamol:  
  - Analgesic  
  - Aqueous solubility: 14 mg/mL
Batch-to-Batch Consistency

Batch-to-batch consistency with commercial METHOCEL™:

Reproducible modified-release performance.


<table>
<thead>
<tr>
<th>Commercial Batch No.</th>
<th>%Me</th>
<th>%HP</th>
<th>50% Cumulative Volume Particle Size (µm)</th>
<th>%NaCl</th>
<th>2% Viscosity (mPa·s)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
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<td>102.1</td>
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<tr>
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<td>Average</td>
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<td>Std Deviation</td>
<td>0.4</td>
<td>0.3</td>
<td>6.6</td>
<td>0.1</td>
<td>414</td>
</tr>
</tbody>
</table>
Pilot Plant HPMC vs. Commercial METHOCEL™

• Expanded design space boundaries with pilot plant HPMC.
  – HP substitution was purposefully varied.
• Premise:
  – There is ‘insufficient’ batch-to-batch variability in commercial METHOCEL to investigate performance design space proactively.
  – We cannot explore the allowable pharmacopeial design space.
    • Where are the boundaries of robustness?
    • What if we miss optimal performance ‘sweet spots’?

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### Table: Sample identification

<table>
<thead>
<tr>
<th>Sample Identification</th>
<th>%Me</th>
<th>%HP</th>
<th>50% Cumulative Volume Particle Size (µm)</th>
<th>%NaCl</th>
<th>2% Viscosity (mPa-s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prototype No. 1</td>
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</table>

See previous section for FRCs of commercial batches investigated.

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Modified-Release Performance

Pilot plant HPMC data “brackets” commercial METHOCEL data for HP substitution and paracetamol release.

Paracetamol release increases with increasing HP substitution.

Efficiently determined that formulation is robust.

Using Science to improve the excipients properties
Balancing Performance Attributes

Flowability
- ↑ Particle size
- ↑ Sphericity
- ↑ Permeability
- ↑ Density

Modified Release
- ↓ Particle size
- ↑ Surface area
- Hydrophilicity
  Tunable by substitution
- Erodability
  Tunable by molecular weight

Compactibility
- ↓ Particle size
- ↓ Sphericity
- ↓ Density
- ↑ Surface area
Evolution of METHOCEL™ Premium

Innovating to Address Industry Needs:

- METHOCEL™ CR
- METHOCEL™ DC2

- Established over 50 years
- Premium quality product line
- Proven track record

- Engineered morphology
- Enhanced flow
- Direct compression

- Lower-cost, more consistent manufacturing processes

- Particle size guarantee
- Tighter specifications
- Robust, optimized MR performance
Morphology and Flow Performance

METHOCEL™ DC2 is a chemically pure hypromellose, meeting all compendial requirements.

Red indicates presence of additional ingredient.
Matrix Tablet Manufacture

METHOCEL™ DC2 accelerates the manufacturing process

WET GRANULATION – 7 STEPS
1. weigh + disperse raw materials
2. wet granulate
3. dry granules
4. mill to size
5. add extragranular materials
6. blend / lubricate
7. compress

DIRECT COMPRESSION – 3 STEPS
8. weigh + disperse raw materials
9. blend / lubricate
10. compress

TIME SAVINGS
COST SAVINGS

Engineered Morphology
Improved Flow & Tablet Attributes
Modified Release
More Efficient Production

Pharma & Food Solutions
Direct Compression of HPMC Matrix Tablets Containing Metformin HCl Materials with Different Particle Size Distributions
### Metformin HCl Particle Size by Lot

<table>
<thead>
<tr>
<th>Metformin HCl Lot</th>
<th>Malvern D10 (µm)</th>
<th>Malvern D50 (µm)</th>
<th>Malvern D90 (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>255</td>
<td>600</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
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<tr>
<td>5</td>
<td>18</td>
<td>176</td>
<td>532</td>
</tr>
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</table>

- Significant particle size variability for different lots of metformin HCl from one or more suppliers.
Dampened Impact of Metformin HCl Particle Size Variability on Matrix Tablet Variability

- More tablet weight variability was observed from metformin HCl lot-to-lot with the competitive direct compression grade of HPMC.
- Less tablet weight variability was observed, in general, with METHOCEL™ K100M DC2 HPMC.
Modified-release performance was comparable for all metformin HCl and HPMC materials studied.
Summary

Material characteristics are a critical piece to the formulation development based on QbD

HPMC chemistry (e.g., HP%) can modify the performance of the polymer and some models can be more sensitive than others to the variation in chemistry type.

Optimized physical properties can be beneficial in creating a more functional excipient for MR in DC – METHOCEL™ DC2

METHOCEL™ DC2:
- is more flowable due to particle morphology engineering
- Matrix tablets containing DC2 exhibited more reproducible properties.
Questions?

Thank You!

www.dowpharmaandfood.com