Pharma Solutions

METHOCEL™ as a Wet and Dry Granulation Binder

A technical review
Formulating the Medicines
That Provide People with Immediate Relief

When you’re developing immediate release tablet and capsule medicines, we know what you’re looking for: good tablet hardness at low binder concentration, versatility and compliance with applicable government requirements.

Producing a tablet with a high concentration of the active drug requires a binder that is highly effective at low concentrations. For this, choose METHOCEL™ Premium LV products from DuPont Nutrition & Biosciences, which deliver the necessary tablet hardness without increasing friability and without negatively impacting the release of the drug.

Why Wait When we Can Help you Deliver Now

METHOCEL™ products provide important binding and adhesive properties during the granulation step of the manufacturing process for immediate release tablet and capsule products. They offer several important benefits for every formulator:

• Now that’s the Tablet we’re Looking For:
  METHOCEL™ polymers produce hard tablets at very low concentrations – as low as 3% when used in formulations for wet granulation processes (low shear, high shear, and fluid bed) and between 6% and 12% for dry granulation (roller compaction) – without increasing friability. With METHOCEL™, minimize tablet size while maximizing the ability to use other excipients to optimize other tablet characteristics, which makes these polymers ideal in formulations with high active drug concentrations.

• Whatever You Need, We Can Help:
  METHOCEL™ products offer flexibility when manufacturing tablets. Wet and dry granulation processes provide important characteristics to the finished product, including better product flow on tablet presses and capsule-filling equipment, better compressibility and overall improved physical characteristics of tablets, uniform drug content within the dosage form, and fewer industrial hygiene constraints. METHOCEL™ is highly effective in both granulating technologies. These polymers also are compatible with virtually all active ingredients and other excipients, and hydrate quickly in process liquids to minimize mixing and preparation time. At the appropriate concentration, METHOCEL™ can be used to add needed viscosity to the granulating liquid to minimize mixing and preparation time. METHOCEL™ products also can be used in solutions or dry-blended into the powder mass that is to be granulated and then hydrated by spraying water.

• Follow the Rules for Success:
  METHOCEL™ Premium grades comply with the compendia specifications of the Pharmacopoeia of the U.S., Europe, and Japan (current editions) and the Food Chemicals Codex.

Viscosity of aqueous solutions containing METHOCEL™ at varying concentration and molecular weight

<table>
<thead>
<tr>
<th>Concentration, % Binder</th>
<th>Viscosity, mPa•s</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>100</td>
</tr>
<tr>
<td>0.25</td>
<td>200</td>
</tr>
<tr>
<td>0.5</td>
<td>300</td>
</tr>
<tr>
<td>1</td>
<td>400</td>
</tr>
<tr>
<td>2</td>
<td>500</td>
</tr>
<tr>
<td>2.5</td>
<td>1000</td>
</tr>
<tr>
<td>5</td>
<td>2000</td>
</tr>
<tr>
<td>10</td>
<td>3500</td>
</tr>
</tbody>
</table>

Viscosity, mPa•s // Concentration, % Binder
**METHOCEL™ Can help you get there**

Methocel has been extensively tested across a variety of different types of model active ingredients utilizing a range of commonly used granulation techniques.

**Acetaminophen: high-dose, low-solubility drug in the wet-granulation**

In a formulation with 50% acetaminophen, METHOCEL™ demonstrated good hardness at concentrations of 3% and 6% of total tablet weight. In some formulations, METHOCEL™ polymers can even provide optimum tablet properties at concentrations of 1% and lower. This ability to provide good hardness at low concentrations makes METHOCEL™ ideal for formulations that contain a high percentage of active drug or other excipients.

**Hardness of compressed tablets containing acetaminophen and granulated with 6% dry binder in low-shear and high-shear granulators**

<table>
<thead>
<tr>
<th>Binder</th>
<th>Low Shear</th>
<th>High Shear</th>
</tr>
</thead>
<tbody>
<tr>
<td>METHOCEL™ A15 Prem LV</td>
<td>7.13</td>
<td>14.27</td>
</tr>
<tr>
<td>METHOCEL™ E5 Prem LV</td>
<td>21.41</td>
<td></td>
</tr>
<tr>
<td>METHOCEL™ K3 Prem LV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hardness of compressed tablets containing acetaminophen and granulated with 6% dry binder in low-shear and high-shear granulators**

<table>
<thead>
<tr>
<th>Binder</th>
<th>Low Shear</th>
<th>High Shear</th>
</tr>
</thead>
<tbody>
<tr>
<td>METHOCEL™ A15 Prem LV</td>
<td>7.13</td>
<td>14.27</td>
</tr>
<tr>
<td>METHOCEL™ E5 Prem LV</td>
<td>21.41</td>
<td></td>
</tr>
<tr>
<td>METHOCEL™ K3 Prem LV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Low Shear**

**High Shear**

**Fluid Bed**
The desirable hardness characteristics of METHOCEL™ also result in friability performance that is well within acceptable limits at both 3% and 6% binder levels. The drug-release performance represents an average of six test runs. In all cases performance of METHOCEL™ binders was within the USP specifications and comparable to that of PVP binders.
Vitamin C (ascorbic acid): high-dose, high-solubility drug in the wet-granulation

In a formulation with 75% ascorbic acid, the hardness values of METHOCEL™ products were equivalent or superior to those achieved with another polymer, polyvinylpyrrolidone (PVP), for all granulating techniques and at both binder levels. Low-shear and high-shear granulations demonstrated comparable hardness values, except for PVP formulations. For PVP, low-shear processing resulted in harder tablets than high-shear processing for dry binder. At 6% binder level in solution, fluid-bed granulations from all products demonstrated excellent tablet hardness, in all cases better than low-shear or high-shear granulations.

Hardness of compressed tablets containing ascorbic acid and granulated with 6% dry binder in low-shear and high-shear granulators

Hardness, strong-cobb units // Binder // Hardness, kiloponds

Friability of compressed tablets containing ascorbic acid and granulated with 6% dry binder in low-shear and high-shear granulators

Friability, % weight loss // Binder
METHOCEL™ at 3% binder level achieved good tablet hardness, though not as consistently high as at 6%. Regardless of the granulation process used, tablets prepared using METHOCEL™ cellulose ethers had friability values below 0.7%. METHOCEL™ A15 Premium LV, E5 Premium LV and K3 Premium LV all demonstrated friability performance that was superior to PVP. The drug-release performance again represents an average of six test runs. In all cases using binders in solution, at least 80% of the active ingredient is released within 15 minutes.

For dry binder additions, at least 80% of the active ingredient is released within 30 minutes.
Methazolamide: low-dose, low-solubility drug in the wet-granulation

In a formulation of 71% methazolamide, METHOCEL™ K3 Premium LV produced the best tablet hardness values at a binder level of 3% using a high-shear granulation process. At 6% binder level, hardness values were essentially equivalent for all binder materials, although low-shear granulation processes tended to perform better than high-shear processes.

Friability of Compressed Tablets Containing Methazolamide and Granulated with 3% or 6% Binder in a Solution of Fluid-Bed Granulator

Tablet friability, % weight loss // Binder
Fluid-bed granulation offered even less differentiation between the three METHOCEL™ products, with performance again equivalent to the PVP binder. The binder level was not a factor for fluid-bed granulation as additional binder did not consistently result in harder tablets. All binders used in this portion of the study produced tablet with low friability—less than 0.6% and well below the 1% industry norm. In terms of drug release from the tablet, all tablets surpassed USP specifications by a significant margin.

Drug release from compressed tablets containing methazolamide and granulated with 6% dry binder in a high-shear granulator

Drug released, % // Time, min

Drug release from compressed tablets containing methazolamide and granulated with 3% dry binder in a high-shear granulator

Drug released, % // Time, min
Niacinamide: high-dose, high-solubility drug in the roller-compaction

A study looked at three formulations with niacinamide (88.5%, 82.5% and 70.75%) plus METHOCEL™. The level of pressure applied to the compactor rolls was important to the quality of the finished tablets. In general, low roller pressures resulted in tablets with higher hardness. At the lowest binder level (6.25%), hardness values of tablets produced at 1- and 3-ton pressures were marginal, and friability was excessive. At the highest binder level (25%), hardness was generally improved and friability (with the exception of PVP) was good. At most binder levels and roller pressures, hardness and friability values for the METHOCEL™ products were better than PVP.

Tablet drug-release times were primarily a function of binder concentration and molecular weight rather than roller pressure. For the METHOCEL™ products, the time required to release 90% of the drug at the lowest binder level ranged from 6–8 minutes for the lower molecular weight products (E5 Premium LV and K3 Premium LV) to 5–12 minutes for the higher molecular weight products (E15 Premium LV and A15 Premium LV).

The time required to release 90% of the drug at the intermediate binder concentration increased to 16–18 minutes for E5 Premium LV and K3 Premium LV to 19–40 minutes for E15 Premium LV and A15 Premium LV.

The highest binder concentration required 44 and 59 minutes for K3 Premium LV and E5 Premium LV, respectively, and 290 and 142 minutes for A15 Premium LV and E15 Premium LV, respectively, for 90% drug release.

Times to 90% release for PVP were generally lower than the METHOCEL™ products at the lowest concentration, but the release times were not as sensitive to increases in binder concentration. However, the physical properties of these tablets were poor; i.e., the tablets exhibited capping.

Times to 90% release for the HPC-EF were between the low and high molecular weight METHOCEL™ products.
Hardness of compressed tablets containing niacinamide and prepared using roller compaction at 3 tons pressure

Hardness, strong-cobb units // Binder // Hardness, kiloponds

Time to 90% drug release from compressed tablets containing niacinamide and prepared using roller compaction at 3 tons pressure

Time to 90% drug release, minutes // Binder

Rate of drug release from compressed tablets containing niacinamide with 12.5% binder and prepared using roller compaction at 3 tons pressure

Drug released, % // Time, min