METHOCEL Cellulose Ethers
in Aqueous Systems
for Tablet Coating
Meet All Coating Quality Specifications, Improve Other Tablet Properties, and Maximize Production Speed

METHOCEL* Premium cellulose ethers produce tough, printable, economical, and highly consistent tablet coatings whether they are aqueous, hydroalcoholic, or solvent-based. Coatings are micro-thin, noncaloric, nonnutritive, nonallergenic, and more resistant to microorganism growth than those formulated with natural gums, sugar, and most other cellulosics.

Beyond producing coatings of the highest quality, METHOCEL products can improve other tablet physical properties and allow the coating process to be performed with optimum speed and efficiency.

This brochure explains the use of METHOCEL products in tablet coating systems in more detail. It also offers discussions of a general nature on the formulation and application of coatings in an effort to speed your development work. We hope you find it useful in anticipating and avoiding some of the common obstacles encountered during formulation and production.

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A Review of the Principle Advantages of METHOCEL in Tablet Coatings

Given the wide variety of routes available to a tablet coating of acceptable quality, why has the family of METHOCEL Premium products become the starting point for so many different applications?

**Formulation Versatility and the Ability To “Fine Tune”**

One reason for the popularity of METHOCEL is simply that these products have been used successfully in tablet coatings for over 25 years. Their performance is well documented and there is a large body of data to reference and rely upon. This speeds development and reduces its expense.

Also important is that with seven separate products and the ability to blend different grades, this polymer family produces an extremely wide range of required viscosities, solids content, and film properties. As a result, the decision to begin formulating a coating system with METHOCEL is not only rewarded with a coating that’s acceptable, but one that has been optimized by several measures.

**Improve Product Appearance, Help Assure Consumer Acceptance**

First of all, coatings based on METHOCEL Premium cellulose ethers improve product appearance. They produce a glossy, quality finish that eliminates dusting. Films of METHOCEL make clear, sharp coatings that are nonionic and compatible with FD&C dyes, lakes, and pigments. They are excellent surfaces for printing, while clearly enhancing and displaying scoring, logos, and other distinguishing features of a tablet’s surface.

Plus, although aqueous polymer films do not deliver the extraordinary high gloss of a sugar coating, tablet appearance is maintained at high levels with METHOCEL by careful process adjustments. Plasticizer selection, application rates, polymer concentration, and application of a second coat to specifically enhance sheen allow an even higher tablet gloss.

Coatings of METHOCEL also offer excellent barrier properties, limiting the migration of water and oxygen to protect sensitive cores. Properly done, an aqueous coating of METHOCEL can be applied to multi-vitamin tablets, for example, without causing the cores to discolor or break down. Further evidence to support the excellent barrier properties of these films can be seen in their use as coatings for food products, such as nuts. Films of METHOCEL effectively improve shelf life of nutmeats.

Of course a primary objective with coatings is to ease swallowing. Clear coatings of METHOCEL begin to hydrate in the mouth, then become slick to allow a tablet to slide easily down the throat. Studies with simulated esophageal passages have documented improved swallowing ease with tablets bearing a coating with METHOCEL as compared with uncoated tablets.

In short, with METHOCEL Premium products you easily achieve a quality image that promotes consumer acceptance.

**Improve Tablet Physical Properties**

Beyond providing the easy-to-swallow, micro-thin coatings consumers demand, METHOCEL also improves many other product properties. Compared to sugar, METHOCEL is a much better film former. Coatings can double tablet compressive strength and reduce friability while only increasing tablet size by 1-3 mil and product weight by 1-3%. Your products stand up to the rigors of handling and shipping. So the quality appearance achieved at the plant is maintained right to the consumer’s home.

Another advantage with METHOCEL Premium products is the availability of low pH grades (pH 4 to 5) to inhibit bacterial growth yet maintain their viscosity under normal storage conditions. This feature, along with the fact that METHOCEL is compatible with a wide variety of preservatives and alone is relatively resistant to bacterial degradation, makes it easy to meet shelf life requirements.

**Production Speed and Simplicity**

Coatings made with METHOCEL can minimize coating cycle time too. They allow the use of high productivity spray application equipment. And spraying and drying can be done in a single pan. (Also consider that the low viscosity of METHOCEL E5 Premium LV permits high solids in the coating solution so less water must be removed.)
By permitting the use of automated equipment, coatings based on METHOCEL can contribute to lower labor costs in two ways. First, since the same procedures are used with each product there’s less need for involvement by highly skilled and experienced personnel. Coating is no longer an “art form” but rather a highly controlled process. Second, fewer total people are involved in the process.

In short, METHOCEL meets all the primary goals for tablet coatings. Plus it improves other tablet properties while making sure production speed and economy are maintained.

**Technical Assistance Every Step of the Way**

A final reason for the popularity of METHOCEL really has little to do with the product family. It involves the years of experience and knowledge we have accumulated and can bring to bear on your specific applications. Some of this information is contained on the pages that follow. But necessarily it is somewhat general in scope. Rest assured, however, that after several decades of involvement with the formulation of coating systems for virtually every pharmaceutical product category, chances are we can help meet your specific coating needs quickly, efficiently, and with optimum results. Look to the rest of this brochure for additional evidence to support the conclusion that METHOCEL is worth further investigation.
An Overview of METHOCEL Products For Tablet Coating

METHOCEL Premium products represent the hypromellose product family of the highest quality. Here’s why.

• METHOCEL is manufactured according to the stringent requirements of Good Manufacturing Practices (GMPs).
• Dow’s manufacturing facilities are registered and regularly inspected by the FDA.
• METHOCEL products are produced from dedicated processes and equipment to assure the highest purity.
• Dow offers a Certificate of Analysis with every shipment so you have documentation of product quality and the consistency of that quality from shipment to shipment.

In short, when hypromellose is the product type of choice, METHOCEL Premium products should be the brand of choice to best ensure the production of consistently high quality products day in and day out.

Available Grades

In tablet coating applications, only the Premium (USP, EP, JP) grades of METHOCEL “E” cellulose ethers should be used. These products will meet the requirements of FDA and USP as well as EP, JP if so specified. See Table 1.

Product Description of METHOCEL Premium Products

<table>
<thead>
<tr>
<th>Physical form</th>
<th>free-flowing white/off-white powder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle size</td>
<td>100% pass through 30 mesh screen; 99% pass through 40 mesh screen</td>
</tr>
<tr>
<td>Packaging</td>
<td>available in 50-lb multi-wall bags or 50-kg fiber drums</td>
</tr>
</tbody>
</table>

†Previously referred to as hydroxypropyl methylcellulose or HPMC.
<table>
<thead>
<tr>
<th>Product Description²</th>
<th>METHOCEL E3 Premium LV</th>
<th>METHOCEL E5 Premium LV</th>
<th>METHOCEL E6 Premium LV</th>
<th>METHOCEL E15 Premium LV</th>
<th>METHOCEL E50 Premium LV</th>
<th>METHOCEL A15 Premium LV</th>
<th>METHOCEL K3 Premium LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methoxyl, %</td>
<td>28-30</td>
<td>28-30</td>
<td>28-30</td>
<td>28-30</td>
<td>28-30</td>
<td>27.5-31.5</td>
<td>19-24</td>
</tr>
<tr>
<td>Hydroxypropyl, %</td>
<td>7-12</td>
<td>7-12</td>
<td>7-12</td>
<td>7-12</td>
<td>7-12</td>
<td>0</td>
<td>7-12</td>
</tr>
<tr>
<td>Moisture, % as packaged, max</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>5.0</td>
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<tr>
<td>Ash, max %</td>
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<td>3.0</td>
<td>3.0</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Sodium chloride, max %</td>
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<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.5</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Arsenic, as As, max</td>
<td>3 ppm</td>
<td>3 ppm</td>
<td>3 ppm</td>
<td>3 ppm</td>
<td>3 ppm</td>
<td>3 ppm</td>
<td>3 ppm</td>
</tr>
<tr>
<td>Heavy metals, as Pb, max</td>
<td>10 ppm</td>
<td>10 ppm</td>
<td>10 ppm</td>
<td>10 ppm</td>
<td>10 ppm</td>
<td>10 ppm</td>
<td>10 ppm</td>
</tr>
<tr>
<td>Viscosity⁴, 2.0% in water, mPa•s</td>
<td>2.4-3.6</td>
<td>4-6</td>
<td>5-7</td>
<td>12-18</td>
<td>40-60</td>
<td>12-18</td>
<td>2.4-3.6 cps</td>
</tr>
</tbody>
</table>

¹ Also available in European Pharmacopoeia, EP, and Japanese Pharmacopoeia, JP grades.
² Meets all requirements in USP XXI monograph for hypromellose.
³ Also available as METHOCEL E5 Premium LV low pH.
⁴ Millipascal-seconds, mPa•s, is equivalent to cP (centipoise).
⁵ All solution viscosities are measured with Ubbelohde viscometers at a 2% concentration in water at 20°C (68°F).
The following review of the process involved with aqueous polymeric film coatings is offered for those not intimately involved in the manufacturing process. As a result it is purposely basic and is not intended for the very experienced reader.

**A Matter of Equilibrium**

The use of polymer film coatings has often been attempted for the first time with a sense of concern by the formulator. Will the coating have the proper characteristics? Will it coat easily? Will the product still be stable and acceptable? Particularly when formulating aqueous coatings, many are concerned that the stability of water-sensitive drugs will be affected. As a result, many turn to organic solvent coating systems. Today, however, aqueous film coatings are being used more often on a wide range of pharmaceutical products, many of which were considered to be very sensitive to water.

To use aqueous coatings on different drug substrates, you simply need to understand the coating process. It is most easily viewed as a simple, black box thermodynamic model as shown in Figure 1.

First, consider the amount of fluid being applied to the tablet surface as the hydraulic load. One can calculate the need for the amount of incoming air, the temperature of the air, and the humidity of the air required to evaporate the incoming water. The goal is to enable the coating equipment to evaporate the water at the same rate as it is being put into the process.

![Figure 1: “Black Box” Model](image)

\[
(C_p, \text{air})(AFR)(\Delta T) = (212^\circ F - T_{in})(C_p, \text{sol}) + (\text{Water vol})(H_{vap})
\]

- \(C_p, \text{air}\) — heat capacity of air
- \(AFR\) — air flow rate
- \(\Delta T\) — difference between inlet and outlet air temperature
- \(T_{in}\) — initial temperature of coating solution
- \(C_p, \text{sol}\) — heat capacity of solution
- \(H_{vap}\) — heat of vaporization

8
Too high a temperature can cause spray drying of the coating solution or instability of the drug due to high tablet core temperatures.

In conclusion, it is simply necessary to monitor the amount of liquid being applied to the coating surface, the ability of the air to evaporate the material under the fixed conditions of air flow rates, humidity, air temperature, and the tablet surface area. (A more complete thermodynamic model is discussed in an article published by Pharmaceutical Technology entitled “A Thermodynamic Model for Aqueous Film Coating,” April 1987, by Glen C. Ebey.)

Whether you complete a thorough thermodynamic analysis of the process or simply monitor important parameters like exhaust air temperature and the various fluid and air flow rates, aqueous coating can be done with relative ease.

With this in mind let’s review the individual factors which must be controlled by the formulator to assure the quality of the coating.

**The Coating Solutions**

Regardless of the delivery system, the coating solution must be formulated to have a sprayable solution viscosity. Generally this means a viscosity of the coating solution in the range of 150-400 mPa\(\cdot\)s, although higher viscosities may be possible under certain equipment conditions. Formulations may contain optional surfactants, plasticizers, or pigments. It should be noted, however, that these additional excipients can affect the viscosity of the coating solution. Yet the major factor controlling the formulation is the viscosity of the polymer grade being used and the concentration of polymer in the solution.

A variety of solvents may be used with tablet coating systems of METHOCEL hypromellose. At its inception, organic solvent systems of methylene chloride/alcohol blends were used. This allowed very fast drying at relatively low temperatures or air volumes.

In some cases, hydroalcoholic solvent systems are used where the water content in the solvent mixture may range from 20-80% by weight.

Hypromellose is not soluble in absolute alcohol but may be applied if more than 20% water is included in the alcohol.

The use of alcohol/water solvents also allowed for relatively fast coating but was slower than the methylene chloride/ alcohol system.

Finally, in more recent times, aqueous coating has become the preferred choice. This did require increased air handling and heat exchange to facilitate rapid coating. Aqueous systems can be formulated at varying water or solids content depending on the choice of polymer, molecular weight, and the use of pigments. The effect of formulation variables on film properties will be discussed later, but in general the higher the coating solids content the faster the tablet may be coated.
Typical Formulation Ingredients

Polymer

METHOCEL cellulose ethers are available in a variety of pharmaceutical grades as shown on page 7. Most often, METHOCEL E Premium products, hypromellose 2910 USP grade, are preferred for use in aqueous film coatings. These products tend to have the best clarity, color, and film properties. METHOCEL E products are available in a range of molecular weights. The viscosity of a 2% solution of these products are available as 3, 5, 6, 15, and 50 mPas.

METHOCEL K products can also be considered for tablet coating, but they are not highly recommended except when sugar coatings are also involved. See page 23 for further discussion of the use of METHOCEL K products.

In those countries where only methylcellulose is approved as a food coating material, METHOCEL A15 Premium LV can be used for tablet coating. This product also produces a good coating on tablet surfaces with similar properties to the hypromellose product. All METHOCEL Premium products are available in USP, European Pharmacopoeia, and Japanese Pharmacopoeia grades.

Solvent

METHOCEL products can be formulated in organic, hydroalcoholic, and aqueous solvent systems. As mentioned, each solvent system has a specific impact on the coating process. Any of the METHOCEL products may be formulated in these solvent systems. It is recommended, however, that METHOCEL E products be used in organic or hydroalcoholic systems where better polymer compatibility is desired.

The viscosity-concentration relationship for different solvents varies slightly with the choice of solvents. The information given in Figures 2, 3, 4, 5, 6, 7, 8, 9, and 10 may be useful in predicting polymer concentrations necessary to achieve sprayable coating solution viscosities.
Figure 3: Viscosity Concentration for METHOCEL in an 80:20 Wt/Wt Water-Ethanol Mixture

Figure 4: Viscosity Concentration for METHOCEL in a 60:40 Wt/Wt Water-Ethanol Mixture

Figure 5: Viscosity Concentration for METHOCEL in a 40:60 Wt/Wt Water-Ethanol Mixture

Figure 6: Viscosity Concentration for METHOCEL in a 20:80 Wt/Wt Water-Ethanol Mixture
**Plasticizer**

The function of a plasticizer in a coating formulation is to soften films or make them less brittle. This is particularly important when using very low molecular weight grades of hypromellose. Generally, water-soluble plasticizers are chosen for use in aqueous systems and solvent-soluble plasticizers are used with organic solvent systems. Using a plasticizer can lead to smoother films, increase adhesion to the tablet surface, reduce logo bridging, and actually reduce cracking or chipping by improving film toughness.

**Pigments**

Pigments are used to allow coloration of tablets. The use of aluminum lake or iron oxide pigments has essentially replaced the use of soluble dyes. Pigments or pigment dispersions are added to polymer solutions in amounts required to achieve the desired coloring while hiding or masking taste effects. Generally, the level of pigment used will be from 50-200% of the polymer weight in a coating solution.
Figure 9: Viscosity Concentration for METHOCEL in a 40:60 Wt/Wt Methylene Chloride-Ethanol Mixture

Figure 10: Viscosity Concentration for METHOCEL in a 20:80 Wt/Wt Methylene Chloride-Ethanol Mixture

Surfactants

Surfactants are sometimes used to aid in color dispersion and development of the tablet coating. The use of surfactants may also depress the viscosity of the polymer solution. Reduction of pigment flocculation through the use of surfactants can also improve the coating gloss. We generally do not recommend the use of surfactants except to solve specific performance problems.
Evaluation of Films Containing METHOCEL in Tablet Coating

Many methods have been used and reported on the evaluation of polymer films for tablet coating. Besides actual tablet coating evaluations we have found that the physical evaluation of free films provides useful information. The following data and observations have been made through testing of 1 mil dry films made by casting on glass and drying at 50°C. While there is a substantial amount of data scatter, trends may be clearly seen when formulation parameters were changed. Film testing was done on an Instron, testing in 50% RH at 75°F. Measurement of tensile at break, work to break, elongation at break, and Young’s Modulus were recorded and evaluated. We find that toughness is the best predictor of overall film performance as it includes both the film strength and ability to deform without breakage. Young’s Modulus has been reported as useful in predicting adhesion. The lower the Young’s Modulus the better the film adhesion to tablet substrates.

**Formulation Factors That Affect Film Properties**

**Polymer Molecular Weight (Viscosity Grade)**

It has often been reported that polymer molecular weight will dramatically affect the strength of films. Since the molecular weight of polymers and the 2% viscosity can be directly correlated we will use viscosity and molecular weight interchangeably. See Figure 11. The names for METHOCEL products specify the 2% aqueous solution viscosity so it is more useful to think of molecular weight in terms of viscosity.

In general, as viscosity decreases the strength of a film will decrease. It will also become more brittle.

**Figure 11: Approximate Molecular Weight/Viscosity Correlation for Hypromellose, 20°C**

\[
\begin{align*}
\text{M}_{\text{n}} & = \text{Number average molecular weight} \\
\text{M}_{\text{w}} & = \text{Weight average molecular weight}
\end{align*}
\]
Figure 12: Film Properties of Low Molecular Weight METHOCEL E Products

Figure 13: Film Properties of Low Molecular Weight METHOCEL E Products

Figure 14: Film Properties of Low Molecular Weight METHOCEL E Products

Figure 12 shows how the tensile strength of a film decreases with decreasing viscosity. The shaded area represents the 90% confidence limits for data from many different lots and viscosities. Enough data have been taken to use these results as a standard for comparison of new products or blends. In Figure 13 the increasing brittleness at low viscosity is shown by the reduction in elongation. At 3 mPAs it becomes very difficult to remove the films from glass plates because of the film brittleness. Figure 14 shows the combined effects of strength loss and brittleness by depicting the reduction in film toughness (work to break) with decreasing molecular weight.
Most companies that coat tablets wish to use the lowest viscosity possible to maximize production efficiency. One can see, however, that there is a trade-off in physical properties with lowering molecular weight. This is why METHOCEL E3P LV is seldom used alone as the coating polymer.

Reduction of film properties usually causes problems like logo bridging or cracking. The level at which this becomes a problem is very dependent on the tablet substrate, geometry, and engraving. For example, one of our customers experienced a 10-fold increase in the incidence of cracking when the polymer viscosity varied from 6 to 5 mPa·s.

Although a wide variety of viscosity grades are available, intermediate viscosity grades may be available on request or can be manufactured through blending (Figures 15 and 16).
Blending Different Molecular Weight Grades of METHOCEL

Experimentation has shown that wide blends of viscosity grades often give better results than the narrower molecular weight distribution of a manufactured product. For example we have found that a blend of METHOCEL E5P LV and METHOCEL E50P LV to achieve a nominal viscosity of 15 mPa•s generally outperformed the typical METHOCEL E15P LV product (Figure 17). While blending of product viscosities is usually not necessary, improvements in coverage, cracking, or logo bridging may be achieved on difficult tablet substrates.
Effects of Plasticizers

The use of plasticizers with hypromellose film coatings is very common. However, many different types have been reported in use. We chose to evaluate the effect of various plasticizers on film properties of METHOCEL as well as evaluate the optimum plasticizer level.

Since the most common level of plasticizer in use today is about 20% based on polymer solids, we chose to evaluate a variety of plasticizers with hypromellose at that level. A control of METHOCEL E5 Premium LV with no plasticizer was included for reference. As expected, most plasticizers made the films less brittle and increased elongation results. Interestingly, the higher molecular weight polyethylene glycols often used in film coating actually decreased elongation (Figure 18). Other plasticizers like oleic acid, triacetin, and propylene glycol (PG) had little effect.

Figure 18: Effects of Plasticizers on METHOCEL E5 Premium LV Films (Elongation)

Figure 20: Effects of Plasticizers on METHOCEL E5 Premium LV Films (Toughness)
Again, as expected, the use of plasticizer reduced the tensile strength of all the films (Figure 19). An evaluation of film toughness, however, shows that equivalent to improved performance was seen with the low molecular weight polyethylene glycols from PEG 300 to PEG 1450 (Figure 20). All of the plasticizers tended to reduce the value for Young’s Modulus and may indicate an increase in adhesion (Figure 21). Finally, in aqueous systems, it is generally recommended that water-soluble plasticizers be used. In nonaqueous systems, plasticizers like triethylcitrate, triacetin, castor oil, acetylated monoglycerides, and oleic acid may be preferred.
The amount of plasticizer used is very important to film properties. If the film is over-plasticized it will lose toughness or may exceed the capacity of the polymer to hold the plasticizer. For example, increasing the level of propylene glycol in a film of METHOCEL demonstrated that an optimum level is 20-30% based on polymer solids. Levels of propylene glycol greater than this do not significantly degrade film properties, possibly due to compatibility limitations or volatility of the plasticizer. With the less volatile polyethylene glycol PEG 600 and PEG 1450, an optimum is reached at 20-30% plasticizer based on polymer solids. Beyond this optimum a continual decrease in film toughness is experienced. In Figure 22 the optimum film toughness is shown for METHOCEL E50 Premium LV. With the lower molecular weight METHOCEL E5 Premium LV the optimum is more difficult to interpret.

**Polymer Blends**

It may at times be advantageous to blend polymers of varying types. Hydroxypropyl cellulose (HPC), for example, has been used in film coating. While HPC typically is much more brittle than hypromellose it does have the property of being a better adhesive. Used alone the film may be tacky and cause problems in sticking or picking of tablets. But when used in combination with hypromellose, the HPC product imparts better adhesion. For example, when HPC-EF and HPC-LF were added to METHOCEL ESP LV in increasing concentrations, the films lost strength (Figure 23), toughness (Figure 24), and became brittle (Figure 25). It was noticed, however, that the films adhered very tightly to glass plates. It was theorized and has been shown in practice that the use of HPC in hypromellose films will increase adhesion. This can be predicted from the reduction in Young’s Modulus seen in Figure 26. We recommend that if adhesion needs to be increased to solve problems such as logo bridging, that HPC-EF or -LF be used at a maximum of 25% of the total polymer solids. Additional amounts may weaken the films too much to be useful.

Other polymer blends have been used at times by the industry. Blends of methylcellulose and polyvinyl pyrrolidone (PVP) have been used commercially. While PVP has poor film formation properties, it can be used at very high concentrations with very low viscosity in water. This could be a method of increasing polymer concentration without detrimentally raising solution viscosity. Care should be taken, however, to evaluate the properties of the film or coated tablet to ensure successful formulation.

**Figure 22: Effects of Plasticizer Concentration on METHOCEL E Premium LV Films (Toughness)**

![Figure 22: Effects of Plasticizer Concentration on METHOCEL E Premium LV Films (Toughness)](image)
**Figure 23:** Film Tensile Strength of Blends of METHOCEL E5P LV Hypromellose/Hydroxypropyl Cellulose

![Graph showing film tensile strength](image)

**Figure 24:** Film Strength of Blends of METHOCEL E5P LV Hypromellose/Hydroxypropyl Cellulose

![Graph showing film strength](image)

**Figure 25:** Film Elongation of Blends of METHOCEL E5P LV Hypromellose/Hydroxypropyl Cellulose

![Graph showing film elongation](image)

**Figure 26:** Young’s Modulus of Blends of METHOCEL E5P LV Hypromellose/Hydroxypropyl Cellulose

![Graph showing Young’s modulus](image)
Very often it is desirable to apply opaque, pigmented coatings. Pigmented coatings can provide additional light stability to dosage forms and help differentiate tablets by color. Most pigments are supplied as color dispersions in alcohol, propylene glycol, or water. Pigments used in tablet coatings generally are either aluminum lakes or iron oxides, with titanium dioxide and talc used in white or pastel colors.

When pigments are used in tablet coatings they have a significant effect on the film properties. As with any plastic, when pigments are added a reduction in flexibility and strength is usually experienced. Additionally, because the pigments are usually dispersed in a plasticizer like propylene glycol, the plasticization effect may be entirely dependent on the ratio of pigment to polymer used in the formulation. In the plasticizer section of this brochure it was shown that additional levels of propylene glycol in an unpigmented film did not necessarily lead to reduced film properties.

To examine the effect of the plasticizer supplied in pigment dispersions, a series of pigmented films was prepared using pigment and METHOCEL E15 Premium LV at a ratio of 1 to 2. A variety of commercial pigments were used and film properties plotted in Figure 27 versus the amount of plasticizer contributed by the pigment dispersion. A control unpigmented METHOCEL E15 Premium LV is plotted as well.

It is clearly seen that the pigmented films exhibit a distinct loss of strength from the unpigmented control. The very high levels of propylene glycol found in some of the pigment dispersions did not detrimentally affect film strength.

Normally, pigmented films are formulated with additional plasticizer even though there may be an excess available from the pigment dispersion. To evaluate the effect of additional plasticizer, an additional 20% polyethylene glycol 600 (PEG 600) was added to the pigmented film coatings. In every case an increase in film properties (Figure 28) was noted with the additional plasticizer. This strongly suggests the use of the optimal 20-30% additional polyethylene glycol plasticizer when formulating pigmented films.

Microbiological Considerations

When working with aqueous solutions, the possibility of microbiological contamination is a valid concern. It has been reported in the literature that many cellulose-based polymers can support microbiological growth. With cellulose ethers the higher the level of chemical substitution, the more resistant to enzymatic breakdown the polymer becomes. METHOCEL E products have a relatively high level of substitution but will support microbiological growth in the very low viscosity grades. It is therefore important to take reasonable care in the preparation of coating solutions to keep all the equipment and excipients clean. Usually GMP standards will suffice. METHOCEL Premium products are supplied to meet USP guidelines for microbiological attributes and are certified to be free of the USP pathogenic organisms. The production process for METHOCEL products is essentially self-sterilizing so no significant contamination of METHOCEL has ever occurred.

It is normally recommended that aqueous solutions be made and used within one week’s time. Additional protection can be obtained by the use of preservatives like propylparaben or methylparaben or the addition of alcohol to the solution.
**Use of METHOCEL in Sugar Coatings**

METHOCEL products have found application in sugar coatings as a seal coating or as a film modifier. As a subcoating, METHOCEL E5 Premium LV or METHOCEL E15 Premium LV can be used with or without plasticizer to place a protective layer over the tablet core. In cases where additional protection from moisture is desired, ETHOCEL* ethylcellulose can be combined with METHOCEL in a co-solvent blend of methylene chloride/alcohol and applied to the tablet cores. At 25% ETHOCEL Standard 10 Premium and 75% METHOCEL E15 Premium LV, little effect is seen on drug dissolution. At higher levels of ethylcellulose (e.g., >75%) a delay in drug diffusion is experienced.

METHOCEL products may be used in sugar coatings to reduce coating brittleness. In cases where hypromellose is dispersed in sugar systems, we recommend the use of METHOCEL K3 Premium LV or possibly METHOCEL E3 Premium LV for sugar compatibility. Compatibility is improved if the polymer is fully hydrated before the addition of sugar. Use of corn syrup for some of the sugar solids will also improve polymer compatibility in sugar systems. These hypromellose polymers may also replace the conventional use of acacia and/or gelatin in sugar coatings.

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Preparation of the Coating Solution

Proper preparation of the coating solution is necessary to achieve good coating in a reasonable amount of time. METHOCEL polymers are supplied as a fine powder and will rapidly hydrate in cold water. The hydration is so rapid that without proper agitation, clumps of gels with dry powder inside can form. Once formed, additional agitation and time are needed to completely hydrate all the polymer.

Several methods are useful in aiding the timely preparation of coating solutions.

1. Dispersion in hot water. Since METHOCEL products are not soluble in hot water, lump-free dispersing can be easily accomplished by dispersion in hot water. Temperatures in excess of 80°C are recommended, but even temperatures of 60-80°C will slightly aid the polymer dispersion. The polymer dispersion is then cooled to cause polymer hydration. The cooling may be accomplished externally in jacketed vessels or part of the water may be reserved as cold water and added after polymer dispersion.

2. Blending of ingredients. Another method to minimize polymer agglomeration consists of separating polymer particles by dilution with other coating excipients. Combinations of dry pigments, dry plasticizer, and polymer can often be added directly to process water.

3. Dispersion in a nonsolvent. When formulating hydroalcoholic or organic solvent coatings of METHOCEL, solutions are easily made by dispersing the polymer in alcohol (a non-solvent) and then hydrated by the addition of water. In organic systems METHOCEL can be dispersed in alcohol and then hydrated by the addition of methylene chloride.

4. Direct addition to room temperature water. This method, while the most difficult, is often used in large scale coating operations due to equipment and heat transfer limitations. METHOCEL products may be added directly to process water if a slow controlled addition of the polymer is used in combination with good agitation. Care must be taken to control the agitation level to minimize foaming and allow sufficient time for complete polymer hydration.
A Word about Foaming

Solutions of METHOCEL products have a tendency to foam under agitation because these polymers are surface active. Air entrapped in ingredients or that is introduced by excessive agitation can increase this tendency. However, once foaming had occurred, it can be reduced by defoamers like Dow Corning AF products or by settling over time.

When mixing solutions, the level of agitation should be changed as thickening occurs. Agitation should move the fluid surface in the vessel and start to pull a small vortex. As thickening occurs, the agitator speed will need to be increased to maintain sufficient mixing. Proper blade placement and baffling are necessary so consultation with equipment suppliers is recommended. A quiescent period of 15-45 minutes is usually recommended after mixing to allow most of the entrapped air to move to the surface.

A Word about Filtration

It is often beneficial to subject coating solutions to filtration. This ensures that any lumps or incompletely hydrated polymers are removed. Use of a 60 to 80 mesh screen can normally be accomplished with commercial filtration devices. Gravity flow is possible, but air pressurization is preferred for rapid filtration.

Application Rate

The rate of coating solution delivery is an important process control variable. While fast application of the coating solution is important to minimize batch times it must be remembered there are limitations for each type of equipment and coating solution being utilized. Practical limits can be determined by utilizing the basic thermodynamic relationships and monitoring exhaust air temperature. The flow rate of coating solutions is generally controlled by a positive displacement pump, although other coating systems may rely upon an air pressure pot delivery system. When using positive displacement pumps, viscosity of the coating solution is not a critical factor in the flow rate. However, when using a pressure pot delivery system, the viscosity of the coating solution will affect the delivery rate. It should also be recognized that the temperature of the coating solution will affect viscosity of the coating solution. As with most polymers, when the solution temperature increases (while staying below the thermal gelation temperature) the coating viscosity will decrease. The application of shear to concentrated polymer solutions can also reduce viscosity.

Air Atomization Pressure and Flow Rates

The amount of air being applied and the amount of pressure being utilized to atomize the liquid droplets can determine the efficiency and effectiveness of the coating system. It is important to make the smallest possible droplet size to ensure rapid drying. Air atomization is generally preferred with aqueous systems because it enhances initial liquid evaporation. Small droplets are necessary to achieve a fine, smooth surface on coating tablets. Changes in air flow rates and air atomization pressure can affect delivery rates when using a system other than a positive displacement pump.
**Spray Systems**

The numbers and types of spray nozzles utilized in any coating pan are of critical importance and information should be obtained from the equipment manufacturer. It is particularly important that nozzles be selected that can achieve a proper pattern for uniform coating of the tablet surfaces. Nozzle fan angles, the number of nozzles, and the distance from the tablet bed must be optimized so uniform side-to-side coating of the tablet bed is achieved without tending to overwet tablets or spray dry the solution. We recommend you seek information from both the equipment manufacturers for nozzles and coating pans for further information.

**Coating Equipment**

Modern film coating pans are manufactured by a variety of suppliers. Each supplier has its own configuration for the coating operation. Basic differences revolve around movement of air through the tablet bed. Some manufacturers move air upward through the tablet bed while others pass the air downward through the fluid bed. Some pans are fully perforated around the entire circumference while others have areas or regions of perforation. While there are some basic differences between these designs, each has its own beneficial features and can be effectively utilized for aqueous film coating. Some of the typical manufacturers of equipment today are: Driam of West Germany, Thomas Engineering, Vector Corporation, and Key Industries in the U.S.

Fluid bed coating of tablets may also be desirable for certain formulations. A variety of fluid bed coating equipment is manufactured with many application methods such as top spray, bottom spray, side spray, and tangential rotary spray. Fluid bed equipment is available from Glatt Air Techniques, Vector Corporation, and Aeromatic, as well as other companies.

**Drying Air**

The volume, temperature, and humidity of the drying air are critical in optimization of the coating process. Generally it is desirable to deliver the greatest possible amount of air at the desired 70-90°C temperature without causing over-fluidization of the tablet bed. Often older equipment is limited by air handling capacity or heating capacity. Therefore we recommend measurement of air flow rates and consultation with equipment manufacturers if coating capacity appears limited. Air flow rates should be monitored during the coating process as exhaust air filters can become restricted with over-spray, dust, and tablet particles.

The condition of inlet air also affects the drying capacity. High humidity air dries tablets less effectively than dry air. Thus a process optimized for one day's atmospheric conditions may need daily adjustment if the inlet air is not conditioned and controlled.

Normally, inlet air is controlled to the range of 70–90°C. Higher or lower temperatures may be desired for specific temperature-sensitive products or for fast coating application.

**The Tablet Load**

The pan loading and tablet dimensions will also affect coating efficiency. Most coating pans must be filled to an operative volume for tablet coating. Too few or too many tablets lead to inconsistent coating quality. Even the shape of tablets will affect the optimal loading and drying efficiency.
of the coating operation. Care must be taken in selection of the tablet shape to be coated. Friable tablets or soft tablets may be very difficult to coat. Tablets using a high level of waxy or hydrophobic ingredients may be difficult to coat due to poor adhesion or poor wetting.

**Conclusion**

Reliable, tough, printable, and economic tablet coatings can be applied quickly and efficiently, meeting USP, EP, JP, and FDA requirements, from aqueous systems based on METHOCEL E Premium products.

Where desired, the carriers for such coatings can be blends of water with alcohol or other solvents ... up to 100% organic solvent if the coater has not yet initiated aqueous coating.

Dow has been making cellulose ethers for pharmaceutical applications since 1938. Years of experience in solving application needs and developing new products that optimize desired performance are available to Dow customers and prospects.

These resources include a comprehensive bibliography of medical articles on the use of METHOCEL products in pharmaceuticals. In addition, Dow maintains several drug master files, a repository of information that you and the FDA can use to gain quick approval of new formulations. Specialized technical services such as individual consultation or problem-solving assistance by experts who specialize in pharmaceutical applications or METHOCEL products are available on request.

**For More Information**

To request additional information, complete literature, or product samples, you can reach a Dow representative by calling the phone numbers listed on the back cover. Or visit our web site at [www.methocel.com](http://www.methocel.com).
Health Considerations

METHOCEL cellulose ether products resemble naturally occurring plant and seaweed gums in many of their chemical, physical, and functional properties since all these materials possess a basic carbohydrate structure.

Gums have a long history of use in food and pharmaceutical products. METHOCEL cellulose ether products have had extensive evaluation and testing in both acute and long-term feeding studies in a number of species, including humans. Their use as food additives in a wide variety of food items and their broad use in pharmaceutical products attest to the safety of METHOCEL Premium cellulose ether products.

Dow has been making cellulose ethers for pharmaceutical applications since 1938. Years of experience in solving application needs and developing new products that optimize desired performance are available to Dow customers and prospects.

While dusts from METHOCEL products could conceivably cause temporary mechanical irritation to the skin and eyes under extreme conditions, and may be considered as a nuisance when breathed, the products are not expected to present a significant health hazard in handling. Although no special precautions typically need to be observed to handle the products safely, the use of an approved dust Respirator in dusty atmospheres is advised.

METHOCEL products are organic polymers that will burn under the right conditions of heat and oxygen supply. Fires can be extinguished by conventional means.

Storage

In storage or use of any dusts or fine powders, good housekeeping is required to prevent dusts in air from reaching possibly explosive levels.

Caution

Under certain conditions, a fine dust of this material in air may cause a dust explosion when exposed to heat, sparks, or open flame. See “METHOCEL Cellulose Ethers Technical Handbook” when handling large quantities. The National Fire Protection Association’s NFPA 654, “Standard for the Prevention of Fire and Dust Explosions in the Chemical, Dye, Pharmaceutical and Plastic Industries,” should also be followed.

With METHOCEL cellulose ether products with particle sizes of 74µ or less (finer than 200 mesh), critical levels are reached at concentrations of 28 gm/m³ (0.03 oz/ft³). The minimum ignition energy to cause a dust explosion is in the range of 28 mJ. Static of a human body has about 25 mJ.

It is also highly desirable to control dusts in order to prevent accidents caused by slippery floors and equipment.

As a USP grade item, Premium METHOCEL cellulose ethers should not be stored next to peroxides or other oxidizing agents, poisons, pesticides, or ill-smelling articles.
Accidental Spills

To prevent employee falls and accidents, floor spills of dry powder should be thoroughly vacuumed or swept up. Any slight residual product on the walls or floor can then be flushed with water into a sewer. If the spill is a viscous solution it should be further diluted with water before disposal.

Disposal

Dow studies show that METHOCEL cellulose ether products do not biodegrade (that is, they show no 5-, 10-, or 20-day BODs) in aquatic environments. They should therefore present no ecological hazard to aquatic life.

Since METHOCEL cellulose ether products and their formulations present no significant ecological problems they can be disposed of by industrial incineration or in an approved landfill, providing all federal, state, and local regulations are observed. Dow recommends that the material be buried in an approved landfill; incineration should be done under carefully controlled conditions to avoid possibility of dust explosion.

Customer Notice

Dow encourages its customers to review their applications of Dow products from the standpoint of human health and environmental quality. To help ensure that Dow products are not used in ways for which they are not intended or tested, Dow personnel will assist customers in dealing with ecological and product safety considerations. Your Dow sales representative can arrange the proper contacts.
For more information, complete literature, and product samples, you can reach a Dow representative at the following numbers:

From the United States and Canada: .................call 1-800-447-4369
..............................fax 1-989-832-1465

In Europe: .............................................toll-free +800 3 694 6367†
.................................................call +32 3 450 2240
.................................................fax +32 3 450 2815

From Latin America and Other Global Areas: .......call 1-989-832-1560
..............fax 1-989-832-1465

†Toll free from Austria (00), Belgium (00), Denmark (00), Finland (990), France (00), Germany (00), Hungary (00), Ireland (00), Italy (00), The Netherlands (00), Norway (00), Portugal (00), Spain (00), Sweden (00), Switzerland (00), and the United Kingdom (00).

Or you can contact us on the Internet at www.methocel.com

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