DIRECT COMPRESSION

WITH THE RIGHT INGREDIENTS IT’S A SIMPLE, COST-EFFECTIVE MANUFACTURING PROCESS

™Trademark of The Dow Chemical Company (“Dow”) or an affiliated company of Dow
WITH OUR FAMILY OF POLYMERS – METHOCEL™, POLYOX™ AND ETHOCEL™ – ENJOY THE SIMPLICITY AND BENEFITS OF DIRECT COMPRESSION, A MANUFACTURING PROCESS THAT HELPS GET PRODUCTS TO THE PATIENTS WHO NEED THEM IN LESS TIME AND FOR LESS MONEY.

SPEEDED AND SAVINGS SOUNDS GOOD TO US

At Dow Wolff Cellulosics, we put a lot of ingenuity into products that help pharmaceutical companies create novel medicines quickly and more cost effectively. That way, they can invest more time and money into developing life-changing and life-saving medicines.

WE’LL SHOW YOU THE WAY TO A BETTER TABLET

METHOCEL™ Premium Direct Compression (DC) grade hypromellose polymers offer an advanced level of consistency and predictable performance. Whether the desired result is durability, presentation, faster processing speed or a consistent drug release profile, depend on METHOCEL™ Premium DC to get there.

METHOCEL™ Premium DC is customized for direct compression providing:
- Excellent processing and dissolution profile without the need for wet granulation
- Greater tablet consistency and uniformity
- Multifunctional performance
- Low tablet-to-tablet weight variability
- Minimal tendency to separate
- Superior flow and tablet content uniformity while ensuring consistent drug delivery in controlled release formulations

METHOCEL™ Premium Direct Compression provides:
- Lower manufacturing costs by as much as 30% through the elimination of the wet granulation process
- Shortened development time – direct compression tablet manufacturing is the industry’s preferred choice with quicker scale-up
- Better for heat and moisture sensitive active pharmaceutical ingredients

SOMETHING FOR EVERYONE

Along with METHOCEL™ Premium DC grade polymers, we also offer additional excipients to meet direct compression formulation needs.

POLYOX™ water-soluble resins: Excellence in tablet binding
POLYOX™ demonstrates excellent binding properties in direct compression systems. In the case of matrix applications, it provides similar function (i.e., swelling in the stomach, forms gel structure and slowly releases active pharmaceutical ingredients from inside) as METHOCEL™. POLYOX™ is an ideal choice in matrix systems using osmotic technologies because it swells much faster but erodes quicker than METHOCEL™. It also has excellent flowability and good compaction properties, making it a good choice for a hydrophilic matrix. In addition, the lubricity of POLYOX™ also assists in tableting operations.

ETHOCEL™ Premium: Direct compression for controlled-release drugs
As a non-water soluble polymer, ETHOCEL™ Premium can help to further control the dissolution profile of controlled release medicines when blended with a water soluble matrix agent such as METHOCEL™ Controlled Release or METHOCEL™ Premium DC. ETHOCEL™ is available in three Fine Particle (FP) grades enabling its use as a direct compression binder without the use of solvents. The ETHOCEL™ FP grade has a smaller particle size than ETHOCEL™ Premium and provides suitable properties and performance for matrix applications. In manufacturing, the FP grade is uniformly mixed with the other system components and then the solid dose form is produced using economical direct compression. Upon compression, the finely-milled particles of ETHOCEL™ FP fuse into a semi-continuous, water-insoluble matrix requiring no solvents, heat, or additives. In the final pill, the water-soluble components of the system are released via diffusion from the water-insoluble structure. With three fine particle grades of ETHOCEL™ available, achieve a range of diffusion path sizes and lengths. The result? A solid dose form with excellent integrity and repeatable dissolution performance. If ETHOCEL™ FP is in the formulation, then the release profile is under your control.

With our family of polymers – METHOCEL™, POLYOX™ and ETHOCEL™ – enjoy the simplicity and benefits of direct compression, a manufacturing process that helps get products to the patients who need them in less time and for less money.
METHOCEL™ Premium DC has been developed to achieve the production economies of direct compression while assuring the multi-functional performance you expect from the time-proven METHOCEL™. These polymers improve powder system flowability while maintaining the excellent compressibility, tablet hardness, and controlled release performance. A number of evaluations have been performed to verify the performance of METHOCEL™ Premium DC.

Model One: Metoprolol tartrate system - improved tablet weight consistency, dissolution performance comparable to analogous METHOCEL™ CR grade

A metoprolol tartrate formulation was developed to compare performance in a system with known difficulties in direct compression processing. Metoprolol tartrate, a very soluble drug, is a "sticky" material, and the 150 micron average particle size further inhibits good flow. In addition, the formulation was developed with 10% active drug to challenge content uniformity.

Flow measurements obtained from the aeroflow tester showed significantly better flowability with METHOCEL™ DC. The aeroflow tester evaluates the avalanching behavior of a powder or powder blend and measures the time between successive avalanches. This measurement, known as the mean time to avalanche (MTA), is an indication of the flowability of the powder. A lower MTA indicates a better flowing powder. The MTA for the formulation containing the METHOCEL™ Premium DC was 5.5 seconds, compared to 9.1 seconds for the same system using METHOCEL™ Premium CR Grade polymer.

In use at the tablet press, METHOCEL™ DC Grade polymer yielded considerably lower tablet-to-tablet weight variability. Dissolution testing comparing the performance of the METHOCEL™ DC and CR Grade polymers yielded remarkably similar dissolution profiles.

### TABLE 2: Consistency of Tablet Weight, 10% Metoprolol Tartrate System, METHOCEL™ K4M Premium Hypromellose, Controlled Release Grade and Direct Compression Grade

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<th>Average Tablet Weight, mg</th>
<th>Standard Deviation</th>
<th>% Relative Standard Deviation</th>
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<tr>
<td>METHOCEL™ K4M Premium CR Grade</td>
<td>377.9</td>
<td>31.4</td>
<td>8.3</td>
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<td>METHOCEL™ K4M Premium DC Grade</td>
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<td>4.1</td>
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Formulation:
Metoprolol tartrate, 150 micron mean particle size (10%); METHOCEL™ K4M Premium CR grade or DC Grade hypromellose (25%); Lactose (54.5%); Starch 1500 (10%); Magnesium stearate (0.5%). Formed via direct compression on a 16 station Monesty Beta press.
Model Two: Granular acetaminophen - consistent release from a large particle size active

A second model system used granular acetaminophen with an average particle size of 400 microns. Acetaminophen is a sparingly soluble drug, well known to have poor compressibility behavior. Like the metoprolol tartrate model, this system used METHOCEL™ Premium CR and DC Grades.

The model 5 kg batch included:
- Granular acetaminophen, 400 micron mean particle size (30%)
- METHOCEL™ Premium CR Grade or DC Grade (25%)
- Lactose (34.5%)
- Starch 1500 (10%)
- Magnesium stearate (0.5%)

The model formulation was tableted via direct compression on a 16 station Manesty Beta press. In this batch, the average particle size was 400 microns. While large particle size provides very good flow properties, it introduces the potential for particle segregation and inconsistencies in tablet compressibility, hardness, and dissolution profiles. Acetaminophen is a sparingly soluble drug, well known to have poor compressibility behavior. Dissolution testing showed extremely comparable release profiles for the two forms of the METHOCEL™ K4M Premium Polymer, as illustrated in the chart.

Reduced waste, greater tablet consistency with significant potential cost savings

As the metoprolol tartrate and acetaminophen studies have shown, METHOCEL™ Premium DC can provide excellent value when designing drug formulations specifically for direct compression processing. They can help provide greater consistency in dosage physical properties, help improve processing speed and performance, and help yield predictable and consistent drug release profiles. Moreover, METHOCEL™ Premium DC can be an excellent choice to replace conventional polymers when the goal is to improve processing and dosage properties.

### TABLE 2: CONSISTENCY OF TABLET WEIGHT, 10% METOPROLOL TARTRATE SYSTEM, METHOCEL™ K4M PREMIUM HYDROXYPROLLOSE, CONTROLLED RELEASE GRADE AND DIRECT COMPRESSION GRADE

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