

**Introducing METHOCEL™ DC Grade  
Hypromellose Polymers for Direct  
Compression of Controlled Release  
Dosage Forms**

Achieve Excellent Processing, Physical Properties  
and Dissolution Profiles without the Need for  
Wet Granulation

Direct Compression



**Now, Enjoy the Simplicity of Direct Compression and Meet All Other Controlled Release Objectives**



METHOCEL™ Premium Direct Compression (DC) Grade Hypromellose Polymers have been developed to achieve the production economies of direct compression while assuring the multi-functional performance you expect from this time-proven excipient family. These polymers improve powder system flowability while maintaining the excellent compressibility, tablet hardness, and controlled release performance for which METHOCEL™ products have long been known.

Two direct compression grades are currently available: METHOCEL™ K4M Premium DC and METHOCEL™ K100M Premium DC. Both polymers have been modified to optimize direct compression performance while maintaining the same nominal solution viscosities, degrees of methoxyl and hydroxypropyl substitution, and other important properties of their Controlled Release (CR) Grade counterparts. Chemically identical to original METHOCEL™ Premium products, you are assured of working with familiar materials. These DC grades meet all the specifications of the US Pharmacopoeia, the European Pharmacopoeia and the Japanese Pharmacopoeia.



**Table 1: Properties of METHOCEL™ Premium Hypromellose Direct Compression Grade Products**

	<b>METHOCEL™ K4M Premium DC Grade Hypromellose</b>	<b>METHOCEL™ K100M Premium DC Grade Hypromellose</b>
<sup>1</sup> Methoxyl %	19.0 – 24.0	19.0 – 24.0
<sup>1</sup> Hydroxypropyl %	7.0 – 12.0	7.0 – 12.0
USP Substitution Type	2208	2208
Apparent Viscosity, Brookfield, 2% in Water @ 20°C, mPa·s	2663 – 4970	72,750 – 135,800
<sup>1</sup> Bulk Density (g/mL)	0.12 – 0.15	0.12 – 0.15
<sup>1</sup> Moisture, %	5% max.	5% max.

<sup>1</sup>Typical values, not to be construed as sales specifications

## Lab studies show excellent flow, processing and tablet properties

METHOCEL™ DC Grade polymers are primarily designed to help improve powder flowability in order to facilitate direct compression methods and take advantage of the approximate 30% manufacturing cost savings and faster scale-up that are typical when the wet granulation step can be eliminated.

A number of evaluations have been performed to verify the performance of the new METHOCEL™ DC Grade polymers.

### Metoprolol Tartrate System: Improved Tablet Weight Consistency, Dissolution Performance Comparable to Analogous Controlled Release 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.

#### Metoprolol Tartrate Formulation, 5 kg Batch

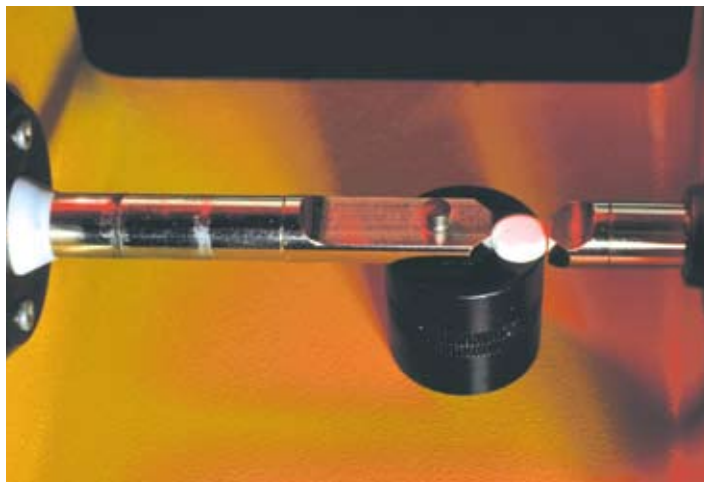
Metoprolol tartrate, 150 micron mean particle size (10%)  
 METHOCEL™ K4M Premium CR Grade or DC Grade hypromellose (25%)  
 Lactose 54.5%)  
 Starch 1500 (10%)  
 Magnesium stearate (0.5%)

The formulation was mixed and tested for flowability using an Aeroflow tester. Tablets were formed via direct compression on a 16 station Manesty Beta press.

Flow measurements obtained from the Aeroflow tester showed significantly better flowability with the DC Grade. 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 mean time to avalanche (MTA) for the formulation containing the METHOCEL™ Premium DC Grade polymer was 5.5 seconds, compared to 9.1 seconds for the same system using METHOCEL™ Premium CR Grade polymer.

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

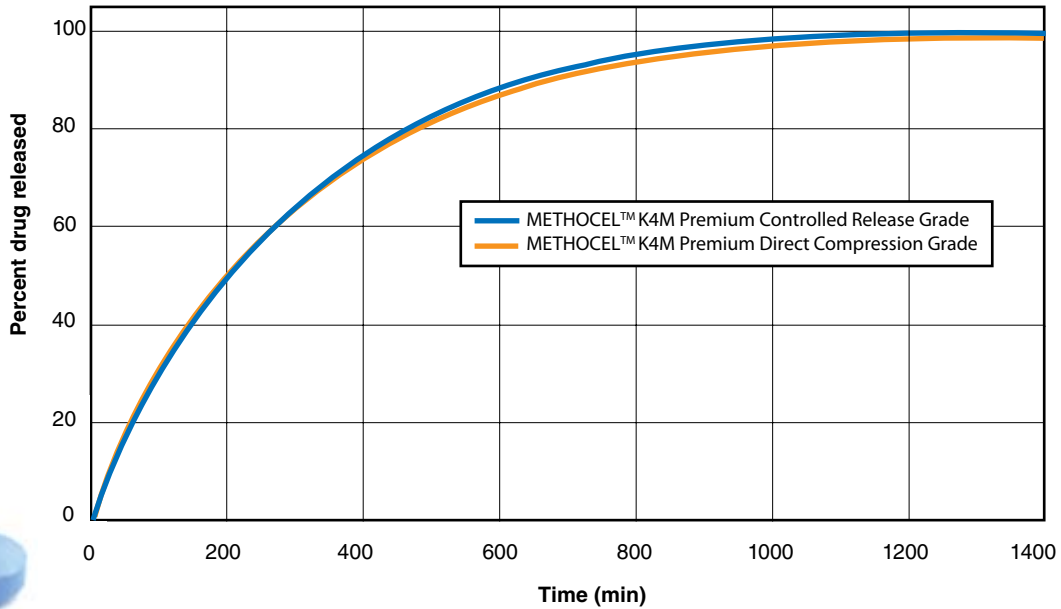
	Average Tablet Weight, mg	Standard Deviation	% Relative Standard Deviation
METHOCEL™ K4M Premium Controlled Release Grade	377.9	31.4	8.3
METHOCEL™ K4M Premium Direct Compression Grade	401.0	4.1	1.0



In use at the tablet press, the DC Grade METHOCEL™ polymer yielded considerably lower tablet-to-tablet weight variability, as shown in Table 2.

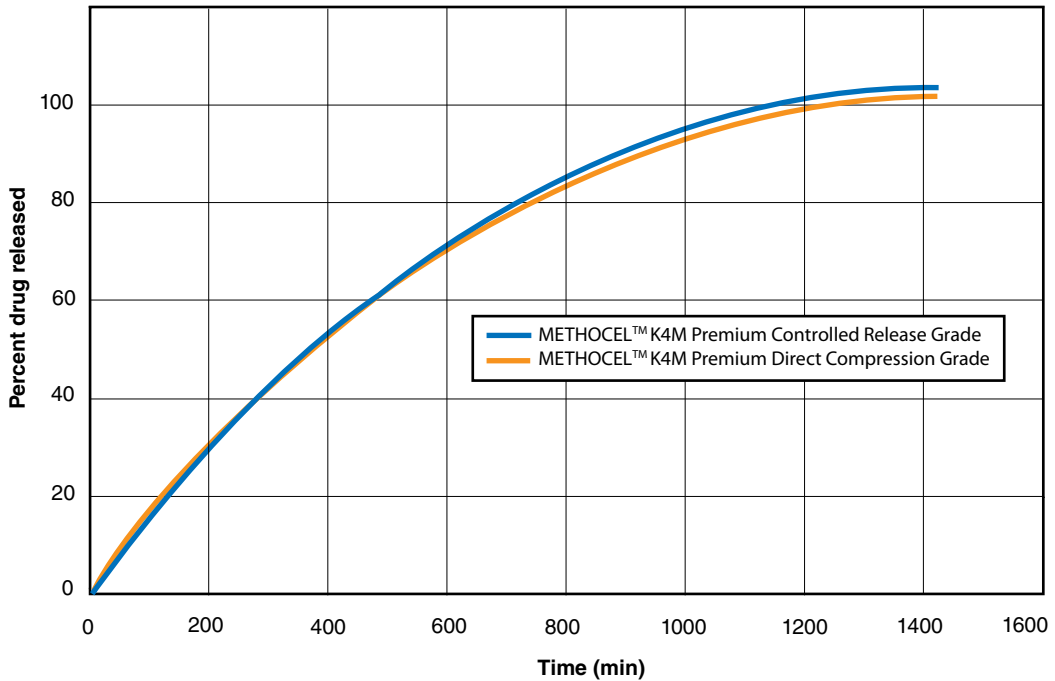
Dissolution testing comparing the performance of the DC and CR Grade METHOCEL™ polymers yielded remarkably similar dissolution profiles. See Figure 1.

**Figure 1: Comparison of Metoprolol Tartrate Release Profiles, METHOCEL™ K4M Premium Hypromellose, Controlled Release Grade and Direct Compression Grade**



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 Manesty Beta press.

**Figure 2: Comparison of Granular Acetaminophen Release Profiles, METHOCEL™ K4M Premium Hypromellose, Controlled Release Grade and Direct Compression Grade**



Formulation: Granular acetaminophen, 400 micron mean particle size (30%); METHOCEL™ K4M Premium CR Grade or DC Grade hypromellose (25%); Lactose (34.5%); Starch 1500 (10%); Magnesium stearate (0.5%). Formed via direct compression on a 16 station Manesty Beta press.



**Granular Acetaminophen  
System: 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 CR and DC Grades of METHOCEL™ K4M Premium hypromellose. While the large particle size provides very good flow properties, it introduces the potential for particle segregation and inconsistencies in tablet compressibility, hardness, and dissolution profiles.

**Granular Acetaminophen  
Formulation, 5 kg Batch**

Granular acetaminophen, 400 micron mean particle size (30%)  
METHOCEL™ K4M Premium CR Grade or DC Grade hypromellose (25%)  
Lactose (34.5%)  
Starch 1500 (10%)  
Magnesium stearate (0.5%)

The model formulation was mixed, then tableted via direct compression on a 16 station Manesty Beta press.

Dissolution testing again showed extremely comparable release profiles for the two forms of the METHOCEL™ K4M Premium polymer, as shown in Figure 2.





**Developmental System Exhibits  
Reduced Waste, Greater Tablet  
Consistency with Significant  
Potential Cost Savings**

As the metoprolol tartrate and acetaminophen studies have shown, METHOCEL™ DC Grade polymers 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™ DC Grade polymers can be an excellent choice to replace conventional polymers when the goal is to improve processing and dosage properties. This is illustrated in the following example.

A customer was working with a system containing 14% of a freely-soluble active drug with a 50 micron average particle size, and 40% METHOCEL™ K100M Premium CR Grade hypromellose. Initial evaluations showed the need to improve powder flow to improve consistency of tablet weight and hardness, as well as to shorten batch start-up times and reduce waste generation.

METHOCEL™ K100M Premium DC Grade hypromellose was evaluated as a performance-improving replacement for the CR Grade polymer. In a 20 kg batch trial using a Fette 1200 tableting press (24 station, 40 rpm), the DC Grade METHOCEL™ polymer overcame the previous shortcomings and yielded several significant improvements:

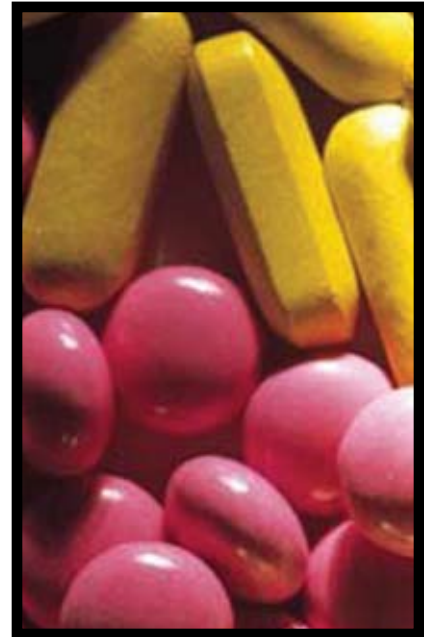
- 22-65% reduction in tablet weight relative standard deviation (See Table 3.)

- Compression force relative standard deviation reduced from 11-14% to 6-8%, resulting in more consistent tablet-to-tablet weight and hardness
- Significant reduction in formulation waste upon start-up, with a significant potential net cost savings

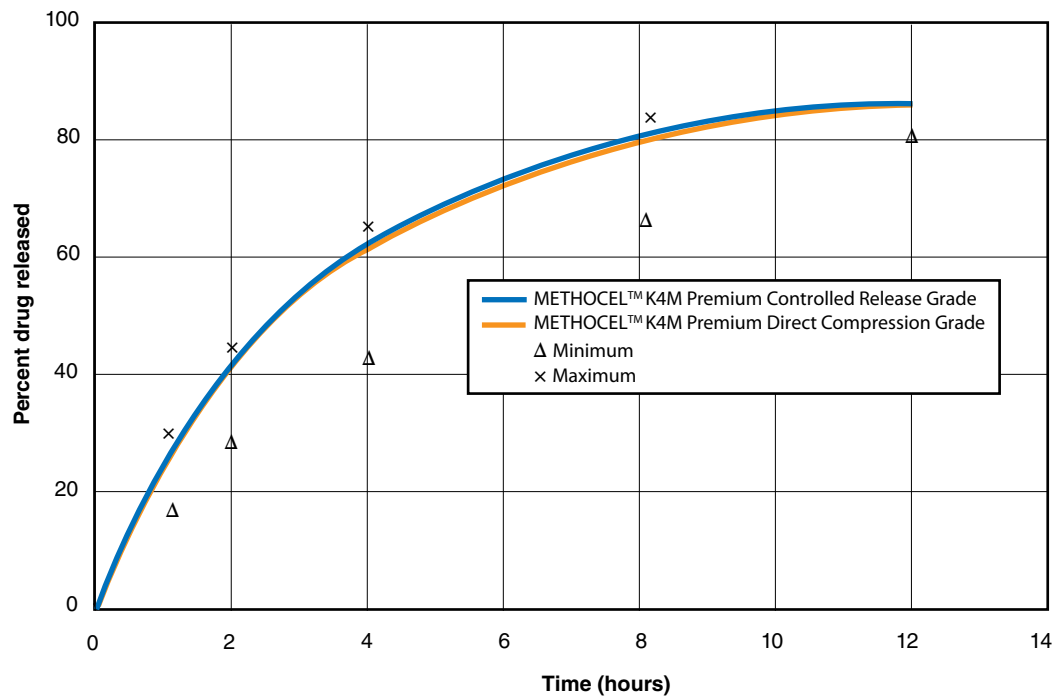
In addition, release profiles for the DC Grade and the CR Grade METHOCEL™ polymer systems were comparable. See Figure 3.

**Table 3: Comparison of Tablet Weight Relative Standard Deviation, METHOCEL™ K100M Premium Hypromellose, Controlled Release Grade and Direct Compression Grade**

Formulation	Tablet Weight Relative Standard Deviation		
	Batch Beginning	Batch Middle	Batch End
METHOCEL™ K100M Premium Controlled Release Grade Formulation	1.39	2.96	2.50
METHOCEL™ K100M Premium Direct Compression Grade Formulation	1.08	1.02	1.33



**Figure 3: Comparison of Developmental System Release Profiles, METHOCEL™ K100M Premium Hypromellose, Controlled Release Grade and Direct Compression Grade**



**Learn More about METHOCEL™ Premium Direct Compression Grade Hypromellose Polymers:  
Contact Dow Today**

This literature can provide only a brief overview of METHOCEL™ Premium DC Grade Hypromellose Polymers. There's much more to learn, and we're adding daily to our knowledge base on these exciting new products.

To learn how they might fit into your current or developing formulation, contact us at the phone, fax, or web contacts below. We look forward to hearing from you!

---

**For more information, complete literature, and product samples,  
you can reach a Dow representative at the following numbers:**

**From North America:**

call 1-800-447-4369  
fax 1-989-832-1465

**In Europe:**

toll-free +800 3 694 6367<sup>†</sup>  
call +32 3 450 2240  
fax +32 3 450 2815

**In Latin America:**

call +55 11 5188 9222  
fax +55 11 5188 9749

**In the Pacific:**

call +60 3 7958 3392  
fax +60 3 7958 5598

**All Pacific countries except Indonesia & Vietnam:**

toll-free call 800 7776 7776<sup>††</sup>  
toll-free fax 800 7779 7779<sup>††</sup>

<sup>†</sup>Toll-free from Austria (00), Belgium (00), Denmark (00), Finland (990), France (00), Germany (00), Hungary (00), Ireland (00), Italy (800 783825) 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.dowexcipients.com](http://www.dowexcipients.com)**

NOTICE: No freedom from any patent owned by Seller or others is to be inferred. Because use conditions and applicable laws may differ from one location to another and may change with time, Customer is responsible for determining whether products and the information in this document are appropriate for Customer's use and for ensuring that Customer's workplace and disposal practices are in compliance with applicable laws and other governmental enactments. Seller assumes no obligation or liability for the information in this document. NO WARRANTIES ARE GIVEN; ALL IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE ARE EXPRESSLY EXCLUDED.

Published October 2008

