



PTR-062-2 (Supersedes PTR-062-1)

## Benecel™ Hydroxypropylmethylcellulose

### *For Nutraceutical Modified Release Dosage Forms*

Benecel hydroxypropylmethylcellulose (HPMC) is a high-purity, water-soluble, non-ionic cellulose ether frequently used in the nutraceutical industry. Benecel HPMC complies with the monograph requirements for purity in the current editions of the Food Chemicals Codex, the EC Commission Directive and the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Most recently, hydroxypropylmethylcellulose has been additionally referred to as hypromellose.

This bulletin describes two high viscosity grades of Benecel HPMC used to modify release of nutraceutical active ingredients:

EP/USP Nominal Harmonized Viscosity Range of 2% Solution (mPa·s)

K35M	26,250 – 49,000
K200M	150,000 – 280,000

Because HPMC is a non-ionic polymer, hydration and viscosity are not affected by the pH of either acidic (0.1N HCl) or neutral solutions (pH 7 buffer). The particle sizing of these grades is a maximum of 8% of the dry powder retained on a 120 mesh (0.125 mm) screen. Tests have shown a volume mean diameter of 0.090 to 0.095 mm, using light scattering (Helos particle analyzer of Sympatec Inc.)

Further product information and typical properties are provided in our *Product Data Sheet, BENECEL High Purity Methylcellulose* and our *Product Brochure, BENECEL High Purity Methylcellulose/Hydroxypropylmethylcellulose Physical and Chemical Properties*.

The studies presented below highlight the release characteristics and tablet physical properties of two typical model formulations, containing either a glucosamine/chondroitin sulfate combination or Vitamin B6 (pyridoxine hydrochloride). Moreover performance comparisons are presented for Benecel and competitive HPMC products.

### Glucosamine/Chondroitin Sulfate

Glucosamine and chondroitin sulfate are popular joint maintenance supplements, however they require the administration of multiple doses per day. Longer acting formulations can reduce dosing frequency and enhance patient convenience. Modified release formulations were therefore developed with 15 and 20% Benecel HPMC. The studies focused on direct compression with high (78 to 83%) active levels of these highly soluble ingredients. Release profiles were also compared to release from tablets prepared with low shear wet granulation.

Measured using a Brookfield viscometer. This viscosity is too high to be reliably measured using a Ubbelode viscometer.



## Formulations:

Each tablet contained 500mg of glucosamine and 400mg of chondroitin sulfate. The formulations are given below. Tablet weights were 1080 and 1150mg, for HPMC contents of 15 and 20%, respectively.

Glucosamine	43.5 or 46.3%
Chondroitin sulfate	34.8 or 37.1%
Benecel™ HPMC	15 or 20%
Stearic acid	1.6 to 1.7%

**Methods:** First, the glucosamine, chondroitin sulfate and Benecel HPMC were passed through a 20-mesh sieve and blended for 5 minutes in a two-quart V-blender. Vegetable-source stearic acid was then added to the blend through a 20-mesh screen and blended for an additional 3 minutes. Tablets were directly compressed on an instrumented Manesty Beta press fitted with 0.750" x 0.343" (.065 concavity) tooling. The press was run at 37.5 rpm with the compression force set at 15 or 25kN.

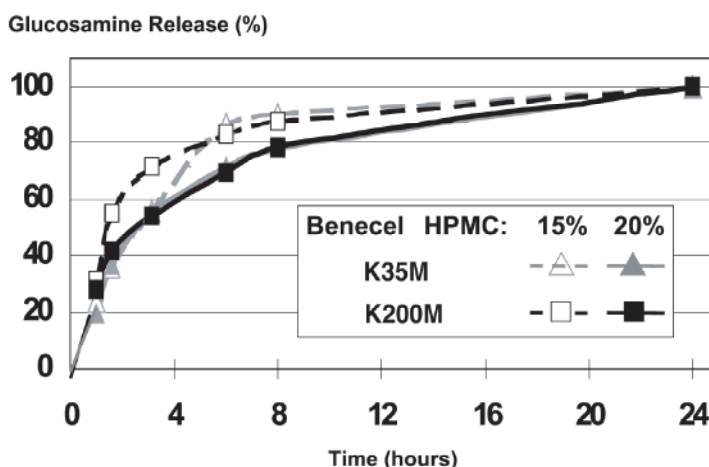
For the wet granulation study, the powder blend was wet-massed in a low-shear Hobart mixer using water as the granulation solvent. The wet mass was then tray dried in a convection oven before milling (Fitzmill fitted with .065" screen, medium speed with knives forward). The reduced granulation was placed in a V-blender and screened stearic acid was added. The materials were then blended for 3 minutes. Tablets were made using the same tooling as used for the direct compression formulas.

For each batch, 10 tablets were tested for thickness, weight, and diametral crushing force using the Schleuniger\* Tablet Tester 6D of Vector Corporation. Friability was determined from 250 rotations of 10 tablets using the Model 10809 Vanderkamp™ friabilator of Van-Kel Industries.

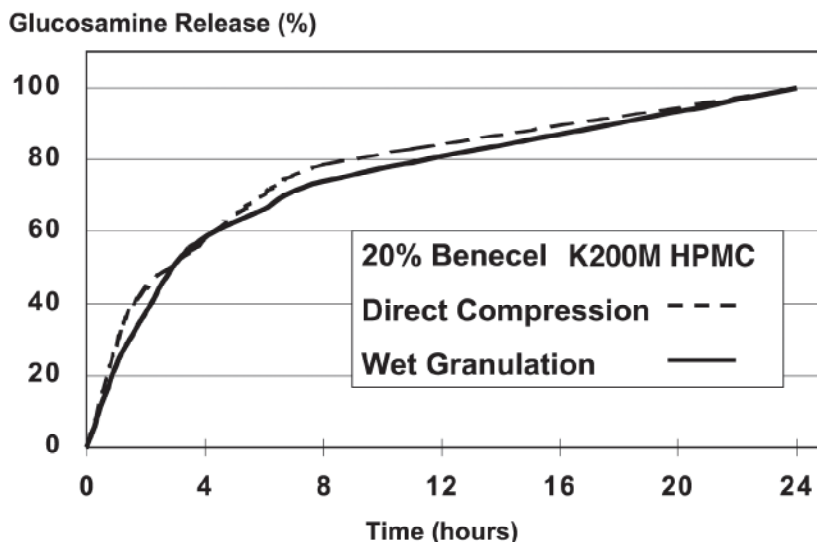
Glucosamine release rates were determined in a Van-Kel USP Apparatus I (basket) at 100 rpm. Samples were withdrawn at regular intervals and glucosamine concentration was determined by reverse phase HPLC coupled with a differential refractive index detector. The dissolution medium used was USP pH 1.5 buffer (0.1N HCl).

**Modified Release Rates:** Figure 1 shows the resulting glucosamine release profiles using Benecel K35M and K200M. Increasing the HPMC content from 15 to 20% provided some further retardation of the release rate. In contrast, increasing the viscosity of HPMC by a factor of approximately 3.5 had no effect on release rates as indicated by the similar release profiles for Benecel K35M and K200M. Figure 2 shows that nearly identical release results were obtained for 20% Benecel K200M in direct compression and low shear wet granulation.

**Figure 1**  
**Glucosamine Release Profiles**  
**Benecel K35M and K200M HPMC: 15 and 20% Use Levels**  
**Direct Compression, 25kN Compression Force**

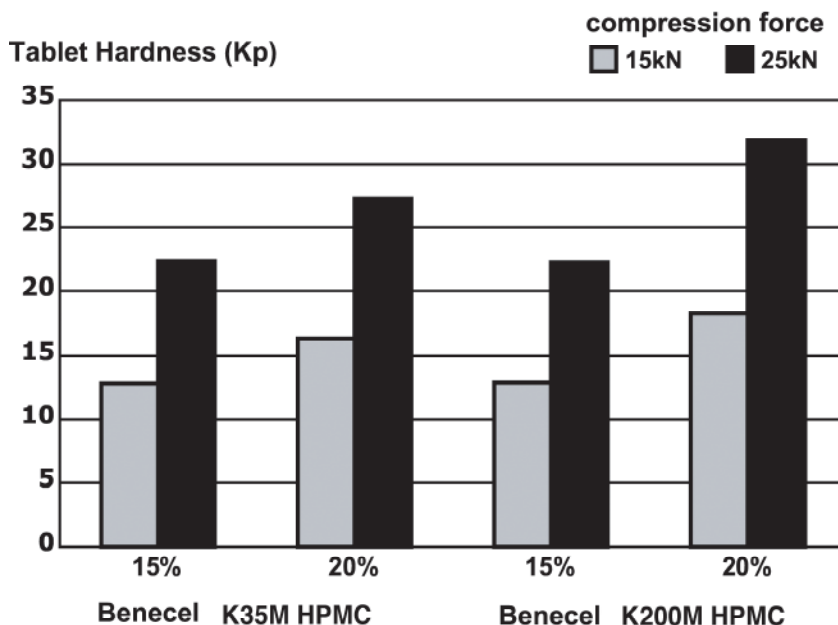


**Figure 2**  
**Glucosamine Release Profiles**  
**Benecel™ K35M and K200M HPMC: 20% Use Level**  
**Direct Compression and Low Shear Wet Granulation**  
**25kN Compression Force**

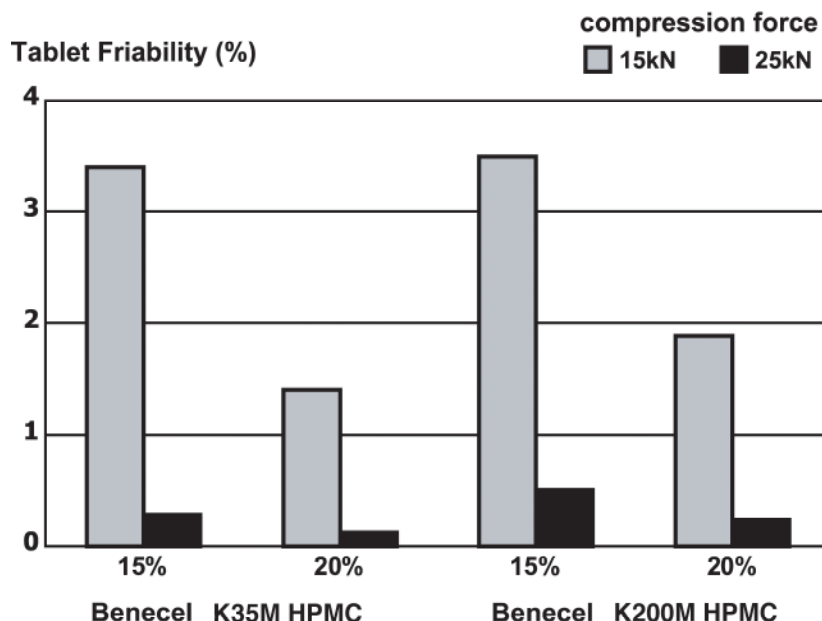


**Tablet Physicals:** The hardness and friability results are shown in Figures 3 and 4, respectively, for tablet compression forces of 15 and 25kN. The tablet hardness ranged from 13 to 18 Kp for 15kN compression force, and increased to 22 to 32 Kp for 25kN compression force. Higher levels of HPMC provided higher hardness values. Acceptable friability performance (less than 0.5%) is shown for the higher compression force.

**Figure 3**  
**Glucosamine/Chondroitin Sulfate Tablet Hardness**  
**Benecel K35M and K200M HPMC**  
**Direct Compression**

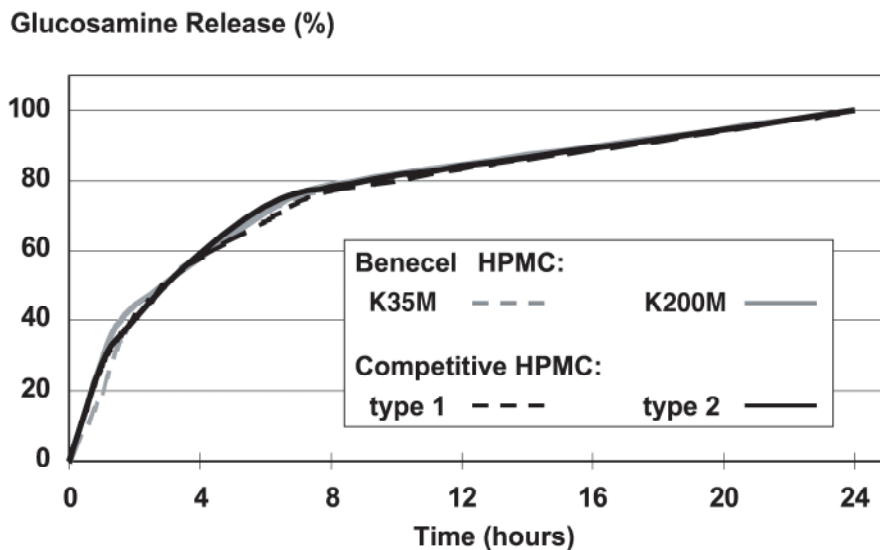


**Figure 4**  
**Glucosamine/Chondroitin Sulfate Tablet Friability**  
**Benecel™ K35M and K200M HPMC**  
**Direct Compression**

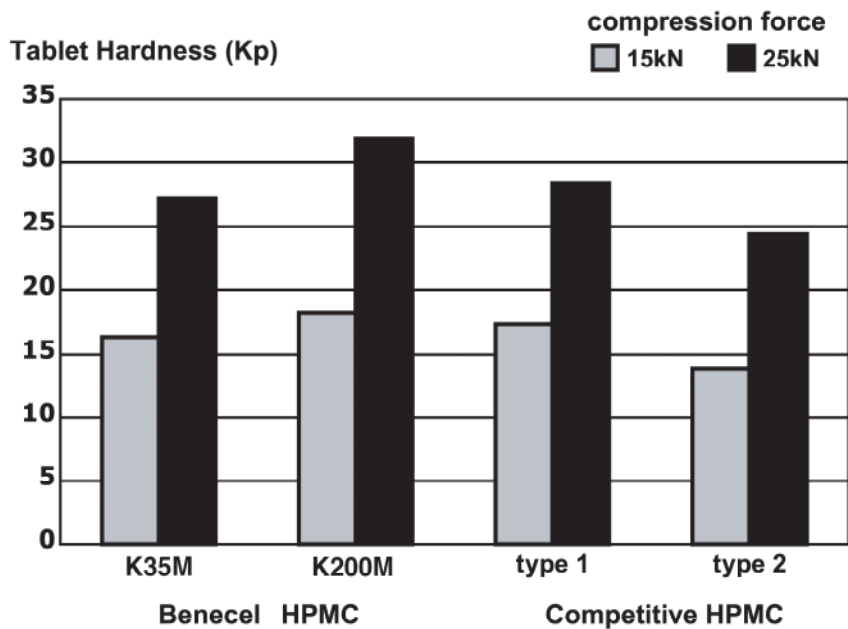


**Competitive HPMC:** The release profiles and tablet physicals obtained for both Benecel K35M and K200M HPMC grades were compared with two competitive high viscosity types of HPMC. Test results shown in Figure 5 through 7 show similar release performance, hardness and friability.

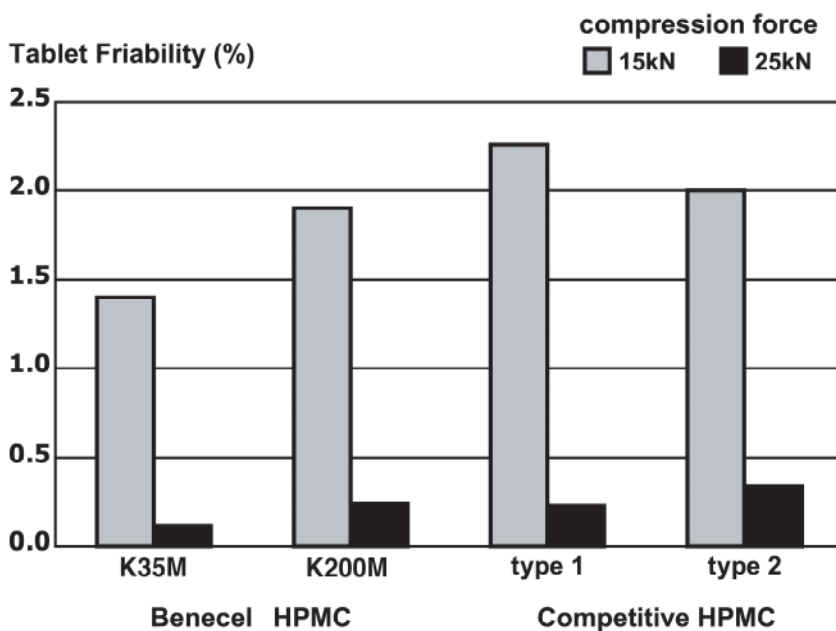
**Figure 5**  
**Glucosamine Release Profiles**  
**Benecel K35M and K200M HPMC and**  
**2 Competitive High Viscosity Types of HPMC**  
**20% Use Level, 25kN Direct Compression**



**Figure 6**  
**Glucosamine/Chondroitin Sulfate Tablet Hardness**  
**Benecel™ K35M and K200M HPMC and**  
**2 Competitive High Viscosity Types of HPMC**  
**20% Use Level, Direct Compression**



**Figure 7**  
**Glucosamine/Chondroitin Sulfate Tablet Friability**  
**Benecel K35M and K200M HPMC and**  
**2 Competitive High Viscosity Types of HPMC**  
**20% Use Level, Direct Compression**



**Conclusion:** Benecel™ HPMC is well suited for modified release formulation of nutraceutical tablets as exemplified by this direct compression system, which presents the dual challenges of highly water soluble actives and high active content. Benecel provides good release retardation and excellent tablet hardness and friability. The robustness of these systems is highlighted by the nearly identical results obtained by direct compression and low shear wet granulation.

## Vitamin B<sub>6</sub>

As a second model system, vitamin B<sub>6</sub> was formulated for modified release to further demonstrate the utility of Benecel K200M HPMC as a directly compressible controlled release polymer. Due to its very high water solubility, vitamin B<sub>6</sub> is a challenging substance for modified release.

### Formulations:

Each 300mg tablet contained 75mg of vitamin B<sub>6</sub>. The formulations are given below:

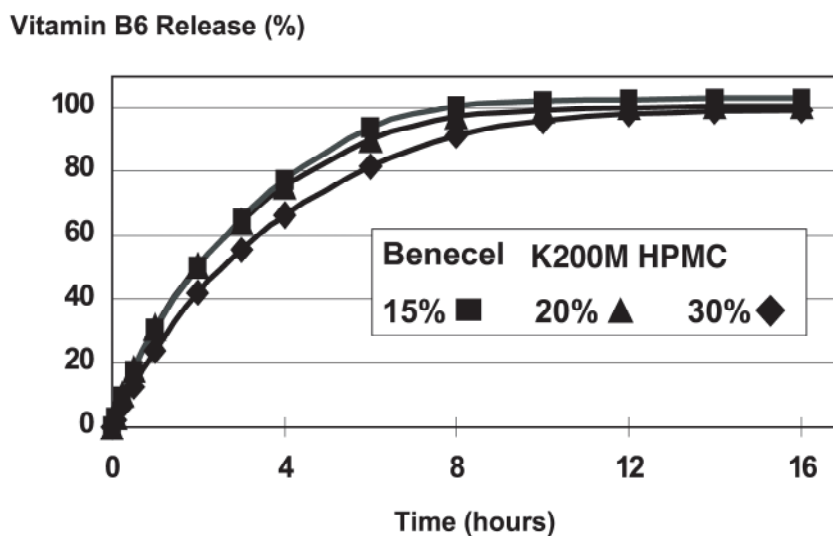
Vitamin B <sub>6</sub>	25%	25%	25%
Benecel K200M HPMC	15%	20%	30%
Microcrystalline cellulose	58%	53%	43%
Stearic acid	2%	2%	2%

**Methods:** The vitamin B<sub>6</sub>, Benecel K200M HPMC and Avicel\* PH 102 microcrystalline cellulose (MCC) of FMC Corporation were hand screened (20 mesh) and then blended for 5 minutes in a V-blender. Vegetable-source stearic acid was then hand screened through a 20 mesh sieve and added to the powder blend and mixed for a further 3 minutes. Using  $\frac{3}{8}$ " standard concave tooling, tablets were directly compressed at 5, 15 and 25kN on an instrumented Manesty Beta press. Tablet hardness and friability were determined as described in the glucosamine/chondroitin sulfate study.

Vitamin B<sub>6</sub> dissolution rates were determined in a Van-Kel USP Apparatus I (basket) at 100 rpm. Samples were withdrawn automatically at regular intervals and vitamin B<sub>6</sub> concentration was determined spectrophotometrically. The dissolution medium was USP pH 1.5 buffer (0.1 N HCl).

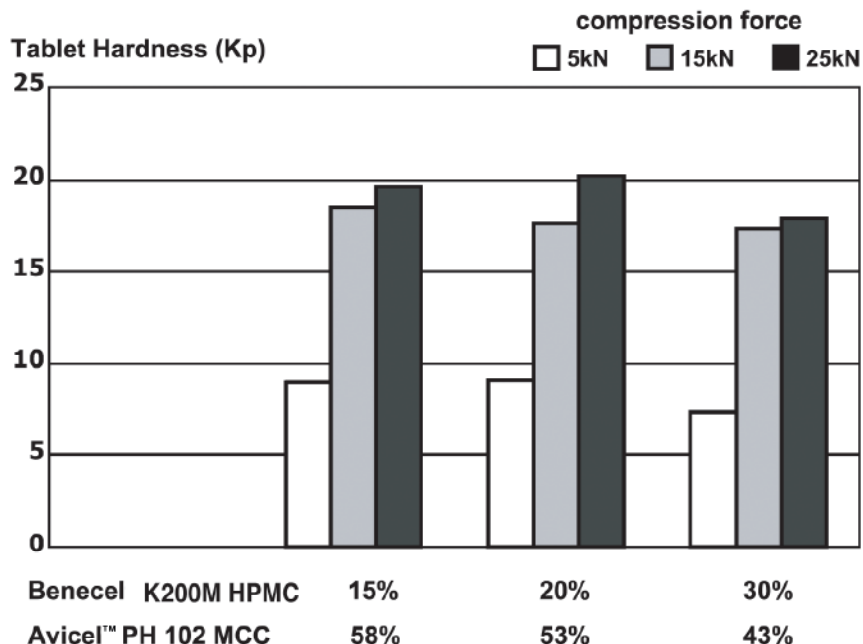
**Modified Release Profiles:** Release results are summarized in Figure 8. Two-hour release was between 40 and 50% of the vitamin B<sub>6</sub> dose. Four-hour release showed 66 to 78% release of the dose. It can be seen that even relatively low levels, Benecel HPMC is effective in retarding the release of this highly soluble active.

**Figure 8**  
**Vitamin B<sub>6</sub> Release Profiles**  
**Benecel K200M HPMC**  
**Direct Compression, 25kN Compression Force**



**Tablet Physicals:** As shown in Figure 9, tablet hardness did not vary significantly over the range of Benece<sup>l</sup>™ HPMC levels studied. This may be due to the high level of MCC included in these formulations. Friability was zero for all formulations and compression forces tested.

**Figure 9**  
**Vitamin B<sub>6</sub> Tablet Hardness**  
**Benece<sup>l</sup> K200M HPMC**  
**Direct Compression**



**Conclusion:** This vitamin B<sub>6</sub> formulation further demonstrates the utility of Benece<sup>l</sup> HPMC for modified release of challenging, highly soluble actives. Direct compression techniques can be used to simplify tablet production.

**Materials:**

1. Benece<sup>l</sup> K35M and K200M hydroxypropylmethylcellulose, marketed by Ashland Specialty Ingredients, Ashland Inc., Wilmington, DE.
2. Glucosamine sulfate, potassium, marketed by Ashland Nutritional Products, Irvine, CA.
3. Chondroitin sulfate, sodium, marketed by Technical Sourcing International, Missoula, MT.
4. Stearic acid, NF and Magnesium stearate, NF, marketed by The Crompton Corporation (formerly Witco Chemical Corporation), Middlebury, CT.
5. Pyridoxine HCl (B<sub>6</sub>), marketed by Spectrum Chemicals & Laboratory Products, Gardenia, CA.