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Benecel™ Hypromellose

For use in Modified Release Drug Dosage Forms: Performance Similarity to Competitive Grades

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Objective

To demonstrate the performance of Benecel hypromellose as a matrix forming polymer in various modified release formulations and show performance similarity to leading competitive grades of hypromellose.

Introduction

For hydrophilic matrix tablets, drug release is modified as the polymer is hydrated, forming a diffusion barrier around the tablet. Controlling factors mediating drug release include drug solubility and concentration, polymer concentration, swelling and erosion, effects of pH and other excipients and processing variables.

The grades of Benecel hypromellose for modified release contain a methoxyl content of 20.0-24.0% and a hydroxypropoxyl content of 7.0-12.0%. These conform to the US Pharmacopeia requirement for type 2208 substitution of hypromellose, and are therefore designated as Benecel K types.

The Brookfield viscosity of these grades is defined by the two digits which follow the K designation. The first of these 2 digits is a multiplier, the second digit defines the order of magnitude. As examples, K4M would define nominal viscosity of 4 x 10^3 = 4 000 mPa·s, and K100M would define a viscosity of 1 x 10^5 =100000 mPa·s. The following grades were evaluated in the studies reported here:

Benecel Hypromellose	
Grade	**European Pharmacopoeia Viscosity (mPa·s)**
K4M	3,600
K15M	18,000
K100M	100,000

Differences in viscosity measurement techniques account for the differences in the values shown in the table on page 1. Also shown are three analogous competitive hypromellose grades from a leading producer. These competitive grades will be shown to provide similar performance in the studies that follow.

The Ashland nomenclature for a nominal viscosity of this product is based on a standard Brookfield method, using the RVT spindle at 20 rpm on 2% solutions maintained at 20°C, based on dried product. Full specifications for the product, including viscosity following the guidance of the European Pharmacopoeia and the US Pharmacopeia, are available (1), as is further product characterization (2). For further formulation options, two other grades of Benecel hypromellose are available, K35M and K200M (1).

The studies reported here characterize the performance of Benecel™ hypromellose in modified release hydrophilic matrix model drug systems. For this purpose, two model drug systems were employed: (a) soluble theophylline, a weak base with solubility ~0.8 mg/ml, combined with the soluble filler lactose and (b) naproxen, a weak acid, with low solubility at neutral or acidic pH, combined with an insoluble filler, microcrystalline cellulose (MCC). Comparable performance of the three analogous competitive grades is shown. Various dissolution conditions were also studied, including varying paddle speed, USP apparatus and the pH and ionic strength of the dissolution media.

Procedures

Theophylline Model: The three grades of Benecel hypromellose and three analogous competitive grades were studied in separate direct compression formulations with theophylline.

To prepare the formulations, 25% hypromellose, 26.7% theophylline, and 47.8% spray-dried lactose were presieved through a 20 mesh screen and dry-blended in a V-blender for 5 minutes. These mixtures were then lubricated with 0.5% magnesium stearate (20 mesh presieved), with further blending for 2 minutes. Prior to compression, powder flow was assessed by measuring the mean time to avalanche (AeroFlow™ powder flowability analyzer of TSI Incorporated).

Tablets (400 mg) were compressed with a compaction force of 25 kN on an instrumented rotary press (Manesty BetaPress) equipped with 0.375" flat faced beveled edge tooling. Tablets were measured for diametral crushing strength on a Model HT-500 Hardness Tester of Key International Inc. Friability was measured using 10 tablets per lot at 250 rotations.

Tablet dissolution was performed in a USP apparatus I (basket) at 100 rpm in pH 6.8, 0.05M phosphate buffer USP. To assess robustness under various hydrodynamic conditions, selected dissolution tests were also run at 150 rpm in USP apparatus I and at 50 rpm in USP apparatus II (paddle). Further studies compared dissolution at pH = 6.8 and 1.5. To assess salt effects, media with two different ionic strengths (μ) were studied: (a) μ = 0.075 (pH 6.8, 0.05M phosphate buffer USP) and (b) μ = 0.15 (via adjustment with sodium chloride, pH = 6.8 also).

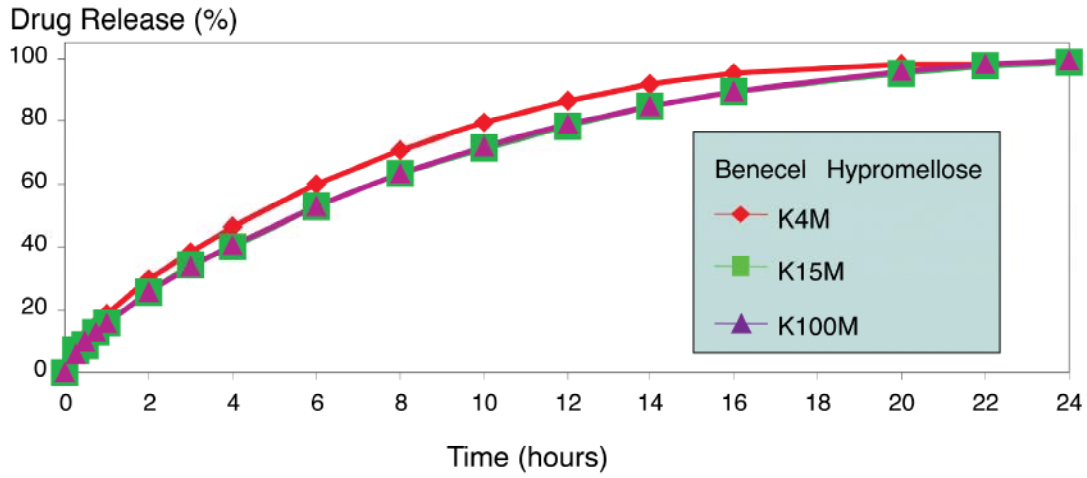
Naproxen Model: To assess performance with a low soluble drug, naproxen, a direct compression formulation comprising 30% hypromellose, 20% naproxen, 49.5% silicified, high density MCC and 0.5% magnesium stearate was prepared using similar techniques as noted above. Dissolution was performed in pH 7.4, 0.1M phosphate buffer using the USP apparatus I.

Similarity in dissolution profiles for Benecel hypromellose and three analogous competitive grades of hypromellose was assessed by calculating the f_2 similarity factor, as described by Moore and Flanner (3). The effect of the various dissolution conditions was also assessed with the f_2 similarity analysis. Release profiles are deemed similar if the f_2 factor is found be greater than 50.

Results

Theophylline Model: Figure 1 shows the relative release profiles for the three grades of Benecel hypromellose. In general, high molecular weight grades provide slower release. As noted by previous investigators, there is a viscosity threshold beyond which further viscosity increases lead to negligible *in vitro* dissolution rate decrease. Roshdy, Schnaare et al (4), however, have shown significant *in vivo* dissolution differences among theophylline formulations comprising high molecular weight hypromellose types. The differences in the *in vivo* performance were related to
gel strength.

Figure 1
Theophylline Model
Relative Release Profiles for Three Grades of Benecel™ Hypromellose
Test Conditions — Basket, 100 rpm, pH 6.8, 0.05M Phosphate Buffer



Figures 2 through 4 show the comparable performance of the Benecel hypromellose grades and the three analogous competitive grades. Table 1 provides the high f_2 similarity factors, demonstrating similar performance.

Figure 2
Theophylline Model Relative Release Profiles for
Benecel K4M Hypromellose and Competitive Grade 4 000
Test Conditions — Basket, 100 rpm, pH 6.8, 0.05M Phosphate Buffer

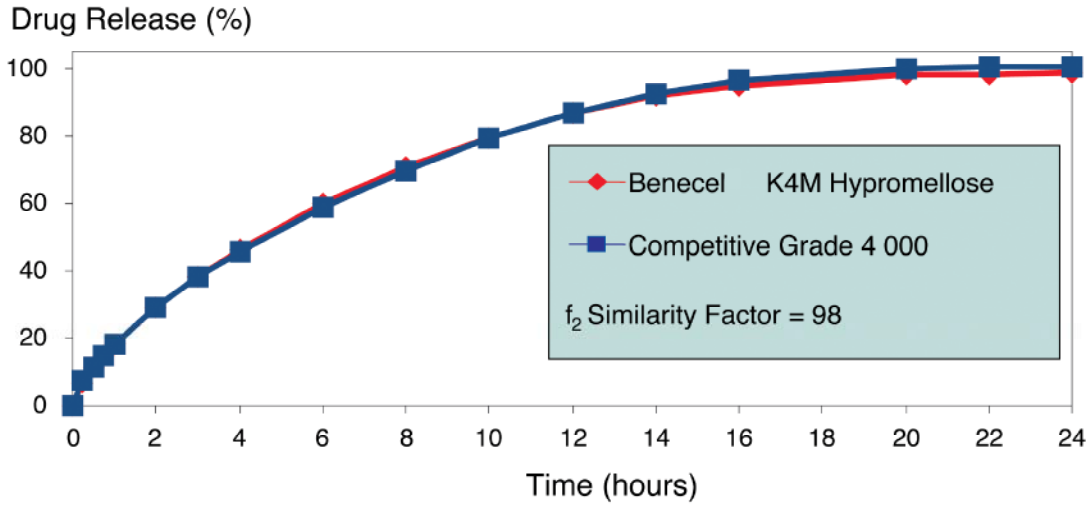


Figure 3
Theophylline Model Relative Release Profiles for
Benecel™ K15M Hypromellose and Competitive Grade 15 000
Test Conditions — Basket, 100 rpm, pH 6.8, 0.05M Phosphate Buffer

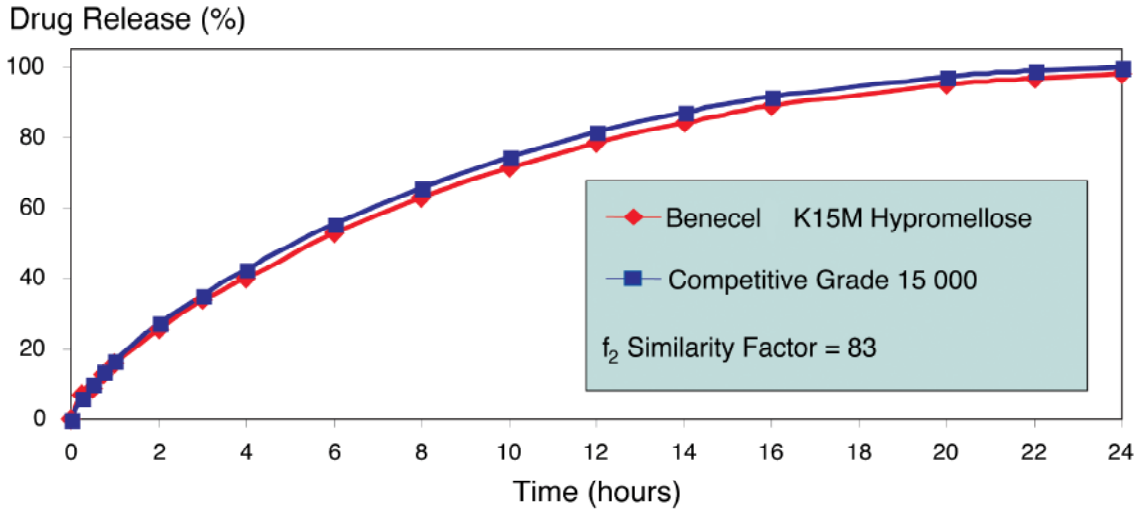


Figure 4
Theophylline Model Relative Release Profiles for
Benecel K100M Hypromellose and Competitive Grade 100 000
Test Conditions — Basket, 100 rpm, pH 6.8, 0.05M Phosphate Buffer

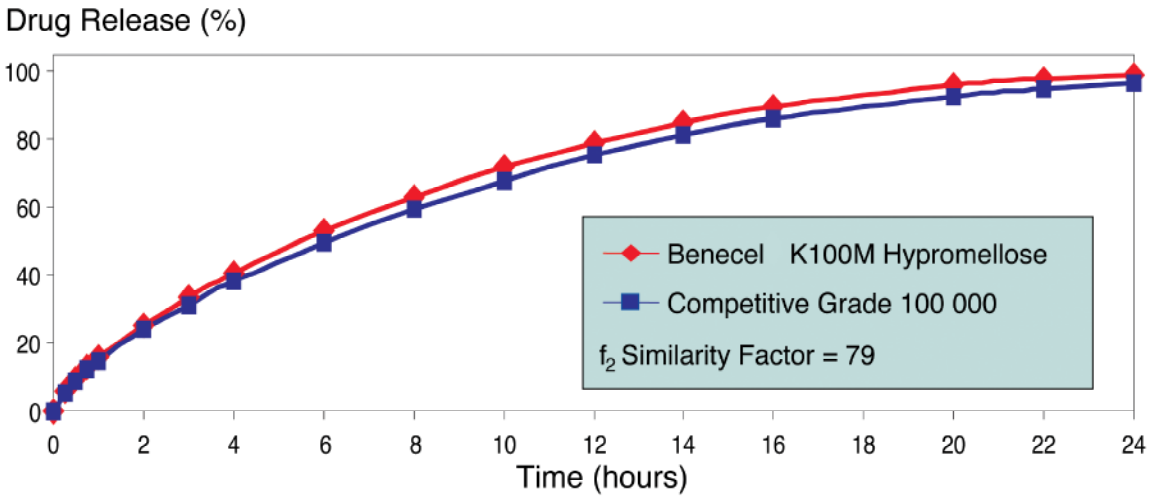
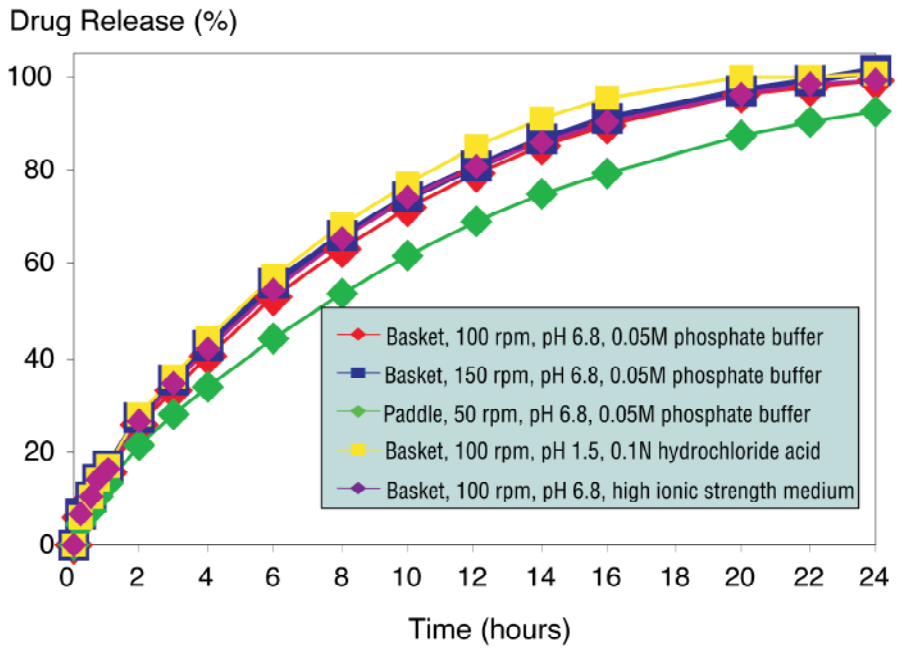


Table 1
Theophylline Release Profiles – Similarity of Formulations with Benecel™ Hypromellose and Analogous Competitive Grades

Test Conditions	Benecel Hypromellose	Competitive Hypromellose	f_2 Similarity Factor
Basket, 100 rpm, pH 6.8, 0.05M phosphate buffer	K4M	4 000	98
	K15M	15 000	83
	K100M	100 000	79
Basket, 150 rpm, pH 6.8, 0.05M phosphate buffer	K100M	100 000	85
Paddle, 50 rpm, pH 6.8, 0.05M phosphate buffer	K100M	100 000	98
Basket, 100 rpm, pH 1.5, 0.1M phosphate buffer	K100M	100 000	84
Basket, 100 rpm, pH 6.8, high ionic strength medium	K100M	100 000	78

Figure 5 shows the release profiles provided by Benecel K100M hypromellose with varying dissolution conditions, demonstrating that the release profiles were not affected by raising the basket speed, or changing the pH or ionic strength of the dissolution media. Due to different hydrodynamic conditions, a slower release dissolution was found when using the paddle apparatus at 50 rpm. Table 1 shows the high f_2 similarity factors demonstrating similar performance with the competitive hypromellose grade 100 000. The similarities in release profiles under a variety of hydrodynamic conditions and in different dissolution media indicates that these hypromellose grades are functionally similar in this typical swellable matrix system, providing diffusion and erosion control on drug release.

Figure 5
Theophylline Model
Relative Release Profiles for Benecel K100M Hypromellose
Various Test Conditions



Variation among competitive excipients may impact parameters related to the manufacturability of tablets. This may manifest as critical differences in compactibility, powder flow or maximum achievable die fill weight. Table 2 shows comparable physical properties of the tablets and powders (density and flow via mean avalanche time and compressibility index) for the Benecel™ hypromellose grades and the analogous competitive grades.

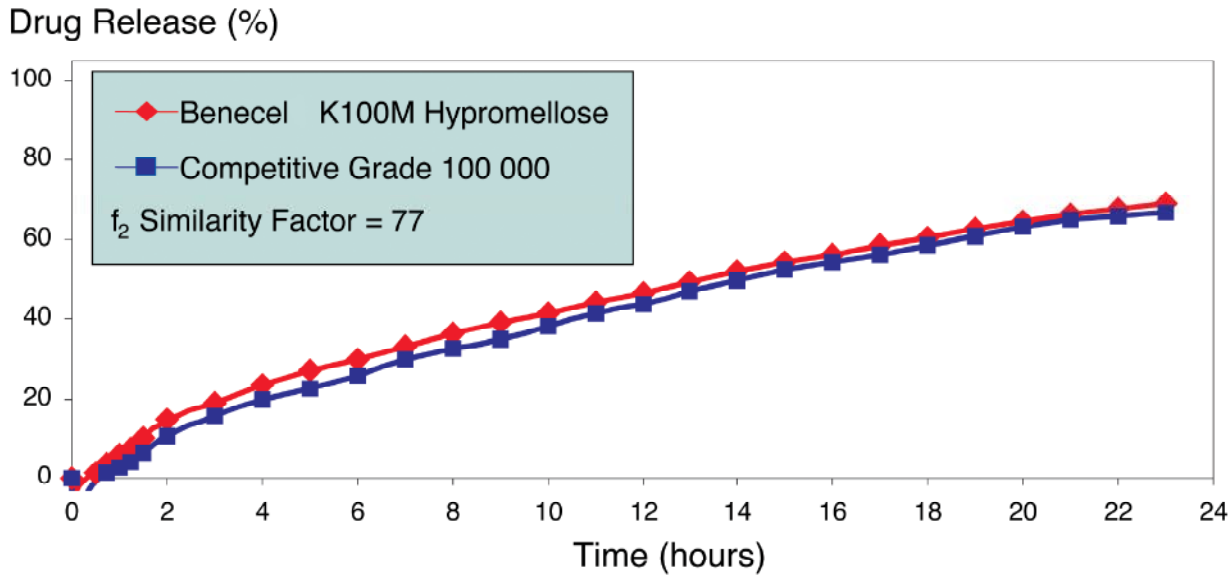
Table 2
Theophylline Tablet and Powder Characterization —
Similarity of Formulations with Benecel Hypromellose and Analogous Competitive Grades

Hypromellose Grade		Crushing Strength[1] (kP)	Friability (%)	Mean Time to Avalanche (s)	Compressibility Index (%)	Bulk Density (mg/ml)
Benecel	K4M	30.7 (1.2)	0.10	4.1	22	0.496
Competitive	4 000	29.2 (0.7)	0.05	3.6	22	0.486
Benecel	K15M	29.1 (1.1)	0.05	4.2	26	0.465
Competitive	15 000	30.9 (1.2)	0.03	3.8	24	0.467
Benecel	K100M	28.4 (0.1)	0.08	3.8	24	0.446
Competitive	100 000	29.2 (1.3)	0.10	3.7	25	0.470

[1]Standard deviations for n=10 samples shown in parentheses.

Naproxen Model: As with the theophylline formulations, naproxen release profiles in Figure 6 are nearly superimposable for Benecel K100M hypromellose and competitive hypromellose grade 100 000. The f_2 similarity factor for this comparison is very high, with a value of 77.

Figure 6
Naproxen Model Relative Release Profiles for
Benecel K100M Hypromellose and Competitive Grade 100 000
Test Conditions — Basket, 100 rpm, pH 7.4, 0.1M Phosphate Buffer



Conclusions

This study shows that Benecel™ hypromellose and analogous competitive grades provide similar diffusion and erosion control on drug release in typical, swellable matrix systems.

Two drug models were studied, soluble theophylline with lactose and low soluble naproxen with MCC.

Powder flow and tablet compactibility of the various formulations were also comparable.

Furthermore, dissolution behavior was evaluated under a wide range of hydrodynamic and media conditions. In all cases, the Benecel hypromellose grades were similar to the analogous competitive grades.

Further studies will expand this work, to explore wet granulation and varying polymer levels. Early studies have shown similar performance of Benecel hypromellose in direct compression and wet granulation.

References

1. Benecel Hypromellose for Pharmaceutical Applications, Ashland Product Data 4233.

2. Moore, J.W. and H.H. Flanner, H.H, 1996, Mathematical Comparison of Dissolution Profiles. Pharmaceutical Technology, 20(6):64-74, 2000.

3. Roshdy M. N., Schnaare, R.L. et al., The Effect of Controlled Release Tablet Performance and Hydrogel Strength on In Vitro / In Vivo Correlation. Pharmaceutical Development and Technology, 7(2): 155 – 168, 2002.

Materials

1. Benecel hypromellose, grades K4M, K15M, K35M, K100M, and K200M, marketed by Ashland Specialty Ingredients, Ashland Inc., Wilmington, DE.
2. Theophylline anhydrous, USP, marketed by BASF Corporation, Mount Olive, NJ.
3. HyQual* magnesium stearate, NF, marketed by Mallinckrodt Inc., a Division of Tyco International, St. Louis, MO.
4. Fast-Flo* spray-dried lactose, NF, marketed by Foremost Farms USA, Rothschild, WI.
5. ProSolv HD* 90 silicified microcrystalline cellulose, NF, marketed by J. Rettenmaier & Söhne GmbH & Co. KG, Rosenberg, Germany.
6. Naproxen, USP, marketed by Spectrum Chemicals, New Brunswick, NJ.