PTR-077

Dissolution Performance and Robustness of New Hypromellose Controlled-release Polymers

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Introduction

In some instances, it is difficult to develop good *in vitro-in vivo* correlations for controlled-release matrix systems due to variations in gastrointestinal tract (GIT) hydrodynamic conditions and GIT fluid compositional factors such as fat, bile salt content, and ionic strength (1). It is postulated that variability in release profiles and lack of robustness can be exacerbated by using blends of different molecular weight grades of hypromellose HPMC. Benecel™ K250 PH PRM, K750 PH PRM, and K1500 PH PRM HPMC grades were developed to obviate the need for blending and offer a potential solution to the problem of dissolution variability. Benecel PH PRM grades of HPMC are of intermediate viscosity and have tight, unimodal MW distribution.

In this study, the dissolution performance and robustness of matrix tablets developed with Benecel K250 PH PRM, K750 PH PRM and K1500 PH PRM HPMC grades under varying hydrodynamic stress conditions and in dissolution media of varying ionic strengths are investigated. Formulations containing blends of Benecel K4M and K100LV Pharm HPMC to achieve analogous viscosities were used as comparators. Glipizide (GLIP, aqueous solubility ~ 37 mg/L) and carbamazepine (CBZ, aqueous solubility ~ 17.7 mg/L) were chosen as model low-solubility drugs.

Experimental Methods

Wet granulation. 1 kg batches comprising polymer (30%), drug (25% for GLIP and 67% for CBZ), and microcrystalline cellulose were wet granulated in a high shear mixer. The granules were dried, milled, and lubricated with 0.5% magnesium stearate. Matrix tablets (400 mg for GLIP and 600 mg for CARB) were compressed on an instrumented Manesty Beta Press.

Drug-release profile. Dissolution was tested at 37°C with 7.5 pH phosphate buffer with 0.1% Tween 80 for GLIP and 1% SLS in DI water for CARB. The hydrodynamic effects were simulated by running the dissolution with an USP Apparatus I at 100 and 150 rpm or with USP Apparatus III (Bio Dis, Varian Inc., Cary, NC) at 5 and 25 dpm. The effect of fluid composition was determined by running the dissolution in media of varying pH (2 hrs in 0.1 N HCl and then in corresponding buffer) and ionic strength (adjusted with NaCl).

Cloud point. This value was determined using a Mettler Toledo FP900 Cloud Point Analyzer at 1.0% concentration in differing dissolution media, plotting the light transmission through the polymer solution as a function of the temperature.

Rheology (Gel Strength). The GLIP tablets were placed in the aqueous and alcoholic dissolution media for 2 hrs at 37°C. The deformation of the gel layer that formed on the tablet was analyzed using a TA Instruments rheometer (Model # AR-G2) in compression mode and an aluminum probe with a diameter of 6.4 mm. The compression stress (resistance of the gel layer) applied to the tablet was plotted against the true compression strain (the degree of gel layer deformation).

Materials

1. Glipizide, marketed by Ria International, East Hanover, NJ
2. Carbamazepine, marketed by Ria International, East Hanover, NJ
3. Benecel™ hypromellose (HPMC), marketed by Ashland, Wilmington, DE
4. Avicel* PH 101 microcrystalline cellulose (MCC), marketed by FMC, Philadelphia, PA
5. HyQual* magnesium stearate, marketed by Mallinckrodt Inc., a division of Tyco International, St. Louis, MO

Results and Discussion

Figures 1, 2 and 3 show dissolution, erosion and swelling profiles for glipizide tablets tested under standard (USP Apparatus I, 100 rpm) dissolution conditions. Variation is observed with tablets prepared with equivalent viscosity Benecel™ K4M/K100LV HPMC blend as compared with tablets prepared with custom viscosity Benecel K250 PH PRM HPMC, K750 PH PRM HPMC and K1500 PH PRM HPMC grades. Similar results were obtained with carbamazepine (Figure 4). Figures 5 and 6 show the impact of increasing hydrodynamic stress on the dissolution rate and variability of glipizide tablets made with Benecel K750 PH PRM HPMC and the equivalent 750 cps viscosity Benecel K4M/K100LV HPMC blend. Increasing the basket stirring rate from 100 to 150 rpm in USP apparatus I had only a marginal effect on Benecel K750 PH PRM HPMC. However, variability increased greatly for formulations containing the blend of HPMC grades with standard deviation (SD) of individual time points exceeding 15%. Extreme variability, including controlled-release failure, was seen when formulations containing a Benecel K4M/K100LV HPMC blend were subject to testing in USP apparatus III (reciprocating cylinder) at 5 and 25 dips per minute (dpm; Figure 6). By contrast, the custom Benecel K750 PH PRM HPMC grade with tight, unimodal distribution showed extremely robust dissolution behavior with a small increase in rate when agitation was increased from 5 to 25 dpm (Figure 6). These results may be of particular significance when considering the *in vivo* behavior of HPMC matrix tablets dosed under fed and fasted conditions, when significant mechanical attribution and hydrodynamic stress is expected in fed conditions (2). Similar trends were also observed with carbamazepine (Figures 7 and 8).

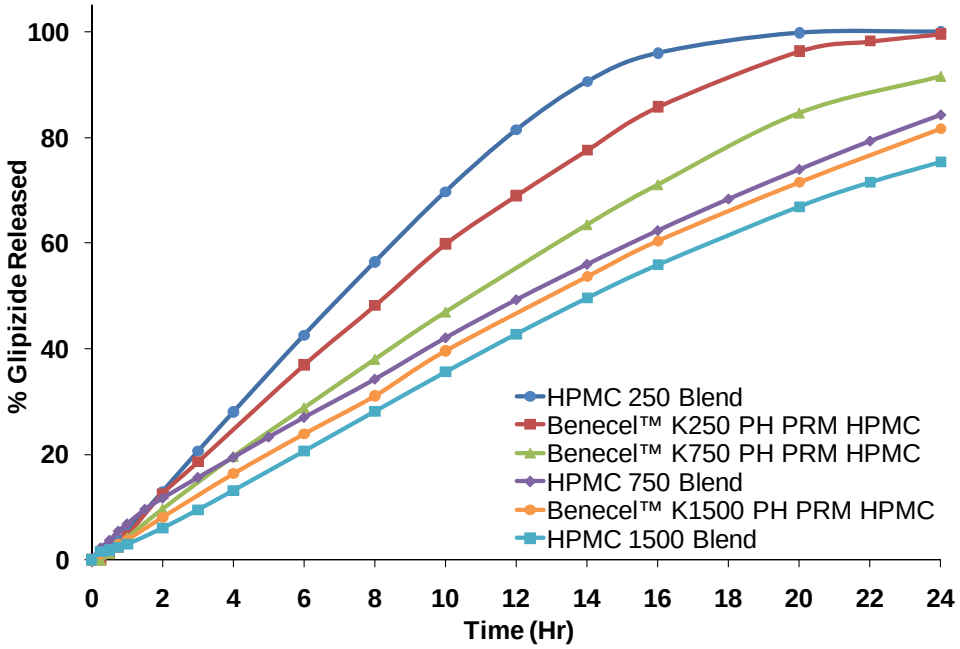

Figure 1. The effect of the Benecel PH PRM HPMC grades and their equivalent viscosity Benecel K4M/K100LV HPMC blends on the dissolution profile of GLIP matrix tablets.

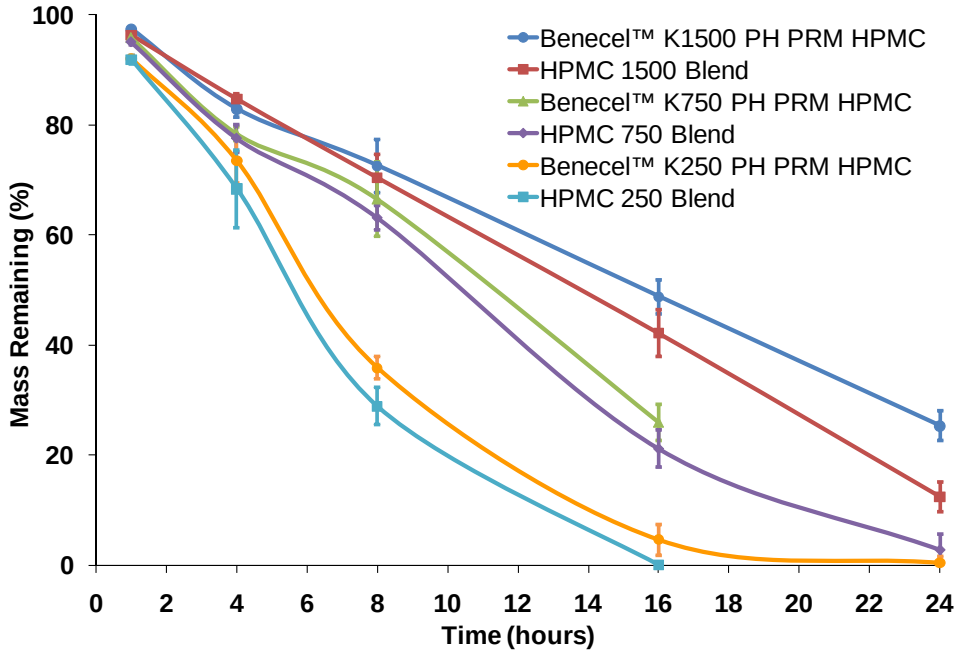

Figure 2. The effect of the Benecel™ PH PRM HPMC grades and their equivalent viscosity Benecel K4M/K100LV HPMC blends on the erosion profile of GLIP matrix tablets.

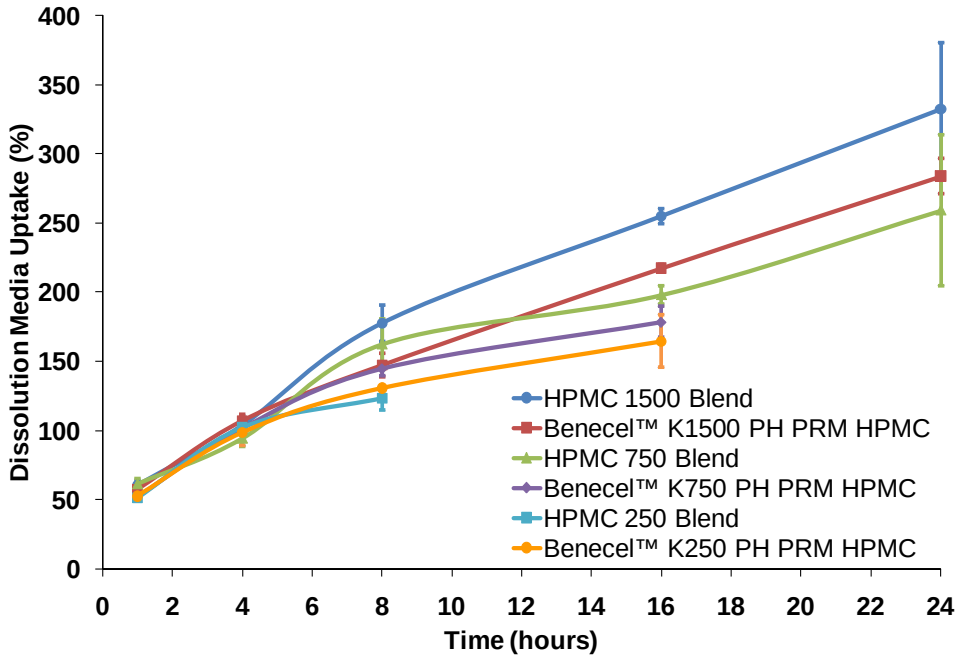

Figure 3. The effect of the Benecel PH PRM HPMC grades and their equivalent viscosity Benecel K4M/K100LV HPMC blend on the swelling profile of GLIP matrix tablets.

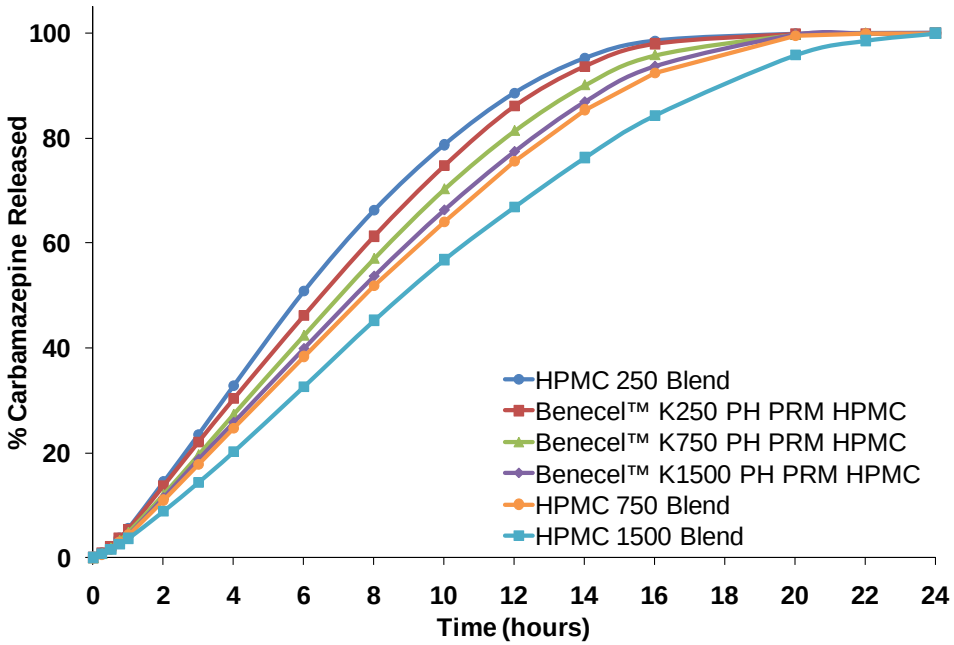

Figure 4. The effect of the Benecel™ PH PRM HPMC grades and their equivalent viscosity Benecel K4M/K100LV HPMC blends on the dissolution profile of CBZ matrix tablets under USP Apparatus I at 100 rpm.

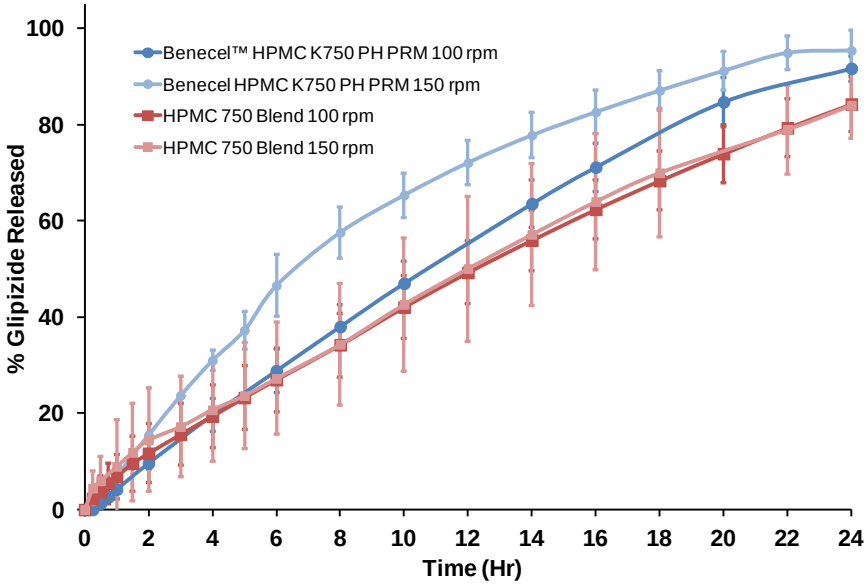

Figure 5. The hydrodynamic effects on GLIP tablets made with Benecel K750 PH PRM HPMC grade and its equivalent viscosity Benecel K4M/K100LV HPMC blend under USP Apparatus I (basket) at 100 and 150 rpm.

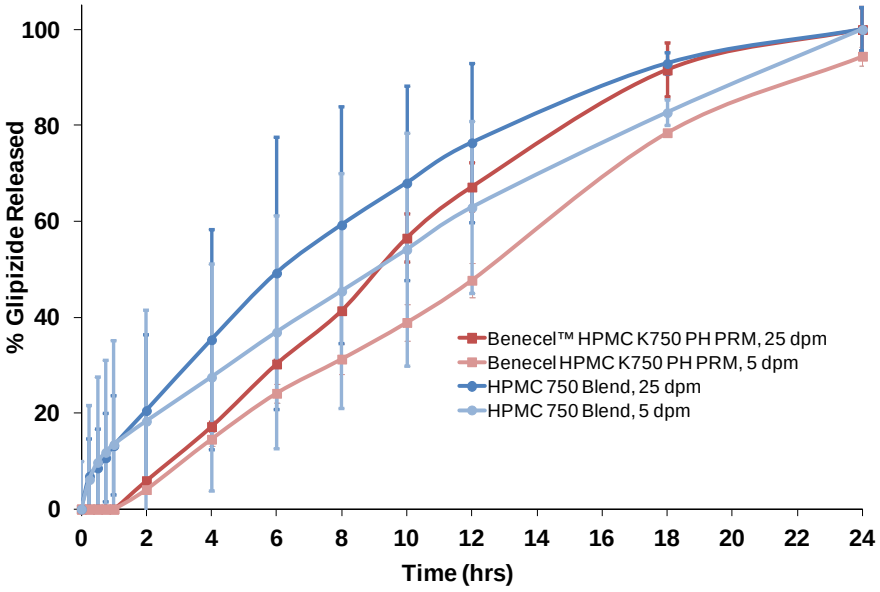

Figure 6. The hydrodynamic effects on GLIP tablets made with Benecel™ K750 PH PRM HPMC grade and its equivalent viscosity Benecel K4M/K100LV HPMC blend under USP Apparatus III (reciprocating cylinder) at 5 and 25 dips per minute.

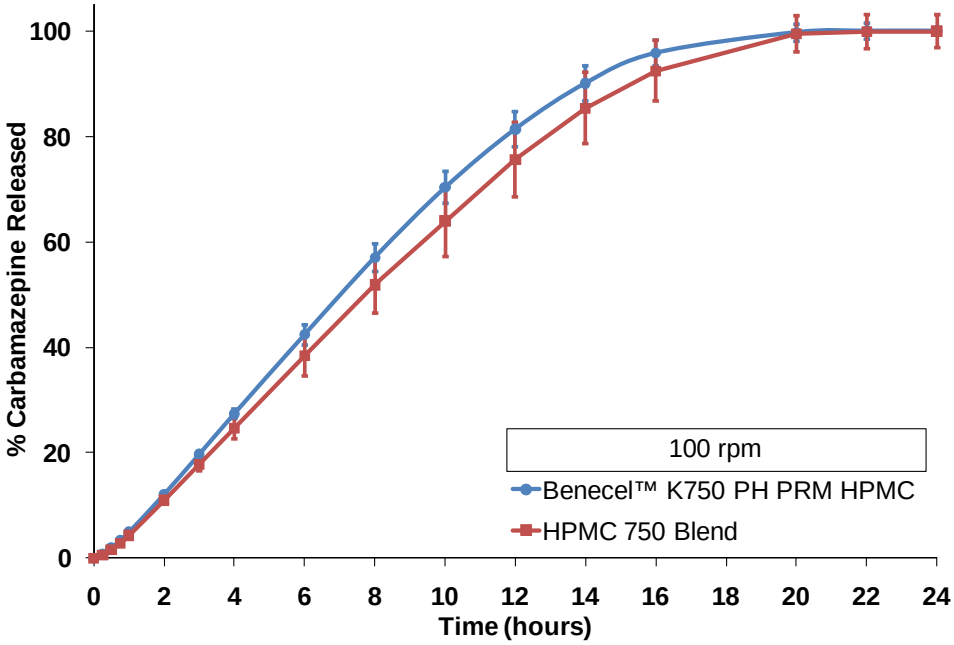

Figure 7. The effect of Benecel K750 PH PRM HPMC grade and its equivalent viscosity Benecel K4M/K100LV HPMC blend on the dissolution profile variability of CBZ matrix tablets under USP Apparatus I at 100 rpm.

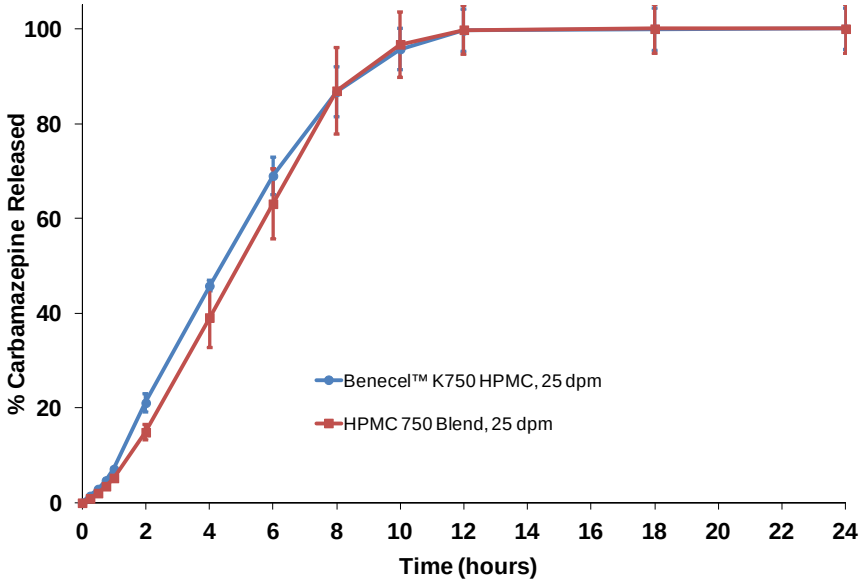

Figure 8. The hydrodynamic effects on CBZ tablets made with the Benecel™ K750 PH PRM HPMC grade and its equivalent viscosity Benecel K4M/K100LV HPMC blend under USP Apparatus III (reciprocating cylinder) at 25 dips per minute.

When subjected to pH change from acidic simulated gastric fluid (SGF) to pH 7.5 simulated intestinal fluid (SIF), no significant differences were seen between formulations made with Benecel K750 PH PRM HPMC or the equivalent viscosity K4M/K100LV HPMC blend (Figure 9). However, when subjected to increasing levels of ionic strength, the glipizide tablets made with Benecel K750 PH PRM HPMC (Figure 10) and the carbamazepine tablets made with Benecel K750 PH PRM HPMC (Figure 11) continued to release drug in a robust and predictable manner, while tablets made with the equivalent viscosity K4M/K100LV HPMC blend resulted in extreme variability and showed evidence of polymer salting out and dose dumping (Figure 10).

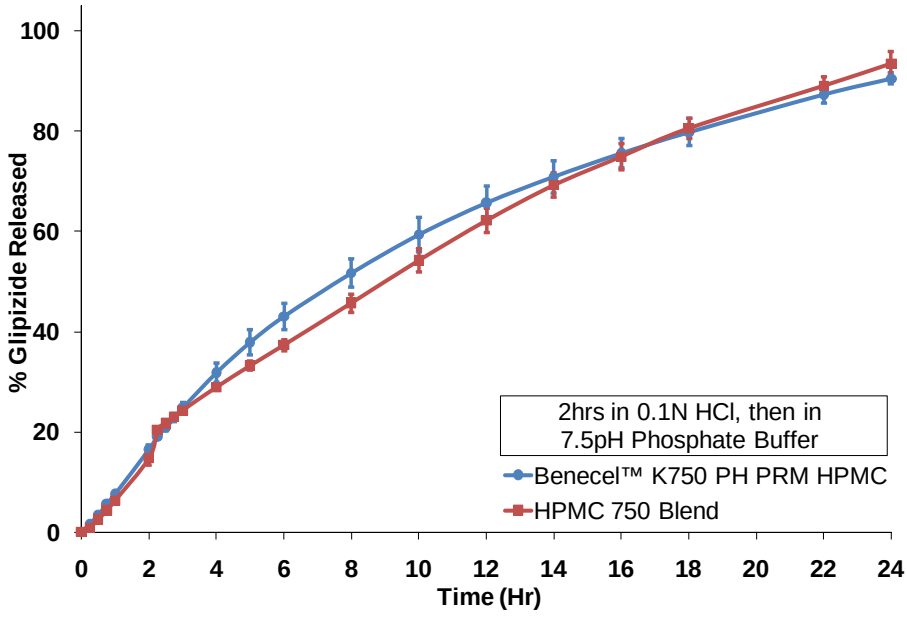

Figure 9. The fluid composition effects on GLIP tablets made with the Benecel K750 PH PRM HPMC grade and its equivalent viscosity Benecel K4M/K100LV HPMC blend under acid/base environment.

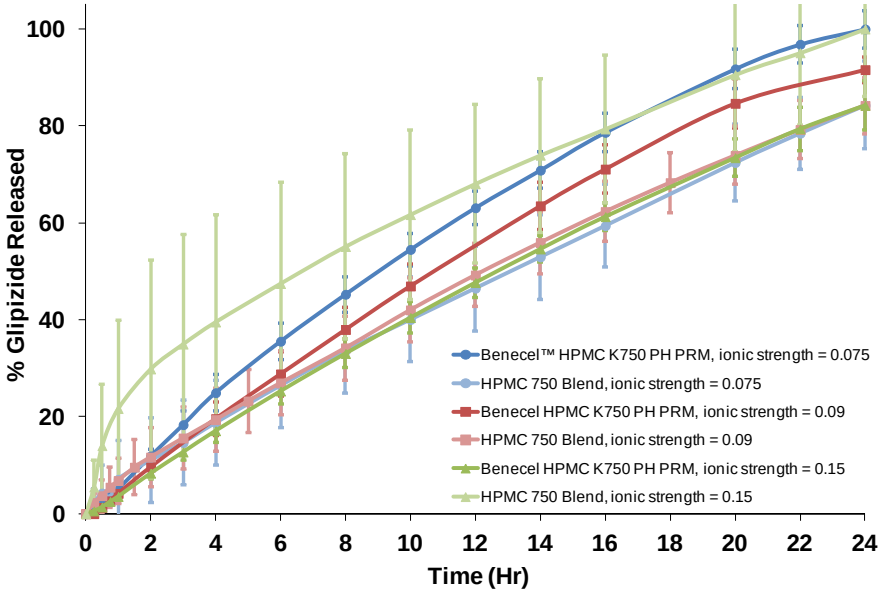

Figure 10. The fluid composition effects on GLIP tablets made with Benecel™ K750 PH PRM HPMC and its equivalent viscosity Benecel K4M/K100LV HPMC blend under media ionic strengths of 0.075, 0.09, and 0.15.

These differences in release profile for unimodal custom Benecel K750 PH PRM HPMC and the equivalent viscosity Benecel K4M/K100LV HPMC blend were further studied by examining cloud points (Figure 12) of the respective polymer solutions at different ionic strengths and by measuring the gel strengths (Figure 13) of hydrated matrix tablets. The bimodal Benecel K4M/K100LV HPMC blend showed greater susceptibility to cloud point depression in the presence of ionic strength media variability than did the unimodal Benecel K750 PH PRM HPMC. Additionally, gel strength was found to be significantly higher for the custom Benecel K750 PH PRM HPMC grade.

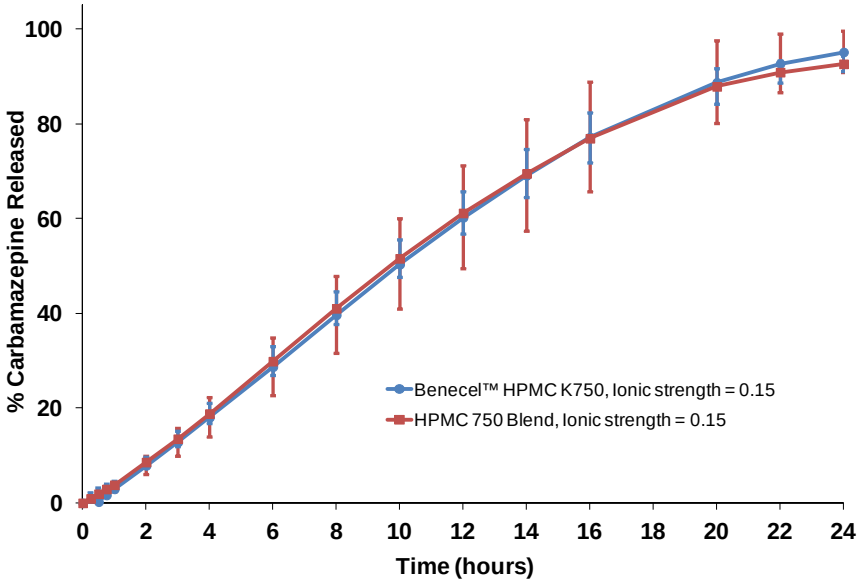

Figure 11. The fluid composition effects on CBZ tablets made with Benecel K750 PH PRM HPMC grade and its equivalent viscosity Benecel K4M/K100LV HPMC blend under media ionic strength of 0.15.

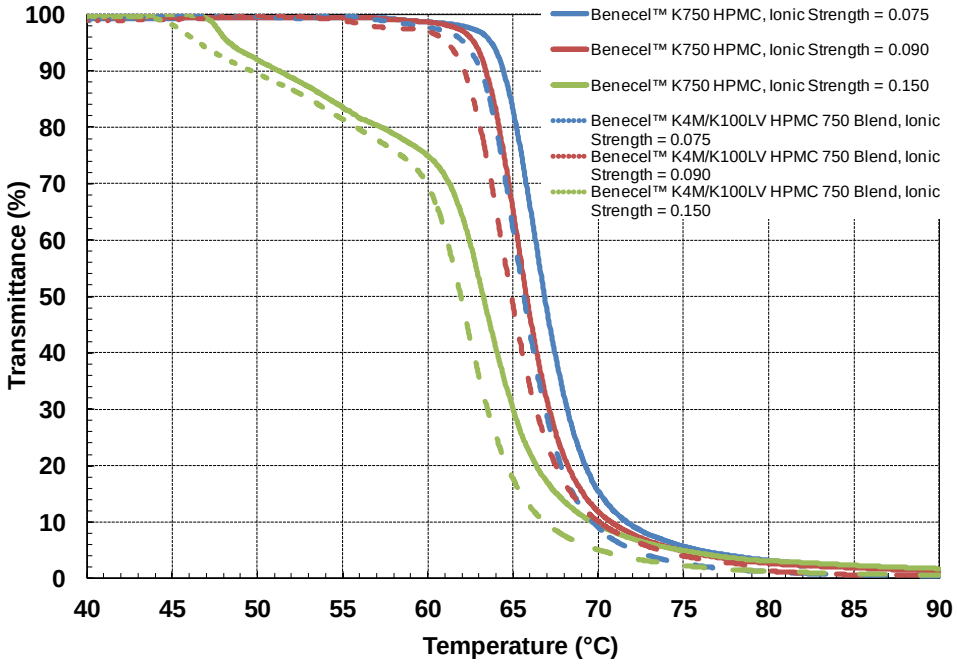

Figure 12. The effect of the Benecel™ K750 PH PRM HPMC grade and its equivalent viscosity Benecel K4M/K100LV HPMC blend on the cloud point in 7.5 pH phosphate buffer with 0.1% Tween 80 at different ionic strengths (0.075, 0.09, and 0.15).

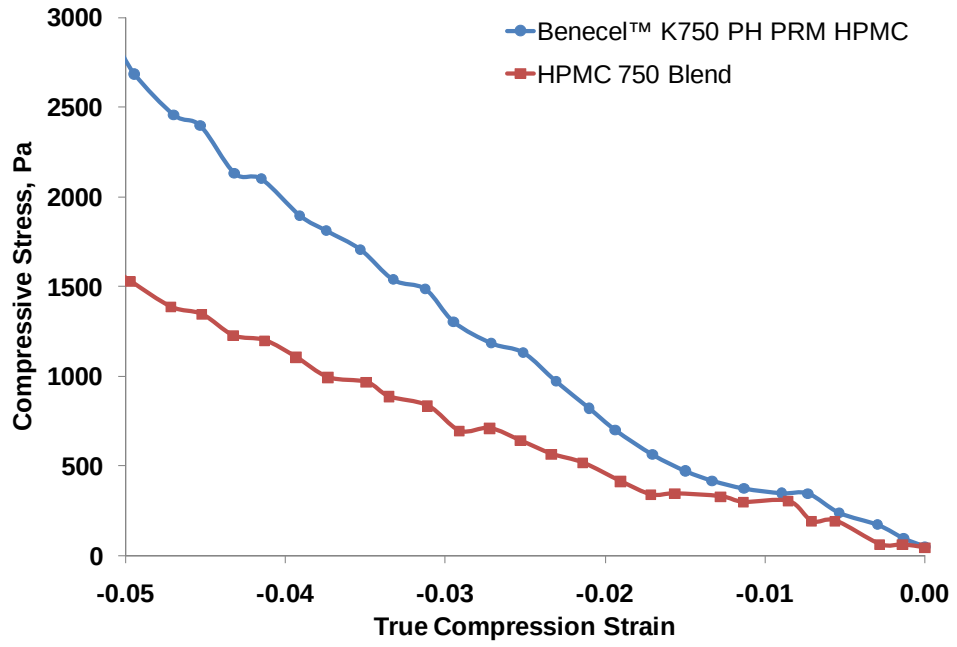

Figure 13. The effect of the Benecel K750 PH PRM HPMC grade and its equivalent viscosity Benecel K4M/K100LV HPMC blend on the gel strength in 7.5 pH phosphate buffer with 0.1% Tween 80.

Conclusions

The custom grades (Benecel™ K250 PH PRM, K750 PH PRM, and K1500 PH PRM HPMC) were more robust in the simulated gastrointestinal environment in comparison with blends of similar viscosities. For erosion-dependent dosage forms, both average MW and the MW distribution are important for matrix erosion and swelling. Bimodally distributed blends result in greater variability and, in some cases, failure to control release as compared to HPMC grades with unimodal MW distribution.

References

1) Rohrs, B.R., Skoung, J.W., Halstead, G.W., 1997. Dissolution assay development for in vitro-in vivo correlations: theory and case studies. In: Young, D., Devane, J., Butler, J. (Eds.), *Advances in Experimental Medicine and Biology. In vitro-in vivo correlations*, Vol. 423. pp. 17-30.
2) Tewari, D., Lewis, R.K., Harcum, W.W., Dürig, T., 2008. *Hydrodynamic Robustness of Hypromellose and Methylcellulose Based Modified Release Matrix Systems*. Ashland Pharmaceutical Technology Report (PTR-69).

** This work was presented at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting and Exposition, October 23-27, 2011, Washington, DC, USA.