PTR 082

Impact of Molecular Weight and Molecular Weight Distribution of Hypromellose in Reducing Drug Release Variability from Erosion Dependent Matrix Systems

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Introduction

Hypromellose (HPMC) is a versatile controlled release polymer that has found wide-spread adoption in controlled release dosage forms. Generally, higher molecular weight (MW) grades are preferred for highly soluble drugs, where drug release is predominantly controlled through diffusion of drug through swollen gel layer. Lower MW grades are preferred for low soluble drugs where matrix erosion is required for effective release of the drug (Table 1).

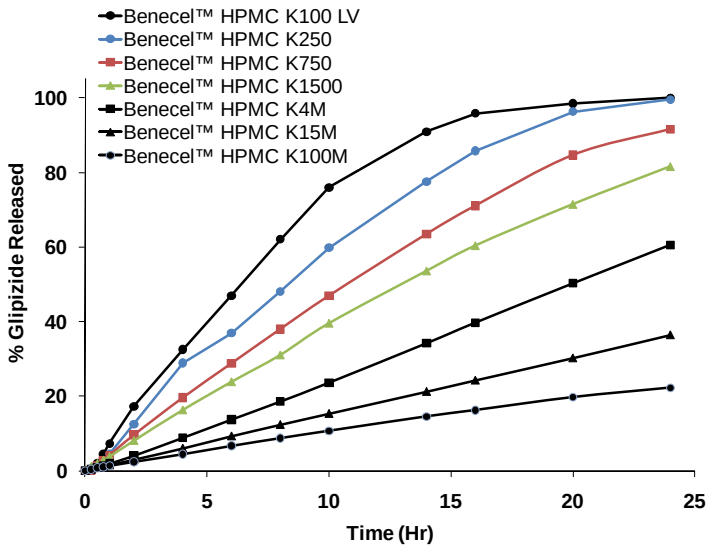
Table 1. Commercially used grades of Benecel™ HPMC

Type	Viscosity 2% (CPS)	MW (kDa)	Dominant Release Mechanism
K100M Pharm	100,000	1150	Swelling/Diffusion
K15M Pharm	15,000	750	Swelling/Diffusion
K4M Pharm	4,000	500	Swelling/Diffusion/Erosion
K100 LV Pharm	100	120	Erosion

Note: This work was presented at the American Association of Pharmaceutical Scientists, November 14 – November 18, 2010, New Orleans, Louisiana, USA.

Among the issues that arise when blending is employed to achieve intermediate MW and release behaviors are the potential increase in release profile variability and reduced predictability. Custom MW grades of HPMC were made to fill the current gap and eliminate the need for blending (Figure 1b).

Figure 1b. Release profile for custom Benecel™ HPMC grades



The current study compares the release behavior of matrix tablets prepared from two intermediate MW HPMC grades (Benecel HPMC K1500 PH PRM and Benecel HPMC K750 PH PRM) with high and low MW HPMC blends of equal viscosity. Two low solubility drugs, i.e. glipizide (37.2 mg/L in water) and carbamazepine (17.7 mg/L in water) were chosen for this study.

Experimental Methods

Batches (1kg) comprising 25% Glipizide (GLIP), 30% polymer, and 44.5% microcrystalline cellulose were wet granulated in high shear mixer. After drying, milling, and lubrication with 0.5% magnesium stearate, 400 mg tablets were compressed on an instrumented Manesty Beta Press, equipped with AIM-Metropolitan Computing Corporation data acquisition system. Dissolution studies were done with dissolution apparatus I in 0.5% solution of polysorbate 80 in pH 7.5 phosphate buffer.

Carbamazepine tablets (600 mg) were made by wet granulation of 66.7% carbamazepine with 2% HPC EF in a low shear mixer, followed by direct compression with 30% polymer, 0.8% microcrystalline cellulose, and 0.5% magnesium stearate on the aforementioned tabletting instrument. Dissolution studies were done with dissolution apparatus I in 1% sodium lauryl sulfate aqueous solution.

Materials

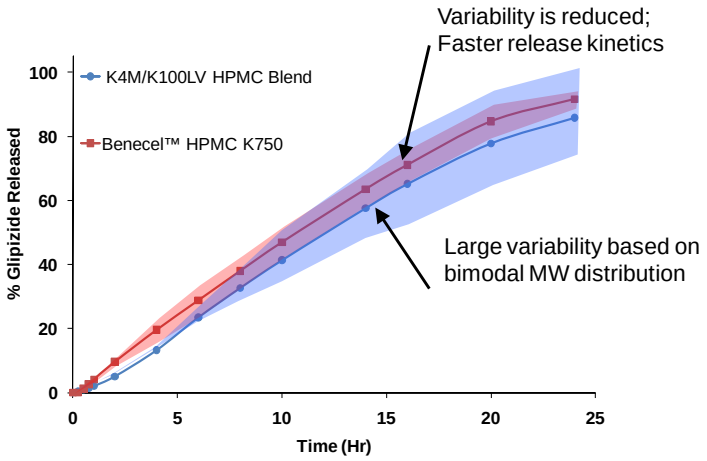
1. Glipizide, marketed by Ria International, NJ.
2. Carbamazepine, marketed by Ria International, NJ.
3. Benecel hypromellose (HPMC), marketed by Ashland Incorporated, Wilmington, DE
4. HyQual® magnesium stearate, NF, marketed by Mallinckrodt Inc., a Division of Tyco International, St. Louis, MO.

Results and Discussion

Release profiles for various Glipizide tablet formulations made with the custom Benecel HPMC grades and equivalent viscosity blends of Benecel HPMC K4M and K100 LV are shown in Figure 2. Release profiles for repeat lots of Benecel HPMC K1500 PH PRM were superimposable with a $t_{50\%}$ of 12 hrs and standard deviations at individual time points of less than 5%. It can be seen that tablets made of equivalent viscosity

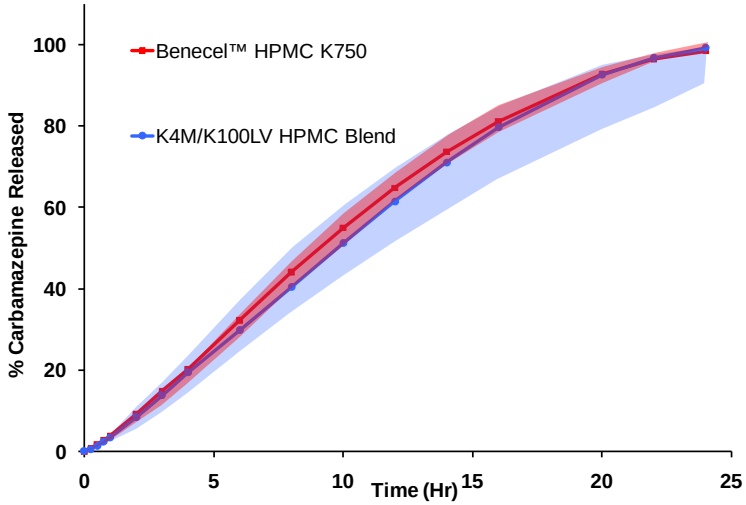
blends of Benecel™ HPMC K4M and K100 LV had slower and more variable drug release with $t_{50\%}$ of 15-18 hours and standard deviations at individual time points of up to 15%. Similar trends are evident for the formulations made with Benecel HPMC K750 PH PRM (Figure 2).

Figure 2. Glipizide release profiles for Benecel HPMC K750 PH PRM



Carbamazepine tablets made with repeat lots of new Benecel HPMC K750 PH PRM also exhibited consistent release profiles with a $t_{50\%}$ of 9 hrs and standard deviations at individual time points of less than 5% (Figure 3). However, it can be seen that tablets made of equivalent viscosity blends of HPMC K4M and K100 LV had much more variable drug release with $t_{50\%}$ of 8-12 hours and standard deviations at individual time points of up to 7%.

Figure 3. Carbamazepine release profiles for Benecel HPMC K750 PH PRM



For hydrophilic matrix polymers erosion rate is known to vary with MW in non linear inverse manner:

$$\text{Erosion} - \text{Rate} = KM_n^{-a}$$

In addition, the opposite relationship applies to matrix swelling, i.e., polymer solubility increases with MW up to a limiting MW threshold (1). However, it is clear from Figures 2 and 3 and Table 2. that in addition to average MW, the MW distribution also plays a key role in matrix erosion and swelling. In the case of the bimodally distributed HPMC blends, the higher MW fraction (Benecel HPMC K4M Pharm) appears to dominate, resulting in slower release kinetics. In addition, variability from the bimodally distributed blends is greater than unimodal Benecel HPMC K1500 PH PRM and K750 PH PRM.

Table 2. MW Distribution of Blended and New Benecel™ HPMC Grades

	Viscosity (cps)	M_W ($x10^5$ Da)	Poly Dispersity Index
Blend	250	2.25	5.99
	750	3.28	7.98
	1500	4.10	6.52
Custom	250	1.96	3.55
	750	2.53	4.16
	1500	2.96	3.96

Conclusion

Unimodal custom MW grades of Benecel HPMC behave fundamentally differently when compared to equivalent viscosity bimodal blends. Matrix tablets comprising equivalent viscosity HPMC blends showed significantly higher variability and the release profiles were dominated by the higher MW component. The use of unimodal custom Benecel HPMC grades may therefore be a useful tool in the development of more robust and predictable controlled release matrix tablets.

References

1. Brady, Dürig, and Shang. Polymer Properties and Characterization pp 211, in Developing Solid Dosage Forms: Pharmaceutical theory and practice. Elsevier, 2009.