Customizing HPMC to Minimize Drug Variability

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alexsl/getty imagesThe authors evaluated the performance and robustness of controlled-release tablets made with HPMC blends of unimodal and bimodal molecular weight distribution.

Hypromellose (HPMC) is a controlled-release polymer that has found widespread 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 through a swollen gel layer. Lower MW grades are preferred for low-solubility drugs where matrix erosion is required for effective release of the drug (see **Table I**). As a result of the historically limited number of commercially available MW grades, formulators would blend various MW grades to tailor release profiles to meet specific therapeutic objectives and to accommodate the wide spectrum of drug solubilities encountered in daily practice. Among the issues that arise when blending is used to achieve intermediate MW and release behaviors are the potential increase in release profile variability, reduced predictability, and lack of robustness. Dissolution variability due to blending is exacerbated in the presence of variations in gastrointestinal (GI) tract hydrodynamic conditions and GI fluid compositional factors such as fat, bile salt content, and ionic strength. It is difficult to develop good *in vitro-in vivo* correlations for controlled-release matrix systems due to variations in GI conditions.

Benecel HPMC Grade	Nominal viscosity (2%, mPa.s)	Molecular weight (kDa)	Dominant release mechanism
K100M Pharm HPMC	100,000	1150	Swelling/ diffusion
K15M Pharm HPMC	18,000	750	Swelling/ diffusion
K4M Pharm HPMC	4000	500	Swelling/ diffusion/erosion
K100LV Pharm HPMC	100	120	Erosion

Table I: Commercially used grades of Benecel hypromellose (HPMC).

Benecel K250 PH PRM HPMC, K750 PH PRM HPMC, and K1500 PH PRM HPMC (Ashland) grades were developed to obviate the need for blending (see **Figure 1**) and offer a potential solution to the problem of dissolution variability. These custom Benecel HPMC grades are of intermediate viscosity and have tight, unimodal MW distribution.

In this study, the dissolution performance and robustness of matrix tablets developed with these custom Benecel HPMC grades under varying hydrodynamic stress conditions and in dissolution media of varying ionic strengths were investigated. Formulations containing blends of Benecel K4M and K100LV PHARM HPMC to achieve analogous viscosities were used as comparators (see **Table II**). Glipizide (GLIP; aqueous solubility ~ 37 mg/L) and carbamazepine (CBZ; aqueous solubility ~ 17.7 mg/L) were chosen as model low-solubility drugs.
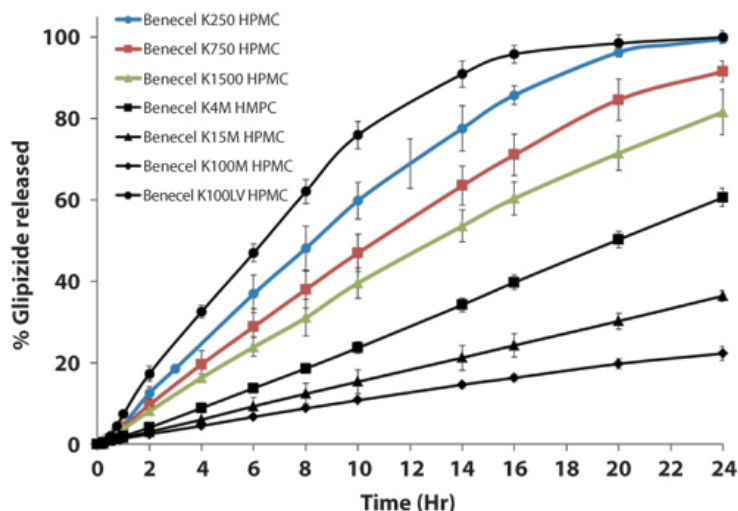
Figure 1: Glipizide drug release profiles with different Benecel HPMC grades.

Methods

Wet granulation. One kg batches comprising polymer (30%; blends of Benecel K4M and K100LV PHARM HPMC or the equivalent custom viscosity grade), drug (25% for GLIP and 67% for CBZ), and quantity sufficient 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 CBZ) were compressed on a Manesty Beta Press equipped with an AIM-Metropolitan Computing Corporation data acquisition system. Blend ratios were calculated according to the following formula:

$$\eta^{1/8} = \eta_1^{1/8} c_1 + \eta_2^{1/8} + c_2$$

Where, η = viscosity of the polymer and c = weight fraction of the polymer.

Drug-release profiles. Dissolution was tested at 37 °C with 7.5 pH phosphate buffer with 0.1% polysorbate 80 for GLIP and 1% sodium lauryl sulfate in distilled water for CBZ. The hydrodynamic effects were simulated by running the dissolution with a United States Pharmacopeia (USP) Apparatus I at 100 and 150 revolutions per minute (rpm) or with USP Apparatus III (Bio Dis, Varian Inc.) at 5 and 25 dips per minute (dpm). The effect of fluid composition was determined by running the dissolution in media of varying pH (2 hr in 0.1 N HCl and then in corresponding buffer) and ionic strength (adjusted with NaCl).

Lots	Viscosity	Methoxyl, %	Hydroxypropyl, %
K750 lot 1	680	22.1	8.1
K750 lot 2	650	22.7	8.1
K750 lot 3	790	23.4	8.5
750 cps blend 1	K4M: 3756 K100LV: 86	K4M: 21.5 K100LV: 22.2	K4M: 8.6 K100LV: 9.3
750 cps blend 2	K4M: 3816 K100LV: 101	K4M: 21.6 K100LV: 22.3	K4M:8.6 K100LV: 9.8
750 cps blend 3	K4M: 3776 K100LV: 83	K4M: 21.6 K100LV: 21.9	K4M:8.5 K100LV: 8.9

Table II: Substitution and viscosity data for custom Benecel K750 and analogous blends used in the study.

Erosion profiles. Tablet erosion and uptake of the dissolution medium were determined gravimetrically under the same dissolution conditions as used for dissolution testing. Three tablets were used per time point. At predetermined times, the tablets were removed and patted to remove excess surface water. After determining the wet weight, the tablets were dried at 70 °C for 10 days, before reweighing to determine the dry weight (1).

Water uptake and mass loss were determined gravimetrically according to **Equation 1**:

[Eq. 1]

Dissolution medium uptake (%) =
$$\frac{100 \text{ (Wet weight - remaining dry weight)}}{\text{Remaining dry weight}}$$

Remaining mass (%) =
$$\frac{100 \text{ (remaining dry weight)}}{\text{Original dry weight}}$$

Cloud point. The cloud point value was determined using a FP900 cloud point analyzer (Mettler Toledo) 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 pH 7.5 phosphate buffer with 0.1% polysorbate 80 for 2 hr at 37 °C. The deformation of the gel layer on the tablet was analyzed using a rheometer (Model # AR-G2, TA Instruments) 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).

Results and discussion

Effect on dissolution profiles. Release profiles for repeat lots of Benecel K750 HPMC were superimposable with a $t_{50\%}$ of 12 hr and standard deviations at individual time points of less than 5%. It can be seen that tablets made of equivalent viscosity blends of Benecel K4M HPMC and K100 LV HPMC had slower and more variable drug release with $t_{50\%}$ of 15-18 hr and standard deviations at individual time points of up to 15% (see **Figure 2**). **Table II** details substitution and viscosities of the lots that were compared in the study. For hydrophilic matrix polymers, erosion rate is known to vary with MW in a nonlinear inverse manner (**Equation 2**):

[Eq. 2] *Erosion rate* $= KM_n^{-a}$

where K is a constant that is polymer-, solvent-, and temperature-dependent, Mn is number average molecular weight, and a is calculated from the slope of the erosion curve. In addition, the opposite relationship applies to matrix swelling (i.e., polymer solubility increases with MW up to a limiting MW threshold) (2). However, **Figure 2** shows 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, variability is greater than that of unimodally distributed custom grades, irrespective of the viscosity. Furthermore, slower release kinetics are obtained for bimodal blends where the higher MW fraction (Benecel K4M HPMC) dominates. This observation was seen for 750 cps and 1500 cps blends in comparison with custom made K750 and K1500. In contrast, for blends where the lower MW fraction (Benecel K100LV HPMC) dominates, comparatively faster release kinetics are obtained, as observed for the 250 cps blend in comparison with custom made K250 (data not shown).
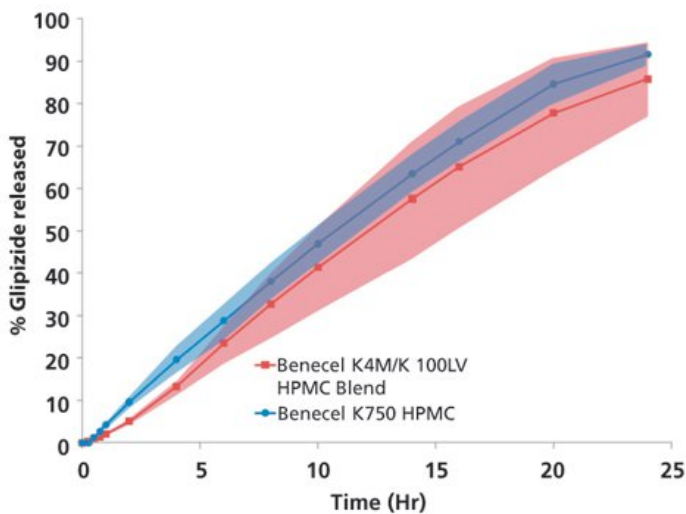

Figure 2: Drug-release profiles of glipizide tablets made with Benecel K750 HPMC and Benecel K4M/K100LV HPMC blend. HPMC is hypromellose.

Carbamazepine tablets made with repeat lots of custom Benecel K750 HPMC also exhibited consistent release profiles with a $t_{50\%}$ of 7 hr and standard deviations at individual time points of less than 5% (see **Figure 3**). However, it can be seen that tablets made of equivalent viscosity blends of Benecel K4M HPMC and Benecel K100LV HPMC had much more variable drug release with $t_{50\%}$ of 8-12 hr and standard deviations at individual time points of up to 7%.
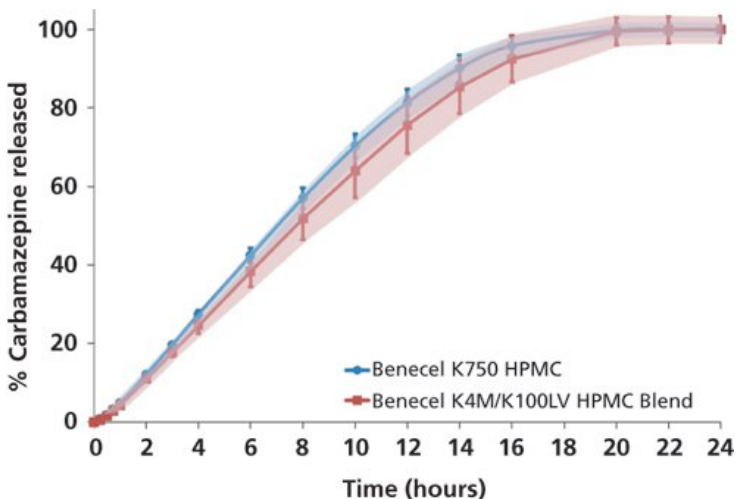

Figure 3: Drug-release profiles of carbamazepine tablets made with Benecel K750 HPMC and Benecel K4M/K100LV HPMC blend. HPMC is hypromellose.

Effect of hydrodynamic stress conditions. Table III shows the impact of increasing hydrodynamic stress on the variability of glipizide and carbamazepine tablets made with Benecel K750 HPMC and the equivalent 750 cps viscosity Benecel K4M/K100LV HPMC blend, at the 8-hr time point. Increasing the basket stirring rate from 100 to 150 rpm in the USP Apparatus I had only a marginal effect on Benecel K750 HPMC. However, variability increased greatly for formulations containing the blend of HPMC grades with standard deviation of individual time points exceeding 15%. Extreme variability, including controlled-release failure, was seen when formulations containing a blend of Benecel K4M/K100LV HPMC were subjected to testing in USP apparatus III (reciprocating cylinder) at 5 and 25 dpm. By contrast, the custom Benecel K750

HPMC with tight, unimodal distribution showed extremely robust dissolution behavior with a small increase in rate when agitation was increased from 5 to 25 dpm. 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 attrition and hydrodynamic stress is expected in fed conditions (3).

Drug	Benecel HPMC Grade or Equivalent	100 rpm	150 rpm	25 dpm	5 dpm
Carbamazepine	K750 HPMC	2.6	0.2	5.2	2.1
	K4M/K100LV HPMC Blend	5.4	4.3	9.1	1.95
Glipizide	K750 HPMC	4.6	5.3	0.3	3.12
	K4M/K100LV HPMC Blend	6.6	12.6	24.7	24.21

Table III: Maximum standard deviation under various testing conditions at the 8-hour time point. HPMC is hypromellose, rpm is revolutions per minute, dpm is dips per minute.

Effect of pH and ionic strength. 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 HPMC or the equivalent viscosity K4M/K100LV HPMC blend. However, when subjected to increasing levels of ionic strength, the tablets made with Benecel K750 HPMC and glipizide and with carbamazepine continued to release drug in a robust and predictable manner, while tablets made with the equivalent viscosity Benecel K4M/K100LV HPMC blend resulted in increased variability and showed evidence of polymer salting out and dose dumping.
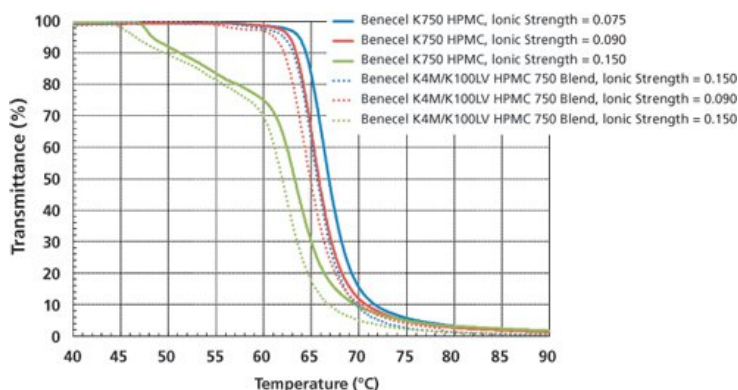

Figure 4: Cloud point effects of the polymer solutions at different ionic strengths. HPMC is hypromellose.

These differences in release profile for unimodal custom Benecel K750 HPMC and the equivalent viscosity K4M/K100LV HPMC blend were further studied by examining cloud points (see **Figure 4**) of the respective polymer solutions at different ionic strengths and by measuring the gel strengths (see **Figure 5**) of hydrated matrix tablets. The bimodal K4M/K100LV HPMC blend showed greater susceptibility to cloud point depression in the presence of media of different ionic strengths as opposed to the unimodal Benecel K750 HPMC. Additionally, gel strength was found to be significantly higher for the custom Benecel K750 HPMC.
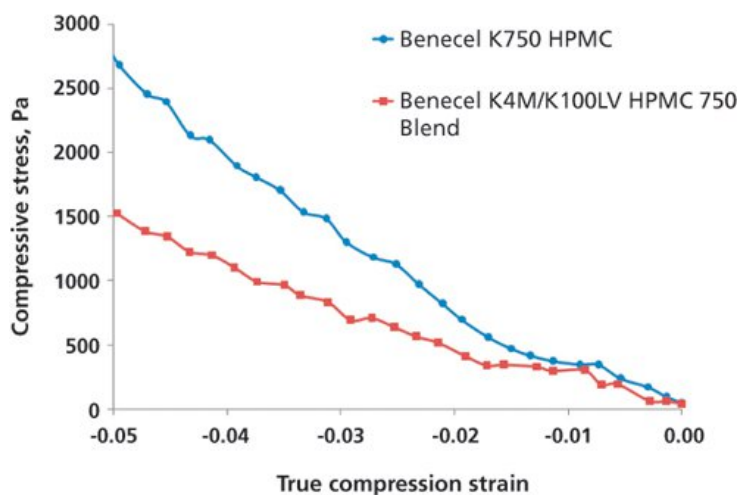

Figure 5: Gel strengths of hydrated matrix tablets made with Benecel K750 HPMC and Benecel K4M/K100LV HPMC blend. HPMC is hypromellose.

While the cloud point effects in **Figure 4** appear modest, these effects need to be understood in the context of the dilute polymer solvent system, which is far removed from the physical reality of hydrating gel matrices where free water is limited. Mechanistically, hydrating gel matrix tablets can be understood as a solvent-lean environment, in which HPMC is only marginally soluble. For such systems, the net free energy of solution increases as molecular weight increases. This molecular weight dependent solubility of HPMC under marginal solvent conditions would be further exacerbated with an increase in ionic strength. It is, therefore, expected that the HPMC blends, having a larger component of higher MW HPMC and displaying earlier onset of clouding, as seen in **Figure 4**, will show dramatically different gel properties.

In essence, salting out of the higher MW polymer species results in insoluble gel domains, leading to disruption in gel network integrity and faster, highly variable erosion, which is also reflected in lower gel strength (see **Figure 5**).

Conclusion

The custom Benecel (K250, K750, and K1500) HPMC grades have fundamentally different behaviors when compared with equivalent viscosity bimodal blends. Matrix tablets comprising equivalent viscosity HPMC blends showed significantly higher variability and the release profiles were dependent on the MW of the higher percentage component of the blend. In addition, custom Benecel HPMC grades 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 with HPMC grades with unimodal MW distribution.

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