

## The Influence of Hydrodynamic Conditions on Verapamil Hydrochloride Release from Hydrophilic Matrices Using Ionic and Non-ionic Polymers

### PURPOSE

Hypromellose (HPMC) is the most widely used rate-controlling polymer in hydrophilic matrices for oral extended release (ER) drug delivery, providing robust, versatile formulations and simplified production.<sup>1&2</sup> The combination of HPMC with one or more ionic, nonionic or insoluble polymers in the formulation may provide additional functionalities which complement the performance of HPMC matrix systems.<sup>3&4</sup> Using polymer blends may improve formulation robustness, reducing the dependence of drug release profiles on external variables such as mechanical stress, food effects, or hydrodynamic conditions in the gastrointestinal tract. In vitro measurement of drug release from hydrophilic matrix tablets across a range of hydrodynamic conditions may provide valuable insight on the sensitivity of drug release to these variables.

The purpose of this study was to investigate the effects of hydrodynamic conditions on drug release rates from a matrix tablet with a soluble active ingredient, verapamil HCl, using different combinations of HPMC with the ionic polymers polyvinyl acetate phthalate (PVAP) and carbomer [cross-linked poly (acrylic acid)].

### METHODS

Eight verapamil HCl 480 mg ER matrix tablet compositions were formulated using two viscosity grades of HPMC (METHOCEL™, premium cellulose ethers, K100LV Premium CR and K4M Premium CR), two polymer levels (15% and 30% w/w) and two polymer blend ratios (100% HPMC and 50:50 ratio of HPMC: ionic polymers) as shown in Table 1. Powders were blended in a 4-quart V-blender (Patterson-Kelley, USA) and directly compressed to tablets with hardness of 10 kp ± 2 kp using an instrumented Piccola rotary press (Riva, Argentina) equipped with 19.0 mm x 8.4 mm oblong tooling at target weights of 575 mg (15% polymer) or 701 mg (30% polymer).

**Table 1. Verapamil HCl 480 mg ER Matrix Formulations**

Ingredient	% Composition Formulation Containing Ionic Polymers				% Composition Formulations with HPMC			
	F5	F6	F7	F8	F1	F2	F3	F4
Verapamil HCl (Nicholas Piramal, India)	83.5	68.5	83.5	68.5	83.5	68.5	83.5	68.5
METHOCEL™ K100LV CR (International Flavors and Fragrances Inc., USA)	7.5	15.0			15.0	30.0		
METHOCEL™ K4M CR (International Flavors and Fragrances Inc, USA)			7.5	15.0			15.0	30.0
Ionic Polymers*	7.5	15.0	7.5	15.0				
CAB-O-SIL M5P (Cabot Corp., USA)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Magnesium Stearate (Mallinckrodt, USA)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
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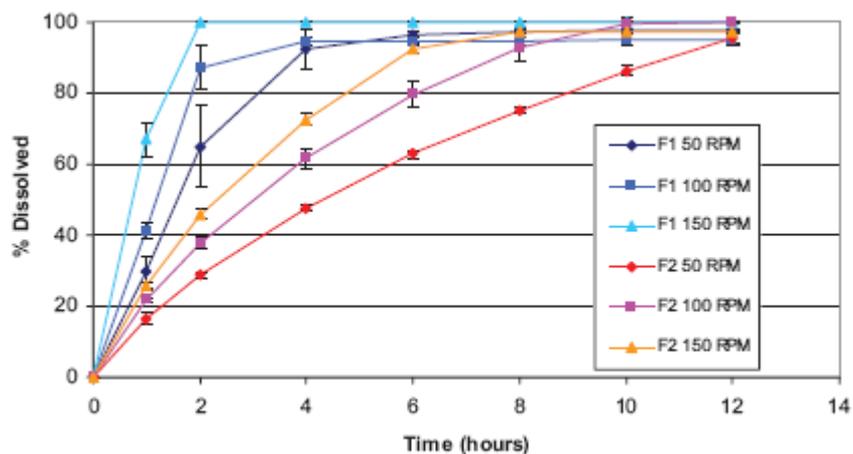
\* Combination of PVAP (Phthalavin enteric coating polymer (Colorcon) and Carbopol 974P NF (Lubrizol Advanced Materials, USA).

Dissolution testing was conducted for 12 hours using apparatus II at agitation speeds of 50, 100 and 150 rpm in media specified in the USP31-NF26 monograph for verapamil HCl ER tablets (test 1; simulated gastric fluid TS without enzyme for 1 hour followed by simulated intestinal fluid TS without enzyme for 11 hours). Drug release profiles were measured spectrophotometrically at a wavelength of 273nm and were compared using the  $f_2$  similarity factor.<sup>5</sup> To determine the effect of polymer blend on matrix gel strength, polymer tablets comprised of either METHOCEL™ K4M or the polymer blend were subjected to textural analysis using a texture analyzer (TA.XT Plus with probe TA-52R, Stable Micro Systems Ltd., UK). The force-displacement profiles were used to compare the textural properties of the hydrated tablets as reported previously.<sup>6</sup>

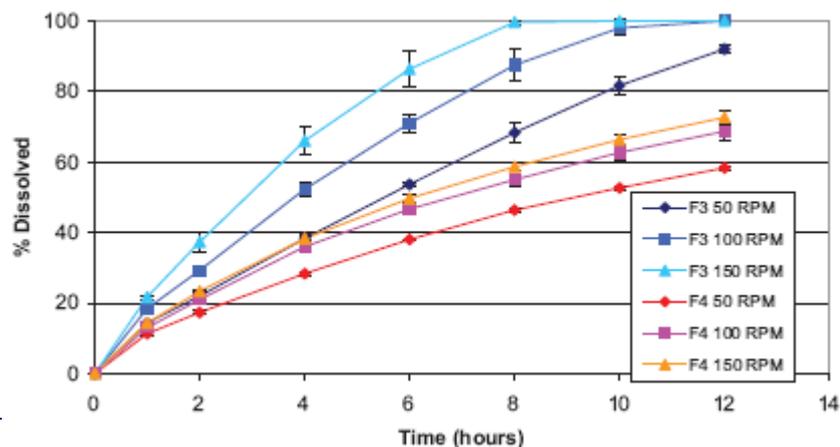
## RESULTS

Verapamil HCl release from HPMC-only matrices was slower when polymer concentration increased from 15% to 30%. In addition, drug release was slower when polymer viscosity grade was increased from K100LV CR to K4M CR (Figures 1 & 2). The release profiles of the HPMC-only matrices (F1-F4) increased significantly when the paddle speed increased from 50 to 150 rpm (Figures 1 & 2).

**Figure 1. Dissolution Profile of Verapamil HCl ER Matrix Tablets Containing 15% and 30% METHOCEL™ K100IV Formulations Using Apparatus II at 50, 100 and 150 rpm**



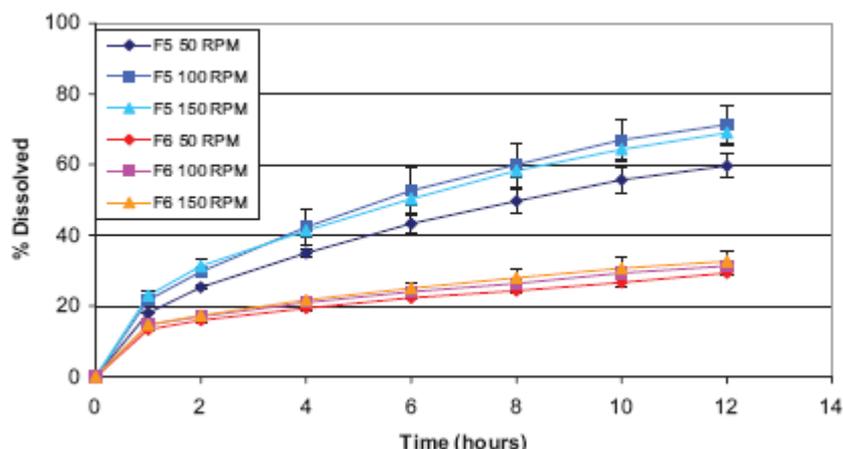
**Figure 2. Dissolution Profile of Verapamil HCl ER Matrix Tablets Containing 15% and 30% METHOCEL™ K4M Formulations using Apparatus II at 50, 100 and 150 rpm**



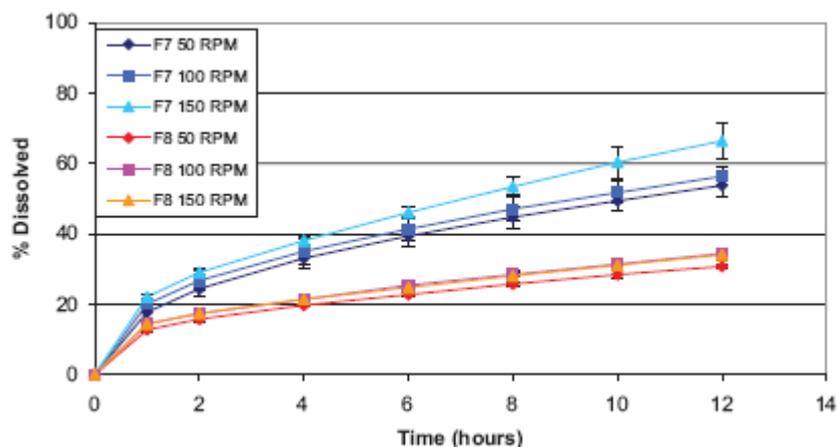
Increased paddle speed caused increased hydrodynamic effects on hydrated HPMC matrices, which may be related to faster erosion of the outer surface of the matrices as rate of agitation is increased and thus faster drug release.

The use of a 50:50 blend of METHOCEL™ and ionic polymers at either 15% (F5, F7) or 30% polymer level (F6, F8) resulted in significantly slower drug release compared to HPMC-only formulations at equivalent polymer levels (Figures 3 & 4). Moreover, the use of polymer blends resulted in drug release profiles which were insensitive to paddle speed, generating similar ( $f_2 > 50$ ) drug release profiles at 50, 100 and 150 rpm. This behavior was observed for formulations containing K100LV CR or K4M CR within the polymer blends. In addition, the viscosity grade of HPMC used in the polymer blends did not influence the drug release profiles. However, the total polymer level in the blend formulations (15% vs. 30%) did significantly affect the drug release rate.

**Figure 3. Dissolution Profile of Verapamil HCl ER Matrix Tablets Containing 15% and 30% METHOCEL™ K100IV Containing Polymer Blend Formulations Using Apparatus II at 50, 100 and 150 rpm**

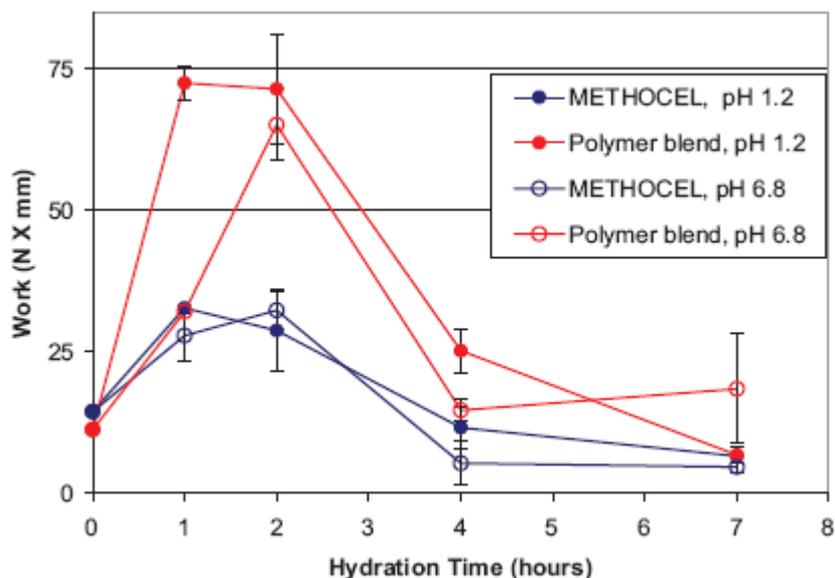


**Figure 4. Dissolution Profile of Verapamil HCl ER Matrix Tablets Containing 15% and 30% METHOCEL™ K4M Containing Polymer Blend Formulations Using Apparatus II at 50, 100 and 150 rpm**



The reduced drug release rates observed with polymer blend formulations and their lack of sensitivity to agitation speed are attributed to the synergistic interaction between HPMC and ionic polymers leading to higher gel strength of the hydrated matrices. The textural analysis of hydrated METHOCEL™ K4M or polymer blend compacts indicated that the polymer blend compositions exhibited higher gel strength than HPMC in both simulated gastric and intestinal media (Figure 5).

**Figure 5. Gel Strengths of Hydrated Compacts of METHOCEL™ K4M or 50:50 METHOCEL™ – Ionic Polymer Blend**



## CONCLUSIONS

A combination of HPMC with the ionic polymers PVAP and carbomer in verapamil HCl ER matrices provided more robust ER matrix formulations than HPMC-only matrices across a range of hydrodynamic conditions. Drug release from HPMC-only matrices was highly dependent on viscosity grade, total level of polymer used, and the agitation speed. However, the use of polymer blends resulted in drug release profiles which were insensitive to agitation speed regardless of HPMC viscosity grade. The slower drug release profiles observed with polymer blend formulations may be attributed to the higher gel strength and slower erosion rate in these matrices. In summary, the combination of HPMC with ionic polymers in ER matrices provides robust formulations which are insensitive to hydrodynamic conditions.

*Reprint of poster presented at AAPS – Nov 2008. Authors: Lawrence M. Martin, Sandip B. Tiwari and Ali R. Rajabi-Siahboomi.*

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North America	Europe/Middle East/Africa	Asia Pacific	Latin America
<b>+1-215-699-7733</b>	<b>+44-(0)-1322-293000</b>	<b>+65-6438-0318</b>	<b>+54-11-4552-1565</b>

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