



Control of Dissolution Rate of Immediate Release Tablets Containing Starch 1500® with a Combination of Different Types and Grades of Methocel®

N. Do and T. Farrell (Colorcon, Inc.)

OBJECTIVE

To demonstrate the feasibility of using Methocel® of different hydration rates, viscosity grades and concentrations to control the release rate of immediate release (IR) tablets.

INTRODUCTION

Dissolution testing of pharmaceutical products was introduced as a regulatory requirement with its prime function as an *in vitro* control of bioequivalence of different formulations. Several formulation variables such as polymer concentration and viscosity have been used to modulate drug release from hydrophilic swellable matrix tablets. Hydroxypropyl methylcellulose (HPMC) is the polymer most widely used as the gel-forming agent to form a gel barrier through which the drug diffuses.^{1,2,3}

A binary polymer combination of Methocel was used to control the release rate of immediate release tablets. Methocel K and E are brands of HPMC with different hydration rates and Methocel A is a brand of methylcellulose (MC). Methocel K has the fastest relative rate of hydration followed by Methocel E and Methocel A has the slowest hydration rate. The matrix tablets were also formulated with only low viscosity grades of Methocel, i.e., Methocel K3, E5, E15 and A15.

Drug release from hydrophilic matrix tablets can also be influenced by the water solubility of drug and its concentration in the formula. Ranitidine hydrochloride, caffeine (ASA substitute), guaifenesin (cyclobenzaprine hydrochloride substitute) and amlodipine besylate were selected as model drugs in an active drug concentration/water solubility matrix for the study.

MATERIALS & METHODS

Active Ingredients

Drug Name	Water Solubility	Formula Conc.
Ranitidine HCl	Freely soluble	60%
Caffeine	Sparingly soluble	60%
Guaifenesin	Soluble	4.5%
Amlodipine Besylate	Slightly soluble	4.5%

Tablet Formulation

Ingredient	Percent
Active ingredient	60% or 4.5%
Methocel®	varied
Starch 1500® : Emcocel® 90M (1:1 ratio)	qs
Cab-O-Sil®	0.25%
Magnesium stearate	0.25%

Drug Name	Methocel Type			
	K3	E5	E15	A15
Ranitidine HCl	3-8%		1-5%	
Caffeine		1-6%	0.5-3%	
Guaifenesin		3-8%		1-5%
Amlodipine B.		3-8%		1-5%

Manufacturing Process: Direct compression on a 10-station instrumented Piccola tablet press
Dissolution Methods

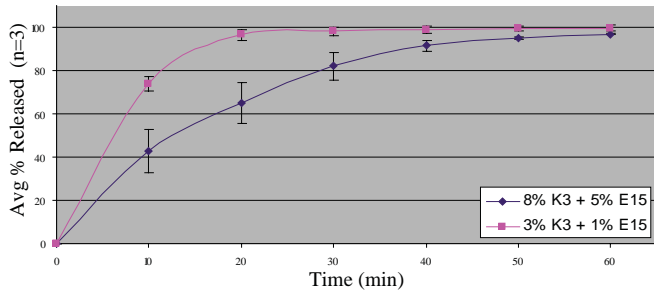
Drug Name	USP Apparatus	Speed	Medium	Vol.
Ranitidine HCl	II (Paddle)	50 rpm	Water	900ml
Caffeine	II (Paddle)	100 rpm	Water	900ml
Guaifenesin	II (Paddle)	50 rpm	Water	900ml
Amlodipine B.	II (Paddle)	75 rpm	0.01N HCl	500ml

RESULTS & DISCUSSION

A statistical design of experiments was developed using Fusion Pro™ software and by response surface methodology to evaluate the effect of Methocel type and viscosity grade on the release rate of matrix IR tablets. The model terms are ranked on a relative scale of zero to one, where one is the rank of the term with the strongest effect across its experiment range.

Dissolution Profile Range & Model Term Pareto Ranking

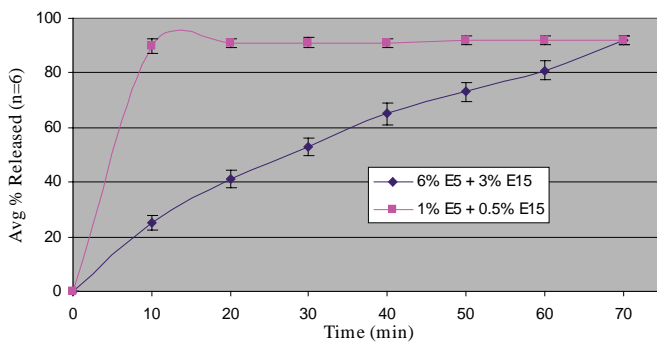
Dissolution of Ranitidine HCl – High Dose/High Water Solubility



Model Term Name	Model Term Pareto Rank			
	10 min (p=0.0004)	20 min (p<0.0001)	30 min (p=0.0016)	40 min (p=0.0183)
A Methocel K3	1.000	0.986	0.762	-----
B Methocel E15	0.975	1.000	1.000	1.000
A*B	0.425	-----	-----	-----

Methocel K3 with a fast hydration capability had a stronger effect on the release rate at the beginning of the profile while the effect of Methocel E15 was significant only at the late phase of the profile. A high concentration of Methocel K3 was also required to compensate for the low viscosity of the polymer.

Dissolution of Caffeine – High Dose/Low Water Solubility

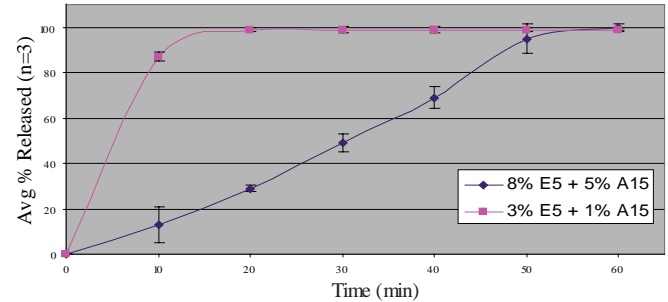


Model Term Name	Model Term Pareto Rank			
	10 min (p<0.0001)	20 min (p<0.0001)	30 min (p=0.0002)	40 min (p=0.0001)
A Methocel E5	1.000	1.000	1.000	1.000
B Methocel E15	0.533	0.617	0.631	0.431
(A) ²	0.220	-----	0.297	0.458
A*B	0.207	-----	0.378	0.370

Methocel E5 and E15 have similar rate of hydration but different gel viscosity characteristics. However, with a low water solubility drug, no significant difference in

dissolution control was observed between the two viscosity grades of Methocel. The larger effect of Methocel E5 was attributed to its higher concentration than Methocel E15.

Dissolution of Amlodipine Besylate – Low Dose/Low Water Solubility

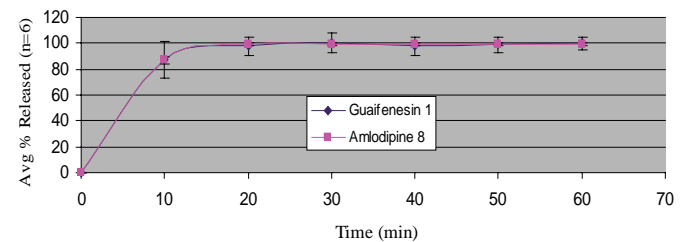


Model Term Name	Model Term Pareto Rank			
	10 min (p<0.0001)	20 min (p<0.0001)	30 min (p=0.0001)	40 min (p=0.0018)
A Methocel E5	1.000	1.000	1.000	1.000
B Methocel A15	0.353	0.366	0.311	0.321
(A) ²	0.243	-----	0.385	0.535
A*B	0.226	-----	-----	0.308

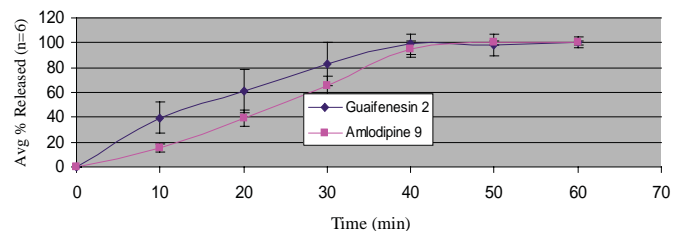
Methocel A15, a methylcellulose polymer, has the slowest rate of hydration among other HPMC products. In a low-dose drug formula, Methocel A15 was less effective than Methocel E5 in the release of low water solubility drugs. The consistently low effect of Methocel A15 in the entire profile was attributed to both slow hydration rate and low concentration of the polymer in the formula.

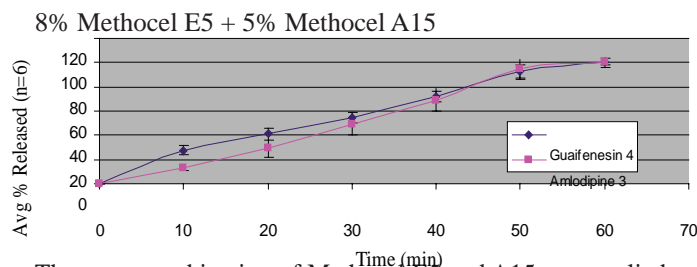
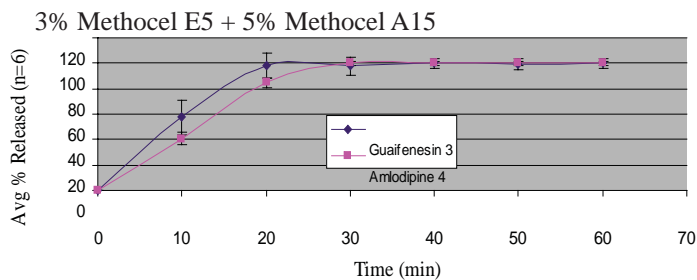
Comparative Dissolution of Guaifenesin (low dose/high water solubility) vs. Amlodipine B. (low dose/low water solubility)

3% Methocel E5 + 1% Methocel A15



8% Methocel E5 + 1% Methocel A15





The same combination of Methocel E5 and A15 was applied to low dose drugs but having different water solubility. The dissolution profile of guaifenesin, a high water solubility drug, followed a similar trend as with amlodipine besylate, a low water solubility drug. However, a slightly faster release rate with a larger variability among dissolution profiles was observed with guaifenesin tablets. High soluble drugs will compete with the polymer for the available water necessary for the gelation of the polymer that could affect the viscosity consistency of the matrix. In this case, the hydrophobic characteristics of Methocel A15 seemed to have a synergistic effect with Methocel E5 not only for a better control of the release rate but also for a lower variability of individual dissolution profiles.

CONCLUSIONS

In a high-dose formula containing a highly water soluble drug, a fast hydrated HPMC polymer, Methocel K3, had a stronger effect on the early phase of the dissolution profile compared to

Methocel E15. Higher concentration of Methocel was also required due to its low gel viscosity.

The release rate of a low water solubility drug in a high-dose formula was not affected by the viscosity difference between Methocel E5 and E15. Polymer concentration in the formula was the main factor for the control of dissolution rate.

With its faster hydration rate, Methocel E5 had a stronger effect over Methocel A15 with a low-dose formula and low water solubility drug. Although Methocel A15 had a higher gel viscosity, a high concentration was required in the formula to be effective.

A combination of Methocel E5 and A15 had a similar effect on the release rate of low dose drugs with either low or high water solubility characteristic. A slightly faster release rate and larger variability among dissolution profiles were observed with high water solubility drugs. A synergistic combination of Methocel E5 and A15 appeared to have a better control on the release rate and minimize the variability among individual dissolution profiles.

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World Headquarters

Colorcon
415 Moyer Blvd., P.O. Box 24, West Point, PA 19486-0024
Tel: 215-699-7733 Fax: 215-661-2605 Website: www.colorcon.com/pharma e-mail: info@colorcon.com

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