

## Modulating Dissolution Profiles of Immediate Release Tablets Using METHOCEL™ E5 LV and a Direct Compression Process

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### PURPOSE

Hypromellose (HPMC) is the polymer most widely used to modulate drug release from hydrophilic swellable matrix tablets.<sup>(1-3)</sup> The drug release rate of tablets depends on several formulation variables such as the concentration and viscosity of the polymers as well as the concentration and water solubility of the drugs. The purpose of this study was to investigate the ability of a single METHOCEL™ premium cellulose ether, E5 LV grade to modulate the dissolution profiles of immediate release tablets prepared by direct compression.

### METHODS

A matrix was developed for the study to include model drugs of three doses by three water solubility levels (Table 1).

**Table 1: Study Design with Dose/Water Solubility Matrix**

Water Solubility of Drugs	Concentration of Drug in Formula/ Dose/ Lowest Water Solubility		
	60% Active	25% Active	5% Active
High	Ranitidine HCl 300 mg (100 mg/mL)	Ranitidine HCl 75 mg (100 mg/mL)	Cyclobenzaprine HCl 10 mg (100 mg/mL)
Intermediate	Caffeine 200 mg (22 mg/mL)	Propranolol HCl 80 mg (33 mg/mL)	Propranolol HCl 10 mg (33 mg/mL)
Low	ASA 300 mg (1 mg/mL)	Theophylline 75 mg (1 mg/mL)	Amlodipine Besylate 10 mg (1 mg/mL)

#### Tablet Formulation:

Ingredient	Percent
Active Drug	60%, 25% or 5%
Starch 1500® : Microcrystalline cellulose (1:1 ratio)	qs
METHOCEL™ E5 LV	0, 4, 6, 8 and 10%
Colloidal silicon dioxide	0.25% *
Magnesium stearate	0.25% **
Opadry® II 85 Series™ PVA-based, high productivity film coating 8F18422, white	qs

\* 0.50% colloidal silicon dioxide for ranitidine HCl 300 mg

\*\* 0.50% magnesium stearate for ranitidine HCl 300 mg and 0.5% stearic acid for ASA

#### Manufacturing Process

Direct compression using a 10-station instrumented Piccola tablet press at 30 rpm.

#### Film Coating Process

All tablets were coated to a 3% weight gain (WG) in a Thomas 15" side-vented, fully-perforated coating pan with Opadry II 85F18422 white at 20% solids concentration (Table 2).

**Table 2: Film Coating Parameters**

Process Parameter	Target Value
Inlet air temperature	60°C
Exhaust air temperature	45°C
Tablet bed temperature	48°C
Air flow	306 m <sup>3</sup> /hr (180 ft <sup>3</sup> /min)
Spray rate	8.0 g/min
Spray nozzle size	1 mm
Number of guns	1
Atomization air pressure	1.7 bar (25 psi)
Pattern air pressure	1.7 bar (25 psi)
Pan speed	15 rpm
Pan load	1 kg

#### Dissolution Methods

The uncoated tablets were tested for comparative dissolution profiles as a function of METHOCEL E5 LV concentration, drug concentration and water solubility of the drugs in the formula.

Dissolution profiles were generated with film coated tablets containing 4% and 10% METHOCEL E5 LV to evaluate the effect on Opadry II 85F Series on the dissolution rate of tablets.

**Table 3: Dissolution Methods**

Drug Name	USP Apparatus	Speed (rpm)	Medium	Vol. (mL)
Ranitidine HCl	II (paddle)	50	deionized water	900
Cyclobenzaprine HCl	I (basket)	50	0.1N HCl	900
Caffeine	II (paddle)	100	deionized water	900
Propranolol HCl	I (basket)	100	dilute HCl (1 in 100)	1000
ASA	I (basket)	50	acetate buffer pH 4.5	500
Theophylline	II (paddle)	50	deionized water	900
Amlodipine Besylate	II (paddle)	75	0.01N HCl	500

**RESULTS**

For the sake of brevity, tablet hardness and dissolution profiles are presented for four out of nine model systems, at the corners of the dose-solubility matrix.

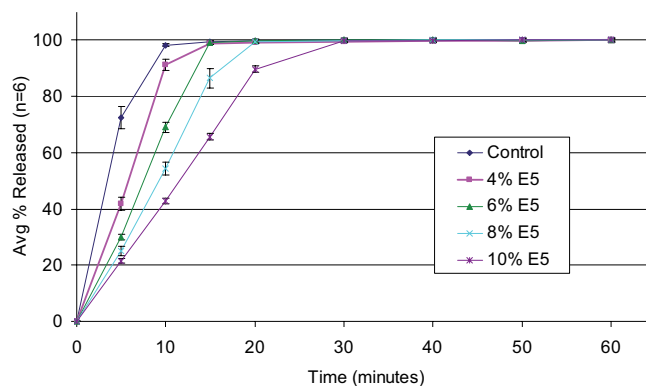
The tablet hardness was maintained within a narrow range of crushing strength for each of the formulae in the study to eliminate the effect of tablet hardness on the dissolution rate (Table 4).

**Table 4: Tablet Hardness of Four Model Formulae**

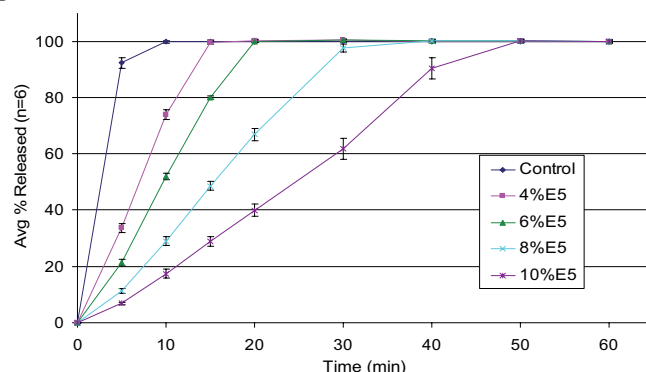
% METHOCEL E5 LV	Average Tablet Crushing Strength (kp) (n=10)			
	Cyclobenzaprine HCl 10 mg	Amlodipine Besylate 10 mg	Ranitidine HCl 300 mg	ASA 300 mg
Control	10.2	18.6	12.1	10.0
4%	10.5	17.6	12.0	10.5
6%	11.0	16.8	12.1	10.1
8%	10.9	17.7	12.5	9.8
10%	10.9	16.8	12.2	11.0

The dissolution rate of tablets decreased as the concentration of METHOCEL E5 LV increased. The effect of METHOCEL is more significant with tablets containing low water solubility drugs and higher concentration of drugs within the same solubility classification. (Figures 1-4)

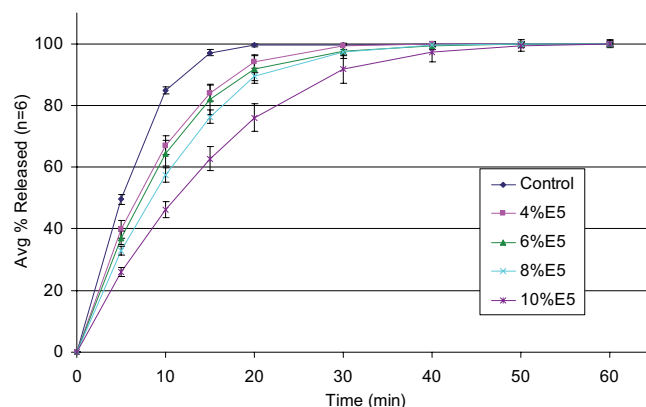
**Figure 1: Dissolution Profiles of Cyclobenzaprine HCl Tablets 10 mg (5% active; dissolution medium = 0.1 N HCl) [Low Dose, High Solubility]**



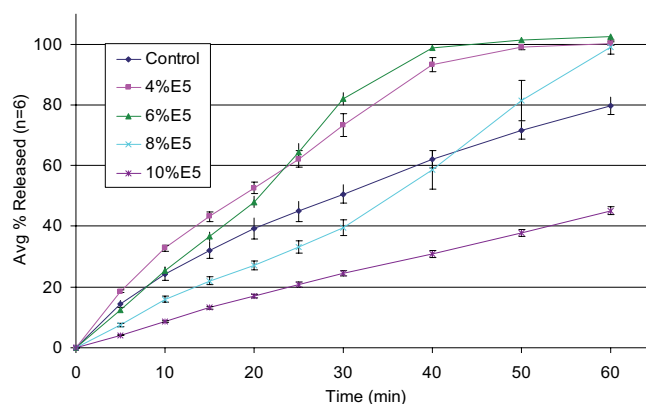
**Figure 2: Dissolution Profiles of Amlodipine Besylate Tablets 10 mg (5% active; dissolution medium = 0.01 N HCl) [Low Dose, Low Solubility]**



**Figure 3: Dissolution Profiles of Ranitidine HCl 300 mg (60% active; dissolution medium = deionized water) [High Dose, High Solubility]**



**Figure 4: Dissolution Profiles of ASA 300 mg (60% active; dissolution medium = pH 4.5 acetate buffer) [High Dose, Low Solubility]**



The dissolution rate of ASA tablets also was determined to be dependent on the concentration of METHOCEL E5 LV in the tablets; however, in this case, it was observed that the dissolution rate of control tablets was slower than that of tablets containing 4% and 6% METHOCEL E5 LV. As the concentrations of METHOCEL E5 LV were increased to 8% and 10%, the dissolution rate decreased progressively below that of the control. It is believed that the dissolution rate enhancement of the ASA tablets containing 4% and 6% METHOCEL E5 LV was due to the surfactant effect of METHOCEL E5 LV as previously reported for poorly soluble drugs.<sup>(4)</sup> At the higher METHOCEL LV E5 concentrations, it is suggested that the dissolution rate slowing effects of polymer gelation and polymer-polymer chain entanglement offset the surfactant properties imparted by the polymer.

In all cases, the dissolution profiles of tablets containing 4% and 10% METHOCEL E5 LV were similar whether they were film coated with Opadry II 85 white or not.

## **CONCLUSIONS**

The dissolution rate of all tablets decreases with increasing concentration of METHOCEL E5 LV. The slow-down effect of METHOCEL E5 LV also depends on the water solubility characteristics of the drug – i.e. lower water solubility drugs had slower dissolution rates at the highest METHOCEL E5 LV concentrations. Film coating with Opadry II 85 Series has no effect on the dissolution profiles of all tablets containing METHOCEL E5 LV.

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