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## Effect of Hypromellose as a Pore-Former in Aqueous Ethylcellulose Dispersion: Characterization of Dispersion Properties

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### Abstract Summary

Hypromellose (HPMC) is commonly used as a pore former in an aqueous ethylcellulose (EC) dispersion. The characteristics of EC dispersion with different levels of HPMC were investigated. Flocculation that occurred at HPMC levels in excess of 5% w/w was disrupted with adequate stress, similar to those encountered during coating processes.

### Introduction

Ethylcellulose (EC) is a commonly used barrier membrane for achieving extended release with multiparticulate formulations. Modulating the dissolution profile of such formulations is often desired and achieved using hydrophilic polymers for pore formation in the EC barrier film. Hypromellose (HPMC, Methocel) is commonly used as a pore former in EC barrier films. Flocculation may occur when utilizing HPMC as a pore former in an aqueous EC dispersion though the exact mechanism is unknown (Wong and Bodmeier, 1996). This study will characterize the addition of Methocel E5 on dispersion properties of Surelease<sup>®</sup> (an aqueous dispersion of ethylcellulose), and evaluate possible interactions arising between the EC dispersed particles and HPMC.

### Experimental Methods

HPMC (Methocel E5, Dow Chemical Co., Michigan, US) was used as a pore-former for EC dispersion (Surelease E-7-19040, Colorcon, West Point, PA, US). HPMC solutions of appropriate concentrations were mixed in the Surelease dispersion.

#### Sedimentation:

The colloidal stability of diluted dispersions was investigated by monitoring the sedimentation rate of the dispersion in closed bottles over a period of 2 weeks. The sedimentation ratio,  $F$ , was calculated as the volume of the sediment (ml)/volume of total mixture (ml).

#### Zeta potential:

The zeta potential ( $\zeta$ ) ( $n = 6$ ), which is a measure of dispersion stability was calculated from the electrophoretic mobility determined using a Zetasizer (ZEN 3600, Malvern Instrument, UK) at  $25.0 \pm 0.5^\circ\text{C}$ .

#### pH:

The pH ( $n = 3$ ) of the dispersion was measured using a PerpHecT LogRmeter (Model 310, Thermo Orion, US).

#### Particle size:

The particle size ( $n = 6$ ) of the dispersions was determined using a laser light scattering Zetasizer (ZEN 3600, Malvern Instrument, UK).

#### Rheology:

Rheological properties of the dispersions were studied using a Dynamic Stress Rheometer (DSR-200, Rheometrics Inc., Piscataway, NJ, USA) equipped with a cup and bob of 32.0 mm and 29.5 mm diameters respectively. Steady shear stress viscosity ( $n = 6$ ) was measured at a controlled temperature of  $25 \pm 1^\circ\text{C}$  (PolyScience Digital Temperature Controlled, 9110-RH, Niles, IL, USA). The response of the dispersion mixtures to sinusoidal variations in stress was also determined by performing dynamic stress sweep at a constant angular frequency of 1 rad s<sup>-1</sup> over a stress range of 0.02 to 300 Pa. Viscoelastic parameters including storage modulus ( $G'$ ) and loss modulus ( $G''$ ) were computed.



## Results and Discussions

Surelease is an aqueous EC dispersion that is stabilized electronically by presence of charged ammonia molecules surrounding the polymer particles.

Destabilization of the dispersion can be monitored by the rate at which particles sediment, the change in particle size distribution and viscosity with time.

The mean size of EC particles remained small and unaffected by presence of HPMC (Table 1). In contrast,  $|\zeta|$  decreased significantly from 60 to 53 with 2.5 %w/w HPMC. Higher HPMC content resulted in a further drop in  $|\zeta|$  (Table 1). The decrease in  $|\zeta|$  value indicates reduced dispersion stability.

**Table 1. Effect of HPMC on Particle Size and Zeta Potential of Surelease**

Amount of HPMC (%)	Mean size ( $\mu\text{m}$ ) ( $\pm\text{S.D.}$ )	$ \zeta $ (mV) ( $\pm\text{S.D.}$ )*
0.0	0.189 $\pm$ 0.003	60.1 $\pm$ 9.9
2.5	0.192 $\pm$ 0.005	52.9 $\pm$ 9.2
5.0	0.191 $\pm$ 0.004	49.1 $\pm$ 8.5
7.5	0.191 $\pm$ 0.005	50.3 $\pm$ 8.5
10.0	0.191 $\pm$ 0.006	47.3 $\pm$ 8.6
15.0	0.190 $\pm$ 0.005	49.4 $\pm$ 8.7
20.0	0.190 $\pm$ 0.005	45.0 $\pm$ 8.3

\*actual values of  $\zeta$  are negative

This was also evident visually from the sedimentation of dispersions containing 2.5 – 5%w/w HPMC. Interestingly, the dispersions containing more than 5 %w/w HPMC did not show clear separation up to 2 weeks. This could be explained by the thickening effect of HPMC on the dispersion as shown from the rheology experiments (Table 2). The colloidal stability of diluted dispersions monitored for a period of 2 weeks by measuring the sedimentation rate is shown in Table 3.

**Table 2. Effect of HPMC on pH, Viscosity and Sedimentation Behavior of Surelease Dispersions**

Amount of HPMC (%)	pH	Viscosity (mPas)	F (%)
0.0	10.17	7.30 $\pm$ 0.31	-
2.5	10.35	13.3 $\pm$ 1.9	95
5.0	10.23	40.6 $\pm$ 3.9	91
7.5	10.16	136 $\pm$ 33	-
10.0	9.97	1050 $\pm$ 180	-
15.0	10.20	7780 $\pm$ 6600	-
20.0	9.98	72400 $\pm$ 17000	-

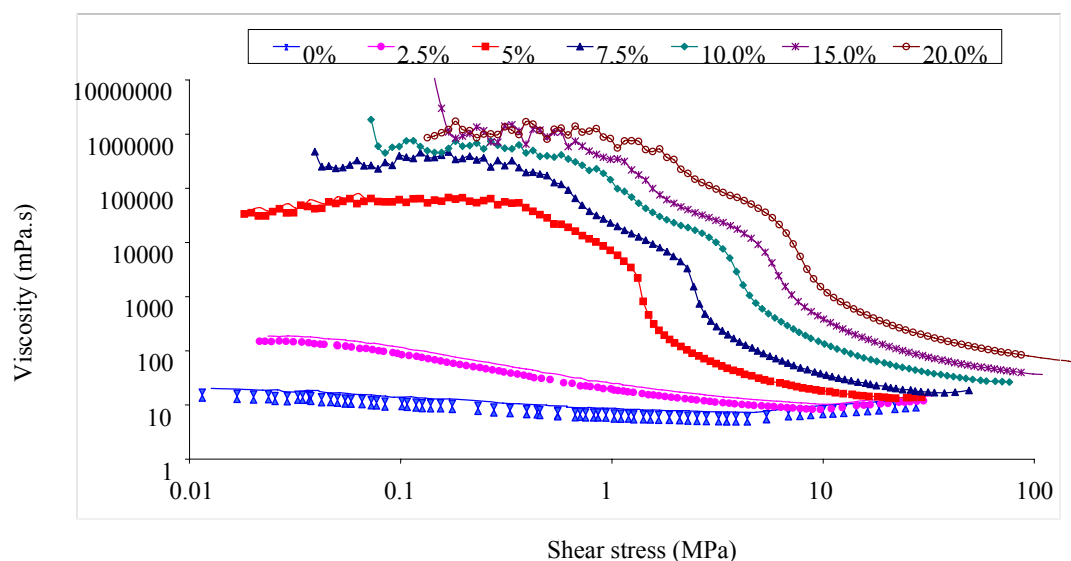
**Table 3. Effect of HPMC on Sedimentation Behavior of Surelease Dispersions**

Time (days)	Sedimentation Ratio (F, %)		
	2.5% HPMC	5% HPMC	20% HPMC
0	-	-	-
3	95	91	-
7	95	91	-
14	95	91	-

At 15 %w/w concentration, Surelease dispersions have very low viscosity and exhibit mild shear thinning behaviour over the applied stress (Figure 1).

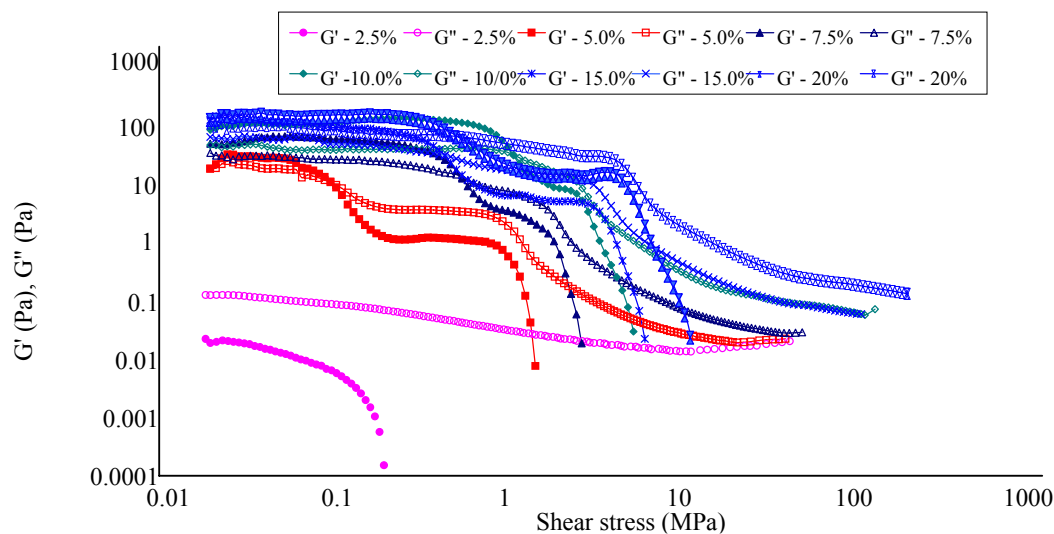
Addition of 2.5 %w/w HPMC caused an upward shift in the viscosity flow curve and greater shear thinning at low applied stress. At concentrations of 5 %w/w and above, the viscosity flow profiles changed drastically, portraying a more pronounced shear thinning behaviour. This pronounced shear thinning consists of 2 stages. In the initial phase, the floccules deformed and aligned with the shear field leading to a decrease in viscosity. On further application of shear, disruption of the floccules took place with a decrease in effective volume fraction (Bujannenez and Dickson 1994). The rate of increase in viscosity was more marked with low HPMC concentration (2.5%w/w), indicating gradual build up of network structure. At higher concentrations, substantial volume of HPMC was present to restrict movement of the EC particles by decreasing particle velocity or trapping them in a three-dimensional network, thereby reducing rate and extent of separation (Pal, 1996).

**Figure 1. Steady State Flow curves of Surelease Dispersions Containing 0 – 20 %w/w HPMC.**



The build-up of internal network causing flocculation is supported by the viscoelastic response of the mixtures subjected to oscillatory stress (Figure 2). Both the  $G'$  and  $G''$  values of Surelease dispersions containing 2.5 %w/w were markedly lower compared to mixtures with higher amount of HPMC. However, as the HPMC content increased, the  $G'$  and  $G''$  values became less concentration dependent. Dispersions with 5 - 20 %w/w HPMC possess solid-like structure, with  $G' > G''$  at low shear stress. This solid-like structure was disrupted with increasing shear resulting in a more fluid-like structure. This transition which is absent for dispersion containing 2.5%w/w HPMC is characterized by a  $G'/G''$  crossover (Figure 2).

**Figure 2. Shear Stress Dependence of the Storage ( $G'$ ) and Loss ( $G''$ ) Modulus of Surelease Dispersions Containing 2.5 - 20 %w/w HPMC.**



## Conclusion

Flocculation of aqueous EC dispersion can occur when sufficient amount of HPMC is added as a pore former. This arises as a result of interaction between the polymer chains and latex particles which contribute to dispersion instability. However, the interactions between the latex particles and HPMC were disrupted with adequate stress, similar to those encountered during coating processes.

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