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Hypromellose as a Pore Former in Aqueous Ethylcellulose Dispersion: Stability and Film Properties

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Introduction

Hypromellose (HPMC) is one of the most commonly used pore formers for ethylcellulose (EC) barrier films. The purpose of this research was to understand the effect of HPMC as a pore-former on: stability of aqueous EC dispersion (Surelease®); quality of the free films prepared from these mixtures, and interactions between the HPMC and EC dispersion.

Materials & Methods

HPMC (Methocel®) was used as a pore-former for EC dispersion (Surelease). HPMC solutions of appropriate concentrations were mixed in the Surelease dispersion.

Characterization of dispersion properties: Colloidal stability of diluted dispersions was investigated by monitoring the sedimentation rate in closed bottles (2 weeks). The zeta potential (ζ) (n = 6), a measure of dispersion stability, was calculated from the electrophoretic mobility determined using a Zetasizer at 25.0 ± 0.5 °C. The pH (n = 3) of the dispersion was measured using a PerpHecT LogRmeter. The particle size (n = 6) of the dispersions was determined using a laser light scattering Zetasizer. Rheological properties of the dispersions were studied using a Dynamic Stress Rheometer equipped with a cup and bob of 32.0 mm and 29.5 mm diameters respectively. Steady shear stress viscosity (η, n = 6) was measured at a controlled temperature of 25 ± 1 °C.

Preparation of film: Films (100 µm thick) were prepared by casting pre-determined amounts of dispersions (12.5 % w/w concentration) on leveled polytetrafluoroethylene (PTFE) coated glass plates. The dried films were cut into strips of specific sizes and equilibrated at ambient room condition (for at least 72 h) prior to testing.

Evaluation of mechanical properties: The mechanical properties of the films (n=10, 22 ± 2°C, 55 ± 2%RH) were evaluated using a Universal Tensile Tester mounted with a 500 N capacity load cell. The test procedure was based on the ASTM D 882 - 75d method. The initial gauge length was set at 25 mm and the extension speed was 10 mm/min. Tensile strength, % elongation at break, and elastic modulus were computed from the load - strain profile and film dimensions.

Determination of water vapor permeability: The film samples (average thickness of 100 µm) were fastened between two chambers (25°C; 80%RH) and nitrogen gas was passed at a rate of 200 ml/min. All samples were pre-dried with air at flow rate of 100 ml/min, 25°C for 15 min to remove residual moisture. Water vapor transmission rate (g water/day/100cm2) was determined by the dew point and flow rate of nitrogen.

Coating of pellets: The drug-loaded pellets were coated with EC dispersions containing 5 or 10 %w/w HPMC. Chlorpheniramine maleate (CPM) loaded beads were coated using a fluid bed, equipped with a bottom-spray nozzle.

***In vitro dissolution studies*:** Drug release from coated pellets (n=3) was characterized by dissolution test (USP XXII, method I) using 900 ml of deionised water, at 37 ± 1 °C. The basket speed was 100 rpm. At predetermined time intervals, samples were collected and assayed spectrophotometrically at 265 nm.

Results & Discussion

Sedimentation was observed for dispersions containing > 7.5 %w/w HPMC (Figure 1). The extent of separation became smaller as the amount of HPMC increased (Figure 2a). This was due to HPMC causing greater restriction on the movement of the EC particles by decreasing particle velocity or trapping them in a three-dimensional network (Pal, 1996). Steady state viscosity flow curves (Figure 2b) also suggest that the formation of floccules were observed.

Figure 1. Surelease Dispersions Containing 2.5 – 20% w/w HPMC

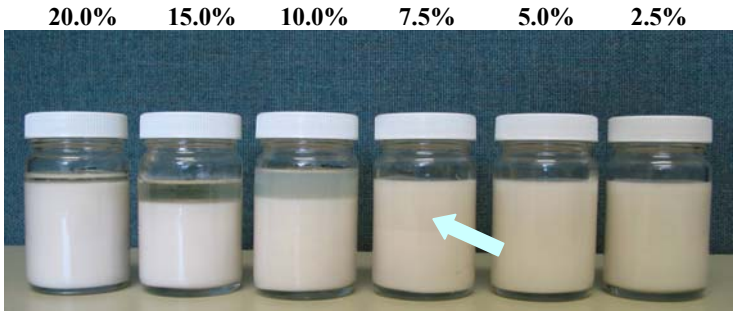
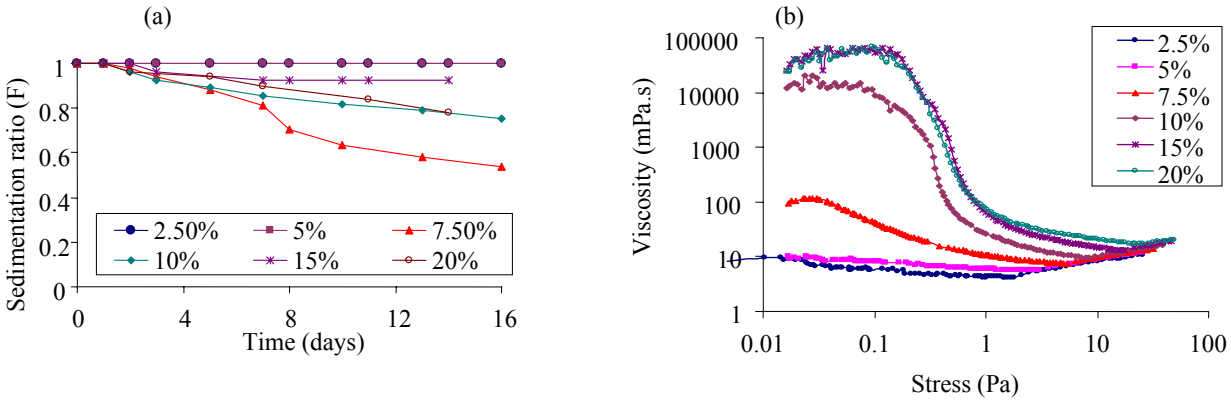


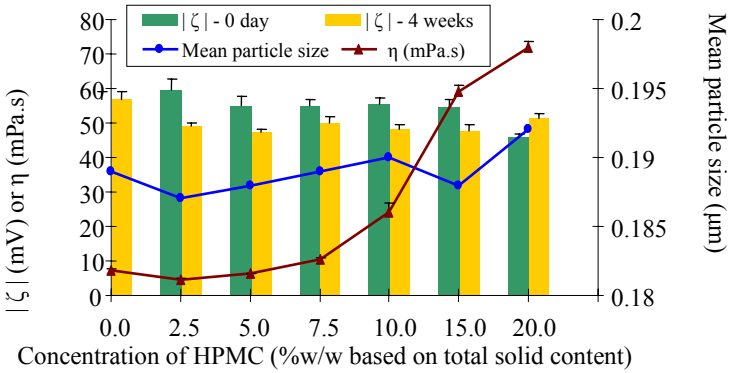
Figure 2. Effect of HPMC Concentration (2.5 – 20% w/w) on (a) Sedimentation and (b) Viscosity Curves



EC dispersions containing 10% w/w or more HPMC exhibited pronounced shear thinning; the rheological profiles are representative of a system with network formation. The zeta potential of freshly prepared EC-HPMC dispersions, with the exception dispersion containing 20 %w/w HPMC, were similar to dispersion without pore-former (Figure 2). After 4 weeks of storage, dispersions which showed sedimentation were redispersed before aliquot volumes of sample were diluted for zeta potential measurement.

Figure 3 showed that a 9 - 17% drop in $|\zeta|$ values for all the dispersions, except for that containing 20 %w/w HPMC.

Figure 3. Effect of HPMC Concentration on Zeta Potential ($|\zeta|$), Particle Size, and Viscosity (η) of EC Dispersion



Ability to redisperse the particles is characteristic of a flocculated system since the attractive forces between the particles are relatively weak (Li and Tians, 2002). On standing, the particles are attracted to each other loosely to reform floccules which when settled, form boundary between the sediment and supernatant. However, the decrease in $|\zeta|$ value may indicate reduced dispersion stability. In order to investigate how the occurrence of flocculation affect the quality of EC coats, the mechanical properties and water vapor permeability of films prepared from EC dispersions with 5 - 10 %w/w HPMC were compared and shown in Figure 3 and Table 1. Films cast from redispersed suspension containing 5 %w/w HPMC that were stored in sealed vessels for 3 days or 2 weeks, respectively showed significantly lower tensile strength and elastic modulus ($p < 0.05$, Figure 4) values

Figure 4. Effect of HPMC Concentrations and Storage Time of Dispersions on the (a) Tensile Strength (TS), % Elongation (%E) (b) Elastic Modulus (EM) and Water Vapor Permeability (WVP) of EC Films

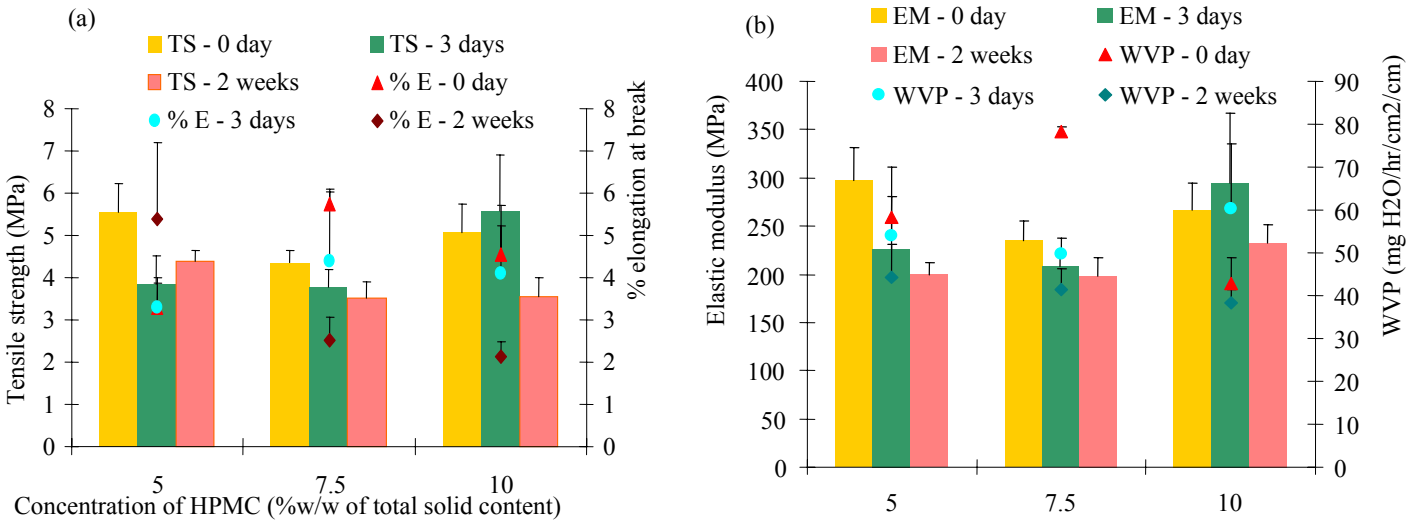


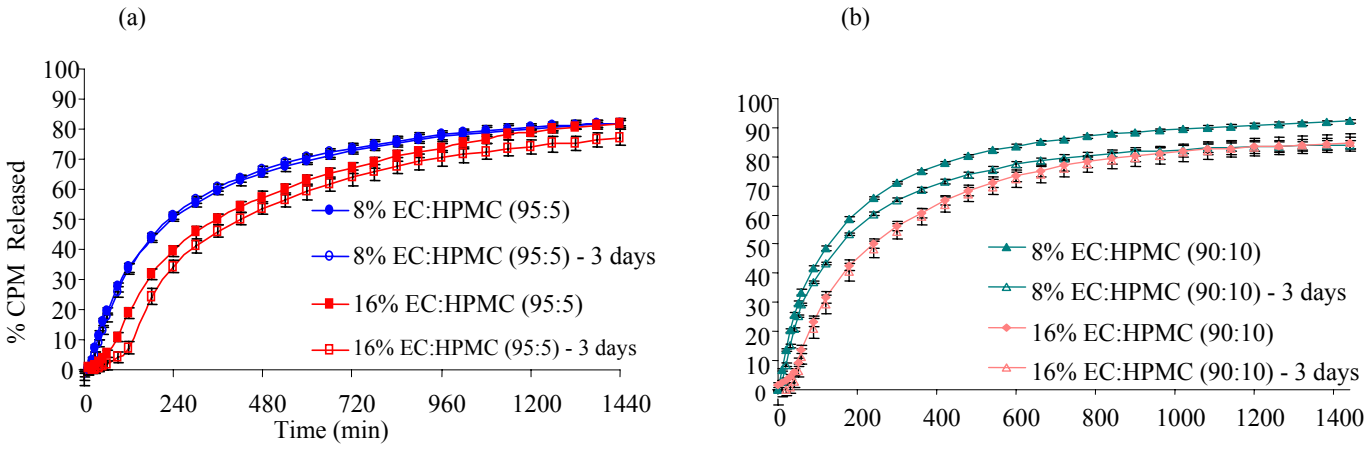
Table 1. Mechanical Properties of EC films Containing 0 - 10 % w/w HPMC

HPMC %	Tensile Strength (MPa)	% Elongation at Break (MPa)	Elastic Modules
0	6.18 ± 0.96	6.78 ± 1.6	252 ± 34
5	5.54 ± 0.69	3.30 ± 0.8	297 ± 34
7.5	4.35 ± 0.29	5.74 ± 2.3	235 ± 20
10	5.08 ± 0.65	4.56 ± 0.8	267 ± 28

A similar trend was observed for dispersions containing 7.5 or 10 %w/w HPMC which showed flocculation on standing for 3 days (Figures 1 and 3). A two tailed t-test analysis exhibited significant differences ($p < 0.05$) between tensile strength and elastic modulus, except for EC:HPMC (90:10) films cast from dispersions that were used immediately or after 3 days of storage. In addition to decreased film strength and hardness, films prepared from dispersions after 2 weeks of storage also exhibited less flexibility with lower % elongation (Figure 4a). The moisture permeability result reflected large variation and less obvious trend (Figure 4b).

Dispersions freshly prepared or left standing for 3 days were also applied onto CPM beads. The dissolution profiles of the coated beads suggested that the interaction between HPMC and EC dispersions has no effect on the mechanism of release (Figure 5a and b). The $f1$ and $f2$ values derived from statistical analysis were less than 10 and more than 50 respectively, thus further concurred that film coats produced by dispersions with different storage times (up to 3 days) were equivalent in their controlled release characteristic. This observation applied to both flocculated (10% HPMC) and non-flocculated systems (5% HPMC).

Figure 5. Dissolution Profiles of CPM Beads Coated with (a) EC:HPMC (95:5) and (b) EC:HPMC (90:10)



Conclusions

HPMC can interact with latex particles, causing flocculation of aqueous EC dispersion when added in sufficient quantity. However, these interactions between the latex particles and HPMC were easily disrupted with adequate stress. Despite the statistically significant differences in mechanical properties of both flocculated and non flocculated EC:HPMC dispersions produced similar release profiles when applied to chlorpheniramine beads.

References

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