The Influence of Pore-Former on Drug Release from Ethylcellulose Coated Multiparticulates

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Abstract Summary

In this study, the addition of hydrophilic pore-former - hypromellose (HPMC) to an ethylcellulose film coating, applied in an isopropyl alcohol-water (9:1) solution was studied. The pore-former addition resulted in modulation and complete drug release over 24-hour dissolution testing. Dissolution rate increased with increasing concentration of pore-former.

Introduction

Ethylcellulose (EC) is a water-insoluble polymer, having a relatively small degree of swelling due to its hydrophobicity.[1] Incomplete drug release, as well as a long lag time, has been reported in some instances from EC coated multiparticulates, even at low coating weight gains.[2] The objective of this work was to investigate the influence of HPMC as a pore-former on the release of chlorpheniramine maleate from multiparticulate beads coated with ethylcellulose from an organic solution.

Experimental Methods

Drug Layering of Sugar Spheres

Chlorpheniramine maleate (CPM) was coated onto 18/20 mesh SureSpheres®, drug layering substrate (Colorcon), to a target drug load of 30 mg/g using a Pam-Glatt fluid bed coater (FBE-125 equipped with a Würster column, 360 mm length) using HPMC (METHOCEL™ E6, premium cellulose ethers, Dow Wolff Cellulosics) as a binder. The aqueous drug layering solution comprised CPM (70 %), METHOCEL E6 (30 %) in purified water.

Ethylcellulose Coating of Drug Layered SureSpheres

Coating solutions of ETHOCEL™, premium ethylcellulose polymers, Standard 10 (Dow Chemical Company) and various low viscosity grades of HPMC E-series (2910) polymers were prepared in an isopropanol (IPA): purified water (90:10) solvent mixture. The HPMC content ranged from 0%-30% in the polymer blend. Dibutyl sebacate (Vertellus), 10% w/w with respect to the total polymer content, was added as a plasticizer. The concentration of the film coating compositions in the solvent mixture was 7% in all cases. CPM beads were coated to a 10% w/w film weight gain in each case using a Glatt GPCG 1.1 fluid bed coater (Pam Glatt Pharma Technologies).

Experimental Methods (cont'd)

Viscosity Determination

Viscosity of a 7% coating solution in a 90:10 solvent mixture of IPA: purified water was determined using a Brookfield viscometer (DV-II+ Pro).

Dissolution Testing

Drug release from coated pellets was determined using an automated dissolution bath (Erweka DT 800), USP Apparatus I at 100 rpm in 1000 mL of purified water at 37 ± 0.5ºC. An online dual beam spectrophotometer (PerkinElmer) was used for the detection of CPM at a wavelength of 262 nm over a 24-hour period. Purified water was used as a reference.

Evaluation of Cast Films

Films were cast from an acetone: isopropanol (65:35) mixture on glass plates using a draw knife (Gardner Casting Knife) to a targeted dry film thickness of 150 µm ± 10%. Films were dried at room temperature in a chemical safety hood. Mechanical properties of cast films (n=10) were evaluated using a tensile testing instrument (Instron Model 5542, Norwood, MA USA) at an extension rate of 1mm/min.

Stability Study

Coated pellets were loosely packaged in 100cc HDPE bottles (45g per bottle, without desiccant). The bottles were induction (foil) sealed, stored for six months at accelerated ICH conditions of 40ºC/75%RH, and evaluated for drug release.

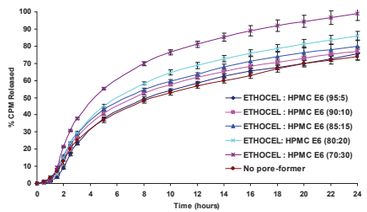
Results and Discussion

Effect of Pore-Former (HPMC) Concentration

The release rate of CPM increased with increasing HPMC concentration in the film (**Figure 1**). It has been postulated that relaxation and swelling of EC films increased as the amount of HPMC in the film increased. HPMC is believed to hydrate and subsequently produce water-logged regions (pores) within the film. Some HPMC migrates into the dissolution medium, thereby creating regions with higher film permeability to the drug. A previous study also suggested that the extent of permeability enhancement and drug release depended on the concentration of HPMC in the film.[3]

Results and Discussion (cont'd)

Figure 1. Effect of pore-former level on CPM release



Effect of Pore-Former (HPMC) Viscosity Grade

There was a modest increase in CPM release rate with increasing HPMC viscosity, indicating that higher molecular weight grades of HPMC may absorb more water and swell to a greater extent, leading to higher permeability (**Figure 2**). Low viscosity grades of HPMC yielded coating solutions of lower viscosity (**Table 1&2**), which typically allowed for more rapid coating application. However, for all the viscosity grades, at the concentrations used, the slight increase in viscosity of the coating solution did not significantly impact coating process time.

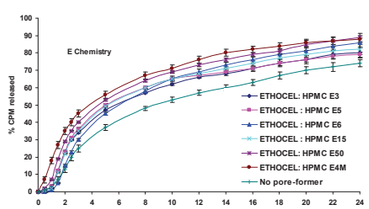
Table 1. Coating solution viscosity (cP)

Coating composition: EC/HPMC ratio		Viscosity (cP)
ETHOCEL Std 10 Prem	METHOCEL E6	
95	5	74.5
90	10	75.3
85	15	82.5
80	20	111.0
70	30	100.5

Table 2. Coating solution viscosity (cP)

Composition:		Viscosity (cP)
ETHOCEL (0.8)	METHOCEL (0.2)	
ETHOCEL Std 10 Prem.		79.8
ETHOCEL Std 10 Prem.	METHOCEL E3	94.5
ETHOCEL Std 10 Prem.	METHOCEL E5	108.0
ETHOCEL Std 10 Prem.	METHOCEL E6	111.0
ETHOCEL Std 10 Prem.	METHOCEL E15	170.0
ETHOCEL Std 10 Prem.	METHOCEL E50	197.2

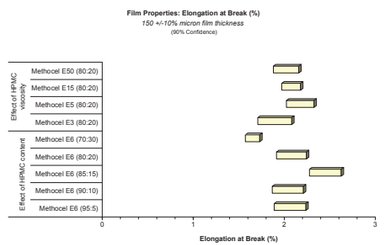
Figure 2. Effect of HPMC viscosity on CPM release [coatings comprised of ETHOCEL (0.80): METHOCEL (0.2)]



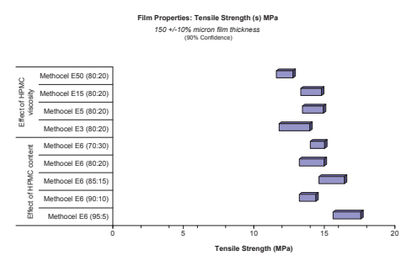
Effect of pore-former (HPMC) on Mechanical Properties of EC Cast Films

Elongation at break increased with the addition of HPMC. Such an effect has also been reported by other researchers.[4] Increasing HPMC to 30%, however, resulted in a significantly reduced elongation at break (**Figure 3a**). HPMC levels exceeding 5% in EC/HPMC composite films resulted in films of lower tensile strength. These results are in agreement with other reports documented in literature.[5] For all other HPMC concentrations evaluated, statistically similar values for tensile strength were obtained (**Figure 3b**). The viscosity of the HPMC had no significant impact on either the elongation or the peak stress.

Figure 3. Effect of HPMC on mechanical properties of EC cast films.



(a) Elongation at Break

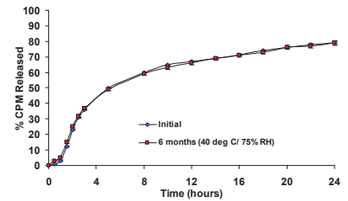


(b) Tensile strength

Stability Study

The multiparticulate beads showed no signs of cracking or discoloration during storage. There was no significant change in drug release for pellets stored at six months at accelerated conditions of 40ºC/75%RH (**Figure 4**).

Figure 4. Effect of storage conditions on drug release from EC (0.8): HPMC 5 cP (0.2) coated CPM pellets [f_2=85.91]



Conclusions

The addition of HPMC to ETHOCEL barrier membrane coatings resulted in complete drug release over 24 hours. Dissolution rate and extent of drug release increased with increasing HPMC content and also modestly with increasing molecular weight of the HPMC. HPMC of lower viscosity provided coating solutions of lower viscosity. The HPMC content influenced film mechanical properties, while the HPMC viscosity did not significantly impact film mechanical properties. CPM beads coated with EC solutions containing HPMC yielded stable release profiles at six months storage at accelerated conditions.

The results demonstrate the utility of HPMC as a pore-former in modulating drug release from organically applied ethylcellulose film coatings, thereby ensuring complete terminal drug release.

References

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