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The Influence of Solvent Type on Extended Release Coating with Ethylcellulose Barrier Membranes

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ABSTRACT SUMMARY:

The influence of four different solvent combinations on chlorpheniramine maleate release from ethylcellulose barrier membrane coated beads was investigated. Solvent type influenced viscosity of ethylcellulose solutions, however drug release profiles from the coated beads were not affected.

INTRODUCTION:

Although interest in aqueous dispersions of cellulose ethers continues to increase, solvent-based ethylcellulose (EC) extended release coating applications also continue to grow. Factors such as plasticizer type [1] and choice of solvent or co-solvents may have significant impact on the film permeability, porosity and mechanical strength of the deposited EC film [2-4].

EC is insoluble in water and soluble in various organic solvents [5]. While some solvents are excellent in dissolving the EC polymer, they have limited or no application in the pharmaceutical industry because of their unacceptable effect on environment and health. The objective of this work was to investigate the influence of four acceptable solvent combinations on EC solution viscosity and consequent drug release from coated beads.

EXPERIMENTAL METHODS:

Drug Layering of SureSpheres™

Chlorpheniramine maleate (CPM) was coated onto 18/20 mesh (850-1000 µm) SureSpheres (Colorcon, Inc., USA) to a target drug load of 37 mg/g using a Vector fluidized bed coater (FL-M-60 equipped with Wurster column) using Hypromellose 2910 (METHOCEL™ E6 Premium, Dow-Wolff Cellulosics, USA) as a binder. Drug layering was carried out at an inlet temperature of 58-60°C, fluid delivery rate of 118 ml/minute, atomizing air pressure of 20 pounds per square inch (psi) and an air volume of 900 cubic feet per minute (cfm).

EC Coating of Drug-Layered SureSpheres

ETHOCEL™ Standard 10 Premium EC (Dow-Wolff Cellulosics) was dissolved in various solvent combinations (Table 1). Solution rheology of each solution was examined using a stress controlled rheometer AR G2 (Cup and bob configuration, TA Instruments, USA). Dibutyl sebacate (10% w/w with respect to the polymer) was then added as a plasticizer leading to a final coating solution solids content of 7% w/w. CPM beads were coated to 5, 7, 10, 15 and 20% weight gains using a GPCG 1.1 fluid-bed apparatus (Pam-Glatt Pharma Technologies, India). Coating process parameters that were used are listed in Table 2.

Table 1. Solvent Combinations

1	Acetone: Isopropanol (IPA)	65:35
2	Dichloromethane (DCM): IPA	50:50
3	Water: IPA	10:90
4	Water: Ethanol	10:90

Note: Viscosity determination: (v/v); Coating solution: (w/w)

Table 2. Coating Parameters used for EC Coating

Solvent combinations	1	2	3	4
Charge (g)	600	600	600	600
Air volume (m/s)	10-12	10-12	10-12	10-12
Inlet air temperature (°C)	30-42	34-36	40-42	40-42
Exhaust air temperature (°C)	28-30	30-32	34-35	34-35
Product temperature (°C)	28-32	30-33	35-36	35-36
Fluid delivery rate (g/min)	5-12	5-10	5-8	5-8
Atomization air pressure (bar)	1.0	1.5	1.5	1.5
Coating solids content (%)	7	7	7	7

Dissolution Testing:

Drug release was measured from 1 gram of coated pellets using a USP compliant automated dissolution bath (Erweka DT 800, Apparatus I (Germany)) at 100 rpm. The dissolution medium was 1000 ml of purified water at 37 ± 0.5°C. An online dual beam spectrophotometer (Perkin-Elmer, USA) was used for the detection of CPM at a wavelength of 262 nm over a 24 hour period.

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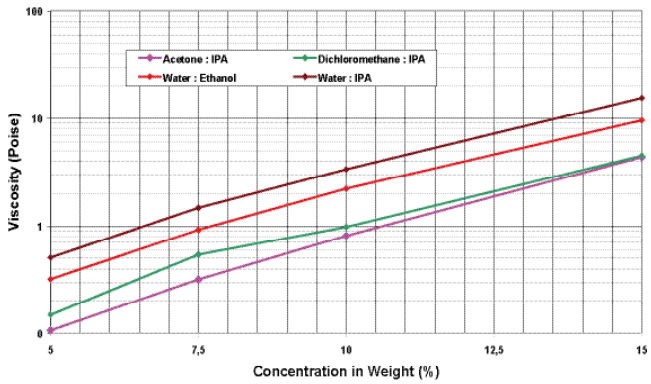
RESULTS AND DISCUSSION:

In EC coating applications, a good solvent system provides low solution viscosity, for ease of application, and allows polymer to solvate and relax, yielding films with good mechanical strength able to reproducibly control drug release. Figure 1 shows that solution viscosity for all solvent combinations increased as the solids content increased. Viscosity, however, at each EC concentration depended on the solvent system used. EC dissolved in water:IPA (10:90) resulted in the highest viscosity at each EC concentration and acetone:IPA (65:35) resulted in lowest solution viscosities.

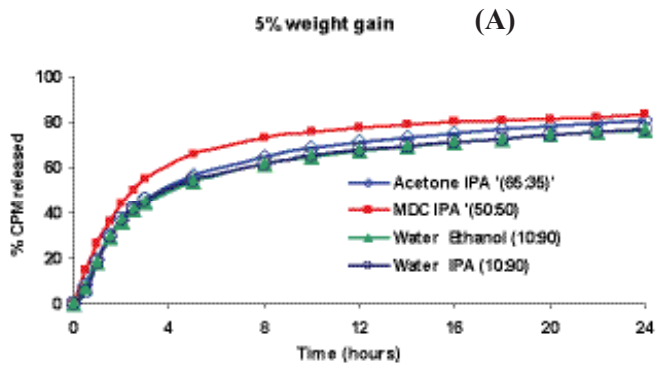
Figure 1. Viscosity of Ethylcellulose Solutions

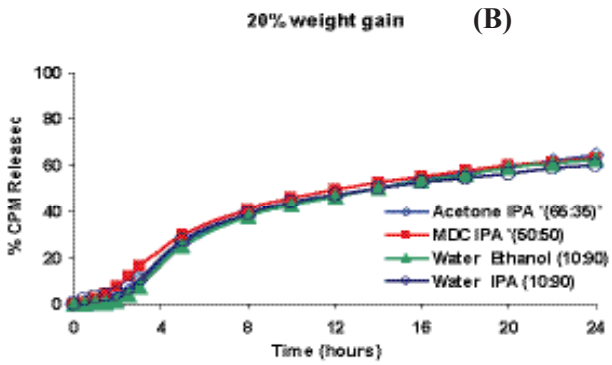


Polymer - solvent interactions are assumed to be at a maximum when the solubility parameter of the polymer and solvent are equal [6]. The solubility parameters and dielectric constants of EC and the solvents used in this study are listed in Table 3. Solubility parameters calculated for the solvent combinations acetone:IPA, DCM:IPA, water:IPA and water:ethanol, were 21.4, 21.7, 29.2 and 28.2,respectively. Calculated solubility parameters for acetone: IPA and DCM: IPA were closest to EC, suggesting that these mixtures should be better solvents for the polymer.

Figure 2 shows drug release from CPM layered beads coated with EC using the four solvent mixtures (Table 1). The release profiles were highly reproducible with standard deviations less than 3% (n=6). Figures 2A/B indicate that the choice of solvent combinations studied here did not significantly affect drug release from the EC coated CPM beads.

Figure 2. CPM Release Profiles from EC Coated Beads: (A) 5% WG and (B) 20% WG





It has been reported that EC films from solvent-mixtures comprising water may be porous, resulting in faster drug release rates [4]. The porous film has been described to result from a premature desolvation or precipitation of EC during film formation due to differences in the latent heat of vaporization [7] of water and the organic solvent. Contrary to these reports, no significant differences in drug release profiles were observed, where 10% water with IPA or ethanol were used in this study. This may be a result of low water concentration in the binary solvent mixture leading to similar EC film formation using laboratory scale coating equipment.

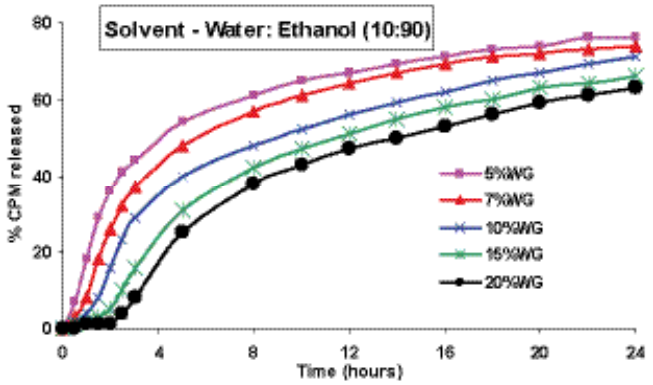
Results of this study showed that regardless of solvent combination used, drug release decreased progressively (for example the time taken for 50% drug release increased from 4 hours to 14 hours for water : ethanol) as the coating weight gains increased from 5% to 20% (Figure 3). This relationship, along with a time-lag in drug release observed (Figures 2B & 3), as coating weight gain exceeded 10%, indicated that drug release is proportional to path length or film thickness.

Table 3. Selected Physical Properties of EC and Solvents used in this Study

	Dielectric constant[8]	Solubility parameter [6,8] (δ)	Boiling point (°C)
Ethylcellulose	3.2- 4.0	21.1	-
Ethanol	24.3*	26.0	78.5
Acetone	20.7*	20.3	56.5
Dichloromethane	9.1**	19.8	40.0
Isopropanol	19.9*	23.5	82.5
Water	78.5	48.0	100.0

* Determined at 25°C
** Determined at 20°C

Figure 3. Effect of EC Weight Gain on Drug Release



CONCLUSIONS:

Solvent composition had an influence on solution viscosity of ethylcellulose, which may affect coating process efficiency. Drug release profiles were not affected by the solvent compositions for the four different solvent mixtures investigated here. Future work will investigate the physico-mechanical properties of ethylcellulose films prepared from each solvent mixture.

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