Ethylcellulose Controlled Release Coating: 
Effects of Plasticizers, Additives, and Solvents

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Introduction
Ethylcellulose (EC) is a water-insoluble polymer, which has been used successfully for coating applications in drug delivery with controlled release. As reported in the literature, variables that significantly impact resulting film properties include the molecular weight, solvent system, additives, and amount of EC applied. This study examined dissolution profiles of drug through EC coatings with different amounts and types of the plasticizers dibutyl sebacate (DBS) and triethyl citrate (TEC). The effect of a pore former, hypromellose, was also examined. The influence of solvent selection was investigated by measuring the viscosity of various EC solutions.

Experimental Methods

Materials Used
- ETHOCELL™ Standard 10 Premium ethylcellulose (The Dow Chemical Company, USA)
- METHOCEL™ E5 Premium LV hypromellose (The Dow Chemical Company, USA)
- Diphenhydramine HCl (Kango Chemical Company)
- Dibutyl sebacate (Morflex, USA)
- Triethyl citrate (Addrich Chemical Company, Inc.)
- 30-35 mesh non-pearl beads (Pallaulin)
- Ethanol, 190 proof (Spectrum, USA)
- Toluene, 190 proof (Spectrum, USA)
- Trikene (Fishier Scientific)
- Methoxe (Fishier Scientific)
- Methanol (Sciencerific)

Drug coating on non-pareils: Diphenhydramine HCl was applied to 30-35 mesh non-pearl beads using a Uni-Glatt Wurster fluidized bed from Glatt Air Techniques, Inc. The EC coating solution was applied to a 10% weight gain on the non-pareils. Coating conditions used with the Uni-Glatt are listed below:

Intet temperature: 70°C
Outlet temperature: 50°C
Spray rate: 1 gm/min

Ethylcellulose coating on drug containing non-pareils: All EC coating solutions were applied in the diphenhydramine HCl coated non-pareils in a Mini-Glatt Wurster fluidized bed from Glatt Air Techniques, Inc. Typical coating conditions used are listed below:

Intet temperature: 70°C
Outlet temperature: 50°C
Spray rate: 1 gm/min

Coating Formulation
10% (w/w) solutions of EC Std. 10 Premium, 1% (w/w) dibutyl sebacate or triethyl citrate in ethanol
10% (w/w) solutions of EC Std. 10 Premium with 3% (w/w) dibutyl sebacate or triethyl citrate in ethanol
10% (w/w) solution of EC Std. 10 Premium with 1% (w/w) hypromellose in ethanol
10% (w/w) solution of EC Std. 10 Premium with 1% (w/w) hypromellose in 40/60 Ethyl Acetate/Ethanol
10% (w/w) solution of EC Std. 10 Premium with 1% (w/w) hypromellose in 80/20 Toluene/Ethanol
10% (w/w) solution of EC Std. 10 Premium with 1% (w/w) hypromellose in 9.5% Ethanol with 0.4% hypromellose
10% (w/w) solution of EC Std. 10 Premium with 1% (w/w) hypromellose in 190 proof Ethanol (undenatured)

Results and Discussion

Previous work shows that EC films without a plasticizer are brittle and have low integrity. Adding small amounts of plasticizers and other additives can increase the flexibility and thus the integrity of EC films. These additives can also affect the drug release rate through the films. Additives can affect the drug release rate through the films. Additives can affect the drug release rate through the films.

Solution testing: Dissolutions were tested with a Distek TCS2000B dissolution system with a Hewlett-Packard 8452A Diode Array Spectrophotometer. For diphenhydramine HCl, the wavelength used for diphenhydramine HCl was 228 to 232 nm. All dissolutions were done in 500 mL deaerated DI water (Distek MD 1 De-Gasser). The media temperature was 37 ± 0.5°C and USP Apparatus I was used (rotating baskets) with a rotation speed of 100 rpm. Each dissolution curve represents an average of six runs.

Measurement of 15% and 5% Solution Viscosities: Solution viscosities were determined using a Ubbelohde viscometer in a constant temperature water bath set at 25°C (± 0.1°C). The average efflux time of three trials was recorded and used in the following equation to calculate solution viscosity (cP):

\[ \text{Viscosity} = k \times d \times t \]

where k is the standard viscometer constant, d is density of the solvent in solution, t is efflux time of ethylcellulose solution.

Figure 1 shows a picture of a typical Ubbelohde viscometer.

Figure 1 – Typical Ubbelohde Viscometer

Figure 2 – Dissolution results for Diphenhydramine HCl coated non-parels in DI water with 13% weight gain EC and different levels of TEC (n=5).

Figure 3 shows dissolution profiles from beads containing diphenhydramine HCl coated with EC along with 1% and 3% TEC added. There is not a large difference in drug dissolution rates. Using 1% TEC as a baseline, the 11 and 12 values for the two dissolution curves are 4.3 and 7.7, respectively, thus suggesting they are similar.

The dissolution rates of diphenhydramine HCl through EC coatings with 1% and 3% DBS are shown in Figure 3. Similar to the EC coatings with TEC, there is not a large difference in drug dissolution rates with the two levels of DBS. The 11 and 12 values for these dissolution curves, with 1% DBS as a baseline, are 10.5 and 59.1, respectively.

Figure 4 can be used to compare the dissolution curves of diphenhydramine HCl with EC formulations containing both 1% and 3% DBS and TEC as well as 1% HPMC.

EC solution viscosities were compared at 15% and 5% concentration levels in various solvents and solvent blends. As Table I indicates, there are differences in solution viscosity based on solvent use, with EC in toluene having the highest solution viscosity and EC in acetone the lowest. This information can help when evaluating solvents to use with EC. One study found differences in dissolution rates from EC films cast with different solvents.3 In good solvents, the EC coils are well-relaxed, as opposed to compacted in a poor solvent. The relaxed EC coils form a stronger network, producing a stronger film which results in slower drug release rates. A good solvent for EC can be defined as one that has a solubility parameter similar to that of EC.

Figure 4 shows the dissolution results for Diphenhydramine HCl coated non-parels in DI water with 13% weight gain EC and different levels of TEC (n=5).

EC solution viscosities can be good indicators if a solvent is good or bad. The extended EC chains in a good solvent increase the viscosity of the solution due to the breaking of intramolecular association and chain-stiffening of the EC.4 Chain-stiffening occurs because more solvent molecules can link to the monomer segments in an extended chain than in a folded or tightly coiled chain. In good solvents, the extended chains are thermodynamically favored over coiled chains.

Figure 5 describes solution viscosities for beads containing diphenhydramine HCl coated with EC along with 1% and 3% TEC, and either 1% or 3% DBS added. There is not a large difference in drug dissolution rates. Using 1% TEC as a baseline, the 11 and 12 values for the two dissolution curves are 4.3 and 7.7, respectively, thus suggesting they are similar.

Table I – Solution viscosities of 15% and 5% ETHOCELL™ Standard 10 Premium in various solvents

<table>
<thead>
<tr>
<th>Solvent Combination</th>
<th>15% Viscosity (cP)</th>
<th>5% Viscosity (cP)</th>
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<tbody>
<tr>
<td>Ethanol with 0.4% hypromellose</td>
<td>132.5</td>
<td>231.3</td>
</tr>
<tr>
<td>Acetone</td>
<td>10.5</td>
<td>33.1</td>
</tr>
<tr>
<td>40/60 Ethyl Acetate/Ethanol</td>
<td>6.1</td>
<td>15.1</td>
</tr>
<tr>
<td>80/20 Toluene/Ethanol</td>
<td>480.4</td>
<td>2401.1</td>
</tr>
<tr>
<td>9.5% Ethanol with 0.4% hypromellose</td>
<td>2401.1</td>
<td>283.2</td>
</tr>
<tr>
<td>577.3</td>
<td>577.3</td>
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</tbody>
</table>

Conclusions

The use of EC as an effective rate controlling polymer was demonstrated. Adding small percentages of the plasticizers TEC and DBS, or the pore former hypromellose, to EC coating solutions does not have a large influence on drug release rate. Solution viscosity of EC solutions varies with the solvent that is used and can be an indication if the solvent is a good or poor solvent for EC. Good solvents will have a higher solution viscosity than bad solvents. Solution viscosity can be used to screen potential solvent candidates prior to using them in coating formulations.

References

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