Effect of Hydroxyl Group Content in Ethyl Cellulose on Permeability in Free Films and Coated Membranes

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ABSTRACT: The change in the water permeability, glass transition temperatures, and mechanical properties of ethyl cellulose with different degrees of substitution are presented. Studies of the hydroxyl group content on the polymer chains indicate that the mechanical properties of a free film decrease as the hydroxyl group content increases. This is thought to be due to the lower solubility of ethyl cellulose with a lower degree of substitution, as determined by the interaction constant in ethanol and the ability of the film with a high hydroxyl group content to hold more water. Furthermore, an increase in hydroxyl group content increases water permeability. Finally, a study of spray-coated pellets has been performed and reveals a similar effect. The higher the hydroxyl group content, the higher the release rate and, at the same time, the decrease in Vickers hardness. © 1999 John Wiley & Sons, Inc. J Appl Polym Sci 72: 529–535, 1999

Key words: ethyl cellulose; degree of substitution; water permeability; mechanical testing

INTRODUCTION

Cellulose derivatives have attracted considerable attention in the pharmaceutical industry during the last decade. Ethyl cellulose (EC), hydroxypropyl cellulose, and hydroxypropyl methyl cellulose polymers are used as coating materials in different extended release formulations.^{1,2} Apart from the influence of molecular length on properties, the substituents are one of the most important features of these cellulose derivatives. The type of alkyl groups, the distribution of substituents in the anhydroglucose unit, and the distribution of substituents along the cellulose chain are thought to influence the physical properties substantially. Several papers discussing the physical and mechanical properties of free films and coatings

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made of EC, such as Sakellariou and colleagues³ have been published. Very few reports have, however, related physical properties to the distribution of the substituents of alkyl celluloses.⁴⁻⁶ The main reason is probably the difficulty involved in preparing alkyl cellulose derivatives with the controlled distribution of substituents.

In the present work, the change in the water permeability, glass transition temperatures, and mechanical properties of free EC membranes with a different degree of ethyl substitution are examined. A study of pellets coated with EC is also included.

EXPERIMENTAL

Materials

EC (Ethocel Standard Premium N10) samples were obtained from Dow Chemical Co. Ethanol

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Sample	Hydroxyl Content ^a (wt %)	Degree of Substitution (D.S.)	Intrinsic Viscosity $(ml g^{-1})$	$\frac{\bar{M}_n{}^{\mathrm{b}}}{(\mathrm{g}\;\mathrm{mol}^{-1})}$	${ar M_w}^{ar W_w}^{ m b}$ (g mol $^{-1}$)
EC1	3.11	2.572	79.6	19,000	78,000
EC2	2.97	2.590	82.0		
EC3	2.93	2.596	82.2	20,000	80,000
EC4	2.91	2.598	80.3	19,000	79,000
EC5	2.88	2.602	81.3	19,000	80,000
EC 6	2.76	2.618	83.2	18,000	80,000

Table I	Properties	of	Studied	EC
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^a Determined by NIR analysis.

^b Determined by SEC with PS calibration.

(99.5% v/v) (AB Svensk Sprit, Sweden) was used as a solvent. Deionized water, purified by reverse osmosis (MAXIMA Ultra Pure Water, Elga, UK) and tritium-labeled water (Amersham, UK), was used in the permeation study. All the chemicals were used without further purification.

Determination of Hydroxyl Group Content

Near-infrared (NIR) reflectance spectroscopy was used to determine the hydroxyl group content in the EC samples. NIR spectra were obtained on an NIRSystems 6500 instrument (NIRSystems, Washington, DC), equipped with a rotating drawer interface for diffuse reflectance spectroscopy. Spectra were collected, as log 1/R in the 1100-2500 nm wavelength, on untreated samples, where R is equal to the reflectance of the samples. Spectra were analyzed using a regression program. The relative standard error of prediction was 2%.

Determination of the Molar Mass

Size exclusion chromatography (SEC) was used to determine the molar masses. The samples were dissolved in tetrahydrofuran at room temperature, 1 mg mL⁻¹. The solutions were filtered through a polytetrafluoroethylene membrane, and 300 μ L were injected into a Waters 150 CV SEC instrument equipped with an RI (refractive index) detector. The instrument was calibrated using narrow molar mass distribution polystyrene standards.

Interaction Constants

Specific viscosity was determined by measuring the kinematic viscosity of the pure ethanol and ethanol solutions of the polymer between 2 and 6 mg mL⁻¹. All the measurements were executed at 25°C with a KPG Ubbelohde Viscometer (Schott-Geräte GmbH, Hofheim, Germany) with an internal capillary of 0.63 mm. To obtain good accuracy, a mean value of five measurements was used. The intrinsic viscosity, $[\eta]$, and Huggins constant, k', were then calculated using linear regression analysis according to eq. $(1)^7$:

$$\eta_{\rm sp}/c = [\eta] + k' [\eta]^2 c$$

where η_{sp} is specific viscosity and *c* is concentration of the solution.

Preparation of EC Films

The EC powder materials, listed in Table I, were dissolved in ethanol, 10% (w/w), and stirred for 40 h. The films were obtained by spraying polymer solution onto a rotating poly(methyl methacrylate) cylinder at 20°C and 15% relative humidity. The spraying apparatus was similar to equipment described previously by Allen and colleagues.⁸ After spraying, the films were peeled off the cylinder and kept in a desiccator before being used in the experiments.

Mechanical Properties

To evaluate mechanical properties, tensile tests were performed on a Hounsfield H2000 universal testing instrument with a 200 N load cell. The EC film specimens were mounted between the two grips. The length of the samples was 40 mm, the width 10 mm, and the typical thickness (as measured with a micrometer) was 25 μ m. The extension rate was 4 mm min⁻¹, and all experiments were conducted at 22°C and 45% relative humidity. Six or more measurements were made on two

Bed weight	100 g
Coating solution	25 g EC
	475 g ethanol (99.5%)
Spraying rate	$19 \mathrm{~g~min^{-1}}$
Atomizing air pressure	2.5 bar
Fluidizing air flow rate	$35 { m m}^3 { m h}^{-1}$
Inlet air temperature	$70^{\circ}C$
Outlet air temperature	40°C

Table II	Coating	Conditions	Controlled	During
Film Coa	ating of th	ne Pellets		

separate occasions. The stress-strain curves were recorded, and the modulus of elasticity was calculated from the initial, linear part of the curve.

Permeability

Water permeability of the EC membranes was measured using tritium-labeled water. The apparatus and method have been previously described by Lindstedt and colleagues.⁹ In concise terms, the apparatus is a cell with two chambers, separated by the film segment of interest. A small amount of tritiated water was added to the donor cell and, at specified time intervals, a small volume of water was taken from the receiver compartment and analyzed in a scintillator counter (1414 LSC, Win Spectral, Wallac). The amount of water removed from the receiver was replaced by new, fresh water to avoid any pressure gradient across the membrane.

Karl Fisher titration was used to analyze the total amount of water in the dry films and in films soaked in water.

Glass Transition Temperature (T_g)

 T_g 's were determined using DSC differential scanning calorimetry; (DSC, Mettler-Toledo, TA8000). A small piece of the EC film, ~ 4 mg, was put in an aluminium cup and heated from 75°C to 200°C at a rate of 10°C min⁻¹. After cooling at 10°C min⁻¹, the sample was heated once again, and T_g was determined from the second run. Three samples from each film were tested to ensure reproducibility.

Preparation of Pellets

Film coating on metoprolol succinate pellets (size fraction 0.40-0.63 mm) was conducted on laboratory-scale, fluid-bed Wurster apparatus (Astra Hässle workshop). Three EC samples (EC1, EC4,

and EC6) were dissolved in ethanol and stirred for 40 h. The coating conditions are presented in Table II. The coated pellets were then kept in a dry area at room temperature before being characterized.

Characterization of Pellets

An Aerosizer-LD v7.04 (Amherst Process Instrument, Amherst, MA). was used to determine the size and distribution of the particles. The thickness of the film was measured in an Axioplan microscope (Zeiss, Jena, Germany), and the Vickers hardness of the coating layer was defined on a Shimadzu microhardness tester HMV-2000 (Shimadzu Co., Kyoto, Japan). The release of metoprolol was measured in USP¹⁰ dissolution apparatus no. 2 (rotating paddle, at a speed of 100 rpm) interfaced with a diode-array spectrophotometer operating at 274 nm (8452 A, Hewlett-Packard, Palo Alto, CA). The test medium was 500 mL of distilled water at 37°C. Using the same media, swelling of the particles was estimated using a method described previously by Hjärtstam and Hjertberg.¹¹

RESULTS AND DISCUSSION

In a good solvent, the attractive forces between polymer segments and solvent molecules are strong. The polymer molecules then assume a less



Figure 1 Interaction constant of EC in ethanol, with an increasing hydroxyl group content in the polymer chain.



Figure 2 Effect of increasing the hydroxyl group content in EC films on the modulus of elasticity in the dry (\bigcirc) and hydrated state (\bigcirc) .

densely packed conformation, and a low value for the Huggins constant, k', would thus be expected.^{12,13} Figure 1 reveals the Huggins constant of an EC/ethanol solution as a function of the hydroxyl group content. The hydrogen-bonding capacity of ethanol is very good, and it appears that the value of k' is increased as the hydroxyl group content in the EC chain increases. In fact, the change in k' is substantial, considering the small change in the number of hydroxyl groups, an increase from 0.38 to 0.43 hydroxyl groups per anhydroglucose unit is coupled with an increase in Huggins constant from 0.38 to 0.51.

There has been some difference of opinion as to whether the good solvents correspond to high or low Huggins constant values.¹⁴ However, most experimental evidence supports the expectation that, in theta solvents, k' = 0.5-0.7 and in good solvents k' < 0.5-0.7.¹⁵ The increase in k' thus indicates decreasing solvent power as the hydroxyl group content in the EC chains increases. One explanation could be that a higher hydroxyl group content increases the amount of intramolecular hydrogen bonding, leading to decreasing flexibility in the polymer chain.

In Figure 2, the effect of unsubstituted hydroxyl groups on the modulus of elasticity is shown. As can be seen, the E-modulus decreases significantly with a small increase in the hydroxyl group content. One plausible explanation could be the decrease in solvent quality, as shown in Figure 1, as a result of the increase in the Huggins constant. The observed decrease in mechanical properties is similar to the findings of Rowe^{16,17} that, the poorer the solvent, the lower the modulus of elasticity. This means that a solvent producing a low Huggins constant value is favorable when it comes to the mechanical properties. The main reason for this is that the opportunity for the polymer molecules to move freely is higher in a good solvent, particularly at the later stages of the film-forming process, and this results in less internal stress in the final film.

The open symbols in Figure 2 represent the EC films obtained after drying in a dessicator, whereas the closed symbols are data obtained after hydrating some of the EC films in water at 37°C. As expected, water acts as a plasticizer for EC, by interacting with the intermolecular forces between the chains and thus reducing the modulus of elasticity. The results of the Karl Fisher titration, presented in Table III, show that the EC film with the highest hydroxyl group content also has the highest level of total water incorporated in the film in both the hydrated and the dry states. The difference in the amount of water between the films is very small, but the possibility that some of the reduction in the E-modulus is a result of water cannot be disregarded.

Even though data on the modulus of elasticity are in good agreement with data presented elsewhere,^{18,19} it should be noted that the mechanical properties are highly dependent on the rate of testing, the temperature, humidity, size, and shape of specimen. Data presented in Figure 2 are, however, comparable within the group, because they were obtained from experiments using the same conditions.

The molecular structure of the starting material, cellulose, contains three replaceable hydroxyl groups per anhydroglucose repeat unit. The hydroxyl groups produce both inter- and intramolecular interactions, thereby leading to a highly crystalline material with restricted mobil-

Table III Amount of Total Water

Sample	"Dry" Film ^a (%)	Soaked Film (%)
EC1 EC4 EC6	7.1 ± 0.7 5.9 ± 0.4 5.6 ± 0.3	$9.8 \pm 2.4 \ 7.1 \pm 1.8 \ 6.7 \pm 0.7$

^a Films kept in desiccator for 4 wk.



1.10 1.05 Water permeability (10⁻¹² m²/s) 1.00 0.95 0.90 0.85 0.80 0.75 0.70 2.7 2.8 2.9 3.0 3.1 3.2 Hydroxyl groups (% w/w)

Figure 3 Variation in T_g of EC with increasing hydroxyl group content.

ity.²⁰ The restricted mobility results in an increase in T_g . The substitution of ethoxyl groups should lead to a decrease in interaction. The increased bulkiness of the side groups connected *via* ether oxygen increases the flexibility of the chain and the structural irregularities that are introduced cancel out the crystallinity. As a result, T_g is shifted to lower temperatures. The T_g 's for the EC samples studied herein are given in Figure 3. As can be seen, the transition temperatures increases somewhat as the hydroxyl group content increases, probably as a result of increased interaction.

If the molecular mechanisms responsible for the results in T_g were responsible for the elasticity of modulus of the film in the same way, an increase in E-modulus would be expected, because the T_g increases. However, as revealed in Figures 2 and 3, the opposite is true. The reason could be the extensive formation of intermolecular hydrogen bonds and entanglements in the films made of EC with the highest solubility in ethanol and, as previously described as the film with the highest hydroxyl group content has the highest water content, it will help to reduce the modulus of elasticity.

When the hydroxyl group content increases, it could be assumed that the EC film would become more hydrophilic. This change in hydrophilicity is expected to lead to an increase in water permeability.²¹ In Figure 4, the results relating to water

Figure 4 Water permeability of EC films with increasing hydroxyl group content.

permeability across the EC membrane are given. As revealed, the water permeability does in fact increase somewhat, because the total hydroxyl group content in the EC chain increases.

Although a great deal of information can be derived from an evaluation of free films, it is the functional performance of these films after deposition on substrates that is of practical significance. To evaluate the effect of water permeability on drug release, a study was conducted of metoprolol succinate pellets coated with EC. Three EC samples were chosen: EC1, EC4, and EC6. Characteristics of the pellets after coating are presented in Table IV. The thickness of the coated membrane and the particle size are almost the same for all three samples. The mechanical properties of the coat were evaluated using a microhardness tester and by way of comparison the tensile strength measured on free films is included in Table V. It is interesting to note that there appears to be very good agreement between

Table IV Pellet Characteristics

Sample	$\begin{array}{c} Release \\ Rate \\ (mg \ min^{-1}) \end{array}$	Thickness (µm)	Particle Size (µm)	Vickers Hardness
EC1 EC4 EC6	$0.070 \\ 0.058 \\ 0.053$	19 19 19	497.7 ± 6.4 488.9 ± 3.0 495.0 ± 6.6	$21.1 \pm 1.9 \\ 26.0 \pm 1.9 \\ 27.2 \pm 1.5$

Sample	Vickers Hardness	Tensile Strength (N mm ⁻²)
EC1 EC4	21.1 ± 1.9 26.0 ± 1.9	$21.5 \pm 1.5 \\ 25.5 \pm 2.4$
EC6	27.2 ± 1.5	30.9 ± 1.8

Table V	Vickers	Hardness	Compared	with
Tensile S	Strength			

the Vickers hardness of coated film and the tensile strength of the corresponding free film.

In Figure 5, swelling of the pellets is shown. Despite the differences in hydrophilicity and mechanical properties, there appears to be no significant difference in swelling behavior between the three materials chosen. A more rapid development in the swelling would have been expected from the coating with a higher hydroxyl group content, because the water permeability is higher and the modulus of elasticity is lower. If there is a small deviation in swelling between the pellets, it will eventually be incorporated with the pure error of the experiment. Figure 6 shows the drug release from the pellets. The release rate increases in the order EC1 > EC4 > EC6 (i.e., as the hydroxyl group content increases). Herein, we have one explanation of the swelling results. The water imbibition into the nonporous membranes produces an increase in hydrostatic pressure af-



Figure 5 Volume increase in the pellets coated with EC1 (\bullet), EC4 (\blacksquare), and EC6 (\diamond).



Figure 6 Release of metoprolol succinate from pellets coated with EC1 (\bigcirc), EC4 (\blacksquare), and EC6 (\blacklozenge).

fecting the membrane and thereby a volume increase in the pellets.^{22,23} As soon as the release begins, the swelling expansion decreases.¹¹ The EC1 pellet has the highest release rate and the hydrostatic pressure in the core is thus reduced. According to Figure 5, the swelling in the three pellets appears to be equal. We can conclude, however, that the swelling in EC1 would most probably have been greater if the drug release were similar to the release rate in pellets EC4 and EC6.

Finally, there is a good agreement between the release rate through the coating and the data from the study of water permeability on free films. Whether the transport of the drug is controlled by diffusion and/or convection is impossible to say from this experiment. Further study of the release rate from pellets in media with different osmotic pressure is needed.

CONCLUSIONS

In this article, we investigated how the substitution of hydroxyl groups in EC affects mechanical properties and water permeability. These properties are very important when it comes to practical use in pharmaceutical applications. An increase from 0.38 to 0.43 hydroxyl groups per anhydroglucose unit resulted in a film with a significantly lower modulus of elasticity and higher water permeability. From dissolution profiles of coated pellets, it is apparent that the release rate of metoprolol is in agreement with the water permeability of free films. Furthermore, when the Vickers hardness of the membrane coat is examined, it can be concluded that an increase in hydroxyl group content causes an increase in hardness.

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