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ETHYLCELLULOSE -- A POLYMER REVIEW

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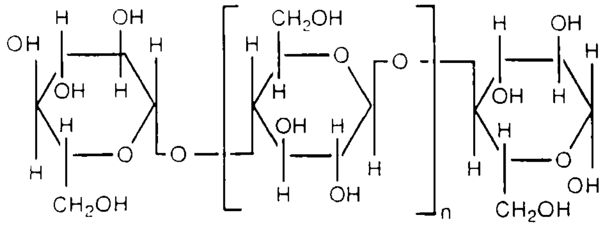
TABLE OF CONTENTS

1. INTRODUCTION

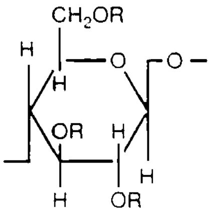
Cellulose ether polymers have a wide diversity of applications ranging from organic soluble thermoplastic products to water-soluble food additives. The importance of cellulose ethers has increased in recent years because of economic factors that have adversely affected the supply and pricing of natural gums and low viscosity products such as starch derivatives. The rising prices of petroleum-based polymers and chemicals engender interest in cellulose as a renewable resource. This is reflected by the growth of cellulose ether polymers which reached an estimated United States volume of about 60,000 metric tons in 1976 (U.S. production capacity is estimated at nearly 79,000 metric tons) (1).

Although many polymers are used in the pharmaceutical industry, the most widely used are the cellulose derivatives: methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, ethylcellulose, cellulose acetate phthalate and hydroxypropyl methylcellulose phthalate. All are derived from, and hence possess, the polymeric backbone of cellulose, which contains a basic repeating structure of ß-anhydroglucose units; each unit having three replaceable hydroxyl groups (Figure 1).

The number of substituent groups of these hydroxyls can be designated either by a weight percentage or by the number of points where the groups are attached - a concept known as degree of substitution (DS). If all the three available positions on each anhydroglucose unit are substituted, the DS is designated as 3. In certain circumstances, the added substituent may also contain a hydroxyl group. A term ‘molar substitution’ (MS) is used to describe the total number of moles of a group that become attached to the cellulose backbone or to the side chain. A derivative may, for example, have an MS of 4 but a DS of 1; however, in no case can its DS exceed 3. In this case, the length of the pendant chain will be the ratio of MS to the DS (2).



Cellulose n - 1000 approx



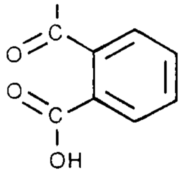
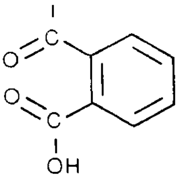
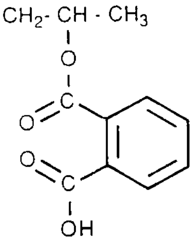
Polymer	Substituent Groups |R|		
Methylcellulose	- H	$-CH_3$	
Hydroxypropyl methylcellulose	- H	$-CH_3$	$-CH_2-\underset{OH}{\underset{\vert}{CH}}-CH_3$
Hydroxypropylcellulose	- H	$-CH_2-\underset{OH}{\underset{\vert}{CH}}-CH_3$	
Ethylcellulose	- H	$-CH_2CH_3$	
Cellulose Acetete Phthalate	- H	$-\overset{O}{\overset{\Vert}{C}}-CH_3$	
Hydroxypropylmethylcellulose Phthalate	- H	$-CH_3$	$-CH_2-\underset{OH}{\underset{\vert}{CH}}-CH_3$
			

Fig.1 The molecular structure of cellulose and the cellulose derivatives.

2. MANUFACTURE

Either chemical grade cotton linters or wood pulp can be used to prepare ethylcellulose. Commercially, however, sodium hydroxide concentrations of 50% w/w or greater are used to prepare the alkali cellulose. Staged additions of solid sodium hydroxide during the reactions can be used to reduce side reactions. The formation of alkali cellulose serves two purposes: first, it forms alkoxide ions by reaction with hydroxyl groups, and secondly, the alkali expands the cellulose lattice, thus, increasing accessibility to the cellulose hydroxyl groups.

$C_6H_{10}O_5.NaOH + C_2H_5Cl$ ----------> $C_6H_9O_5.C_2H_5 + NaCl + H_2O$

Alkali cellulose Ethyl chloride Ethylcellulose

Ethyl chloride is added to the alkali cellulose in nickel-clad reactors at 90-150°C and 828 to 965 kPa (120 to 140 psi) for 6-12 hours. Diluents such as benzene or toluene can be used. The resulting sodium chloride is rinsed away with water. The product is spin-dried to a water content of 55-60% and subsequently homogenized and compacted in a screw extender (1).

There are two main suppliers of ethylcellulose in the U.S.. Ethylcellulose resins are white to light-tan granular powders with bulk density of approximately 0.4 g/cc (3). The differences in physical properties of the ethylcellulose products result largely from variation in the degree of etherification. The ethoxyl substitution values of commercial products range from a DS of 2.2 to 2.6 ethoxyl groups per anhydrous glucose units. This corresponds to an ethoxyl content of 44.5 to >49% (1).

Ethylcellulose products are also produced and marketed in a number of different viscosity grades. Viscosity increases as the length of the polymer molecule increases (4).

3. GENERAL PROPERTIES

i. Solubility

Ethylcellulose is soluble in a wide variety of solvents, thus making it easier to use when solution application is desirable. Among the useful solvents are the esters, aromatic hydrocarbons, alcohols, ketones, and chlorinated solvents (1-6). Ethylcellulose is most soluble in solvents that have nearly the same cohesive energy density or solubility parameter as the material itself. The solubility parameter ranges vary with degree of substitution (DS) as shown in Table I (7).

Solutions of ethylcellulose in aromatic hydrocarbons are highly viscous; consequently, solutions of low concentrations are practical when these solvents are used individually. On the other hand, solvents like ethanol and methanol yield solutions having lower viscosity; however, film properties are too poor for practical purposes. The mixtures of aromatic hydrocarbons with ethanol or methanol yield solutions having a lower viscosity than is obtainable with either solvent type when used alone. Furthermore, this mixed solvent system also deposit films having good strength. This is shown by the data from the 80-20 toluene-ethanol solvent included in Table II for comparison.

The amount of ethanol required to obtain a solution with minimum viscosity for a given concentration of ethylcellulose, is proportional to the number of hydroxyl groups that remain unsubstituted. For example, ethylcellulose with a DS of 2.17-2.35 (44.0 - 46.5% w/w ethoxyl content) dissolves in a 60:40% w/w toluene-ethanol mixture, whereas having a DS of 2.35-2.62 (46.5 - 51.0% w/w ethoxyl content) is most soluble in an 80:20% w/w toluene-ethanol mixture.

The lower molecular weight aliphatic esters and ketones yield ethyl cellulose solutions of relatively low viscosities and form films of good strength and extensibility. However, it is preferable, in most cases, to use these solvents with a small proportion of one of the lower molecular weight alcohols because of the lower viscosities obtainable from such mixtures. (Table III) (4).

TABLE I

Solubility Parameter Ranges for Ethylcellulose

		Solubility parameter range MPa$^{1/2}$		
DS	Ethoxyl content %w/w	Poorly	Moderately hydrogen-bonded solvents	Strongly
2.28-2.38	45.5-46.8	0	17.4-22.1	19.4-23.3
2.42-2.53	47.5-49.0	16.6-22.7	15.1-22.1	19.4-29.7
>2.53	>50.0	17.4-19.4	16.0-20.1	19.4-23.3

* Reprinted from reference 7

TABLE II

Viscosity and Film Properties of Ethylcellulose

(15 g Resin in 100 cc Solvent)

	Solution Properties @ 25°C		Film Properties	
Solvent	Viscosity cps	Specific Gravity	Yield Pt. Kg/cm^2	Elongation %
n-Butanol	1900	0.848	425	6
Butyl acetate 90%	590	0.901	430	7
Ethanol, Formula 30	560	0.850	—[1]	—[1]
Ethyl Acetate, 99%	360	0.924	440	9
Ethylene dichloride	470	1.238	420	5
Methyl ethyl ketone	320	0.845	428[2]	7[2]
Toluene	1930	0.890	440	12
80-20 Toluene-ethanol	260	0.887	440	7

[1] Too brittle to test properly

[2] Films show "orange peel"

* Reprinted from reference 4

Table III

Solvent Compositions for Minimum Solution Viscosity for Ethylcellulose

Solvent Mixture	Solvent Composition
Aromatic/ethanol	20% ethanol
Aromatic/ester	No change by varying ester
Esters/ethanol	20% ethanol
Ketones/ethanol	20% ethanol
Aromatic naphthas/ethanol	30% ethanol
Aliphatic naphthas/ethanol	30 % ethanol

* Reprinted from reference 4

ii. Viscosity and Molecular Weight

The suitability of a polymer in film coating is determined by its apparent viscosity (η_{app}), which represents viscosity of a specified concentration of the polymer dissolved in a specified solvent at a specified temperature (Table IV) (8). Since viscosity control is achieved by controlling the chain length, i.e. the degree of polymerization (DP) or the number of anhydroglucose units during the production process, the apparent viscosity (η_{app}) can be regarded as an indirect measure of the molecular weight of the polymer. The relationship between the molecular weight and the apparent viscosity (measured in mPas) can be expressed in the form:

$$\text{Molecular weight} = k(\eta_{app})^n \text{..........(Equation 1)}$$

where k and n are constants for each polymer determined by regression analysis and which depend on the method used to measure the molecular weight of the polymer (e.g. osmotic pressure, light scattering or gel permeation chromatography). Representative values for k and n for the polymers

TABLE IV

Apparent Viscosity Specifications for Some Polymers

Polymer	Solvent	Concent. (% w/w)	Temp. (°C)	Specifications
Methylcellulose	Water	2	20	± 20% of nominal
HPMC	Water	2	20	± 20% of nominal
HPC	Water	10	25	> 145 mPas
Ethylcellulose		5		
(<46.5% w/w ethoxyl)	Toluene:ethanol (60:40)		25	3.0-5.5[1]
(>46.5% w/w ethoxyl)	Toluene:ethanol (80:20)		25	6.0-8.0[2] ± 10% of nominal

[1] (for nominal 4)

[2] (for nominal 7)

* Reprinted from reference 8

methylcellulose, hydroxypropyl methylcellulose and ethylcellulose are 32.49 x10^3 and 0.48; 23.56 x 10^3 and 0.45; and 66.96 x10^3 and 0.56, respectively (9-11).

Eq. 1, though empirical, is useful. However, since the relatively high concentrations of polymers used for apparent viscosity determinations invariably means that there will be an appreciable amount of molecular interaction and the fact that commercial polymers do have a wide molecular weight distribution,it is customary to make viscosity measurements in much more dilute solutions using fractionated samples of the polymer in order to provide more basic information on the molecular weight-viscosity relationship. The data thus obtained can be fitted to the Mark-Houwink equation:

$$[\eta] = k\ M^{\alpha}..........\text{(Equation 2)}$$

TABLE V

Constants for Mark-Houwink Equation for Some Polymers Used in Film Coating

Polymer	Solvent	Temperature (^0C)	K ($x\ 10^{-5}dlg^{-1}$)	α
Methylcellulose	Water	25	316.0	0.55
Hydroxypropylcellulose	Ethanol	25	2.6	0.92
Ethylcellulose	Chloroform	25	11.8	0.89
	Benzene	25	29.2	0.81

* Reprinted from reference 8

where $[\eta]$ is the intrinsic viscosity of the polymer, M is its molecular weight, and k and α are the constants that depend on the solvent and solution temperature. In this equation, α is indicative of the degree of polymer-solvent interaction and hence the general form of the polymer molecule in solution. If the polymer molecule in solution is coiled tightly into a spheroid, α should have the value of zero; but if it is extended, as in the case of a good solvent, the value is unity. Representative values of K and α for some of the solvents used are given in Table V. It is interesting to note that recent work (11) on ethylcellulose has shown that molecular weights calculated for commercial samples of ethylcellulose, using the Mark-Houwink constants, were comparable to those obtained by gel permeation chromatography.

iii. Effect of Molecular Weight on Mechanical Properties of Films

The dependence of the mechanical properties of polymers on their molecular weight is qualitatively the same for all polymers. At low molecular weight increases, their strength also increases until some critical molecular weight when there is no further increase. Theoretically, this inflection in the curve should occur at DP of 200-250 corresponding to a molecular weight of 4-5x10^4 for the cellulose derivatives. However, in practice it has been found that for the commercial film-coating polymers, the inflection occurs at a molecular weight of 7-8x10^4. It is reported (10,11) that this discrepancy is due to the presence of very low molecular weight components ($<5x10^3$) within the molecular weight distribution, which are known to have a deleterious effect on the mechanical properties of polymers disproportionate to their concentration on a weight basis.

iv. Softening (Glass Transition) Temperature

This is the temperature at which a film strip laid on a heated metal bar begins to soften. It is closely related to a more fundamental property of glass-transition temperature and is of importance to a formulator, since it gives an indication of the tackiness likely to be encountered with film coatings either during high temperature drying or during the heat sealing process used in strips or blister packing. The high thermal softening points or glass-transition temperatures of hydroxypropylcellulose, hydroxypropyl methylcellulose and ethylcellulose (120, 180 and 140°C, respectively) make them ideal polymers. With ethylcellulose, the softening temperature is related to the degree of substitution, a minimum occurring at a DS of 2.55 (48.5% ethoxy content) (4).

v. Stability

Ethylcellulose is the most stable of the cellulose derivatives. It is resistant to alkalis, both dilute and concentrated, but is sensitive to acids. It takes up very little water from moist air or during immersion, and this evaporates readily leaving ethylcellulose unchanged.

Light, visible or ultraviolet, has no discoloring action on ethylcellulose. Application of heat up to its softening point has little effect on ethylcellulose.

Ethylcellulose formulations, if not stabilized are subject to oxidative degradation in the presence of sunlight or ultraviolet light and at elevated temperatures. Therefore, heat and light stabilizers are often added, particularly in unpigmented formulations. Octyl phenol and butylated hydroxy phenol have performed effectively as antioxidants, and Uvinul 400 (2,4 Dihydroxy-benzophenone, GAF Corp.) has been used effectively as an ultraviolet light absorber. Generally. a combination of 1 to 2% antioxidant plus 0.5 to 1.0% of ultraviolet absorber (based on lacquer solids) gives adequate protection against both heat and light degradation. Pigmented formulations seldom require light stabilization (4).

Acid acceptors should be added to ethylcellulose formulations containing components such as chlorinated resins and plasticizers, which form acid degradation products. Epoxy types are especially useful because of their excellent capacity to absorb free acids (5).

vi. Plasticizers

Ethylcellulose alone yields very tough films of excellent tensile strength, flexibility, and elongation characteristics; yet such films lack suppleness. Also, ethylcellulose alone softens and flows at too high a temperature to be practical in molding operations or in other applications requiring good thermo-plasticity. Therefore, plasticizers or softening agents are added to ethylcellulose to obtain the proper degree of suppleness, to lower the softening point, and to improve thermoplasticity.

A basic requirement of any plasticizer is compatibility with the polymer with which it is formulated. Compatibility is a property related to a specific polymer/plasticizer system and is a manifestation of the solubility of the polymer in the plasticizer. Solubility measurements thus provide a measure of plasticizer compatibility. An indication of solubility, and hence, compatibility in a plasticizer/polymer system can be obtained by comparing the solubility parameters of each compound. It can be seen on comparing the solubility parameters of a variety of plasticizers (Table VI) (7) with those of ethylcellulose (Table I) that compatibility will be at a maximum with the phthalic acid esters and dibutyl sebacate, but with glycerol and propylene glycol phase separation will occur. Furthermore, it can be seen from Table VII that the most effective plasticizer is defined as one which gives the greatest decrease in glass-transition temperature (8).

In addition, the solubility parameters of many of the polymers and the plasticizers are not available and this approach cannot quantify the degree of interaction and compatibility. Both these limitations can be overcome by using intrinsic viscosity measurements. This relies on the fact that, when there is good interaction between the plasticizer and the polymer, the polymer chains will extend at random, and hence the intrinsic viscosity of the polymer in the plasticizer will be higher. Data for ethylcellulose dissolved in the phthalate esters, and hydroxypropyl methylcellulose (HPMC) dissolved in the polyols are given in Table VIII (12). It can be seen from the data that, of the phthalate esters, diethyl phthalate is the most compatible with ethylcellulose, while for HPMC, propylene glycol is the most compatible.

Among the plasticizers having the greatest softening effect are dibutyl phthalate, castor oil, butyl phthalyl butyl glycolate, and butyl stearate. In most formulations of ethylcellulose resins, 5-30% plasticizer (based on the total solids) is sufficient to produce a satisfactory film flexibility.

The choice of plasticizer generally depends on other components of the formulation and the temperature range or applications rather than on the particular ethylcellulose product. For use in compositions that are resistant to low

TABLE VI

Solubility Parameters for Some Plasticizers

Plasticizer	Solubility parameter ($MPa^{1/2}$)	Solvent group
Dibutyl sebacate	18.8	M
Dibutyl phthalate	19.0	M
Diethyl phthalate	20.5	M
Dimethyl phthalate	21.9	M
Propylene glycol	25.8	S
Glycerol	33.8	S

M, S moderately and strongly hydrogen-bonded solvents respectively

* Reprinted from reference 7

temperatures,, long chain ester-type plasticizers are recommended. Examples of such esters are dibutyl sebacate, butyl stearate, glycol esters of coconut oil fatty acids, and butyl ricinoleate.

4. APPLICATIONS IN PHARMACEUTICAL FORMULATIONS

Binder in tablets. Ethylcellulose may be blended dry or by dissolving in a solvent such as alcohol. However, tablets made with ethylcellulose as a binder tend to exhibit poor dissolution and poor drug absorption.

Coating material for stabilization. Ethylcellulose, dissolved in isopropanol, is used to coat ascorbic acid granules to prevent oxidation and also to mask unpleasant taste.

Table VII

Glass-transition measurements for ethylcellulose/phthalate ester and hydroxypropyl methylcellulose/polyol systems (plasticizer concent. 20% w/w)

Plasticizer	Glass-transition temperature (^{0}C)
1. Ethylcellulose/phthalate ester	
No plasticizer	135
Dimethyl phthalate	96
Diethyl phthalate	84
Dibutyl phthalate	105
2. Hydroxypropyl methylcellulose/polyol	
No plasticizer	177
Glycerol	128
Propylene glycol	108
Polyethylene glycol 200	110

* Reprinted from reference 8

Slow drug release from films. Caffeine and salicylic acid, incorporated into ethylcellulose films, have been shown to exhibit diffusion-controlled release (13).

Coating for drug microcapsules and beads. Ethylcellulose has been used to coat particles to form microcapsules and beads. The release of the drug is a function of the coating thickness.

Thickening agent in creams, lotions or gels. Ethylcellulose may be used in these types of formulations, provided an appropriate solvent is used.

Coating material for tablets. Ethylcellulose by itself forms a water-soluble film. However, it is commonly used with hydroxypropyl methylcellulose to alter the

TABLE VIII

Intrinsic viscosity measurements for ethylcellulose/phthalate ester and hydroxypropyl methylcellulose/polyol systems

Plasticizer	Intrinsic viscosity (dlg^{-1})
1. Ethylcellulose/phthalate esters	
Dimethyl phthalate	1.38
Diethyl phthalate	1.43
Dibutyl phthalate	0.95
2. Hydroxypropyl methylcellulose/polyols	
Glycerol	Could not be measured
Propylene glycol	1.73
Polyethylene glycol 200	1.32
Polyethylene glycol 300	1.25
Polyethylene glycol 400	0.71
Polyethylene glycol 600	0.10

* Reprinted from reference 12

solubility of the film. Other water-soluble materials may be used for this as well.

Coating material for controlled release. Ethylcellulose is available as aqueous polymer dispersions (pseudo-latex) for use in controlled release (Aquacoat® and Surelease®) that allows for high solids content (30 and 25% w/w, respectively) with relatively low viscosity. The effectiveness of these dispersions has been demonstrated in the literature (15-17).

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