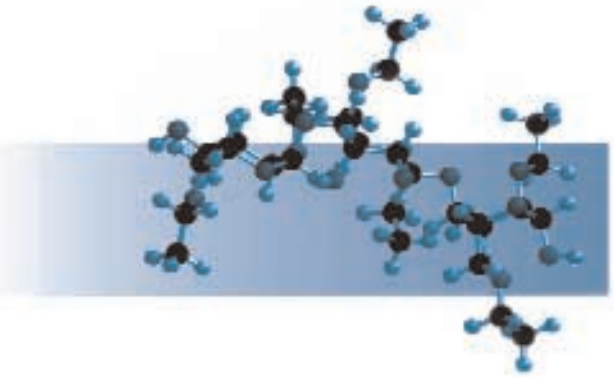
ETHOCEL PREMIUM POLYMERS

FOR PHARMACEUTICAL APPLICATIONS

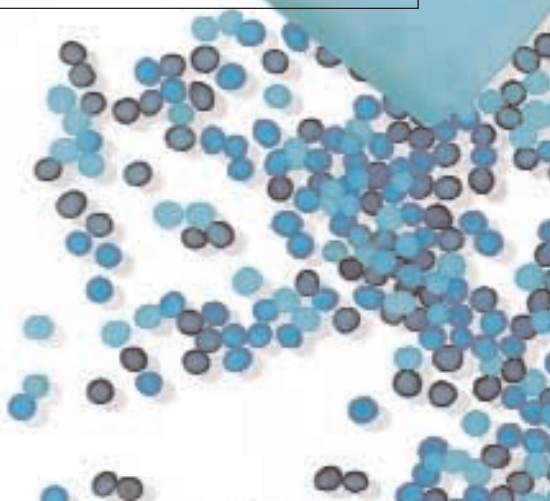
Proven organosoluble polymers for controlled release coatings, microencapsulation, granulation, and flavor masking



Contents

ETHOCEL* Premium ethylcellulose polymers are a family of organosoluble thermoplastics that have been widely used in pharmaceuticals since their commercial introduction in the mid-1930s. ETHOCEL Premium ethylcellulose products are among only a very small number of water-insoluble excipient polymers that are approved and accepted globally for pharmaceutical applications.

ETHOCEL Premium ethylcellulose products are essentially tasteless, odorless, colorless, noncaloric, and very inert physiologically. They form strong, tough films at low concentrations. By themselves, they offer an attractive range of physical properties, and they can be blended with other materials to achieve intermediate characteristics. This unusual combination of qualities makes them useful in a broad array of pharmaceutical formulations.



An Overview of the Use of ETHOCEL Premium Ethylcellulose in Pharmaceutical Applications

Even as a trend toward water-based systems continues, the use of ETHOCEL Premium polymers is still growing. In view of their long history of use, the extensive literature supporting them in many different applications, and the undeniable utility of water-insoluble systems, their continued acceptance is not surprising at all. Here's a closer look at why so many pharmaceutical formulators choose ETHOCEL Premium ethylcellulose over other excipients.

Globally accepted

ETHOCEL Premium polymers are recognized and used globally for many different functional purposes in scores of pharmaceutical products. Perhaps the best evidence of widespread acceptance of ETHOCEL Premium polymers is the bibliography on the uses and functional properties of ETHOCEL in pharmaceutical applications, which includes nearly 500 citations from the international literature. This bibliography is available from Dow by requesting Form Number 192-1152.

Globally approved

ETHOCEL Premium polymers comply with the specifications of 21 CFR 172.868, 21 CFR 73.1, 21 CFR 73.1001, and 21 CFR 573.420. They also comply with a number of other FDA regulations governing use in food packaging, paper, and adhesives. ETHOCEL Premium polymers meet the requirements of the Food Chemicals Code, the International Codex Alimentarius, and the National Formulary (NF). They also meet the requirements of the Japanese Standards of Pharmaceutical Ingredients (JSPI), and will meet the requirements of the European Pharmacopeia (EP) when finalized. See Table 3 for more complete U.S. regulatory information.

Many polymer choices for formulation flexibility

We offer nine different ETHOCEL Premium ethylcellulose polymers for pharmaceutical applications. These include a variety of molecular weights, which translate into a range of viscosities in solution. By selecting among these variables, you can meet an extensive range of product or process requirements. Further, you can blend ETHOCEL polymers to achieve intermediate properties.

The ethanol route to solvent-based systems

ETHOCEL polymers exhibit good solubility in ethanol, as well as many additional aliphatic and cyclic alcohols. If you are already familiar with and equipped to handle other common organic solvents, it's important to note that ETHOCEL products are soluble in a remarkably wide variety of solvent types. Blends of ethanol and other solvents in varying proportions can often be used to optimize the properties of solutions of ETHOCEL polymers.

Useful in many applications

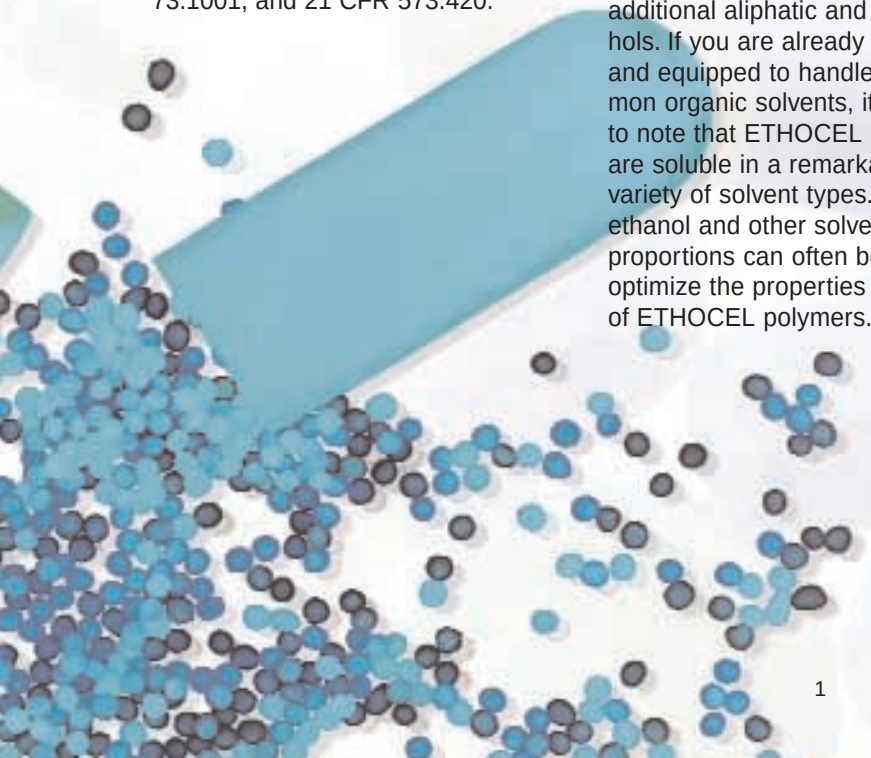
ETHOCEL Premium ethylcellulose polymers are most frequently used in controlled release solid dosage formulations. They are also useful as granulation binders, as film-formers to improve tablet integrity and appearance, and in taste masking. These applications are discussed in greater detail in later sections of this literature.

Very high, consistent product quality

When you formulate with ETHOCEL ethylcellulose, you can rely on very high quality and consistent product properties over time. ETHOCEL polymers are produced according to current Good Manufacturing Practices. Using Statistical Process Control, our production process is managed very precisely, and the results are reflected in finished product quality. For example, we achieve tight control over the degree of ethoxyl substitution and solution viscosity, two of the most critical variables in the final properties of any ethylcellulose product.

Excellent compatibility

ETHOCEL polymers have been used without difficulty in a wide variety of pharmaceutical systems incorporating an even greater number of basic ingredient materials. Their non-ionic, water-insoluble nature keeps a whole spectrum of potential reactions at arm's length. ETHOCEL ethylcellulose polymers exhibit good stability within the pH range of 3 to 11, so they can be used with both acidic and alkaline ingredients. As further evidence of their broad compatibility, ETHOCEL polymers are essentially odorless and tasteless. Even one of the most common uses in pharmaceuticals—providing barrier properties—is broadly suggestive of the non-reactive nature of ETHOCEL polymers.



ETHOCEL Premium ethylcellulosic polymers are essentially tasteless, odorless, noncaloric, and chemically inert. These products have been used in the pharmaceutical industry for almost half a century.

The properties of ETHOCEL polymers make them ideal for use in a variety of pharmaceutical applications. Their water-insolubility makes them a natural choice when working with water-sensitive pharmaceutical active ingredients. ETHOCEL polymers are used in a number of ways, primarily in controlled release systems such as tablet/bead coatings, taste masking, sustained release matrix tablets, granulation, micro-encapsulation, and as a binder in dry and direct compression tablets.

ETHOCEL polymers are among a very small number of organosoluble and water insoluble excipients. Among those choices, ETHOCEL polymers are noted for their versatility as an excellent film former and binder, and often perform multiple tasks in a single drug formulation. And when you specify ETHOCEL ethylcellulosic polymers you get the consistent product properties and performance from lot to lot.

Where hydrophobic films are needed

When you specify an ETHOCEL cellulose ether product, you get that performance from fast-curing films that won't bottleneck production rates. Consider coatings or matrices of ETHOCEL ethylcellulose when you need a water vapor barrier to improve product shelf life or prevent hydrolysis of ingredients. Where taste masking is needed, thin films of ETHOCEL polymers often provide excellent barrier properties.

Controlled release tablet and bead coating

ETHOCEL polymers have a long history in film and bead coating for controlled release applications. ETHOCEL forms a strong film with good adhesion. These polymers can provide a versatile diffusion barrier whose properties can be modified by film thickness, the level of pore-forming additives, or by modifying the solvent(s) used and molecular weight of ETHOCEL.

ETHOCEL polymers can be applied with conventional coating techniques such as pan and fluidized bed coating.

Micro-encapsulation of pharmaceutical actives

ETHOCEL polymers are commonly used to micro-encapsulate pharmaceutical actives for sustained release or taste masking applications. This can be accomplished by coacervation or fluidized bed coating techniques. The coated particles of ETHOCEL provide a tough controlled release film which can be compressed directly into tablets.

Controlled release matrix systems

When you need one or more of the advantageous characteristics of multi-particulate systems, ETHOCEL polymers offer excellent routes to controlling drug release.

As water insoluble excipients, ETHOCEL polymers can effectively control the release of an active by modifying the size and length of the diffusion path. In this role, an ETHOCEL polymer is typically used in combination with a water-soluble active and/or water-soluble excipient such as a METHOCEL* cellulose ether, and/or DOW polyethylene glycol. By varying the type and amount of insoluble/soluble excipient ratio and the particle size, a wide variety of release rate profiles can be achieved. Micro-encapsulated particles of ETHOCEL can also use these techniques.

Solvent and extrusion granulation

ETHOCEL polymers can be used for solvent granulation of water-sensitive materials. Tablets made with ethylcellulose-granulated materials are strong, have low friability, and can provide a wide range of dissolution rates.

Dissolution times may be extended or modified by varying the amount of ETHOCEL ethylcellulose in the granulation or by adding a water-soluble excipient to the granulating fluid containing the ETHOCEL. Because they're thermoplastic materials, ETHOCEL polymers may also be used for extrusion granulation.

Tablet binding for dry and direct compression

ETHOCEL polymers are also used as tablet binders in roller compaction granulation or direct compression tableting. In these applications they produce hard tablets with very low friability. When used in small but effective amounts, ETHOCEL ethylcellulose will not adversely affect tablet disintegration or dissolution rates.

A Guide to the Family of ETHOCEL Polymers

ETHOCEL ethylcellulose is derived from cellulose. Like cellulose, the backbone of the molecule of ETHOCEL is based on repeating anhydroglucose units. The basic structure is shown in Figure 1.

Specific properties of the various ETHOCEL polymers are determined by the number of anhydroglucose units in the polymer chain and the degree of ethoxyl substitution.

ETHOCEL polymers are white to light tan granular powders with a bulk density of approximately 0.4 g/cc. These polymers are packaged in fifty-pound bags.

Six different ETHOCEL Premium ethylcellulose products are available for pharmaceutical applications, as shown in Table 1. ETHOCEL Standard 7, 10, and 100 Premium are also available in a fine particle size designated ETHOCEL Std 7 FP, Std 10 FP, and Std 100 FP Premium. These products were designed specifically for pharmaceutical formulations when the ETHOCEL is used in an unsolubilized form such as in direct compression controlled release tablets, granulation and/or agglomeration. In these applications, the particle size distribution influences the release rate and tablet compressibility.

Figure 1 — Structure of ETHOCEL Ethylcellulose

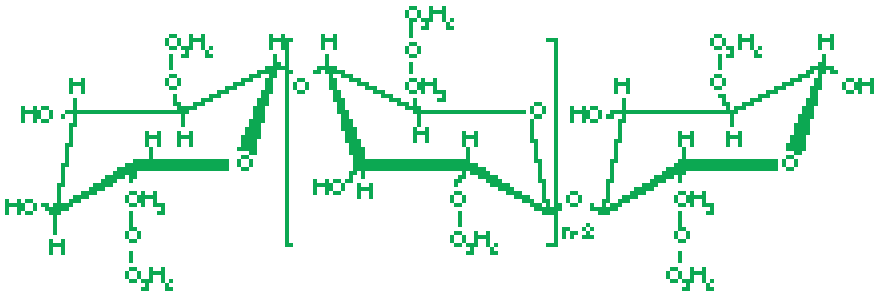


Table 1 — ETHOCEL Premium Polymers for Pharmaceutical Applications

Product Viscosity Designation	Solution Viscosity[1] Range, cP	Ethoxyl Content, %
ETHOCEL Standard 4 Premium	3-5.5	48.0-49.5
ETHOCEL Standard 7 Premium[2]	6-8	48.0-49.5
ETHOCEL Standard 10 Premium[2]	9-11	48.0-49.5
ETHOCEL Standard 20 Premium	18-22	48.0-49.5
ETHOCEL Standard 45 Premium	41-49	48.0-49.5
ETHOCEL Standard 100 Premium[2]	90-110	48.0-49.5

[1]Note: Viscosities are for 5% solutions measured at 25°C in an Ubbelohde viscometer. The solvent is 80% toluene and 20% alcohol.

[2]ETHOCEL Standard 7, 10, and 100 Premium are also offered as a fine particle; designation ETHOCEL Standard 7 FP Premium, ETHOCEL Standard 10 FP Premium, and ETHOCEL Standard 100 FP Premium.

Selecting the right ETHOCEL polymer

Although certainly not all-inclusive, Table 2 provides starting point recommendations for various formulating technologies. Contact your Dow representative for recommendations specific to your own system.

Regulatory status

ETHOCEL Premium ethylcellulose complies with the compendial specifications of the National Formulary (XVIII), (Ethylcellulose) the Food Chemicals Codex (Ethylcellulose). They also meet the requirements of the Japanese Standards of Pharmaceutical Ingredients (JSPI), and will meet the requirements of the European Pharmacopeia (EP) when finalized. ETHOCEL Premium ethylcellulose polymers meet the requirements of the FDA food regulations outlined in Table 3. Letters of compliance for certain uses can be requested of your Dow sales representative.

Effects of viscosity

Polymers of greater molecular weight yield more viscous solutions. The corresponding films formed are generally tougher and possess higher yield strengths than those created from lower molecular weight materials. Film permeability can also be adjusted by varying the nominal viscosity of the polymer used, often in conjunction with adjustment of film thickness and plasticizer level.

Table 2 — Selection of ETHOCEL Polymers for Pharmaceutical Applications

Application	ETHOCEL Polymer
Controlled release coatings	ETHOCEL Standard 7, 10, or 20 Premium ETHOCEL blended with METHOCEL E5 or E15LV Premium cellulose ether
Micro-encapsulation	ETHOCEL Standard 45, or 100 Premium
Tablet coating	ETHOCEL Standard 7, 10, or 20 Premium
Granulation	ETHOCEL Standard 10, 20, or 45 Premium
Binder/direct compression	ETHOCEL Standard 7 FP Premium, 10 FP Premium, or 100 FP Premium

Table 3 — FDA Compliance of ETHOCEL Premium Ethylcellulose Polymers

Food Additive Regulation Number	Application
21 CFR 73.1	Diluents in color additive mixtures for food use exempt from certification
(b) (1) (i), (ii) and (b) (2)	Diluent used in inks for marking certain foods Ethylcellulose as defined in 172.868
21 CFR 73.1001	Diluents in color additive mixtures for drug use exempt from certification
(b)	Externally applied drugs Ethylcellulose as defined in 172.868
21 CFR 172.868	Ethylcellulose — for use as:
(b) (1)	A binder and filler in dry vitamin preparations
(b) (2)	A component of protective coatings for vitamin and mineral tablets
(b) (3)	A fixative in flavoring compounds
21 CFR 573.420	Ethylcellulose
(b)	For use as a binder or filler in dry vitamin preparations or to be incorporated into animal feed

Solution and Film Properties

The following tables and figures provide information on solution and film properties for ETHOCEL polymers. These data should be useful for starting point work with ETHOCEL Premium polymers in both laboratory evaluation and formulation development.

Solubility in organic solvents

ETHOCEL Premium polymers are soluble in a very wide variety of organic solvents, beginning with aliphatic alcohols such as ethanol and isopropanol. They are compatible with most other familiar organic solvent chemistries, including ether alcohols, ketones, aromatic hydrocarbons, and many more. Table 4 provides a partial listing of solvents in which ETHOCEL Premium polymers are soluble; these solvents may be acceptable for use in pharmaceutical applications. References 1-7 in Table 5 cite additional sources of information on the solubility properties of ethylcellulose. Your Dow technical representative also has information on solubility in other solvents.

Solution viscosity-concentration relationships

Figure 2 shows the relationship between solution viscosity and concentration for ETHOCEL Standard Premium polymers in 80/20 toluene/alcohol (the solvent blend specified in the NF).

Using this figure, you can select the polymer viscosity required to obtain a solution of desired viscosity and concentration. You can also use it to determine the solids content at a given solution viscosity, or to estimate the dilution required to obtain a given viscosity.

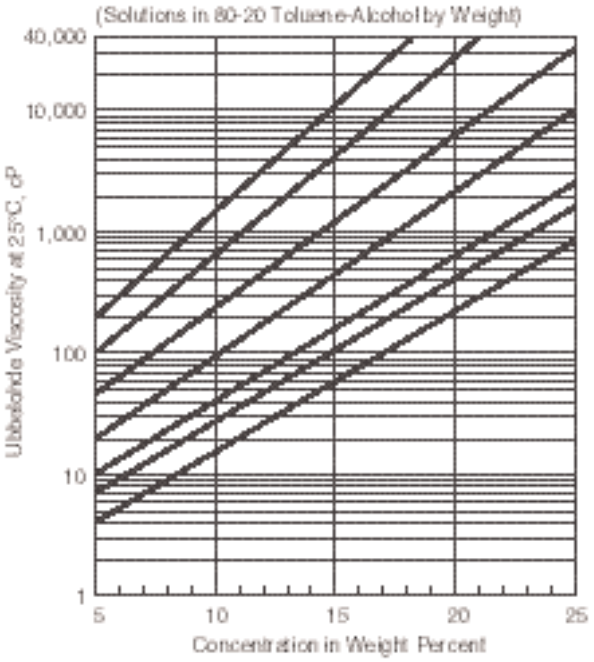
Figure 3 provides viscosity-concentration profiles for a number of solvent blends that may be useful in pharmaceutical applications.

Table 4 — Starting-Point Listing of Solvents for ETHOCEL Premium Polymers in Pharmaceutical Applications

Solvent % Volume / % Volume	Relative Evaporation Rate[1]
20 Methylene chloride / 80 Ethanol	1.81
50 Methylene chloride / 50 Ethanol	2.83
80 Methylene chloride / 20 Ethanol	6.48
Ethanol	.66
70 Acetone / 30 n-Propanol	2.11
65 Acetone / 35 Isopropanol	2.29
50 Acetone / 50 DOWANOL* PM glycol ether	0.69
85 Methyl acetate / 15 Methanol	4.73
80 Methyl acetate / 20 n-Propanol	3.03
65 Methyl acetate / 35 DOWANOL PM glycol ether	0.98
70 Methyl isobutyl ketone / 30 Methanol	1.63
65 Methyl isobutyl ketone / 35 Ethanol	1.72

Caution: Some solvent blends, especially those containing acetone, have very low flash points and should only be used with caution and appropriate safeguards.
[1] n-butyl acetate = 1.00
* Trademark of The Dow Chemical Company

Figure 2 — Viscosity-Concentration Chart for Solutions of ETHOCEL Standard Premium Polymers



Note: On the left-hand vertical axis, origins of viscosity plots indicate nominal viscosities of 5% solutions; these viscosities correspond to the Product Viscosity Designations found in Table 1.

Figure 3 — Viscosity / Concentration Profiles for ETHOCEL Standard 10 Premium Cellulose Ether

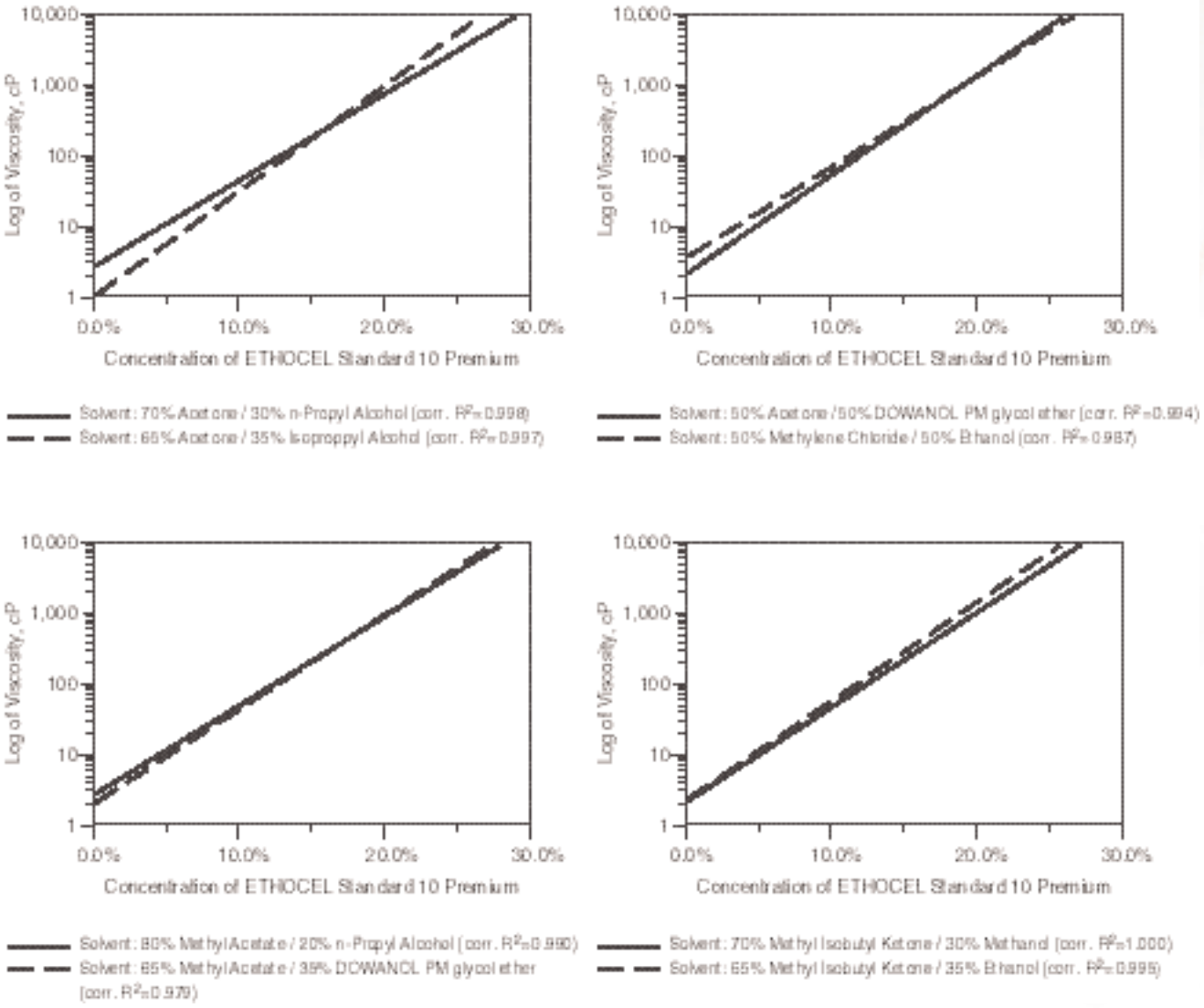


Table 5 — References on Solubility Properties of Ethylcellulose

1. Kent, D.J., and Rowe, R.C., *J. Pharm. Pharmacol.,* 1978, 30, 808-810.
2. Rowe, R.C., *J. Pharm. Pharmacol.,* 1986, 38, 214-5.
3. Sakellariou, P., Rowe, R.C., and White, E.F.T., *Int. J. Pharm.,* 1986, 31, 175-7.
4. Arwidsson, H., and Nicklasson, M., *Int. J. Pharm.,* 1989, 56, 187-193.
5. Robinson, D.H., *Drug Dev. Ind. Pharm.,* 1989, 15, 2597-2620.
6. Arwidsson, H., and Nicklasson, M., *Int. J. Pharm.,* 1990, 58, 73-7.
7. Archer, W.L., *Ind. Eng. Chem. Res.,* 1991, 30, 2292-2298.

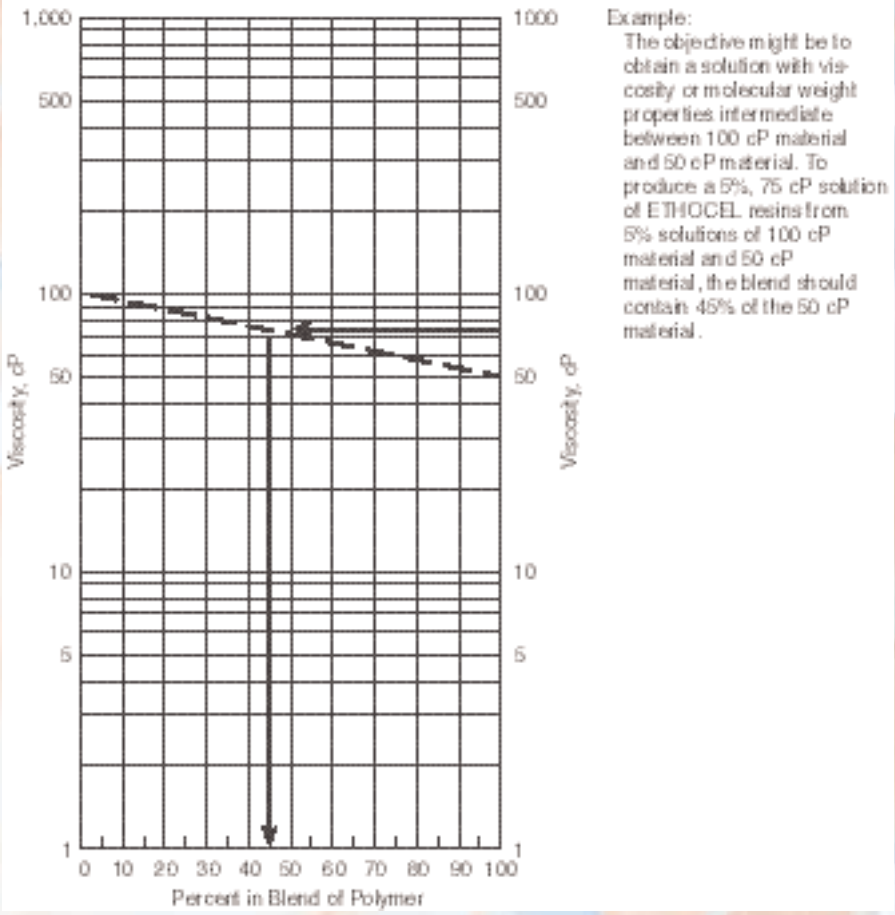
Blending for intermediate viscosities/molecular weights

If you need a solution of intermediate viscosity, or an intermediate molecular weight, you can blend different ETHOCEL polymers. Refer to Figure 4.

To achieve an intermediate viscosity, find on the vertical axes the viscosities for the two solutions at the same conditions. (Any other viscosity units may be substituted for centipoise, as long as both solutions are measured in the same units.)

Connect the two viscosities with a line, as indicated by the dashed line on the chart. On the right hand vertical axis, find the desired final solution viscosity and draw a horizontal line over to the dashed line (solid horizontal line on chart). At the point of intersection, drop down to the horizontal axis on the bottom of the chart. There, read the percentage by weight of material from the right hand vertical axis needed in the blend.

Figure 4—Blending Chart for Intermediate Viscosities/ Molecular Weights of ETHOCEL Polymers



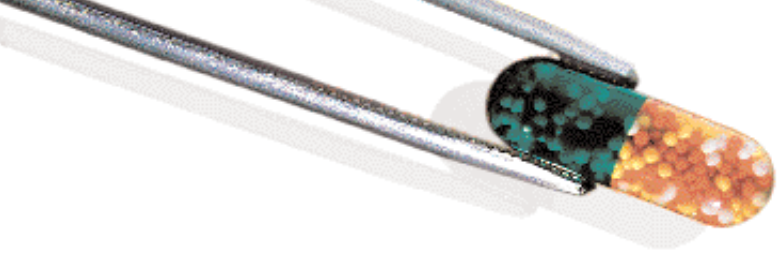
Solvent evaporation rates

Evaporation rates of solvents from solution of ETHOCEL Premium polymers depend on many factors, including the type of solvent(s) and the specific ETHOCEL polymer in solution. Comparative predicted evaporation rate data are available for both pure solvents and blends.

Viscosities in alcohol-aromatic hydrocarbon mixtures

Blends of lower molecular weight aliphatic alcohols and aromatic hydrocarbons may be used to yield low-viscosity solutions of ETHOCEL Premium polymers. Figure 5 compares the viscosity-lowering performance of various alcohols for ETHOCEL Standard 100 Premium, using toluene as the reference hydrocarbon solvent.

As shown, minimum viscosities are obtained when the alcohols make up 30-35% of the solvent mixture. But note that with the lower molecular weight alcohols such as ethanol and methanol, relatively low solution viscosities are maintained even when the percentage of alcohol in the solvent blend is very high. Additional tests have shown that the relationships indicated in Figure 5 change very little when the concentration of ETHOCEL is changed or when other aromatic solvents are substituted for toluene. Therefore, in alcohol-aromatic solvent blends, the viscosity of a solution of an ETHOCEL polymer will be dependent primarily on the kind of alcohol used, and on its percentage in the solvent blend.



Film properties

Effective at low percentages of total formulation weight, cast ETHOCEL Premium cellulose ethers yield strong films. Film properties depend on the specific ETHOCEL polymer chosen, on the solvent or solvent blend used for processing, and on the type and amount of plasticizer.

Effect of polymer choice – The higher viscosity ETHOCEL polymers tend to yield stronger, tougher films than lower viscosity products. Figure 6 puts these into perspective for films derived from a complete range of ETHOCEL products in their respective reference of toluene/alcohol solvent blends.

Effect of solvent – Table 6, by contrast, compares viscosity and film properties for a single product—ETHOCEL Standard 10 Premium polymer—as derived from several solvents which could be used in pharmaceutical processing.

Figure 5 — Viscosity vs. Alcohol Content of Solvent for ETHOCEL Standard 100 Premium Cellulose Ether

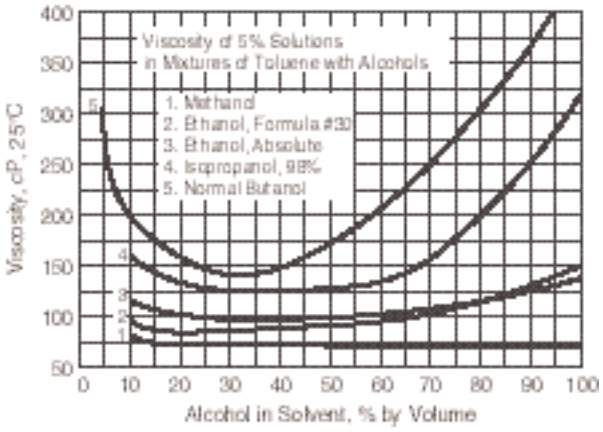
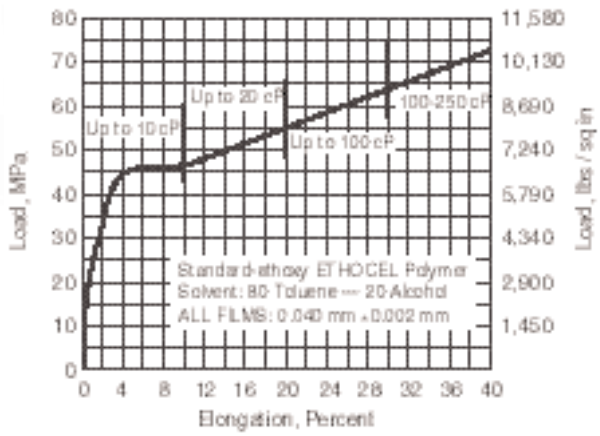


Figure 6 — Load-Elongation Curves for ETHOCEL Premium Ethylcellulose



Note: These curves are representative only of the solvent mixtures shown above; performance or curves will vary with different solvents.
Note: Dashed vertical lines represent approximate yield points for the product viscosity ranges indicated.

Table 6 — Viscosity and Film Properties of Unplasticized ETHOCEL Standard 10 Premium Cellulose Ether in Solvent Blends at 25°C (20 g Resin in 100 ml Solvent)

Solvent % Volume / % Volume	Viscosity, cP	Tensile Strength MPa	Tensile Strength psi	Elongation at Break, %
70 Acetone / 30 n-Propanol	671.0	42.7	6186	7.13
65 Acetone / 35 Isopropanol	1066.7	41.2	5971	17.78
50 Acetone / 50 DOWANOL PM glycol ether	1199.3	32.3	4673	2.51
80 Methyl acetate / 20 n-Propanol	785.6	36.1	5227	4.82
65 Methyl acetate / 35 DOWANOL PM glycol ether	1025.3	32.6	4716	3.07
50 Methylene chloride / 50 Ethanol	1092.0	28.0	4059	2.11
70 Methyl isobutyl ketone / 30 Methanol	769.3	32.7	4735	11.77
65 Methyl isobutyl ketone / 35 Ethanol	1240.7	34.6	5007	15.35

Safe Handling of ETHOCEL Polymers

Material Safety Data Sheets on ETHOCEL polymers are available from Dow to help customers further satisfy their own handling needs and those that may be imposed by regulatory agencies. This information should be read PRIOR to handling or use of the product.

The materials...solvents in particular ...used in formulating with ETHOCEL polymers may constitute separate hazards from toxicity or flammability. Be certain to get handling and safety recommendations for each such product from its supplier.

Health considerations

ETHOCEL cellulose ether polymers are thermoplastic polymers having a polymer "backbone" obtained from cellulose, a naturally-occurring carbohydrate polymer. Dust from ETHOCEL cellulose ether polymers could conceivably cause temporary mechanical irritation to the eye under extreme conditions. They are considered as nuisance dusts when inhaled. A local exhaust system to control dust during opening and dumping of bags is recommended.

The Dow Chemical Company advises against the use of ETHOCEL ethylcellulose polymers in any form in the preparation of parenteral or intravenous injections, because the material is not readily metabolized. Significant injury may result from impurities in the blood stream, especially if the ethylcellulose has not been properly dissolved.

Combustibility

Dust or fine powders of ETHOCEL polymers in air can reach explosive levels and care must be taken to prevent this. ETHOCEL polymers are organic materials and will burn under the right conditions of heat and oxygen supply. ETHOCEL resins will melt upon exposure to an open flame. Once melted and ignited, these resins will support combustion. Fires involving powders of ETHOCEL polymers can be extinguished by any available extinguishing agent.

Spills and disposal

To prevent accidents, good housekeeping requires that spills of ETHOCEL polymers should be thoroughly vacuumed or swept up. ETHOCEL polymers are not water soluble and do not biodegrade. The polymer should, therefore, present no ecological hazard to aquatic life.

If incineration is the chosen method of disposal, in compliance with all applicable laws and regulations, carefully controlled conditions should be maintained to avoid the possibility of a dust explosion.

If it is necessary to dispose of a formulation which included ETHOCEL polymers, it is recommended that the suppliers of all formulation ingredients be consulted before deciding on a suitable disposal method.

In disposal of any wastes, be certain all applicable federal, state, and local regulations are met.

Storage and handling

The shelf life for ETHOCEL polymers is two years. ETHOCEL polymers should be stored at temperatures not exceeding 32°C (90°F) in a dry area away from all sources of heat.

In storage or use, good housekeeping is required to prevent dusts or fine powders of ETHOCEL polymer from reaching explosive levels in air. When handling ETHOCEL polymers in large quantities or in bulk, general precautions outlined in NFPA[1] 1 No. 63, "Fundamental Principles for the Prevention of Dust Explosions in Industrial Plants," are recommended. For additional information, see NFPA Nos. 68, 69, and 654.

As with any organic chemical material, ETHOCEL cellulose ethers should not be stored next to peroxides or other oxidizing agents. Premium grades of ETHOCEL polymers are intended for use in foods, in food-contact, or in pharmaceuticals. As such, these products are subject to the Good Manufacturing Practices (21 CFR 110, 21 CFR 210, and 21 CFR 211) of the Food and Drug Administration. Materials in this use should not be stored near hazardous or non-food chemicals. To prevent odor transference, ETHOCEL Premium polymers should not be stored adjacent to any foul smelling material.

[1]National Fire Protection Association, Battery March Park, Quincy, MA 02269

Customer notice

Dow encourages its customers and potential users of Dow Products to review their applications of such products from the standpoint of human health and environmental quality. Dow personnel will assist customers in dealing with product safety considerations. Your Dow sales representative can arrange the proper contacts. Dow product literature, including Material Safety Data Sheets, should be consulted prior to use of Dow products. These may be obtained from your Dow sales representative or sales office.

For more information, complete literature, and product samples you can reach a Dow representative by calling the following phone numbers.

From the United States and Canada		call 1-800-447-4369
From Mexico		call 95-800-447-4369
In Europe	FAX + 31/20.691.6418	call + 31/20.691.6268

Or you can contact us on the Internet at ETHOCEL@DOW.COM

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