Hydroxypropyl Cellulose

1 Nonproprietary Names

BP: Hydroxypropylcellulose
JP: Hydroxypropylcellulose
PhEur: Hydroxypropylcellulosum
USPNF: Hydroxypropyl cellulose

2 Synonyms

Cellulose; hydroxypropyl ether; E463; hyprolose; *Klucel*; *Methocel*; *Nisso HPC*; oxypropylated cellulose.

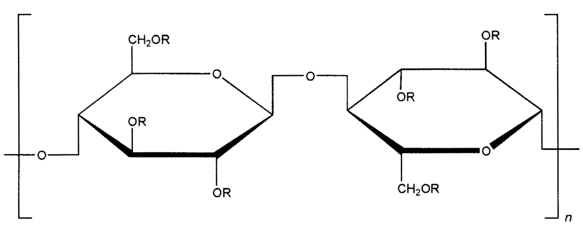
3 Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether [9004-64-2]

4 Empirical Formula Molecular Weight

The PhEur 2002 and USPNF 20 describe hydroxypropyl cellulose as a partially substituted poly(hydroxypropyl) ether of cellulose. It may contain not more than 0.6% of silica or another suitable anticaking agent. Hydroxypropyl cellulose is commercially available in a number of different grades that have various solution viscosities. Molecular weight ranges from 50 000–1 250 000; *see also* Section 10..

5 Structural Formula



R is H or $[CH_2CH(CH_3)O]_mH$

6 Functional Category

Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations; *see* Table I.

In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film-coating, and extended-release-matrix former. Concentrations of hydroxypropyl cellulose of 2–6% w/w may be used as a binder in either wet-granulation or dry, direct-compression tableting processes.[1–5] Concentrations of 15–35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release.[6] The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the viscosity of hydroxypropyl cellulose and hence decreases the release rate of a drug. Typically, a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Aqueous solutions containing hydroxypropyl cellulose along with an amount of methyl cellulose or ethanolic solutions may be used.[7–9] Stearic acid or palmitic acid may be added to ethanolic hydroxypropyl cellulose solutions as plasticizers. A low-substituted hydroxypropyl cellulose is used as a tablet disintegrant; see Hydroxypropyl Cellulose, Low-substituted.

Hydroxypropyl cellulose is also used in microencapsulation processes and as a thickening agent. In topical formulations, hydroxypropyl cellulose is used in transdermal patches and ophthalmic preparations.[10–12]

Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

Table I: Uses of hydroxypropyl cellulose.

Use	Concentration (%)
Extended release-matrix former	15–35
Tablet binder	2–6
Tablet film coating	5

8 Description

Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder. *See also* Sections 4 and 5.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for hydroxypropyl cellulose.

Test	JP 2001	PhEur 2002	USPNF 20
Identification	+	+	+
Characters	—	+	—
Apparent viscosity	+	+	+
Appearance of solution	+	+	—
pH (1 in 100)	5.0–7.5	5.0–8.5	5.0–8.0
Loss on drying	⩽5.0%	⩽7.0%	⩽5.0%
Residue on ignition	⩽0.5%	—	⩽0.2%
Sulfated ash	—	⩽1.6%	—
Arsenic	⩽2 ppm	—	⩽3 ppm
Chlorides	+	⩽0.5%	—
Lead	—	—	⩽0.001%
Heavy metals	⩽20 ppm	⩽20 ppm	20 μg/g
Silica	—	⩽0.6%	—
Organic volatile impurities	—	—	+
Sulfate	⩽0.048%	—	—
Assay of hydroxypropoxy groups	53.4–77.5%	—	⩽80.5%

10 Typical Properties

Acidity/alkalinity: pH = 5.0–8.5 for a 1% w/v aqueous solution.

Density (bulk): ≈0.5 g/cm^3

Interfacial tension: 12.5 mN/m for a 0.1% w/v aqueous solution compared with mineral oil.

Melting point: softens at 130°C; chars at 260–275°C.

Moisture content: hydroxypropyl cellulose absorbs moisture from the atmosphere, the amount of water absorbed depending upon the initial moisture content and the temperature and relative humidity of the surrounding air. Typical equilibrium moisture content values at 25°C are 4% w/w at 50% relative humidity and 12% w/w at 84% relative humidity. *See* Table III. *See also* Figure I.

Table III: Moisture content of *Klucel* (Aqualon).

Grade	Molecular weight	Moisture (%)
Klucel EF	≈80 000	0.59
Klucel LF	≈95 000	2.21
Klucel JF	≈140 000	1.44
Klucel GF	≈370 000	1.67
Klucel MF	≈850 000	1.52
Klucel HF	≈1 150 000	4.27

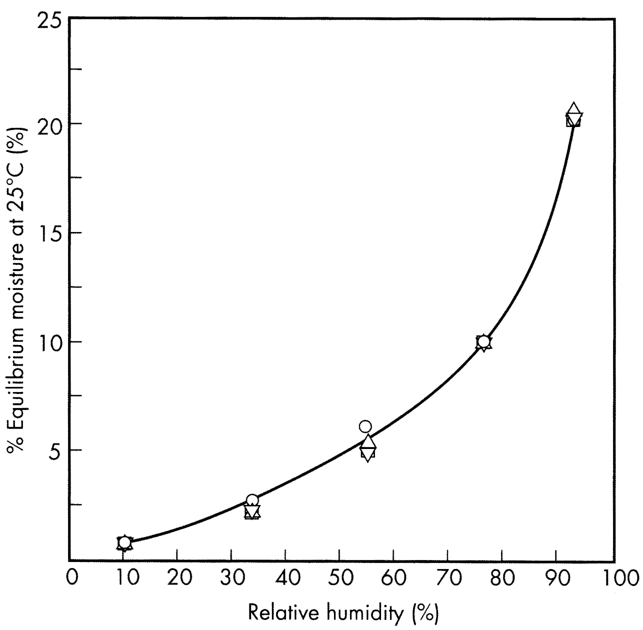


Figure 1: Equilibrium moisture content of various grades of hydroxypropyl cellulose.
○ *Klucel GF* (Aqualon, Lot #4996).
▽ *Klucel JF* (Aqualon, Lot #4753).
△ *Klucel LF* (Aqualon, Lot #4965).
□ *Klucel EF* (Aqualon, Lot #1223).

Particle size distribution:
Klucel (regular grind), 95% through a US #30 mesh (590 μm), and 99% through a US #20 mesh (840 μm)
Klucel (X-grind), 100% through a US #60 mesh (250 μm), and 80% through a US #100 mesh (149 μm)

Refractive index: n_D^{20} = 1.3353 for a 2% w/v aqueous solution.

Solubility: soluble 1 in 10 parts dichloromethane, 1 in 2.5 parts ethanol, 1 in 2 parts methanol, 1 in 5 parts propan-2-ol, 1 in 5 parts propylene glycol, and 1 in 2 parts water; practically insoluble in aliphatic hydrocarbons, aromatic hydrocarbons, carbon tetrachloride, petroleum distillates, glycerin, and oils.

Hydroxypropyl cellulose is freely soluble in water below 38°C, forming a smooth, clear, colloidal solution. In hot water, it is insoluble and is precipitated as a highly swollen floc at a temperature between 40 and 45°C. Hydroxypropyl cellulose is soluble in many cold or hot polar organic solvents such as dimethyl formamide, dimethyl sulfoxide, dioxane, ethanol, methanol, propan-2-ol (95%), and propylene glycol. There is no tendency for precipitation in hot organic solvents. However, the grade of hydroxypropyl cellulose can have a marked effect upon solution quality in some organic liquids that are borderline solvents, such as acetone, butyl acetate, cyclohexanol, dichloromethane, lactic acid, methyl acetate, methyl ethyl ketone, propan-2-ol (99%), and *tert*-butanol. The higher-viscosity grades of hydroxypropyl cellulose tend to produce slightly inferior solutions. However, the solution quality in borderline solvents can often be greatly improved by the use of small quantities (5–15%) of a cosolvent. For example, dichloromethane is a borderline solvent for *Klucel HF* and solutions have a granular texture, but a smooth solution may be produced by adding 10% methanol.

Hydroxypropyl cellulose is compatible with a number of high-molecular-weight, high-boiling waxes and oils, and can be used to modify certain properties of these materials. Examples of materials that are good solvents for hydroxypropyl cellulose at an elevated temperature are acetylated monoglycerides, glycerides, pine oil, polyethylene glycol, and polypropylene glycol.

Specific gravity: 1.2224 for particles; 1.0064 for a 2% w/v aqueous solution at 20°C.

Surface tension: *see* Table IV.

Table IV: Surface tension (mN/m) of aqueous solutions of *Nisso HPC* (Nippon Soda Co. Ltd.) at 20°C.

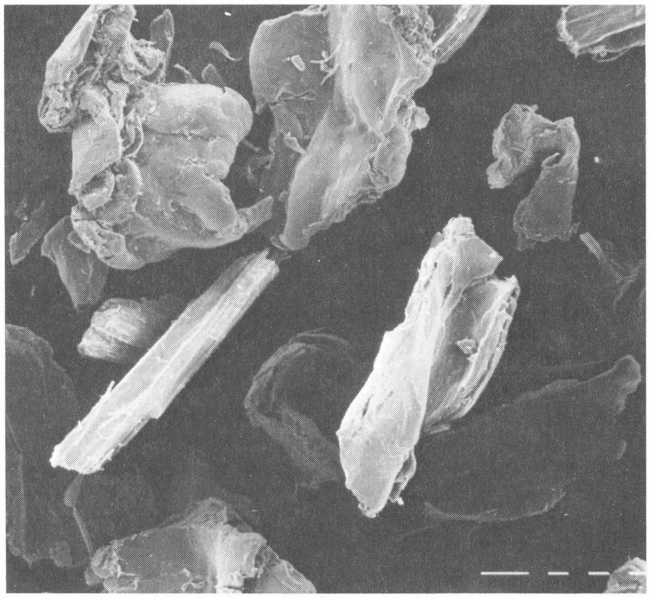
Grade	Surface tension (mN/m) at 20°C for aqueous solutions of stated concentration			
	0.01%	0.1%	1.0%	10.0%
Nisso HPC-L	51.0	49.1	46.3	45.8
Nisso HPC-M	54.8	49.7	46.3	—

Viscosity (dynamic): a wide range of viscosity types are commercially available; *see* Table V. Solutions should be prepared by gradually adding the hydroxypropyl cellulose to a vigorously stirred solvent. Increasing concentration produces solutions of increased viscosity. *See also* Section 11 for information on solution stability.

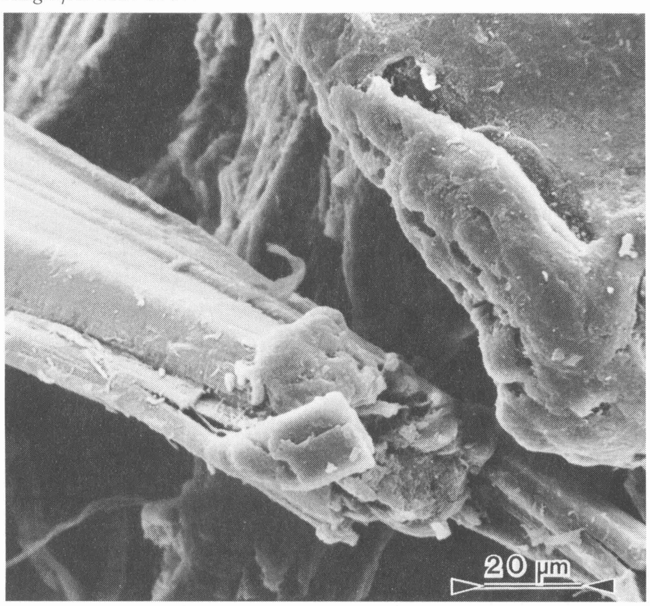
Table V: Viscosity of aqueous solutions of *Klucel* (Aqualon) at 25°C.

Grade	Viscosity (mPa s) of various aqueous solutions of stated concentration			
	1%	2%	5%	10%
Klucel HF	1500–3000	—	—	—
Klucel MF	—	4000–6500	—	—
Klucel GF	—	150–400	—	—
Klucel JF	—	—	150–400	—
Klucel LF	—	—	75–150	—
Klucel EF	—	—	—	200–600

SEM: 1
Excipient: Hydroxypropyl cellulose (*Klucel*)
Manufacturer: Aqualon
Magnification: 60 ×



SEM: 2
Excipient: Hydroxypropyl cellulose (*Klucel*)
Manufacturer: Aqualon
Magnification: 600 ×



11 Stability and Storage Conditions

Hydroxypropyl cellulose powder is a stable material, although it is hygroscopic after drying.

Aqueous solutions of hydroxypropyl cellulose are stable at pH 6.0–8.0, with the viscosity of solutions being relatively unaffected. However, at low pH aqueous solutions may undergo acid hydrolysis, resulting in chain scission and hence a decrease in solution viscosity. The rate of hydrolysis increases with increasing temperature and hydrogen ion concentration. At high pH, alkali-catalyzed oxidation may degrade the polymer and result in a decrease in viscosity of solutions. This degradation can occur owing to the presence of dissolved oxygen or oxidizing agents in a solution.

Increasing temperature causes the viscosity of aqueous solutions to decrease gradually until the viscosity drops suddenly at about 45°C owing to the limited solubility of hydroxypropyl cellulose. However, this process is reversible and on cooling the original viscosity is restored.

The high level of substitution of hydroxypropyl cellulose improves the resistance of the polymer to degradation by molds and bacteria.[9] However, aqueous solutions are susceptible to degradation under severe conditions and a viscosity decrease may occur. Certain enzymes produced by microbial action will degrade hydroxypropyl cellulose in solution.[13] Therefore, for prolonged storage, an antimicrobial preservative should be added to aqueous solutions. Solutions of hydroxypropyl cellulose in organic solvents do not generally require preservatives.

Ultraviolet light will also degrade hydroxypropyl cellulose and aqueous solutions may therefore decrease slightly in viscosity if exposed to light for several months.

Aqueous hydroxypropyl cellulose solutions have optimum stability when the pH is maintained between pH 6.0 and 8.0, and also when the solution is protected from light, heat, and the action of microorganisms.

Hydroxypropyl cellulose powder should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Hydroxypropyl cellulose in solution demonstrates some incompatibility with substituted phenol derivatives, such as methylparaben and propylparaben. The presence of anionic polymers may increase the viscosity of hydroxypropyl cellulose solutions.

The compatibility of hydroxypropyl cellulose with inorganic salts varies depending upon the salt and its concentration; *see* Table VI. Hydroxypropyl cellulose may not tolerate high concentrations of other dissolved materials.

Table VI: Compatibility of hydroxypropyl cellulose (*Nisso HPC*) with inorganic salts in aqueous solutions.[a]

Salt	Concentration of salt (% w/w)						
	2	3	5	7	10	30	50
Aluminum sulfate	S	S	I	I	I	I	I
Ammonium nitrate	S	S	S	S	S	I	I
Ammonium sulfate	S	S	I	I	I	I	I
Calcium chloride	S	S	S	S	S	T	I
Dichromic acid	S	S	S	S	S	S	S
Disodium hydrogenphosphate	S	S	I	I	I	I	I
Ferric chloride	S	S	S	S	S	I	I
Potassium ferrocyanide	S	S	S	I	I	I	I
Silver nitrate	S	S	S	S	S	S	T
Sodium acetate	S	S	S	S	I	I	I
Sodium carbonate	S	S	I	I	I	I	I
Sodium chloride	S	S	S	S	I	I	I
Sodium nitrate	S	S	S	S	S	I	I
Sodium sulfate	S	S	I	I	I	I	I
Sodium sulfite	S	S	I	I	I	I	I
Sodium thiosulfate	T	T	T	I	I	I	I

(a) S, completely soluble; T, turbid white; I, insoluble.

The balance of the hydrophilic–lipophilic properties of the polymer, which are required for dual solubility, reduces its ability to hydrate with water and it therefore tends to be salted out in the presence of high concentrations of other dissolved materials.

The precipitation temperature of hydroxypropyl cellulose is lower in the presence of relatively high concentrations of other dissolved materials that compete for the water in the system; *see* Table VII.

Table VII: Variation in precipitation temperature of hydroxypropyl cellulose (*Klucel H*) in the presence of other materials.

Ingredients and concentrations	Precipitation temperature (°C)
1% *Klucel H*	41
1% *Klucel H* + 1.0% sodium chloride	38
1% *Klucel H* + 5.0% sodium chloride	30
0.5% *Klucel H* + 10% sucrose	41
0.5% *Klucel H* + 30% sucrose	32
0.5% *Klucel H* + 40% sucrose	20
0.5% *Klucel H* + 50% sucrose	7

13 Method of Manufacture

A purified form of cellulose is reacted with sodium hydroxide to produce a swollen alkali cellulose that is chemically more reactive than untreated cellulose. The alkali cellulose is then reacted with propylene oxide at elevated temperature and pressure. The propylene oxide can be substituted on the cellulose through an ether linkage at the three reactive hydroxyls present on each anhydroglucose monomer unit of the cellulose chain. Etherification takes place in such a way that hydroxypropyl substituent groups contain almost entirely secondary hydroxyls. The secondary hydroxyl present in the side chain is available for further reaction with the propylene oxide, and 'chaining-out' may take place. This results in the formation of side chains containing more than 1 mole of combined propylene oxide.

14 Safety

Hydroxypropyl cellulose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hydroxypropyl cellulose is generally regarded as an essentially nontoxic and nonirritant material.[14] However, the use of hydroxypropyl cellulose as a solid ocular insert has been associated with rare reports of discomfort or irritation, including hypersensitivity and edema of the eyelids. Adverse reactions to hydroxypropyl cellulose are rare. However, it has been reported that a single patient developed contact dermatitis due to hydroxypropyl cellulose in a transdermal estradiol patch.[15]

The WHO has not specified an acceptable daily intake for hydroxypropyl cellulose since the levels consumed were not considered to represent a hazard to health.[16] Excessive consumption of hydroxypropyl cellulose may, however, have a laxative effect.

LD_{50} (rat, IV): 0.25 g/kg[17]
LD_{50} (rat, oral): 10.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hydroxypropyl cellulose dust may be irritant to the eyes; eye protection is recommended. Excessive dust generation should be avoided to minimize the risk of explosions.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets; topical and transdermal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Hydroxyethyl cellulose; hydroxypropyl cellulose, low-substituted; hypromellose.

18 Comments

Hydroxypropyl cellulose is a thermoplastic polymer that can be processed by virtually all fabrication methods used for plastics.

It is also used in hot-melt extruded films for topical use. When it is produced with chlorpheniramine maleate, the matrix is stabilized, allowing film processing at lower temperatures.[18] Mucoadhesive hydroxypropyl cellulose microspheres have been prepared for powder inhalation preparations.[19]

19 Specific References

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21 Author

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22 Date of Revision

10 October 2002.