Handbook of PHARMACEUTICAL EXCIPIENTS

Second Edition

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Hydroxypropyl Methylcellulose

1. Nonproprietary Names

BP: Hypromellose
PhEur: Methylhydroxypropylcellulosum
USP: Hydroxypropyl methylcellulose

2. Synonyms

Cellulose, hydroxypropyl methyl ether; *Culminal MHPC*; E464; HPMC; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; *Pharmacoat*.

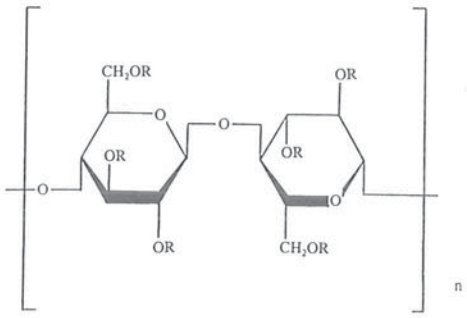
3. Chemical Name and CAS Registry Number

Cellulose, 2-Hydroxypropyl methyl ether
[9004-65-3]

4. Empirical Formula Molecular Weight

The PhEur 1992 describes hydroxypropyl methylcellulose as a partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose. It is available in several grades which vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hydroxypropyl methylcellulose defined in the USP XXII specifies the substitution type by appending a four digit number to the nonproprietary name, e.g. hydroxypropyl methylcellulose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CHOHCH_3$), calculated on a dried basis. Molecular weight is approximately 10 000-1 500 000.

5. Structural Formula



Where R is H, CH_3 or $[CH_3CH(OH)CH_2]$.

6. Functional Category

Coating agent; film-former; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl methylcellulose is widely used in oral and topical pharmaceutical formulations.

In oral products, hydroxypropyl methylcellulose is primarily used as a tablet binder,[1] in film-coating[2-7] and as an extended release tablet matrix.[8-12] Concentrations of between 2-5% w/w may be used as a binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of water-soluble drugs from a matrix.

Depending upon the viscosity grade, concentrations between 2-10% w/w are used as film-forming solutions to film-coat tablets. Lower viscosity grades are used in aqueous film-coating solutions while higher viscosity grades are used with organic solvents.

Hydroxypropyl methylcellulose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. Compared with methylcellulose, hydroxypropyl methylcellulose produces solutions of greater clarity, with fewer undispersed fibres present, and is therefore preferred in formulations for ophthalmic use. Concentrations of between 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye-drops and artificial tear solutions.

Hydroxypropyl methylcellulose is also used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hydroxypropyl methylcellulose is used as an adhesive in plastic bandages and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

8. Description

Hydroxypropyl methylcellulose is an odorless and tasteless, white or creamy-white colored fibrous or granular powder.

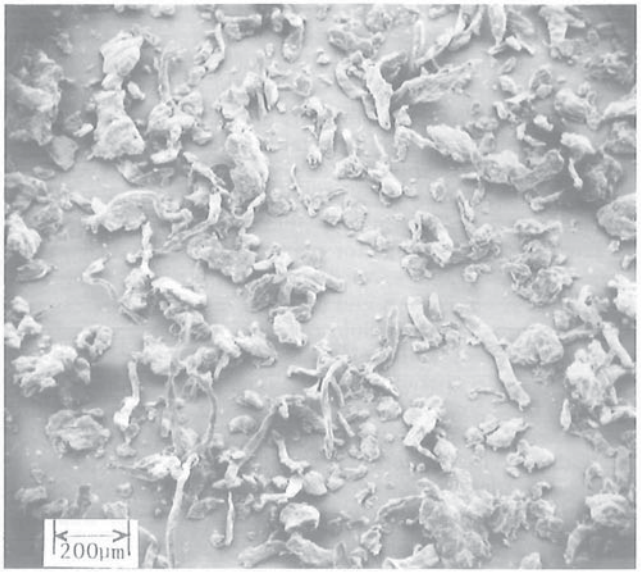
9. Pharmacopeial Specifications

Test	PhEur 1992	USP XXII (Suppl 2)
Identification	+	+
Appearance of solution	+	—
pH (1% w/w solution)	5.5-8.0	—
Apparent viscosity	+	+
Loss on drying	⩽ 10.0%	⩽ 5.0%
Residue on ignition		
for viscosity grade > 50 mPa s	—	⩽ 1.5%
for viscosity grade ⩽ 50 mPa s	—	⩽ 3.0%
for type 1828 of all viscosities	—	⩽ 5.0%
Sulfated ash	⩽ 1.0%	—
Arsenic	—	⩽ 3 ppm
Chlorides	⩽ 0.5%	—
Heavy metals	⩽ 20 ppm	⩽ 0.001%
Methoxy content		
Type 1828	—	16.5-20.0%
Type 2208	—	19.0-24.0%
Type 2906	—	27.0-30.0%
Type 2910	—	28.0-30.0%
Hydroxypropoxy content		
Type 1828	—	23.0-32.0%
Type 2208	—	4.0-12.0%
Type 2906	—	4.0-7.5%
Type 2910	—	7.0-12.0%

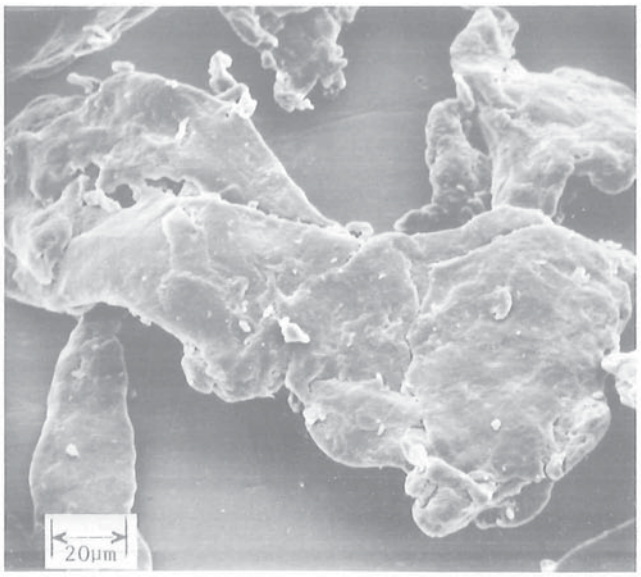
10. Typical Properties

Acidity/alkalinity:
pH = 5.5-8.0 for a 1% w/w aqueous solution.

SEM: 1
Excipient: Hydroxypropyl methylcellulose
Manufacturer: Shin-Etsu Chemical Co Ltd
Lot No.: 83214
Magnification: 60x
Voltage: 10kV



SEM: 2
Excipient: Hydroxypropyl methylcellulose
Manufacturer: Shin-Etsu Chemical Co Ltd
Lot No.: 83214
Magnification: 600x
Voltage: 10kV



Ash: 1.5-3.0%, depending upon the grade.
Autoignition temperature: 360°C
Density (tapped): 0.50-0.70 g/cm^3 for *Pharmacoat*.
Melting point: browns at 190-200°C; chars at 225-230°C. Glass transition temperature is 170-180°C.
Moisture content: hydroxypropyl methylcellulose 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. *See also* HPE Data.
Solubility: soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane, and mixtures of methanol and dichloromethane. Certain grades of hydroxypropyl methylcellulose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. *See also* Section 11.
Specific gravity: 1.26
Viscosity (dynamic): a wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared although hydroxypropyl methylcellulose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hydroxypropyl methylcellulose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions, *see* Table I.
To prepare an aqueous solution, it is recommended that hydroxypropyl methylcellulose is dispersed and thoroughly hydrated in about 20-30% of the required amount of water. The water should be vigorously stirred and heated to 80-90°C then the remaining hydroxypropyl methylcellulose added. Cold water should then be added to produce the required volume.
When a water-miscible organic solvent such as ethanol, glycol, or mixtures of ethanol and dichloromethane is used, the hydroxypropyl methylcellulose should first be dispersed into the organic solvent, at a ratio of 5-8 parts of solvent to 1 part of hydroxypropyl methylcellulose. Cold water is then added to produce the required volume.

Table I: Dynamic viscosity (mPa s) of *Pharmacoat 603* (Shin-Etsu Chemical Co Ltd) solutions in various solvents at 20°C.

Solvent	Viscosity (mPa s) at 20°C Concentration (% w/w)			
	2	6	10	14
Dichloromethane: ethanol (50:50)	4	28	150	580
Ethanol: water (50:50)	8	32	120	350
Water	3	15	45	100

	HPE Laboratory Project Data		
	Method	Lab #	Results
Moisture content	MC-20	15	2.10% [a]
Moisture content	MC-20	15	3.10% [b]
Moisture content	EMC-1	15	*See* Fig. 1. [a]

Supplier: a. Dow Chemical Company; b. Aqualon.

11. Stability and Storage Conditions

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

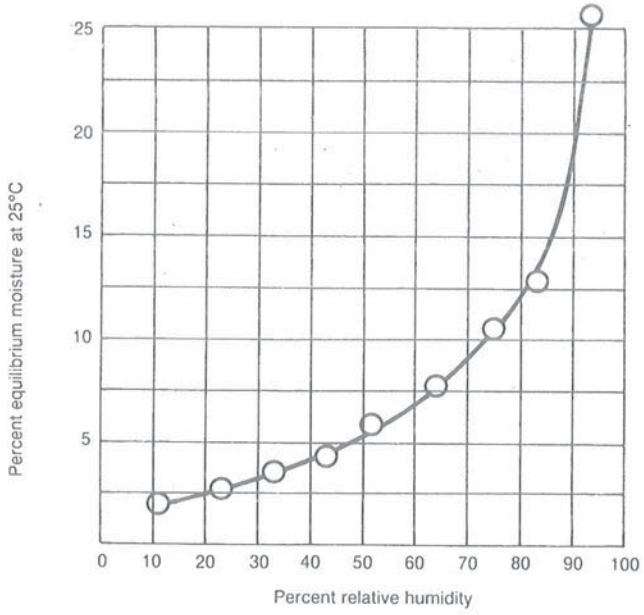


Fig. 1: Equilibrium moisture content of hydroxypropyl methylcellulose, *Methocel E15* (Dow Chemical Company, Lot No.: QP0502-801-E).

Solutions are stable between pH 3-11. Increasing temperature reduces the viscosity of solutions. Hydroxypropyl methylcellulose undergoes a reversible sol to gel transformation upon heating and cooling respectively. The gel point is 50-90°C, depending upon the grade of material.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.[13] However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative. When used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used for this purpose. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking.

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

12. Incompatibilities

Hydroxypropyl methylcellulose is incompatible with some oxidizing agents. Since it is nonionic, hydroxypropyl methylcellulose will not complex with metallic salts and ionic organics to form insoluble precipitates.

13. Method of Manufacture

A purified form of cellulose, obtained from cotton waste or wood pulp, is reacted with sodium hydroxide solution to produce a swollen alkali cellulose which is chemically more reactive than untreated cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produce methylhydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules.

14. Safety

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

Hydroxypropyl methylcellulose is generally regarded as a nontoxic and nonirritant material although excessive oral consumption may have a laxative effect.[14] The WHO has not specified an acceptable daily intake for hydroxypropyl methylcellulose since the levels consumed were not considered to represent a hazard to health.[15]

LD_{50} (mouse, IP): 5 g/kg[16]

LD_{50} (rat, IP): 5.2 g/kg

15. Handling Precautions

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

16. Regulatory Status

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

17. Pharmacopeias

Br, Eur, Fr, Gr, It, Jpn, Neth, Port, Swiss and US.

18. Related Substances

Hydroxyethyl Cellulose; Hydroxypropyl Cellulose; Hydroxypropyl Methylcellulose Phthalate.

19. Comments

Powdered or granular, surface-treated grades of hydroxypropyl methylcellulose are also available which are dispersible in cold water. The dissolution rate of these materials can be controlled by a shift in pH and they are thus useful for slow-release or enteric coated formulations.

20. Specific References

1. Chowhan ZT. Role of binders in moisture-induced hardness increase in compressed tablets and its effect on *in vitro* disintegration and dissolution. J Pharm Sci 1980; 69: 1-4.
2. Rowe RC. The adhesion of film coatings to tablet surfaces - the effect of some direct compression excipients and lubricants. J Pharm Pharmacol 1977; 29: 723-726.
3. Rowe RC. The molecular weight and molecular weight distribution of hydroxypropyl methylcellulose used in the film coating of tablets. J Pharm Pharmacol 1980; 32: 116-119.
4. Banker G, Peck G, Jan S, Pirakitikulr P. Evaluation of hydroxypropyl cellulose and hydroxypropyl methyl cellulose as aqueous based film coatings. Drug Dev Ind Pharm 1981; 7: 693-716.
5. Okhamafe AO, York P. Moisture permeation mechanism of some aqueous-based film coats. J Pharm Pharmacol 1982; 34(Suppl): 53P.
6. Alderman DA, Schulz GJ. Method of making a granular, cold water dispersible coating composition for tablets. US Patent 4816298, 1989.
7. Patell MK., Taste masking pharmaceutical agents. US Patent 4916161, 1990.
8. Hardy JG, Kennerley JW, Taylor MJ, Wilson CG, Davis SS. Release rates from sustained-release buccal tablets in man. J Pharm Pharmacol 1982; 34(Suppl): 91P.

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