

HANDBOOK OF PHARMACEUTICAL EXCIPIENTS

THIRD EDITION



APhA
American
Pharmaceutical
Association

(PP)
Pharmaceutical Press

EDITED BY
ARTHUR H. KIBBE

**Handbook of
PHARMACEUTICAL
EXCIPIENTS**

Third Edition

Edited by
Arthur H. Kibbe, Ph.D.

Professor and Chair
Department of Pharmaceutical Sciences
Wilkes University School of Pharmacy
Wilkes-Barre, Pennsylvania



American Pharmaceutical Association
Washington, D.C.



London, United Kingdom

Published by the American Pharmaceutical Association
2215 Constitution Avenue NW, Washington, DC 20037-2985, USA
www.aphanet.org
and the Pharmaceutical Press
1 Lambeth High Street, London SE1 7JN, UK
www.pharmpress.com

© 1986, 1994, 2000 American Pharmaceutical Association and Pharmaceutical Press

First edition 1986
Second edition 1994
Third edition 2000

Printed in the United States of America

ISBN: 0-85369-381-1 (UK)
ISBN: 0-917330-96-X (USA)

Library of Congress Cataloging-in-Publication Data

Handbook of pharmaceutical excipients / edited by Arthur H. Kibbe.--3rd ed.
p. ; cm.

Includes bibliographical references and index.

ISBN 0-917330-96-X

1. Excipients--Handbooks, manuals, etc. I. Kibbe, Arthur H. II. American
Pharmaceutical Association.

[DNLM: 1. Excipients--Handbooks. QV 735 H236 2000]

RS201.E87 H36 2000

615'.19--dc21

99-044554

A catalogue record for this book is available from the British Library.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, without the prior written permission of the copyright holder. The publisher makes no representation, express or implied, with regard to the accuracy of the information contained in this book and cannot accept any legal responsibility or liability for any errors or omissions that may be made.

Managing Editor: Melanie Segala
Copyeditor: Paul Gottehrer
Indexer: Lillian Rodberg
Compositor: Roy Barnhill
Cover Designer: Tim Kaage

Hydroxypropyl Methylcellulose

1. Nonproprietary Names

BP: Hypromellose
JP: Hydroxypropylmethylcellulose
PhEur: Methylhydroxypropylcellulosum
USP: Hydroxypropyl methylcellulose

2. Synonyms

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

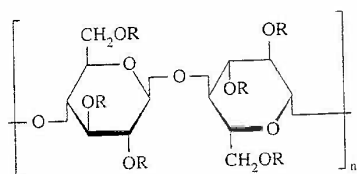
3. Chemical Name and CAS Registry Number

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

4. Empirical Formula Molecular Weight

The PhEur 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 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 (OCH₃). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH₂CHOHCH₃), calculated on a dried basis. Molecular weight is approximately 10 000-1 500 000.

5. Structural Formula



Where R is H, CH₃, or [CH₃CH(OH)CH₂].

6. Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; 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 drugs from a matrix at levels 10-80% w/w in tablets and capsules.

Depending upon the viscosity grade, concentrations between 2-20% 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 fibers 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 in the manufacture of capsules, 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

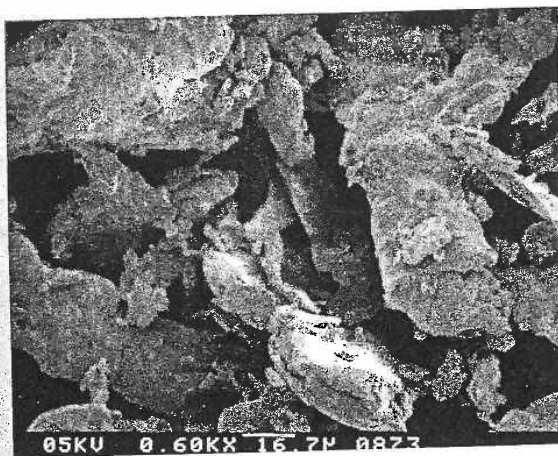
Hydroxypropyl methylcellulose is an odorless and tasteless, white or creamy-white colored fibrous or granular powder.

9. Pharmacopeial Specifications

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

SEM: 1

Excipient: Hydroxypropyl methylcellulose
 Manufacturer: Dow Chemical Co
 Lot No.: ME20012N11
 Magnification: 600×
 Voltage: 5kV

**10. Typical Properties****Acidity/alkalinity:**

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

Ash: 1.5-3.0%, depending upon the grade.

Autoignition temperature: 360°C

Density (bulk): 0.341 g/cm³

Density (tapped): 0.557 g/cm³

Density (true): 1.326 g/cm³

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 Fig. 1.

Particle size distribution: See Table I.

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, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. 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 II.

To prepare an aqueous solution, it is recommended that hydroxypropyl methylcellulose is dispersed and thoroughly hy-

SEM: 2

Excipient: Hydroxypropyl methylcellulose
 Manufacturer: Dow Chemical Co
 Lot No.: ME20012N11
 Magnification: 60×
 Voltage: 5kV

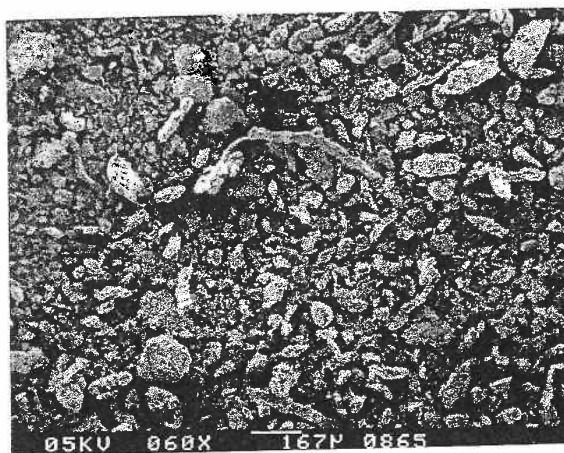


Table I: Typical particle size distribution for hydroxypropyl methylcellulose.

	Average particle size (µm)	Cumulative frequency oversize (%)	Weight retained (%)
Lot LC15012N11	250	5.6	5.60
	200	18.8	13.20
	137	26.6	7.8
	115	35.4	8.8
	90	54.4	19.0
	64	85.8	31.4
	pan	100	14.0
Lot LA29012N02	250	2.8	2.8
	200	15.6	12.8
	137	20.6	5.0
	115	26.4	5.8
	90	42.8	16.4
	64	68	25.2
	pan	100	33

Note: Using an ATM Sonic Softener.

drated 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.

11. Stability and Storage Conditions

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

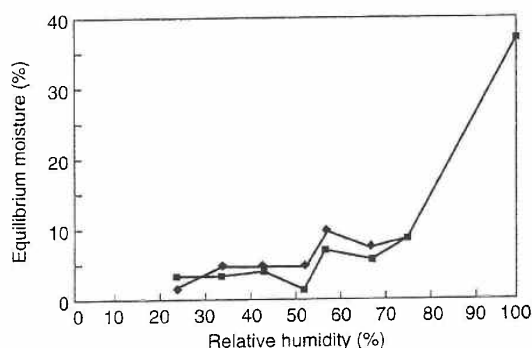


Fig. 1: Absorption desorption isotherm for hydroxypropyl methylcellulose.

◆ : sorption
■ : desorption

Table II: Typical viscosity values for 2% (w/v) aqueous solutions of Methocel (Dow Chemical Co.) Viscosities measured at 20°C.

Methocel grade	Nominal	Viscosity (mPa s)
K100LVP ^(a)	100	80-120
K4MP ^(a)	4000	3000-5600
K15MP ^(a)	15 000	12 000-21 000
K100MP ^(a)	100 000	80 000-120 000
E4MP ^(a)	4000	3500-5600
E10MP CR ^(a)	10 000	8000-13 000
E3 PREM.LV		2.4-3.6
E5 PREM.LV		4-6
E6 PREM.LV		5-7
E15 PREM.LV		12-18
E50 PREM.LV		40-60
K3 PREM.LV		2.4-3.6

^(a) Dow Chemical Company.

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 and concentration 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 or ionic organics to form insoluble precipitates.

13. Method of Manufacture

A purified form of cellulose, obtained from cotton linters 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⁾

LD₅₀ (mouse, IP): 5 g/kg⁽¹⁶⁾

LD₅₀ (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

China, Eur, Int, Jpn, Pol, and US.

18. Related Substances

Hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropyl methylcellulose phthalate; methylcellulose.

19. Comments

Powdered or granular, surface-treated grades of hydroxypropyl methylcellulose are also available which are dispersible in cold water. These are not recommended for oral use.

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.
9. Hogan JE. Hydroxypropylmethylcellulose sustained release technology. *Drug Dev Ind Pharm* 1989; 15: 975-999.
10. Shah AC, Britten NJ, Olanoff LS, Badalamenti JN. Gel-matrix systems exhibiting bimodal controlled release for oral delivery. *J Controlled Release* 1989; 9: 169-175.
11. Wilson HC, Cuff GW. Sustained release of isomazole from matrix tablets administered to dogs. *J Pharm Sci* 1989; 78: 582-584.
12. Dahl TC, Calderwood T, Bormeth A, Trimble K, Piepmeier E. Influence of physicochemical properties of hydroxypropyl methylcellulose on naproxen release from sustained release matrix tablets. *J Controlled Release* 1990; 14: 1-10.
13. Banker G, Peck G, Williams E, Taylor D, Pirakitikulr P. Microbiological considerations of polymer solutions used in aqueous film coating. *Drug Dev Ind Pharm* 1982; 8: 41-51.
14. Final report on the safety assessment of hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropyl methylcellulose and cellulose gum. *J Am Coll Toxicol* 1986; 5(3): 1-60.
15. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-fifth report of the joint FAO/WHO expert committee on food additives. *Tech Rep Ser Wld Hlth Org* 1990; No. 789.
16. Sweet DV, editor. Registry of Toxic Effects of Chemical Substances. Cincinnati, US Department of Health, 1987.

21. General References

- Doelker E. Cellulose derivatives. *Adv Polymer Sci* 1993; 107: 199-265.
- Dow Chemical Company. Technical literature: *Methocel*, 1993.
- Malamataris S, Karidas T, Goidas P. Effect of particle size and sorbed moisture on the compression behavior of some hydroxypropyl methylcellulose (HPMC) polymers. *Int J Pharmaceutics* 1994; 103: 205-215.
- Papadimitriou E, Buckton G, Efentakis M. Probing the mechanisms of swelling of hydroxypropylmethylcellulose matrices. *Int J Pharmaceutics* 1993; 98: 57-62.
- Parab PV, Nayak MP, Ritschel WA. Influence of hydroxypropyl methylcellulose and of manufacturing technique on *in vitro* performance of selected antacids. *Drug Dev Ind Pharm* 1985; 11: 169-185.
- Radebaugh GW, Murtha JL, Julian TN, Bondi JN. Methods for evaluating the puncture and shear properties of pharmaceutical polymeric films. *Int J Pharmaceutics* 1988; 45: 39-46.
- Rowe RC. Materials used in the film coating of oral dosage forms. In: Florence AT, editor. *Critical Reports on Applied Chemistry*, volume 6. Oxford, Blackwell Scientific Publications, 1984; 1-36.
- Sebert P, Andrianoff N, Rollet M. Effect of gamma irradiation on hydroxypropylmethylcellulose powders: consequences on physical, rheological and pharmacotechnical properties. *Int J Pharmaceutics* 1993; 99: 37-42.
- Shin-Etsu Chemical Co Ltd. Technical literature: *Metolose*, 1977.
- Shin-Etsu Chemical Co Ltd. Technical literature: *Pharmacoat* hydroxypropyl methylcellulose, 1990.
- Wan LSC, Heng PWS, Wong LF. The effect of hydroxypropylmethylcellulose on water penetration into a matrix system. *Int J Pharmaceutics* 1991; 73: 111-116.

22. Authors

RJ Harwood.