Hypromellose Phthalate

1 Nonproprietary Names

BP: Hypromellose phthalate
JP: Hydroxypropylmethylcellulose phthalate
PhEur: Hypromellosi phthalas
USPNF: Hypromellose phthalate

2 Synonyms

Cellulose phthalate hydroxypropyl methyl ether; HPMCP; hydroxypropyl methylcellulose benzene-1,2-dicarboxylate; 2-hydroxypropyl methylcellulose phthalate; methylhydroxypropylcellulose phthalate.

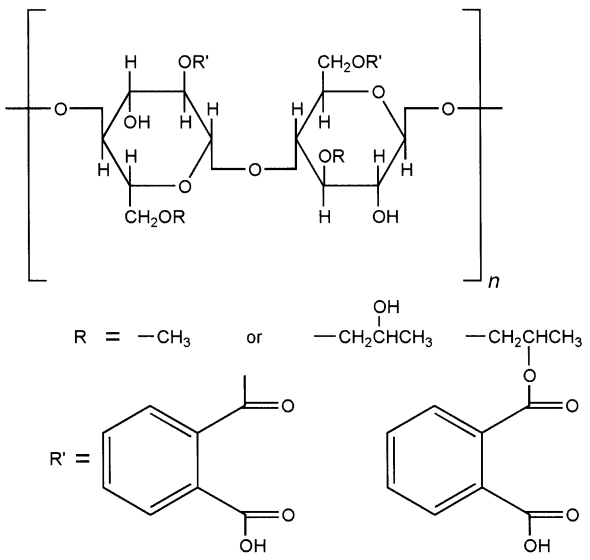
3 Chemical Name and CAS Registry Number

Cellulose, hydrogen 1,2-benzenedicarboxylate, 2-hydroxypropyl methyl ether [9050-31-1]

4 Empirical Formula Molecular Weight

Hypromellose phthalate is a cellulose in which some of the hydroxyl groups are replaced with methyl ethers, 2-hydroxypropyl ethers, or phthalyl esters. Several different types of hypromellose phthalate are commercially available with molecular weights in the range 20 000–200 000. Typical average values are 80 000–130 000.[1]

5 Structural Formula



6 Functional Category

Coating agent.

7 Applications in Pharmaceutical Formulation or Technology

Hypromellose phthalate is widely used in oral pharmaceutical formulations as an enteric coating material for tablets or granules.[2–8] Hypromellose phthalate is insoluble in gastric fluid but will swell and dissolve rapidly in the upper intestine. Generally, concentrations of 5–10% of hypromellose phthalate are employed with the material being dissolved in either a dichloromethane : ethanol (50 : 50) or an ethanol : water (80 : 20) solvent mixture. Hypromellose phthalate can normally be applied to tablets and granules without the addition of a plasticizer or other film formers, using established coating techniques. However, the addition of a small amount of plasticizer or water can avoid film cracking problems; many commonly used plasticizers, such as diacetin, triacetin, diethyl and dibutyl phthalate, castor oil, acetyl monoglyceride, and polyethylene glycols, are compatible with hypromellose phthalate. Tablets coated with hypromellose phthalate disintegrate more rapidly than tablets coated with cellulose acetate phthalate.

Hypromellose phthalate can be applied to tablet surfaces using a dispersion of the micronized hypromellose phthalate powder in an aqueous dispersion of a suitable plasticizer such as triacetin, triethyl citrate, or diethyl tartrate along with a wetting agent.[9]

Hypromellose phthalate may be used alone or in combination with other soluble or insoluble binders in the preparation of granules with sustained drug-release properties; the release rate is pH-dependent. Since hypromellose phthalate is tasteless and insoluble in saliva, it can also be used as a coating to mask the unpleasant taste of some tablet formulations.

8 Description

Hypromellose phthalate occurs as white to slightly off-white, free-flowing flakes or as a granular powder. It is odorless or with a slightly acidic odor and has a barely detectable taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for hypromellose phthalate.

Test	JP 2001	PhEur 2002	USPNF 20
Identification	+	+	+
Characters	—	+	—
Water	≤5.0%	≤5.0%	≤5.0%
Viscosity (20°C)	+	—	+
Residue on ignition	≤0.20%	≤0.20%	≤0.20%
Chloride	≤0.07%	≤0.07%	≤0.07%
Heavy metals	≤10 ppm	≤10 ppm	≤0.001%
Free phthalic acid	≤1.0%	≤1.0%	≤1.0%
Organic volatile impurities	—	—	+
Phthalyl content	—	21.0–35.0%	21.0–35.0%
Type 200731	27.0–35.0%	—	—
Type 220824	21.0–27.0%	—	—

10 Typical Properties

Angle of repose:
37° for *HP-50*
39° for *HP-55*
38° for *HP-55S*[10]

Density:
1.82 g/cm^3 for *HP-50*
1.65 g/cm^3 for *HP-55*

Density (bulk):
0.278 g/cm^3 for *HP-50*
0.275 g/cm^3 for *HP-55*
0.239 g/cm^3 for *HP-55S*

Density (tapped):
0.343 g/cm^3 for *HP-50*
0.306 g/cm^3 for *HP-55*
0.288 g/cm^3 for *HP-55S*[10]

Melting point: 150°C. Glass transition temperature is 137°C for *HP-50* and 133°C for *HP-55*.[11]

Moisture content: hypromellose phthalate is hygroscopic; it takes up 2–5% of moisture at ambient temperature and humidity conditions. For the moisture sorption isotherm of *HP-50* measured at 25°C, *see* Figure 1.

Particle size distribution: *see* Figure 2.

Solubility: readily soluble in a mixture of acetone and methyl or ethyl alcohol (1 : 1), in a mixture of methyl alcohol and dichloromethane (1 : 1), and in aqueous alkali. Practically insoluble in water and dehydrated alcohol and very slightly soluble in acetone. The solubilities of the *HP-50* and *HP-55* grades, in various solvents and solvent mixtures, are shown in Table II.[10]

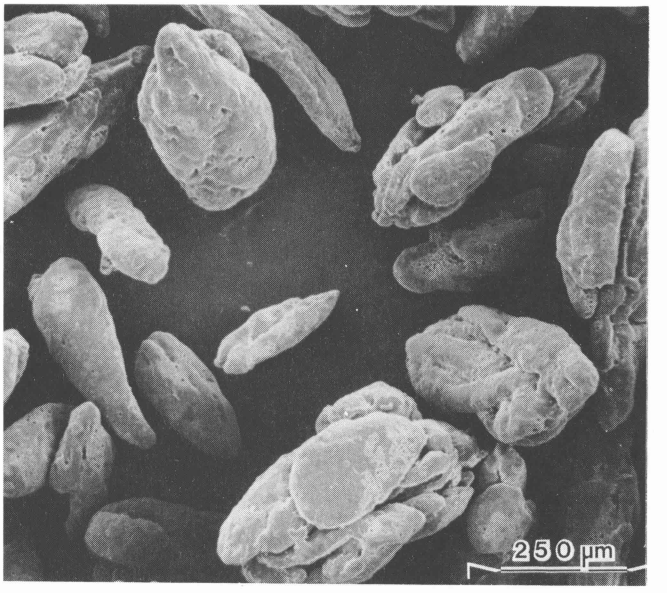
Viscosity: *see* Figures 3 and 4.

Table II: Solubility of hypromellose *HP-50* and *HP-55* (Shin-Etsu Chemical Co. Ltd.).

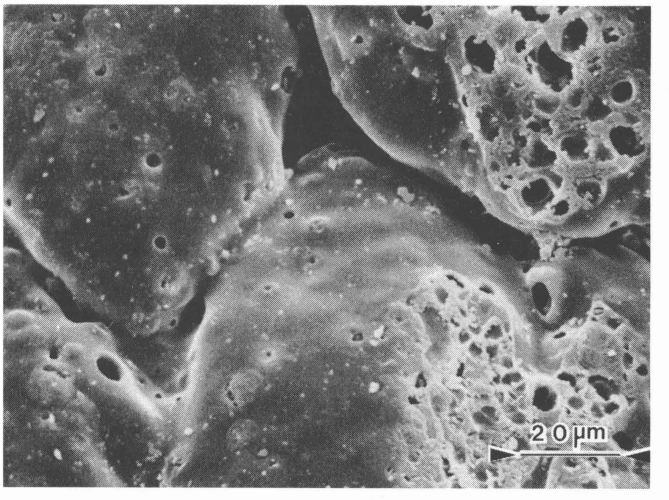
Solvent	Solubility	
	HP-50	*HP-55*
Acetone	S/I	S
Acetone : dichloromethane	S/I	S
Acetone : ethanol	S/S	S
Acetone : methanol	S	S
Acetone : 2-propanol	S/S	S
Acetone : water (95 : 5)	S	S
Benzene : methanol	S	S
Dichloromethane	S/I	S/I
Dichloromethane : ethanol	S	S
Dichloromethane : methanol	S	S
Dichloromethane : 2-propanol	S/S	S
Dioxane	S	S
Ethanol	S/I	S/I
Ethyl acetate	X	S/I
Ethyl acetate : ethanol	S/S	S
Ethyl acetate : methanol	S	S
Ethyl acetate : 2-propanol	S/I	S
Methanol	S/I	S/I
Methyl ethyl ketone	S/I	S
2-Propanol	X	S/I

Note: solubilities are for the pure solvent, or a (1 : 1) solvent mixture, unless otherwise indicated.
S = soluble, clear solution.
S/S = slightly soluble, cloudy solution.
S/I = swells but insoluble.
X = insoluble.

SEM: 1
Excipient: Hypromellose phthalate (*HP-55*)
Manufacturer: Shin-Etsu Chemical Co. Ltd.
Magnification: 60 ×



SEM: 2
Excipient: Hypromellose phthalate (*HP-55*)
Manufacturer: Shin-Etsu Chemical Co. Ltd.
Magnification: 600 ×



11 Stability and Storage Conditions

Hypromellose phthalate is chemically and physically stable at ambient temperature for at least 3–4 years and for 2–3 months at 40°C and 75% relative humidity.[10] It is stable on exposure to UV light for up to 3 months at 25°C and 70% relative humidity. Drums stored in a cool, dry place should be brought to room temperature before opening to prevent condensation of moisture on inside surfaces. After 10 days at 60°C and 100% relative humidity, 8–9% of carbyoxybenzoyl group were hydrolyzed. In general, hypromellose phthalate is more stable than cellulose acetate phthalate. At ambient storage conditions, hypromellose phthalate is not susceptible to microbial attack.

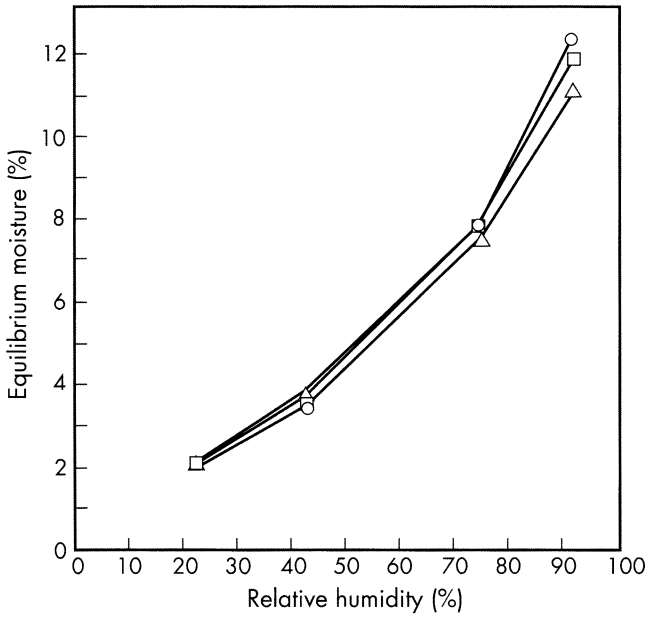


Figure 1: Equilibrium moisture content of hypromellose phthalate (Shin-Etsu Chemical Co. Ltd.) at 25°C.[10]
○: *HP-50*
□: *HP-55*
△: *HP-55S*

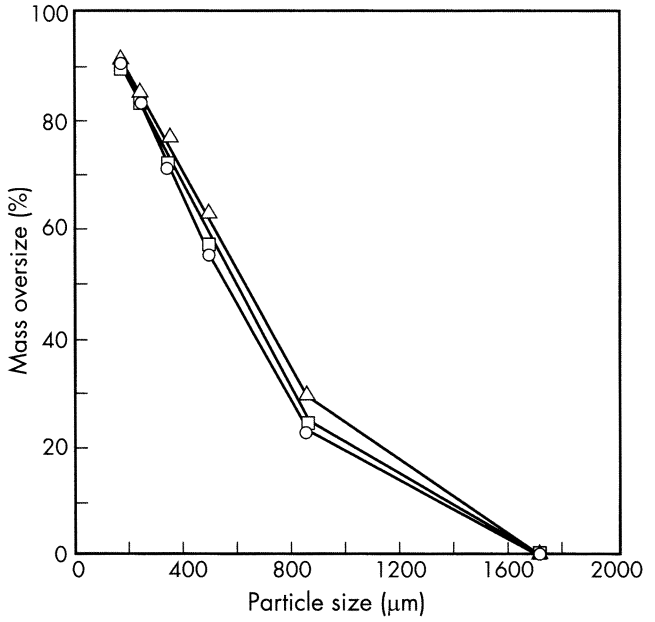


Figure 2: Particle size distribution of hypromellose phthalate (Shin-Etsu Chemical Co. Ltd).[10]
○: *HP-50*
□: *HP-55*
△: *HP-55S*

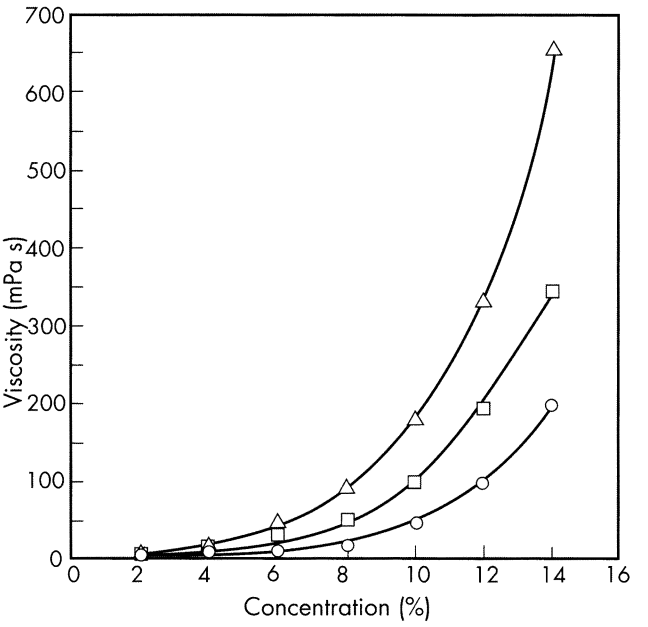


Figure 3: Dynamic viscosity of hypromellose phthalate (*HP-50*) (Shin-Etsu Chemical Co. Ltd.) in various solvent mixtures at 20°C.[10]
○: Acetone : ethanol (1 : 1)
□: Dichloromethane : ethanol (1 : 1)
△: Ethanol : water (1 : 1)

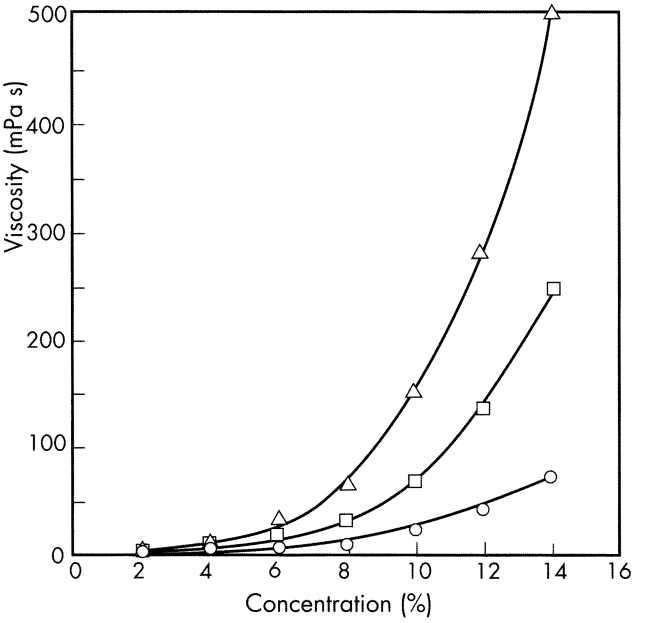


Figure 4: Dynamic viscosity of hypromellose phthalate (*HP-55*) (Shin-Etsu Chemical Co. Ltd.) in various solvent mixtures at 20°C.[10]
○: Acetone : ethanol (1 : 1)
□: Dichloromethane : ethanol (1 : 1)
△: Ethanol : water (8 : 2)

12 Incompatibilities

Incompatible with strong oxidizing agents.

Splitting of film coatings has been reported rarely, most notably with coated tablets that contain microcrystalline

cellulose and calcium carboxymethylcellulose. Film splitting has also occurred when a mixture of acetone : propan-2-ol or dichloromethane : propan-2-ol has been used as the coating solvent, or when coatings have been applied in conditions of low temperature and humidity. However, film splitting may be avoided by careful selection of formulation composition, including solvent, by use of a higher molecular weight grade of polymer, or by suitable selection of plasticizer.

The addition of more than about 10% titanium dioxide to a coating solution of hypromellose phthalate, which is used to produce a colored film coating, may result in coating with decreased elasticity and resistance to gastric fluid.[10]

13 Method of Manufacture

Hypromellose phthalate is prepared by the esterification of hypromellose with phthalic anhydride. The degree of alkyloxy and carboxybenzoyl substitution determines the properties of the polymer and in particular the pH at which it dissolves in aqueous media.

14 Safety

Hypromellose phthalate is widely used, primarily as an enteric coating agent, in oral pharmaceutical formulations. Chronic and acute animal feeding studies on several different species have shown no evidence of teratogenicity or toxicity associated with hypromellose phthalate.[12–16] Hypromellose phthalate is generally regarded as a nonirritant and nontoxic material.

LD_{50} (rat, oral): >15 g/kg[12]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Although no threshold limit value has been set for hypromellose phthalate, it should be handled in a well-ventilated environment and the generation of dust should be minimized.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Cellulose acetate phthalate; hypromellose.

18 Comments

Various grades of hypromellose phthalate are available with differing degrees of substitution and physical properties, e.g., grades *HP-50*, *HP-55*, and *HP-55S* (Shin-Etsu Chemical Co Ltd). *See* Table III.

The number following 'HP' in each grade designation refers to the pH value (× 10) at which the polymer dissolves in aqueous buffer solutions. The designation 'S' in *HP-55S* indicates a higher molecular weight grade, which produces films with a greater resistance to cracking.

Table III: Types of hypromellose phthalate available from Shin-Etsu Chemical Co. Ltd.

Property	Grade of hypromellose phthalate		
	HP-50	HP-55	HP-55S
Substitution type	220824	200731	200731
Hydroxypropoxy content	6–10%	5–9%	5–9%
Methoxy content	20–24%	18–22%	18–22%
Phthalyl content	21–27%	27–35%	27–35%
Molecular weight	84 000	78 000	132 000

In the USA, the substitution type is indicated by a six digit number: the first two digits represent the approximate percentage content of methoxy groups; the next two digits represent the approximate percentage content of hydroxypropoxy groups; and the final two digits represent the approximate percentage content of phthalyl groups.

To dissolve hypromellose phthalate in acetone : alcohol or dichloromethane : alcohol solvent systems, the hypromellose phthalate should first be well dispersed in alcohol before adding acetone or dichloromethane. When using acetone : dichloromethane, hypromellose phthalate should be first dispersed in the dichloromethane and then the acetone added to the system.

19 Specific References

1 Rowe RC. Molecular weight studies on hydroxypropyl methylcellulose phthalate (HP55). *Acta Pharm Technol* 1982; **28**(2): 127–130.
2 Ehrhardt L, Patt L, Schindler E. Optimization of film coating systems [in German]. *Pharm Ind* 1973; **35**: 719–722.
3 Delporte JP, Jaminet F. Influence of formulation of enteric coated tablets on the bioavailability of the drug [in French]. *J Pharm Belg* 1976; **31**: 263–276.
4 Patt L, Hartmann V. Solvent residues in film forming agents [in German]. *Pharm Ind* 1976; **38**: 902–906.
5 Stafford JW. Enteric film coating using completely aqueous dissolved hydroxypropyl methyl cellulose phthalate spray solutions. *Drug Dev Ind Pharm* 1982; **8**: 513–530.
6 Thoma K, Heckenmüller H, Oschmann R. Resistance and disintegration behaviour of gastric juice resistant drugs [in German]. *Pharmazie* 1987; **42**: 832–836.
7 Thoma K, Heckenmüller H. Impact of film formers and plasticizers on stability of resistance and disintegration behaviour [in German]. *Pharmazie* 1987; **42**: 837–841.
8 Takada K, Oh-Hashi M, Furuya Y, *et al.* Enteric solid dispersion of ciclosporin A (CiA) having potential to deliver CiA into lymphatics. *Chem Pharm Bull* 1989; **37**: 471–474.
9 Muhammad NA, Boisvert W, Harris MR, Weiss J. Evaluation of hydroxypropyl methylcellulose phthalate 50 as film forming polymer from aqueous dispersion systems. *Drug Dev Ind Pharm* 1992; **18**: 1787–1797.
10 Shin-Etsu Chemical Co. Ltd. Technical literature: *Hydroxypropyl methylcellulose phthalate*, 1993.
11 Sakellariou P, Rowe RC, White EFT. The thermomechanical properties and glass transition temperature of some cellulose derivatives used in film coating. *Int J Pharm* 1985; **27**: 267–277.
12 Kitagawa H, Kawana H, Satoh T, Fukuda Y. Acute and subacute toxicities of hydroxypropyl methylcellulose phthalate. *Pharmacometrics* 1970; **4**(6): 1017–1025.
13 Kitagawa H, Satoh T, Yokoshima T, Nanbo T. Absorption, distribution and excretion of hydroxypropyl methylcellulose phthalate in the rat. *Pharmacometrics* 1971; **5**(1): 1–4.
14 Ito R, Toida S. Studies on the teratogenicity of a new enteric coating material, hydroxypropyl methylcellulose phthalate (HPMCP) in rats and mice. *J Med Soc Toho-Univ* 1972; **19**(5): 453–461.

15 Kitagawa H, Yano H, Fukuda Y. Chronic toxicity of hydroxypropylmethylcellulose phthalate in rats. *Pharmacometrics* 1973; 7(5): 689–701.
16 Kitagawa H, Yokoshima T, Nanbo T, Hasegawa M. Absorption, distribution, excretion and metabolism of ^{14}C-hydroxypropyl methylcellulose phthalate. *Pharmacometrics* 1974; 8(8): 1123–1132.

20 General References

Deasy PB, O'Connell MJM. Correlation of surface characteristics with ease of production and *in vitro* release of sodium salicylate from various enteric coated microcapsules prepared by pan coating. *J Micoencapsul* 1984; **1**(3): 217–227.
Doelker E. Cellulose derivatives. *Adv Polym Sci* 1993; **107**: 199–265.
Rowe RC. Materials used in the film coating of oral dosage forms. In: Florence AT, ed. *Critical Reports on Applied Chemistry,* vol. 6. Oxford: Blackwell Scientific, 1984: 1–36.
Sertsou G, Butler J, Hempenstall J, Rades T. Solvent change co-precipitation with hydroxypropyl methylcellulose phthalate to improve dissolution characteristics of a poorly water-soluble drug. *J Pharm Pharmacol* 2002; **54**: 1041–1047.

21 Authors

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