

Handbook of Pharmaceutical Excipients

Eighth edition

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Cellulose Acetate Phthalate

1 Nonproprietary Names

BP: Cellacefat

JP: Cellacefat

PhEur: Cellulose Acetate Phthalate

USP–NF: Cellacefat

2 Synonyms

Acetyl phthalyl cellulose; *Aquacoat CPD*; CAP; cellacefat; cellulose acetate benzene-1,2-dicarboxylate; cellulose acetate hydrogen 1,2-benzenedicarboxylate; cellulose acetate hydrogen phthalate; cellulose acetate monophthalate; cellulose acetophthalate; cellulose acetylphthalate; cellulose acetate phthalas.

3 Chemical Name and CAS Registry Number

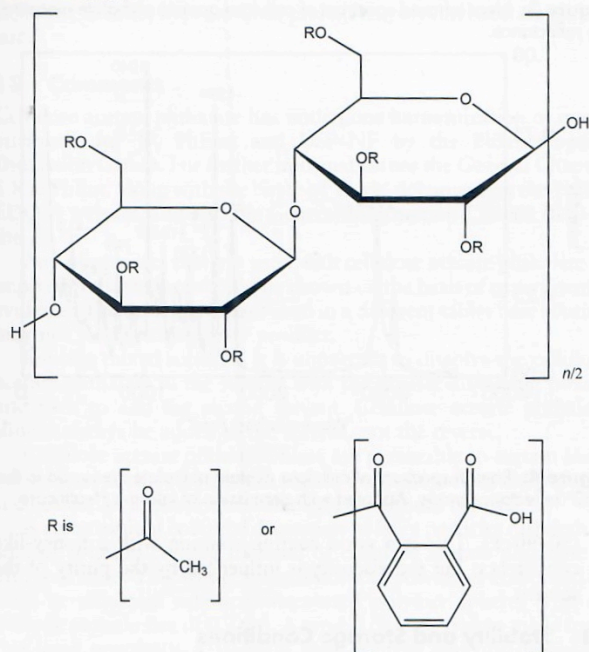
Cellulose, acetate, 1,2-benzenedicarboxylate [9004-38-0]

4 Empirical Formula and Molecular Weight

Cellulose acetate phthalate is a cellulose in which some of the hydroxyl groups are acetylated and some are phthalylated.

5 Structural Formula

Cellulose acetate phthalate is a reaction product of phthalic anhydride and a partial acetate ester of cellulose. It contains 21.5–26.0% of acetyl (C_2H_3O) groups and 30.0–36.0% of phthalyl (*o*-carboxybenzoyl, $C_8H_5O_3$) groups, calculated on the anhydrous acid-free basis.



6 Functional Category

Coating agent; microencapsulating agent; tablet and capsule binder.

7 Applications in Pharmaceutical Formulation or Technology

Cellulose acetate phthalate is used as an enteric film-coating material, as a microencapsulation agent, or as a matrix binder for tablets and capsules.^(1–8) Such coatings resist prolonged contact with the strongly acidic gastric fluid, but dissolve in the mildly acidic or neutral intestinal environment.

Cellulose acetate phthalate is commonly applied to solid-dosage forms either by coating from organic or aqueous solvent systems, or by direct compression. Concentrations generally used are 0.5–9.0% of the core weight. The addition of plasticizers improves the water resistance of this coating material, and formulations using such plasticizers are more effective than when cellulose acetate phthalate is used alone.

Cellulose acetate phthalate is compatible with many plasticizers, including acetylated monoglyceride; butyl phthalylbutyl glycolate; dibutyl tartrate; diethyl phthalate; dimethyl phthalate; ethyl phthalylethyl glycolate; glycerin; propylene glycol; triacetin; triacetin citrate; and tripropionin. It is also used in combination with other coating agents such as ethyl cellulose in controlled-release preparations.

8 Description

Cellulose acetate phthalate occurs as a hygroscopic, white to off-white, free-flowing powder, granule, or flake. It is tasteless and odorless, or might have a slight odor of acetic acid.

9 Pharmacopeial Specifications

The pharmacopeial specifications for cellulose acetate phthalate have undergone harmonization of many attributes for JP, PhEur, and USP–NF.

See Table I. See also Section 18.

Table I: Pharmacopeial specifications for cellulose acetate phthalate.

Test	JP XVII	PhEur 9.2	USP 40–NF 35 S1
Identification	+	+	+
Characters ^(a)	+	+	—
Free acid	≤3.0%	≤3.0%	≤3.0%
Heavy metals ^(a)	≤10 ppm	—	≤0.001%
Residue on ignition	≤0.1%	—	≤0.1%
Sulfated ash	—	≤0.1%	—
Viscosity (15% w/v solution)	45–90 mPa s	45.0–90.0 mPa s	45.0–90.0 mPa s
Water	≤5.0%	≤5.0%	≤5.0%
Assay	+	+	+
Acetyl groups	21.5–26.0%	21.5–26.0%	21.5–26.0%
Phthalyl (<i>o</i> -carboxybenzoyl) groups	30.0–36.0%	30.0–36.0%	30.0–36.0%

(a) These tests have not been fully harmonized at the time of publication.

10 Typical Properties

Density (bulk) 0.260 g/cm³

Density (tapped) 0.266 g/cm³

Melting point 192°C. Glass transition temperature is 160–170°C.⁽⁹⁾

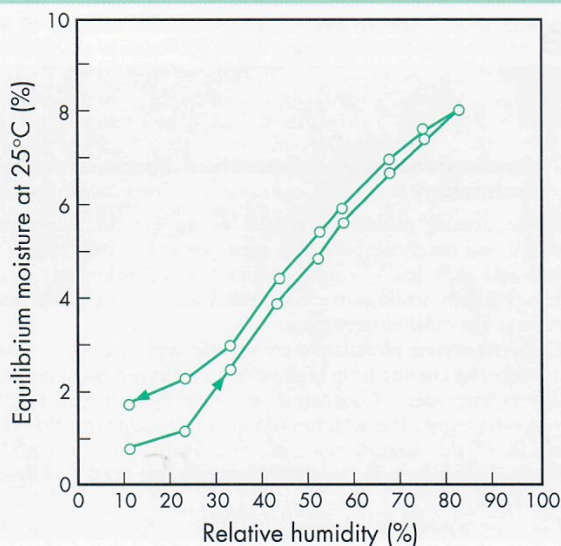


Figure 1: Sorption-desorption isotherm of cellulose acetate phthalate.

Moisture content Cellulose acetate phthalate is hygroscopic and precautions are necessary to avoid excessive absorption of moisture. Equilibrium moisture content has been reported as 2.2%, but moisture content is a function of relative humidity.⁽¹⁰⁾ See also Figure 1.

Solubility Practically insoluble in water, alcohols, and chlorinated and nonchlorinated hydrocarbons. Soluble in a number of ketones, esters, ether alcohols, cyclic ethers, and in certain solvent mixtures. It can be soluble in certain buffered aqueous solutions as low as pH 6.0. Cellulose acetate phthalate has a solubility of $\leq 10\%$ w/w in a wide range of solvents and solvent mixtures; see Table II and Table III.

Table II: Examples of solvents with which cellulose acetate phthalate has $\leq 10\%$ w/w solubility.

Acetone
Diacetone alcohol
Dioxane
Ethoxyethyl acetate
Ethyl glycol monoacetate
Ethyl lactate
Methoxyethyl acetate
 β -Methoxyethylene alcohol
Methyl acetate
Methyl ethyl ketone

Table III: Examples of solvent mixtures with which cellulose acetate phthalate has $\leq 10\%$ w/w solubility.

Acetone : ethanol (1 : 1)
Acetone : water (97 : 3)
Benzene : methanol (1 : 1)
Ethyl acetate : ethanol (1 : 1)
Methylene chloride : ethanol (3 : 1)

Spectroscopy

IR spectrum see Figure 2.

NIR spectrum see Figure 3.

Raman spectrum see Figure 4.

Viscosity (dynamic) A 15% w/w solution in acetone with a moisture content of 0.4% has a viscosity of 50–90 mPa s

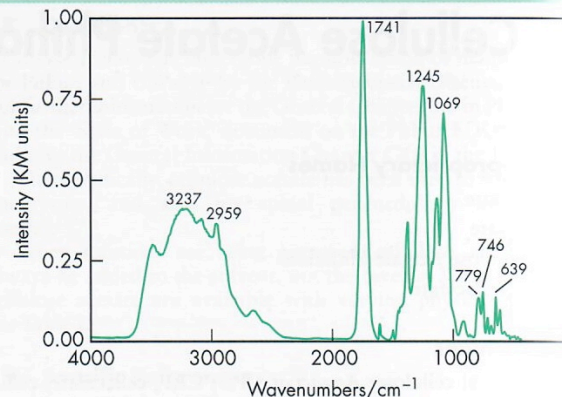


Figure 2: Infrared spectrum of cellulose acetate phthalate measured by diffuse reflectance. Adapted with permission of Informa Healthcare.

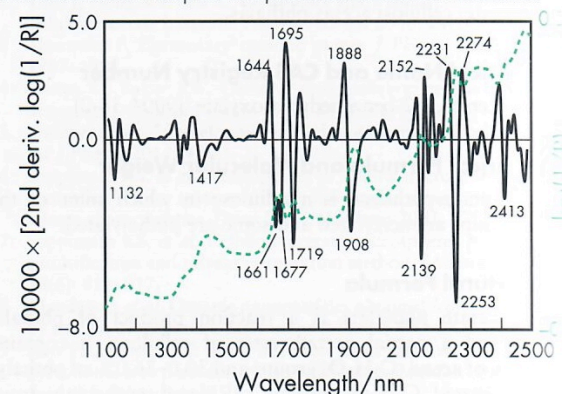


Figure 3: Near-infrared spectrum of cellulose acetate phthalate measured by reflectance.

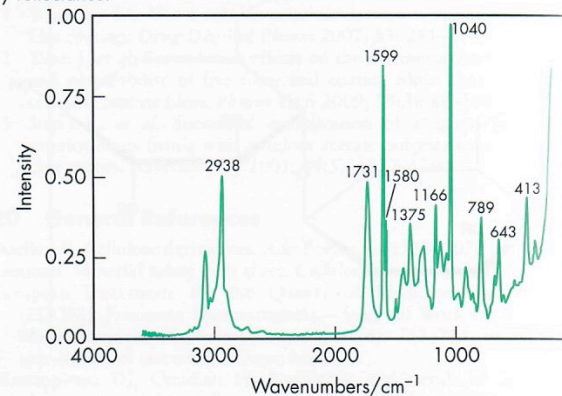


Figure 4: Raman spectrum of cellulose acetate phthalate measured in 180° reflectance mode. Adapted with permission of Informa Healthcare.

(50–90 cP). This is a good coating solution with a honey-consistency, but the viscosity is influenced by the purity of the solvent.

11 Stability and Storage Conditions

Slow hydrolysis of cellulose acetate phthalate will occur under prolonged adverse conditions such as high temperatures and high humidity, with a resultant increase in free acid content, viscosity, and odor of acetic acid. However, cellulose acetate phthalate is stable if stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Cellulose acetate phthalate is incompatible with ferrous sulfate, ferric chloride, silver nitrate, sodium citrate, aluminum sulfate, calcium chloride, mercuric chloride, barium nitrate, basic lead acetate, and strong oxidizing agents such as strong alkalis and acids.

13 Method of Manufacture

Cellulose acetate phthalate is produced by a reaction between the partial acetate ester of cellulose and phthalic anhydride in the presence of a tertiary organic base such as pyridine, or a strong acid such as sulfuric acid.

14 Safety

Cellulose acetate phthalate is widely used in oral pharmaceutical products and is generally regarded as a nontoxic material, free of adverse effects. However, it may be irritant to the eyes, mucous membranes, and upper respiratory tract.

Results of long-term feeding in rats and dogs have indicated a low oral toxicity. Rats survived daily feedings of up to 30% in the diet for up to 1 year without showing a depression in growth. Dogs fed 16 g daily in the diet for 1 year remained normal.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Cellulose acetate phthalate should be handled in a well-ventilated environment; use of a respirator is recommended when handling large quantities. Eye protection and gloves are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (oral tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian Natural Health Products Ingredients Database.

17 Related Substances

Cellulose acetate; hypromellose phthalate; polyvinyl acetate phthalate.

18 Comments

Cellulose acetate phthalate has undergone harmonization of many attributes for JP, PhEur, and USP–NF by the Pharmacopeial Discussion Group. For further information see the General Chapter 5.8 in PhEur, along with the ‘State of Work’ document on the PhEur EDQM website, and also the General Information Chapter G10 in the JP.

Any plasticizers that are used with cellulose acetate phthalate to improve performance should be chosen on the basis of experimental evidence. The same plasticizer used in a different tablet base coating may not yield a satisfactory product.

In using mixed solvents, it is important to dissolve the cellulose acetate phthalate in the solvent with the greater dissolving power, and then to add the second solvent. Cellulose acetate phthalate should always be added to the solvent, not the reverse.

Cellulose acetate phthalate films are permeable to certain ionic substances, such as potassium iodide and ammonium chloride. In such cases, an appropriate sealer subcoat should be used.

A reconstituted colloidal dispersion of latex particles rather than solvent solution coating material of cellulose acetate phthalate is also available. This white, water-insoluble powder is composed of solid or semisolid submicrometer-sized polymer spheres with an average particle size of 0.2 μm . A typical coating system made from this latex powder is a 10–30% solid-content aqueous dispersion with a viscosity in the 50–100 mPa s (50–100 cP) range.

Therapeutically, cellulose acetate phthalate has been reported to exhibit experimental microbicidal activity against sexually transmitted disease pathogens, such as the HIV-1 retrovirus.^(11,12)

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21 Author

ME Quinn.

22 Date of Revision

4 May 2017.

Hypromellose Phthalate

1 Nonproprietary Names

BP: Hypromellose Phthalate
JP: Hypromellose Phthalate
PhEur: Hypromellose Phthalate
USP–NF: Hypromellose Phthalate

2 Synonyms

Cellulose phthalate hydroxypropyl methyl ether; *Deepcoat*; *HPMCP*; hydroxypropyl methylcellulose benzene-1,2-dicarboxylate; 2-hydroxypropyl methylcellulose phthalate; hypromellose phthalate; *Mantrocel HP-55*; methylhydroxypropylcellulose phthalate.

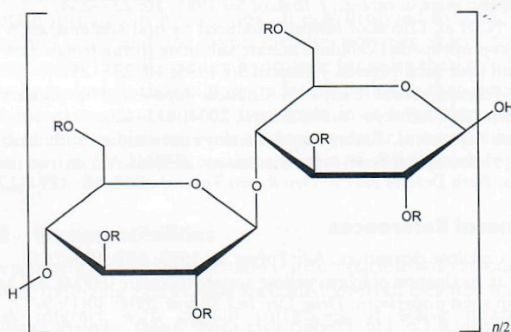
3 Chemical Name and CAS Registry Number

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

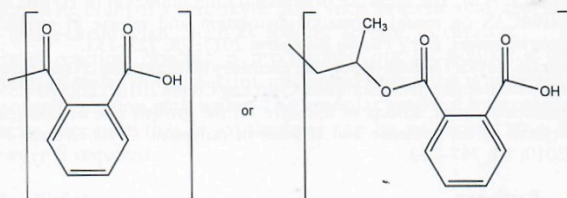
4 Empirical Formula and Molecular Weight

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



R = H, CH₃, CH₂CH(OH)CH₃,



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 together 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. Hypromellose phthalate has also been co-precipitated with a poorly soluble drug to improve dissolution characteristics.⁽¹⁰⁾

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

The pharmacopeial specifications for hypromellose phthalate have undergone harmonization of many attributes for JP, PhEur, and USP–NF.

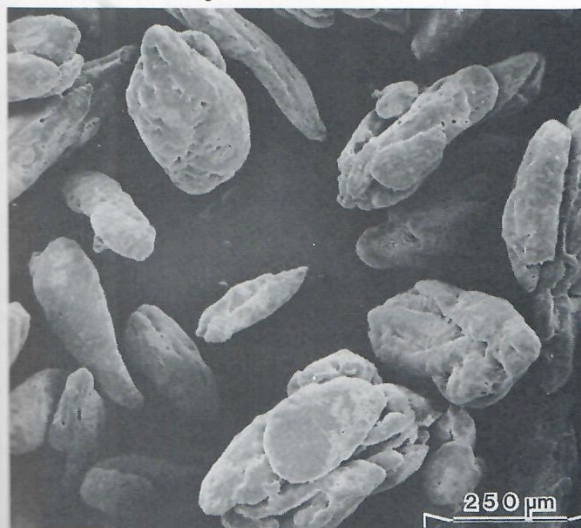
See Table I. See also Section 18.

Table I: Pharmacopeial specifications for hypromellose phthalate.

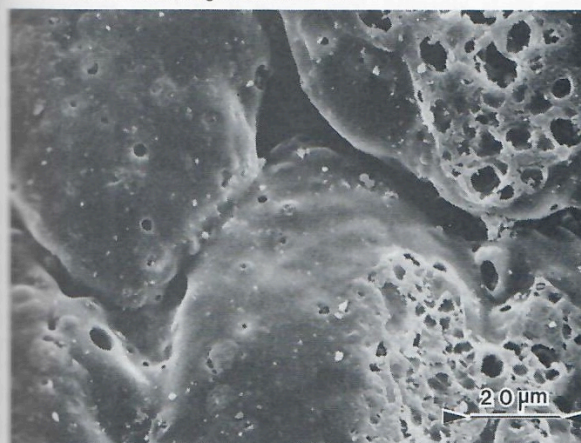
Test	JP XVII	PhEur 9.2	USP 40–NF 35 S1
Identification	+	+	+
Characters	–	+	–
Water	≤5.0%	≤5.0%	≤5.0%
Viscosity (20°C)	+	+	+
Residue on ignition	≤0.2%	≤0.2%	≤0.2%
Chloride	≤0.07%	≤0.07%	≤0.07%
Heavy metals ^(a)	≤10 ppm	–	≤0.001%
Free phthalic acid	≤1.0%	≤1.0%	≤1.0%
Phthalyl content	+	21.0–35.0%	21.0–35.0%
Type 200731	27.0–35.0%	–	–
Type 220824	21.0–27.0%	–	–

[a] This test has not been fully harmonized at the time of publication.

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×.



10 Typical Properties

Angle of repose

- 37° for HP-50;
- 39° for HP-55;
- 38° for HP-55S.⁽¹¹⁾

Density

- 1.82 g/cm³ for HP-50;
- 1.65 g/cm³ for HP-55.⁽¹¹⁾

Density (bulk)

- 0.278 g/cm³ for HP-50;
- 0.275 g/cm³ for HP-55;
- 0.239 g/cm³ for HP-55S.⁽¹¹⁾

Density (tapped)

- 0.343 g/cm³ for HP-50;
- 0.306 g/cm³ for HP-55;
- 0.288 g/cm³ for HP-55S.⁽¹¹⁾

Melting point 150°C. Glass transition temperature is 137°C for HP-50 and 133°C for HP-55.⁽¹²⁾

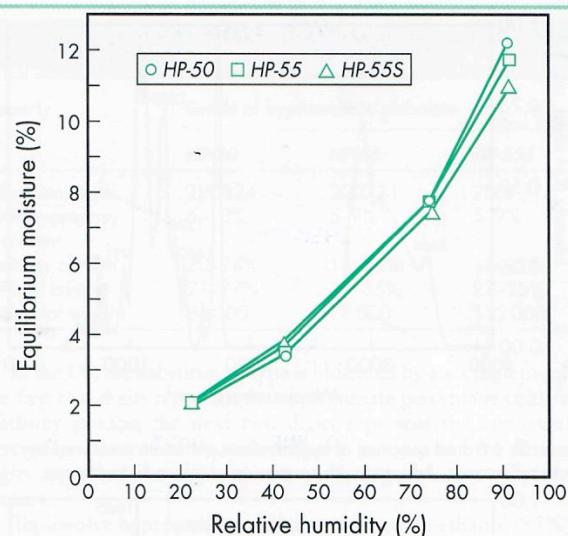


Figure 1: Equilibrium moisture content of hypromellose phthalate (Shin-Etsu Chemical Co. Ltd) at 25°C.⁽¹¹⁾

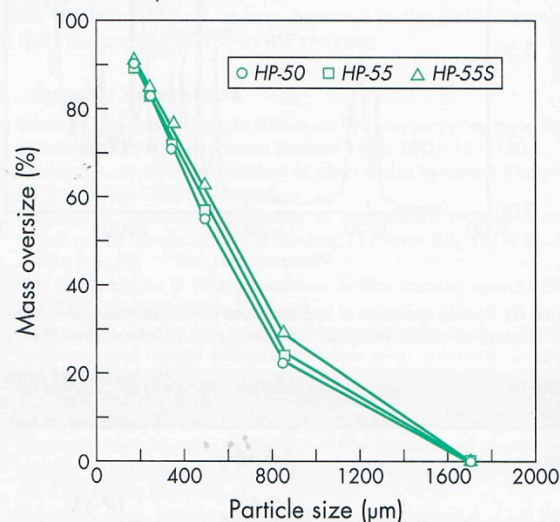


Figure 2: Particle size distribution of hypromellose phthalate (Shin-Etsu Chemical Co. Ltd).⁽¹¹⁾

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.⁽¹¹⁾

Spectroscopy

IR spectrum see Figure 3.

Raman spectrum see Figure 4.

Viscosity see Figures 5 and 6.

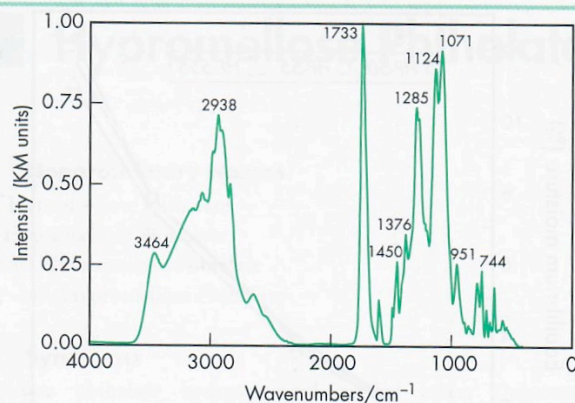


Figure 3: Infrared spectrum of hypromellose phthalate measured by diffuse reflectance. Adapted with permission of Informa Healthcare.

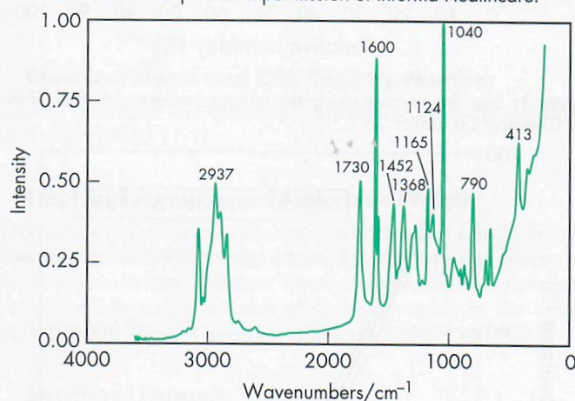


Figure 4: Raman spectrum of hypromellose phthalate measured in the 180° reflectance mode. Adapted with permission of Informa Healthcare.

Table II: Solubility of hypromellose phthalate (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 (95%)	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
Propan-2-ol	X	S/I

Note: solubilities are for the pure solvent, or a (1 : 1) solvent mixture, unless otherwise indicated.

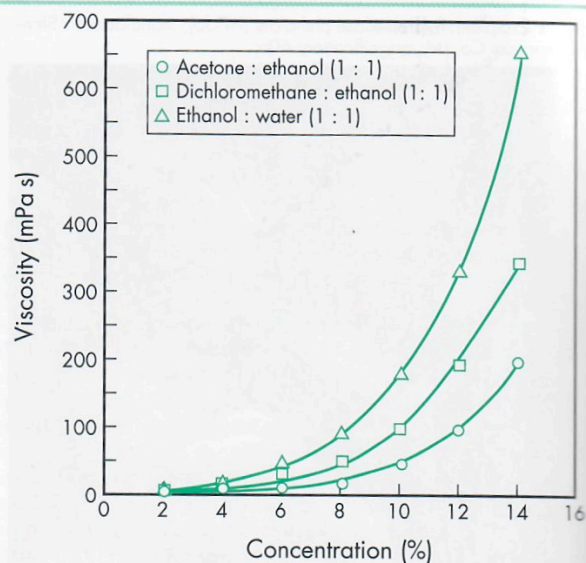


Figure 5: Dynamic viscosity of hypromellose phthalate (HP-50) (Shin-Etsu Chemical Co. Ltd) in various solvent mixtures at 20°C.⁽¹¹⁾

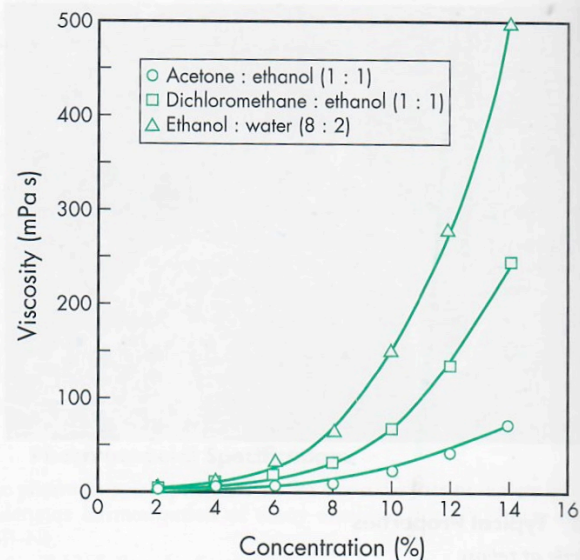


Figure 6: Dynamic viscosity of hypromellose phthalate (HP-55) (Shin-Etsu Chemical Co. Ltd) in various solvent mixtures at 20°C.⁽¹¹⁾

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.⁽¹¹⁾ 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 carboxybenzoyl 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.

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.⁽¹¹⁾

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.⁽¹³⁻¹⁷⁾ Hypromellose phthalate is generally regarded as a nonirritant and nontoxic material.

LD₅₀ (rat, oral): >15 g/kg⁽¹³⁾

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 Database (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian Natural Health Products Ingredients Database.

17 Related Substances

Cellulose acetate phthalate; hypromellose.

18 Comments

Hypromellose phthalate has undergone harmonization of many attributes for JP, PhEur, and USP-NF by the Pharmacopeial Discussion Group. For further information see the General Chapter 5.8 in PhEur, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter G10 in the JP.

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 ($\times 10$) 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 US, 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-ethanol (95%) 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.

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22 Date of Revision

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