Shin-Etsu

Hypromellose Phthalate NF

HPMCP

Enteric Coating Material

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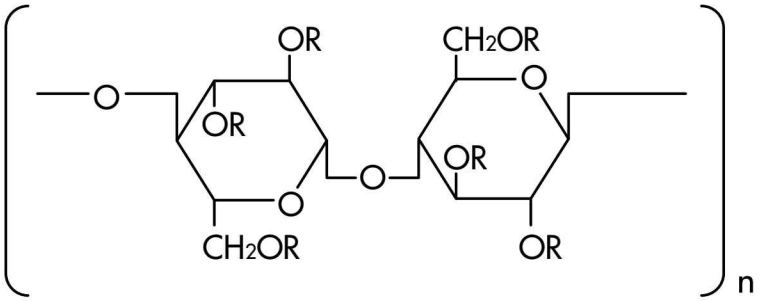
Introduction

An enteric coating agent is used to protect drugs from degradation by gastric acid or to protect gastric mucosa from irritating drugs. HPMCP (Hypromellose Phthalate), since its introduction into the market in 1971 as an alternative cellulose derivative for enteric coating, has been demonstrated to be an effective and safe material by many researchers and is widely used as an enteric coating agent by the pharmaceutical industry. HPMCP has been admitted into the U.S. National Formulary (USP/NF), European Pharmacopoeia (EP), and Japanese Pharmacopoeia (JP).

The chemical structure of HPMCP is a monophthalic acid ester of Hypromellose (hydroxypropyl methylcellulose), and the threshold pH value for rapid disintegration of HPMCP can be controlled by varying the phthalyl content. Two types of HPMCP with different in pH-solubilities, HP-55 and HP-50, are available. Moreover, HP-55S, a special type of HP-55, which is distinguished by its higher molecular weight, greater film strength and higher acid resistance properties, has also been introduced. A suitable grade of HPMCP for a particular purpose should be selected in accordance with each preparation.

We are continuing our effort to improve the quality of our products and to develop new application technologies to satisfy the needs of our customers. Detailed technical information is available in a separate publication, "Technical Information".

Description

Trade name	HPMCP
Generic name	Hypromellose Phthalate (Hydroxypropylmethylcellulose Phthalate)
Abbreviation	HPMCP
IUPAC name	Cellulose, 2-hydroxypropyl methyl ether, hydrogen benzene-1,2-dicarboxylate
CAS RN®	9050-31-1
Compendial status	NF (National Formulary) EP (European Pharmacopoeia) JP (Japanese Pharmacopoeia)
Structure	

R = -H
-CH_3
-$CH_2CH(CH_3)OH$
-COC_6H_4COOH

pH-dissolution mechanism

An enteric coating agent is used to protect drugs from degradation by gastric acid or to protect gastric mucosa from irritating drugs. Thus, an enteric coating agent is insoluble in gastric juice, and it immediately dissolves when the enteric preparation transfers to the small intestine.
HPMCP contains a carboxybenzoyl (phthalyl) group but its backbone structure is a water-soluble polymer (HPMC). The phthalyl group can define the soluble nature of HPMCP, which is insoluble in water due to its hydrophobicity and soluble in weak acid to neutral medium.
Additionally, there is no insolubilization during storage.

The pH-dissolution mechanism of HPMCP is shown in Fig. 1. HPMCP having a phthalyl group in its undissociated form has very low solubility in water due to its hydrophobic nature; as the pH is raised, the equilibrium shifts to the formation of the ionized form with increasing water solubility. Thus, the pH at which HPMCP becomes soluble can be controlled by adjusting the phthalyl content. HP-55 and HP-50 were dissolved at pH around 5.5 and 5.0, respectively.

The pH-dissolution properties of HPMCP depend on the types of buffer solutions differing in ionic strength and electrolyte concentration. HP-55 was dissolved at pH around 5.5 and HP-50 was dissolved at pH around 5.0 (Fig. 2).

Fig. 1 Dissociation of carboxybenzoyl (phthalyl) group

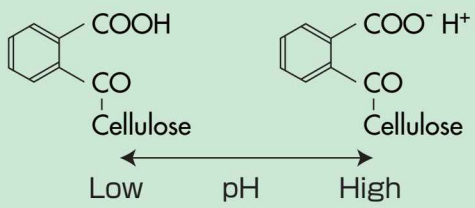
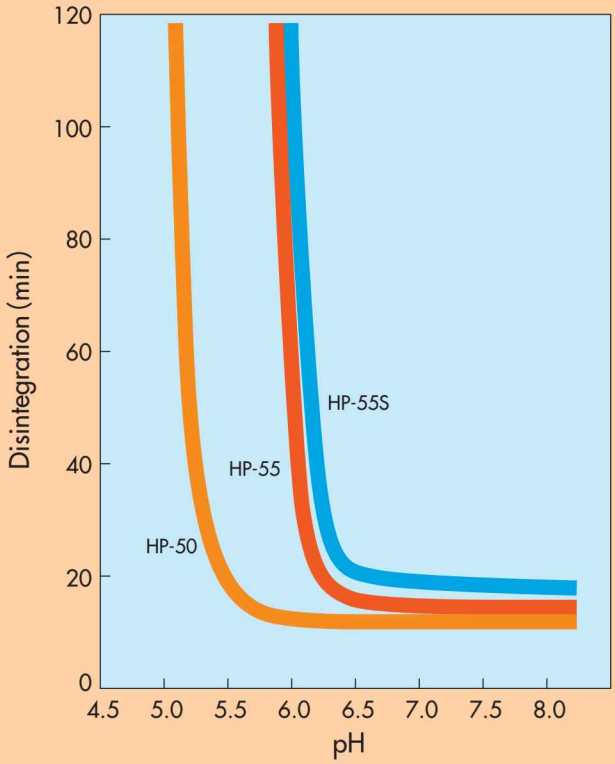


Fig.2 USP Phosphate buffer & USP Phthalate buffer*
[NaOH - KH_2PO_4, NaOH - $C_6H_4(COOH)COOK$]



According to the disintegration test method, dissolution time was measured for cast film from organic solvent solution (thickness: 100 μm; size: 10 × 10 mm)

Solubility

An organic solvent, typically a water-ethanol system, is used for making a coating solution of HPMCP. Solubility in water-ethanol is shown in Fig. 3, and viscosity curves in water-ethanol are shown in Fig. 4. Table 1 shows solubility in other solvents.

The viscosity of the coating solution usually shows 100 mPa·s or less. Thus, a typical polymer concentration for HP-55, HP-50 and HP-55S are 9 %, 8 % and 6 %, respectively.

Fig. 3 Solubility in water-ethanol at 20℃

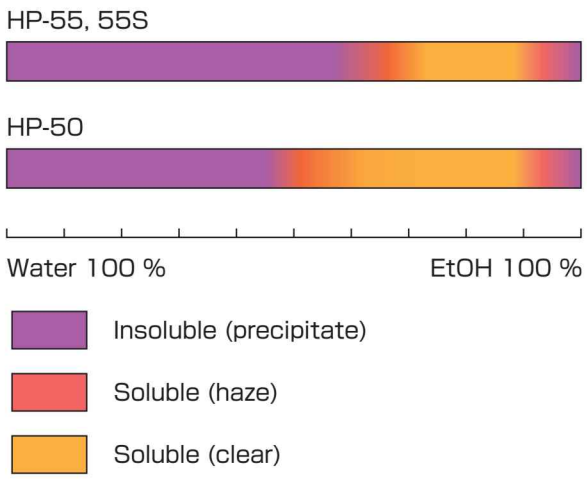
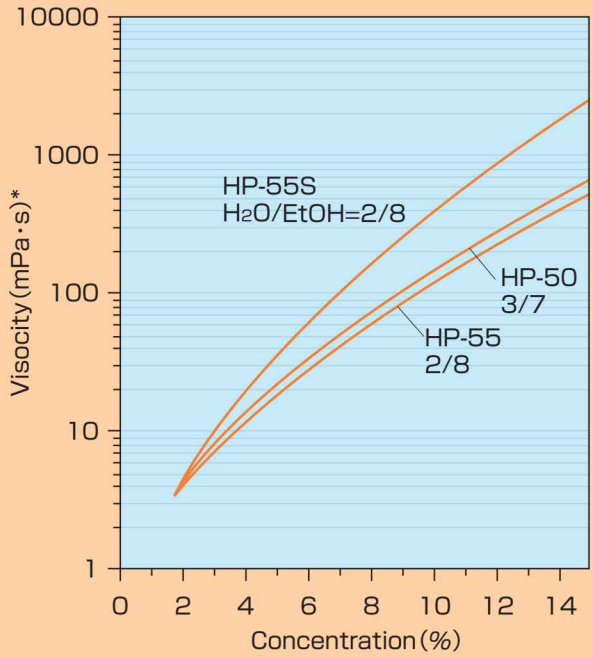


Fig. 4 Viscosity curves in water-ethanol



*Rotating viscometer (Brookfield BL type) at 20℃

Table 1 Solubility in various organic solvents

	HPMCP		Shin-Etsu AQOAT
	HP-55 HP-55S	HP-50	AS-MG
Acetone	○	△	○
Acetone/water (95:5)*	○	○	○
Acetone/ethanol (1:1)*	○	○	○
Dichloromethane	△	△	△
Dichloromethane/ ethanol (1:1)*	○	○	○
Dioxane	○	○	○
Methanol	△	△	○
Isopropanol	△	×	×
Ethanol	×	×	×
Ethanol/water (8:2)*	○	○	○
Ether	×	×	×

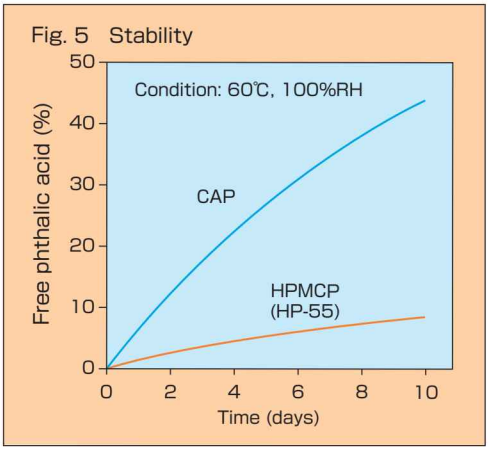
○ : soluble △ : swollen or partially soluble × : insoluble
* : mixing ratio by weight

Stability

Stability of HPMCP powder (Accelerated test under high humidity condition)

HPMCP is known as a highly stable polymer.
However, ester bonding of phthalic acid in the HPMCP structure can release free phthalic acid by hydrolysis under extreme conditions. In the case of 60 ℃ , 100 %RH, Cellacefate (cellulose acetate phthalate; CAP) having the same phthalyl group in the structure showed a faster hydrolysis than that of HPMCP (Fig. 5).

Fig. 5 Stability



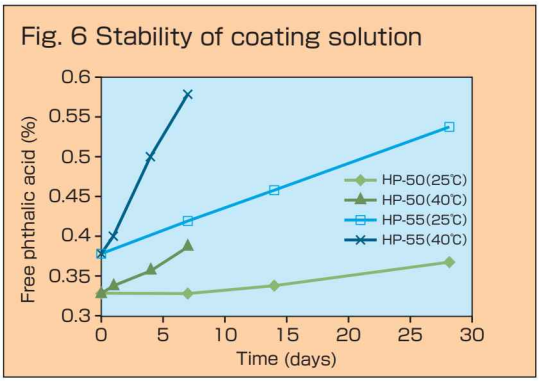
Stability of HPMCP coating solution

Stability of the ethanol-water coating solution of Hypromellose Phthalate (HP-55 and HP-50) was shown in Fig.6. The prepared solutions with below formulation were stored at 25 ℃ and 40 ℃, and free phthalic acid contents were analyzed. At 25 ℃, hydrolysis proceeded moderately slow.

Evaluated solution	
HPMCP (HP-50 or HP-55)	6.7 %
Triethyl citrate	1.3
Ethanol	80
Water	12

Prepared coating solution was stable at 25 ℃

Fig. 6 Stability of coating solution



Stability of coated tablets with HPMCP

Tablets were coated with 8 % of HPMCP (HP-50, HP-55 and HP-55S) and stored at 2 accelerated conditions (50 ℃ with closed bottle and 40 ℃, 75 %RH with opened bottle) for 3 months. The amounts of penetrated quantity of simulated gastric fluid (SGF) for 2 hours were evaluated. The results were shown in Fig. 7 and Fig. 8.

Fig. 7 50 ℃ with closed bottle

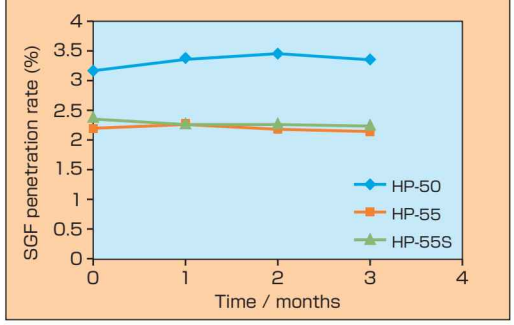
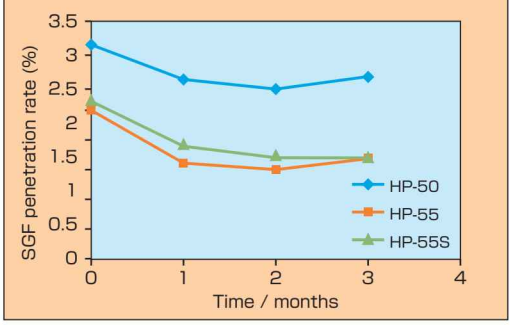


Fig. 8 40 ℃, 75 %RH with opened bottle



The coated tablets with HPMCP were able to maintain the acid resistance for 3 months under 2 accelerated conditions. HPMCP can be recognized as a highly stable polymer.

Directions

Preparation of the coating solution

Preparation of a HPMCP water-ethanol coating solution is according to the following procedure.

1) Disperse HPMCP in ethanol.

2) Add the prescribed amount of water to the dispersion under stirring.

In the case of a direct preparation of the mixed solvent, gradually add HPMCP powder to the mixed solvent to avoid aggregates forming.

The other components of the coating solution

The other components, such as pigment, plasticizer, talc, etc., are added to the HPMCP coating solution, when it is required. Typical components are shown in the following.

Plasticizer

Triethyl citrate is effective, but other plasticizers including cetanol, fats and oils such as castor oil, olive oil and monoglycerides of fatty acids can also be used, alone or in combination. The addition of these plasticizers in the amount of 5 - 10 % (based on HPMCP) may be effective to prevent crack generation in the film or to improve acid resistance.

In the case of a high loading of TiO_2 (more than 10 %) based on the HPMCP, it requires a little higher plasticizer.

Pigment

Pigments such as TiO_2 and lake color are usually used. A remarkable decrease in acid resistance may sometimes occur, especially when TiO_2 is added to HPMCP in an amount of 10 % or more.

Talc

The addition of talc is effective to avoid a sticking problem with pellet coating in the fluidized bed. Normally, the addition level is 10 - 30 %.

Applications

○ Tablet coating

Formulation of the coating solution

HP-55	9.0 %
Ethanol	72.8 %
Purified water	18.2 %

Operating conditions

Machine	New Hi-Coater HCT-48N (Fruend Corp.) Pan size 48 cm
Charge	5 kg of placebo tablet (8 mm, 200 mg)
Pan speed	16 min^{-1}
Spray gun	Air spray gun ATF Nozzle 1.2 mm
Atomizing air	150 l/min, 200 kPa
Drying air	60 ℃
Tablet bed	34 ℃
Exhaust air	37 ℃
Spray feed rate	50 g/min

Results

Spraying time	89 min
Consumption of the coating solution	4444 g (8 % based on 5 kg)
Coating amount	15.2 mg/tab
Coating yield	95 %

Performance of the coated tablet

Acid resistance*1	No change (0/100 tabs)
Fluid uptake*2	2.2 %
Disintegration time*3	7.2 min

*1 According to the disintegration test method using simulated gastric fluid (pH 1.2) with water soluble red dye for 2 hours. After the test, the number of colored defects among the 100 tablets was counted.
*2 After the acid resistance test, average weight increase was measured.
*3 Disintegration time in simulated intestinal fluid (pH 6.8).

pH dependency of disintegration time

pH	McIlvaine's buffer	Clark-Lubs' buffer
4.5	> 120 min	-
4.75	> 120	> 120 min
5.0	> 120	> 120
5.25	62	> 120
5.5	24	78
5.75	14	40
6.0	-	26

Coating experiment of tablet

○ Granule coating

Formulation of the coating solution

HP-55	6.0 %
Talc	1.8 %
Ethanol	73.8 %
Purified water	18.4 %

Operating conditions

Machine	Flow Coater FLO-1 (Fruend Corp.)
Charge	1.5 kg of pancreatin granule
Spray gun	Air spray gun Schlick
	Nozzle 1.2 mm
Gun position	25 cm from the granule bed surface
Atomizing air	200 l/min, 250 kPa
Drying air	75 ℃
Granule bed	50 ℃
Exhaust air	45 ℃
Spray feed rate	50 g/min

Results

Spraying time	125 min
Consumption of the coating solution	
	6250 g
	(25 % as HPMCP based on 1.5 kg)
Coating amount	280 mg/g-granule
Coating yield	86 %

Performance of the coated tablet

Acid resistance*4	4.3 %
Disintegration time	10.1 min
Remaining amylase activity*5	96 %

*4 According to the dissolution test method using simulated gastric fluid (pH 1.2) for 2 hours. After the test, dissolution of the pancreatin protein was measured by UV.

*5 After 1 hour acid resistance test, amylase activity was measured.

Coating experiment of granule

Product Information

Table 2 Grades of HPMCP

Grade	Nominal phthalyl content	Specification of Phthalyl content	Viscosity type	Specification of Viscosity	pH Solubility
HP-50	24 %	21.0～27.0 %	55 mPa・s	44～66 mPa・s	≧ 5.0
HP-55	31 %	27.0～35.0 %	40 mPa・s	32～48 mPa・s	≧ 5.5
HP-55S			170 mPa・s	136～204 mPa・s	

Package

25 kg - Fiber drum with polyethylene double bag inside
1 kg - Polyethylene double bag

Precautions for Safe Handling

Warning: May form flammable or explosive dust-air mixtures.

When handling, avoid accumulation and suspension of dust in the air.
Store away from heat sources, sparks, and flame. Do not permit grinding, welding, or smoking near this material.
General precautions outlined in the National Fire Protection Association's NFPA654 "Standard for the Prevention of Fire and Dust Explosions from the Manufacturing, Processing, and Handling of Combustible Particulate Solids" and NFPA 77 "Recommended Practice on Static Electricity" are recommended.
(Minimum Explosive Dust Concentration: 85 g/m^3, Mukai *et al.,* 1995)

CAUTION: May cause eye irritation.

Avoid contact with eyes, skin and clothing.
Wash thoroughly after handling.
Wash contaminated clothing before re-use.
Use only with adequate exhaust ventilation.
Follow an organized housekeeping plan.
Keep floors and equipment clean.

Emergency and first aid procedures

If inhaled: Remove to fresh air. Give artificial respiration if breathing stops. Get immediate medical attention.
In case of eye contact: Flush eyes with plenty of fresh water while holding eyelids open. Get immediate medical attention.
In case of skin contact: Wash off with flowing water.

In case of material spills and leakages

The following steps should be taken.
- Wear an approved respirator, rubber gloves, rubber boots and safety goggles.
- Vacuum or sweep up spillage. Prevent dustgeneration. Place spillage in an appropriate container for waste disposal.
- Ventilate area and wash spill site.
- Wash contaminated clothing before reuse.

Storage

Keep dry. Store away from excess heat and sunlight. Store in sealed containers.

Disposal

Contents: Dispose of unused contents in accordance with all applicable federal, state and local laws.
Consult the distributor for further information.
Container: Do not re-use container. Dispose of empty container by incineration or the procedures approved by federal, state and local authorities.

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Carefully read and understand the safety data sheet (SDS) before using this product.

N O T E :

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