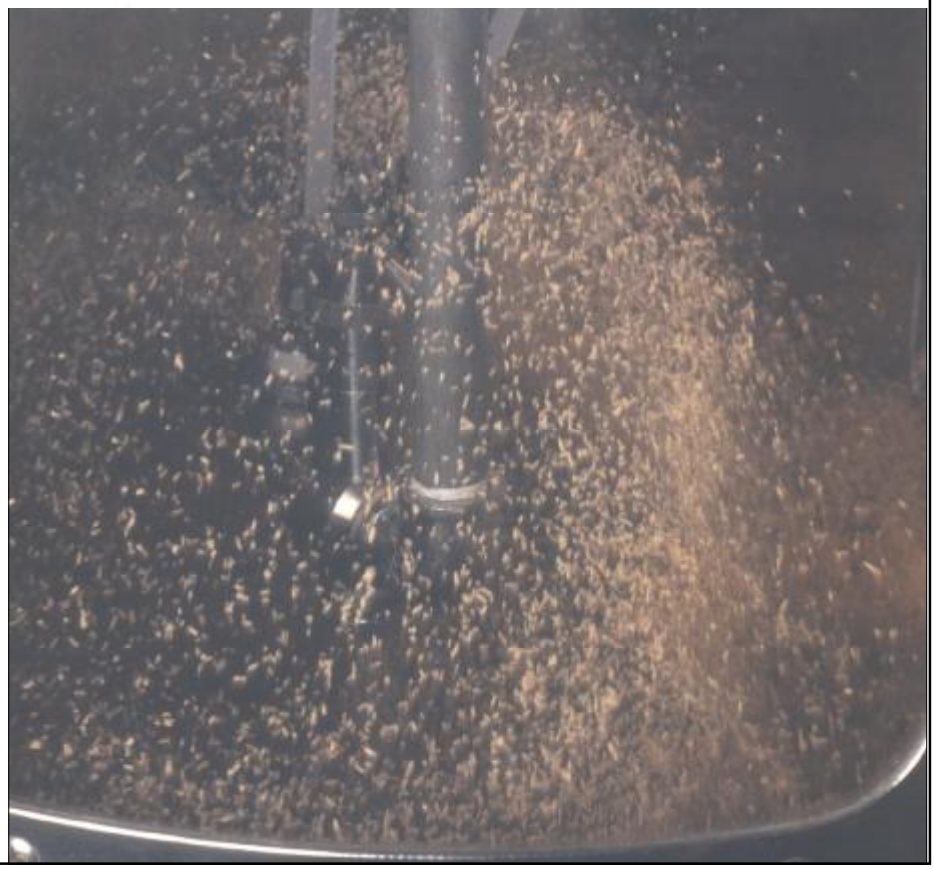
ShinEtsu

USP
Hypromellose Phthalate

HPMCP

Enteric Coating Material



Please note:

- The information and data contained herein are believed to be correct and are given in good faith. However, no liability is accepted therefore, and no warranty or freedom from any patent is to be inferred.
- The general specifications for the products are those in use at the time of printing of this brochure and are subject to change in the future.
- Please contact us if you have any questions or require more information.

An enteric coating agent is used to protect drugs from degradation by gastric acid or to present them from causing side effects in the stomach. HPMCP (hydroxypropyl methylcellulose phthalate) , since its introduction into the market in 1971 as a cellulose derivative for enteric coating, has been demonstrated to be effective 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 (US/NF). European Pharmacopeia (EP), and Japanese Pharmacopeia (JP).

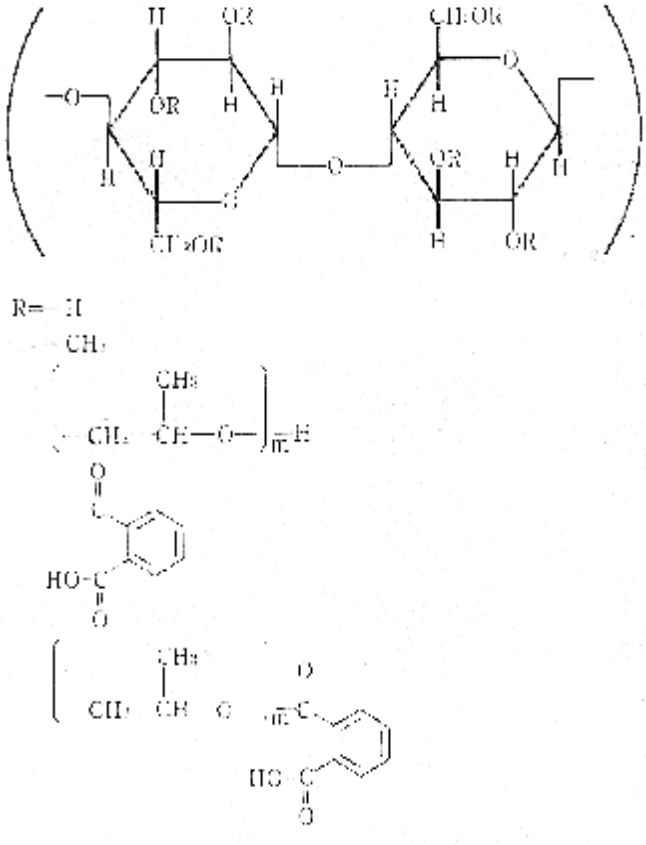
The chemical structure of H PMCP is a phthalic half ester of hvdroxypropyl methylcellulose, and the threshold pH value for rapid disintegration of HPMCP can he controlled by varying the phthalyl content. Two types of HPMCP with different solubility. HP-55 and HP-50, are available. Moreover HP-55S, a special type of HP-55 which is distinguished by its higher molecular weight, higher film strength and higher resistance to simulated gastric fluid, has also been introduced. A suitable grade of HPMCP for a particular purpose should be selected in accordance with the properties of the formulations.

We are continuing our efforts to improve the quality of our products and to develop new application technologies to satisfy the needs of our customers. For further technical information. refer to a separate publication “Technical Information”.

Designation	Hypromellose Phthalate (HPMCP)
Admissions to Compendia	NF, EP, JP
Chemical name	Cellulose, 2-hydroxypropyl methyl ether, phthalic acid ester (CAS 9050-31-1)
Trade name	HPMCP

	Grade	Nominal Phthalyl Content	pH solubility in McIlvaine's Buffer Solution	Labelled Viscosity (cSt)*
HPMCP	50	24%	≧ 5.0	55
	55	31%	≧ 5.5	40
	55S			170

Structural formula



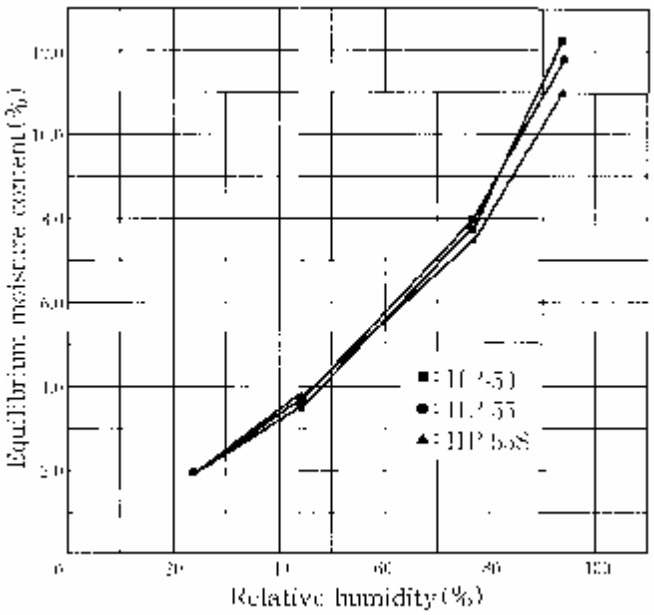
1) True specific gravity 1.28

2) Apparent density 0.20-0.40g/cm^3 tapped

3) Equilibrium moisture content

The relationship between relative humidity and equilibrium moisture content of each type of HPMCP is shown in Fig. 1.

Fig. 1: Relationship between Relative Humidity and Equilibrium Moisture Content at 25°C for Each Type of HPMCP



4) Molecular weight and molecular weight distribution

The weight-average molecular weight (Mw), number-average molecular weight (Mn) and the ratio of Mw to Mn (Mw/Mn) of HPMCP determined by the gel-permeation chromatography (GPC) method are shown in Table 1.

Table 1: Molecular Weight of Each Type of HPMCP Evaluated by GPC

	HP-55	HP-55S	HP-50
$MwX10^{-4}$	8.4	13.2	7.8
$MnX10^{-4}$	2.1	3.6	2.4
Mw/Mn	4.1	4.0	3.3

Note: Polystyrene was used as a standard material

5) Solubility in organic solvents

HPMCP dissolves in many kinds of organic solvents. The solubilities of each type of HPMCP at room temperature in typical organic solvents are compared with those of CAP and Shin-Etsu AQOAT (HPMCAS; Hydroxypropyl Methylcellulose Acetate Succinate) in Table 2. HPMCP is different from CAP in that it is soluble in an ethanol/water mixed solvent.

Table 2 Solubility of HPMCP in Organic Solvent

	HPMCP		Shin-Etsu AQOAT	CAP
	HP-55 HP-55S	HP-50	AS-MG	
Acetone	š	r	š	š
Acetone/water(95:5)*	š	š	š	š
Acetone/ethanol(1:1)*	š	š	š	š
Methylene chloride	r	r	r	r
Methylene chloride/ ethanol(1:1)*	š	š	š	š
Dioxane	š	š	š	š
Methanol	r	r	š	X
Iso-propanol	r	X	X	X
Ethanol (dehydrated)	X	X	X	X
Ethanol/water(8:2)*	š	š	š	X
Ether	X	X	X	X

Note r :soluble š :swelling or partially soluble
X:insoluble *:mixing ratio by weight

6) Properties of HPMCP film

The tensile strength, elongation, surface hardness and water vapour permeability of HPMCP films prepared by the casting method are shown in Table 3. Film of 100 μm in thickness, die-cut in the No.1 dumbbell model, was tested after 3 days of conditioning at 25 C and 50°c relative humidity (RH.). The tests were carried out according to JIS K-6301 under conditions of 25°c and 50% R.H. The water vapour permeability was measured at 25°c and 0-75% R.H. Compared with the other HPMCP types, HP-55S had a higher tensile strength due to its higher degree of polymerization.

Table 3 Mechanical Strength, Surface Hardness and Water Vapour Permeability of HPMCP Film

	Tensile strength (kg/mm^2)	Elongation (%)	Surface hardness (as pencil hardness)	Water vapour permeability (g/m^2 24hr)
HP-55	7.9	5.6	2H-3H	86
HP-55S	8.5	8.3	2H-3H	95
HP-50	7.7	6.1	2H-3H	99

The specifications for HPMCP are listed in Table 4 . HPMCP meets all the requirements of US/NF Hydroxypropyl Methylcellulose Phthalate, EP Hypromellose Phthalate or JP Hydroxypropyl Methyl-cellulose Phthalate.

Shin-Etsu Chemical performs strict quality control to meet GMP guidelines.

Table 4: Specifications of HPMCP

Item/Grade	HP-55	HP-55S	HP-50
Labelled viscosity (cst)	40	170	55
Description and solubility	conforms		
Identification (Infrared Absorption)	conforms		
Viscosity (cst)	32-48	136-204	44-66
Water	not more than 5.0%		
Residue on ignition	not more than 0.20%		
Chloride	not more than 0.07%		
Heavy Metals	not more than 0.001%		
Free phthalic acid	not more than 1.0%		
Phthalyl content	27.0-35.0%		21.0-27.0%
Methoxy content	18.0-22.0%		20.0-24.0%
Hydroxypropoxyl content	5.0-9.0%		6.0-10.0%

The test methods of items 1. through 9. are in accordance with the US/NF monograph for Hypromel-lose Phthalate. Items 10. and 11. are Shin-Etsu specifications in which the test methods are in ac-cordance with the US/NF monograph for Hypromellose .

Although HPMCP was developed and used originally as an enteric coating agent, its favourable properties have led to extension of its range of applications into other fields, including sustained-release preparations, binders and microcapsule bases. In the above-mentioned applications, HPMCP is usually used alone, but can be used in combination with other polymers, as in the case of the sustained-release preparations.
The descriptions of HPMCP given here apply mainly to coating applications.

• Solvents for HPMCP
The following mixed solvents are used in general: methylene chloride/ethanol, acetone/ethanol (1:1 by weight). ethanol/water (8:2 for HP-55, 8.5:1.5 for HP-55S. 7:3 for HP-50 by weight).

• Pigment
Pigments such as titanium dioxide and lakes are usually used. A remarkable decrease in the simulated gastric fluid resistance may sometimes be observed, especially when titanium dioxide is added to HPMCP in an amount of 10 wt. or more (based on HPMCP).

• Plasticizer
Triethyl citrate is effective, but other plasticizers including polyethylene glycol, cetanol, fats and oils such as olive oil, castor 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 wt.% (based on HPMCP) may be effective to delay crack generation in the film or to improve the simulated gastric fluid resistance of the coating agent.

• Others
During the coating operation on granules, the fluidity of particles is often impaired by static electricity. This may be greatly improved by the addition of about 10 wt.% of water to the solvent.

The addition of talc is effective to prevent adhesion of granules and tablets during coating, and may shorten the coating time.

1) Selection of HPMCP type

In selecting the type of HPMCP, it is recommended to take the following points into account

a. HP-55 is applicable as a general enteric coating agent.
b. HP-55S, because of its higher degree of polymerization compared with HP-55, tends to have higher solution viscosity, higher mechanical strength of the film and higher simulated gastric fluid resistance of the coating formulation. These characteristics are effective in reducing the necessary amount for coating and in preventing crack generation in film applied to fragile tablets and granules.
c. HP-5O can be dissolved at a lower pH value and is therefore applicable to preparations which are designed to disintegrate in the upper part of the small intestine.

2) Concentration of coating solution

The optimal concentration of the coating solution is different depending on the type of solvent, coating apparatus, dosage form, etc. However, the concentration ranges shown in Table 5 are generally appropriate for coating.

Table 5: Suitable Concentration Ranges of Coating Solution

Type of Coating/Agent	HP-55 or HP-50	HP-55S
Tabet Coating	6-10 wt.%	5-8 wt.%
Granule Coating	5-7 wt.%	4-6 wt.%

Packaging

- 25kg net: Double layered polythene bag in fibre drum
- 1 kg net: Double layered polythene bag

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