Shin-Etsu

USP

Hypromellose

PHARMACOAT

Film Coating Material and Binder

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.

Film coating was developed as undercoating for sugar coating in the 1950's and film-coated tablets were eventually introduced early in the 1970's. Since then, much development work aimed at increasing the production rate of film-coated tablets and reducing the cost has been done in order to improve the efficiency of pharmaceutical manufacturing, as well as the bioavailability of drugs, and film coating is now a well- established and effective technique.

Shin-Etsu Chemical's PHARMACOAT was developed from hydroxypropyl methylcellulose in 1963, during the early days of film coating, and has been the subject of a continuous program of development and quality improvement since then. Film coatings of this type are now in widespread use throughout the world.

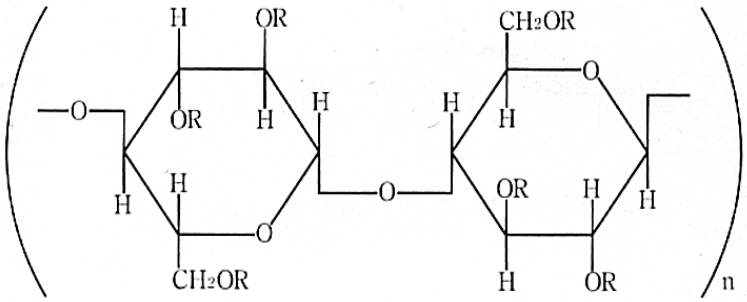
Although drug properties are the key factor in medicinal formulations, the physical font or the finish of a preparation is also important. PHARMACOAT is easy to use as a film coating material and gives an excellent finish. It is very versatile, and is suitable for many applications in the design of film-coated tablet formulations.

In addition, PHARMACOAT is effective as a binder, since it does not interact with drugs, and has superior stability, non-ionic character, etc. PHARMACOAT is widely used as a binder for granulation, and is available in various viscosity grades for granulation purposes.
Shin-Etsu Chemical's PHARMACOAT can make a valuable contribution in various areas of pharmaceutical technology. Detailed technical information is available in a separate publication, "Technical Information".

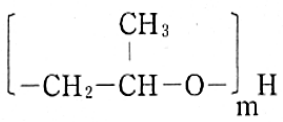
Designation	Hypromellose (Hydroxypropyl Methylcellulose: HPMC) Substitution Type 2910(USP) Substitution Type 2208(USP)
Admissions to Compendia	USP, EP
Chemical name	Cellulose, 2-hydroxypropyl methyl ether (CAS 9004-65-3)
Trade name	Pharmacoat

	Grade			Substitution Type	Labelled Viscosity (cP)*
	Normal Type	Granular Type	White Type		
Pharmacoat	603	-	603W	2910	3
	-	-	645W		4.5
	606	606G	606W		6
	615	-	-		15
	904	-	-	2208	4

Structural formula



R = −H, $-CH_3$ or

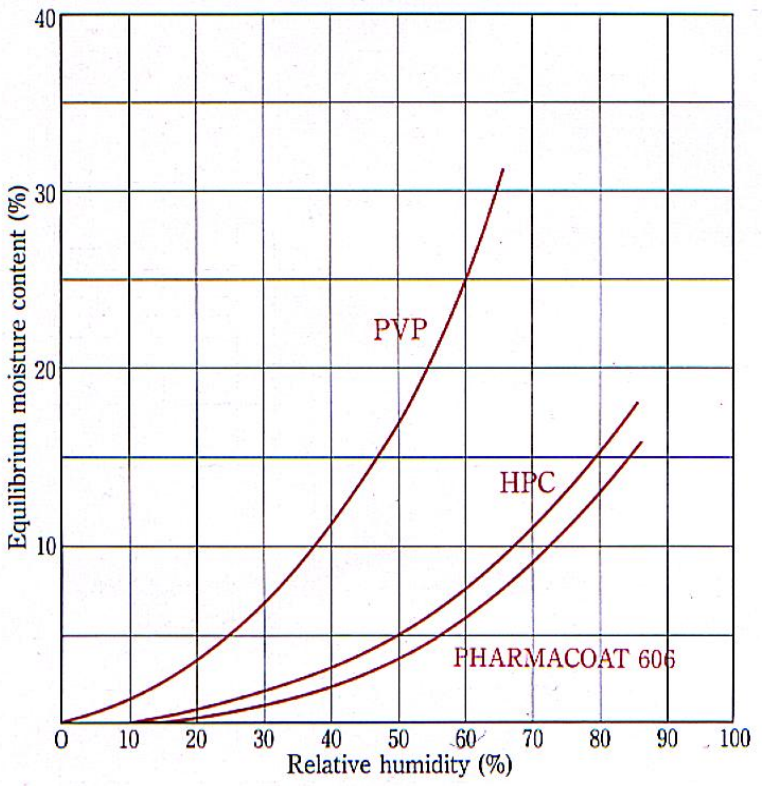


1) Real specific gravity	1.26-1.31
2) Apparent density	0.5-0.7 g/ml (tapped)

3) Equilibrium moisture content

The relationship between relative humidity and equilibrium moisture content of PHARMACOAT, PVP and HPC is shown in Fig. 1. There is no difference in equilibrium moisture content between PHARMACOAT and HPC.

Fig. 1: Relative humidity and equilibrium moisture content at 25°



4) Permeability to moisture

Table 1: Permeability to moisture of film

Material	Moisture permeability
PHARMACOAT 603	207
PHARMACOAT 606	194
PHARMACOAT 615	192

unit: $g/m^2 \cdot 24$ hr-0~75% difference in RH
25°C, 0.1 mm thickness

5) Viscometric properties

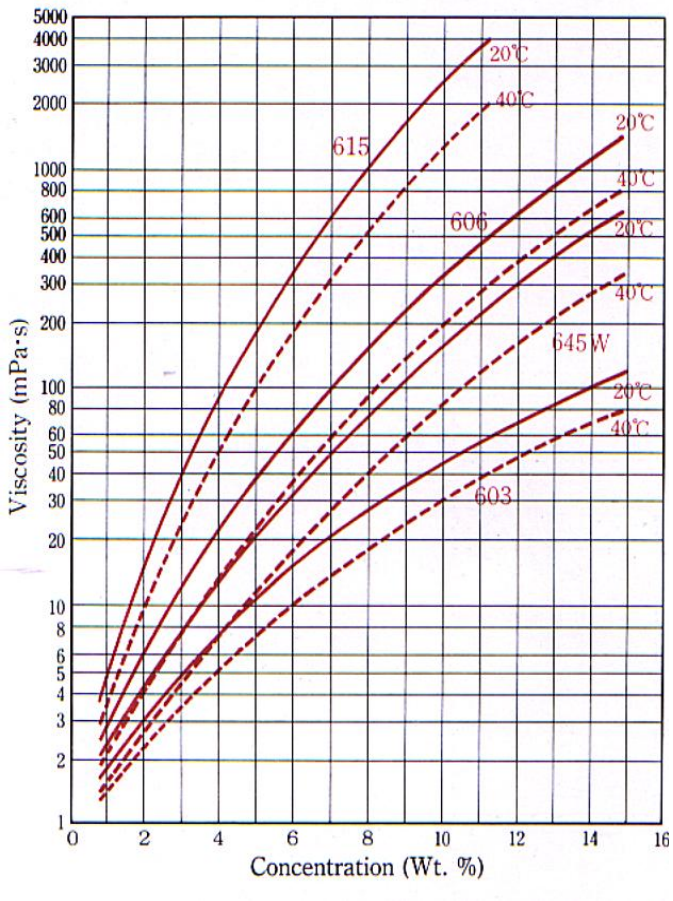
a) Viscosity of aqueous solution

The relationship between concentration and viscosity of PHARMACOAT 603, 645W, 606, and 615 in water at 20°C and 40°C is shown in Fig.2. The type of product and the concentration used should be selected depending on the required usage. For film coating, concentrations reaching 80-100mPa~s are optimum. For use as a binder, a low viscosity grade is effective.

b) Viscosity of organic solvent solutions

PHARMACOAT is soluble in aqueous alcohols such as ethanol and isopropanol containing water in a ratio of more than 1:1, but insoluble in simple alcohols. Organic solutions can be prepared in mixtures of methylene chloride and alcohol. There are various disadvantages to the use of organic solvents in pharmaceutical processing, but if they must be used, we recommend methylene chloride-ethanol and water-ethanol mixtures as solvents.

Fig. 2: Concentration-viscosity relationship of PHARMACOAT



6) Properties of the film

PHARMACOAT film has the hardness and strength characteristic of cellulose derivatives. Although PHARMACOAT film is not brittle, as acrylic polymer is, addition of a plasticizer such as polyethylene glycol (PEG 6,000) is effective when highly flexible film is required.
When PHARMACOAT film is used for film coating, sometimes titanium dioxide or talc is recommended to be added. Addition of inorganic substances such as TiO_2 in a large amount to a grade of PHARMACOAT 603 with low viscosity (molecular weight) causes a marked decrease in the tensile strength, often leading to occurrence of cracking and detachment.

Therefore, when an inorganic substance is added, use of a grade with a relatively high viscosity (molecular weight) such as PHARMACOAT 645W 606 or 615 is recommended. Moreover, addition of a water-insoluble polymer such as ethylcellulose (EC) or hydroxypropyl methylcellulose phthlate (HPMCP) to PHARMACOAT delays dissolution of the film, which is useful for the masking of bitter taste or unacceptable texture, as well as delaying drug dissolution. Table 2 shows the solubility of such a mixed film in simulated gastric fluid and simulated intestinal fluid. The test piece had a thickness of 0.08 mm and a size of l0mm x l0mm. For the test, the apparatus for the USP Disintegration Test was used.

Table 2: Solubility of mixed film in simulated gastric fluid and simulated intestinal fluid

Mixed film	Mixing ratio	Simulated gastric fluid	Simulated intestinal fluid
PHARMACOAT 606/HPMCP	9/1	Soluble	Soluble
	8/2	Soluble	Soluble
	7/3	Soluble	Soluble
	6/4	Low	Soluble
	5/5	Nearly insoluble	Soluble
	4/6	Nearly insoluble	Soluble
	3/7	Nearly insoluble	Soluble

PHARMACOAT meets all the requirements for USP Hydroxypropyl Methylcellulose (Substitution Type 2910 or 2208) or EP Hypromellose. Moreover, in addition to the tests prescribed in the aforementioned Pharmacopoeias, Shin-Etsu carries out tests for foreign matter contamination, microbiological contamination, yellowness index, etc., in order to ensure strict quality control.

PHARMACOAT is manufactured in accordance with the good manufacturing practice (GMP). A certificate of analysis commonly incorporating test results based on the USP, are routinely attached to PHARMACOAT products. Quality specifications are shown in the following table.

Table 3: Quality specifications of PHARMACOAT

Item/Grade	PHARMACOAT 603	PHARMACOAT 606	PHARMACOAT 615	PHARMACOAT 904	Method
Substitution type in USP	2910			2208	
Description and solubility	conforms				USP
Characters	conforms				EP
Identification (A—C) (A—F)	conforms conforms				USP EP
pH	5.5—8.0				EP
Apparent viscosity (cP or mPa s)	2.4 - 3.6	4.8 - 7.2	12.0 – 18.0	3.2 – 4.8	USP or EP
Loss on drying	not more than 5.0%				USP
Residue on ignition	not more than 1.5% not more than 1.0%				USP EP
Arsenic	within the limit not more than 3ppm)				USP
Heavy Metals	within the limit (not more than 0.001%)				USP
Appearance of Solution	conforms				EP
Chlorides	within the limit (not more than 0. 5%)				EP
Methoxyl content	28.0 - 30.0%			19.0 - 24.0%	USP
Hydoroxypropoxyl content	7.0 -12.0%			4.0 -12.0%	USP

PHARMACOAT 904 is especially useful as a binder for sugar coating in addition to its general uses as a coating material and binder for tablets or granules.

PHARMACOAT 603W, 645W and 606W are developed grades with less yellowness to the solution color.

Viscosity ranges are as follows. Other specifications are the same as those for PHARMACOAT type 2910.

	PHARMACOAT 603W	PHARMACOAT 645W	PHARMACOAT 606W
Apparent viscosity (cP or mPa s)	2.5 - 3.5	3.6 - 5.1	5.2 - 7.0

1) Dissolving PHARMACOAT

As PHARMACOAT is a powder with a particle size of 50-70μm, dissolution of a large amount of PHARMACOAT must be done carefully to avoid loss of material through dust formation (dusting). Moreover, as PHARMACOAT has high solubility in water and mixed solvents, it may form lumps, which require a long time to dissolve, if it is added to such solvents all at once.

2) Film coating

Film coating is usually done with aqueous solutions rather than organic solvents, since the cost of the solvent is less, the cost of equipment is less (solvent recovery and disposal are simpler), and the process is safer (better working environment, less risk of explosion and no need for treatment to remove residual solvents in preparations). Accordingly, Shin-Etsu recommends the adoption of coating with an aqueous solution. Machinery which offers a high drying efficiency and short coating time is available.

Many coatings are available for particular purposes such as improving abrasion resistance, improving printability, improving impact strength, masking colour and/or taste, and improving flowability. Coating formulations and quantities differ considerably depending on the purpose, and it is necessary to change the formulation of the coating solution, the drying temperature and the operating parameters of the coating equipment on a case-by-case basis. Shin-Etsu Chemical can provide technical advice on the suitability of various coatings.

3) Dissolution characteristics of PHARMCOAT-coated tablets

The coated tablets must release the drug in simulated gastric fluid. Moreover, it is essential that the drug is dissolved in water and buffer solutions with various salt concentrations and pH values similar to those of simulated gastric fluid. This is because the pH value of human gastric juice shows inter- individual variation depending on age, constitution, etc. and the drug therapeutic effect is required to be maintained irrespective of such differences. PHARMACOAT film has very favourable dissolution characteristics from this point of view, and this is one of the main reasons why PHARMACOAT is widely used as a coating agent.

In the case of agents having pH-dependent dissolution characteristics such as acrylic polymer and polyvinyl polymer, water-soluble polymers or other additives may be required, but PHARMACOAT has uniform dissolution characteristics, making it easy to use.

4) Granulation

PHARMACOAT can also be used as a binder for granulation. The fine particle size (5O-7Oμm on average) allows good admixture with the vehicle (lactose-corn starch) and PHARMACOAT is effective for flow granulation and agitating granulation (dry blend).

A low viscosity grade is more effective as a binder for granulation. Shin-Etsu recommends the use of PHARMACOAT for fine granules and tabletting granules as a highly stable binder which does not interact with drugs.

Packaging	• 50kg net: Double layered polythene bag in fibre drum • 1 kg net: Double layered polythene bag
Outline of Applications	**Coating for tablets and granules** Masking of colour, masking of taste, improvement in hardness, improvement of abrasion resistance, improvement in flowability, improvement in stability and improvement in printability. **Undercoating for sugar coating** Waterproofing and stabilization of dissolution **Undercoating for enteric coating** Prevention of reaction between drugs and coating agents **Binder for tablets and granules** Improvement in granulation yield, improvement in hardness and prevention of interaction with drugs **Formation of membrane and increase in viscosity for aerosols and ointments** Provision of membrane with desired properties and stabilization of suspensions
Limitation of Applications	PHARMACOAT must not be used in preparations for injection.

Regular types of hydroxypropyl methylcellulose or methylcellulose are on sale under the trade name METOLOSE, and are used as binders for solid dosage forms and to increase viscosity. Data on these products will be provided on request.

Table 8: Outline of types of hypromellose (hydroxypropyl methylcellulose) and Methylcellulose

Corresponding name defined by USP Labelled viscosity (USP)	Hypromellose Substitution Type 2208	Hypromellose Substitution Type 2910	Hypromellose Substitution Type 2906	Methylcellulose
3		PHARMACOAT 603, 603W		
4	PHARMACOAT 904			METOLOSE SM-4
4.5		PHARMACOAT 645W		
6		PHARMACOAT 606, 606W, 606G**		
15		PHARMACOAT 615		SM-15
25				SM-25
50		METOLOSE 60SH-50	METOLOSE 65SH-50	
100	METOLOSE 90SH-100			SM-100
400	90SH-400		65SH-400	SM-400
1500			65SH-1500	SM-1500
4000	90SH-4000 90SH-4000SR*	60SH-4000	65SH-4000	SM-4000
10000		60SH-10000		
15000	90SH-15000		65SH-15000	
100000	90SH-100000 90SH-100000SR*			
Range of substituent content Methoxy group Hydroxypropoxy group	19.0-24.0% 4.0-12.0%	28.0-30.0% 7.0-12.0%	27.0-30.0% 4.0-7.5%	27.5-31.5%

*** METOLOSE SR is used for Hydrophilic matrix system, having much tighter specification**
**** PHARMACOAT 606G is a granular type product for quick preparation of the coating solution and dust-free handling**

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