Shin-Etsu

Hypromellose USP

PHARMACOAT®

Film Coating Material and Binder

CONTENTS

Introduction

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.

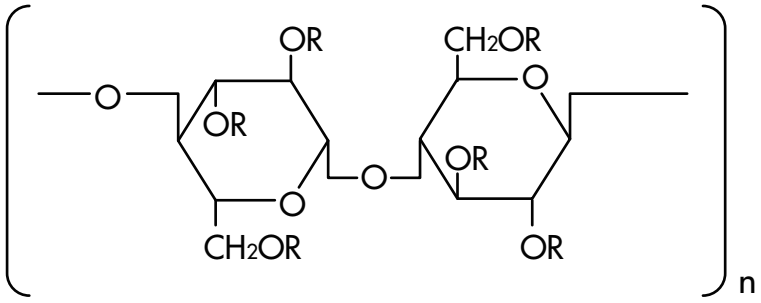
Although drug properties are the key factor in medicinal formulations, the physical form or the finish of a preparation is also important. PHARMACOAT® is easy to use as a film coating material and gives an excellent finish. It is very versatile, and is suitable for many applications in the design of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

In addition, PHARMACOAT® is effective as a binder, since it seldom interacts with drugs, and has superior stability, nonionic 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. Detail technical information is available in a separate publication, "Technical Information".

Description

Trade name	PHARMACOAT®
Generic name	Hypromellose (Hydroxypropylmethylcellulose)
Abbreviation	HPMC
IUPAC name	Cellulose, 2-hydroxypropyl methyl ether
CAS RN®	9004-65-3
Compendial status	USP (The United States Pharmacopeia) EP (European Pharmacopoeia) JP (Japanese Pharmacopoeia)
Structure	



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

Physicochemical Properties

1) True density ····· 1.26 - 1.31 g/cm^3 (measured with helium pycnometer)

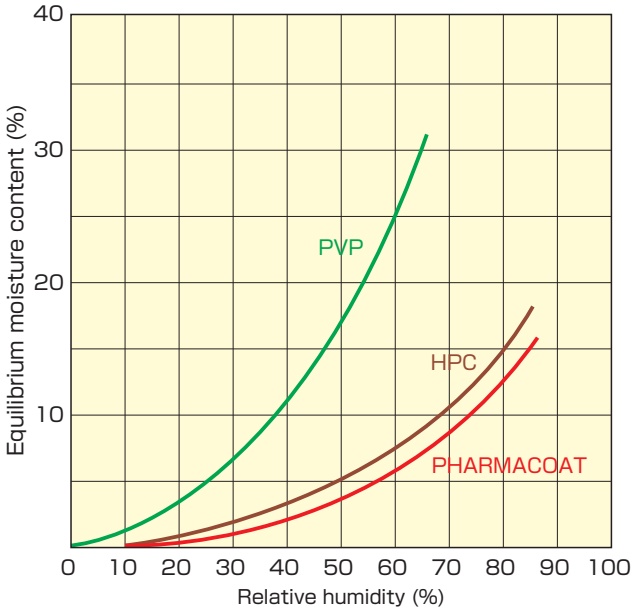
2) Tapped density ····· 0.50 - 0.70 g/mL

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.

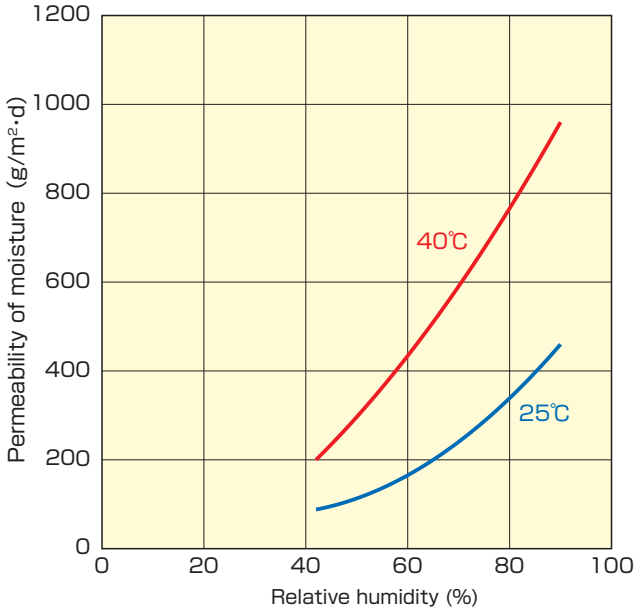
4) Permeability of moisture ·····

The relationship between relative humidity and permeability of moisture is shown in Fig 2.



There is no difference among the grades of PHARMACOAT®

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



Lyssy's method
(Lyssy L80-5000 Water Vapor Permeability Tester)
0.1mm thickness
There is no difference among the grades of PHARMACOAT®

Fig. 2 : Relative humidity and permeability of moisture

5) Molecular weight

Grade	Mw	Mw/Mn
PHARMACOAT® 603	20000	1.80
PHARMACOAT® 645	25000	1.92
PHARMACOAT® 606	32800	1.90
PHARMACOAT® 615	56400	1.96

Mw : weight-average molecular weight (g/mol) Mn : number-average molecular weight (g/mol)

Physicochemical Properties

6) Viscosity behavior

a) Viscosity of aqueous solutions

The relationship between concentration and viscosity of PHARMACOAT® 603, 645, 606 and 615 in water at 20℃ and 40℃ are shown in Fig. 3.

The viscosity grade and the concentration used should be selected depending on the required usage. For film coating, concentrations reaching 80 – 100 mPa·s are optimum. For use as a binder, a low viscosity grade is effective.

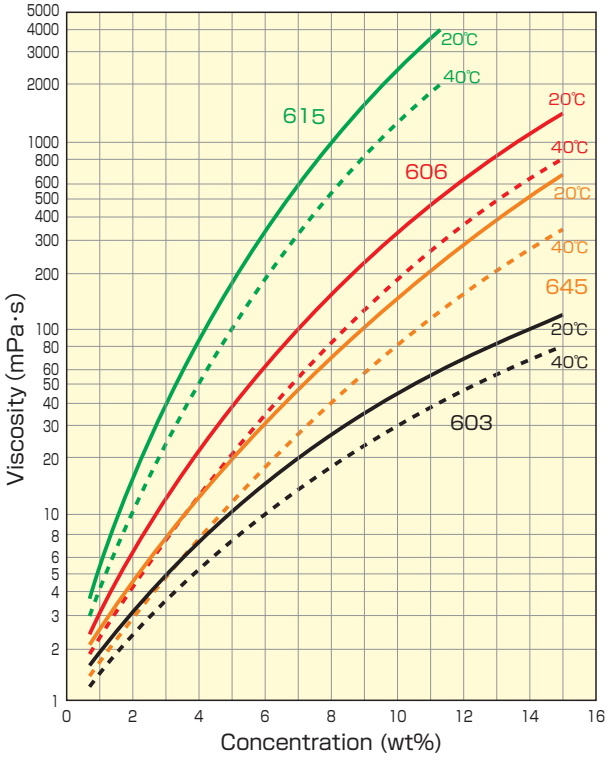


Fig. 3 : Concentration-viscosity relationship of PHARMACOAT®

b) Viscosity of organic solvent solutions

PHARMACOAT® is soluble in aqueous alcohols such as ethanol and isopropanol containing water in a ratio more than 10% water, but insoluble in simple alcohols. Therefore, the mixture of water and ethanol is recommendable with the ratio of 20% water and 80% ethanol. Solubility in the mixture of water and ethanol can be seen in Figs. 4 and 5. Figures 6 and 7 show the viscosity in the water / ethanol system.

When complete organic solvent is required, the mixture of methylene chloride and alcohol is usable. Figures 8 and 9 show the viscosity in the methylene chloride / ethanol system.

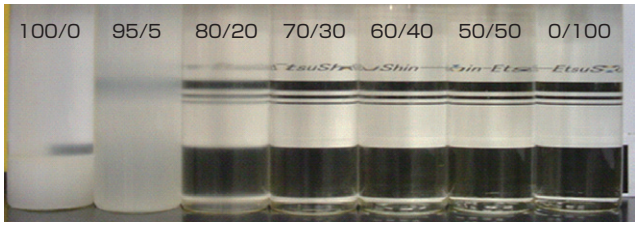


Fig. 4 : Solubility of PHARMACOAT® in ethanol / water. (5 wt%)

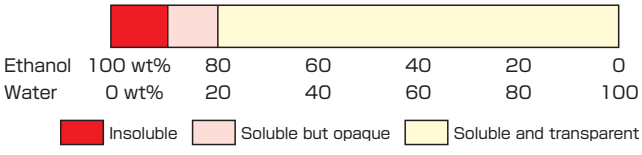


Fig. 5 : Solubility of PHARMACOAT® in ethanol and water

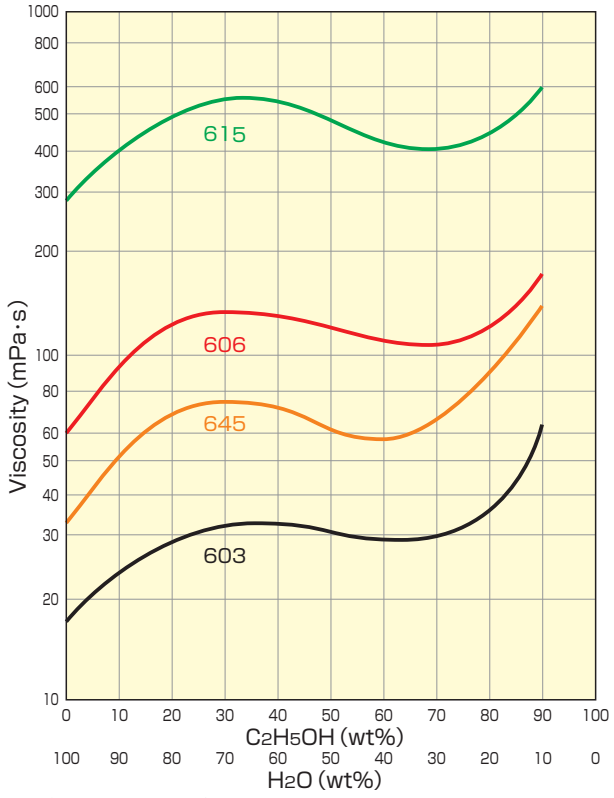


Fig. 6 : Relationship of the mixing ratio in the water/ethanol system and the viscosity of 6% solutions of PHARMACOAT®

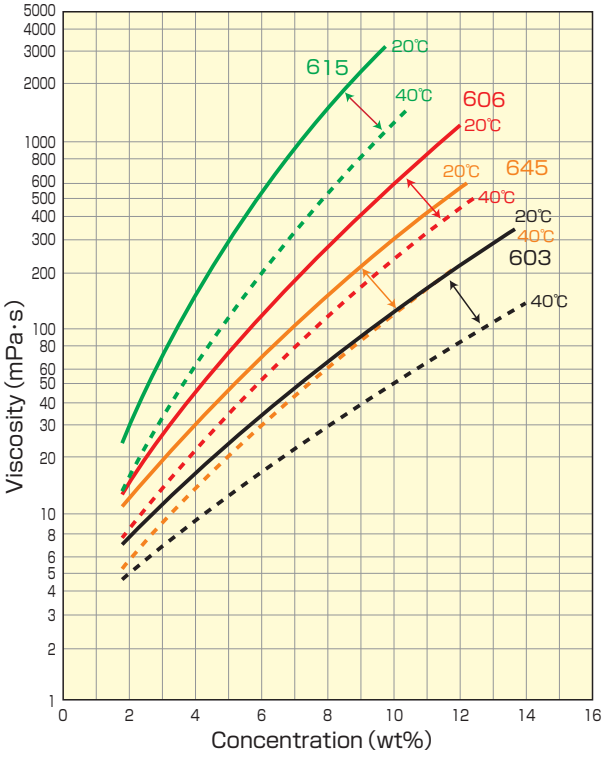


Fig. 7 : Concentration - viscosity relationship of PHARMACOAT® in water/ethanol (50:50)

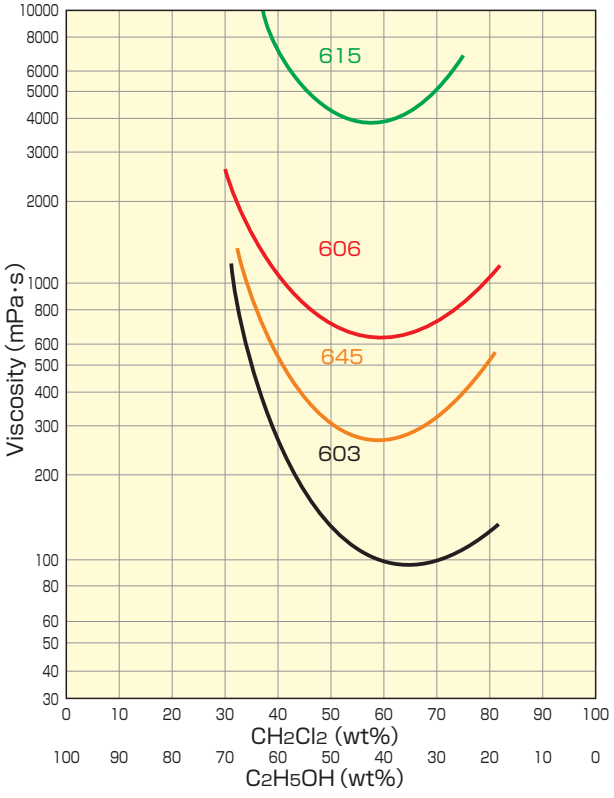


Fig. 8 : Relationship of the mixing ratio in the methylene chloride/ethanol system and the viscosity of 10% solutions of PHARMACOAT®

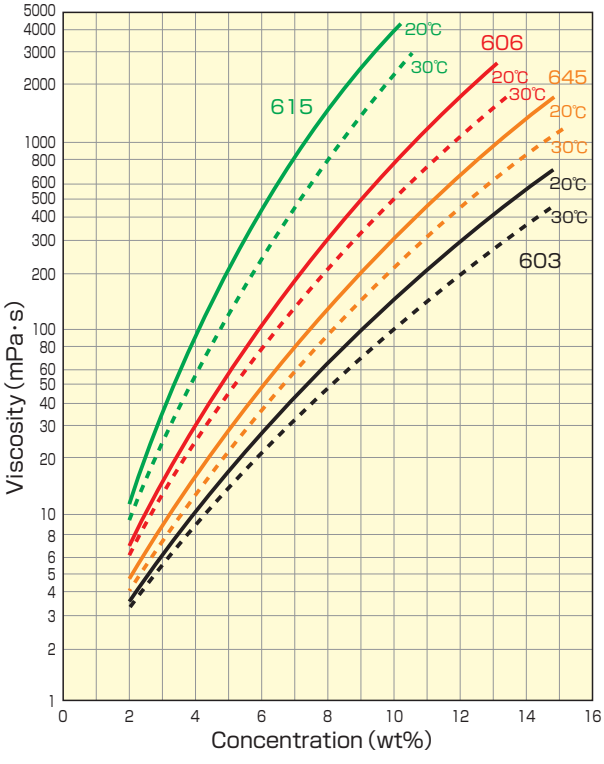


Fig. 9 : Concentration - viscosity relationship of PHARMACOAT® in methylene chloride/ethanol (50:50)

Physicochemical Properties

7) Film properties

PHARMACOAT® film has the tough and flexible characteristics of cellulose derivatives. Although PHARMACOAT® film is not brittle, as acrylic polymer is, addition of a plasticizer such as polyethylene glycol (PEG) is effective when highly flexible film is required.

When PHARMACOAT® film is used for film coating, sometimes titanium dioxide (TiO_2) or talc is recommended to be added. Figures 10 and 11 show the properties of PHARMACOAT® film containing TiO_2. For the experiment, film with a thickness of 0.1 mm, which was obtained by dissolving PHARMACOAT® in methylene chloride/ethanol mixture (50 : 50), adding TiO_2 to the solution and casting it on a glass plate, was used. The measurements were performed under the conditions of 25 ±1℃, 50±5%RH according to JIS K-6301.

Addition of inorganic substance 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 cracking and/or peeling of the films. Therefore, when an inorganic substance is added, use of a grade with a relatively high viscosity (molecular weight) such as PHARMACOAT® 645, 606 or 615 is recommended.

Moreover, addition of a water-insoluble polymer such as Hypromellose Phthalate (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 1 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 size of 10 mm × 10 mm. For the test, the apparatus for the USP Disintegration Test was used. Hypromellose Phthalate (HPMCP) used in this study is HP-50.

Table 1 : Solubility of the films in pH 1.2 and 6.8 buffer solutions

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	Slightly soluble	Soluble
	5/5	Nearly insoluble	Soluble
	4/6	Nearly insoluble	Soluble
	3/7	Nearly insoluble	Soluble

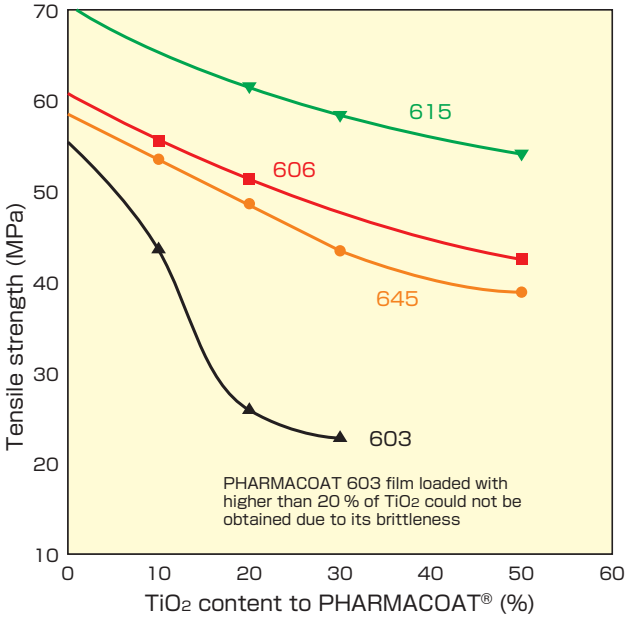


Fig. 10 : Effect of TiO_2 on the tensile strength of PHARMACOAT® films

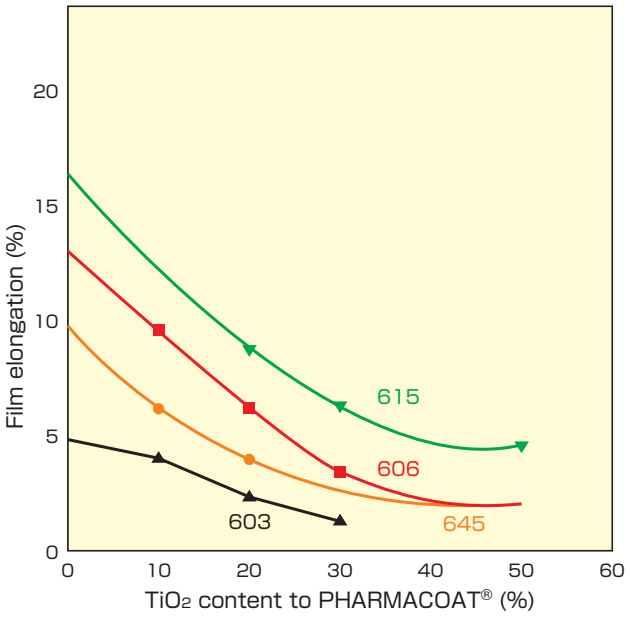


Fig. 11 : Effect of TiO_2 on the elongation of PHARMACOAT® films

Applications

Table 2. Application Guide for PHARMACOAT®

Application	Purpose
Film coating for tablet	Taste masking, Color masking, Coloring, Hardness (improve friability), Stability
Sub-coating for sugar coating	Stability, Prevention of moisture penetration to the core
Sub-coating for enteric coating	Prevention of interaction
Binder for tablet and granule	Compressibility, Compatibility

1) Technique for dissolving PHARMACOAT®

As PHARMACOAT® is a powder with particle size of 50 - 70 μm, 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. Therefore, PHARMACOAT® should be dissolved according to the following procedures.

a) Dissolving in water

Put all of the PHARMACOAT® in about 1/3 of the water, previously heated to above 80℃, while stirring well at higher speed. Because hot water is a poor solvent for PHARMACOAT®, a uniformly wet dispersion is obtained. Then, add cold water to make the prescribed volume while stirring well. After cold water is added, slow down the stirring speed to lower speed and continue until the PHARMACOAT® disssolves completely. When the temperature of the water falls to below 30℃, PHARMACOAT® can dissolve completely and the solution can be used as a coating fluid. If a high-power stirrer is used, PHARMACOAT® can be readily dissolved by adding it gradually to the water at below 30℃ with stirring. Care must be taken to avoid bubble or foam formation.

At 6 - 10% viscosity (less than 100 mPa·s) any bubbles formed disappear when the solution is left to stand for several hours. The following can be employed as antifoaming agents : Shin-Etsu Silicone KM-72 (Polydimethylsiloxane) from Shin-Etsu Chemical / NIKKOL SO-15 (Sorbitan sesquioleate) from Nikko Chemicals / Pulronic F 68 (Polyoxyethlene(160)-polyoxypropylene(30)glycol) from Asahi Denka.

b) Dissolving in organic solvents

(ethanol / water system)

As PHARMACOAT® is insoluble in simple alcohols, first of all pour a prescribed volume of ethanol into a container and put all of the PHARMACOAT® in it while stirring. When a uniform dispersion is obtained, add water gradually and stir gently to form a well-wetted dispersion as the coating solution. If PHARMACOAT® is put all at once into a previously prepared mixed solution, insoluble lumps will be formed.

Although great care is taken to avoid any foreign material contamination, it is recommended to sieve the product and/or filter the product solution before usage.

*If difficulties arise concerning the dissolution apparatus, removal of bubbles in the coating solution or filtration of solutions, Shin-Etsu can offer technical advice based on extensive experience and know-how.

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. Some examples of coating using PHARMACOAT® are given in Table 3. In addition to those illustrated many coatings available for particular purposes such as improving abrasion resistance, improving printability, improving impact strength, masking color and/or taste, and improving flowability. Coating formulation 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.

Applications

Table 3 : Examples of film coating with PHARMACOAT®

1) Example of coating using organic solution

Laboratory scale apparatus

a) Composition of coating solution

PHARMACOAT® 606	6 parts
Ethanol	75.2 parts
Water	18.8 parts

b) Coating conditions

Machine	New Hi-Coater HCT-48N (Freund corporation)
Dimension	480 mm
Pan speed	16 (20 at later atage) min^{-1}
Spray gun	··· air spray gun × 1 (AT type nozzle diameter 1.2 mm)
Drying air	55 - 60℃
Air flow rate	3 m^3/min
Spray speed	40 g/min
Nozzle air	150 L/min
Pressure of spray air	200 kPa
Tablet bed air temperature	46 - 39 ℃
Charge per batch	25,000 tablets, 5 kg (dosage form; 8 mm, 200 mg/tab)

c) Results

Coating time	62.5 min
Coating solution consumption	2500 g
PHARMACOAT® 606 consumption	6 mg/tab
Disintegration time (USP disintegration test, average)	before coating; 2 min 20 sec after coating; 3 min 30 sec

Production scale apparatus

a) Composition of coating solution

PHARMACOAT® 606	6 parts
Ethanol	75.2 parts
Water	18.8 parts

b) Coating conditions

Apparatus	New Hi-Coater HCT-130N (Freund corporation)
Dimension	1300 mm
Pan speed	5 (8 at later stage) min^{-1}
Spray gun	··· air spray gun × 3 (AT type nozzle diameter 1.2 mm)
Drying air	50 - 60℃
Air flow rate	10 ～ 15 m^3/min
Spray speed	140 g/min×3
Nozzle air	140 ～ 150 L/min
Spray air	250 L/min
Tablet bed air temperature	37 - 30℃
Charge per batch	600,000 Tablets, 120 kg (dosage form; 8 mm, 200 mg/tab)

c) Results

Coating time	143 min
Coating solution consumption	60.0 kg
PHARMACOAT® 606 consumption	6 mg/tab
Disintegration time (USP disintegration test)	before coating; 2 min 20 sec after coating; 3 min 30 sec

2) Example of coating using auqeous solution

Laboratory scale apparatus

a) Composition of coating solution

	606	645
PHARMACOAT®	6 parts	10 parts
Water	94 parts	90 parts

b) Coating conditions

Machine	New Hi-Coater HCT-48N (Freund corporation)	
Dimension	480 mm	
Pan speed	16 min^{-1}	
Spray gun	air spray gun X 1 (ATF type nozzle diameter 1.2 mm)	
Drying air	70℃	←
Air flow rate	2.5 m^3/min	←
Spray speed	30 g/min	←
Nozzle air	150 L/min	←
Pressure of spray air	200 kPa	←
Tablet bed temperature	39℃	←
Charge per batch	5 kg	←
Dosage form	6.5 mm, 120 mg/tab	←

c) Results

Coating time (3% coating based on tablet weight)	83 min	50 min
Coating solution consumption	2490 g	1500 g
PHARMACOAT® 606 consumption	3.6 mg/tab.	←
Disintegration time (USP disintegration test)	before coating: 2 min 20 sec	←
	after coating: 3 min 30 sec	←

Production scale apparatus

a) Composition of coating solution

	606	645
PHARMACOAT®	6 parts	10 parts
Water	94 parts	90 parts

b) Coating conditions

Machine	New Hi-Coater HC-130N (Freund corporation)	
Dimension	1300 mm	
Pan speed	8 min^{-1}	
Spray gun	air spray gun X 3 (AT type nozzle diameter 1.2 mm)	
Drying air	80℃	←
Air flow rate	15 m^3/min	←
Spray speed	70 g/min×3	←
Nozzle air	170 L/min	←
Nozzle air + pattern air	250 L/min	←
Tablet bed temperature	46℃	←
Charge per batch	120 kg	←
Dosage form	6.5 mm, 120 mg/tab	←

c) Results

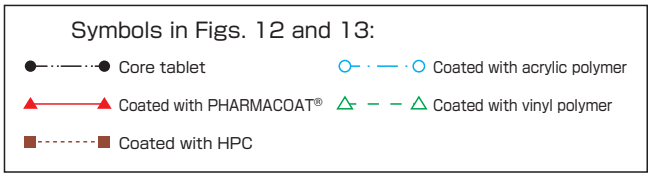
Coating time (3% coating based on tablet weight)	286 min	171 min
Coating solution consumption	60.0 kg	35.9 kg
PHARMACOAT® 606 consumption	3.6 mg/tab	←
Disintegration time (USP disintegration test, average)	before coating: 2 min 35 sec	←
	after coating: 3 min 40 sec	←

3) Dissolution characteristics of PHARMACOAT®- 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 favorable dissolution characteristics from this point of view, and this is one of the main reasons why PHARMACOAT® is widely used as a coating agent.

To illustrate the superior dissolving characteristics, 190 mg vitamin B2 tablets containing 3.2 mg of vitamin B2 were coated with various agents and their dissolution characteristics were compared. Figures 12 and 13 show the results.

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.



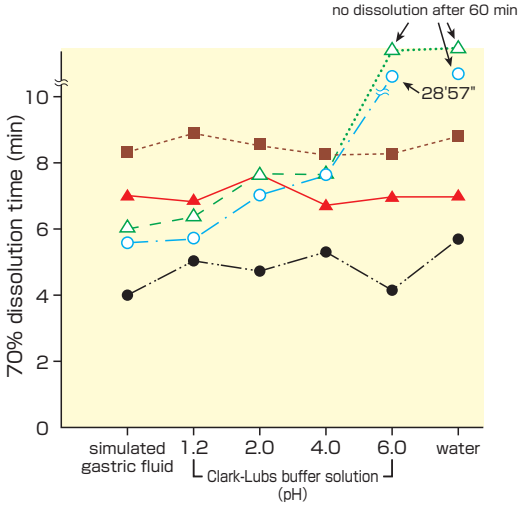
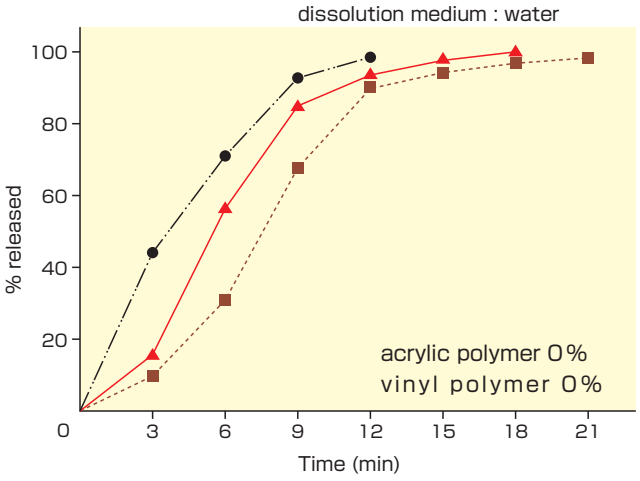
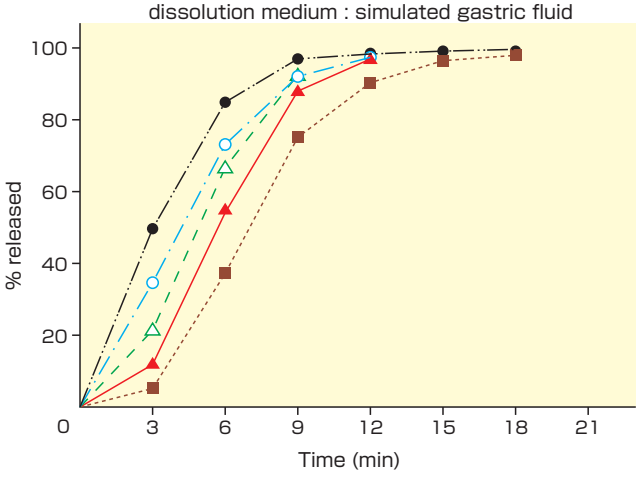


Fig. 12: 70% dissolutioin time of tablets coated with various coating materials





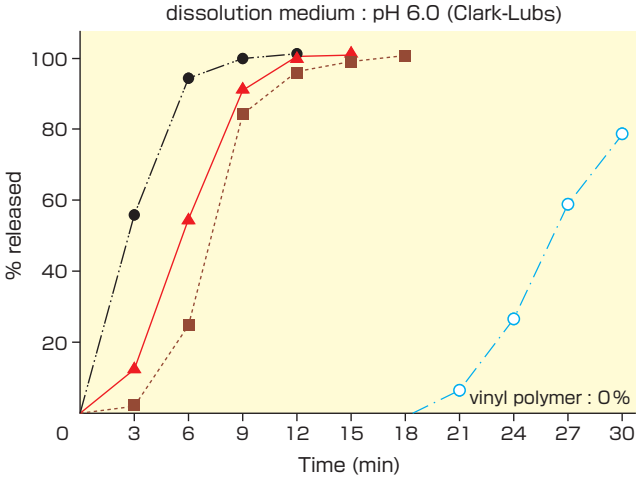


Fig. 13: Results of dissolution tests of coated tablets at various pH values

4) Granulation

PHARMACOAT® can also be used as a binder for granulation. The fine particle size (average 50 - 70 μm) allows good admixture with the other ingredients (lactose/cornstarch) and PHARMACOAT® is effective for fluidized bed granulation and high shear mixer granulation (dry-blend).

Although the details are not given here, a low viscosity grade (typically PHARMACOAT® 603) is also effective as a binder for granulation, which can afford the powders with good compressibility. Shin-Etsu recommends the use of PHARMACOAT® for fine granules and tabletting granules as a highly stable binder which does not interact with active substances.

Table 4: Formulation

	High shear mixier		Fluidized bed	
	Dry form	Solution	Dry form	Solution
Lactose (200 mesh)	3360 g	3360 g	2800 g	2800 g
Cornstarch	1440 g	1440 g	1200 g	1200 g
MCC	200 g	200 g	–	–
PHARMACOAT® 606	150 g	50 g*	200 g	140 g*
Water	1000 g	1000 g	1600 g	1860 g

*Dissolved in granulating liquid

Table 5: Conditions (high shear mixer)

		Dry mixing	Solution
Granulation	Machine	Vertical granulator FM-VG-25 (Powrex Corp.)	
	Granulating time	10 min	
	Blade Chopper	300 min^{-1} 3000 min^{-1}	
Drying	Machine	Flow coater FLO-5 (Freund Corp.)	
	Drying temperature	70℃	
	Air flow	2.2 m^3/min	
	Drying time	30 min	

Conditions (fluidized bed)

		Dry mixing	Solution
Granulation	Machine	Flow coater FLO-5 (Freund Corp.)	
	Drying air temperature	82-83℃	83-84℃
	Exhaust air temperature	28-30℃	29-32℃
	Air flow	2.2 m^3/min	40 m^3/min
	Spray gun	Schlick nozzle 1.8 mm	
	Spray air pressure	300 kPa	
	Gun position	25 cm	40 cm
	Spraying time	25 min	20 min
	Shaking/interval	6 sec/30 sec	
Drying	End point	When the outlet temperature came to 35℃	
	Drying air temperature	The same as at granulation condition	
	Air flow	2.2 m^3/min	
	Shaking/interval	6 sec/180 sec	
	Drying time	15 min	7 min

Table 6: Properties of granules

Granulation method		High shear mixier		Fluidized bed	
		Dry form	Solution	Dry form	Solution
Binder content		3%	1%	5%	3.5%
Mean particle size (μm)		223	203	211	220
Bulk density (g/mL)	Loose	0.635	0.621	0.534	0.450
	Tapped	0.789	0.785	0.612	0.553
Angle of repose (°)		37	37	35	34
Moisture content (%)		2.2	2.6	3.2	2.6

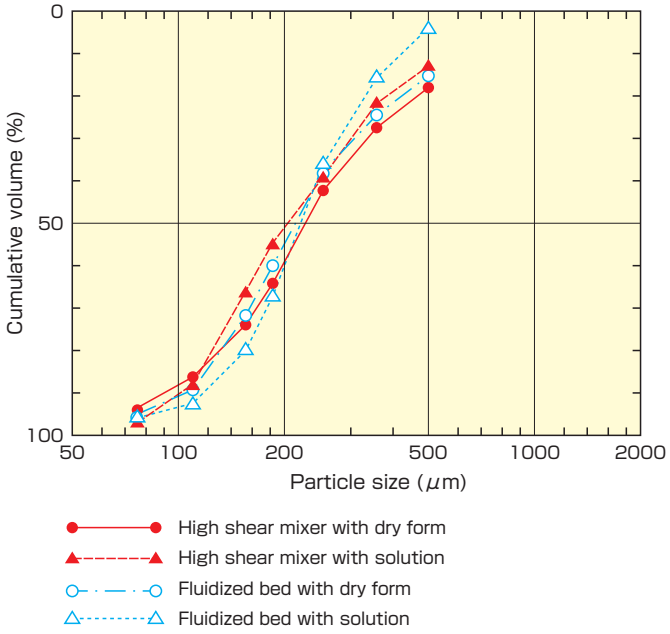


Fig. 14: Cumulative particle size distribution

Products Information

PHARMACOAT® meets all the specifications for the USP Hypromellose (Substitution type: 2910), EP Hypromellose and JP Hypromellose. The grades are shown in Table 7.
Please contact us for the latest product specifications.

Table 7 : Grades of PHARMACOAT®

Grade	Viscosity (mPa·s)	Substitution type	Methoxy content (%)	Hydroxypropoxy content (%)
603	2.4 - 3.6	2910	28.0 - 30.0	7.0 - 12.0
645	3.6 - 5.1			
606	4.8 - 7.2			
615	12.0 - 18.0			

SB-4 (Hypromellose 2208) is especially useful as a binder for sugar coating, which is an alternative source of gelatin and gum arabic in sugar syrup. Please contact us for further information.

Package

- 50kg - Fiber drum with polyethylene double bag inside [Size;465 mm (Φ)×740 mm(H)]
- 1kg - Polyethylene double bag

Precautions for Safe Handling

Warning: May form combustible dust concentrations in air.

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 Concentration: 55 g/m^3, Mukai *et al.,* 1995)

CAUTION: Spilled powder becomes slippery when wet. 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 and organized house keeping 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.
- If spillage is viscous solution, scrape up as much as possible before flushing it with plenty of water.
  Place the scraped spillage in an appropriate container for waste disposal.

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.

****

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

N O T E :

All the information and data in this brochure are accurate and reliable to the best of our knowledge, but they are intended only to provide recommendations or suggestions without guarantee or warranty. All of our products are sold on the understanding that buyers themselves will test our products to determine their suitability for particular applications. Buyers should also ensure that use of any product according to these data, recommendations, or suggestions does not infringe any patent, as Shin-Etsu will not accept liability for such infringement. Any warranty of merchantability or fitness for a particular purpose is hereby disclaimed.

Shin-Etsu Chemical Co.,Ltd

Cellulose & Pharmaceutical Excipients Department

4-1, Marunouchi 1-chome, Chiyoda-ku, Tokyo, Japan,100-0005

Tel: 81-3-6812-2441 Fax: 81-3-6812-2443

http://www.metolose.jp/e

Chinese Distributor: Dalian Diligence Trade Co., Ltd. Room No.1801, Tianxing Roosevelt Center, No.677 Yellow River Road, Shahekou Dist., Dalian, China.

Tel: 0411-8452-1177 Fax: 0411-8452-1199/2288

http://www.dalian-diligence.com

2018.7/1000