Hypromellose Acetate Succinate NF

Shin-Etsu AQOAT®

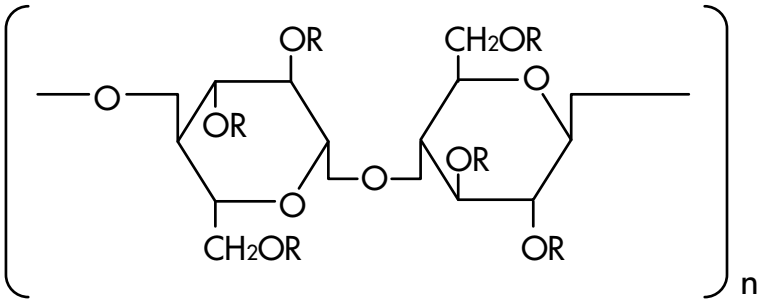
Enteric coating agent, Solid dispersion carrier

CONTENTS

Introduction

Shin-Etsu AQOAT® (pronounced *"Ay-coat"*), Hypromellose Acetate Succinate is an enteric coating material which was first approved in Japan in 1987.
Since January 2004, this product has been approved in Korea, several countries in Europe, and USA as well as in Japan. In 2000, the production plant located in Japan was inspected by the FDA. In 2016, self-determined GRAS status was claimed.
The characteristics of this material suggest several applications in addition to conventional enteric coating.
This brochure briefly describes the properties of Hypromellose Acetate Succinate.
If you have any questions, please contact us for further information.

Description

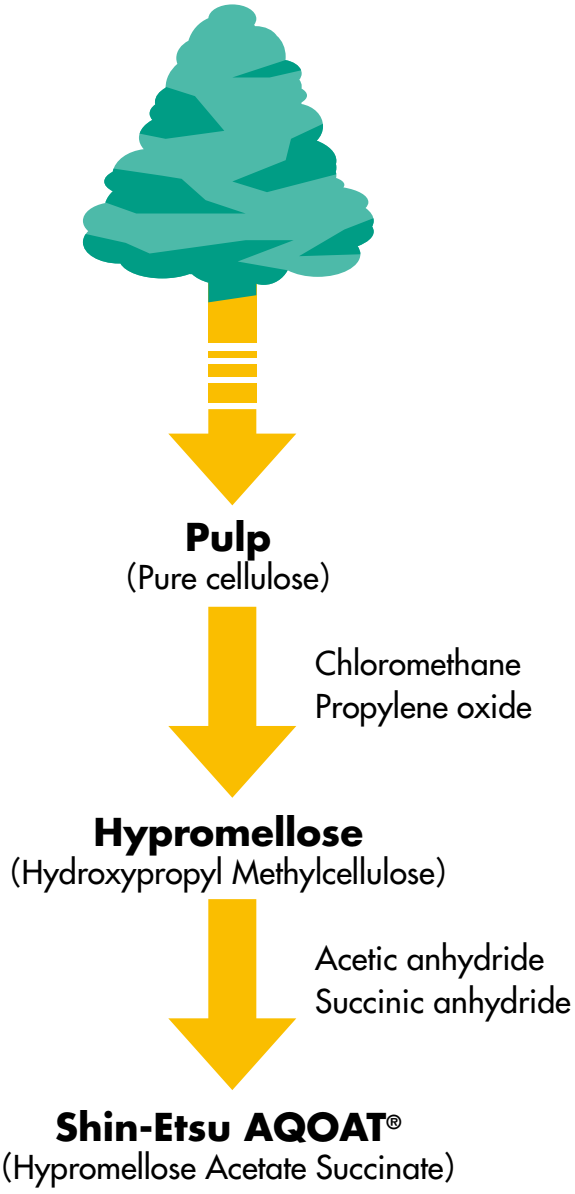
Trade name	Shin-Etsu AQOAT®
Generic name	Hypromellose Acetate Succinate NF Hypromellose Acetate Succinate JP
Abbreviation	HPMCAS
IUPAC name	Cellulose, 2-hydroxypropyl methyl ether, acetate, hydrogen butanedioate
CAS RN®	71138-97-1
Compendial status	JP (Japanese Pharmacopoeia) from October 2012 NF (US National Formulary) from August 2005
Structure	

R = -H
-CH_3
-$CH_2CH(CH_3)OH$
-$COCH_3$
-$COCH_2CH_2COOH$
-$CH_2CH(CH_3)OCOCH_3$
-$CH_2CH(CH_3)OCOCH_2CH_2COOH$

Manufacturing Process

The raw material of Shin-Etsu AQOAT® is highly-purified pulp, which is available from natural trees.
The first step of production is to manufacture "Hypromellose" (also known as HPMC = Hydroxypropyl Methylcellulose) from the pulp. Hypromellose is a non-toxic material which has been used in pharmaceutical, food, and cosmetic industries for many years.

Based on Hypromellose, acetyl and succinoyl groups are introduced to the hydroxyl groups of the backbone, and these constitute Shin-Etsu AQOAT®, Hypromellose Acetate Succinate.



Available grades*

Grade		Acetyl %	Succinoyl %	Mean Particle Size	Labeled Viscosity
Micronized	AS-LF	8	15	5 μm	3 mPa・s
	AS-MF	9	11		
	AS-HF	12	7		
Granular	AS-LG	8	15	1mm	
	AS-MG	9	11		
	AS-HG	12	7		

*The data shows only typical values and not specifications. Please contact us for the latest specification.

Physicochemical Properties

There are six grades available as shown on the previous page. They have different particle sizes and chemical substitution levels. **The following data shows only typical values and not specifications.** The values vary slightly depending on lot, grade, and determination method.

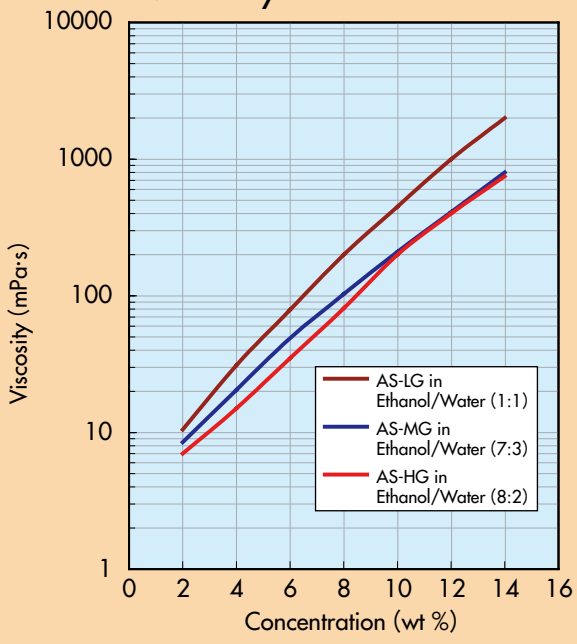
Appearance	White to yellowish powder or granules with a faint, acetic acid-like odor. Tasteless.
True density	1.27 - 1.30 g/cm³ (measured with helium pycnometer)
Bulk density	Micronized grade: 0.2 - 0.3 g/mL, Granular grade: 0.2 - 0.5 g/mL
Tap density	Micronized grade: 0.3 - 0.5 g/mL, Granular grade: 0.3 - 0.6 g/mL
Thermal degradation temperature	200 °C

Solubility

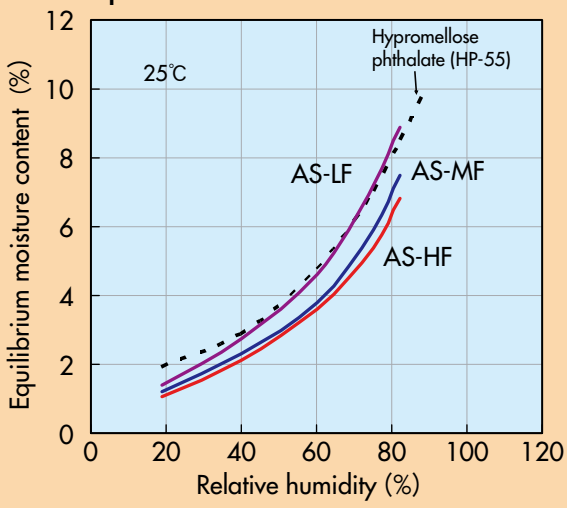
	AS-LF AS-LG	AS-MF AS-MG	AS-HF AS-HG
Acetone	S	S	S
Methanol	S	S	S
99% Ethanol	P	P	P
CH_2Cl_2	P	P	S
Ethanol - Water (8:2)*	S	S	S
Ethanol - Water (1:1)*	S	S	S
CH_2Cl_2 - Ethanol (1:1)*	S	S	S
Diethyl ether	I	I	I
Purified water	I	I	I
10% - NaOH	S	S	S
10% - Na_2CO_3	S	S	S

S = Soluble (solution may be slightly opaque) I = Insoluble
P = Partly soluble or swelling * Weight ratio

Viscosity vs concentration



Equilibrium moisture content



Film Properties

Glass transition temperature*

HPMCAS (All grades)	122℃
HPMCP (HP-55)	138℃
HPMC(P-603)	150℃

*Tg was measured with DSC under the following conditions.
Equipment: DSC Q2000 (TA Instrument)
Heating rate: 10℃/min.
Referred to the second run
N_2 gas atmosphere
Sample size: 3 mg

The film specimens were cast from organic solvent.

Film strength (ASTM)

	AS-LG	AS-MG	AS-HG
Tensile strength at break (MPa)	52	51	55
Elongation (%)	8.4	7.2	4.3

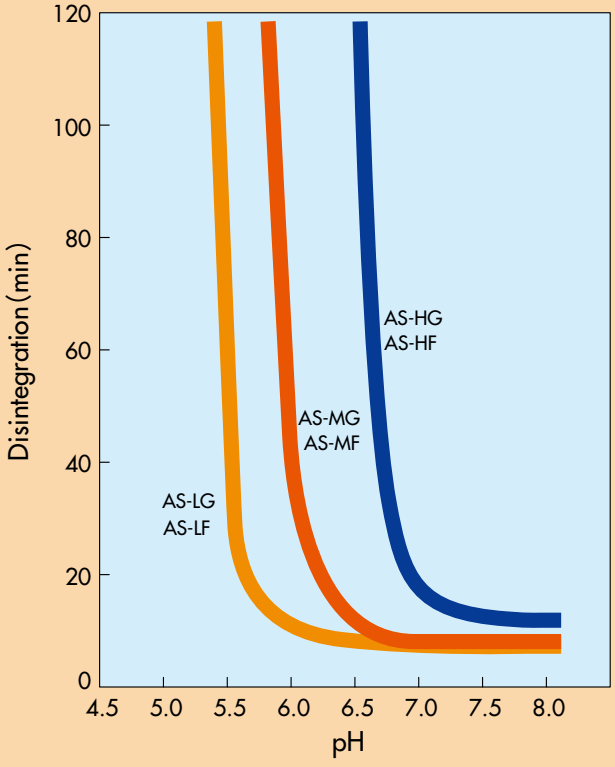
Water vapor permeability (0% / 75% RH)

AS-LG	165 (g/m²/24hrs)
AS-MG	185
AS-HG	210

Film solubility at various pH

Cast films were cut into 1 cm x 1 cm pieces of 100 μm thickness and put into a test buffer in a USP disintegration tester.
Disintegration time of the film specimens was then measured.
The disintegration time is dependent on grades, pH, and buffer solutions.

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



*~pH 5.6 : USP Phthalate buffer
pH 5.8~ : USP Phosphate buffer

Applications

Conventional Aqueous Dispersion Coating

The polymer powder is dispersed in water and sprayed onto the core tablets or granules. Plasticizer is required for film formation. To avoid nozzle clogging, if necessary, chilling of coating dispersion is recommended.

Aqueous Dispersion Coating using "Concentric Dual Feed Spray Nozzle"

This is an improved method to avoid the drawbacks in the conventional method. By spraying the plasticizer and polymer separately with a specially developed spray nozzle, it avoids the nozzle clogging problem encountered with spraying the dispersion at room temperature. In addition, it can increase the polymer concentration which achieves shorter coating time.

Solvent-Based Coating

This is the usual way of coating using organic solvents.
A typical solvent is a mixture of ethanol and water. Plasticizer is not necessary in most cases. This is the simplest method and gives the most uniform and continuous films.

Neutralized Coating

This method is aqueous, but uniform and continuous film can be obtained, which is similar to solvent based coating system.
Complete or partially neutralized coating is available. Stability (color change) should be considered.

Dry Coating

This is a unique coating method using Shin-Etsu AQOAT®.
The powder is applied directly onto tablets or granules, while plasticizer is sprayed separately. The polymeric powder and plasticizer coalesce into a film by heat curing. This process does not require solvents or water, which is especially important when working with water-sensitive drugs. Another benefit is the shorter processing time compared to conventional coatings.

Other applications

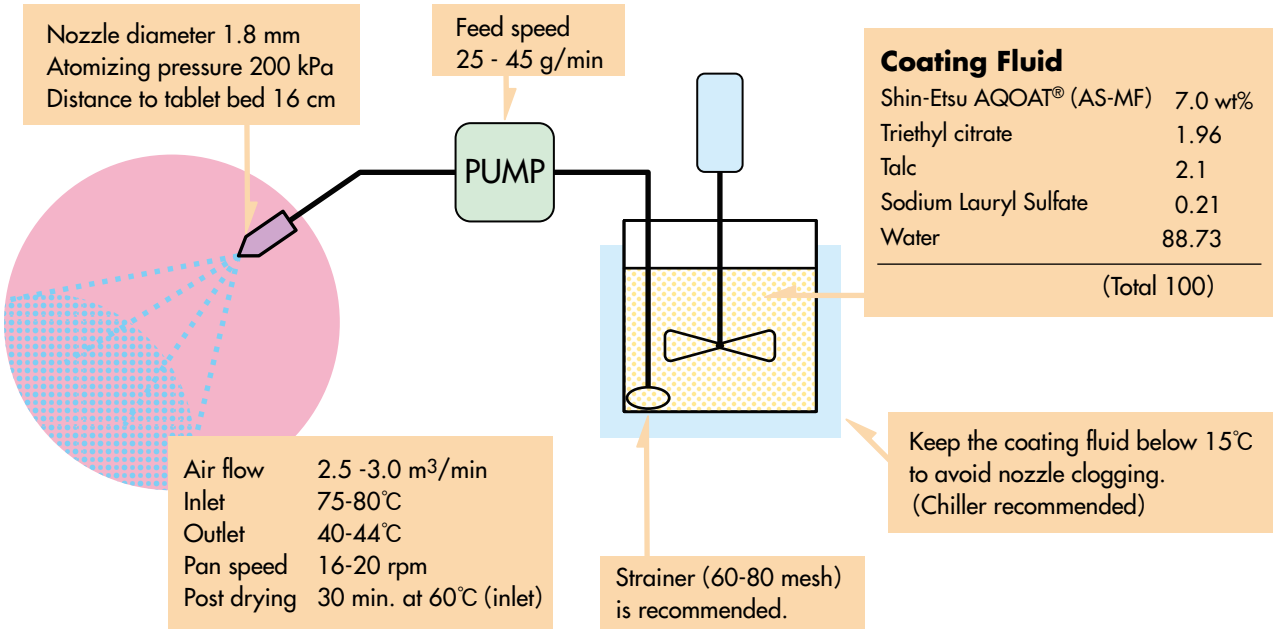
Solid Dispersions

This technique significantly enhances bioavailability of poorly-soluble drugs by increasing solubility.
Please refer to page 15 for details.

Conventional Aqueous Dispersion Coating

100 kg scale

This is the conventional aqueous dispersion coating method for which Shin-Etsu AQOAT® was originally developed. Micronized polymeric powder is dispersed in water and sprayed onto core. Plasticizer is required for the film formation. The following parameters are based on 5 kg scale laboratory operation using a side-vented pan coater for tablets. Since the polymeric powder dispersion has a low viscosity and is less sticky, it should be sprayed at a high speed. Shin-Etsu has technical information in more detail pertaining to the use of other apparatus such as fluidized-bed and lab-scale equipment. Ask your sales representative for further information.



100 kg scale

After coating, the inside of pan is very clean compared to other enteric coating agents. You can save time for cleaning.

◆Ingredients

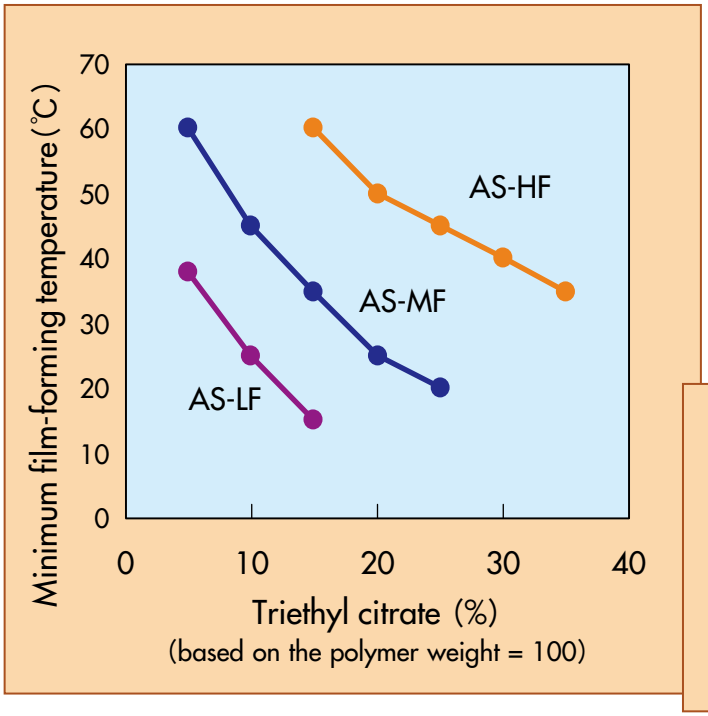
For aqueous dispersion, use a micronized grade. Maximum polymer concentration is 7%. Greater concentrations may clog the spray nozzle.
Triethyl citrate (TEC) is the recommendable plasticizer for Shin-Etsu AQOAT®. The optimum amount of TEC depends on grade (See the following table on this page). Sodium lauryl sulfate is a wetting agent that facilitates the dispersion of the polymer in the suspension.
Talc is added, typically 30% based on polymer, for anti-tacking.

◆Preparation of Coating Fluid

Prior to adding ingredients, water should be below 10-25℃ . Under stirring, dissolve TEC and sodium lauryl sulfate in the water first. After TEC is completely dissolved, add Shin-Etsu AQOAT® and talc gradually.
After the powder is uniformly dispersed, the coating fluid is ready to use. To prevent nozzle clogging, it is recommended to chill the coating fluid with ice bath or electronic chiller, if necessary, to keep under 15℃. Keep stirring gently.




Minimum Film-Forming Temperature of Aqueous Dispersions



Minimum film-forming temperature (MFT) of the aqueous dispersion with Shin-Etsu AQOAT® is dependent on the substitution type of the polymer and the content of plasticizer. The graph shows MFT of aqueous dispersions with various contents of TEC for each grade. The dispersion contains 7.0% of Shin-Etsu AQOAT®, various amount of TEC, and 0.21% of sodium lauryl sulfate in purified water. Based on these characteristics, the regular level of plasticizer is set for each grade, as shown in the following table.

Regular TEC level for aqueous dispersion coating*

AS-LF	20 %
AS-MF	28 %
AS-HF	35 %

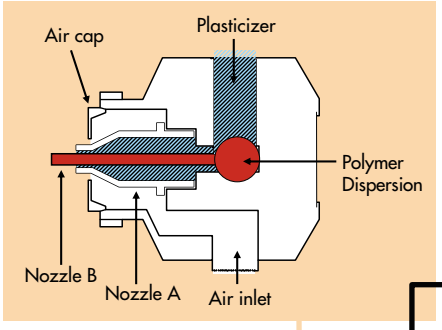
*based on the polymer weight = 100 %

Aqueous Dispersion Coating using "Concentric Dual Feed Spray Nozzle"

Since the nozzle clogging was found to be caused by the strong binding of the polymer and plasticizer, this technique was developed. The key of this method is to spray the two components separately. Using this technique, you don't have the clogging problem, and you don't need to chill the dispersion as in the regular method. As the polymer can be applied in greater concentrations than the regular method, you can achieve shorter processing time.

A newly developed **Concentric Dual Feed Spray Nozzle** is used in this method. Ask your sales representative about the nozzle for your laboratory test.

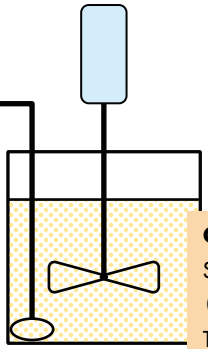
Concentric Dual-Feed Spray Nozzle



Nozzle diameter
(A) 3.0 mm (B) 1.2 mm
Atomizing pressure 300 kPa
Distance to tablet bed 16 cm

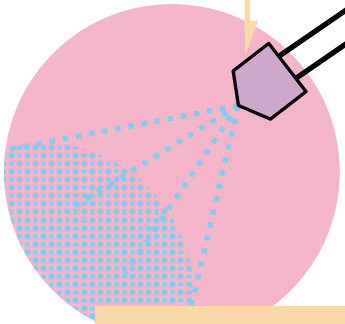
PUMP 1

Feed speed
25 - 50 g/min



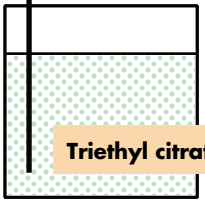
Coating Fluid

Shin-Etsu AQOAT® (AS-MF)	15.0 wt%
Talc	4.5
Sodium lauryl sulfate	0.15
Water	80.35
	(Total 100)

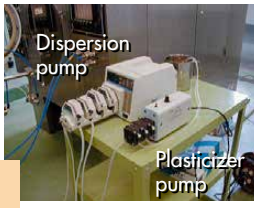


PUMP 2

Plasticizer feed rate
1.1 - 2.1 g/min



Triethyl citrate



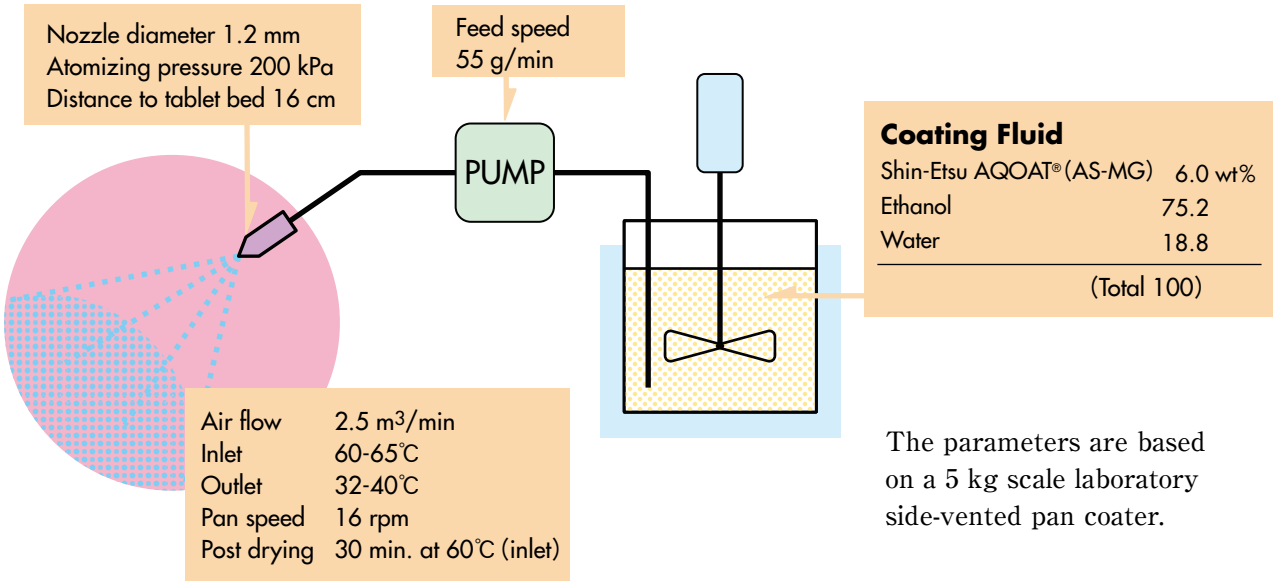
Air flow 2.5 -3 m^3/min
Inlet 70-82℃
Outlet 40-45℃
Pan speed 16-20 rpm
Post drying
30 min. at 60 ℃ (inlet)

Adjust the feed speed so that the polymer and TEC is a proper proportion (See page 8).

The parameters are based on a 5 kg laboratory scale side vented pan coater.

Solvent Based Coating

For preparing a solution with organic solvents, use the granular grades (AS-LG, -MG, or -HG) because the micronized grades may cause the lumping.
Dichloromethane mixture used to be a typical solvent, but nowadays ethanol-water mixtures are preferred due to the environmental issues.
Plasticizer is not necessary in most cases. The coating layer is the most uniform and continuous of all the methods described here.



The parameters are based on a 5 kg scale laboratory side-vented pan coater.

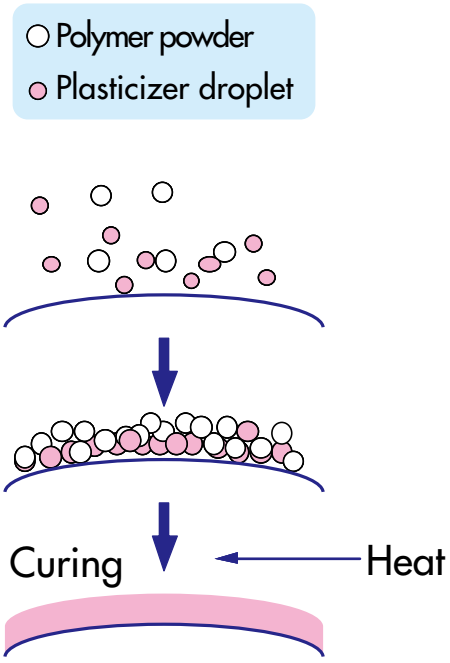
Neutralized Coating

Ammonia is a conventional neutralized agent for this system. The typical coating fluid is as follows.

Shin-Etsu AQOAT® (AS-MG)	7.0 wt%
Talc	2.1
Ammonia	0.13 (as NH_3)
Water	90.77

The optimum level of ammonia depends on the grade. For AS-LG, regularly add ammonia-water so that the pure NH_3 is 2.6 % with regard to the polymer weight. For AS-MG and AS-HG, the optimum level of NH_3 is 1.9 % and 1.1 %, respectively. As the pH of formulation is approximately 7.0, there is no smell of ammonia.
Plasticizer is not necessary in most cases.
The processing parameters are similar to regular aqueous coating such as hypromellose (typically, for a 5 kg batch: inlet 80-83°C, outlet 42°C, spray rate 30 g/min). During the drying process, ammonia is evaporated gradually. Compared to other enteric polymers like hypromellose phthalate, ammonia is more rapidly removed.
The coating layer is uniform and continuous like the one from the solvent-based coating, but the layer absorbs greater amount of acidic media although the tablets appear intact during the gastric resistance test. The coating layer also tends to have a color change during the storage test.
Therefore, please test carefully when applying this method to your core dosage forms before commercializing your product.
Instead of ammonia, basic amino acids such as L-arginine can be used in this system. Polymer is partially neutralized, which brings higher polymer amount and shorter processing time. Please refer our technical information for details.

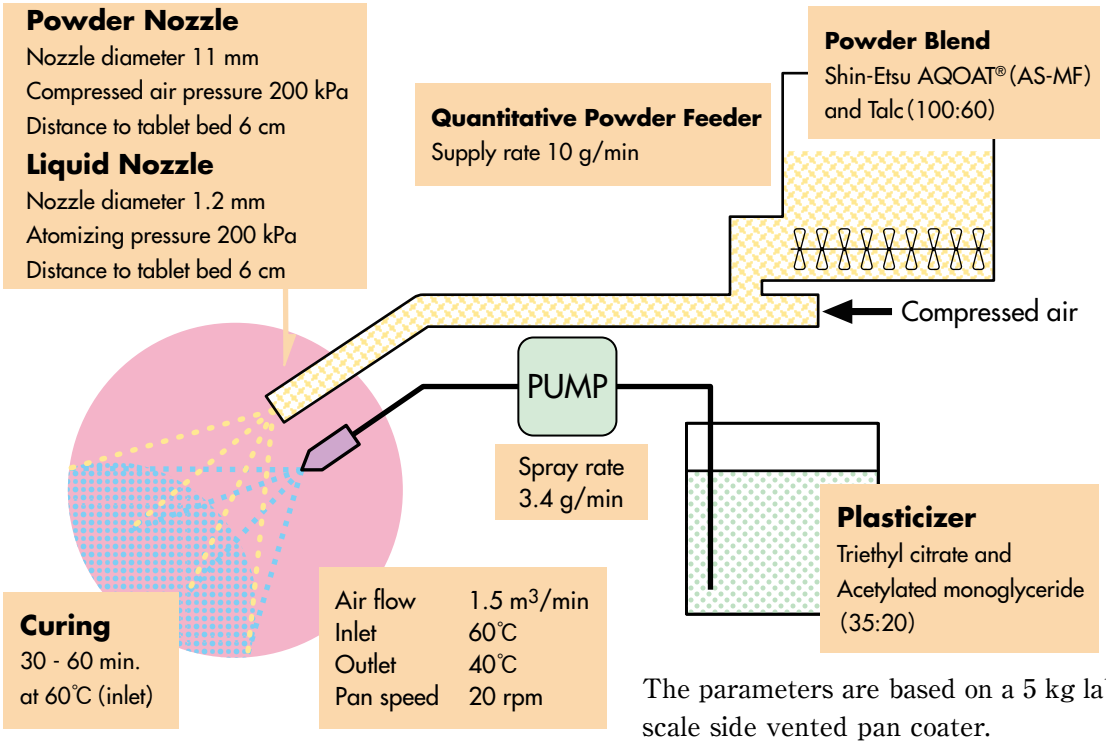
Dry Coating



"Dry coating" is a unique technique in which the polymer powder is directly applied to tablets or granules and the powder layer coalesces to form a film quickly by curing. In 2000, a Japanese pharmaceutical company commercialized this technique using Shin-Etsu AQOAT® for the first time. Greater amount of plasticizer is required, and therefore more coating amount is necessary compared to other coating methods. However, this technique is beneficial especially when your active ingredient is water sensitive and you don't want to use organic solvents.
This technique is applicable for both tablets and granules using a regular apparatus with a powder feeding system. Ask your sales representative for further information.

Basic Formulation

Powder	Shin-Etsu AQOAT® (AS-MF)	100 parts
	Talc	60
Liquid	Triethyl citrate	35
	Acetylated monoglyceride	20



The parameters are based on a 5 kg laboratory scale side vented pan coater.

Pictures of Dry Coating in Laboratory

Tablet Coating
(Side vented pan coater)

Powder feeder

Granule Coating
(Fluidized bed)

Powder feeding

Granule Coating
(Centrifugal granulator)

Plasticizer nozzle

Coating Performance

Data is based on a 5 kg laboratory test using a side vented pan coater for placebo tablets with a diameter of 8 mm.

Comparison between methods

Coating method	Standard polymer concentration in coating fluid (%)	Standard coating amount for gastric resistance (% wt gain)		Processing time (min)	Advantage	Disadvantage
		Polymer	Total solid			
Aqueous (conventional)	7	7	11	154 *1	No solvent	Nozzle clogging
Aqueous (dual-feed)	15	9	14	96 *1	No solvent, faster	Special nozzle required
Ethanol-water	6	8	8	149 *1	Simple, no plasticizer	Cost, residual solvent
Ammonia-neutralized	7	8	11	220 *1	No solvent, no plasticizer	Color change
Dry coating	(100)	10	22	135 *2	No water, faster	Powder feeder required

*1 Includes 30 minute post drying time.

*2 Includes 60 minute curing time instead of post drying.

Stability

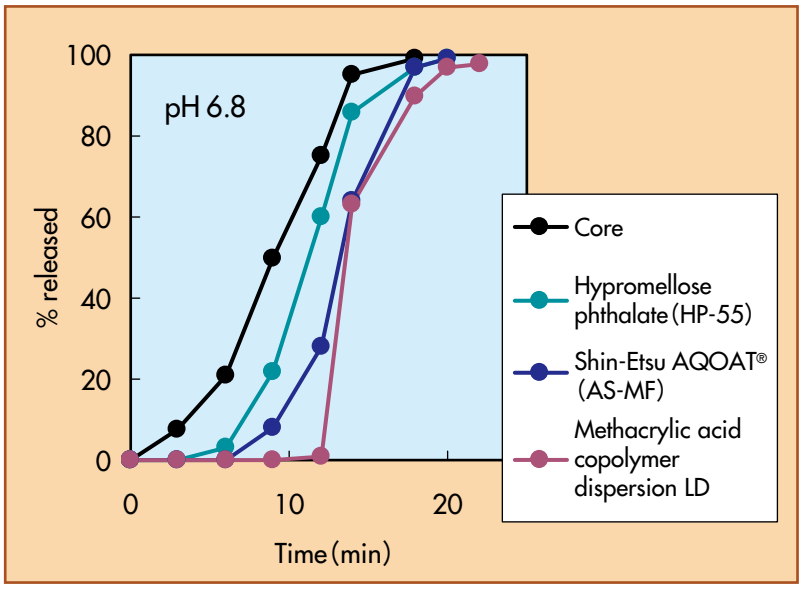
		Aqueous (conventional)	Aqueous (dual feed)	Ethanol-water	Ammonia-neutralized	Dry coating*2
Initial	Gastric resistance*1	3.5	3.4	5.8	11.0	1.9
	Disintegration time (min) at pH 6.8	9	11	9	10	13
After 6 months at 40℃, 75 % RH (closed package)	Gastric resistance*1	3.4	3.9	5.5	4.4	1.5
	Disintegration time (min) at pH 6.8	10	12	9	10	14

*1 Percent uptake of acidic media (pH 1.2) after a 2 hr disintegration test. (All tablets were intact after the test.)

*2 Over coated with carnauba wax.

◆Drug Release at pH 6.8

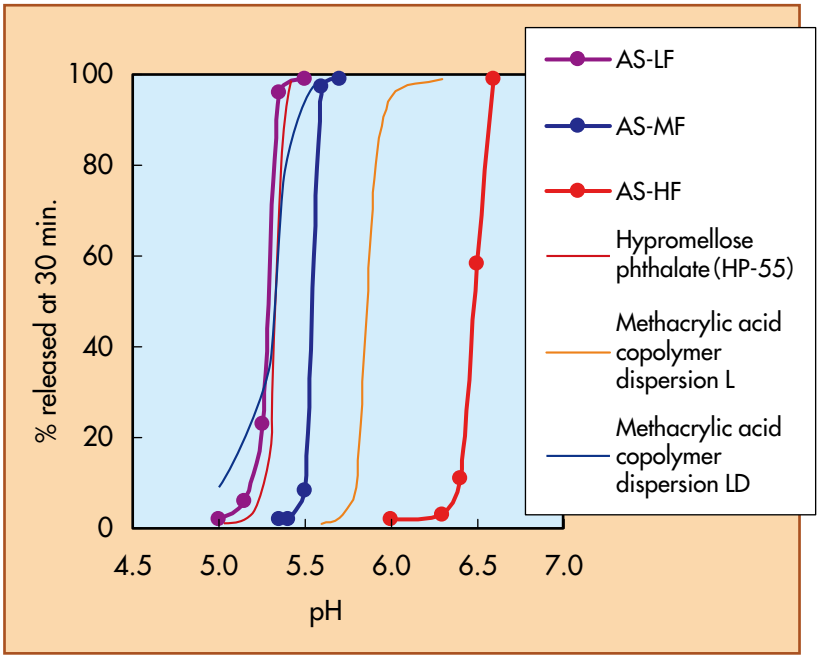
Riboflavin tablets were coated with various enteric coating materials. The coated tablets were intact at pH 1.2 for 2 hrs, and there was no drug release. The right graph shows the drug release at pH 6.8 from the tablets. The coating amount was 9 % for all samples.



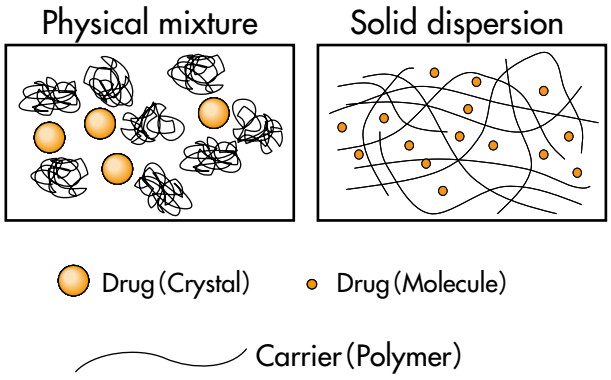
◆Drug Release vs pH

Riboflavin granules were coated with various enteric coating agents using a fluidized bed. Percent release of riboflavin at 30 minutes was measured using a dissolution tester (paddle 100 rpm). USP phosphate buffer and phthalate buffer were used as the test fluids.

The three grades of Shin-Etsu AQOAT® show different patterns of the pH dependency in drug release. AS-LF shows a similar profile to methacrylic acid copolymer dispersion LD or HP-55 (hypromellose phthalate). Other two grades release the drug at higher pH. These characteristics enable this material to be used in a controlled release dosage forms for targeting of drug release at a specific gastro intestinal site.

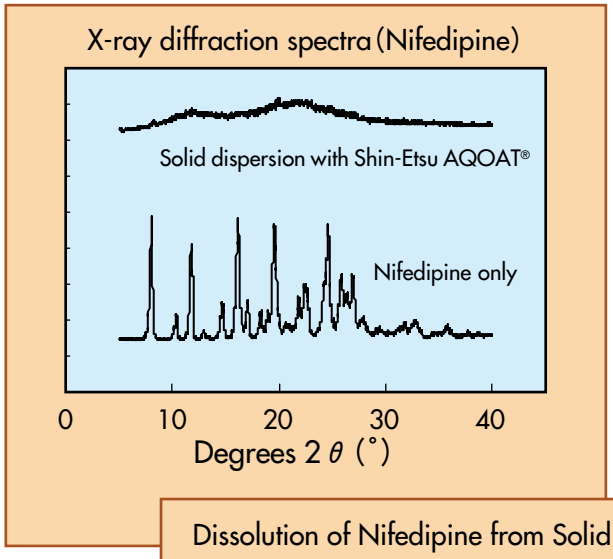


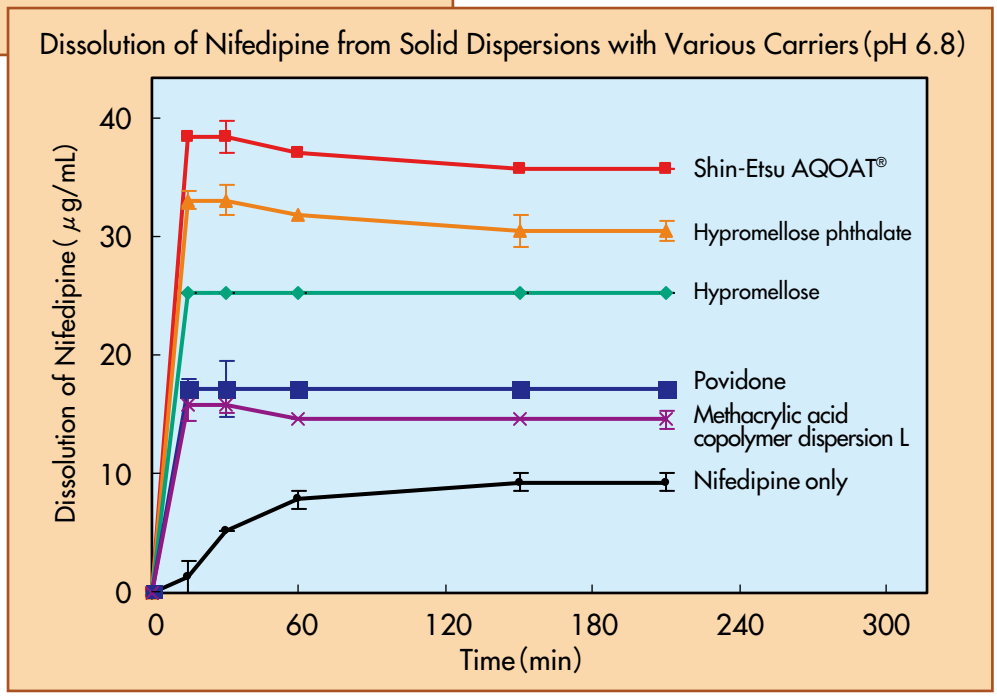
Solid Dispersions



"Solid dispersion" is a technique to enhance bioavailability of poorly-soluble drugs by increasing solubility. For a typical method of preparation, the drug and polymer (carrier) are dissolved together in a common solvent and the solution is spray-dried or coated on some core formulations. The resulting solid is a "molecular matrix" of the polymer and the drug, which demonstrates a significantly greater solubility compared to the original solubility of the drug. It has been reported that in this application Shin-Etsu AQOAT® enhances solubility of a poorly-soluble drug more effectively than other pharmaceutical polymers (Tanno et al., 2004).

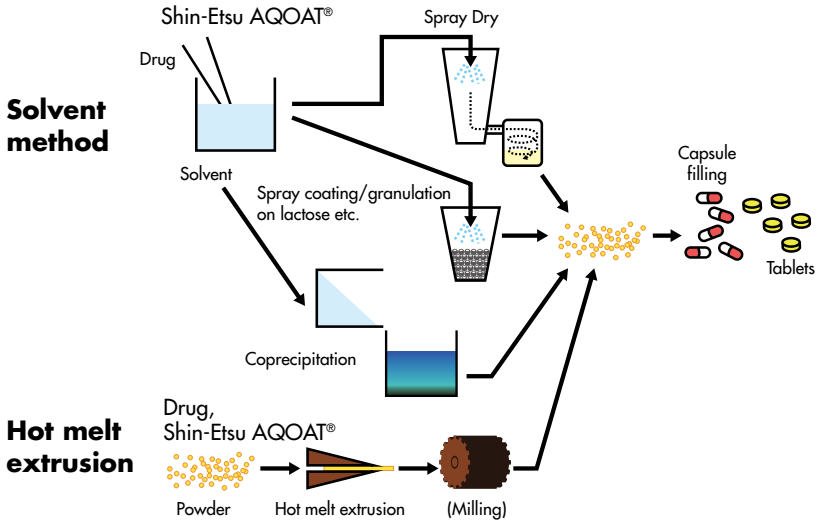
The present graphs show data on solid dispersions of nifedipine, a poorly-soluble drug. The solid dispersions were prepared by spray drying. In the solid dispersion, the crystalline peaks of nifedipine disappeared in the X-ray diffraction analysis. The solid dispersion using Shin-Etsu AQOAT® improved the drug solubility compared to the ones with different carriers.





◆Preparation Methods

Solid dispersion can be prepared by several ways. Shin-Etsu AQOAT® is suitable in every way due to its solubility in organic solvents and relatively low Tg. Depending on the conditions such as solubility and Tg of drug, suitable method can be selected.



◆Formulation Examples

1) Spray coating

Formulation	**wt%**
(Coating fluid)	
Nifedipine	5
Shin-Etsu AQOAT®(AS-MG)	10
(Core)	
L-HPC(LH-B1)	40
Filler	45
(Lactose and corn starch)	

Fluid Bed Granulation
Equipment: Multiplex MP-01(Powrex,Japan)
Inlet air: 60℃
Fluidizing air: 60-71 m^3/hr
Spray rate: 10 g/min
Nozzle pressure: 150 kPa
Solvent: ethanol/water(8/2, w/w)
Conc.: Nifedipine 3 %; HPMCAS 6 %

Tablet Preparation
Granules were compressed into tablets with rotally tabletting machine.
(9 mm-d, 210 mg/tab, Main; 195 MPa, Pre; 65 MPa)

2) Hot melt extrusion

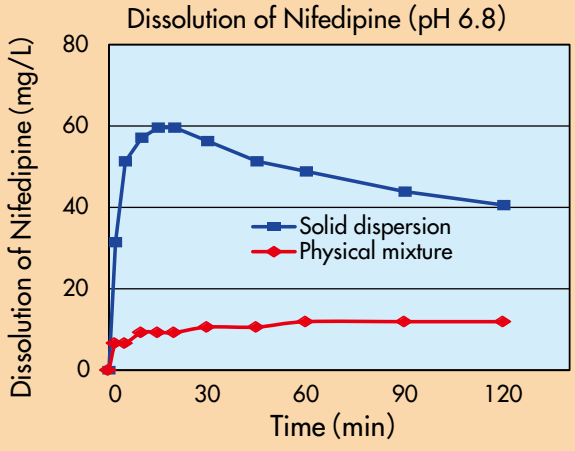
Formulation	**wt%**
Ibuprofen	33
Shin-Etsu AQOAT®(AS-LF)	67

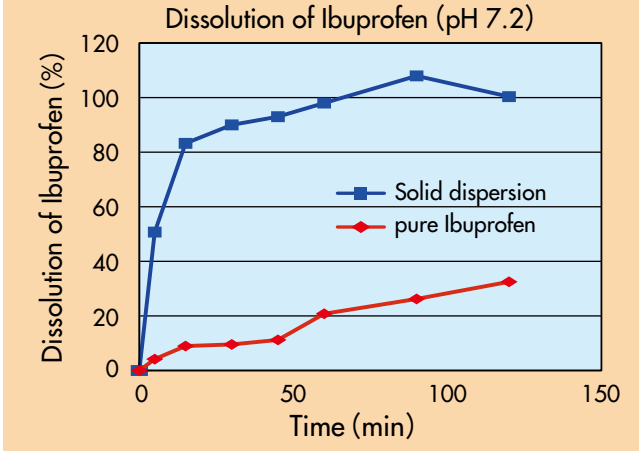
Ibuprofen and AS-LF in a 1:2 wt/wt ratio were blended in a Turbula mixer for 10 min

Hot Melt Extrusion
Processing parameters
Equipment: Pharmalab,Thermo Scientific, UK
Feeder; Brabender, Germany
Length-to-diameter ratio: 40:1 at 0.2 kg/h
Screw speed:150 rpm
Temperature profile; shown as below

Zone No.	1	2	3	4	5	6	7	8	9	Die
Temp. ℃	20	50	70	90	100	100	100	100	100	100

Extruded strands were collected and allowed to cool. The collected samples were cut into pellets using a pelletizer (Varicut,Thermo Scientific,UK).





Product Information

The grades are shown in below table.
Please contact us for the latest product specification.

Grades	Viscosity* (mPa·s)	Methoxy content (%)	Hydroxypropoxy content (%)	Acetyl content (%)	Succinoyl content (%)	Particle	pH Solubility
LF	2.4 – 3.6	20.0 – 24.0	5.0 – 9.0	5.0 – 9.0	14.0 – 18.0	Fine**	≧ 5.5
LG						Coarse	
MF		21.0 – 25.0	5.0 – 9.0	7.0 – 11.0	10.0 – 14.0	Fine**	≧ 6.0
MG						Coarse	
HF		22.0 – 26.0	6.0 – 10.0	10.0 – 14.0	4.0 – 8.0	Fine**	≧ 6.5
HG						Coarse	

* Viscosity of 2 wt% solution of sodium hydroxide solution at 20 ℃

** D_{50} : NMT 10 μm, D_{90} : NMT μm by laser diffraction method

Package

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

Dust explosivity parameters of AQOAT® (AS-HF)

● Kst [1)]	351 bar·m/s
● ST classification [1)]	ST-3
● Maximum explosion pressure [1)]	9.0 bar
● Maximum rate of pressure rise [1)]	710 bar/s
● Minimum explosive concentration [1)]	40 - 50 g/m^3
● Minimum ignition energy [1)]	3 - 5 mJ

1) In house data was determined by Chilworth Technology Inc., New Jersey, USA

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 dust generation. 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 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 :

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