NF
Hypromellose Acetate Succinate

Shin-Etsu AQOAT

Enteric Coating Agent

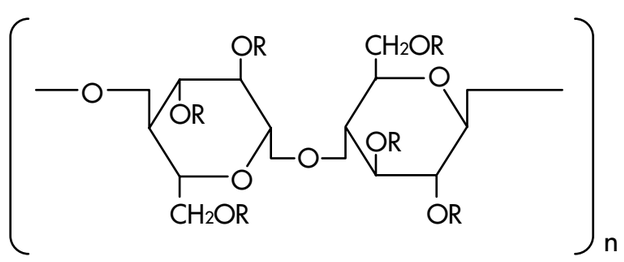
CONTENTS

Introduction

Shin-Etsu AQOAT (pronounced *"Ay-coat"*), Hypromellose Acetate Succinate is an enteric coating material which was first approved in Japan in 1987.
As of 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.
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 Hydroxypropyl Methylcellulose Acetate Succinate JPE
Abbreviation	HPMCAS
IUPAC name	Cellulose, 2-hydroxypropyl methyl ether, acetate, hydrogen butanedioate
CAS registry number	71138-97-1
Compendial status	JPE (Japanese Pharmaceutical Excipients) 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 Methylcelulose) 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 this constitutes Shin-Etsu AQOAT, Hypromellose Acetate Succinate.

Pulp
(Pure cellulose)

Chloromethane
Propylene oxide

Hypromellose
(Hydroxypropyl Methylcellulose)

Acetic anhydride
Succinic anhydride

Shin-Etsu AQOAT
(Hypromellose Acetate Succinate)

Available grades*

Grade		Acetyl %	Succinoyl %	Mean Particle Size	Labeled Viscosity
Micronized	AS-LF	8	15	5μm	3 mm^2/s
	AS-MF	9	11		
	AS-HF	12	6		
Granular	AS-LG	8	15	1mm	
	AS-MG	9	11		
	AS-HG	12	6		

*The data shows only typical values and not specifications. For specifications, see page 17.

Physicochemical Properties

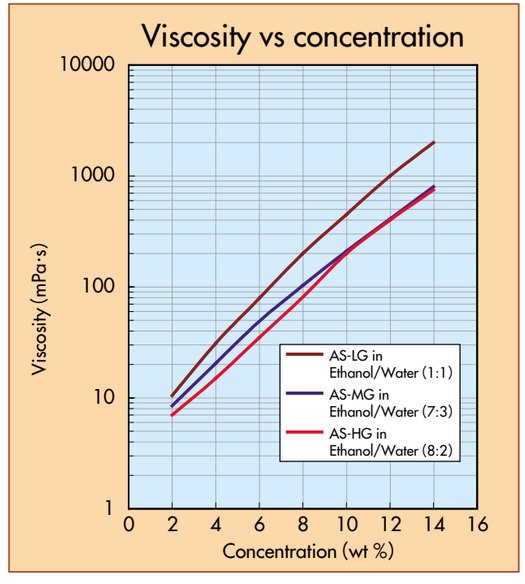
There are six grades available as shown on the previous page. They have different particle sizes and chemical substitution levels. **The following data shows only typical values and not specifications.** The numbers vary slightly depending on lot, grade, and determination method. For specifications, see page 17 of this brochure.

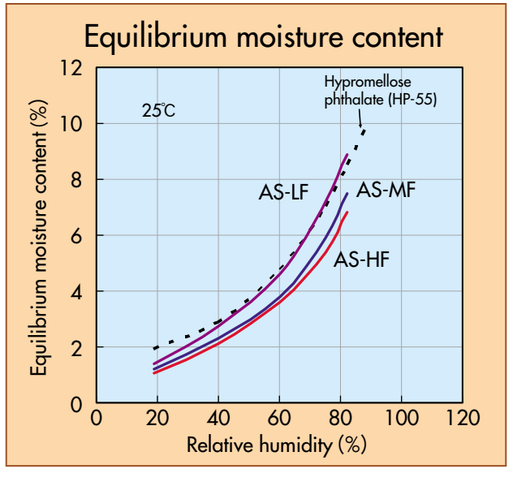
Appearance	White to yellowish powder or granules with a faint, acetic acid-like odor. Tasteless.
True density	1.27 - 1.30 g/cm^3 (measured with helium pycnometer)
Bulk density	Micronized grade: 0.2 - 0.3 g/mL, Granular grade: 0.2 - 0.5 g/mL
Tap density	Micronized grade: 0.3 - 0.5 g/mL, Granular grade: 0.3 - 0.6 g/mL
Molecular weight	18000 (weight-average, measured with SEC-MALLS)
Degree of polymerization	70 (weight-average, measured with SEC-MALLS)
Thermal degradation temperature	200 ℃

Solubility

	AS-LF AS-LG	AS-MF AS-MG	AS-HF AS-HG
Acetone	S	S	S
Methanol	S	S	S
99% Ethanol	I	I	I
CH_2Cl_2	I	P	P
Ethanol - Water (8:2)*	S	S	S
Ethanol - Water (1:1)*	S	P	P
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





Film Properties

Glass transition temperature*

AS-LG	120 (°C)
AS-MG	130
AS-HG	135
Hypromellose phthalate	145
Hypromellose	165

*Film softening temperature in thermo - mechanical analysis

The film specimens were cast from organic solvent.

Film strength (ASTM)

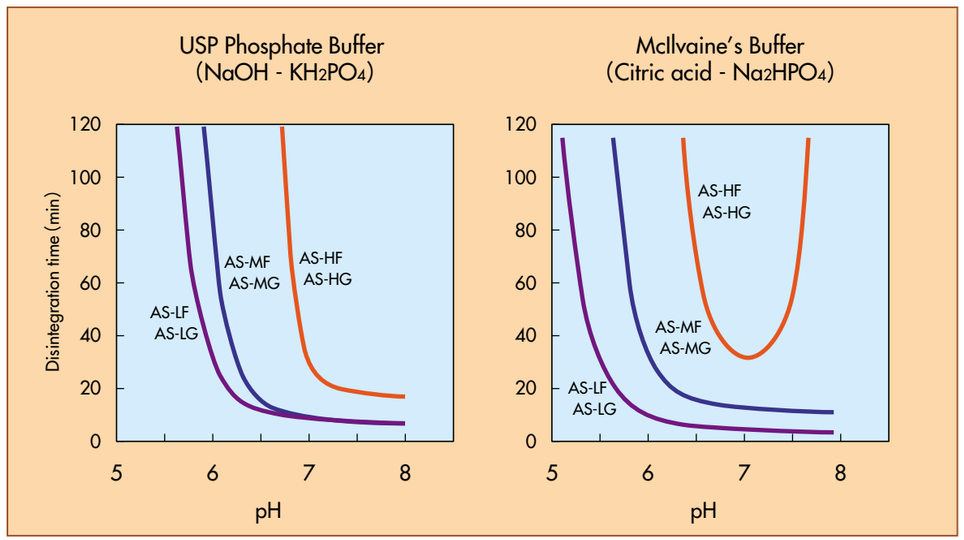
	AS-LG	AS-MG	AS-HG
Tensile strength at break (MPa)	52	51	55
Elongation (%)	8.4	7.2	4.3

Water vapor permeability (0%/75%RH)

AS-LG	165 (g/m^2/24hrs)
AS-MG	185
AS-HG	210

Film solubility at various pH

Cast films were cut into 1 cm x 1 cm pieces of 100μm 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.



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, you avoid the nozzle-clogging problem encountered with spraying the dispersion at room temperature. In addition, you can increase the polymer concentration which achieves shorter coating time.

Variety of Enteric Coating with Shin-Etsu AQOAT

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.

Ammonia-Neutralized Coating

If you want uniform and continuous film coating as in the solvent coating but do not want to use organic solvents, this procedure is available (There may be some limitation in gastric resistance and stability).

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.

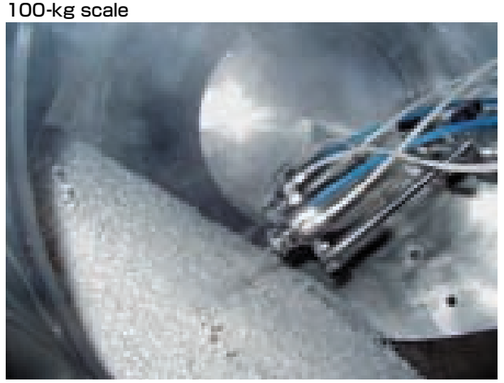
Other applications

Solid Dispersions

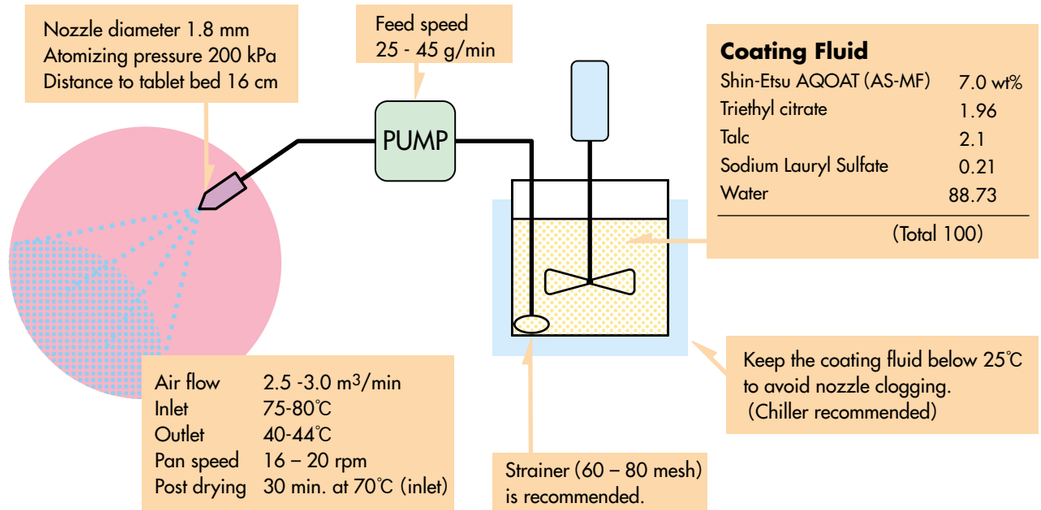
This technique significantly enhances bioavailability of poorly-soluble drugs by increasing solubility.

Conventional Aqueous Dispersion Coating

100-kg scale



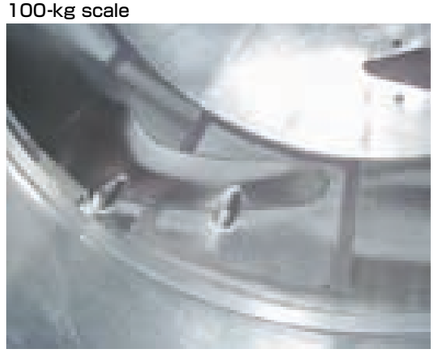
This is the conventional aqueous dispersion coating method for which Shin-Etsu AQOAT was originally developed. Micronized polymeric powder is dispersed in water and sprayed onto core. Plasticizer is required for the film formation. The following parameters are based on 5-kg scale laboratory operation 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 in 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.



Coating Fluid

Shin-Etsu AQOAT (AS-MF)	7.0 wt%
Triethyl citrate	1.96
Talc	2.1
Sodium Lauryl Sulfate	0.21
Water	88.73
	(Total 100)

100-kg scale



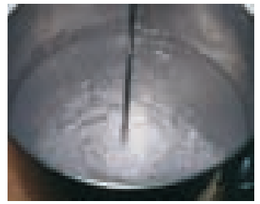
After coating, the inside of pan is very clean compared to other enteric coating agents. You can save time for cleaning.

◆Ingredients

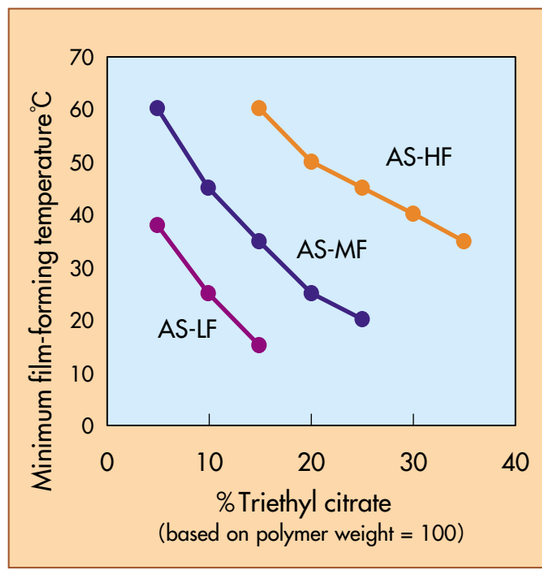
For aqueous dispersion, use a micronized grade. Maximum polymer concentration is 7 %. Greater concentrations may clog the spray nozzle.
Triethyl citrate (TEC) is the only compatible plasticizer for Shin-Etsu AQOAT. The optimum amount of TEC depends on grade (See the following table on this page). Sodium 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 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 25℃. 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 %

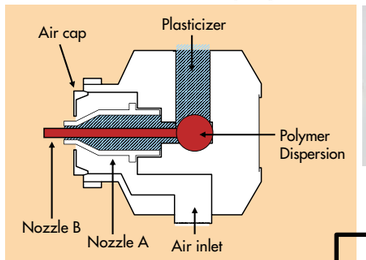
*based on the polymer weight = 100 %

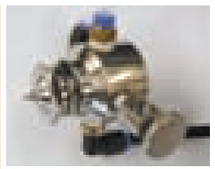
Aqueous Dispersion Coating using "Concentric Dual-Feed Spray Nozzle"

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.

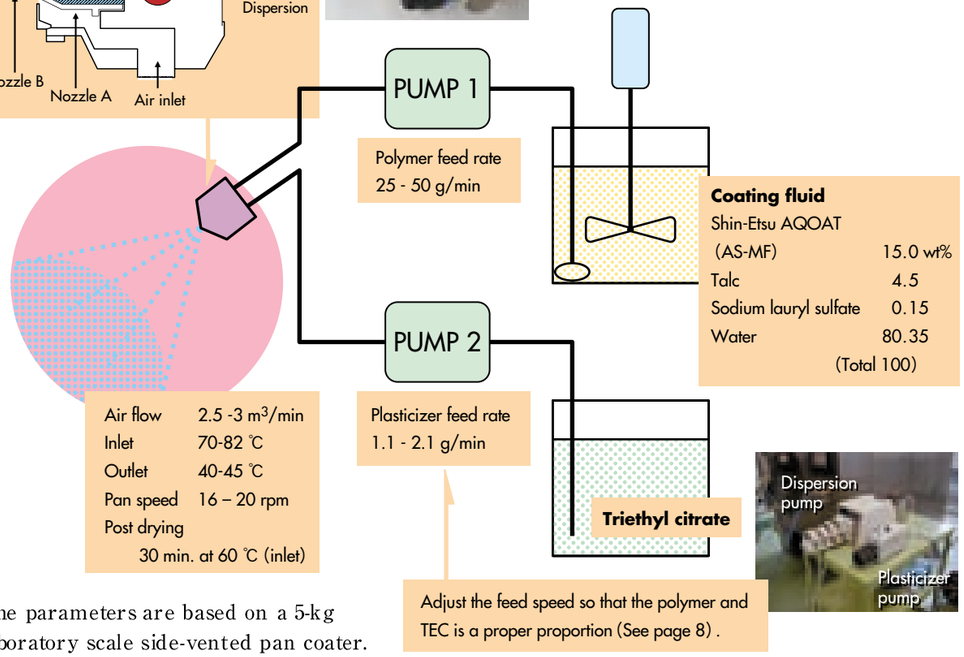
A newly-developed **Concentric Dual-Feed Spray Nozzle** is used in this method. Ask your sales representative about the nozzle for your laboratory test.

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

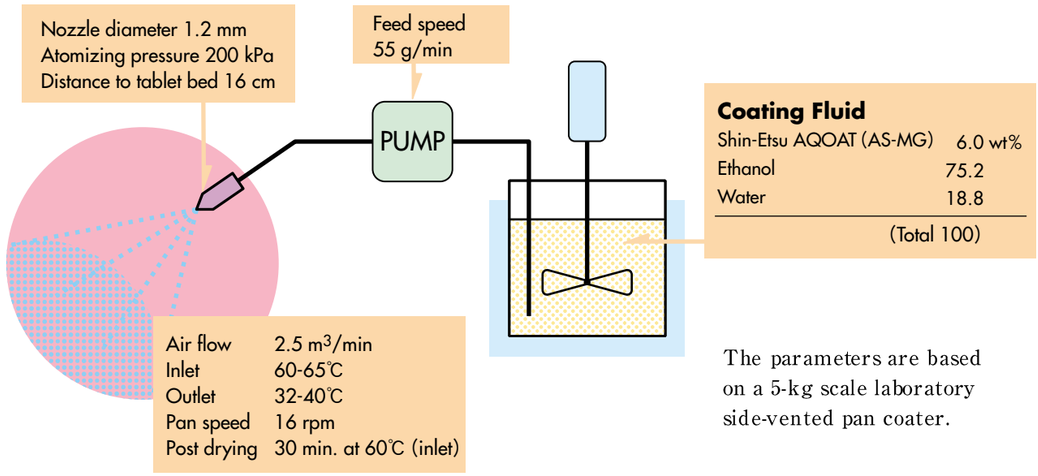


The parameters are based on a 5-kg laboratory scale side-vented pan coater.

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 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.

Ammonia-Neutralized Coating

Ammonia-neutralized coating fluids can also be applied. A typical formulation for the coating fluid is as follows:

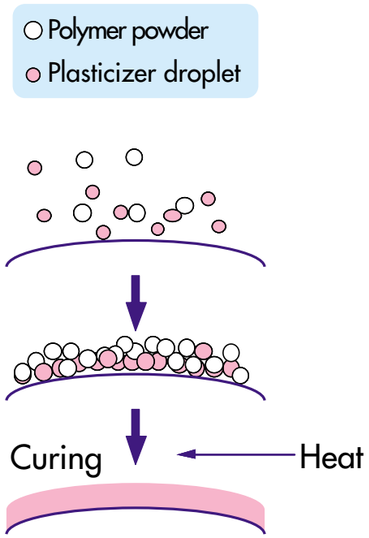
Shin-Etsu AQOAT (AS-MG)	7.0 wt%
Talc	2.1
Ammonia	0.13 (as NH_3)
Water	90.77

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.

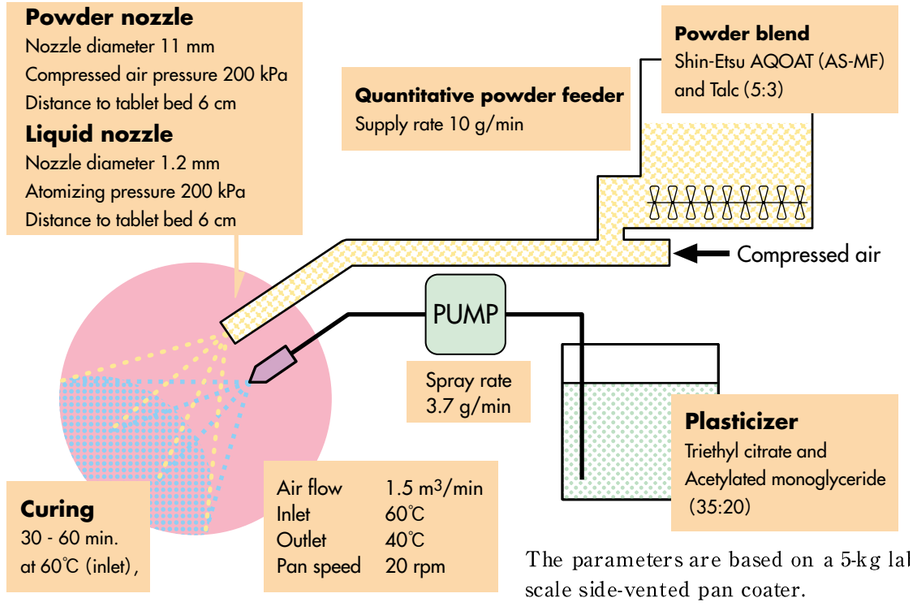
Dry Coating



"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

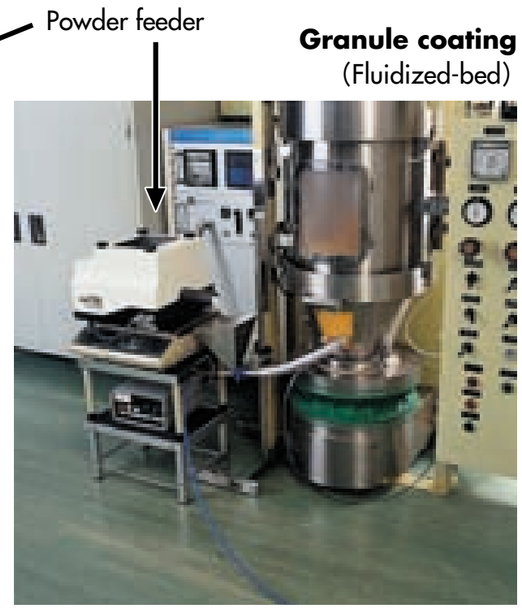
Powder	Shin-Estu AQOAT (AS-MF)	100 parts
	Talc	60
Liquid	Triethyl citrate	35
	Acetylated monoglyceride	20



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

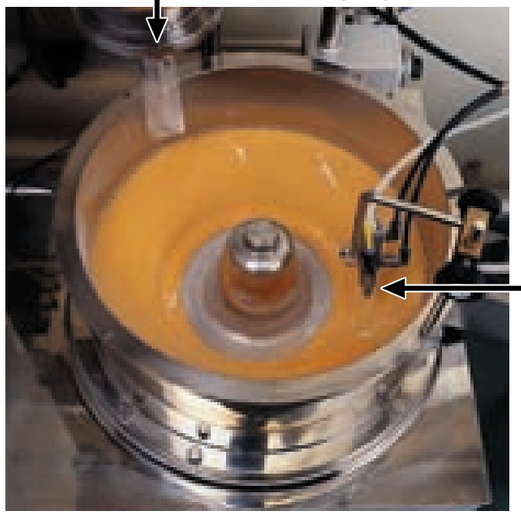
Pictures of Dry Coating In the Laboratory

Tablet coating
(Side-vented pan coater)



Granule coating
(Fluidized-bed)

Granule coating
(Centrifugal granulator)



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.

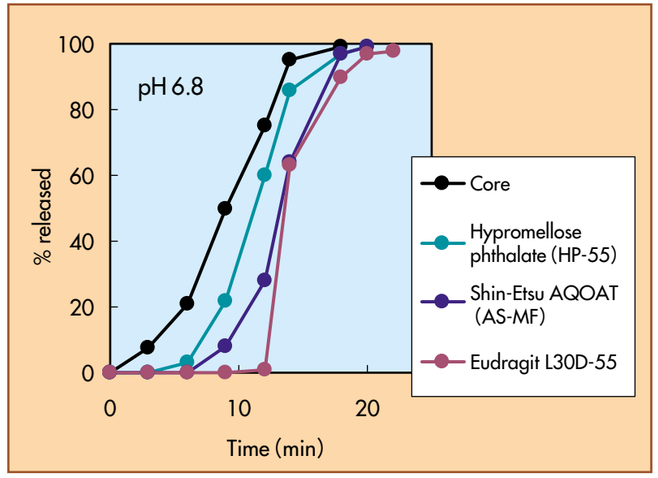
Stability

		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	10	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	9	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

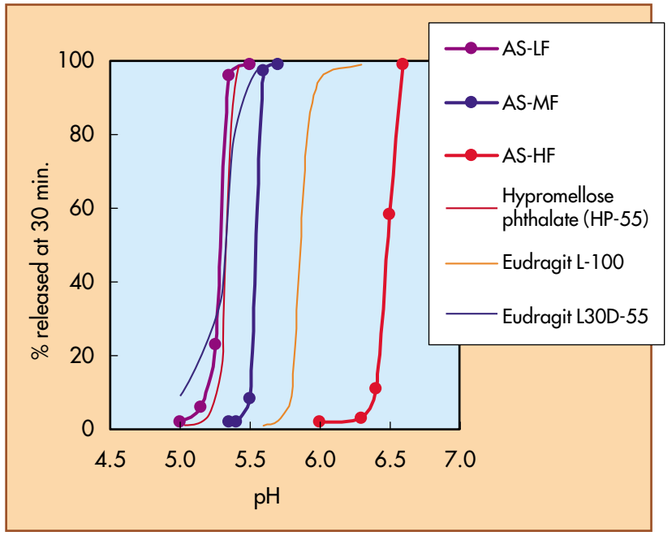
Riboflavin tablets were coated with various enteric coating materials. The coated tablets were intact at pH 1.2 for 2 hrs, and there was no drug release. The right graph shows the drug release at pH 6.8 from the tablets. The coating amount was 9 % for all samples.



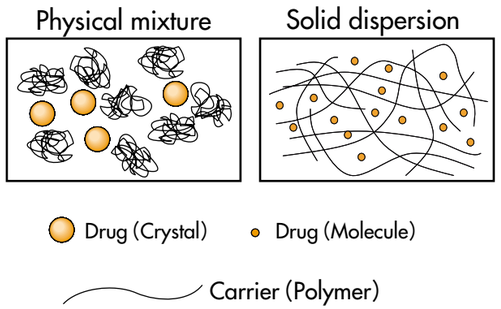
◆Drug release vs pH

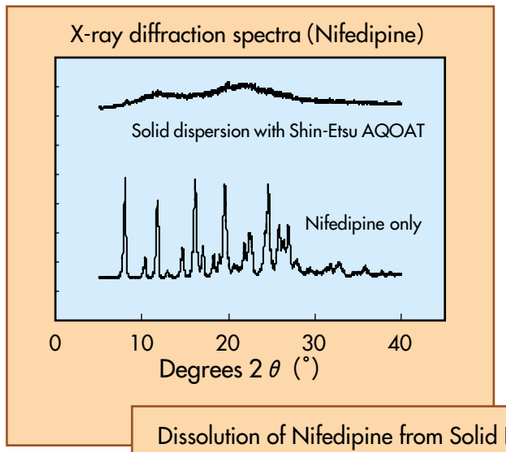
Riboflavin granules were coated with various enteric coating agents using a fluidized-bed. Percent release of riboflavin at 30 minutes was measured using a dissolution tester (paddle 100 rpm). USP phosphate buffer and phthalate buffer were used as the test fluids.

The three grades of Shin-Etsu AQOAT show different patterns of the pH dependency in drug release. AS-LF shows a similar profile to Eudragit L30D-55 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.



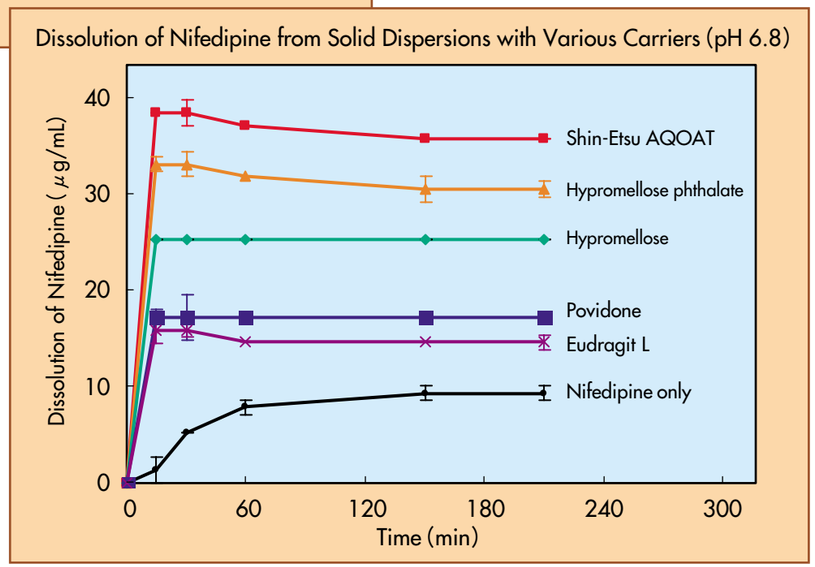
Solid Dispersions





"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 released the greatest amount of the drug compared to the ones with different carriers.



Bibliography

【Conventional aqueous coating, characteristics】
T. Nagai, S. Obara, H. Kokubo, and N. Hoshi, Application of HPMC and HPMCAS to aqueous film coating of pharmaceutical dosage forms. In Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, 2nd Ed., J.W. McGinity Ed., Marcel Dekker, Inc., New York, 1997, pp. 177-225.

【Dissolution mechanism】
A. Takahashi, T. Kato, and F. Kamiya, Dissolution mechanism for hydroxypropyl methylcellulose acetate succinate used in enteric coating of tablets. Kobunshi Ronbunshu 42, 803-808 (1985) [In Japanese].

【Film properties】
S. Obara, and J.W. McGinity, Influence of processing variables on the properties of free films prepared from aqueous polymeric dispersions by a spray technique. Int. J. Pharm. 126, 1-10 (1995).

【Aqueous coating using concentric dual-feed nozzle】
J. Brunemann, Y. Nishiyama, and H. Kokubo, A plasticizer separation system for aqueous enteric coating using a concentric dual-feed spray nozzle., Pharm. Tech. Europe, 14, 41-47 (2002).

【Ammonia-neutralized coating】
M. Baudoux, D. Kapusta, and L. Delattre, Enteric film coating with aqueous solutions of hydroxypropyl methylcellulose acetate succinate. Congr Int. Tech Pharm, 6th, 243-250 (1992)

【Dry coating】
N. Maruyama, Y. Nishiyama, and H. Kokubo, Enteric Coating with Micronized Polymeric Powder, J. Soc. Powder Technol., Japan, 35, 443-446 (1998) [In Japanese].

N. Maruyama, Y. Nishiyama, and S. Obara, Process control of enteric dry coating using an insulation tester. PharmTech Japan, 13, 105-111 (1997) [In Japanese]

S. Obara, N. Maruyama, Y. Nishiyama, and H. Kokubo, Dry coating: an innovative enteric coating method using a cellulose derivative., Eur. J. Pharm. Biopharm, 47, 51-59 (1999).

【Solid dispersion】
F. Tanno, Y. Nishiyama, H. Kokubo, and S. Obara, Evaluation of hypromellose acetate succinate (HPMCAS) as a carrier in solid dispersions, Drug. Dev. and Ind. Pharm, 30, 9-17 (2004).

【Dust explosivity】
H. Mukai, H. Muto, and Y. Onda, The dust explosivity of sevaral kinds of cellulose derivatives. J. Soc. Powder Technol., Japan, 32, 4-9 (1995) [In Japanese].

【Toxicology】
N. Hoshi, H. Yano, K. Hirashima, H. Kitagawa, and Y. Fukuda, General pharmacological studies of HPMCAS in experimental animals. J. Toxicol. Sci. 10 (S2), 129-146 (1985).

N. Hoshi, H. Yano, K. Hirashima, H. Kitagawa, and Y. Fukuda, Toxicological studies of hydroxypropyl methylcellulose acetate succinate - acute toxicity in rats and rabbits, and subchronic and chronic toxicities in rats. J. Toxicol. Sci. 10 (S2), 147-185 (1985).

N. Hoshi, K. Ueno, T. Igarashi, H. Kitagawa, T. Fujita, N. Ichikawa, Y. Kondo, and M. Isoda, Studies of hydroxypropylmethylcellulose acetate succinate on fertility in rats. J. Toxicol. Sci. 10 (S2),187-201 (1985).

N. Hoshi, K. Ueno, T. Igarashi, H. Kitagawa, T. Fujita, N. Ichikawa, Y. Kondo and M. Isoda, Teratological study of hydroxypropylmethylcellulose acetate succinate in rats. J. Toxicol. Sci. 10 (S2), 203-226 (1985).

N. Hoshi, K. Ueno, T. Igarashi, H. Kitagawa, T. Fujita, N. Ichikawa, Y. Kondo and M. Isoda, Teratological study of hydroxypropylmethylcellulose acetate succinate in rabbits. J. Toxicol. Sci. 10 (S2), 227-234 (1985).

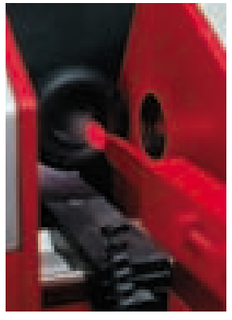
N. Hoshi, K. Ueno, T. Igarashi, H. Kitagawa, T. Fujita, N. Ichikawa, Y. Kondo and M. Isoda, Effects on offspring induced by oral administration of hydroxypropyl methylcellulose acetate succinate to the female rats in pre- and post-natal periods. J. Toxicol. Sci. 10 (S2), 235-255 (1985).

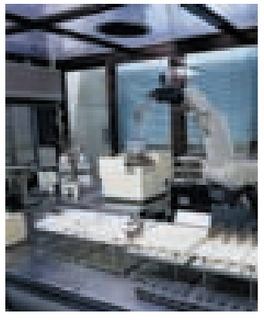
Product Specifications

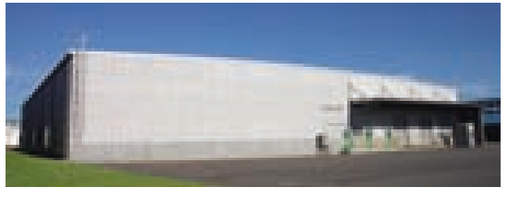
Test item / Grade	AS-LG AS-LF	AS-MG AS-MF	AS-HG AS-HF	Method
Identification (1R)	Conforms			USP/NF
Viscosity	2.4 - 3.6 cP			
Loss on drying	Not more than 5.0%			
Residue on ignition	Not more than 0.20%			
Heavy metals	Not more than 0.001%			
Free acetic acid succinic acid	Not more than 1.0 %			
Acetyl content	5.0 - 9.0 %	7.0 - 11.0 %	10.0 - 14.0 %	
Succinoyl content	14.0 - 18.0 %	10.0 - 14.0 %	4.0 - 8.0 %	
Methoxyl content	20.0 - 24.0 %	21.0 - 25.0 %	22.0 - 26.0 %	
Hydroxypropoxyl content	5.0 - 9.0 %	5.0 - 9.0 %	6.0 - 10.0 %	
Particle size (For AS-LF, MF, and HF only)	Average : Not more than 10 μm 90 % cumulation : Not more than 20 μm			Shin-Etsu Laser Diffraction Method

Package

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







ISO 9001
ISO 14001
Naoetsu Plant
JCQA-0018
JCQA-E-0064

QS,EMS
Accreditations
JAB-R003,RE003

The Manufacture of Shin-Etsu Celluose derivatives are based on the mentioned registered quality standard and environmental management system.

Precautions for Safe Handling

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

When handling in large quantities or bulk, 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 NFPA 654 "Standard for the Prevention of Fire and Dust Explosions from the Manufacturing, Processing, and Handling of Combustile Particulate Solids" and NFPA 77 "Recommended Practice on Static Electricity" are recommended.

Dust explosivity parameters hazard class of AQOAT :

- F grades: St 3

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 water for at least 15 minutes 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 re-use.

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.

****

Carefully read and understand the material safety data sheet (MSDS) 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.

Cellulose & Pharmaceutical Excipients Department
6-1, Ohtemachi 2-chome, Chiyoda-ku, Tokyo 100-0004
JAPAN
TEL: 81-3-3246-5261 FAX: 81-3-3246-5372
http://www.metolose.jp/e

04.9 05.10/1000