Shin-Etsu

USP
Hypromellose

METOLOSE SR

Sustained Release Agent for Matrix System

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.

Shin-Etsu Chemical started the production of water-soluble cellulose ethers such as Hypromellose and Methylcellulose, with the trade name METOLOSE, in 1962, and low viscosity type Hypromellose (Pharmacoat), was developed as a film coating agent in 1963.

Hydrophilic matrix systems designed with water-soluble polymers, such as Hypromellose, were first introduced in the early 1970's. Since then, development work has concentrated on controlled release technology, and many types of advanced polymers and techniques have become available. The hydrophilic matrix system is the simplest sustained release technology for oral dosage forms, consisting essentially of a drug and a water soluble, highly viscous polymer. It does not require any other excipient.

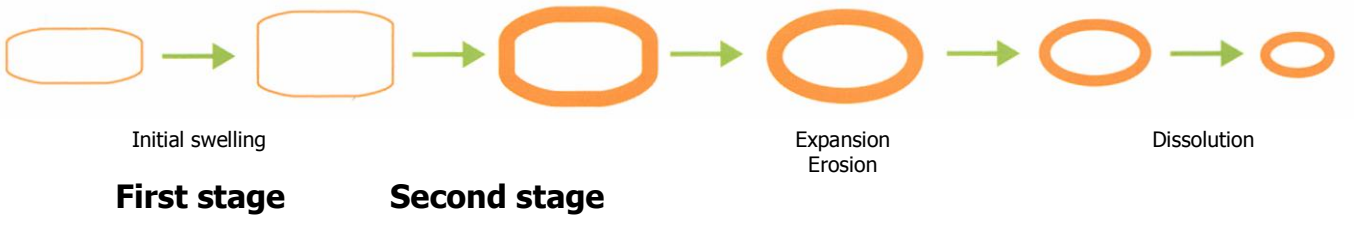
Recent advances in this hydrophilic matrix system have allowed more controllable and reproducible drug release by controlling the chemical and physical properties of the polymer. METOLOSE SR (Hypromellose) is especially suitable for this application, and provides a genuine consistency in the final products.

METOLOSE SR, USP Hypromellose (HPMC), is exclusively designed for a hydrophilic matrix agent having tighter specifications, which is especially suitable for direct compression application.
The matrix system has several advantages as follows,

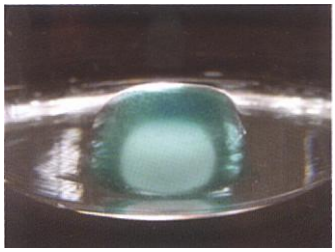
1. It is very simple and easy to establish a formulation.
2. The tablet is completely dissolved and thus achieves good bioavailability.
3. It is easy to control the dissolution profile by selecting a specific grade.
4. The matrix system is an economical method for obtaining controlled release products.

Figure 1 illustrates the schematic dissolution profile of the matrix tablet. After administration, hydrophilic matrix tablets made with METOLOSE SR hydrate to form a gel layer, which regulates the drug release pattern. The most important aspect of this matrix system is the homogeneity of HPMC particle distribution in the tablet. The selection of METOLOSE grades affects the initial wetting, swelling, hydration and gel strength. In the first stage, usually within 30 to 60 minutes after administration, before the completion of the gel layer, the polymer particles on the tablet surface become partially hydrated. Sometimes surface erosion or excess dissolution can be observed in tins period. In the second stage, the gel layer is completed, and a steady dissolution of the active ingredient occurs.

Figure 1. Schematic dissolution profile of the matrix tablet



General information on major factors



Factors affecting the drug release are shown in table 1 and next page

Table 1. Factors affecting the drug release from the matrix tablet

1. Solubility of drug	**Solubility in water** pH dependency
2. HPMC properties	**Substitution type of HPMC** **Viscosity of HPMC** (related to molecular weight) Particle size Particle shape (related to bulk density)
3. Composition	**HPMC content in the tablet** Tablet size Other excipients
4. Preparation	**Direct compression or wet granulation** Compression force Tablet shape Film coating

METOLOSE includes several types with different levels of substitution. Chemical name and CAS registry numbers are listed below.

Table 2. Types of METOLOSE

Type	Methoxy (%)*1	Hydroxypropoxy (%)*1	Name in the USP	CAS registry number
SM	26.0—33.0	—	Methylcellulose	9004-67-5 cellulose, methyl ether
60SH	28.0—30.0	7.0—12.0	Hypromellose, Substitution type 2910	9004-65-3 Cellulose, 2-hydroxypropyl methyl ether
65SH	27.0—30.0	4.0—7.5	Hypromellose, Substitution type 2906	
90SH	19.0—24.0	4.0—12.0	Hypromellose, Substitution type 2208	

*1: the ranges are expressed as the USP specification.

General information on major factors

1. Drug solubility is one of the most influential factors for designing a drug release pattern. Highly water- soluble drugs require higher amounts of HPMC in the tablet.
2. Suitable types of HPMC are the METOLOSE 60SH and 90SH grades, especially 90SH-SR grades, which have a characteristic of quick hydration and gel formation.
3. The higher viscosity of HPMC or amount of HPMC in the tablet can decrease the drug release rate. Generally, an optimum content of METOLOSE in the tablet is at least 20%. If the content is below 20%, there is a risk for initial erosion or excess dissolution in the first stage.
4. Preparation method also affects the dissolution profile due to the difference of HPMC particle distribution in the tablet. In the case of wet granulation, most of the water can be taken up by METOLOSE, resulting in the separation of METOLOSE and the other components. (i.e. large particles with high METOLOSE content and ungranulated drug in the fine particle fraction.) Direct compression methods can avoid such processing factors.

How to adjust the dissolution profile

In case dissolution is too fast:

1. Increase the content of METOLOSE in the tablet formulation.
2. Select higher viscosity grade of METOLOSE.
3. Increase the tablet size.

In case dissolution is too slow:
Opposite adjustments of too fast dissolution.

Figure 2. Dissolution profile: High solubilty in water

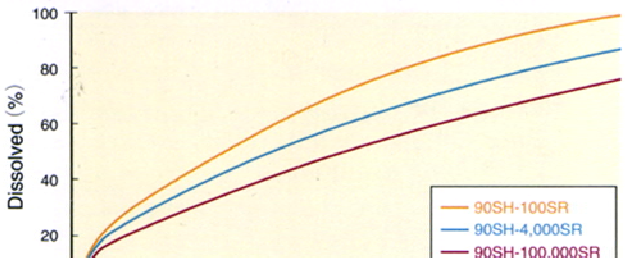
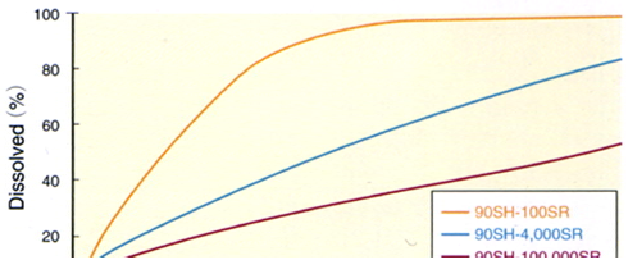


Figure 3. Dissolution profile: Low solubilty in water



Effect of substitution type

Substitution type of METOLOSE affects hydration speed of HPMC particles and gel strength, which can influence the dissolution profile (Figure 4). In the case of Methylcellulose, it takes much longer hydration time as compared with Hypromellose.

Effect of viscosity

Viscosity of HPMC affects gel strength or erosion rate of the gel in the second stage, and hydration speed in the first stage. The higher the viscosity, the stronger the gel strength and the slower the hydration speed (Figure 3). By selecting the viscosity grade the dissolution profile can be easily controlled.

Effect of particle size

Larger particles require longer hydration time, and in this period particles can swell certain volume (Figure 5). METOLOSE SR has an average particle size around 5O μm, which is an ideal particle size for matrix application.

Effect of HPMC content

The content of HPMC in the matrix tablet significantly affects the initial erosion of the tablet in the first stage (Figure 6a, 6b, 6c). To avoid such a risk the content of HPMC should be 20% or higher.

Figure 4. Effect of various substitution types

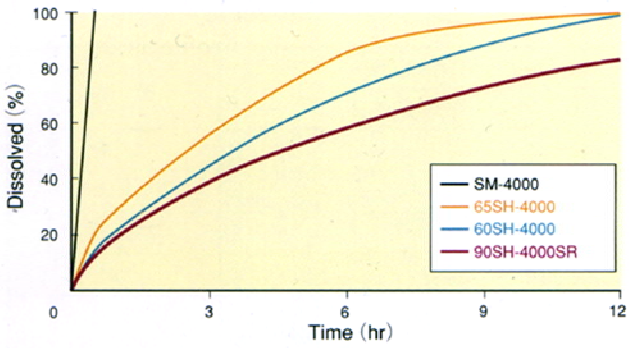


Figure 5. Effect of Particle size /90SH-100,000SR

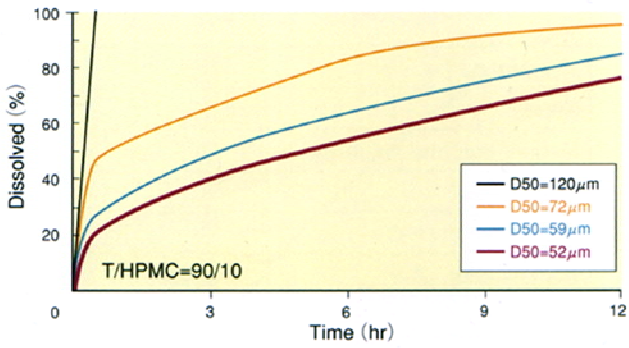


Figure 6a.
Effect of HPMC content/90SH-100SR

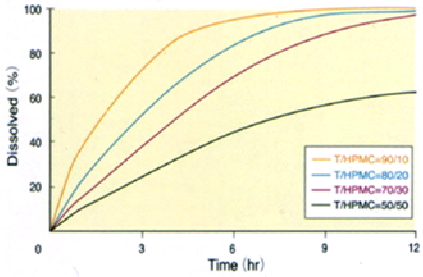


Figure 6b.
Effect of HPMC content/90SH-4,000SR

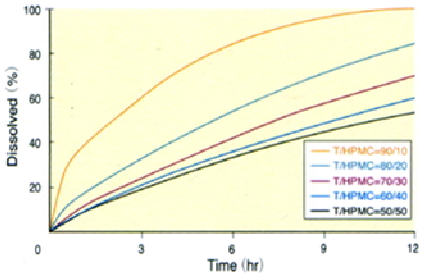
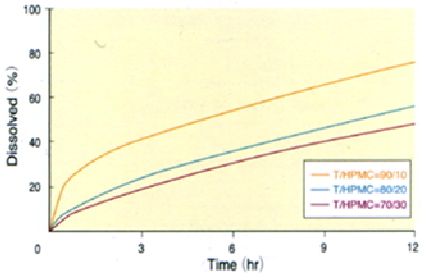


Figure 6c.
Effect of HPMC content/90SH-100,000SR



Formulation (Fig5–Fig6c):

Theophylline	477mg
METOLOSE SR	
Mg-stearate	3mg
Total	480 mg / Tab

Compression & Dissolution conditions are the same in the previous page.

Summary of the major parameters

Increasing the parameters listed in the left side column of the table below could influence the drug release or tablet properties are summarized in the following table. For example, selecting a higher viscosity grade will increase initial erosion but decrease drug release in the second stage, and no change in tablet hardness.

Table 3. Summarized table for factors affecting the drug release from direct compression tablet

	First stage Initial erosion	Second stage Dissolution speed	Tablet hardness (before administration)
Formulation HPMC content ↗	Decrease	Decrease	Increase
Powder properties Average particle size ↗ Bulk density ↗	Increase Increase	Increase Increase	Decrease Decrease
Chemical properties HPO content (9OSH) ↗ Viscosity ↗	Decrease Increase	Increase Decrease	No change No change

METOLOSE includes several types of Hypromellose (USP) and Methylcellulose (USP). Please consult the details of the other types and grades in separate brochure of METOLOSE.

General name	Hypromellose, substitution type 2208		Method
Type	90SH	90SH-SR	
Description and solubility	Conforms		USP
Characters	Conforms		EP
Identification (A-C)	Conforms		USP
Identification (A-F)	Conforms		EP
pH	5.5-8.0		EP
Viscosity	See table below		USP & EP
Loss on drying	Not more than 5.0%		USP
Residue on ignition	Not more than 1 .5%		USP
Residue on ignition	Not more than 1.0%		EP
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
OVI	Conforms *1		USP
Methoxy content	19.0-24.0%	22.0-24.0%	USP
Hydroxypropoxy content	4.0-12.0%	8.0-12.0%	USP
Particle size	- *2	40-60 μm	- *3

*1 This material does not require CVI testing, under the USP-NF (467) stipulation that "... based on knowledge of the manufacturing process and controlled handling and storage ... there is no potential for the specific toxic solvents to be present ... if tested, will comply established standards."
*2 The products can pass through 355 μm sieve, approximately 7Oμm.
*3 Shin-Etsu test method based on the standard sieve analysis.

METOLOSE SR has a tighter specification for substituents with finer particle size as compared with regular METOLOSE, which is exclusively suitable for matrix applications, especially direct compression.

Table 5. Available grades and viscosity specifications

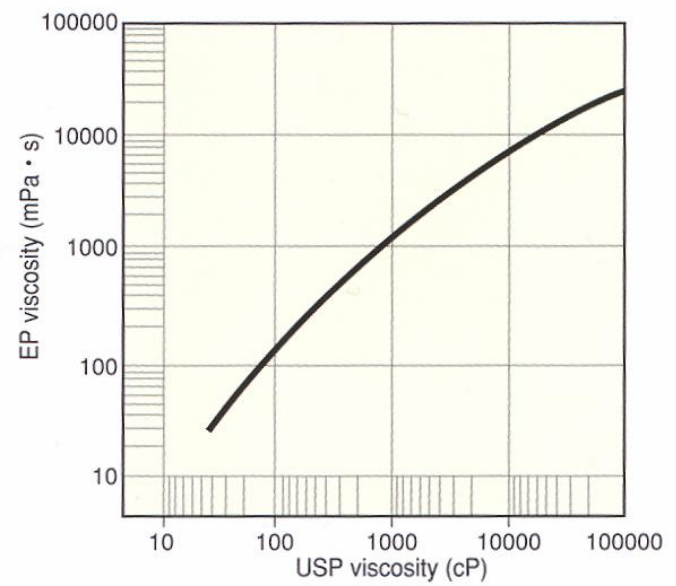
Hypromellose		Labeled Viscosity	USP Specification (cP)*1	EP Specification (mPa•s)*2
90SH	90SH-SR			
š	š	100	80—120	75—140
š		400	300—560	300—560
š	š	4000	3000—5600	3000—5600
š	š	15000	11250—21 000	- *3
š	š	100000	75000—140000	- *3

*1 USP viscosity is 80%-120% for labelled viscosity 100 cP and lower.
USP viscosity is 75%-140% for labelled viscosity over 100 cP.
*2 EP viscosity is 75%-140% for all labelled viscosities.
*3 Due to the difference in viscosity measurement method, it is not possible to prepare products meeting both viscosity specifications for labelled viscosities higher than 4000.

Viscosity

The relationship between the USP viscosity and the EP viscosity is shown in Fig.7. At a higher viscosity of HPMC there is a larger difference between the USP and the EP viscosities.

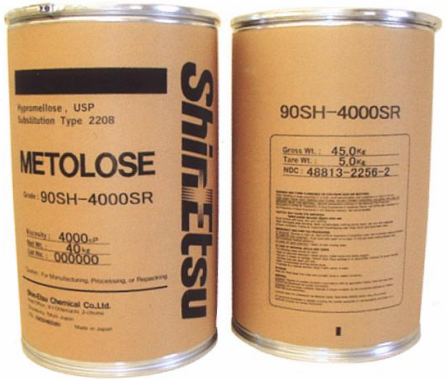
Figure 7. Relationship between the USP viscosity and the EP viscosity



Nomenclature

Substitution type	Labeled viscosity	Other Special powder Property, etc.
SM-	15	
60SH-	50	
90SH-	4000	SR

Packaging



●**Package:**
Double-layered polyethylene bag in fibre drum
●**Net weight:**
40kg depending on grade

METOLOSE includes several types of Hypromellose (USP) and Methylcellulose (USP). Please consult the details of the other types and grades in separate brochure of METOLOSE.

Powder properties

METOLOSE SR is a white to slightly off-white powder and practically odourless and tasteless.

Table 6. METOLOSE SR powder properties

Appearance	White to off-white powders.
Particle size	40–60 μm (sieve analysis) See Fig.8(laser diffraction analysis)
True density	1.26–1.31 g/mL
Bulk density	0.25–0.35 g/mL
Tapped density	0.40–0.55 g/mL
Angle of repose	39–46°
Degradation temperature	280–300 ℃
Self ignition temperature	approx. 360 ℃
Hygroscopicity	See Fig. 9
Dust explosion	Kst = approx. 100 bar·m/s※ 1bar = approx. 0.1MPa

※1 bar≒0.1 MPa

Figure 8. Particle size of METOLOSE SR grade (laser diffraction method)

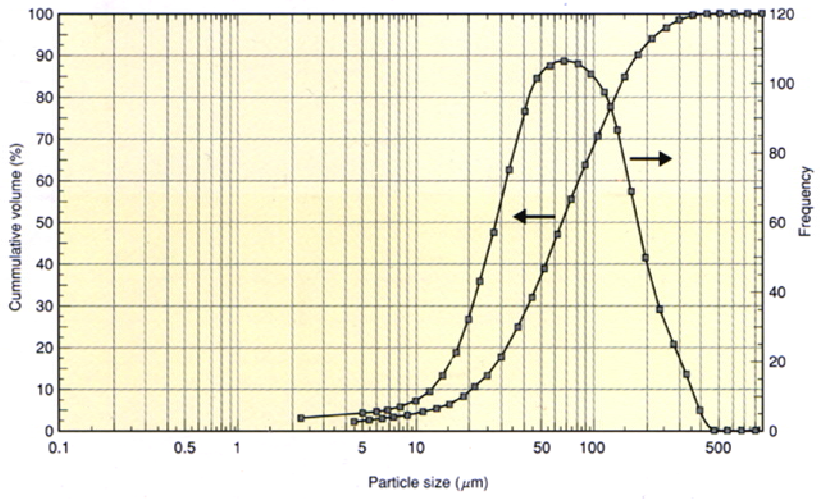
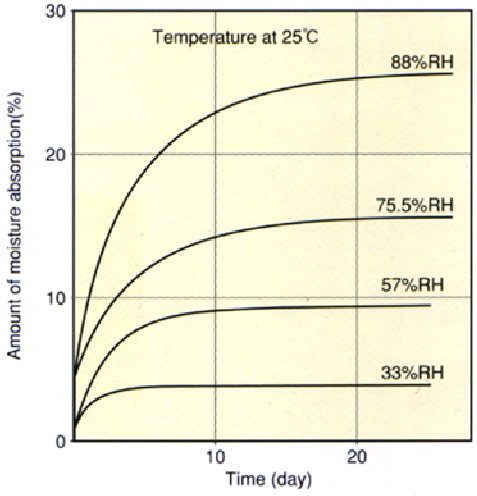


Figure 9. Moisture uptake character of METOLOSE SR grade



Note: Particle size in the table expressed as based on standard sieve analysis. Chart generated by a laser diffraction analysis, which gives larger particle size in comparison with standard sieve analysis.
Note: Regular loss on drying value for METOLOSE SR is around 2.0%. Please take care moisture uptake of laboratory retained sample, which moisture content could profoundly influence the compressibility of METOLOSE SR (see Fig.10).

4 Compressibility

Compressibility of Metolose is recognized as sufficient, however, several factors should be taken into consideration, especially in case of direct compression.

4 Effect of moisture content

Moisture content of METOLOSE has a strong influence on the hardness of the compacts (Figure 10). Water is recognized as a very good plasticizer for water-soluble polymers like METOLOSE SR, thus compression proceeds plastically and results in high tablet hardness.

4 Effect of particle size

Finer particle size shows better compressibility and the threshold value of approximately 100 u m (Figure 11). Fine particles can rearrange inside the die during the process, thus achieve good tablet hardness due to the numerous numbers of bonding points. Large particles over 10011 m, however, are dense and tough and are difficult to deform. The compressibility of the particles over 100 u m precipitously drops to **zero.**

4 Effect of bulk density

Low bulk density products show higher tablet hardness as compared with high density types. Low bulk density and fibrous materials can afford to proceed to be compressed plastically rather than elastically **(Figure 10).**

Figure 10. Effect of moisture content and bulk density

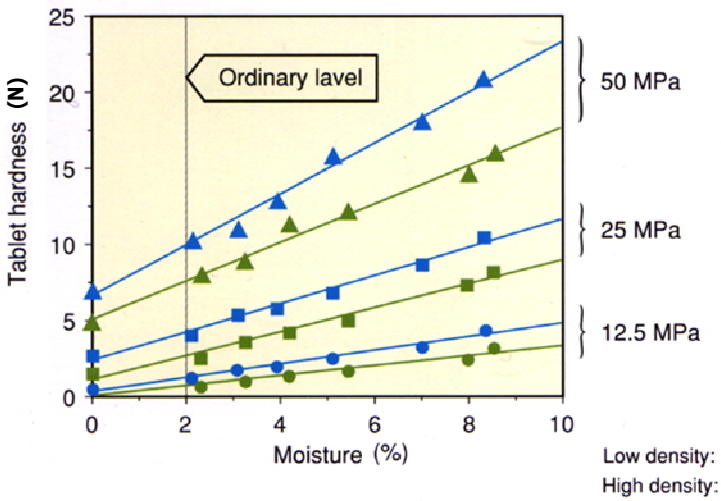
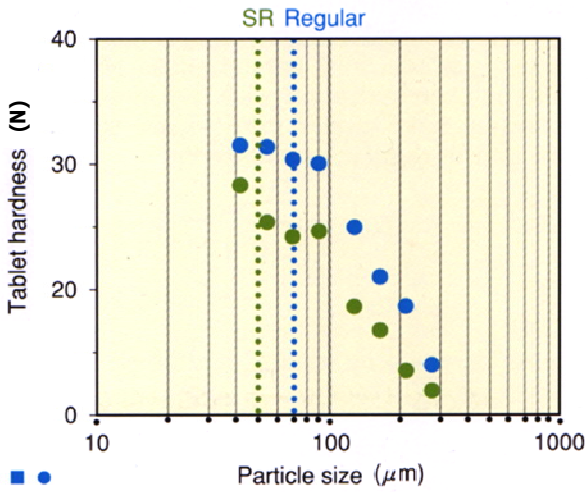


Figure 11. Effect of particle size



Material:
Low density : 0.27 g/mL (apparent bulk density) ... SR grade level
High density : 0.33 g/mL (apparent bulk density)... regular products level
Both having particle size of approx. 80 μm

Condition:
Samples were stored in five desiccators containing different moisture atmosphere for 4 days to prepare different moisture levels

Compression:
Rotary tablet machine HT-P18 (Hata): 10 mm flat, 300 mg / Tab
Compression pressure : 12.5 ~ 50 MPa
Compression speed : 30 min^{-1} with 18 punches

•Dissolving temperature

METOLOSE (Hypromellose & Methylcellulose) has the unique characteristic of thermal gelation; each substitution type has a specified temperature for gelling. Their physical properties affect the dissolving temperatures as shown in Figure 12.

Test method:
METOLOSE powders were dispersed in hot water at the mixing ratio of 1:99 by weight and the mixture was gradually cooled while being stirred. The viscosity was measured at various temperatures.

From the viewpoint of hydro-gel formation, 90SH and 60SH are suitable due to their higher dissolving temperatures above 37℃.

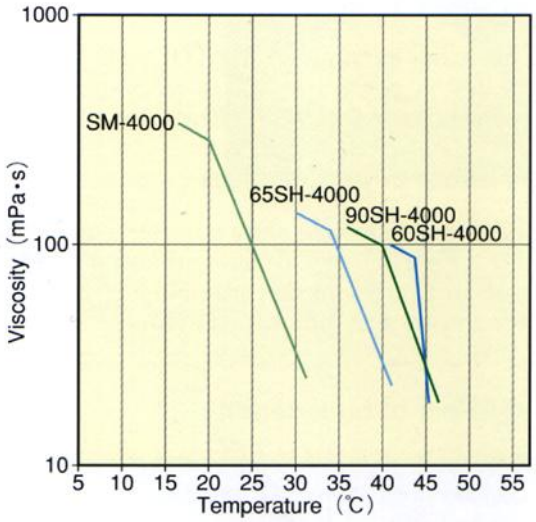


Figure 12. Changes in viscosity during the cooling process of hot water dispersions of METOLOSE

•Swelling characteristics

Full hydration, which is ready to form a gel layer takes a certain period of time. During this period METOLOSE particles can increase their volume and this tendency depends on the substitution level, viscosity grade, and particle size. METOLOSE 60SH and 9OSH show quicker hydration with low swelling volume and METOLOSE SR grades have a finer particle size showing lower swelling volume than that of regular grade shows.

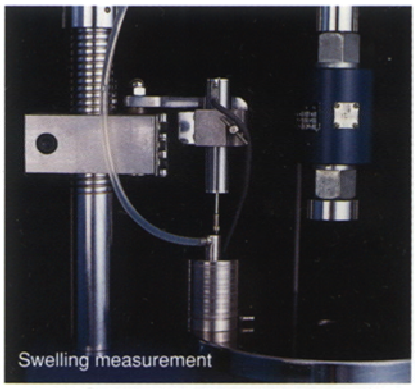


Figure 13. Swelling volume of 4000 cP grades

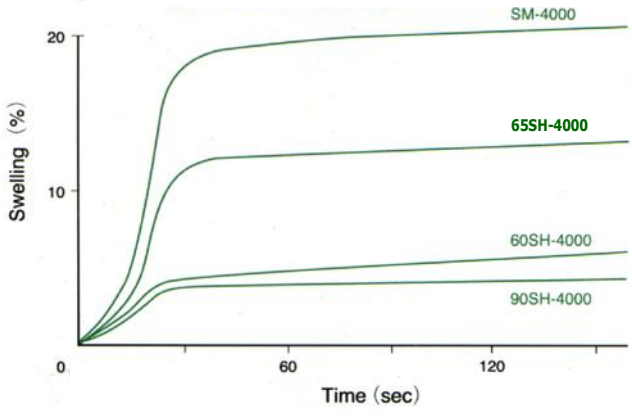
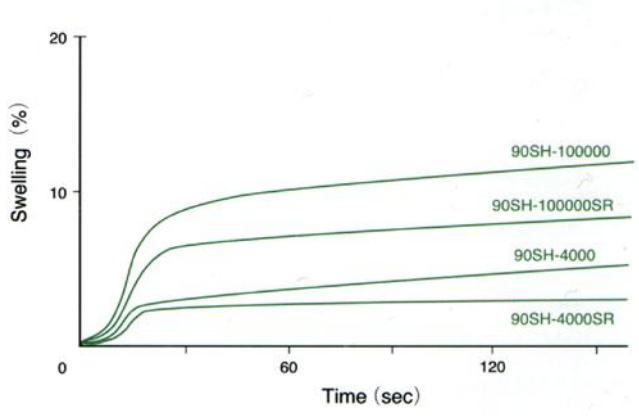


Figure 14. Swelling volume of METOLOSE 90SH types



Please refer separate brochure of METOLOSE about the detailed solution properties. Solution properties

Solution properties

The molecular weight of water-soluble polymer is closely related to their viscosities. The relationship is shown in Figure 15.

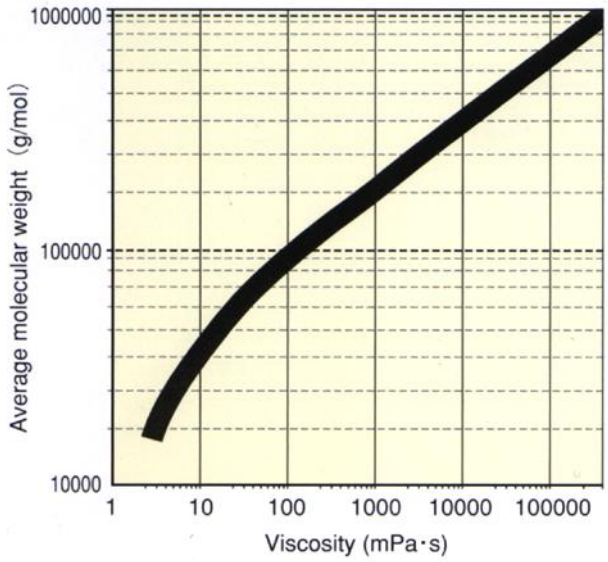


Figure 15. Molecular weight (Mw) vs. Viscosity

Note:
The viscosity in horizontal axis is expressed as capillary method of measurement according to the ASTM (USP method).

The desired viscosity can be obtained by the blending of different viscosity grades according to the instruction as follows. The blending chart has a special scale in viscosity for justification. To achieve viscosity at 1000 mPa s in Fig. 16, for example, the combination of 35% of a 400 mPa grade and 65% of 1500 mPas grade would give a 1000 mPa s product.

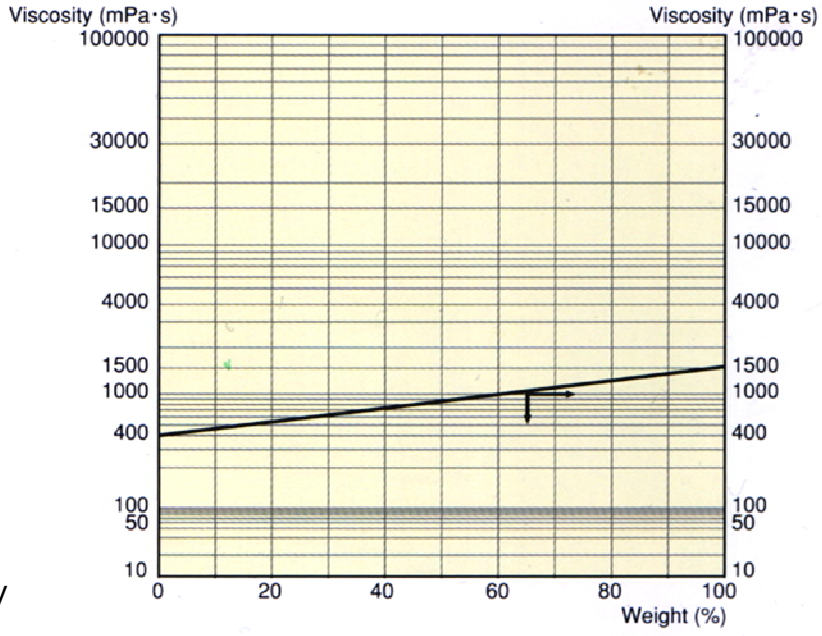


Figure 16.
Blending chart for intermediate viscosity

1)Theophylline (direct compression)
Direct compression is the simplest technique to prepare matrix tablets. This essentially consists of drug substance and METOLOSE.
Drug substance, which usually shows poor flowability, is primarily granulated in a fluidized-bed granulator.

Ingredient	mg/Tablet
Theophylline*	264
90SH-4000SR	64.5
Mg-stearate	1.5
Total	330 mg/Tab

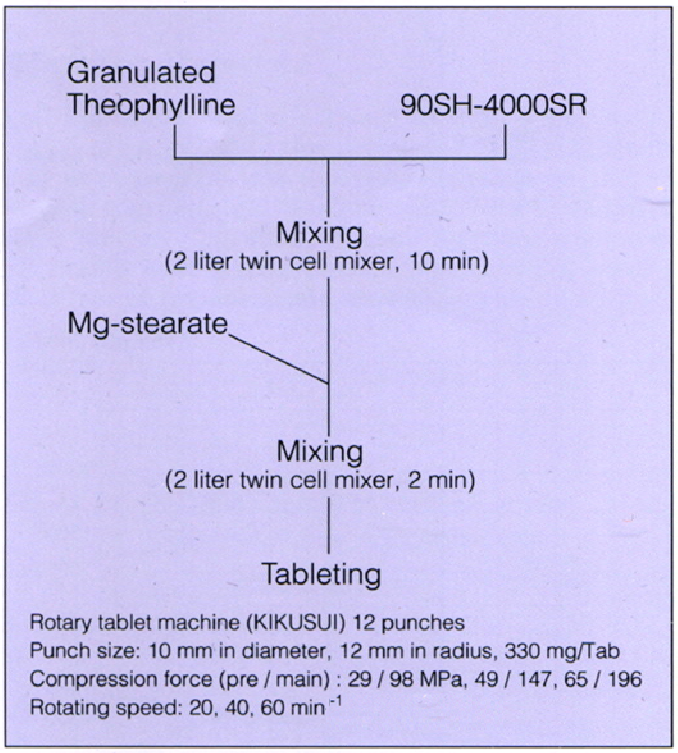
*Theophylline powder was granulated by a fluidized-bed.
(Mixing rate : Thephylline 97%, Pharmacoat 606 3%)

Fluidized-bed granulation
Machine: Fluidized-bed Flowcoater FLO-5 (Freund)
Charge: 3 kg of Thephylline
Supply drying air temperature: 80℃
Exhaust air temperature: 35℃
Binder solution: Pharmacoat 606 7% aq. soln.
Spray feed rate: 60 g/min

Powder properties of granule
Bulk density: 0.34 g/mL
Tapped density: 0.47 g/mL
Average particle size: 170 μm

The resultant Theophylline powder showed good flowability and mixing ability to METOLOSE powders.

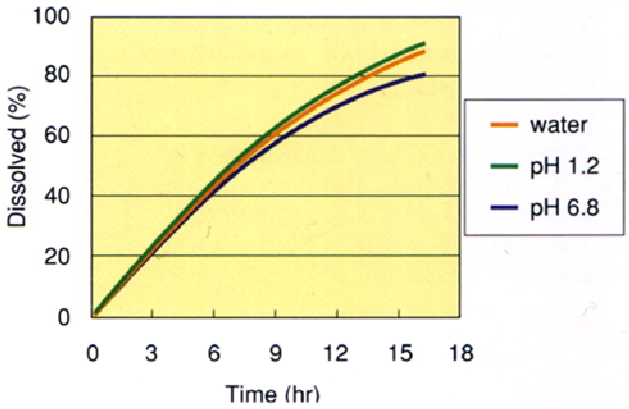
1-2) Mixing procedure of the powders for compression



Rotary tablet machine (KIKUSUI) 12 punches
Punch size: 10 mm in diameter, 12 mm in radius, 330 mg/Tab
Compression force (pre / main) : 29 / 98 MPa, 49 / 147, 65 / 196
Rotating speed: 20, 40, 60 min^{-1}

1-3) Results

Figure 17.
Dissolution profiles of Theophylline tablets in different buffer solutions and water



Dissolution test: According to the USP method
(Paddle method)
Dissolution medium: Purified water, pH1.2, pH6.8, 900 mL
Paddle rotation: 100 (50, 150) min^{-1}
Test periods: 16 hours

Figure 18.
Dissolution profiles of Theophylline tablets with several rotation speed levels

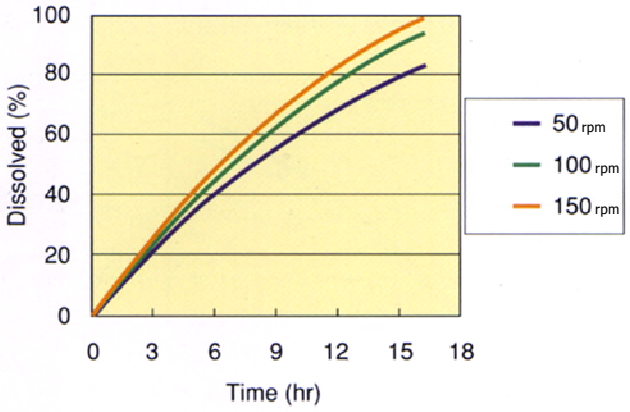


Figure 19.
Dissolution profiles of Theophylline tablets at different compression force

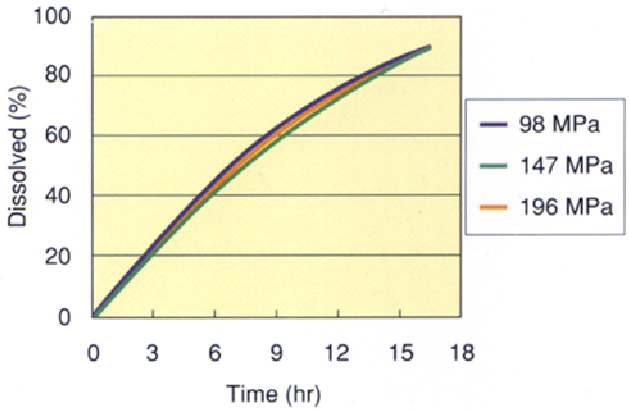


Figure 20.
Tablet weight deviations between 90SH-4000SR and regular product

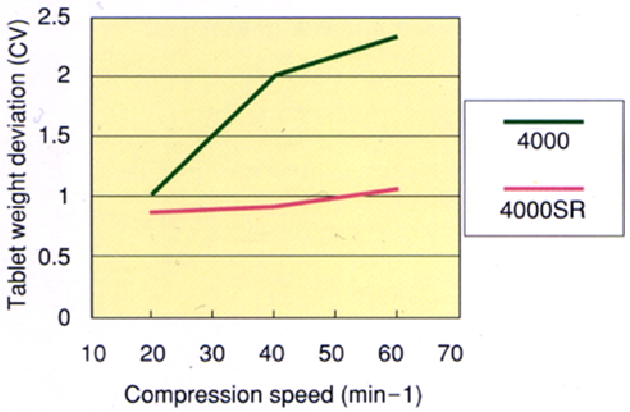


Figure 21.
Tablet hardness of Theophylline direct compression tablet at different turn table speeds (90SH-4000SR)

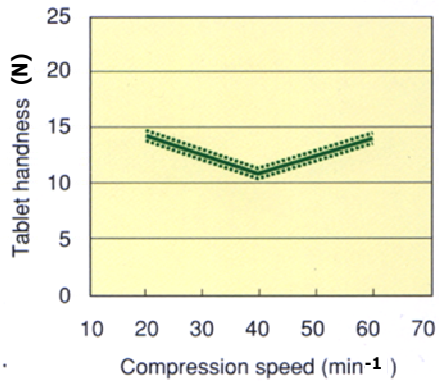
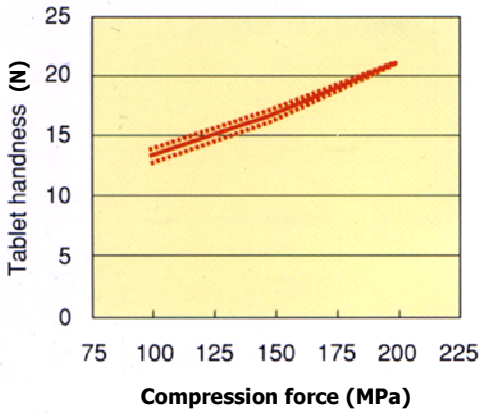


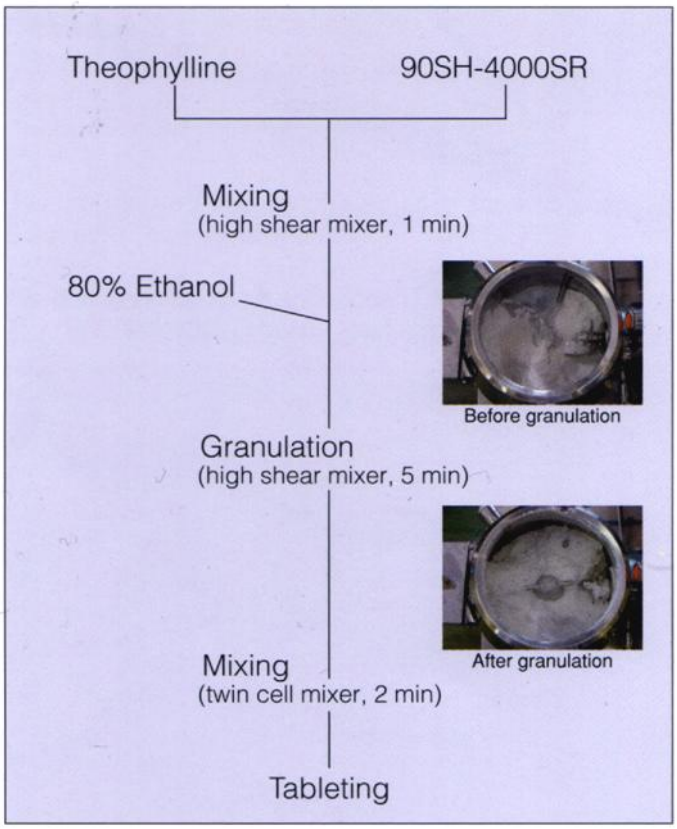
Figure 22.
Tablet hardness of Theophylline direct compression tablet at different compression force (90SH-4000SR)



2)Theophylline (wet granulation)

1-2) Mixing procedure of the powders for compression
Same in 1-1). 80% Ethanol was used as a kneading liquid in order to avoid sticky mass attached to the vessel's wall.

2-2) Mixing procedure of the powders for compression



Granulation with alcoholic solvent mixture could improve powder handling and compressibility of the powders.
80 to 90% Ethanol is suitable for the granulation.

Wet granulation
Machine: High shear mixer Vertical granulator FM-VG-15 (Pwrex)
Charge: 300 g
Agitation (blade / chopper): 600 / 1000 min^{-1}
Kneading liquid: 80% ethanol, 180 g

Powder properties of granule
Bulk density: 0.35 g/mL
Tapped density: 0.48 g/mL
Average particle size: 122 μm

2-3) Results

Figure 23.
Dissolution profiles comparison between direct compression and wet granulation

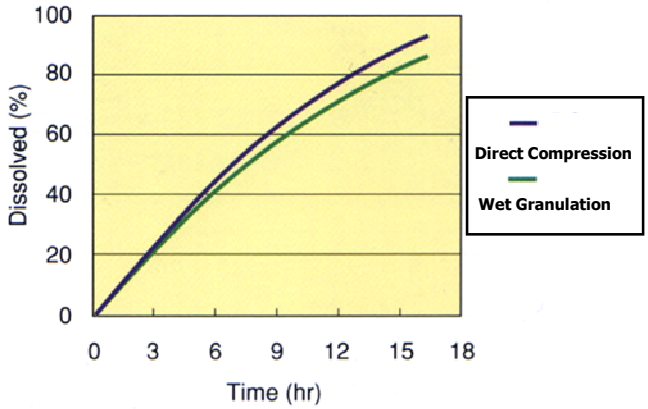


Figure 24.
Tablet weight deviation comparison between direct compression and wet granulation

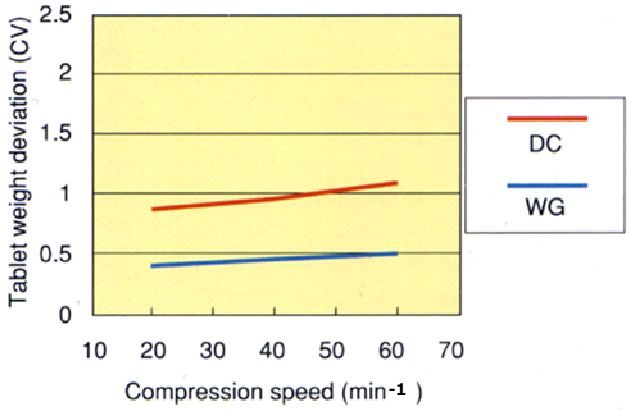
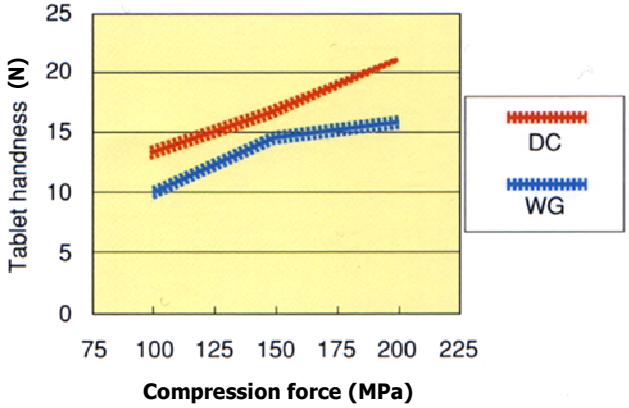


Figure 25.
Tablet hardness of comparison between direct compression and wet granulation



There are a lot of patents concerning sustained release preparations using HPMC, mostly specified active ingredients. Some patents which mainly cover HPMC, excipients and process are listed in Table 8 and Table 9.

Table 8. Some relevant patents

Patent number	Inventor	Title
US 3065143	Christenson *et al.*	Sustained release tablet
US 4259314	Lowey	Method and composition for the preparation of controlled long-acting pharmaceuticals
US 4357469	Schor	Carriers base material for prolonged release therapeutic compositions
US 4369172	Schor *et al.*	Prolonged release therapeutic compositions based on hydroxypropyl/methylcellulose
US 4389393	Schor *et al.*	Sustained-release therapeutic compositions based on high molecular weight hydroxypropylmethylcellulose
US 4540566	Davis *et al.*	Prolonged release drug dosage forms based on modified low viscosity grade hydroxypropylmethyl cellulose
US 4571333	Hsiao *et al.*	Controlled release naproxen and naproxen sodium tablets
US 4678516	Alderman *et al.*	Sustained release dosage form based on highly plasticized cellulose ether gels
US 4695591	Hanna *et al.*	Controlled release dosage forms comprising hydroxypropyl methylcellulose
US 4704285	Alderman	Sustained release compositions comprising hydroxypropyl cellulose ethers
US 4734285	Alderman	Sustained release compositions
US 4803079	Hsiao *et al.*	Controlled release naproxen and naproxen sodium tablets
US 4871548	Edgren *et al.*	Controlled release dosage form comprising different cellulose ethers
US 4973470	Mills *et al.*	Sustained-release pharmaceutical compositions
US 5009895	Lui	Sustained-release pharmaceuticals with high and low viscosity HPMC
EP 280613	Sournac *et al.*	Sustained-release dehydroergotamine tablet of the hydrophilic matrix-type
EP 322222	Gaylord *et al.*	Sustained-release drug dosage forms containing hydroxypropyl methylcellulose and alkali metal carboxylates
GB 2219206	Solomon *et al*	Sustained-release medicinal fomulations containing hydroxypropyl methylcellulose

Table 9. International relevant patents

Patent number	Inventor	Title
WO 8700044	Shah	Therapeutic formulations with bimodal release characteristics
WO 9210169	Lundberg	Manufacturing of a pharmaceutical controlled-release solid unit dosage form containing hydroxypropyl methylcellulose

Please note:

- This patent information based on the current knowledge and experiences of Shin-Etsu, which should not involve non patent infringement. Shin-Etsu takes no responsibility for any infringement of the patents listed above or others, arising from utilisation of data provided by us.

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