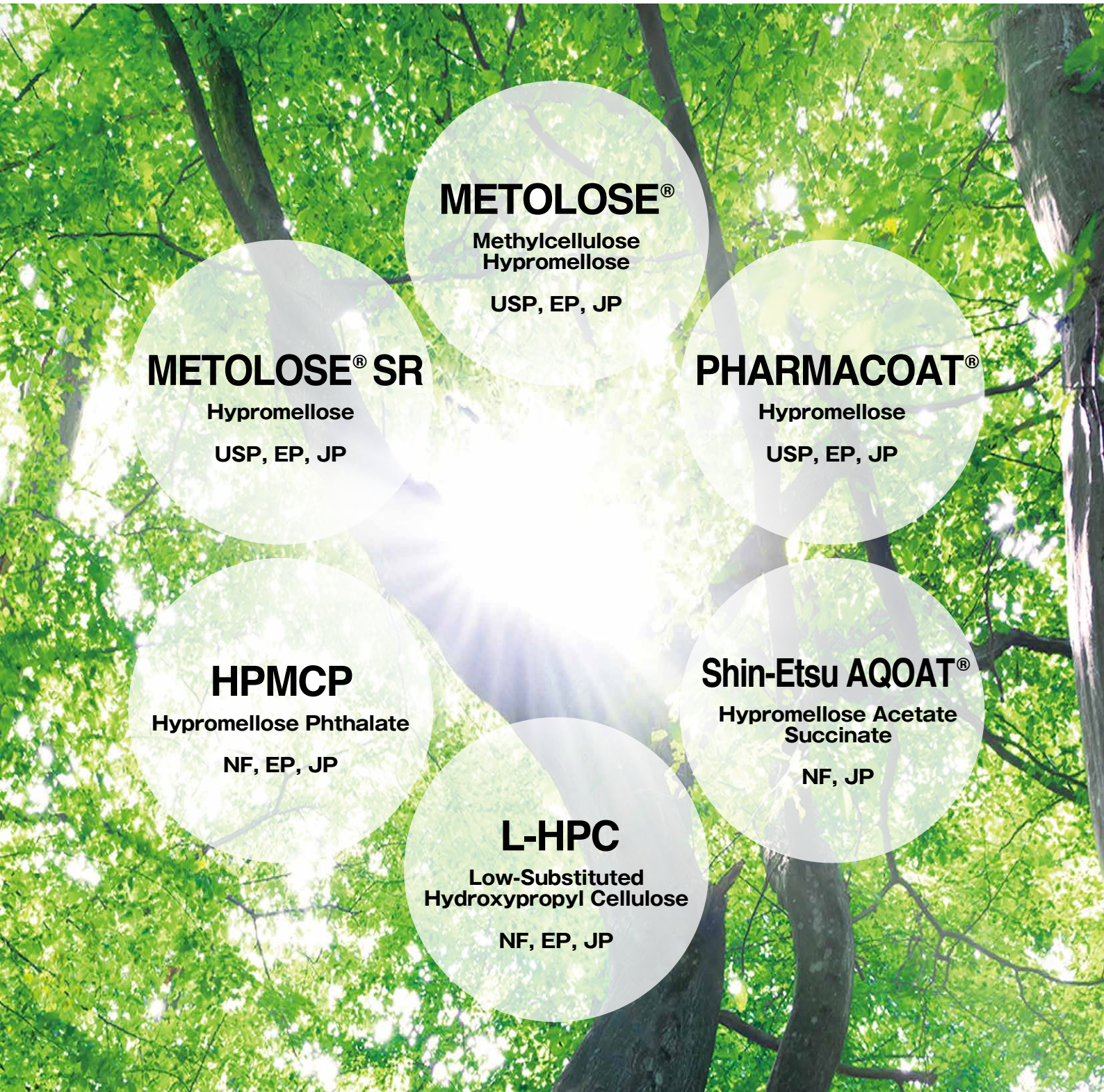
Shin-Etsu

Pharmaceutical Excipients



Product Information

Shin-Etsu Chemical has introduced various excipients for pharmaceutical industry. The following tables indicate the value of different attributes of excipient.

Grade	Specification	Reference data

Please find the detailed information in the individual brochure.
Each brochure can be obtained by internet at http://www.metolose.jp/en.

<Film coating agent,Binder>

PHARMACOAT® Hypromellose, USP, EP, JP

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			

*Viscosity of 2 w/w% aqueous solution at 20°C

Features:
- Low viscosity, suitable for film coating with water or solvent (co-solvent of water and ethanol) coating system.
- Water soluble and non-ionic, less interaction with active pharmaceutical ingredient (API).
- Available as a binder in wet granulation. Low viscosity and soluble polymer, helpful to obtain granules with uniform particle size and good flowability.
- Available also as a solid dispersion carrier.

<Sugar coating binder>

SB-4 Hypromellose, USP, EP, JP

Grade	Viscosity (mPa·s)*	Substitution type	Methoxy content (%)	Hydroxypropoxy content (%)
SB-4	3.2 - 4.8	2208	19.0 - 24.0	4.0 - 12.0

*Viscosity of 2 w/w% aqueous solution at 20°C

Features:
- Available as a binder for sugar coating instead of gelatin. Compared to gelatin, SB-4 has a better stability.

<Thickener>

METOLOSE® Hypromellose, Methylcellulose, USP, EP, JP

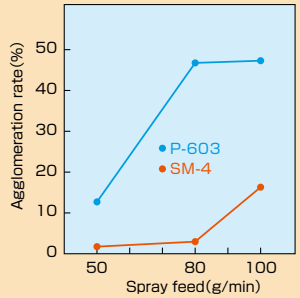
Grade*		Generic name	Methoxy content (%)	Hydroxypropoxy content (%)
SM	4, 15, 25, 100, 400, 1500, 4000	Methylcellulose	26.0 - 33.0	-
60SH	50, 4000, 10000	Hypromellose 2910	28.0 - 30.0	7.0 - 12.0
65SH	50, 400, 4000	Hypromellose 2906	27.0 - 30.0	4.0 - 7.5
90SH	4000, 15000, 100000	Hypromellose 2208	19.0 - 24.0	4.0 - 12.0

*Values in the table are viscosities of 2 w/w% aqueous solution at 20°C

Features:
- Non ionic and water soluble polymer with various viscosity.
- Applicable as film strips and dispersant of liquid formulation.
- SM-4 is recommendable for pellet coating as it less sticky. This thermal gel helps to prevent agglomerations during the coating process even at the higher spray speed.

Pellets which were extruded from 1.0 mm- diameter nozzle were coated with 7% aqueous solution of SM-4 and the result was compared with PHARMACOAT® 603(P-603) in fluidized bed granulator.
The ratio of agglomerated pellets was analyzed from the weight retained on #16 sieve, when the spray speed was changed from 50 g/min to 100 g/min.

Prevention of agglomeration of pellet coating using SM-4



<Sustained release agent>

METOLOSE® SR Hypromellose, USP, EP, JP

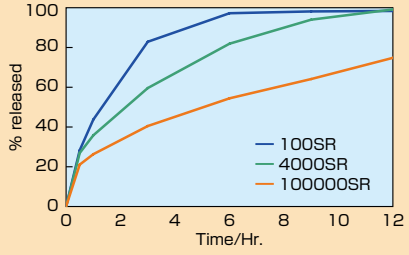
Grades		Viscosity (mPa·s)*	Substitution type	Methoxy content (%)	Hydroxypropoxy content (%)	Particle size (μm)
90SH	100SR	80 - 120	2208	22.0 - 24.0	8.5 - 10.5	D_{20} : 20 - 40 D_{50} : 50 - 80 D_{80} : 100 - 160
	4000SR	3000 - 5600				
	15000SR	11250 - 21000				
	100000SR	75000 - 140000				

*Viscosity of 2 w/w% aqueous solution at 20°C

Features:

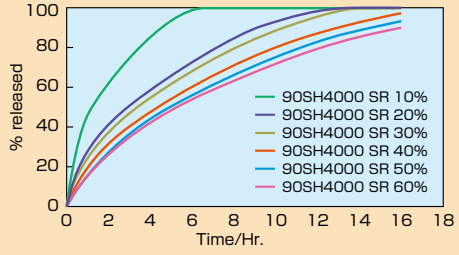
- For Hydrophilic matrix formulation of API and METOLOSE® SR to extend the dissolution. The dosage forms can be obtained by direct compression or granulation process.
- METOLOSE® SR has specifications of particle size which can be suitable for sustained release application.
- Dissolution profile can be easily adjusted by selecting appropriate grade.
- Recommendable amount of METOLOSE® SR is more than 20% in the formulation in order to form the stable gel layer.

Drug release of METLOSE® SR from different viscosity grades



Formulation : Theophylline ····· 429 mg
METOLOSE® SR ····· 48 mg
Mg stearate ····· 3 mg
Preparation : Direct compression
Tested media : water

Drug release of METLOSE® SR from different dosage amount



Formulation : Theophylline ····· 10 mg
METOLOSE®4000 SR, Lactose ····· 467 mg
Mg stearate ····· 3 mg
Preparation : Direct compression
Tested media : water

<Enteric coating agent, solid dispersion carrier>

HPMCP Hypromellose Phthalate, NF, EP, JP

Grade	Phthalyl content (%)	Viscosity (mPa·s)*	pH Solubility
HP-50	21.0 - 27.0	44-66	≧ 5.0
HP-55	27.0 - 35.0	32-48	≧ 5.5
HP-55S		136-204	

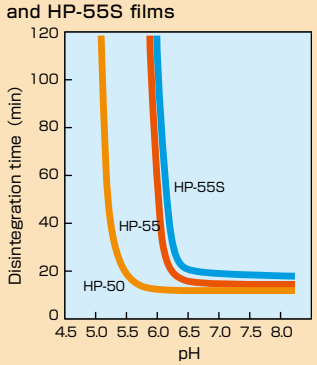
*Viscosity of 10 w/w% solution of methanol and dichloromethane at 20°C

Features:

- Suitable for solvent coating system. As co-solvents, mixture of ethanol and water (80/20 w/w%) or mixture of acetone and water (95/5 w/w%) are recommendable.
- Relatively stable, die to less hydrolysis.
- Available as a solid dispersion carrier for solubility enhancement.

According to the disintegration test method, dissolution time was measured for cast film from organic solvent (thickness: 100 μm; size: 10 x 10 mm)
~ pH 5.6: USP Phthalate buffer
pH 5.8 ~: USP Phosphate buffer

Solubility of HP-50, HP-55 and HP-55S films



Product Information

<Enteric coating agent, solid dispersion carrier>

Shin-Etsu AQOAT® Hypromellose Acetate Succinate, NF, JP

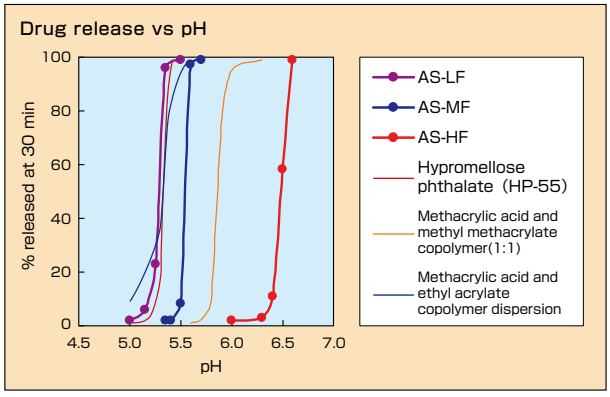
Grades	Viscosity* (mPa · s)	Methoxy content (%)	Hydroxypropoxy content (%)	Acetyl content (%)	Succinoyl content (%)	Particle	pH Solubility
AS-LF	2.4 - 3.6	20.0 - 24.0	5.0 - 9.0	5.0 - 9.0	14.0 - 18.0	Fine**	≧ 5.5
AS-LG						Coarse	
AS-MF		21.0 - 25.0	5.0 - 9.0	7.0 - 11.0	10.0 - 14.0	Fine**	≧ 6.0
AS-MG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

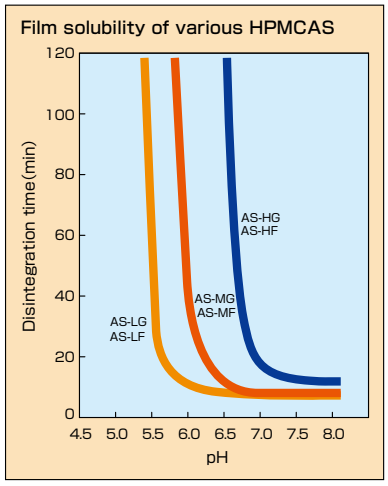
*Viscosity of 2 w/w% solution of sodium hydroxide aqueous solution at 20°C
**D_{50}: NMT10 μm, D_{90}: NMT20 μm by laser diffraction method
Abbreviation; HPMCAS

Features:

・For enteric coating, various coating methods can be applied such as aqueous, organic solvent, ammonia neutralized and dry coating. Coating methods can be selected depending on the characteristic of API. For example, dry coating is suitable for water and solvent sensitive API.

Riboflavin granules were coated with various enteric coating agents. Percent release of riboflavin at 30 minutes was measured in USP Phthalate buffer (～pH 5.6) and USP Phosphate buffer (pH 5.8～)



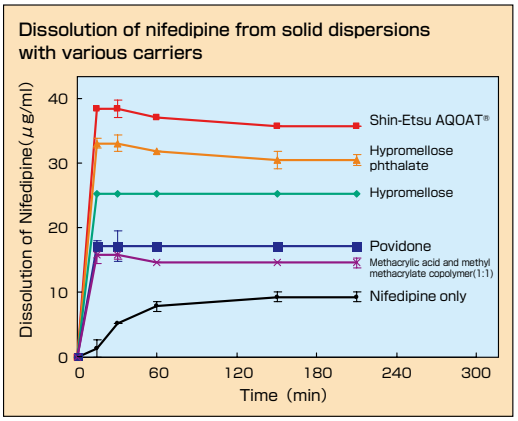


According to the disintegration test method, dissolution time was measured for cast film from organic solvent (thickness: 100 μm; size: 10 x 10 mm)
～ pH 5.6: USP Phthalate buffer
pH 5.8 ～: USP Phosphate buffer

・Shin-Etsu AQOAT® is suitable not only for enteric coating, but also for control release. It is also used in solid dispersion for solubility and bioavailability enhancement.
In order to prepare solid dispersion, various methods are applicable such as spray dry, spray coating, hot melt extrusion (HME), coprecipitation etc. As Shin-Etsu AQOAT® can dissolve into various organic solvents and has relatively low glass transition temperature (Tg), it is one of the most suitable polymers in solid dispersion. Numerous scientific papers reported that Shin-Etsu AQOAT® was able to enhance the drug solubility more effectively compared to other polymers.

Tg of various cellulosic polymers	
HPMCAS (all grades)	122℃
HPMCP (HP-55)	138℃
HPMC (PHARMACOAT® 606)	150℃

Tg was determined by DSC experiment under the following test condition;
Equipment: DSC Q2000 (TA Instruments, JP),
Heating rate: 10°C/min,
Referred to the second heating run N_2 gas atmosphere
Sample size: 3 mg



Nifedipine (NP) and various carriers were dissolved into organic solvents with the ratio of NP/carrier=1:2 by weight and sprayed, dried and milled.
Dissolution test was done with simulated intestinal fluid (pH 6.8).

<Disintegrant, anti-capping agent>

L-HPC Low-Substituted Hydroxypropyl Cellulose, NF, EP, JP

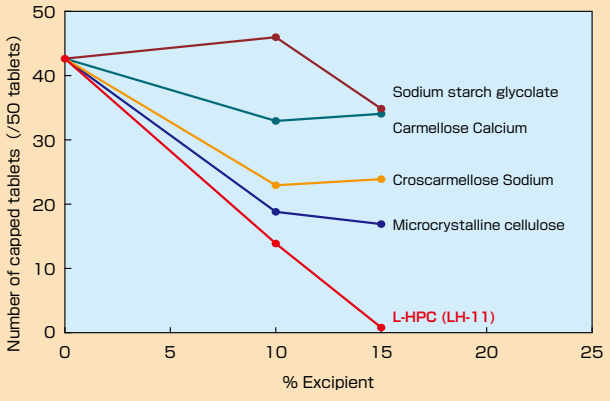
Grades	Hydroxypropoxy content (%)	Mean particle size* (μm)	90% cumulative particle size * (μm)	Application
LH-11	10.0 - 12.9	45-65	150-200	Direct compression (DC), anti-capping
LH-21		35-55	100-150	DC, granulation (high shear)
LH-22	7.0 - 9.9			DC, granulation (high shear)
LH-B1	10.0 - 12.9	45-65	100-150	DC, granulation (fluid bed)
LH-31		17-23	40-100	Granulation (high-shear, extrusion), layering
LH-32	7.0 - 9.9			Granulation (high-shear, extrusion), layering
NBD-020	13.0 - 15.9	35-55	70-130	Granulation (high shear)
NBD-021	10.0 - 12.9			DC, granulation (high shear)
NBD-022	7.0 - 9.9			DC, orally disintegrating tablets

*Shin-Etsu Laser diffraction method

Features:

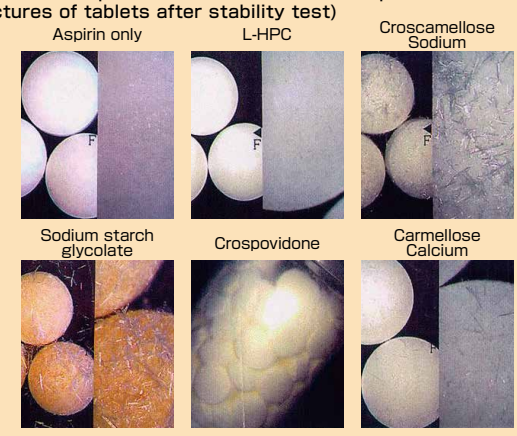
- Water insoluble, swells in water and works as dual functional ingredients, disintegrant and binder for tablets and pellets.
- Suitable grade can be selected depending on process and API characteristics.
- Non-ionic polymer which has less interaction with API and better stability.

Anti-capping effect of L-HPC



Ethenzamide tablets were prepared with various ratio of excipients and friability test was implemented in accordance with USP method.

Pictures of aspirin tablets with various excipients
(Pictures of tablets after stability test)



Aspirin tablets with 20% excipients were stored in closed plastic bottle at 50°C for 3 months.

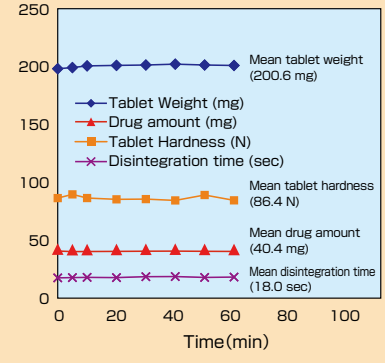
- NBD grades are suitable for direct compression as they have narrower particle size distribution and better flowability. They are able to make less deviation on tablet weight and content uniformity.
- They are also suitable for orally disintegrating tablet (ODT) formulation as they swell very quickly (especially NBD-022 grade). ODT can be prepared by direct compression and spray granulation methods, where filler is granulated with the dispersion of NBD.

Tablet formulation

Paracetamol	20%
Granulated mannitol (Granutol®S)	69.5%
NBD-022	10%
Mg Stearate	0.5%

All components were well blended and compressed into 8 mm diameter and 200 mg weight tablet.
Compression force; pre 3 kN, main 10 kN
Rotation speed; 40 rpm
10 tablets were taken at every 5-10 minutes and weight, tablet hardness, disintegration test in water and drug content were analyzed.

Variations of ODTs quality in DC



Shin-Etsu Pharmaceutical Excipients　Guide to application

This table provides an overview of the general aspects of our cellulose products in pharmaceutical applications.

For your specific formulation, please consult our sales department or the distributor in your area.

◎= Very suitable　○= suitable

		Tablet													Pellet										Liquid and others									
		Film coating 1)	Taste masking 2)	Enteric coating solvent	Enteric coating aqueous & dry	Sugar coating	Sustained release pH independent	Binder solution wet granulation	Quick disintegration 3)	Fast dissolution 4)	Dry binder 5) direct compression & wet granulation	Anti-capping	Orally disintegrating tablet	Film coating 6)	Taste masking	Enteric coating solvent	Enteric coating aqueous & dry	Sustained release pH dependent	Fast dissolution	Pellet extrusion	Powder layering	Thickening	Eye drops 7)	Suspending	Dry syrup	Plaster/Dermal patch	Film making	Capsule making	Dispersing aid for capsule filling	Solid dispersion
PHARMACOAT®	603	○					◎							○										◎					◎
	645	◎	◎				○																	○		○	○		○
	606	◎	◎				◎																	○		◎	○		◎
	615	◎	◎				◎																	○		○	○		◎
	SB-4				◎																					○			
METOLOSE®	SM-4		◎											◎	○											○			
	Other SM's						◎														◎		◎	○	○					
	60SH's					◎	○														◎	○	○		○	◎				
	65SH's						○														○		◎							
	90SH's					○															○		○		○	○				
METOLOSE® SR	All grades					◎																			○					
HPMCP	All grades		◎	◎										◎	◎		○												◎
Shin-Etsu AQOAT®	LF		◎		◎									◎		◎	○												○
	MF		◎		◎									◎		◎	○												○
	HF		○		○									○		○	◎												○
	LG		◎	◎										◎	◎		○												◎
	MG		◎	◎										◎	◎		○												◎
	HG		○	○										○	○		◎												◎
L-HPC	LH-11							○	○	○	◎																		
	LH-21							○	○	○	○																	○	
	LH-22							○	○	○	○																		
	LH-B1							◎	◎																			◎	
	LH-31									◎		○							○	◎	◎								
	LH-32									◎		○							○	◎	◎								
	NBD-022							◎	○	◎	○	◎							○	○	○								
	NBD-021							○	○	◎	○	◎							○	○	○							○	
	NBD-020							○	○	◎	○	○							○	○	○							○	

Notes & Caution

1) Film coating (Tablet)
The term "film coating" used in this table refers to a conventional water-soluble polymer coating.
Special properties, such as taste masking, coloring, light protection, etc. can be achieved by suitable additives.

2)Taste masking
The coating is formulated depending on the intensity of the flavour to be masked.

3)Quick disintegration
A common application of a swelling agent.

4)Fast dissolution
L-HPC makes tablets disintegrate into small particles, which enhance dissolution rate.

5)Dry binder
The term "dry binder" refers to the excipients used as dry powders to enhance the tablet hardness and reduce friability.

6)Film coating (Pellet)
This coating avoids undesired interactions.

7)Eye drops
This application may require specialized properties. Please contact our sales department for assistance. Bulk drug GMP is not applicable.

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