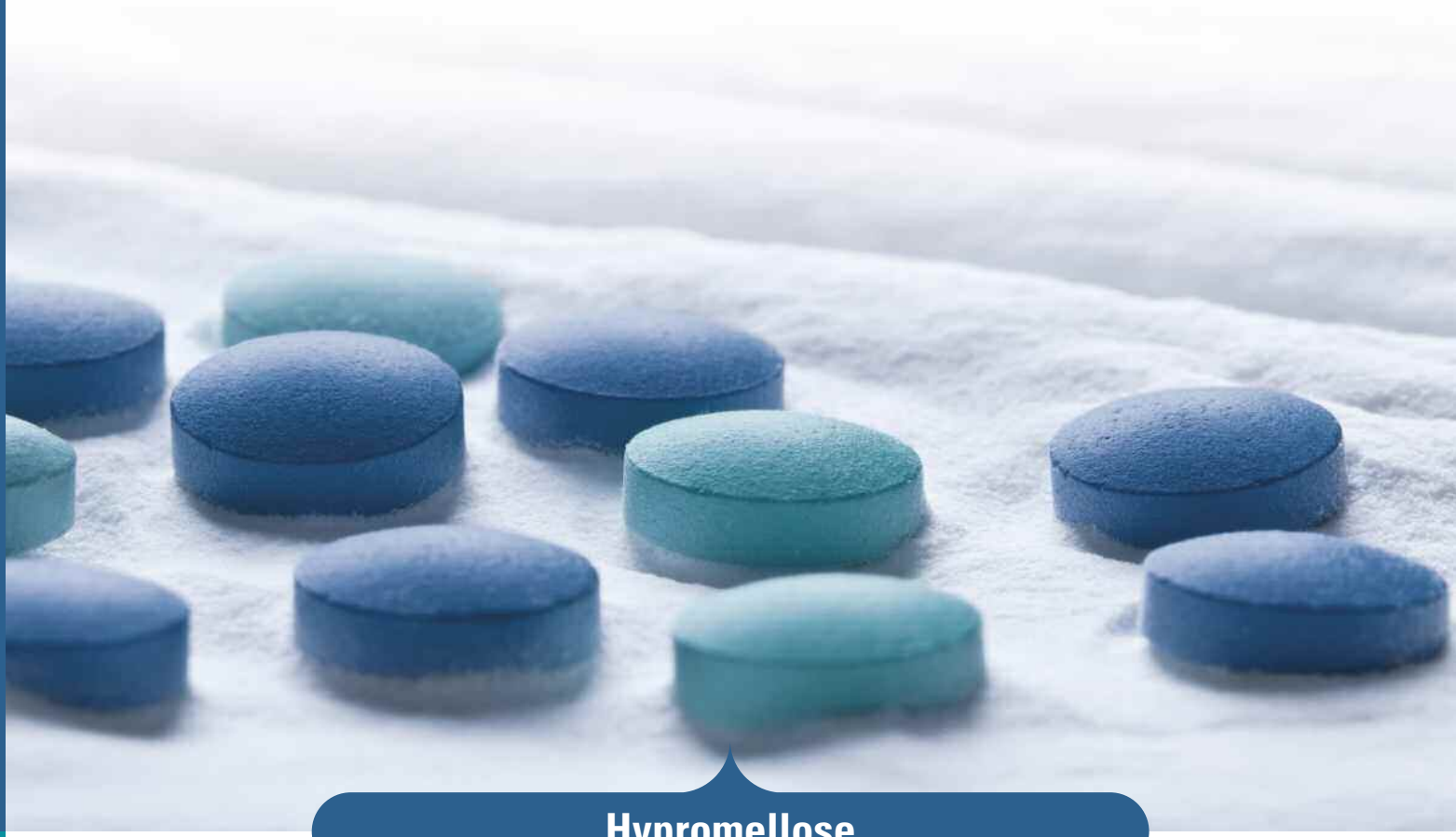
TYLOPUR®



Hypromellose

Shin-Etsu

Content

Introduction

TYLOPUR® is Hypromellose (HPMC) and a versatile pharmaceutical excipient. TYLOPUR® is manufactured at Tyloshin 2 plant at SE Tylose GmbH & Co. KG in Wiesbaden, Germany. This plant operates under GMP conditions and fulfills the requirements of the pharmaceutical industry. SE Tylose is a materials producer with an emphasis on a stable supply of high-quality products.

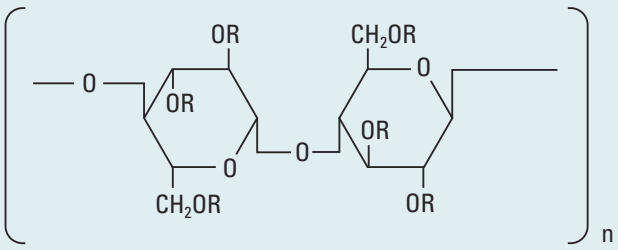
One of TYLOPUR® applications is film coating and it is easy to use as a coating material to provide an excellent finish. In addition, TYLOPUR® is effective as a granulation binder since it does not interact with drugs, has superior stability and has a nonionic character. It is available in various viscosity grades for the granulation process.

TYLOPUR® can also be used as a hydrophilic matrix agent for sustained release tablets. 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, such as hypromellose. Shin-Etsu has focused on controlled release technology and found that by controlling the chemical and physical properties of the HPMC, a more reproducible drug release can be achieved.

Another application of TYLOPUR® is to enhance the solubility of drugs, for example using solid dispersion technologies. TYLOPUR® can also replace gelatine for hard shell capsule manufacturing because of its greater stability.

Shin-Etsu has application laboratories located worldwide and is able to offer you technical services. These laboratories are continuously making valuable contributions to pharmaceutical technology; detailed technical data is available and formulation advices can be offered. We can also provide you with Quality by Design (QbD) samples for your development projects. Please contact your technical sales manager for further information.

Description

Trade Name	**TYLOPUR®**
Generic Name	**Hypromellose** (Hydroxypropylmethylcellulose)
Abbreviation	**HPMC**
Chemical Name	**Cellulose, 2-hydroxypropyl methyl ether**
CAS Registry Number	**9004-65-3**
Compendial Status	**USP** (The United States Pharmacopeia) **EP** (European Pharmacopoeia) **JP** (Japanese Pharmacopoeia)
Structure	 R = -H $-CH_3$ $-CH_2CH(CH_3)OH$

Substitution Types and Major Applications

The substitution type describes the amount of methoxy and hydroxypropoxy substituents on the cellulose backbone of TYLOPUR® and is mentioned in the pharmacopeia monographs. TYLOPUR® includes several grades with different kind of substitution, low viscosity and high viscosity grades.

	TYLOPUR® Hypromellose (USP/EP/JP)			
	Low Viscosity Grades	High Viscosity Grades		
Trade Name	TYLOPUR® 603 TYLOPUR® 645 TYLOPUR® 605 TYLOPUR® 606 TYLOPUR® 615	TYLOPUR® 60SH	TYLOPUR® 65SH	TYLOPUR® 90SH-SR
Substitution Type	2910	2910	2906	2208
Viscosity Range	3 – 15 mPa·s	50 – 13 000 mPa·s	50 – 4000 mPa·s	100 – 100 000 mPa·s
Applications	Tablet/Pellet Coating Granulation Binder	Thickening Suspending Liquid and Semi-solid	Thickening Suspending Liquid and Semi-solid	Sustained Release (Matrix Tablet)

Table 1: Substitution types and major applications of TYLOPUR® grades.

For the complete specification, please see page 22.

Physicochemical Properties

True Density

1.26 – 1.31 g/cm³ (measured with helium pycnometer)

Tapped Density

0.50 – 0.70 g/cm³

Equilibrium Moisture Content

The relationship between relative humidity and equilibrium moisture content of TYLOPUR® is shown in Figure 1 and 2. In Figure 1, Tylopur 606 (low viscosity) was compared with povidone (PVP) and hydroxypropyl cellulose (HPC), and there is no difference between TYLOPUR® and HPC. In Figure 2, high viscosity TYLOPUR® with different substitution were compared and no difference was found.

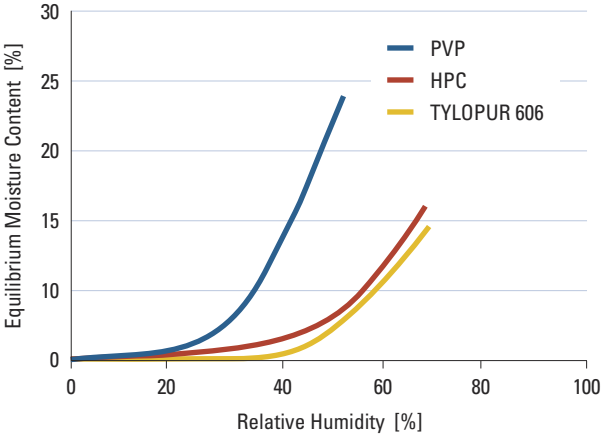


Figure 1: Relative humidity and equilibrium moisture content of TYLOPUR® 606, PVP and HPC at 25 °C.

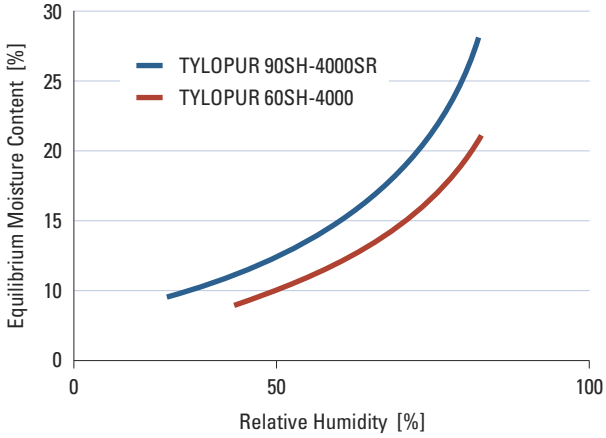


Figure 2: Relative humidity and equilibrium moisture content of TYLOPUR® 60SH and 90SH at 25 °C.

Molecular Weight

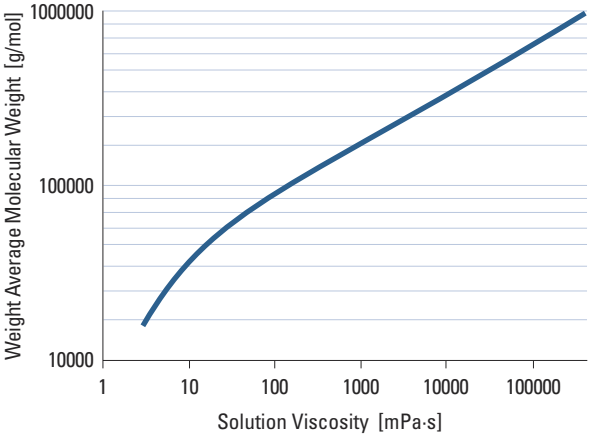


Figure 3: Viscosity versus molecular weight (GPC-MALLS technique).
Equation: $Mw = 40000 \times (\log\eta) + 880 \times (\log\eta)^4$
(η: solution viscosity).

Stability at Various pH Values at 20 °C

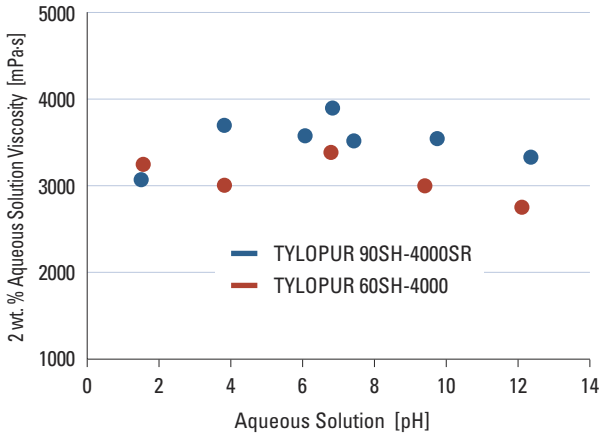


Figure 4: Effect of pH on viscosity for TYLOPUR®.

TYLOPUR® maintains a constant viscosity over the pH range of 3-11. At pH out of this range, the viscosity will be lower. If stored at low pH (acidic), viscosity will gradually decrease due to depolymerization.

Applications

TYLOPUR® is soluble in water and mixed solvents. It may form lumps, which require a long time to dissolve, if it is added to such solvents all at once. Therefore, TYLOPUR® should be dissolved according to the following procedures.

Dissolving in Water

Add all of the TYLOPUR® in about 1/3 of the water, previously heated to above 80 °C, while stirring well. Because hot water is a poor solvent for TYLOPUR® a uniformly wet dispersion is obtained. Then, add cold water to make the prescribed volume while stirring well. When the temperature of the water falls to below 30 °C, TYLOPUR® can dissolves completely and the solution can be used as a coating fluid. If a high-power stirrer is used, TYLOPUR® can be readily dissolved by adding it gradually to the water at below 30 °C with stirring. Care must be taken to avoid bubble or foam formation.

At 6 – 10 % polymer concentration (viscosity less than 100 mPas) any formed bubbles disappear when the solution is left to stand for several hours. Shin-Etsu Silicone KM-72 (Polydimethylsiloxane) from Shin-Etsu Chemical can be employed as antifoaming agents.

Dissolving in Organic Solvents

Pour a prescribed volume of ethanol into a container and add all of the TYLOPUR® in it while stirring. When a uniform dispersion is obtained, add methylene chloride gradually and stir gently to form a well-wetted dispersion as the coating solution.

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

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

1. Low Viscosity Grades

a) Coating

Film coating is usually done with aqueous solutions rather than organic solvents, since the cost of the solvent is lower, the cost of equipment is also lower (solvent recovery and disposal are simpler), and the process is safer (better working environment, less risk of explosion and no need for treatment to remove residual solvents in preparations). Accordingly, Shin-Etsu recommends coating with an aqueous solution. Machinery which offers a high drying efficiency and short coating time is available. Some coating formulations using TYLOPUR® are given in Table 4.

In addition to those examples many coatings are available for particular purposes such as improving abrasion resistance, printability, impact strength, masking color and/or taste, and flowability. Coating formulation and quantities differ considerably depending on the purpose, and it is necessary to change the formulation of the coating solution, the drying temperature and the operating parameters of the coating equipment on a case-by-case basis. Shin-Etsu can provide technical advice on the suitability of various coatings.

I. Laboratory Scale Tablet Coating

Ibuprofen was granulated in a high shear mixer. For the formulation and process conditions please refer to the granulation section of the brochure.

After granulation, tablets were produced according to the formulation (Table 2).

Material	**w/w** [%]	[mg/tablet]
Ibuprofen [1]	80.00	200.00
L-HPC 21 [1]	15.00	37.50
TYLOPUR® 606 [1]	1.00	2.50
L-HPC 21	3.00	7.50
Silicon dioxide colloidal	0.50	1.25
Magnesium stearate [2]	0.50	1.25
[1] granulated with water	*[2] added before compression*	

Table 2: Formulation of ibuprofen tablets.

Tablets were produced with 10-13 kN compression force (9 mm, round, biconvex) on IMA Kilian Pressima.

Parameters	
Tablet weight [mg]	250
Tablet hardness [N]	101
Friability [%]	0.5
Disintegration time [s]	228
Dissolution (>80%) [min]	10

Table 3: Analysis of ibuprofen tablets.

Tablets were coated in a pan coater with TYLOPUR® 606, 645, or 615 grade until 3% weight gain (2 kg batch size each). The formulation of the coating solution is presented in Table 4, the process parameters are presented in Table 5.

Material	**TYLOPUR® 606** **w/w** [%]	**TYLOPUR® 645** **w/w** [%]	**TYLOPUR® 615** **w/w** [%]
HPMC	9.35	11.05	6.75
Talc	2.72	0.99	2.85
TiO_2	1.70	2.55	3.90
Pigment	1.36	1.22	0.15
PEG 6000	1.87	1.19	1.35
Water	83.00	83.00	85.00
Solid content	17	17	15

Table 4: Coating formulation with TYLOPUR® 606, 645 and 615.

Coating Parameters	**TYLOPUR® 606**	**TYLOPUR® 645**	**TYLOPUR® 615**
Nozzle type	Schlick 970	Schlick 970	Schlick 970
Nozzle pressure [bar]	0.65	0.65	0.65
Inlet air temp [°C]	80	80	80
Inlet air flow [m^3/h]	constant	constant	constant
Tablet bed temperature pre-heating [°C]	40	40	40
Tablet bed temperature during coating [°C]	38 – 40	38 – 40	38 – 40
Spray rate [g/min]	4.3 – 6.1	4.2 – 5.9	4.5 – 6.4
Pan speed [rpm]	22	22	22

Table 5: Coating process parameters.

Parameters	**TYLOPUR® 606** coated	**TYLOPUR® 645** coated	**TYLOPUR® 615** coated
Weight [mg]	262.3	258.4	258.8
Disintegration time [s]	728	474	559
Dissolution (>80 %) [min]	10	10	10

Table 6: Analysis of coated tablets.

The analysis of coated tablets showed that all tablets release more than 80% of ibuprofen within the first 10 minutes of the dissolution test (Table 6).

II. Pilot Scale Tablet Coating

TYLOPUR® coating in pilot scale coating, performed in 15 kg batch size. Placebo tablets were coated with TYLOPUR® 605, 645, or 615. Coating parameters are presented in Table 7.

Coating Parameters	TYLOPUR® 606	TYLOPUR® 645	TYLOPUR® 615
Nozzle type	Schlick 930-33/7-1S14	Schlick 970	Schlick 970
Nozzle pressure [bar]	2.9	2.9	2.9
Inlet air temp [°C]	80	80	70
Inlet air flow [m^3/h]	400	400	400
Tablet bed temperature pre-heating [°C]	40	40	42
Tablet bed temperature during coating [°C]	35 – 40	35 – 40	37 – 40
Spray rate [g/min]	9 – 23	6 – 23	4 – 20
Pan speed [rpm]	11	5 (during 5 min) – 12	5 (during 5 min) – 13

Table 7: Tablet coating parameters of scale-up process.

III. Logo Tablet Coating

Logo caffeine tablets were coated in a pan coater with TYLOPUR® 606 grade until 3% weight gain. The tablet core formulation is presented in Table 8 (tablet weight 240 mg with 8 mm diameter). Two coating formulations (with and without lactose) were prepared (Table 9), and the process parameters are presented in Table 10.

Material	w/w [%]
Caffeine	20
L-HPC LH-11	10
MCC 102	30
Lactose	38.5
SiO_2	0.5
Magnesium stearate [1]	1.0
Total	*100*
[1] added before compression	

Table 8: Tablet core formulation.

Material	F1 w/w [%]	F2 w/w [%]
TYLOPUR® 606	7.0	7.0
Lactose	2.1	–
TEC	2.1	–

Table 9: Coating formulation.

Coating Parameters	w/w [%]
Coating equipment	Bosch Solidlab 1
Batch size [g]	560
Inlet temperature [°C]	54
Product temperature [°C]	32
Outlet temperature [°C]	33
Airflow [m^3/h]	38
Drum revolutions [rpm]	20
Spray rate [$g \cdot min^{-1} \cdot kg^{-1}$]	8.9
Nozzle diameter [mm]	0.5
Spray pressure [bar]	0.7
Formation air pressure [bar]	0.2

Table 10: Coating process parameters.

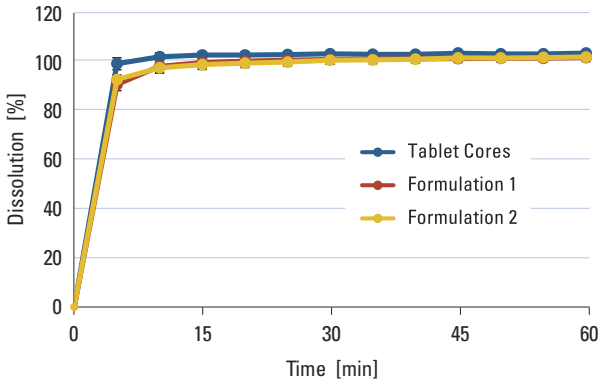


Figure 5: Dissolution of uncoated and coated tablets; according to USP (n=6, Apparatus 2, 50 rpm, 0.1N HCl pH = 1.2, 750 mL, λ = 275 nm).

Coating with TYLOPUR® 606 does not change the dissolution profile. Coating of tablets with a logo is improved when adding lactose to the coating formulation.

IV. Pellet Coating

Pellets offer a great flexibility in pharmaceutical solid dosage forms, from design and development point of view. Successful film coating can be applied onto pellets due to their ideal spherical shape and low surface area-to-volume ratio. TYLOPUR® 603 (HPMC 2910, 3 mPas) can be used for sub- or top/color-coating of functional coatings. Paracetamol layered sugar pellets (#25-30, 0.595-0.707 mm) were coated according to the formulation presented in Table 11. The coating process parameters for fluid bed pellet coating using a wurster setup with TYLOPUR® is presented in Table 12.

Material	w/w [%]
TYLOPUR® 603	7.0
Water	93
Total	*100*

Table 11: Coating formulation.

Coating Parameters	
Coating equipment	Diosna Minilab XP
Batch size [g]	800
Atomizing air [bar]	1.0
Nozzle diameter [mm]	1.2
Inlet tempature [°C]	70
Outlet temperature [°C]	34 – 41
Product temperature [°C]	37.41
Airflow [m^3/h]	30 – 70
Spray rate [g/min]	7.1

Table 12: Coating process parameters.

Paracetamol pellets were coated up to 10 % polymer weight gain. An intermediate sample was collected at 4 % polymer weight gain. After the process, dissolution testing according to USP was performed – Figure 6.

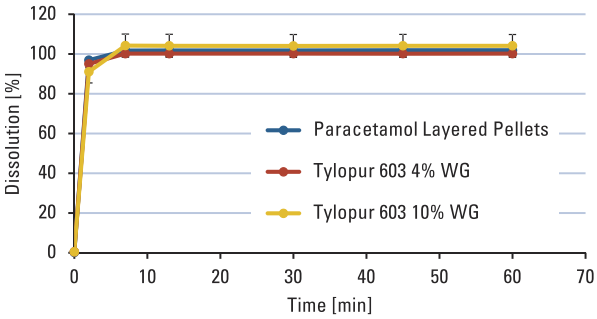


Figure 6: Dissolution of pellets; according to USP (n=3, Apparatus 1, 100 rpm, method B, 0.1N HCl pH = 1.2, 900 mL, λ = 280 nm).

The uncoated paracetamol pellets show virtually the same dissolution as the pellets with 4 % and 10 % polymer weight gain. Coating of paracetamol layered sugar spheres with TYLOPUR® 603 (hypromellose 2910, 3 mPas) up to 10 % polymer weight gain does not affect the dissolution of paracetamol from the pellets.

Summary

The coated tablets/pellets must release the drug in simulated gastric fluid. Moreover, it is essential that the drug is dissolved in water and buffer solutions with various salt concentrations and pH values similar to those of simulated gastric fluid. This is because the pH value of human gastric juice shows inter-individual variation depending on age, constitution, etc., and the drug therapeutic effect is required to be maintained irrespective of such differences. TYLOPUR® film has very favorable dissolution characteristics from this point of view, and this is one of the main reasons why TYLOPUR® is widely used as a coating agent.

TYLOPUR® is an easy to use product to coat tablets and pellets without having a delayed release effect, and this has also been demonstrated in the pilot scale coating experiment.

b) Granulation

TYLOPUR® can also be used as a binder for granulation. The fine particle size (average 50 – 70 µm) allows good admixture with the vehicle (lactose/cornstarch). TYLOPUR® is effective for fluidized bed granulation and high shear mixer granulation. Shin-Etsu recommends the use of TYLOPUR® for fine granules and tableting granules as a highly stable binder, which does not interact with active substances.

Material	High shear mixer	Fluid bed	Fluid bed
Ibuprofen	83.3	83.3	80.8
L-HPC 21	15.5	15.5	15.1
TYLOPUR® 606 (added as 7% aq. solution)	1.2	1.2	4.0

Table 13: Tablet formulations.

Granulation Parameters	
Equipment	Glatt TMG 1-6
Granulating time [min]	6
Blade [rpm]	400 – 300
Chopper [rpm]	300 – 1500
Drying Parameters	
Machine	Diosna Minilab XP
Inlet temp [°C]	65
Air flow [m3/h]	40
Drying time [min]	18

Table 14: Granulation process parameters for High shear mixer.

Granulation Parameters	1 % TYLOPUR® 606	4 % TYLOPUR® 606
Equipment	Diosna Minilab XP	Diosna Minilab XP
Bowl [L]	3	3
Nozzle position / pressure	1.2 mm / 1.5 bar	1.2 mm / 1.5 bar
Air flow [m^3/h]	40	40
Inlet air temperature [°C]	65	65
Product temperature [°C]		
– Warm up	31.0	31.0
– Granulation	25.5	28.3
– Drying	31.0	29.0
Spraying speed [g/min]	5.4 – 11	Up to 12
Filter pressure [bar]	1.5 – 2.0	1.5 – 2.0
Filter cleaning / Pause [s]	5 / 0.5	5 / 0.5
Process time [min]		
– Granulation	20	85
– Drying	8	4

Table 15: Granulation process parameters for Fluidized bed.

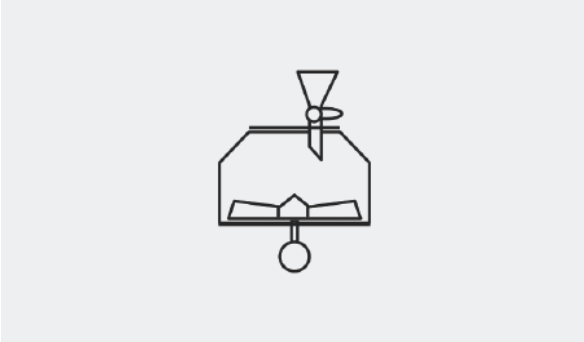


Figure 7: High shear mixer.

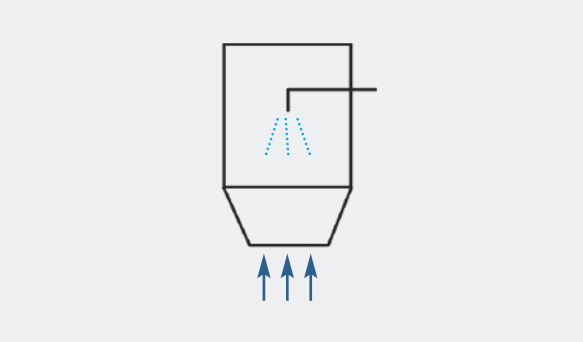


Figure 8: Fluid bed granulation.

Parameters	High shear mixer	Fluid bed 1% TYLOPUR® 606	Fluid bed 4% TYLOPUR® 606
Bulk density [g/cm³]	0.48	0.41	0.30
Angle of repose [°]	44.4	46.4	44.4
Loss on Drying (LOD) [%]	1.2	0.5	1.1
Particle size (x50) [µm]	126	104	188

Table 16: Granules properties.

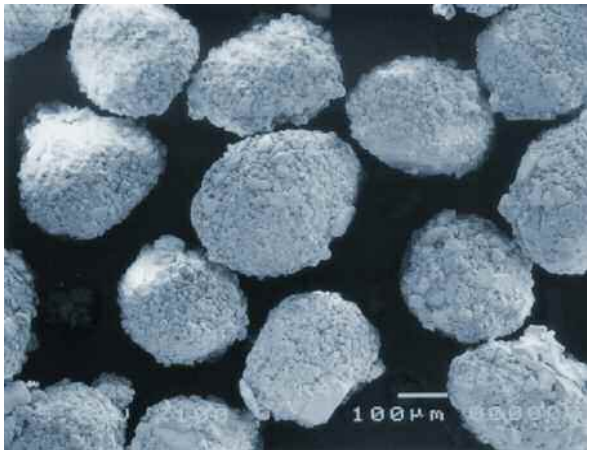


Figure 9: High shear granules.

Figure 10: Fluid bed granules.

Summary

The fluid bed process produces granules with lower bulk density than the high shear mixer process. Upon increasing the TYLOPUR® 606 content in the fluid bed granulation from 1% to 4%, the lowest bulk density and largest particles were obtained. The angle of repose showed nearly no difference when different granulation methods are used.

2. High Viscosity Grades

a) Matrix Tablet

TYLOPUR® high viscosity grades such as the 60SH and the 90SH types can be used for hydrophilic matrix agent and Shin-Etsu can also provide a tighter specification which is especially suitable for sustained release formulations.

The matrix system has several advantages:

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

The dissolution steps of a matrix tablet is presented in Figure 11. HPMC matrix tablets hydrate to form a gel layer, which regulates the drug release pattern. The most important aspect of this matrix system is the homogeneity of the HPMC particle size distribution in the tablet as the selection of the substitution types will affect the initial wetting, swelling, hydration and gel strength.

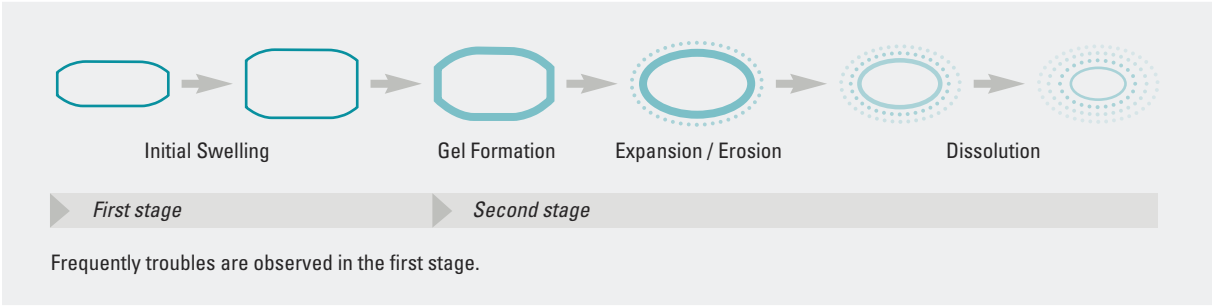


Figure 11: Schematic dissolution of the matrix tablets.

Major factors for formulation of matrix tablets:

Solubility of the drug	– Solubility in water pH dependency
HPMC properties	– Substitution types of HPMC – Viscosity of HPMC – Particle size
Composition	– HPMC content in the tablet – Tablet size – Other excipients
Preparation	– Direct compression or granulation – Compression force – Tablet shape and size – Coating

I. Solubility

For a highly water-soluble drug (Paracetamol solubility is 14.0 mg/mL in water at 25 °C), drug release is regulated by diffusion through the gel layer. In the first 30 minutes an excess amount of drug in the gel layer can be released. For a poorly water-soluble drug (Ibuprofen solubility is 0.021 mg/mL in water at 25 °C), drug release is regulated by erosion of the matrix tablet. The dissolution curve is comparatively linear as compared with highly soluble drugs. The dissolution profiles are shown in Figure 12.

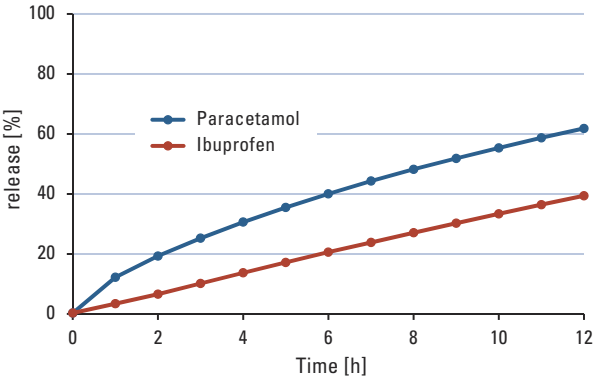


Figure 12: Dissolution profiles of Paracetamol (high solubility) and Ibuprofen (low solubility); according to USP (n=6, Apparatus 2, 50 rpm, 900 mL; paracetamol was tested with 0.1N HCl pH = 1.2 at λ = 280 nm and ibuprofen was tested with phosphate buffer pH = 7.2 at λ = 221 nm).

Material	**w/w** [%]
Paracetamol or Ibuprofen granules [1]	79.5
TYLOPUR® 90SH-4000SR	20.0
Magnesium stearate [2]	0.5

[1] Granules were prepared by wet granulation
[2] added before compression
Compression: 12 mm, 500mg/Tab, 15 kN

Table 17: Tablet formulation.

II. HPMC Properties

Effect of Substitution Type

Substitution type of TYLOPUR® affects hydration speed of HPMC particles and gel strength, which can influence the dissolution profile (Figure 13). Comparing the 60SH and 90SH-SR grades, a slower release is obtained when the 90SH-SR grade is used. In fact, the 90SH-SR grades were designed for the sustained release applications. The 60SH grade has a significant higher methoxy content. A longer hydration time is required. This results in a longer time for gel layer formation, giving initial faster dissolution.

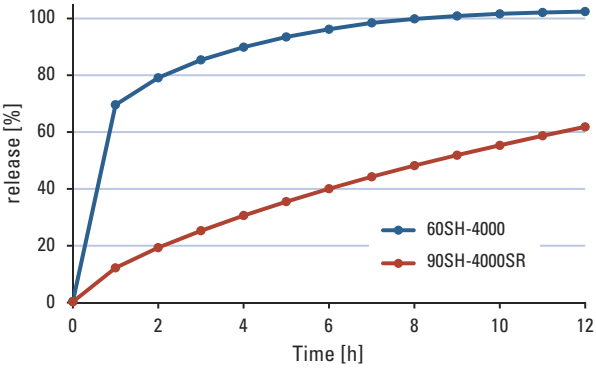


Figure 13: Effect of substitution type on the dissolution of paracetamol tablets; according to USP (n = 6, Apparatus 2, 50 rpm, 0.1N HCl pH = 1.2, 900 mL, λ = 280 nm).

Material	**w/w** [%]
Paracetamol granules [1]	79.5
TYLOPUR®	20.0
Magnesium stearate [2]	0.5

[1] Paracetamol granules were prepared by wet granulation; [2] added before compression
Compression: 12 mm, 500 mg/Tab, 15 kN

Table 18: Tablet formulation.

Viscosity Variation

Paracetamol tablets were prepared using different TYLOPUR® SR grades in order to evaluate their dissolution profile (Table 19). The viscosity of HPMC affects gel strength, hydration speed in the first stage and erosion rate of the gel in the second stage. The higher viscosity grade has stronger gel strength and slower dissolution – Figure 14.

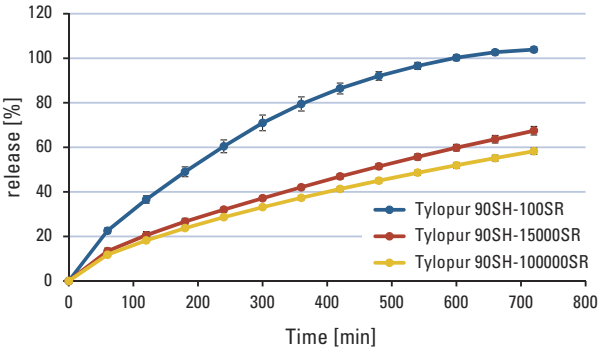


Figure 14: Comparison of the dissolution profiles of TYLOPUR® SR with different viscosity grades; according to USP (n = 6, Apparatus 2, 50 rpm, 0.1N HCl pH = 1.2, 900 mL, λ = 280 nm).

Material	**w/w** [%]
Paracetamol [1]	52.4
TYLOPUR® HPMC 2208 varied	20
Lactose	27.1
Magnesium stearate [2]	0.5

[1] Paracetamol granules were prepared by wet granulation; [2] added before compression
Compression: 18 mm x 9 mm (oblong), 1000 mg

Table 19: Tablet formulation.

Effect of Dissolution Media

In order to see the impact of pH in dissolution profile, the paracetamol tablets were tested with different dissolution media. The dissolution profile of paracetamol tablets was similar (Figure 15) in the different media, showing that the dissolution profile is independent of pH.

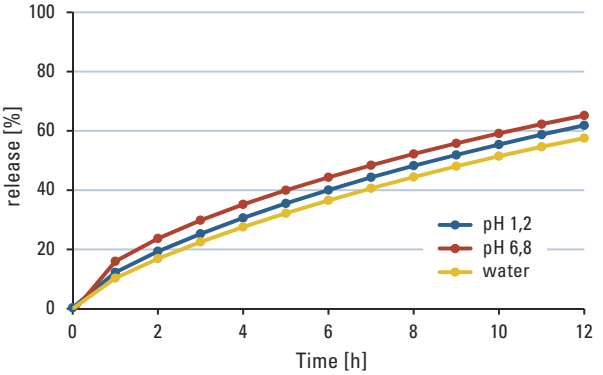


Figure 15: Effect of different media on the dissolution of paracetamol tablets; according to USP ((n = 6, Apparatus 2, 50 rpm, 900 mL).

Material	**w/w** [%]
Paracetamol granules [1]	79.5
TYLOPUR® 90SH-4000SR	20.0
Magnesium stearate [2]	0.5

[1] Paracetamol granules were prepared by wet granulation; [1] added before compression
Compression: 12 mm, 500 mg/Tab, 15 kN

Table 20: Tablet formulation.

III. Composition

HPMC Content in Matrix Tablets

The content of HMPC in the matrix tablet has a significant effect on the dissolution profile. The HPMC content affects the initial erosion of the tablet (first stage). Shin-Etsu recommends 20 % to 40 % content of TYLOPUR® SR for the matrix tablet in order to obtain a delayed release (Figure 16).

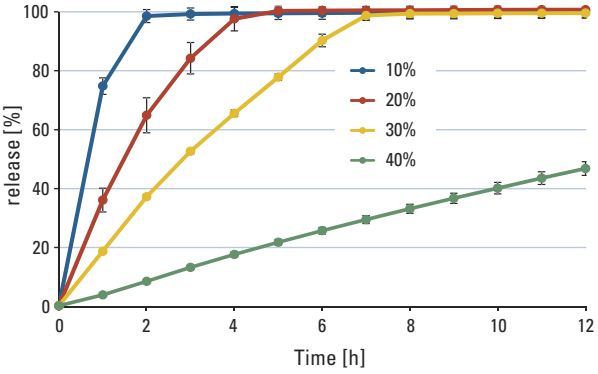


Figure 16: Effect of different HPMC content on the dissolution of ibuprofen tablets, according to USP (n = 6, Apparatus 2, 50 rpm, 0.1N HCl pH = 1.2, 900 mL, λ = 280 nm).

Material	**w/w** [%]
Ibuprofen granules [1]	52.4
TYLOPUR® 90SH-4000SR	10.0 – 40.0
Lactose	7.1 – 37.1
Magnesium stearate [2]	0.5

[1] Ibuprofen granules were prepared by wet granulation; [2] added before compression
Compression: 12 mm,500 mg/ Tab, 15 kN

Table 21: Tablet formulation.

Fillers Consideration

Hydrophilic matrix tablet formulations require the API, the matrix polymer (HPMC 2208, TYLOPUR® SR) and the lubricant. Fillers are added to achieve suitable tablet weight and modify compressibility and powder flow. Three popular fillers are lactose, microcrystalline cellulose (MCC), and calcium phosphate. Depending on the nature of the filler, different dissolution profiles are observed. The effect of the filler on the dissolution profile of matrix tablets is different according to the dissolution media used. In case of acid media, MCC, as an insoluble filler, releases the API slowest and soluble lactose is faster. In case of calcium phosphate, it is easily soluble in the acidic dissolution media required by USP (0.1 N hydrochloric acid pH = 1.2) and releases the API fastest approaching zero-order release. In case of alkaline media, insoluble filler excipients like MCC or dibasic calcium phosphate anhydrous (practically insoluble at pH = 7.2), have a similar effect on the dissolution profile. On the other hand soluble lactose increases the dissolution rate in comparison to MCC or dibasic calcium phosphate.

IV. Preparation

Direct Compression and Granulation

Hydrophilic matrix tablets are easily prepared with API and TYLOPUR® SR (Hypromellose 2208) by different methods such as direct compression, wet granulation and dry granulation.

DC is the most cost-effective production method and can be applied if the other ingredients (such as API) have the following properties:

– Sufficient flowability
– Sufficient compressibility
– Miscibility with TYLOPUR®

TYLOPUR® itself has sufficient flowability and compressibility to be used by DC. However, in some cases the other ingredients do not have the desired properties to use the DC method. Instead, wet or dry granulation, with standard equipments such as High Shear Mixer, Fluid Bed and Roller Compactor, should be used. For wet granulation, a mixture of water and ethanol (20:80 by wt.) is recommended as a solvent.

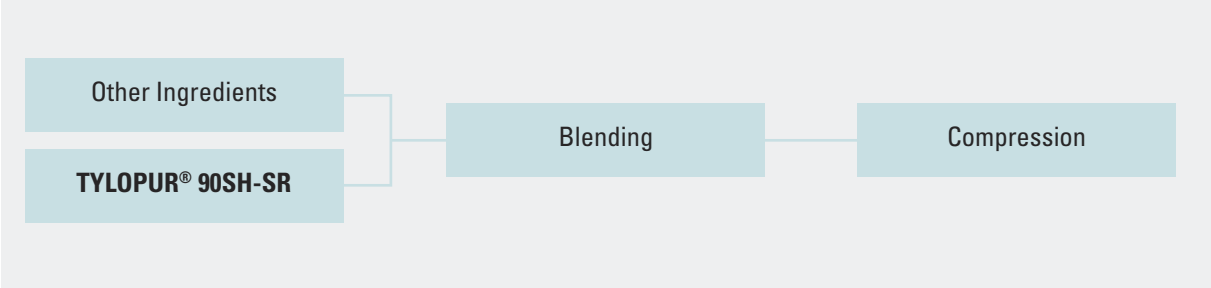


Figure 17: Direct compression.

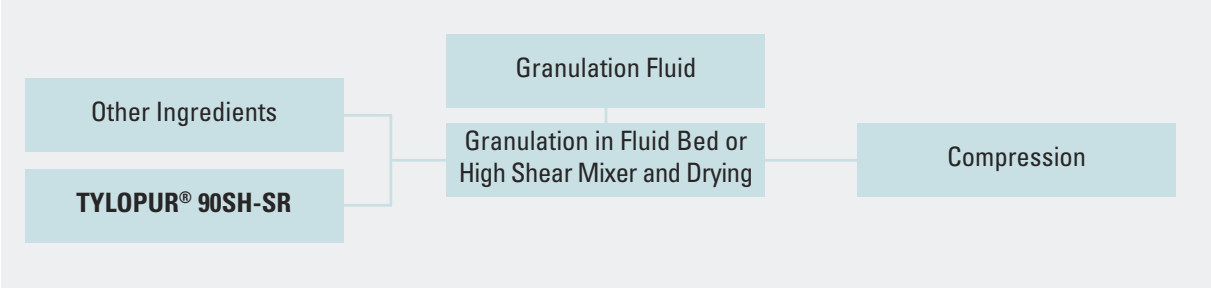


Figure 18: Wet granulation.

Figure 19: Dry granulation – roller compaction.

Example

Paracetamol Sustained Release Matrix Tablet by Direct Compression and Wet Granulation

DC is the simplest technique to prepare matrix tablets. It essentially consists of a drug and TYLOPUR®. Drug substance, which usually shows poor flowability, is primarily granulated in a high shear granulator. With wet granulation of API and excipients, a homogenous mixture is obtained and segregation can be avoided. Furthermore, the flowability of the API is increased by wet granulation process.

Different TYLOPUR® SR grades are compared regarding their dissolution profile when prepared by DC or WG (Figure 20 and 21, respectively).

Material	**w/w** [%]
Paracetamol granules [1]	10.5
TYLOPUR® 90SH-SR	20
Lactose	69.0
Magnesium stearate [2]	0.5
Total	*100*

[1] Paracetamol granules were prepared by wet granulation; [2] added before compression
Compression: 12 mm, 500 mg/ Tab, 15 kN

Table 22: Formulation of tablets prepared by direct compression.

Material	**w/w** [%]
Paracetamol [1]	10
TYLOPUR® 90SH-SR [1]	20
Lactose [1]	69.5
Magnesium stearate [2]	0.5
Total	*100*

[1] Granulated; [2] added before compression;
Compression: 12 mm, 500 mg/Tab, 15 kN

Table 23: Formulation of tablets prepared by wet granulation.

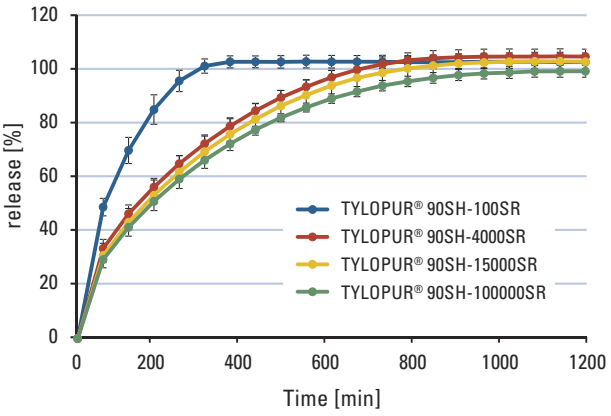


Figure 20: Comparison of the dissolution profiles of tablets prepared by DC; according to USP (n = 6, Apparatus 2, 50 rpm, 0.1N HCl pH = 1.2, 900 mL, λ = 280 nm).

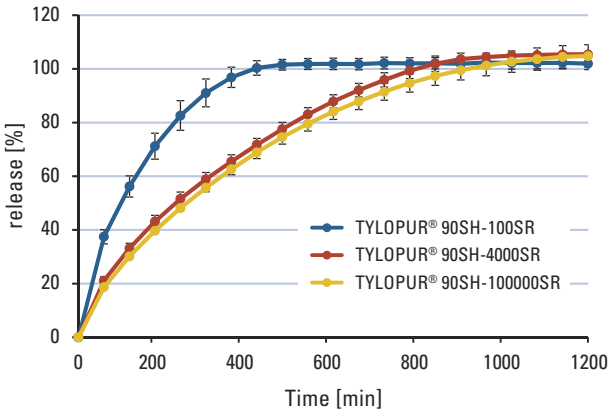


Figure 21: Comparison of the dissolution profiles of tablets prepared by WG; according to USP (n = 6, Apparatus 2, 50 rpm, 0.1N HCl pH = 1.2, 900 mL, λ = 280 nm).

With increasing viscosity, a slower dissolution is observed. The biggest difference in the dissolution profile of a highly soluble API is observed upon changing from the 100SR to the 4000SR grade. TYLOPUR® is suitable for direct compression and wet granulation. Figure 20 and 21 shows that the obtained dissolution profiles are comparable.

Effect of Compaction Force on Dissolution Profile

The paracetamol tablets were prepared using different compaction forces in order to see the impact of this factor on dissolution profile (Figure 22).

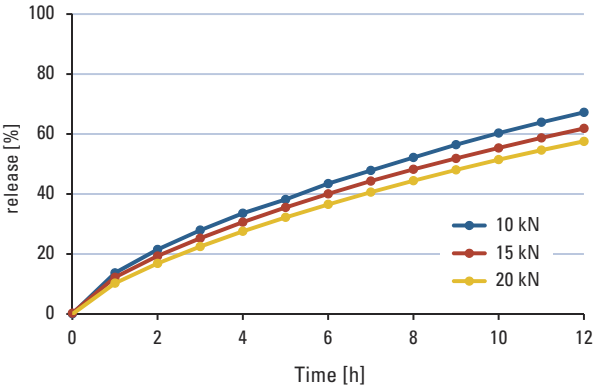


Figure 22: Effect of different compression forces on the dissolution of paracetamol tablets; according to USP (n = 6, Apparatus 2, 50 rpm, 0.1N HCl pH = 1.2, 900 mL, λ = 280 nm).

Material	**w/w** [%]
Paracetamol granules [1]	79.5
TYLOPUR® 90SH-4000	20.0
Magnesium stearate [2]	0.5

[1] Paracetamol granules were prepared by wet granulation; [2] added before compression
Compression: 12 mm, 500 mg/ Tab

Table 24: Tablet formulation.

The compaction force has no effect on the dissolution profile of paracetamol tablets, all the three compaction forces showed a similar dissolution profile.

V. Overview of HPMC Key Quality Attributes in Matrix Tablets

Lower HPO content	– Decrease in initial erosion – Faster drug release – No effect on tablet hardness
Higher viscosity	– Decrease in initial erosion – Slower drug release – No effect on tablet hardness
Bigger particle size or higher bulk density	– Increase in initial erosion – Faster drug release – Lower tablet hardness
Increasing HPMC content (minimum recommend 20 %)	– Decrease in initial erosion – Slower drug release – Higher tablet hardness

Products Specifications

1. Low Viscosity Grades

General Name	Hypromellose					Method
Type	603	645	605	606	615	
Substitution Type	2910					
Identification A. - E. [1]	Conforms					EP
Viscosity [mPas]	2.4 – 3.6	3.6 – 5.1	4.0 – 6.0	4.8 – 7.2	12.0 – 18.0	EP
pH [1]	5.0 – 8.0					EP
Appearance of solution [2]	Conforms					EP
Loss on drying [1]	Not more than 5.0 %					EP
Sulphated ash / Residue on ignition [1]	Not more than 1.5 %					EP
Heavy metals [1]	Not more than 20 ppm					EP
Methoxy content [1]	28.0 – 30.0 %					EP
Hydroxypropoxy content [1]	7.0 – 12.0 %					EP

[1] Harmonized items among the USP, EP and JP [2] Specific local attribute in EP

Table 25: Specifications of low viscosity grades of TYLOPUR®.

2. High Viscosity Grades

General Name	Hypromellose			Method
Type	60SH	65SH	90SH-SR	
Substitution Type	2910	2906	2208	
Description	Conforms			EP
Characters	Conforms			EP
Identification A.-E [1]	Conforms			EP
Viscosity [mPa·s] [1]	See table 27			EP
pH [1]	5.0 – 8.0			EP
Appearance of solution [2]	Conforms			EP
Loss on drying [1]	Not more than 5.0 %			EP
Sulphated ash / Residue on ignition [1]	Not more than 1.0 %			EP
Heavy Metals [1]	Not more than 20 ppm			EP
Methoxy content [1]	28.0 – 30.0	27.0 – 30.0	22.0 – 24.0	
Hydroxypropoxy content [1]	7.0 – 12.0	4.0 – 7.5	8.0 – 12.0	

[1] Harmonized items among the USP, EP and JP [2] Specific local attribute in EP

Table 26: Specifications of high viscosity grades of TYLOPUR®.

TYLOPUR® meets all the requirement for the EP Hypromellose (substitution type: 2910, 2906 and 2208), USP Hypromellose and JP Hypromellose. Moreover, in addition to the tests prescribed in the aforementioned Pharmacopeias, Shin-Etsu carries out tests for foreign matter contamination (including black specs), microbiological contamination, yellowness index, etc., in order to ensure strict quality control. TYLOPUR® is manufactured in accordance with the good manufacturing practice (GMP). A certificate of analysis (CoA) commonly incorporating test results on the EP, are routinely attached to TYLOPUR® products. Quality specifications are shown in the tables 25 and 26.

Labeled viscosity	**Specification**[1] [mPa·s]	**60SH**	**65SH**	**90SH**	**90SH-SR**
4	3.2 – 4.8			●	
50	40.0 – 60.0	●	●		
100	80 – 120				●
400	320 – 480		●		
1500	1125 – 2100		●		
4000	3000 – 5600	●	●		●
13000	7500 – 14000	●			
15000	11250 – 21000				●
100000	75000 – 140000				●

[1] Viscosity is measured with 2 % aqueous solution at 20 °C. Viscosity ranges are 80 % – 120 % of the nominal value for samples with a viscosity less than 600 mPa.s and 75 % – 140 % of the nominal value for samples with 600 mPa.s or higher. Viscosity is hormonized item among the USP, EP and JP.

Table 27: Available grades and viscosity specifications.

Packaging

Standard Package

Fiber drum (40-50 kg) with polyethylene single bag inside.

Customised packaging

We can supply alternative packaging according to your warehouse and manufacturing requirements.

40 - 50 kg Fiber Drum
Ø 450 mm x h 740 mm
(110 litres)

25 kg Fiber Drum
Ø 375 x h 508 mm
(50 litres)

25 kg Carton Box
l 375 x w 375 x h 430 mm

Big Bag Type B
l 1060 x w 710 x h 1250 mm
(up to 1040 litres)

Packing option	TYLOPUR® LV	TYLOPUR® HV 60SH and 65SH	TYLOPUR® HV 90SH-SR
25 kg Fiber Drum	●		
25 kg Carton Box	●		
40 kg Fiber Drum			●
50 kg Fiber Drum	●	●	
Big Bag approx. 1040 L	●	●	●

Table 28: Summary of packing options.

Samples

All samples are packaged in a 1 L sample bottle (approx. 500 g).

Sample Bottle
(500 g)

Application Guide

	TYLOPUR®							
	603	645	605	606	615	60SH	65SH	90SH-SR
Tablets								
Film coating[1]	○	○	●	●	○			
Binder solution (wet granulation)	●	○	○	○				
Sustained release (matrix tablets)						○	○	●
Pellets								
Film coating	●	○	○	○				
Capsules								
Capsule shell		●	●	●	○			
Amorphous solid dispersion								
Solvent free methods (HME)	●	●	●	○				
Solvent methods	●	●	●	○				
Liquids and others								
Thickening						●	○	
Eye drops						○		
Suspending						○	○	
Dry syrup	●	○	○	○	○			
Plaster/dermal patch						○		○
Oral strips		○	●	●	○	●		

[1] refers to a conventional water-soluble polymer coating ● = very suitable ○ = suitable

Table 29: Overview of the pharmaceutical applications with TYLOPUR® products.

For your specific application or further information, please ask your technical sales contact.

Precautions for Safe Handling

Carefully read and understand the Safety Datasheet (SDS) before using this product!

PRODUCT INFORMATION

This substance is not classified as dangerous according Regulation 1272/2008 EC (CLP).
Normal safety precautions for handling chemicals must be observed.
This product does not contain any substance which may be considered hazardous to the health and environmental to the current legislation.

HAZARDS IDENTIFICATION

The product can form flammable or explosive dust clouds in air!
It forms slippery surfaces with water.
Danger of slipping!

HANDLING AND PRECAUTION INFORMATION

Avoid dust formation.
Spilled product has to pick up mechanically under avoiding dust.
Do not breath dust.
Keep away from sources of ignition – No smoking!
The product is hygroscopic.
Protect from atmospheric moisture and water.

PERSONAL PROTECTION

If used properly, protective gloves are normally not required.
If used properly, no need to wear eye protection.
Wash hands before breaks and at the end of the work.
Do not breath dust! In case of insufficient ventilation, use filter apparatus, filter P1.

EMERGENCY AND FIRST AID PROCEDURES

After inhalation, take affected person into fresh air. Consult a physician.
After eye contact, rinse thoroughly with plenty of water, also under the eyelids.
If eye irritation persists, consult a specialist.
After ingestion, rinse mouth. If symptoms persists, call a physician.

STORAGE

Keep dry. Store away from excess heat and sunlight.
Store preferentially in original packaging.

DISPOSAL

Dispose of unused contents and container in accordance with all applicable federal, state and local laws.

Imprint

SE Pharma & Food Materials Distribution GmbH
Industriepark Kalle-Albert
Rheingaustraße 190-196
D-65203 Wiesbaden / Germany

The Manufacture of SE Tylose cellulose derivatives is based on the following registered international quality, environmental and energy management standards.

Wiesbaden Plant ISO 9001 (01 100 84066) ISO 14001 (01 104 7041) ISO 50001 (01 407 7041) HACCP is applied to the relevant manufacturing facilities. It is certified to Kosher and Halal.

Information and Samples

For further information or samples, contact your local distribution partner or Shin-Etsu.

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