Newsletter

July 2022

Shin-Etsu PHARMA

Dear Reader,

2022 is a very special year for Shin-Etsu Chemical Co., Ltd. We are excited to share that we are celebrating the 60th anniversary of the start of our cellulose derivatives production in 1962. With this occasion, we would like to celebrate the long and prosperous years of cooperation with our customers by connecting with you through the new edition of the Shin-Etsu Pharma Newsletter!

Shin-Etsu Pharma Newsletter is an overview of our developments in the field of cellulose ether excipients and their advanced applications. We want to share with you our commitment and dedication to pharmaceutical excipients as our life mission and we look forward to the opportunity to continuing in partnership and in supporting your needs.

Please get in touch with us if you have any questions and we will connect you with someone in your region.

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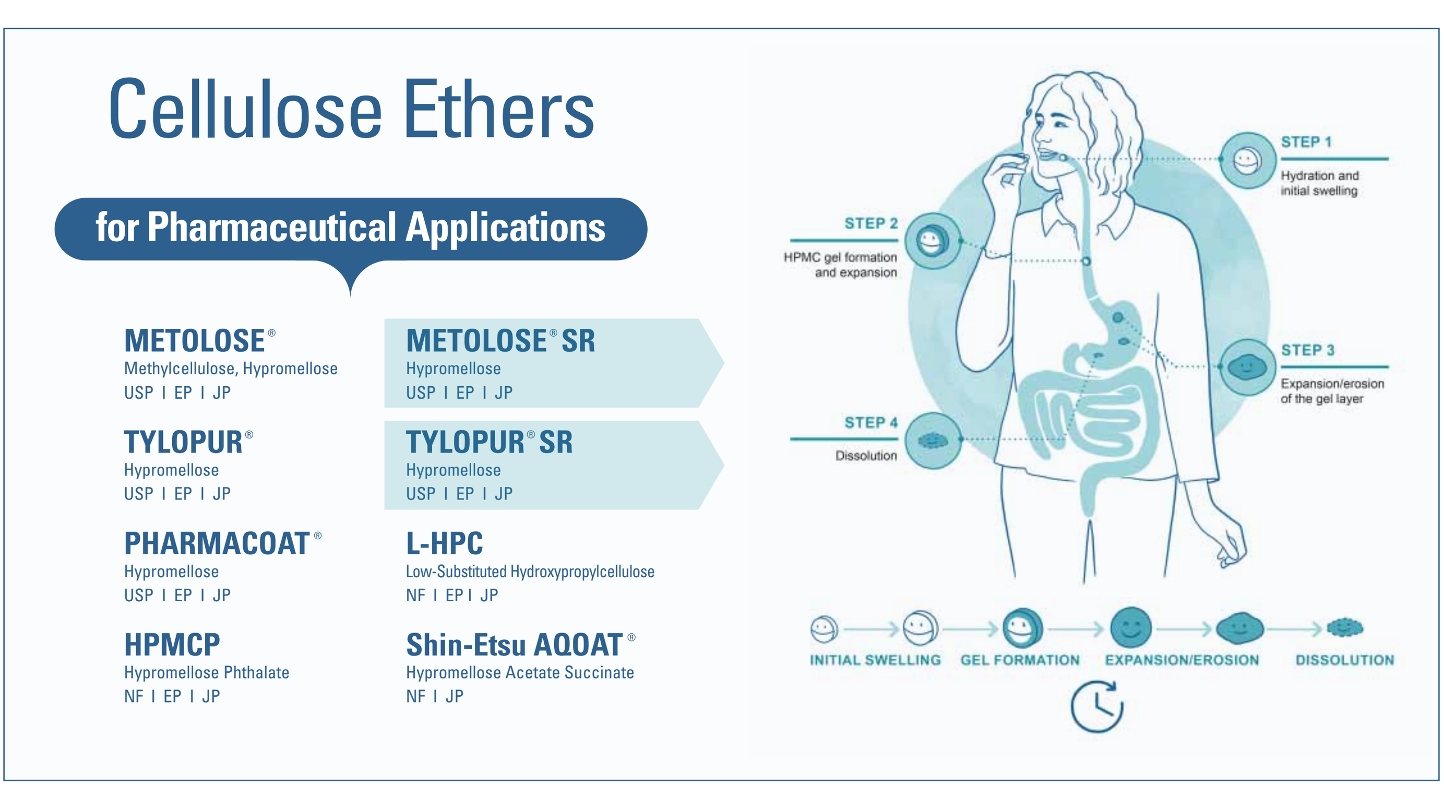
Product Portfolio

METOLOSE® SR and TYLOPUR® SR



Shin-Etsu was established in 1926 and began producing cellulose derivatives in 1962. Pharmaceutical grades of cellulose ethers have been manufactured since 1971.

Regulated grades of cellulose ethers used in pharmaceutical applications are manufactured in Naoetsu, Japan (METOLOSE®, METOLOSE® SR, PHARMACOAT®, L-HPC, HPMCP and Shin-Etsu AQOAT®) and Wiesbaden, Germany (TYLOPUR® and TYLOPUR® SR).

Already in 1962 Shin-Etsu Chemical Co., Ltd. began to produce the water-soluble cellulose ethers methylcellulose and hydroxypropylmethylcellulose (hypromellose), with the trade name METOLOSE®. Hydrophilic matrix systems designed with water-soluble polymers, such as hypromellose, were first introduced to the pharmaceutical industry in the early 1970s.

They are the easiest, cost-effective and most popular way to modify drug release. Hydrophilic matrix systems allow more controllable and reproducible drug release by controlling the chemical and physical properties of the polymer. METOLOSE® SR and its equivalent produced in Germany by SE Tylose TYLOPUR® SR are particularly designed for that purpose.

METOLOSE® SR and TYLOPUR® SR grades feature optimized viscosity, hydroxypropoxy content, and particle size to guarantee highly reproducible dissolution profiles in the production of extended-release matrix tablets. It is fully compliant with USP, JP, EP and applicable in granulation or direct compression processes. Different viscosity grades are available according to the requirements of our customers.

Research Articles

1. Robust Formulation using METOLOSE® SR for Hydrophilic Matrix Tablet

Directly compressed hydrophilic matrix tablets have been widely used as oral controlled-release dosage forms because of their simple formulation, ease of manufacture, and the versatility of their release characteristics. Hypromellose (HPMC) is the compound most commonly used to control drug release, and various hydrophilic matrix tablets using HPMC are highly water soluble, show good gelation performance, and are stable and safe. When hydrophilic matrix tablets are prepared using HPMC, the solubility behavior of HPMC is one of the critical attributes for drug dissolution properties. Additionally, the solubility behavior is affected by the viscosity, hydroxypropoxy (HPO) content and particle size (PS) of HPMC. "Quality by Design" (QbD) principles to formulation development is strongly recommended in the guideline of ICH Q8. It leads to an understanding of how the properties and performance of the dosage forms are influenced by the formulation, including the quality attributes of HPMC. In this study, the effects of HPMC properties on robustness of in vitro drug release were investigated using QbD principles (summarized in Table 1).

A sample kit of METOLOSE® SR (HPMC) consisting of high and low extreme levels of viscosity, hydroxylpropoxy content (HPO) and particle size (PS) were prepared. While one extreme property was set, the other properties were maintained at the standard level. Metformin was used as a model API. API (2%), lactose (78%) and HPMC (100000 m·Pas, 20%) were blended manually and compressed into tablets (11.3 mm-d, flat) by a single punch tablet tester.

The dissolution test was according to the USP paddle method. The effect of the HPMC parameters (viscosity, substitution level and particle size) to the drug release were investigated. There was almost no difference in the drug release from the various METOLOSE® SR parameters when those parameters carried over the upper and lower limit of each specification (Figure 1). It is suggested that the formulation used in this study was highly robust with respect to the properties of METOLOSE® SR.

Sample name	100000ST	100000LV	100000HV	100000LS	100000HS	100000FP	100000CP	
Feature	Standard	Low-viscosity	High-viscosity	Low-HPO	High-HPO	Fine PS	Coarse PS	Shin-Etsu specification
Viscosity (mPa·s)	103000	72800	133000	113000	108000	91000	104000	75000 - 140000
HPO content (%)	9.5	9.5	9.5	7.9	10.6	9.5	9.5	8.5 - 10.5
D_{50} (µm)	63.3	61.4	68.3	61.4	60.7	58.9	73.4	50 - 80

Table 1: A sample kit of METOLOSE® SR (HPMC) consisting of high and low extreme levels of viscosity, hydroxypropoxy (HPO) content and particle size (PS).

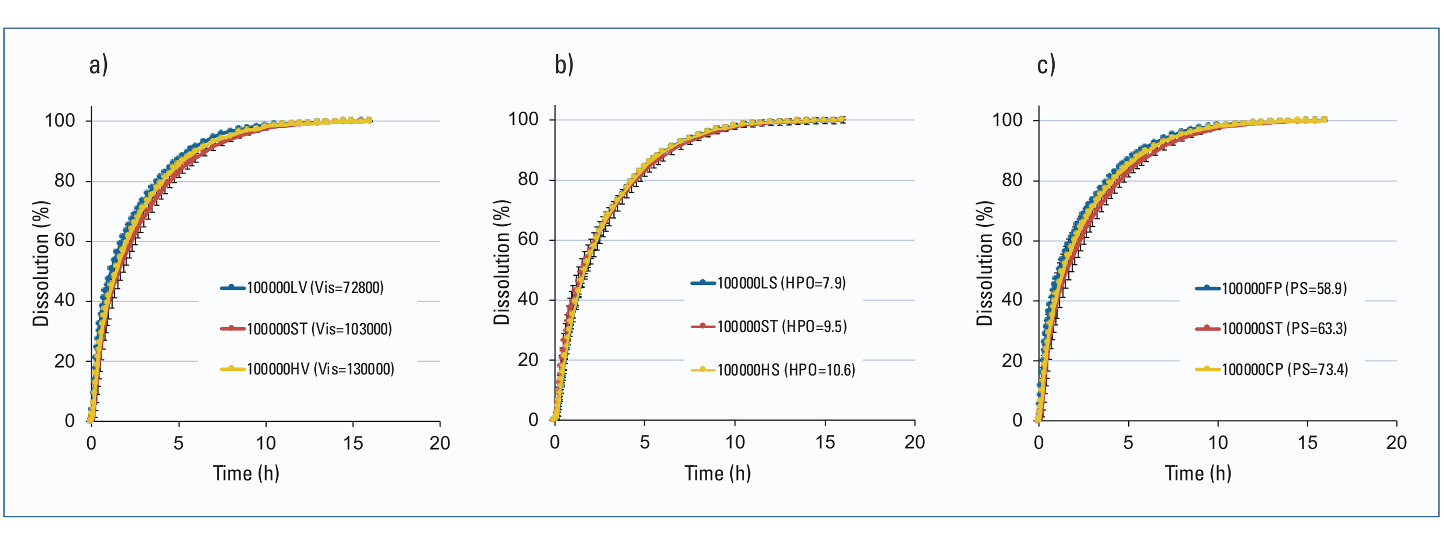


Figure 1: Effect of the METOLOSE® SR properties a) viscosity, b) HPO content and c) particle size on the dissolution profiles of Metformin.

More information in Technical Information SR-011 available on:

www.metolose.jp/en   www.setylose.com

2. Design of Solid Dispersion Tablets using L-HPC as a Disintegrant

There are many strategies to improve the dissolution properties of poorly water-soluble drugs. Amorphous solid dispersion (ASD) is one of the useful techniques to enhance dissolution rate and/or solubility. A manufacturing method of ASD for solid dosage forms has been also investigated. Because it needs a relatively high amount of polymer as a carrier in the tablet, prolonged disintegration time of the tablets containing ASD is expected. Therefore, incorporation of disintegrant is also important to make rapid disintegration and prevent crystallization of the drug.

Low-substituted hydroxypropylcellulose (L-HPC), listed in NF, EP and JP is insoluble in water, however swells in water. L-HPC is widely used as disintegrant in tablets and granules because of its superior swelling property. There are nine Shin-Etsu grades of commercially available products, which have different particle sizes, shapes and chemical substitution levels (Table 2). L-HPC is applicable to various processes. It is an effective disintegrant because of its high swelling property and water absorption speed in water. Moreover, the characteristics of its unique particles show good compressibility, like a dry binder.

Grades	Particle shape	HPO content (%)	Particle size (µm)	Bulk density (g/mL)	Angle of repose (°)	Typical application
LH-11		11	d_{50}: 50 d_{90}: 180	0.33	48	Anti-capping
LH-21		11	d_{50}: 45	0.38	45	Standard grade
LH-22		8	d_{90}: 135	0.37	46	DC, WG
LH-31		11	d_{50}: 20	0.28	49	Pellet extrusion
LH-32		8	d_{90}: 80	0.21	50	Layering
LH-B1		11	d_{50}: 50 d_{90}: 125	0.48	40	DC, FBG (Highly swelling)
NBD-020		14	d_{50}: 45		43	WG
NBD-021		11	d_{90}: 100	0.32	43	DC, WG
NBD-022		8			43	DC, ODTs

Table 2: Powder properties of L-HPC products (Typical value).
HPO: Hydroxypropoxy   FBG: Fluid bed granulation
DC: Direct compression   DG: Dry granulation
WG: Wet granulation   ODT: Orally disintegrating tablet

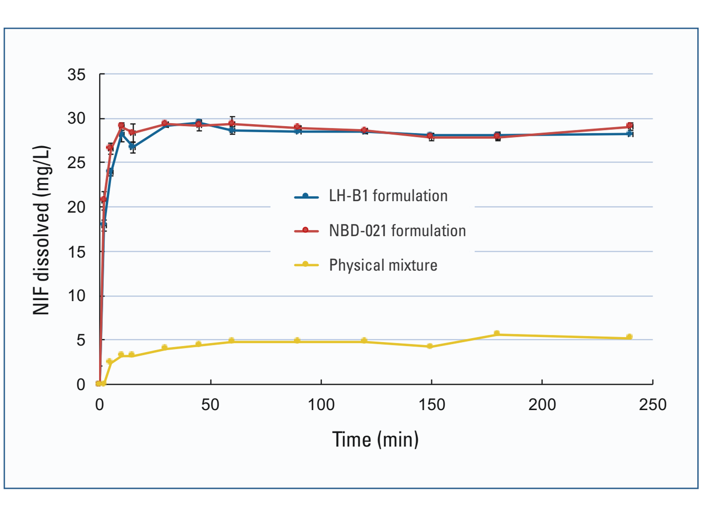


Figure 2: Dissolution profiles of NIF-SDD tablets and the physical mixture.

Spray dried solid dispersion (SDD) with hypromellose acetate succinate (Shin-Etsu AQOAT®, AS-MG) as a polymeric carrier and nifedipine (NIF) as a model drug with the ratio of 2:1 (w/w) were prepared. The tablets containing 54 parts of SDD, anhydrous calcium hydrogen phosphate and L-HPC (LH-B1 or NBD-021), which are excipients with excellent powder flow, were prepared by direct compression (DC) process.

Both tablets containing L-HPC satisfied the tablet properties, such as tablet hardness, disintegration time and friability. Dissolution profiles are shown in Figure 2. Compared to a physical mixture, NIF was immediately released from both tablets, and they showed an excellent super-saturation performance of the NIF:HPMCAS SDD. L-HPC enables the ability to make SDD tablets by DC, and improves tablet properties with SDD, which have poor flowability and disintegration performance.

More information in Technical Information A-072 available on:

www.metolose.jp/en   www.setylose.com

3. Continuous Twin Screw Melt Granulation to Improve Flow and Compaction Properties of Metformin HCl Using Shin-Etsu AQOAT® AS-MMP

Metformin HCl is one of the most prescribed biguanide oral antihyperglycemic drugs usually available in tablet form. As Metformin HCl is poorly flowable and poorly compressible, it is usually wet granulated to develop into a tablet dosage form. However, conventional wet granulation process is a batch process and involves a large number of unit operations, thus increasing cost and footprints. In the present study, twin screw melt granulation (TSMG), an inherently continuous process, has been employed to improve flowability and compaction properties of metformin HCl. Hypromellose Acetate Succinate (Shin-Etsu AQOAT® AS-MMP) with a mid-level particle size and acetyl and succinyl content was chosen as a granulation binder. To optimize processability of melt granulation of metformin HCl with HPMCAS, a preliminary trial consisting of 18 experiments with varying temperatures, feed rates, screw speeds and number of kneading zones was carried out. The effect of adding HPMCAS on flowability, particle size distribution, solid state properties (crystallinity and microscopical analysis) was evaluated. Granules were further compacted into tablets using a single press consisting of a 500 mg dose of metformin HCl. Tensile strength along with dissolution rate was evaluated. From the preliminary experiments, it was found that metformin HCl can only be granulated with 10% AS-MMP or more at a processing temperature of 180 °C, feed rate of 10 g/min and screw speed of 50 RPM consisting of 1 kneading zone. It was found that flowability of metformin HCl can be significantly improved using HPMCAS by melt granulation. Compactibility of metformin HCl can be significantly enhanced by TSMG using AS-MMP with 10% showing optimal concentration with higher tensile strength (Figure 3). From dissolution studies, it was found that with increasing concentrations of AS-MMP, decreases in drug release of metformin HCl occurs. Thus, it can be concluded that HPMCAS can be successfully employed to improve flow and compaction properties of metformin HCl by continuous twin screw melt granulation.

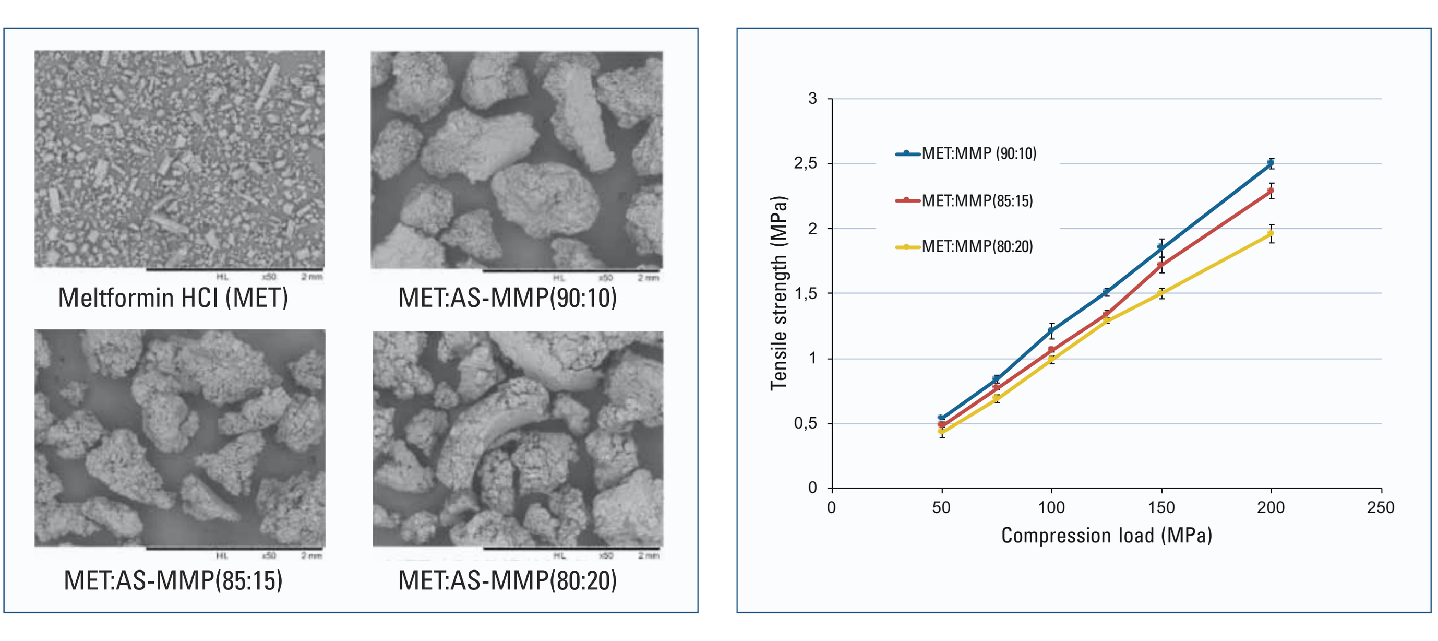


Figure 3: SEM images and tabletability plot depicting the effect of different concentration of HPMCAS-MMP on Metformin HCl by continuous twin screw granulation. Physical mixture of Metformin HCl and AS-MMP cannot form tablets due to capping.

4. Head-to-head comparison of L-HPC and MCC/croscarmellose as binder and disintegrant in roller compaction of a spray-dried ASD with Shin-Etsu AQOAT®

In a recent published article, the Shin-Etsu team in Wiesbaden, Germany, studied the roller compaction of an amorphous solid dispersion (ASD) with Nifedipine and Shin Etsu AQOAT® (ratio 1:2) as carrier polymer to yield tablets with 75 % ASD load after compression. Roller compaction is the preferred granulation technique for spray dried amorphous solid dispersions as moisture is excluded. However, in roller compaction, a phenomenon called work- or granule-hardening is observed. By the compression of the formulation between the rollers during granulation, the granules show a higher density and reduced tabletability compared to other granulation technologies. The extent of loss of tablet tensile strength is described as work- or granule-hardening. Low-substituted hydroxypropyl cellulose (L-HPC) or the combination of MCC/croscarmellose was tested as binder-disintegrant system for roller compaction. Less work hardening during roller compaction and a 45% higher tablet tensile strength was observed in the formulation with L-HPC vs. the widely applied combination of MCC/croscarmellose (Figure 4). An identical dissolution profile for both formulations was observed. This case study demonstrates that L-HPC is an excellent binder and disintegrant in the roller compaction of spray-dried ASDs providing tablets of sufficient tensile strength for further downstream processes and rapid dissolution.

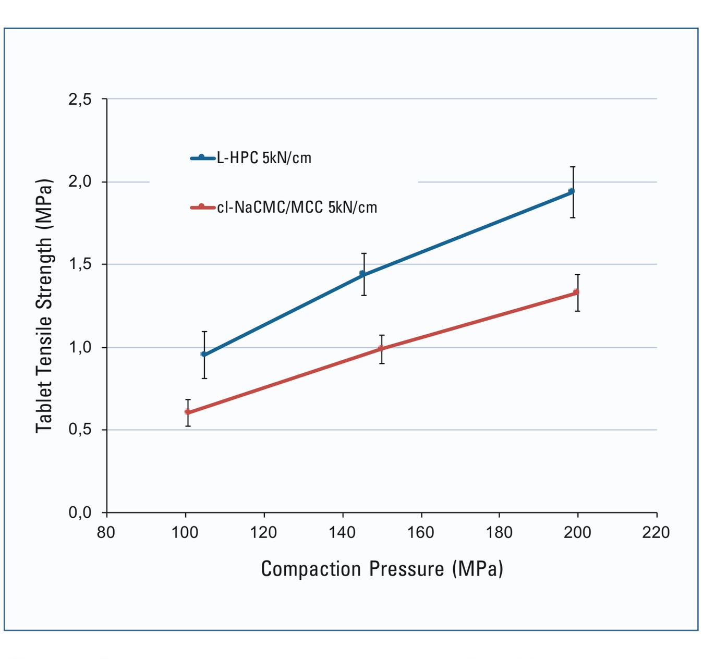


Figure 4: Roller compacted granules tabletability of formulations with L-HPC or MCC/cl-NaCMC.

For more information on the study, please view the full article published in open access:

Downstream processing of spray-dried ASD with hypromellose acetate succinate – Roller compaction and subsequent compression into high ASD load tablets - Int. J. Pharm: X, 3 (2021)

https://doi.org/10.1016/j.ijpx.2021.100099

New Technical Information

Shin-Etsu are continuously striving to deliver new technical data for your formulation development. Please take a look at those new technical information sheets that are available from your local Shin-Etsu representative.

Shin-Etsu AQOAT®

A-071
Impact of process parameters on solid dispersion particle

www.metolose.jp/en   www.setylose.com

A-072
Direct Compression of Spray Dried Solid Dispersion

www.metolose.jp/en   www.setylose.com

Together with HPMCP

H-017 A-054
IR Spectrum of HPMCP and Shin-Etsu AQOAT®

www.metolose.jp/en   www.setylose.com

L-HPC

L-040
Twin Screw Wet Granulation: Suitability of L-HPC and PHARMACOAT®

www.metolose.jp/en   www.setylose.com

L-041
Water Absorption of L-HPC

www.metolose.jp/en   www.setylose.com

Exhibitions 2022

Please come visit us at the following trade shows. We will have technical teams available who will be happy to answer any questions, and we can also book private or confidential meetings.

CRS Controlled Release Society

11th-15th July 2022 – CRD – Montreal, Canada

in-PHARMA JAPAN 2022 – 16th Int'l Pharmaceutical and Cosmetics Ingredients Expo

13th-15th July 2022 – in-PHARMA JAPAN – Tokyo, Japan

EuPFi

20th-22nd September 2022 – EuPFi – Rome, Italy

aaps American Association of Pharmaceutical Scientists

16th-19th October 2022 – AAPS – Boston, USA

SupplySide WEST

31th Oct. - 4th Nov. 2022 – Supply Side West – Las Vegas, USA

CPhI worldwide

1st-3rd November 2022 – CPhI worldwide – Frankfurt, Germany

CPhI india

29th Nov. - 3rd Dec. 2022 – CPhI India – Delhi NCR, India

More Information

www.metolose.jp/en   www.setylose.com   www.linkedin.com   www.youtube.com

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