Newsletter

December 2023

Shin-Etsu PHARMA

Dear Reader,

We are approaching the end of 2023. It was a very exciting year full of activities and information to share with you.
With this Newsletter we would like to highlight the most important ones:

1. Together with four partnering companies we organised the 4th Shin-Etsu Technical Seminar in May 2023 at our SE Tylose site in Wiesbaden, Germany. Now the protocols of the four technologies demonstrated during the seminar are available upon request through our website.
2. Shin-Etsu´s efforts in mitigating the risk of nitrosamine formation in solid oral dosage forms.
3. Our research activities:
   – Recently published article in a peer reviewed journal,
   – Six posters presented this year at AAPS PharmSci 360 in Orlando, Florida, USA
   – ODT blog article posted.

We would be delighted to share more details with you so please do not hesitate to contact us!

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Announcement | Protocols of technologies demonstrated during the 4th Shin-Etsu Technical Seminar on ASD

In May 2023, at our site in Wiesbaden, we held a seminar focusing on amorphous solid dispersion (ASD) organized along with four partnering companies: Alexanderwerk, Frewitt, PROCEPT and Thermo Fisher Scientific – the 4th Shin-Etsu Technical Seminar on Solubility Enhancement: From Screening to Downstreaming. As technology providers in the field of ASD we shared the latest insights on ASD development steps ranging from initial screening to downstream processing including spray drying, hot melt extrusion (HME), roller compaction and milling. The program comprised of practical lab demonstrations featuring the leading polymer for ASDs - Shin-Etsu AQOAT® (HPMCAS). Please feel very much encouraged to download the protocols of the mentioned technologies:

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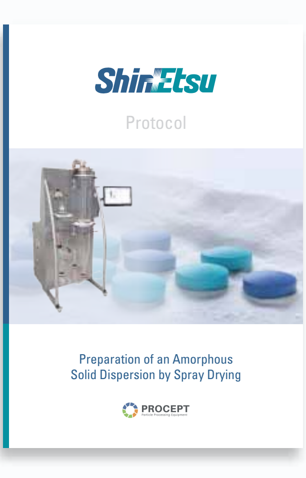

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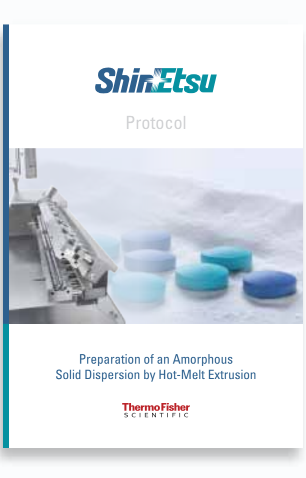

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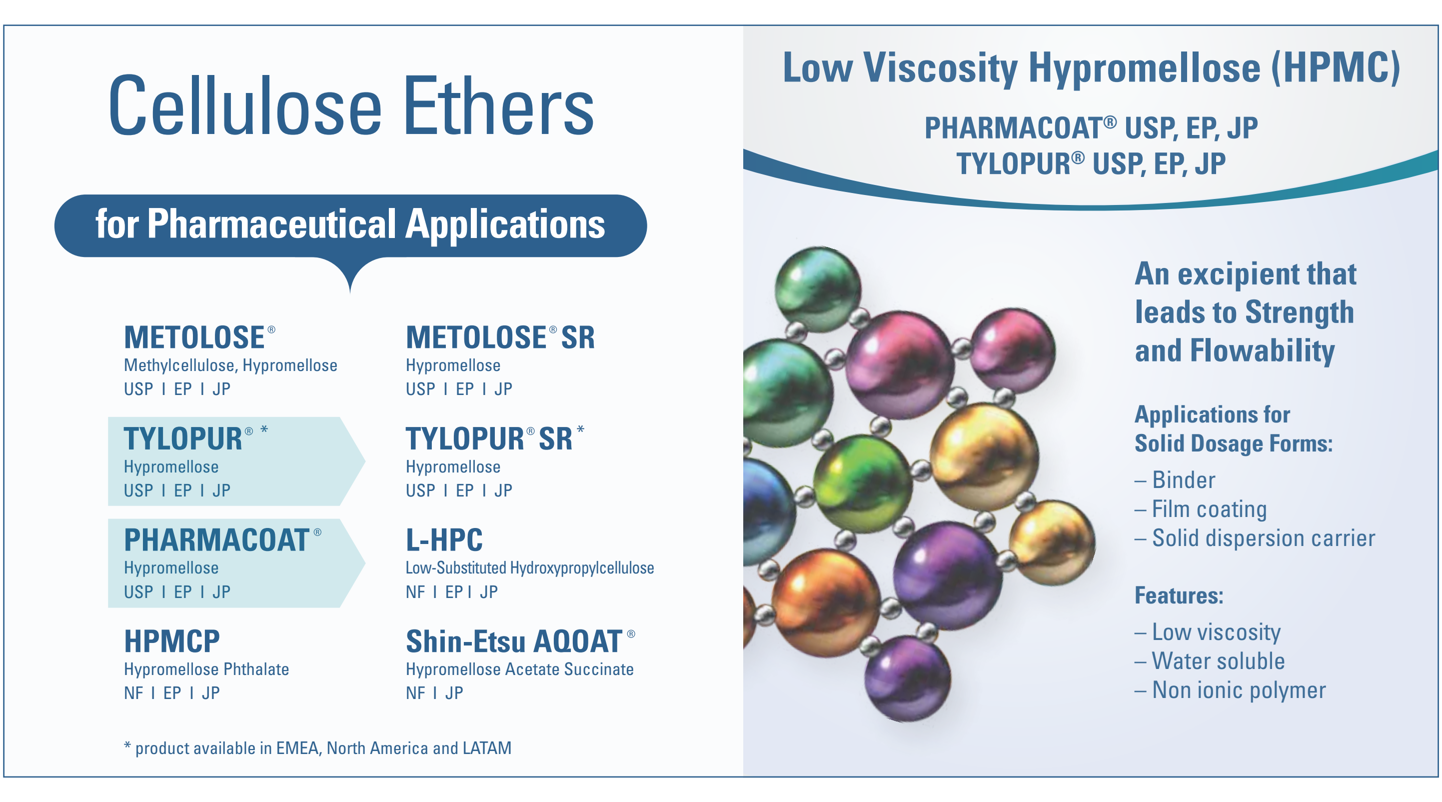
More information:

https://www.setylose.com/en/knowledge-base/previous-seminars

Product Portfolio



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).

Shin-Etsu's PHARMACOAT® was developed in 1963 during the early days of film coating and since then it has been the subject of a continuous development and quality improvement. TYLOPUR® is manufactured at SE Tylose GmbH & Co. KG in Wiesbaden, Germany.

The PHARMACOAT® and TYLOPUR® grades are low viscosity hypromellose substitution 2910 (also named as hydroxypropyl methylcellulose or HPMC). Hydroxypropoxy and methoxy groups are introduced on the cellulose backbone, resulting in water soluble cellulose derivatives. Once dissolved in water, the PHARMACOAT® and TYLOPUR® grades generate clear solutions with different viscosities depending on the amount and grade used. The PHARMACOAT® and TYLOPUR® grades are nonionic cellulose derivatives, have superior stability and non-ionic character. These properties confer good stability with a wide range of active ingredients.

The PHARMACOAT® and TYLOPUR® are easy to use as a film coating material and give an excellent finish. They are very versatile and are suitable for many applications in the design of film-coated tablet formulations. In additiona, PHARMACOAT® and TYLOPUR® are widely used as binders for granulation and are available in various viscosity ranges for that purpose.

Hydroxypropyl methylcellulose films manifest very good properties used for hard capsule manufacturing as an alternative to gelatin. The main advantage of PHARMACOAT® and TYLOPUR® over gelatine are their better moisture stability and its plant derived origin, the optimal solution for patients following a vegetarian or vegan diet.

More information:

https://www.metolose.jp/en/pharmaceutical/tc-5.html

https://www.setylose.com/en/products/healthcare/pharmacoat

https://www.setylose.com/en/products/healthcare/tylopur

Research Articles

1. In vitro-in vivo relationship for amorphous solid dispersions using a double membrane dissolution-permeation setup

The use of amorphous solid dispersions (ASDs) is one commonly applied formulation strategy to improve the oral bioavailability of poorly water-soluble drugs by overcoming dissolution rate and/or solubility limitations. While bioavailability enhancement of ASDs is well documented, it has often been a challenge to establish a predictive model describing in vitro-in vivo relationship (IVIVR). In this study, it is hypothesized that drug absorption might be overestimated by in vitro dissolution-permeation (D/P)-setups, when drug in suspension has the possibility of directly interacting with the permeation barrier. This is supported by the overprediction of drug absorption from neat crystalline efavirenz compared to four ASDs in a D/P-setup based on the parallel artificial membrane permeability assay (PAMPA). However, linear IVIVR ($R^2 = 0.97$) is established in a modified D/P-setup in which the addition of a hydrophilic PVDF-filter acts as a physical boundary between the donor compartment and the PAMPA-membrane. Based on microscopic visualization, the improved predictability of the modified D/P-setup is due to the avoidance of direct dissolution of drug particles in the lipid components of the PAMPA-membrane. In general, this principle might aid in providing a more reliable evaluation of formulations of poorly water-soluble drugs before initiating animal models.

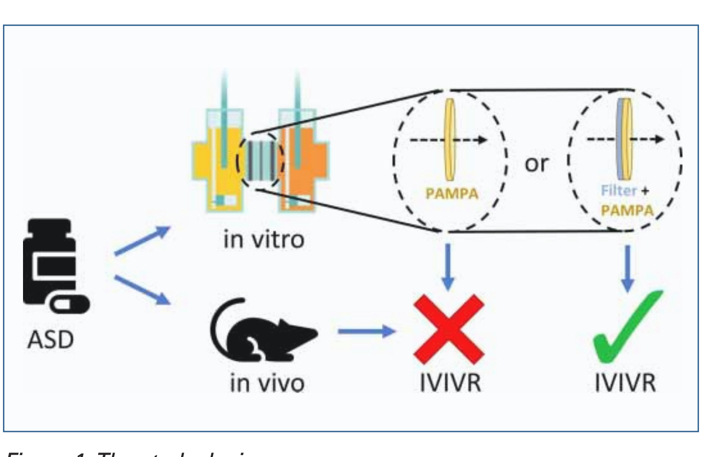


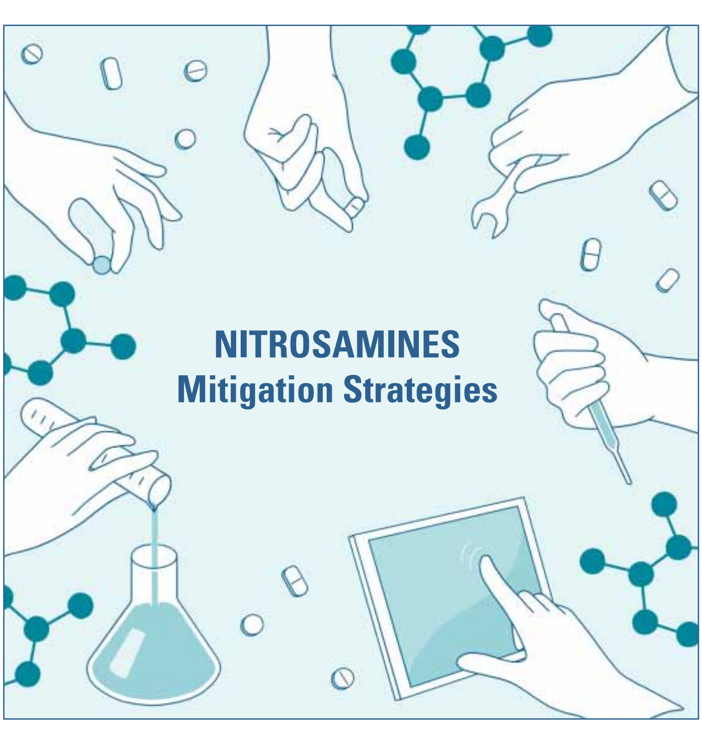
Figure 1: The study design.

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

European Journal of Pharmaceutics and Biopharmaceutics, Volume 188, July 2023, Pages 26-32

https://www.sciencedirect.com/science/article/pii/S0939641123001145?via%3Dihub

2. Strategies to Reduce Nitrosamine Contamination of Drug Products



Nitrosamines contamination of drug products are a concern for pharmaceutical companies. N-Nitrosamines are compounds, which are either proven, or potential carcinogens in humans. With the 2018 report of N-Nitrosodimethylamine (NDMA) found in various Sartan-type drug products, the regulatory bodies imposed a strict limit of acceptable intake of 96 ng/day (nanograms/day) for this specific nitrosamine. In these cases, the API was already contaminated with NDMA during drug synthesis. In recent years, more and more drug products have been found to contain different nitrosamine impurities leading to recalls and shortages of medicines world-wide. [1]

Nitrite testing is a rather new topic for excipient manufacturers there is no historical data available and testing is not harmonized (there are UV, HPLC-UV, IC methods reported for e.g. hypromellose). It is noted by the International Pharmaceutical Excipients Council (IPEC) in their questionnaire on nitrosamines risk assessment, that nitrite test results from suppliers may vary and encourages excipient users to develop their own nitrite test for excipients. [2] Shin-Etsu provides support in the development of analytical methods to enable pharmaceutical companies to test for nitrite in hypromellose.

Shin-Etsu tested their and competitors' cellulose ethers and found the lowest levels in Shin-Etsu hypromellose – low and high viscosity using a validated analysis method, limiting risk of nitrosamine formation in drug products. The data is summarized in a Whitepaper from 2023 and is available for download on SE Tylose website: **https://www.setylose.com/en/knowledge-base/healthcare/white-papers#metolose-sr-10410**

References:

[1] Bharate, S.S. Critical Analysis of Drug Product Recalls Due to Nitrosamine Impurities. J. Med. Chem. 2021, doi:10.1021/acs.jmedchem.0c02120.
[2] IPEC Federation IPEC Questionnaire for Excipient Nitrosamines Risk Evaluation; 2023.

More information:

https://www.setylose.com/en/blog/strategies-to-reduce-nitrosamine-contamination-of-drug-products

https://www.setylose.com/en/knowledge-base/healthcare/white-papers#metolose-sr-10410

3. Shin-Etsu Posters Presented at AAPS PharmSci 360 in Orlando, Florida, USA

Poster A
Assessment of Stability and Erosion Behavior of ASDs by Using VCM Technique

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Poster B
Dissolution Technology Using HPMCAS Solid Dispersion Targeting the Upper Small Intestine

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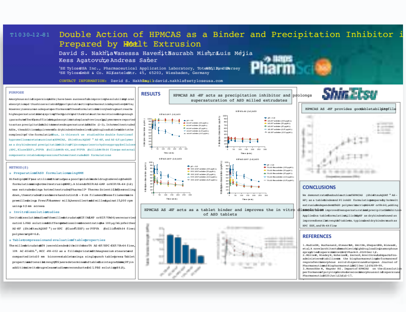

Poster C
Double Action of HPMCAS as a Binder and Precipitation Inhibitor in ASD Tablets

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Poster D
Application of Hypromellose Phthalate (HPMCP) for the development of Esomeprazole 20mg Multiple Unit Pellet System (MUPS)

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Poster E
Effect of Different Neutralizers and Their Concentration on Enteric Coating of Hypromellose Phthalate (HPMCP HP-50) and Drug Release in Various pH

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Poster F
Development of Hydroxypropyl Methylcellulose (HPMC)-Based, Titanium Dioxide (TiO_2)-Free Coating

Download

4. Blog – Improving patient adherence with ODT formulations

In June 2022, Persistence Market Research presented a market outlook of orally disintegrating tablets (ODT) for the next years (2022 - 2025). According to this research "The ODT Market is likely to have a compound annual growth rate (CAGR) of 8.5% over the forecasted period. One of the primary factors driving the growth of Orally Disintegrating Tablets is that these tablets are increasingly being used as an alternative to traditional tablets or capsules".[1]

ODTs are namely orally disintegrating tablets or orodispersible tablets containing a medicinal substance and disintegrating within a matter of seconds in the mouth without any intake of externally administered liquids. Thus, the active pharmaceutical ingredient (API) is delivered via the mouth mucosa avoiding the first-pass metabolism leading to an increased bioavailability for enzymatic sensitive APIs as example. [2] ODTs are defined by the pharmacopoeias as weighing a maximum 500 mg and disintegrating in less than 30 seconds (American pharmacopoeia /USP) or 180 seconds (European pharmacopoeia/EP) in 2 mL of saliva.

References:

[1] Persistence market Research Website - https://www.persistencemarketresearch.com/market-research/orally-disintegrating-tablet-market.asp (accessed June 2023).
[2] Chinwala M. Recent Formulation Advances and Therapeutic Usefulness of Orally Disintegrating Tablets (ODTs). Pharmacy (Basel). 2020;8(4):186 - https://pubmed.ncbi.nlm.nih.gov/33050437/.

For more information, visit our Blog article on SE Tylose website:

https://www.setylose.com/en/blog/improving-patient-adherence-with-odt-formulations

Exhibitions 2024

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.

PHARMA LIVE•EXPO 2024

17th – 17th January 2024 | Mumbai, India
India Pharma Expo

DCAT®

18th – 21st March 2024 | New York, USA
Premier global event for companies engaged in the Bio/Pharmaceutical manufacturing value chain

CRS CONTROLLED RELEASE SOCIETY INDIAN LOCAL CHAPTER

29th February – 1st March 2024 | Dhaka, Bangladesh
CRS India

Global DDF Summit Drug Delivery & Formulation

21st – 23rd May 2024 | Berlin, Germany
15th Global Drug Delivery & Formulation Summit

asia PHARMA EXPO | ASIA LAB EXPO

29th February – 2nd March 2024 | Dhaka, Bangladesh
15th International Exhibition on complete pharma manufacturing

in-PHARMA JAPAN Int'l Pharmaceutical and Cosmetics Ingredients Expo

26th – 28th June 2024 | Tokyo, Japan
International exhibition specialised in pharma and cosmetics ingredients

PBP WORLD MEETING | ResearchPharm® International Exhibition for R&D

18th – 21nd March 2024 | Vienna, Austria
14th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology

CRS CONTROLLED RELEASE SOCIETY

8th – 12th July 2024 | Bologna, Italy
Annual Meeting and Exposition

More Information

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

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