Newsletter March 2023

Shin-Etsu PHARMA

Dear Reader,

we are pleased to share an exciting update on Shin-Etsu Pharma's most recent activities including: the upcoming 4th Technical Seminar on Solubility Enhancement: from Screening to Downstreaming in May 2023 at Shin-Etsu's site in Wiesbaden, Germany; introduction of SmartEx® Plus as our new product for direct compression used, among the others, in orally disintegrating tablets (ODTs) and dispersible tablets; the most recent research articles pursued or contributed to by the Shin-Etsu Pharma Team; as well as the newly released Technical Information.

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Announcement | 4th Technical Seminar on Solubility Enhancement

We are glad to announce our 4th Seminar on Amorphous Solid Dispersion (ASD). As technology provider in the field of ASD, Shin-Etsu, together with partners Alexanderwerk, Frewitt, PROCEPT and Thermo Fisher Scientific will share the latest insights on ASD development steps ranging from initial screening phase up to downstream processing including spray drying, hot melt extrusion (HME), roller compaction, milling and 3D printing.
The program is comprised of practical lab demonstrations featuring the leading polymer for ASDs - Shin-Etsu AQOAT® (HPMCAS) and lectures from invited speakers with expertise in the field.

4th Technical Seminar on Solubility Enhancement
From Screening to Downstreaming

SAVE THE DATE 11th-12th May 2023

Confirmed speakers

Dr. Elisabeth Kersten
Bayer AG
"Postprocessing of HME to tablets"

Dr. Christian Lübbert
Amofor GmbH
"Predicting the physical stability of amorphous solid dispersions"

Dr. Alvaro Goyanes
UCL School of Pharmacy
"3D printing technologies to improve drug solubility"

Prof. Thomas Rades
Solid State Pharmaceutics, University of Copenhagen
"Establishing an in-vitro/in-vivo correlation model for ASDs"

Dr. Daniel Treffer
Founder of Meltprep
"Lossless ASD and implant screening in the mg to g scale"

Dr. Liselotte De Smet
CSO, XEDEV
"Spray-drying of ASDs as a part of formulation development"

Venue

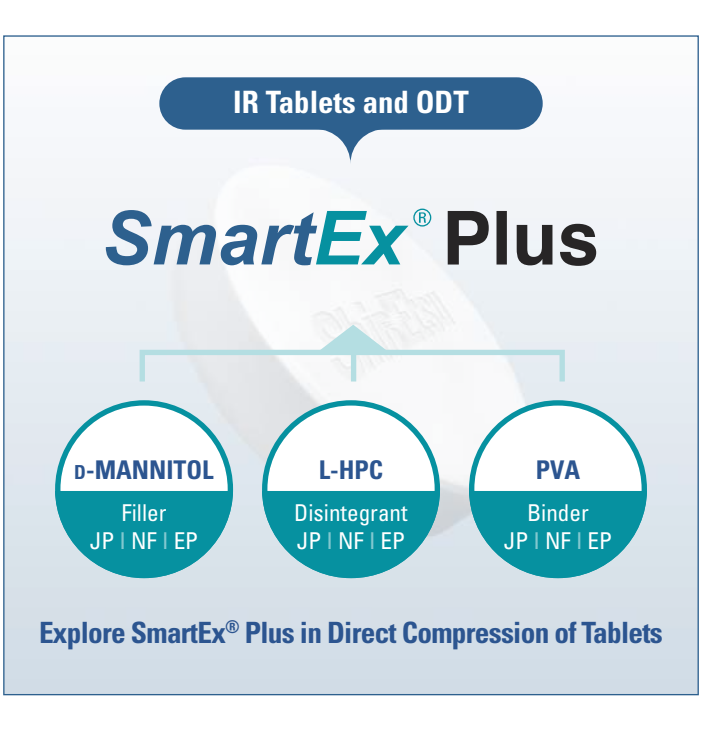
Lecture Venue
Courtyard by Marriott
Ostring 9, Wiesbaden-Nordenstadt
65205 Wiesbaden, Germany

Demonstration Venue
SE Tylose GmbH & Co. KG
Kasteler Straße 45
65203 Wiesbaden, Germany

Networking Event
Johannisberg Castle
65366 Geisenheim
Germany

More information and registration:
www.setylose.com/en/pharma-seminar

Announcement | New Shin-Etsu Product - SmartEx® Plus



SmartEx® Plus was designed by Shin-Etsu to ease the development of orally disintegrating tablets (ODTs) and dispersible tablets. SmartEx® Plus is a co-processed excipient based on mannitol, low-substituted hydroxypropyl cellulose (LHPC) and polyvinyl alcohol (PVA). All the components fulfill the respective compendial requirements from the EP, NF and JP. Registration for a US-DMF number is ongoing.

The good mouthfeel is, besides a fast disintegration time, a key consideration when developing ODTs. That is why SmartEx® Plus combines mannitol, L-HPC and PVA. Mannitol is a water-soluble filler and it brings a good stability and a pleasant taste to the formulations. It has a sweet taste with a cooling effect once tablets disintegrate in the mouth. L-HPC is a non-ionic disintegrant with a defined small particle size, showing good compressible properties. PVA was chosen as a binder as it does not impact the disintegration time. All three excipients are co-processed physically so that SmartEx® Plus provides ideal attributes for ODT development.

One of the major challenges faced by R&D is the stability of the developed tablets. ODTs can either lose their tensile strength or their disintegration time can increase when put under accelerated stability conditions (40°C/75% relative humidity). With SmartEx® Plus excellent stability is achieved without compromising the disintegration time.

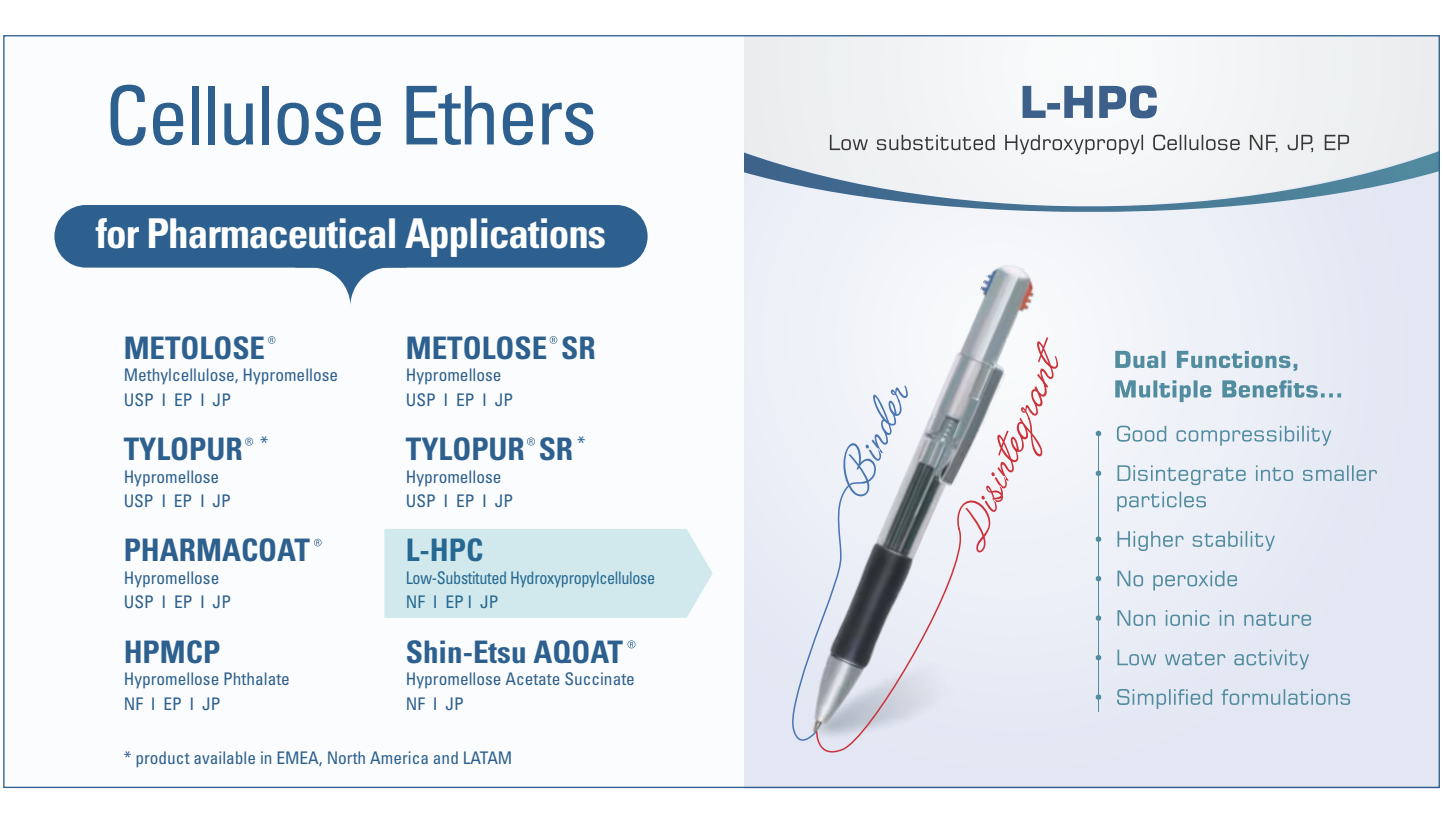
Further applications of SmartEx® Plus include the development of immediate release tablets or dispersible tablets by direct compression.

Its excellent flow properties make SmartEx® Plus a key excipient in continuous manufacturing.

It has never been as easy to develop a robust direct compression process, as only three components are required: API, SmartEx® Plus, and magnesium stearate.

More information and registration:
www.setylose.com/en/products/healthcare/smartex

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).

L-HPC, low-substituted hydroxypropyl cellulose NF, JP, EP, was developed by Shin-Etsu and first approved in 1977 as disintegrant for tablets in Japan. L-HPC is a non-ionic, multi-functional excipient based on a cellulose backbone with a low amount of hydroxypropopyl groups. Thus, L-HPC is not soluble in water but manifests swelling properties in this media.

Typical applications of L-HPC are: binding and disintegrating, stability enhancement, pellet extrusion and continuous manufacturing. On top of that, L-HPC reduces the residual die-wall force and ejection force resolving capping issues, a typical problem in the tableting process.

L-HPC manifests excellent properties as binder for direct compression, wet granulation and dry granulation (roller compaction).

L-HPC can simplify immediate release tablet formulation as only one excipient is needed to assure good tablet hardness and quick disintegration. Thus L-HPC is a key excipient for reducing the tablet size (mini-tablet formulation).

One of the additional benefits of L-HPC is linked to its non-ionic-nature and absence of peroxide leading to a better stability of the drugs by avoiding interactions with the API.

L-HPC is also applicable for pellet extrusion (micronized grades). Here, L-HPC provides wet mass with a "buffer effect" – wet mass accepts a wider range of water content, and plasticizes it to enhance extrusion speed and yield.

For capsule filling, the swelling property of L-HPC actively contributes to improving the disintegration and dissolution of the cake formed during the capsule filling process.

L-HPC also plays a key role in continuous manufacturing. Its optimized particle shape and particle size distribution is designed to maximize the flow property and multifuncionality required for direct compression, wet granulation and dry granulation performed in a continues manner.

There are 9 commercially available grades of L-HPC, which vary in physico-chemical properties fitting various pharmaceutical applications.

More information and registration:
www.metolose.jp/en/pharmaceutical/l-hpc.html
www.setylose.com/en/products/healthcare/l-hpc

Research Articles

1. Downstream Processing of Itraconazole:HPMCAS Amorphous Solid Dispersion: From Hot-Melt Extrudate to Tablet Using a Quality by Design Approach

Despite the importance of hot-melt extrusion in the preparation of amorphous solid dispersions (ASDs) for solubility improvement of poorly soluble drugs, there are few reports on milling of hot-melt extrudates. In a recently published peer-reviewed article, the Shin-Etsu team in Totowa (NJ, USA) in cooperation with Thermo Fisher Scientific in Karlsruhe (Germany) reports on the milling of ASD extrudates using a design of experiments (Scheme 1). The study comprises the preparation of three different milling feedstocks of itraconazole and hypromellose acetate succinate (Shin-Etsu AQOAT(R)) ASD by variation of the downstream process after hot melt extrusion (hand-cut, pelletization, chill roll flakes).

These different feedstocks were subjected to milling in a pilot scale hammer mill and the milled extrudates were compressed into tablets. Interestingly, it was found that by careful selection of milling speed, a similar particle size distribution (PSD) was observed after the milling of hand-cut filaments in comparison with the milling of pellets or chill roll flakes, demonstrating an easy transfer from early-formulation hand-cut processing at the lab scale to industrial-applicable processes. Furthermore, the tablet formulation with milled chill roll flakes showed improved compactibility over milled hand-cut filaments, despite a similar PSD. In summary, the study demonstrates the facile milling of an hot-melt extruded ASD based on HPMCAS as carrier polymer at ambient temperature.

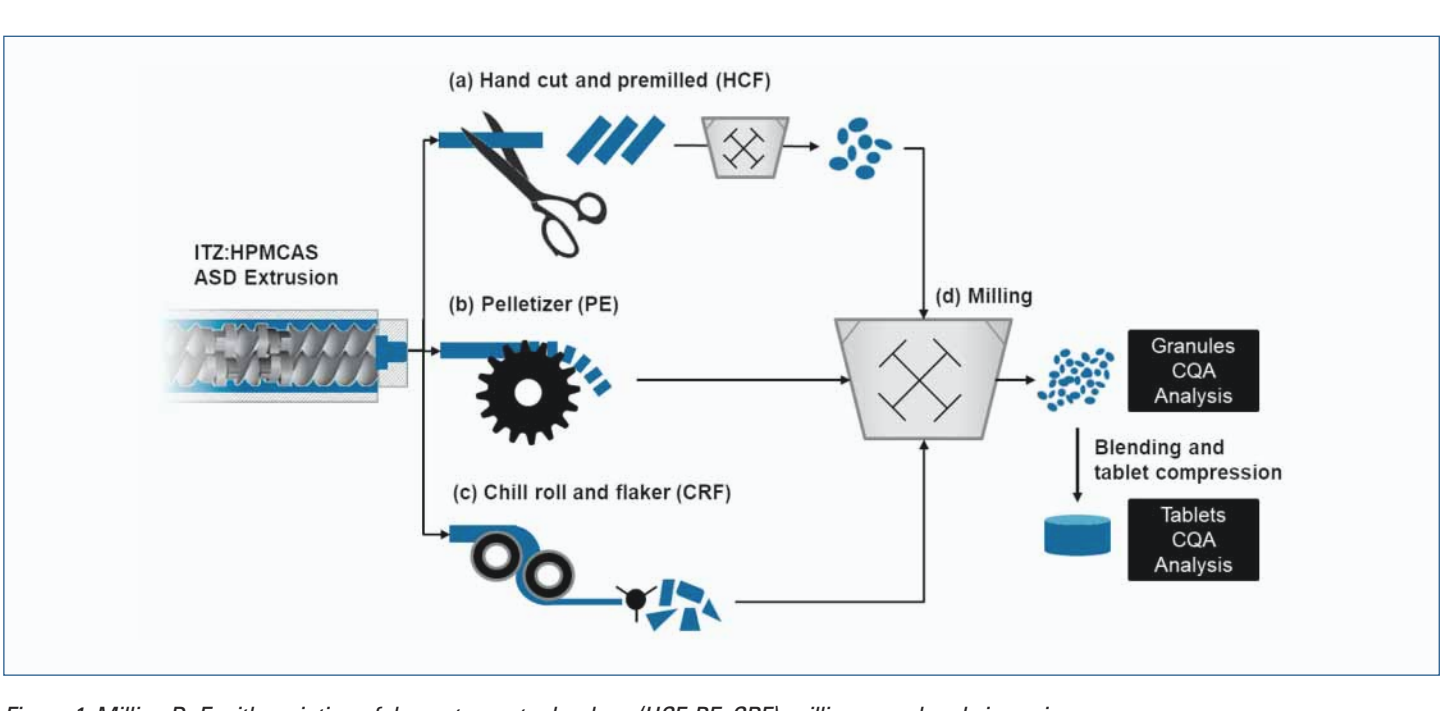


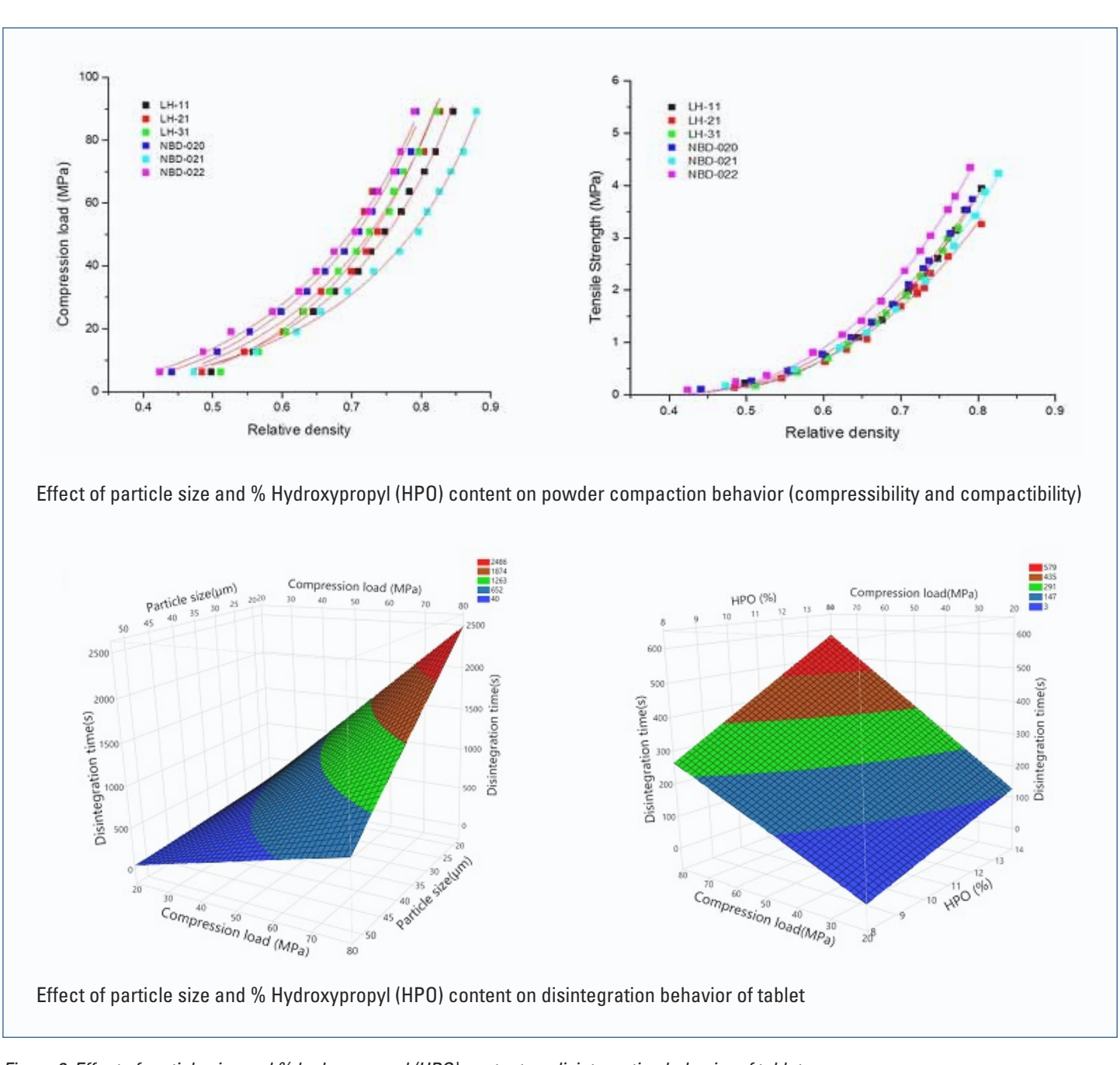
Figure 1: Milling DoE with variation of downstream technology (HCF, PE, CRF), milling speed and sieve size.

For more information on the study, please view the full article published in open access:
Pharmaceutics 2022, 14, 1429: https://doi.org/10.3390/pharmaceutics14071429

2. Effect of Physical Properties and Chemical Substitution of Excipient on Compaction and Disintegration Behavior of Tablet: A Case Study of Low-Substituted Hydroxypropyl Cellulose (L-HPC)

As final attributes of a dosage form largely depend on the properties of the excipients used, understanding the effect of physicochemical properties of excipients is important. In the present study, six different grades of L-HPC (LH-11, LH-21, LH-31, NBD-020, NBD-021, NBD-022) with different particle sizes and %HPO contents were studied, their effect on compaction and disintegration behavior were evaluated. An integrated approach to the statistical evaluation using compaction models and QbD methodology was used to study the variability of L-HPC grades on the quality attributes of tablets. It was found that all tested grades of L-HPC are highly compressible, undergoing predominantly plastic deformation. Additionally, it was found that particle size has a large effect on deformation behavior/compressibility of L-HPC, and LH-31 with smaller particles was found to be less compressible compared to other grades of L-HPC such as LH-21 and LH-11.

The compactibility of L-HPC was found to be equivalent to microcrystalline cellulose, demonstrating its applicability as a binder. From the 32 full-factorial design, it was found that disintegration time of L-HPC tablets was significantly influenced by particle size and %HPO content, while tablet porosity is largely dependent upon the compression load. It was also found that reducing particle size or increasing %HPO significantly increases the disintegration time due to the decrease in water absorption and swelling pressure. From the DoE study, it was found that particle size of L-HPC grades demonstrates a larger degree of effect compared to %HPO on disintegration time, showing a higher coefficient value. Thus, based on the present study, it can be concluded that variability in L-HPC can have a significant influence on critical quality attributes of tablets such as compaction and disintegration behavior, and thus the selection of the correct grade of L-HPC is critical for successful formulation development.



Effect of particle size and % Hydroxypropyl (HPO) content on powder compaction behavior (compressibility and compactibility)

Effect of particle size and % Hydroxypropyl (HPO) content on disintegration behavior of tablet

Figure 2: Effect of particle size and % hydroxypropyl (HPO) content on disintegration behavior of tablet

For more information on the study, please view the full article published in open access:
Macromol 2022, 2(1), 113-130: https://doi.org/10.3390/macromol2010007

3. Stability and intrinsic dissolution of vacuum compression molded amorphous solid dispersions of efavirenz

In this research paper from the University of Copenhagen, co-authored with Shin-Etsu, Losan Pharma and Harke Pharma, the effect of polymer type and polymer loading on stability and intrinsic dissolution of amorphous solid dispersions is discussed. The amorphous solid dispersions of efavirenz, an HIV drug, and the different polymer carriers were prepared by vacuum compression molding using the Meltprep device. Melting point depression studies yielded the solubility of efavirenz in the respective polymer and ASDs were prepared around the solubility limit. ASDs with efavirenz loading below or close to the solubility limit did not crystallize at different stability conditions for seven months. All ASDs above the solubility limit crystallized at high humidity. ASDs above the solubility limit with cellulose derivatives (Shin-Etsu AQOAT® HPCMCAS, PHARMACOAT® HPMC) were kinetically stable at 22°C/23% RH over the course of the study, while others showed signs of crystallization. The intrinsic dissolution study gave insights into the solubility behavior of the ASD discs which depends on polymer solubility and API load in the ASD.

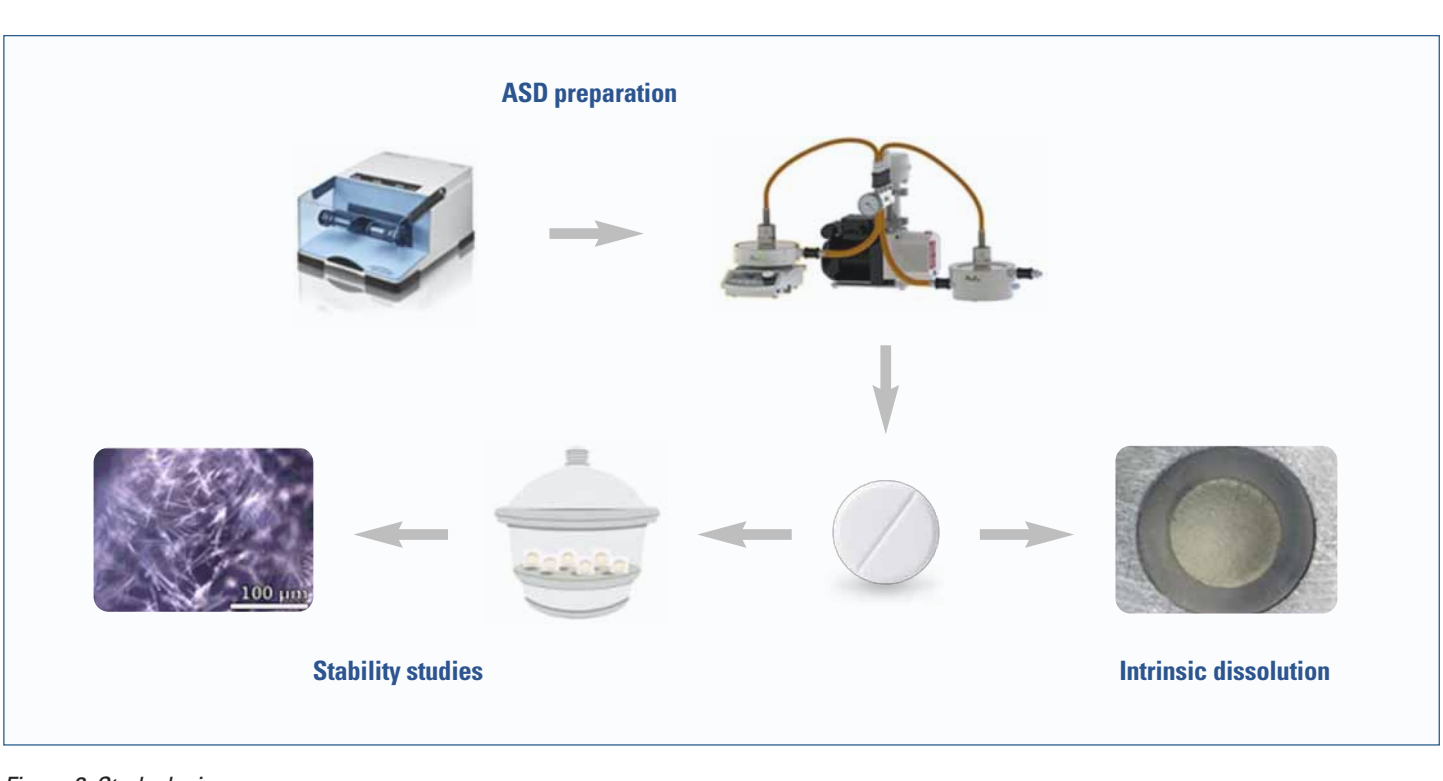


Figure 3: Study design

For more information on the study, please view the full article published in open access:
Int. J. Pharm. 2023, 632, 122564: https://doi.org/10.1016/j.ijpharm.2022.122564

4. Shin-Etsu's solutions for the typical tablet defect

During the manufacturing of tablets, defects like capping, lamination, sticking, etc. can occasionally be encountered. These tablet defects can originate from any upstream operation units and from the tablet press. In the upstream part of the process, the quality and concentration of raw materials as well as process optimization are the key variables for manufacturing of good quality tablets. Tablet defects, if not avoided at the right time, may lead to the recall of product, loss of time and decreased productivity. The attached troubleshooting guide shows the most common tablet defects that can be easily avoided by choosing appropriate Shin-Etsu Pharma excipients.

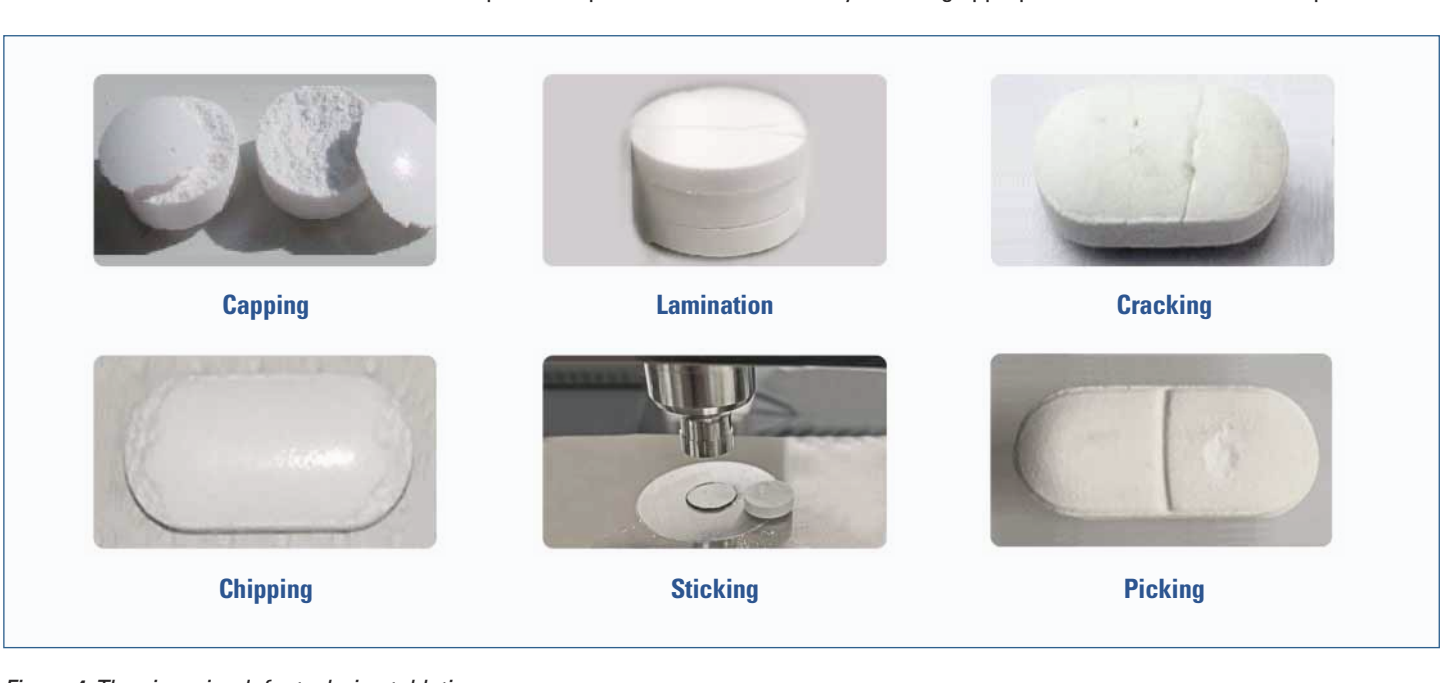


Figure 4: The six major defects during tableting.

More information:
https://www.setylose.com/en/knowledge-base/healthcare/brochures#l-hpc-10253

New Technical Information

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

Shin-Etsu AQOAT®
A-073
Mechanical Properties of Hot Melt Extruded Amorphous Solid Dispersion with Shin-Etsu AQOAT®
www.metolose.jp/en
https://www.setylose.com/en/knowledge-base/healthcare/technical-information#shin-etsu-aqoat-10399

HPMCP
H-023
Application of Hypromellose Phthalate in Extended Release (ER) Matrix Tablet formulation
www.metolose.jp/en
https://www.setylose.com/en/knowledge-base/healthcare/technical-information#hpmcp-10400

METOLOSE® SR
SR-021
Impact of combination of METOLOSE® SR grades in Carbamazepine Extended Release (ER) Matrix Tablet formulation
www.metolose.jp/en
https://www.setylose.com/en/knowledge-base/healthcare/technical-information#metolose-sr-10398

Exhibitions 2023

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.

20th – 21st March 2023 | 4th European Conference on Pharmaceutics – Marseille, France

Talk
Dr. Vanessa Havenith
"Continuous Manufacturing: Rheological Powder Characterisation of Excipients to understand their Behaving during the Feeding Step"
Monday, 20.03.2023 at 16:00 at the Pharmaceutical manufacturing and engineering; Continuous manufacturing Session

Poster
Dr. Andreas Sauer
"Downstream Processing of Itraconazole: HPMCAS Amorphous Solid Dispersion: From Hot-Melt Extrudate to Tablet Using a Quality by Design Approach"
Tuesday, 21.03.2023

DCAT Week — The Premiere Event for the Global Bio/Pharmaceutical Manufacturing Value Chain
20th – 23rd March 2023 | DCAT – New York, USA

公益社団法人 日本薬剤学会 — The Academy of Pharmaceutical Science and Technology, Japan
16th – 18th May 2023 | (APSTJ) – Japan
The 38TH Annual Meeting of the Academy of Pharmaceutical Science and Technology

14th Global DDF Summit — Drug Delivery & Formulation
31st May – 2nd June 2023 | DDF – Berlin, Germany

in-PHARMA JAPAN — Int'l Pharmaceutical and Cosmetics Ingredients Expo
5th – 7th July 2023 | in-Pharma Japan – Tokyo, Japan

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www.youtube.com

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