

Continuous formulation opportunities of electrospun amorphous solid dispersions

E. Szabó¹, P. Záhonyi¹, M. Gyürkés¹, A. Farkas¹, S.K. Andersen², T. Vigh², G. Verreck², I. Csontos¹, G. Marosi¹, Z. K. Nagy¹

¹Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budapest, Hungary

²Janssen R&D, Beerse, Belgium

Introduction

- Dissolution properties of poorly water-soluble drugs can be improved by electrospinning¹.
- The main limitations of the electrospinning technology are the scaling-up and the effective formulation of the product^{2,3}.

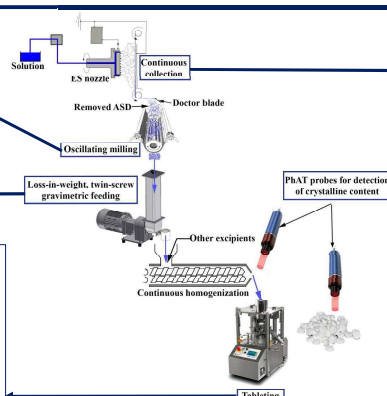
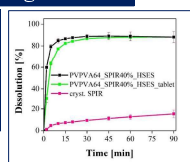
Main goals

- Investigation of the possible continuous downstream processing steps.
- In-situ* homogenisation of fibres and excipients during fibre collection.
- Continuous blending of fibrous materials.

Experiments and results

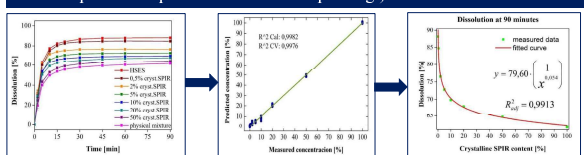
Spironolactone (SPIR) + PVPVA64 model system

- Fully amorphous grindable samples were prepared.
- Feedability enhancement with microcrystalline cellulose.
- Feeding rate: 385 g/h
- Dissolution was successfully improved via electrospinning.



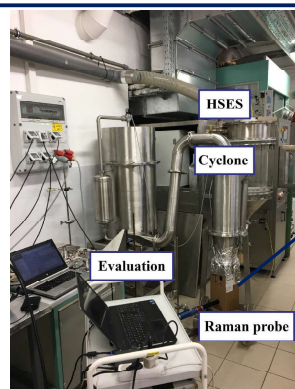
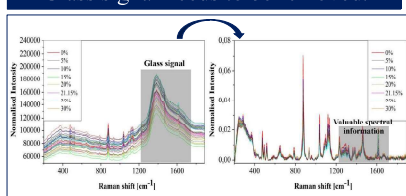
- Collection of fibres proved to be feasible.

- Possible crystalline traces have effect on the dissolution.
- Raman spectroscopy was applied for measuring the crystalline content. (Crystalline SPIR was added manually to the amorphous samples after the electrospinning.)

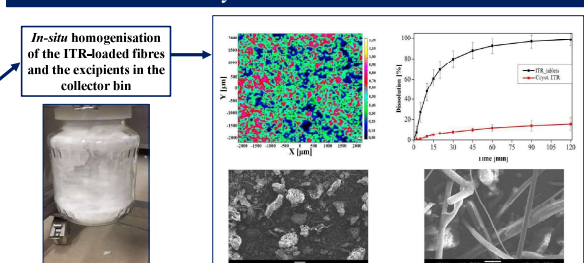


Itraconazole (ITR) + PVPVA64 model system

- Raman spectroscopy may be used for in-line monitoring of the ITR concentration in the blend.
- Glass signal needs to be removed.

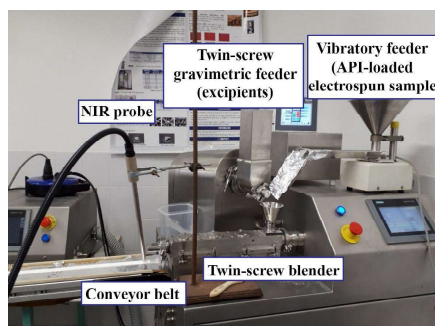
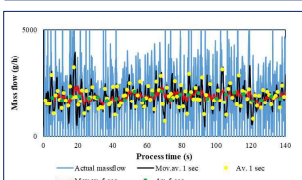


- The blend was microscopically homogeneous according to the Raman mapping.
- The tablets showed good content uniformity based on the small variability of the final dissolved ITR amount.

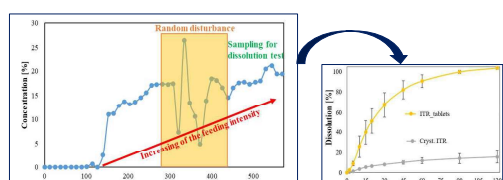


Itraconazole (ITR) + PVPVA64 model system

- Vibratory feeders are more suitable for feeding fibrous materials.



- Real-time detection of itraconazole can be achieved by near-infrared spectroscopy.
- Dissolution of the tablets proved the effectivity of continuous blending.



Conclusion

The feasibility of continuous formulation of continuously produced electrospun amorphous solid dispersions was demonstrated in this work.

References

- D.-G. Yu et al., J. Control. Release, 292, 91-110 (2018)
- B. Démuth et al., Adv. Powder Technol., 28 (6), 1554-1563 (2017)
- E. Szabó et al., Express Polym. Lett., 12 (5), 436-451 (2018)

Acknowledgements

This work was supported by (is related to) the National Research, Development and Innovation Fund of Hungary in the frame of FIEK_16-1-2016-0007 (Higher Education and Industrial Cooperation Center) project.

Contact

szabo.edina@mail.bme.hu



Poster list 2nd APV continuous manufacturing conference

1	On line measurement of granule size distribution in a continuous manufacturing line A. Wilms^{1,2}; P. Kleinebudde¹ 1 Heinrich-Heine University, Institute for Pharmaceutics and Biopharmaceutics, 40225 Düsseldorf, Germany, annika.wilms@hhu.de 2 INVITE GmbH, Drug Delivery Innovation Center, Chempark Building W32, 51368 Leverkusen, Germany
2	Dynamic image analysis to monitor the granule size distribution in roll compaction/dry granulation A. Wilms^{1,2}; P. Kleinebudde¹ 1 Heinrich-Heine University, Institute for Pharmaceutics and Biopharmaceutics, 40225 Düsseldorf, Germany, annika.wilms@hhu.de 2 INVITE GmbH, Drug Delivery Innovation Center, Chempark Building W32, 51368 Leverkusen, Germany
3	Digital design of robust continuous drug substance and drug product processes: A comparison of challenges and approaches D. Barrasso¹, S. K. Bermingham² 1Process Systems Enterprise (PSE) Inc., NJ, USA 2Process Systems Enterprise (PSE) Ltd., London, UK
4	SPRAY FLASH EVAPORATION, A DISRUPTIVE ECO-EFFICIENT PROCESS FOR THE CONTINUOUS ENGINEERING OF NANOPHARMACEUTICS: FROM LABORATORY TO INDUSTRY Denis SPITZER¹ 1NS3E Laboratory, UMR 3208 ISL/CNRS/UNISTRA, ISL, Saint-Louis, France denis.spitzer@isl.eu, www.isl.eu
5	Influence of binder attributes on binder effectiveness in a continuous twin screw wet granulation process via wet and dry binder addition L. Vandevivere¹; C. Portier¹; V. Vanhoorne¹; O. Häusler²; T. De Beer³; C. Vervaet¹ 1Ghent University, Laboratory of Pharmaceutical Technology, Ottergemsesteenweg 460, 9000 Ghent, Belgium 2Roquette Frères, Rue de la Haute Loge, 62136 Lestrem, France 3Ghent University, Laboratory of Pharmaceutical Process Analytical Technology, Ottergemsesteenweg 460, 9000 Ghent, Belgium
6	Continuous formulation opportunities of electrospun amorphous solid dispersions E. Szabó¹, P. Záhonyi¹, M. Gyürkés¹, A. Farkas¹, I. Csontos¹, G. Marosi¹, Z. K. Nagy¹ 1Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budapest., Hungary
7	Investigations on Powder Residence Time in a Rotary Tablet Press Maren Zimmermann, Markus Thommes Laboratory of Solids Process Engineering, TU Dortmund University, Emil-Figge-Str. 68, 44227 Dortmund, Germany maren.zimmermann@tu-dortmund.de, (+49) 231 755 2108
8	Modeling and simulating the continuous blending: Residence Time Distribution and Digital Twins in continuous manufacturing Gyürkés, Martin; Madarász, Lajos; Domokos, András; Farkas, Attila; Nagy, Zsombor Kristóf; Pataki, Hajnalka

Poster list 2nd APV continuous manufacturing conference

1	On line measurement of granule size distribution in a continuous manufacturing line A. Wilms^{1,2}; P. Kleinebudde¹ 1 Heinrich-Heine University, Institute for Pharmaceutics and Biopharmaceutics, 40225 Düsseldorf, Germany, annika.wilms@hhu.de 2 INVITE GmbH, Drug Delivery Innovation Center, Chempark Building W32, 51368 Leverkusen, Germany
2	Dynamic image analysis to monitor the granule size distribution in roll compaction/dry granulation A. Wilms^{1,2}; P. Kleinebudde¹ 1 Heinrich-Heine University, Institute for Pharmaceutics and Biopharmaceutics, 40225 Düsseldorf, Germany, annika.wilms@hhu.de 2 INVITE GmbH, Drug Delivery Innovation Center, Chempark Building W32, 51368 Leverkusen, Germany
3	Digital design of robust continuous drug substance and drug product processes: A comparison of challenges and approaches D. Barrasso¹, S. K. Bermingham² 1Process Systems Enterprise (PSE) Inc., NJ, USA 2Process Systems Enterprise (PSE) Ltd., London, UK
4	SPRAY FLASH EVAPORATION, A DISRUPTIVE ECO-EFFICIENT PROCESS FOR THE CONTINUOUS ENGINEERING OF NANOPHARMACEUTICS: FROM LABORATORY TO INDUSTRY Denis SPITZER¹ 1NS3E Laboratory, UMR 3208 ISL/CNRS/UNISTRA, ISL, Saint-Louis, France denis.spitzer@isl.eu, www.isl.eu
5	Influence of binder attributes on binder effectiveness in a continuous twin screw wet granulation process via wet and dry binder addition L. Vandevivere¹; C. Portier¹; V. Vanhoorne¹; O. Häusler²; T. De Beer³; C. Vervaet¹ 1Ghent University, Laboratory of Pharmaceutical Technology, Ottergemsesteenweg 460, 9000 Ghent, Belgium 2Roquette Frères, Rue de la Haute Loge, 62136 Lestrem, France 3Ghent University, Laboratory of Pharmaceutical Process Analytical Technology, Ottergemsesteenweg 460, 9000 Ghent, Belgium
6	Continuous formulation opportunities of electrospun amorphous solid dispersions E. Szabó¹, P. Záhonyi¹, M. Gyürkés¹, A. Farkas¹, I. Csontos¹, G. Marosi¹, Z. K. Nagy¹ 1Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budapest., Hungary
7	Investigations on Powder Residence Time in a Rotary Tablet Press Maren Zimmermann, Markus Thommes Laboratory of Solids Process Engineering, TU Dortmund University, Emil-Figge-Str. 68, 44227 Dortmund, Germany maren.zimmermann@tu-dortmund.de, (+49) 231 755 2108
8	Modeling and simulating the continuous blending: Residence Time Distribution and Digital Twins in continuous manufacturing Gyürkés, Martin; Madarász, Lajos; Domokos, András; Farkas, Attila; Nagy, Zsombor Kristóf; Pataki, Hajnalka

Continuous formulation opportunities of electrospun amorphous solid dispersions

E. Szabó¹, P. Záhonyi¹, M. Gyürkés¹, A. Farkas¹, S. K. Andersen², T. Vígh², G. Verreck², I. Csontos¹, G. Marosi¹, Z. K. Nagy¹

¹Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budapest., Hungary

²Janssen R&D, Beerse , Belgium

Preparation of polymer-based amorphous solid dispersions by electrospinning is a promising way to improve the dissolution properties of poorly water-soluble drugs [1]. However, scaled-up production and formulation of the fibrous materials can be challenging which are the main limitations of the practical application. Continuous technologies can mean a solution for the scaling-up issues since pilot-scale equipment are also able to satisfy the productivity needs of the pharmaceutical industry [2]. Nonetheless, poor flowability of the fibres makes harder to achieve an appropriate final dosage form with continuous downstream processes. For this reason, possible continuous formulation strategies of drug-loaded electrospun fibres were investigated during this research to generate tablets, the most common solid dosage forms.

For electrospinning experiments, spironolactone and itraconazole were used as a model drug while polyvinylpyrrolidone-vinyl acetate copolymer was chosen as a polymer matrix. In addition, a pilot-scale and a production scale high-speed electrospinning machine were applied to produce fibres in higher amount [3,4,5]. The collection of the fibrous product was accomplished with a rotating collector in case of the pilot-scale equipment while fibres were collected with a cyclone during the production scale experiments.

The possible continuous downstream processing steps were investigated at first where the pilot-scale device was applied. In further experiments, the production scale equipment was used. First, the tableting excipients were measured into the collector bin of the cyclone to perform an in-situ homogenisation of the electrospun material and the powder mixture. The actual drug-loaded fibre concentration was followed by Raman spectroscopy. Dissolution results of the tablets and Raman mapping measurements proved the macroscopic and microscopic homogeneity of the prepared blend, respectively. Furthermore, Raman spectroscopy seemed to be feasible to detect the exact amount of the fibrous material in the powder mixture. Another opportunity is to fulfil the homogenisation process in a continuous blender. The waste can reduce this way since the errors during the electrospinning may be filtered before the blending. In this research, a twin-screw extruder was used for blending. The feeding of the ground fibres was achieved with a vibratory feeder while a gravimetric feeder was applied in case of the mixture of the excipients. Finally, near-infrared spectroscopy was placed to the end of the extruder for measuring the actual concentration. Based on the dissolution tests of tablets, the homogenisation was successfully performed with the twin-screw extruder.

As a conclusion, the continuous blending of electrospun fibres proved to be possible thus the technology can be especially interesting in the practical application point of view.

1. D.-G. Yu et al., J. Control. Release, 292, 91-110 (2018)
2. S. L. Lee et al., J. Pharm. Innov., 10, 191-199 (2015)
3. E. Szabó et al., Express Polym. Lett., 12(5), 436-451 (2018)
4. Z. K. Nagy et al., Int. J. Pharm., 480, 137-142 (2015)
5. P. Vass et al., J. Control. Release, 298, 120-127 (2019)



APV e. V. Kurfürstenstr. 59 · 55118 Mainz · Germany

Telefon: +49 6131 9769-0 · Telefax: +49 6131 9769-69 · E-Mail: apv@apv-mainz.de

Conference: 2nd APV Continuous Manufacturing Conference
Course no.: 6794 from 18 to 19 February 2020 at the Stadthotel Freiburg, Freiburg, Germany
Chairs: Giustino di Pretoro, Janssen Research&Development, Belgium
Dejan Djuric, Bayer, Germany
Horst Dieter Friedel, Bayer, Germany
Geert Verreck, Janssen Research&Development, Belgium
Peter Kleinebudde, Heinrich-Heine-University Düsseldorf, Germany

Programme

Tuesday, 18 February 2020

9:00-18:00 h

09:00-09:15 h

Welcome and introduction by the programme committee

Giustino di Pretoro, Janssen Research&Development, Belgium

Dejan Djuric, Bayer, Germany

Horst Dieter Friedel, Bayer, Germany

Peter Kleinebudde, Heinrich-Heine-University Düsseldorf, Germany

Geert Verreck, Janssen Research&Development, Belgium

Plenary lecture

09:15-10:00 h

Continuous manufacturing in the future

Markus Krumme, Novartis, Switzerland

Session 1: Regulatory perspective on continuous manufacturing

10:00-10:30 h

Coffee break and exhibition and poster presentations

10:30-11:00 h

FDA - guidance for industry continuous manufacturing

Thomas O'Connor, FDA, United States

11:00-11:30 h

Update on ICH Q13

Wendy Zwolenski-Lambert, Novartis and EFPIA EWG, Switzerland

11:30-12:00 h

Eli Lilly - experiences with approval processes in different countries / HA

Ahmad Almaya, Eli Lilly, United States

12:00-13:30 h

Luncheon and exhibition and poster presentations

13:30-14:00 h

Janssen - experiences with approval processes in different countries / HA

Kim Boue, Janssen, Belgium