BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS
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GEORGE A. OLAH DOCTORAL SCHOOL

Development of integrated continuous pharmaceutical technologies

Summary of Ph.D. thesis

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1 LITERATURE REVIEW

Innovation in the pharmaceutical industry has been limited to the research and development of new drug products, meanwhile the structure of the production has not changed in decades and relies on outdated batchwise technologies to date. As it has already been demonstrated in several other industrial sectors, by replacing batch processes to continuous manufacturing (CM) many improvements can be accomplished. Faster, cheaper and more flexible production can be developed with a significantly higher level of quality assurance.[1]

In the recent years the main regulatory agencies recognized the need for a change in drug production and started to promote continuous technologies and encourage pharmaceutical companies to develop and adapt such processes. As a result, by today extensive research is being conducted in the various fields of pharmaceutical technologies from drug substance to drug product manufacturing. Many published papers can be found in the literature dealing with synthetic steps carried out in flow reactors, crystallizations implemented in a continuous manner, and on the formulation side continuous filtration, drying, granulation and blending have all been studied to a lesser or greater extent. Moreover, besides the modification of these traditional processes to continuous operation novel, intrinsically continuous, but not yet widespread technologies are being studied as well.

In order to entirely exploit all the advantages of CM, the processes developed mainly separately need to be connected to reduce idle time between the technological steps as much as possible. According to the number of relevant publications, even the integration of two technological steps is a challenging task.

The multi-step flow synthesis has been developed for a few dozen of active pharmaceutical ingredients (APIs) already. However, very little or no emphasis has been put on the connectability with the following crystallization or any other work-up step. Meanwhile, continuous crystallization of APIs is a widely discussed topic using mixed suspension mixed product removal (MSMPR) crystallizers or plug flow reactors (PFRs). Nonetheless filtration, the inseparable counterpart of crystallization is addressed very few times in the studies, and no thorough evaluation has been conducted with a directly connected system. At the end of the production line continuous blending and direct compression of tablets have been studied in integrated systems several times, but no attention was payed on the preceding filtration process, *i.e.* on the processability of a continuously filtered API in such a continuous process.

[1] S.L. Lee, T.F. O'Connor, X. Yang, C.N. Cruz, S. Chatterjee, R.D. Madurawe, C.M. V Moore, L.X. Yu, J. Woodcock, Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production, J. Pharm. Innov. 10 (2015) 191–199. doi:10.1007/s12247-015-9215-8

The final aim of the continuous pharmaceutical process development would be to form end-to-end systems from the raw materials to the final dosage forms. The development of such systems requires deep process understanding and holistic approach towards optimization. In the literature a few examples can be found for end-to-end manufacturing of drug products, in which cases flow synthesis was connected to continuous formulation of either heat-mold tablets[2] or liquid dosage forms[3]. No example could be found for the production of conventional compressed tablets and for the application of novel technologies in end-to-end systems, such as electrospinning (ES).

After surveying the current 'state of the art' related to integrated continuous pharmaceutical technologies, the main objectives of the experimental work could be set up:

- the development of the multi-step synthesis of an API, which has not been published yet, with special focus on the connectability of the process to the following work-up procedures;
- the direct connection of ES to a flow synthesis as a work-up tool of the reaction mixture, and the development of a system for the continuous collection of electrospun fibers, with which the continuous production of orally applicable final dosage forms is feasible;
- the development of an orally dissolving formulation containing a poorly water-soluble API, carvedilol, and the investigation of the continuous production of the product;
- the integration of MSMPR crystallization with continuous filtration, and the investigation of the effect of process parameters on the quality of the filtered API product;
- the implementation of the continuous blending of the continuously filtered API with excipients, and the production of conventional compressed tablets from the powder blend.

[2] S. Mascia, P.L. Heider, H. Zhang, R. Lakerveld, B. Benyahia, P.I. Barton, R.D. Braatz, C.L. Cooney, J.M.B. Evans, T.F. Jamison, K.F. Jensen, A.S. Myerson, B.L. Trout, End-to-end continuous manufacturing of pharmaceuticals: Integrated synthesis, purification, and final dosage formation, Angew. Chemie. 125 (2013) 12585–12589. doi:10.1002/ange.201305429

[3] A. Adamo, R.L. Beingessner, M. Behnam, J. Chen, T.F. Jamison, K.F. Jensen, J.-C.M. Monbaliu, A.S. Myerson, E.M. Revalor, D.R. Snead, T. Stelzer, N. Weeranoppanant, S.Y. Wong, P. Zhang, On-Demand Continuous-Flow Production of Pharmaceuticals in a Compact Reconfigurable System, Science. 352 (2016) 61–67. doi:10.1126/science.aaf1337

2 METHODS

2.1 Sample preparation

Flow chemistry experiments

Syrris Asia® syringe pumps and a Jasco PU-980 pump were used for the feeding of the solvents and solutions. The microreactors were made of PTFE tubing.

Electrospinning

The API solution was fed by a SEP-10S Plus syringe pump. An NT-35 high voltage direct current generator provided the electrostatic field for the process. The continuous collection of the fibers was accomplished with a rotating grounded wheel.

Film casting of pullulan carrier

Pullulan, Tween 80, red food coloring and optionally citric acid was used. The components were dissolved in water, spread on the surface of a glass plate and casted by an applicator in a predetermined thickness of 30 μm. The film was cut into smaller pieces after 24 hours of drying on room temperature.

Continuous crystallization

Masterflex L/S peristaltic pumps were used to feed the liquid streams into a round-bottom jacketed MSMPR crystallization reactor., in which the temperature was controlled with a Huber Ministat 230 thermostat and a PT100 thermocouple.

Continuous filtration

A Continuous Filtration Carousel (CFC) device (Alconbury Weston Ltd., UK) was used.

Continuous homogenization and tableting

A TS16 QuickExtruder® continuous twin-screw multipurpose equipment (Quick 2000 Ltd., Hungary) was used with 16 mm screw diameter (25 L/D ratio). Single-screw (FPS Pharma, Fiorenzuola d'Arda, Italy) and twin-screw (Brabender® GmbH & Co., Germany) feeders were applied for feeding the powders into the blender. The powder blend was compressed into tablets by a Dott Bonapace CPR-6 eccentric tablet press.

2.2 Analytical methods

HPLC analysis

The measurement of the API content was carried out with an Agilent 1200 series RP-HPLC system, using Supelco Inertsil ODS-2 C18 and Phenomenex Luna 3 μm C18 columns. The eluent was the mixture of water containing 0.5% phosphoric acid and ACN, at a feeding rate of 1-1.5 mL/min.

HPLC-MS measurements

The major impurities in the reaction mixture were identified by an Agilent 1200 LC system coupled with an Agilent 6130 single quadrupole mass spectrometer equipped with an ESI ion source.

NMR measurements

The ^{1}H NMR spectra were recorded on a 500 MHz Bruker DRX-500 instrument, while a 75 MHz Bruker-300 instrument was used for the ^{13}C NMR spectra.

Gel permeation chromatography

The chemical changes of the polymer used for electrospinning was measured with a HPLC system composed of a Waters 515 HPLC pump, a Jetstream 2 Plus column heater and a Jasco RI-4035 Refractive Index Detector; Waters Styragel HT 2 and HT 4 columns were applied for the measurements.

Scanning electron microscopy (SEM)

The structure of the electrospun products was analyzed with a JEOL JSM 6380LA type instrument.

Differential scanning calorimetry (DSC)

The thermograms of the samples were measured by a Setaram DSC 92 apparatus.

X-ray powder diffraction (XRPD)

The diffractograms were measured by an X'pert Pro MDP type PANanalytical X-ray diffractometer.

In vitro dissolution tests

Fibrous ODWs were dissolved in 10 or 20 mL of dissolution media modeling the oral cavity; concentration was followed with HPLC.

Content uniformity measurement (CU)

10 fibrous/tablet samples were dissolved in volumetric flasks; API content was measured with HPLC.

Residual solvent content determination

Residual solvent content of fibrous samples was determined with HPLC (Agilent 1200 LC series) and GC (Perkin Elmer GC system and Agilent 6890 N GC system).

FTIR spectroscopy

The flow synthesis was monitored with a Bruker Alpha FTIR spectrometer equipped with an on-line diamond ATR flow cell and an RT-DLaTGS detector.

Raman spectroscopy

The quantity of the fibrous material collected on the surface of a pullulan carrier film was measured with a Kaiser RamanRxn2® Hybrid spectrometer with PhAT probe

Phase solubility studies

The solubilizer effect of HPβCD on CAR was determined in water and KH_2PO_4 buffer by HPLC.

Disintegration tests

The disintegration of the double-layered orally dissolving formulation was analyzed with a method known in the literature: disintegration time was considered to be the period required for a droplet of water to bore a hole in a product fixed in a frame.

Particle size measurements

The particle size distribution of the crystalline product was measured with a Malvern Mastersizer 3000 Aero S device.

Crystal flowability tests

A metal funnel with a 15 mm circular orifice at the bottom was used for the measurement of the crystalline product.

NIR spectroscopy and spectral evaluation of the continuous blending and tableting experiment

The continuous blending and tableting was monitored with a Bruker MPA FT-NIR spectrometer equipped by a Solvias fiberoptic probe.

3 RESULTS

3.1 Coupling flow synthesis and formulation by electrospinning

In this work phase a benchtop-scale CM apparatus was developed incorporating flow synthesis, formulation by ES and the production of final dosage forms. Acetylsalicylic acid (ASA) was selected as model API, which was synthesized from salicylic acid (SA) with acetic anhydride in the presence of phosphoric acid as an acid catalyst. The reaction mixture was immediately processed by ES, thus ASA was directly turned into solid form and formulated into a fibrous product. By the controlled deposition of the fibers on a carrier film orally dissolving web (ODW) dosage forms could be produced.

Following the batch pre-experiments, the two-step synthesis of ASA was optimized in flow reactors by conducting Design of Experiments (DoE) studies. The aim was to find the appropriate conditions for the synthetic steps to obtain ASA with high yield and purity. Finally, >95% ASA and <3% SA could be obtained by applying the optimal parameters. The second, quenching step was optimized in two different ways: with and without a dissolved polymer, in order to create the possibility to further process the reaction mixture either by ES or by other techniques.

By applying high voltage on the final reaction mixture containing the optimized amount of PVPK30 polymer the synthesized ASA could be formulated into nanofibers with excellent quality. The fibers were collected on the surface of a carrier film, strained on the surface of a special collector wheel with a grounded metal sheet on its circumference. The wheel was rotated slowly, thus the created double-layered formulation was conveyed further to a cutting equipment, which cut the strip into smaller dosage units ready for patient administration (Figure 1).

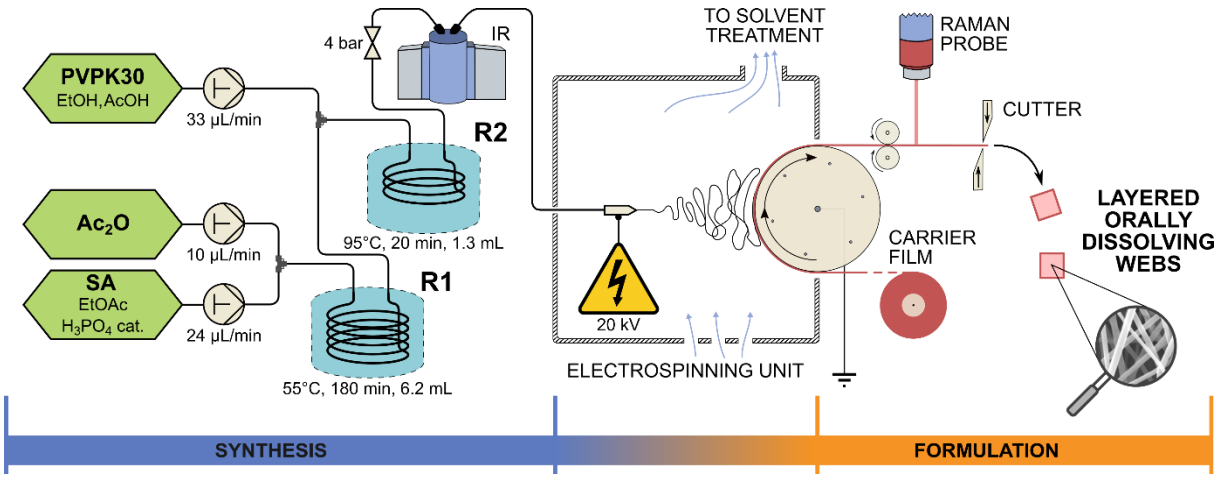

Figure 1. Schematic diagram of the developed system for the production of ASA-loaded fibrous ODWs based on ES. R1 and R2 microreactors, IR Bruker FTIR cell, Kaiser Raman PhAT probe.

The performance of the developed system was evaluated during longer operations regarding purity, content uniformity and residual solvent content. The purity of the optimized reaction mixture was monitored in a 24-hour long experiment, which showed the >95% ASA content with minimal variation (Figure 2c). The content uniformity of the produced dosage units was monitored in an 8-hour long test run and was found to be close to the set target dose with controlled deviation (Figure 2b). The amount of the residual solvents could be decreased under the regulatory limit (5000 ppm) even in the case of the less volatile acetic acid in another 8-hour long experiment (Figure 2a).

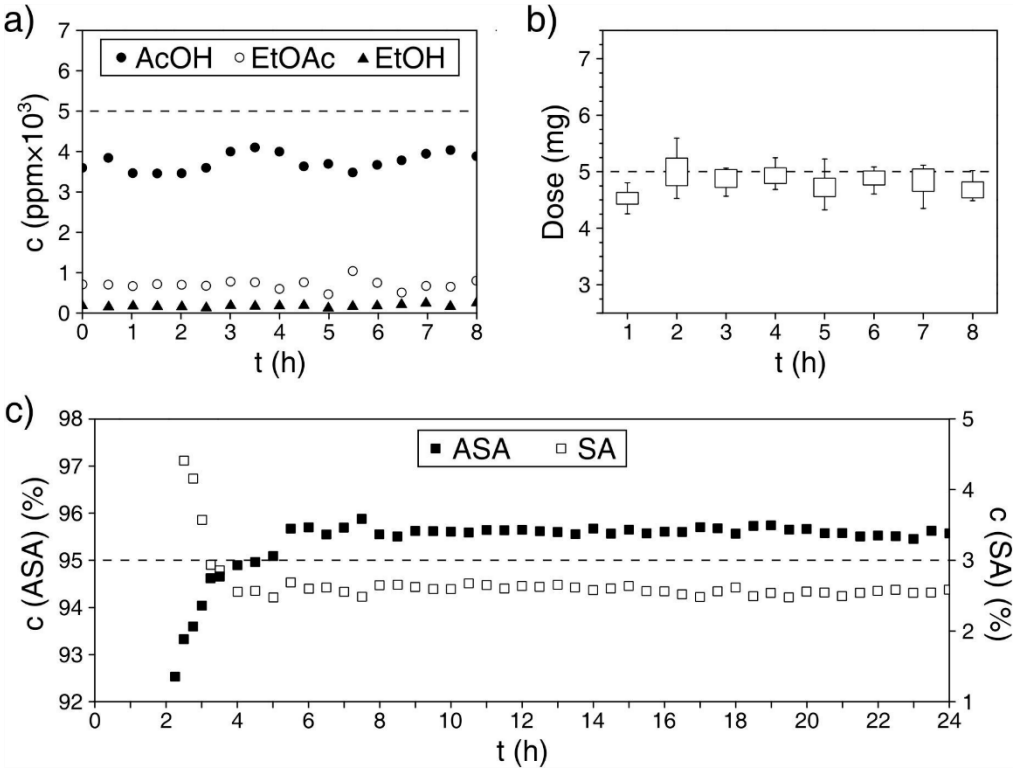

Figure 2. Quality attributes of ODWs over time produced by the CMS: (a) residual solvent content, (b) content uniformity, (c) and purity (HPLC). The dashed lines indicate either regulatory (residual solvent) or specified process (minimal accepted ASA purity and target dose) limits.

3.2 Continuous manufacturing of ODWs containing a poorly soluble drug via electrospinning

In the previous study it was demonstrated how ES can be applied for the continuous processing of a flow reaction mixture to produce ODW final dosage forms. A desktop-size apparatus was built for this purpose, in which the electrospun fibers were deposited on the surface of a carrier film. As the next step, in this work phase our aim was to extend the applicability of the developed apparatus for the formulation of ODWs containing a poorly water-soluble API. Carvedilol (CAR), a non-selective beta blocker was selected as a model compound.

First the solubility of CAR was attempted to be enhanced by adding (2-hydroxypropyl)-β-cyclodextrin (HPβCD) to the formulation. It was found that the application of this solubilizer could increase the solubility of the API above the target dose concentration when citric acid was also used as a pH-modifier. However, the required large amount of HPβCD drastically increased the total weight of the mixture, prohibiting its application in an ODW formulation. Instead, the development of a stable ES process was aimed to produce a nanofibrous amorphous solid dispersion, with which the target dose concentration could be reached through immediate dissolution and supersaturation in the presence of the pH-modifier citric acid.

Several solvents in various combinations were tested during the optimization of the ES of the selected PVPK30-CAR system, and at last the 1:1 (V/V) EtOH-DMF mixture was chosen and applied in further experiments. The optimal concentration of PVPK30 in the EtOH-DMF 1:1 (V/V) mixture was explored by gradually increasing the amount of the dissolved polymer at fixed CAR ratios. Adding 5.125 g PVPK30 to 10 mL solvent mixture along with the appropriate amount of CAR provided fibers with the best quality possessing an average diameter of 0.56 ± 0.11 μm and a process with satisfactory stability at a flow rate of 2 mL/h.

The fibers were collected on the surface of a water-soluble pullulan carrier film. Citric acid, which was necessary for the pH-modification during dissolution was incorporated into the carrier. Immediate and ultrafast dissolution and disintegration was observed during the tests modelling the oral cavity, indicating the applicability of the developed double-layered product as an ODW formulation (Figure 3).

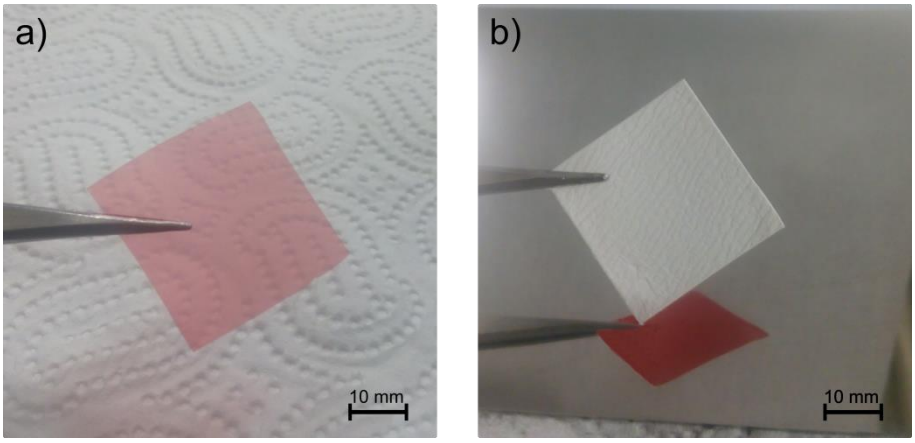

Figure 3. (a) Casted and cut (30 × 30 mm) pullulan film with incorporated citric acid and (b) the final ODW with the nanofibrous layer containing 6.25 mg CAR.

The continuous production of CAR-loaded ODWs was carried out in the CM apparatus described in the previous study. The content uniformity of the dosage units and the residual solvent content of the fibers was monitored in a 4-hour long experiment. The API content of 10 samples from each hour was measured with HPLC, and the results showed low deviation of

the CAR-loading of the ODWs from the target dose strength (Figure 4a). Regarding the amount of residual solvents, trace amount of EtOH was measured even directly after fiber formation. Removing DMF from the fibers was more challenging, as this solvent was significantly less volatile, and the regulatory limit is much stricter than that of EtOH (880 ppm and 5000 ppm, respectively). Nevertheless, by applying additional drying after production on room temperature the DMF content of the fibers could be decreased appropriately (Figure 4b).

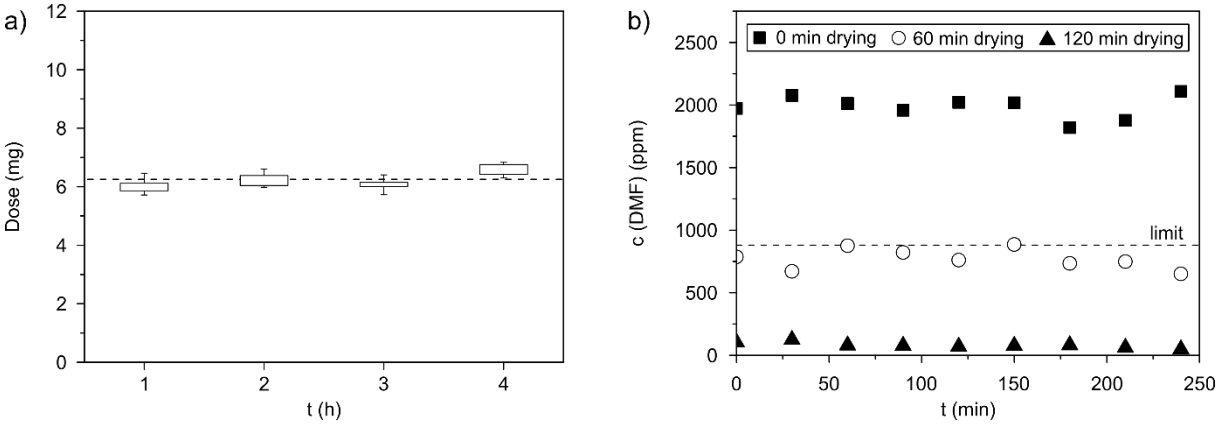

Figure 4. (a) The results of content uniformity measurements of the ODW products prepared using the continuous system in steady state and (b) residual DMF content of the final product during 4-hour long operations of the continuous system at different drying times.

3.3 End-to-end continuous manufacturing of conventional compressed tablets: from flow synthesis to tableting through integrated crystallization and filtration

The flow synthesis of ASA connected directly to ES to obtain good quality ODW dosage forms was presented in the first study. As a step forward, in this work phase we aimed the end-to-end production of the industrially most common conventionally compressed tablets, which has not been described in the literature yet. Thus, the main goal of this work phase was the proof-of-concept demonstration of such a CM system. For this purpose, we needed to resolve the crystallization of the described reaction mixture from the flow synthesis, the filtration and drying of the formed crystals as well as the blending and tableting steps all in continuous and connectable way.

The continuous crystallization of ASA was carried out from the flow reaction mixture of the API in an MSMPR reactor. Heptane was used as antisolvent during the process in a volumetric ratio of 2:1. The crystallizer was directly connected to a continuous filtration device (CFC), thus the inlet tubing of the CFC served as the outlet of the MSMPR reactor. The integrated two-step process was optimized and stable operation was achieved. The effect of the critical crystallization process parameters (residence time, temperature) on the filtered product quality was examined in detail. Steady state could be reached, and crystals with low residual solvent content and with excellent flowability could be produced (Figure 5).

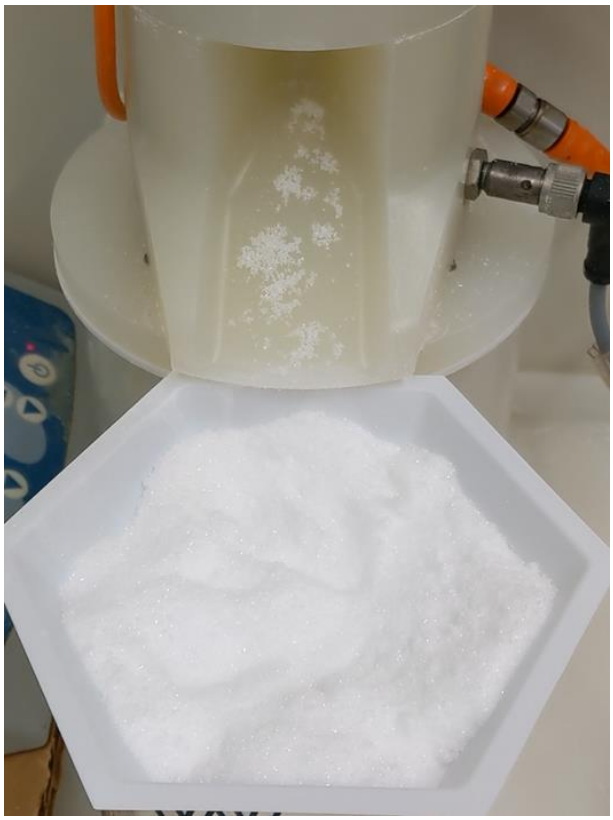

Figure 5. Dry, free-flowing ASA crystals from the integrated continuous crystallization-filtration experiments.

The collected ASA produced during the integrated continuous crystallization-filtration experiments was moved to the continuous blending of the API with MCC and the tableting of the powder mixture into conventional compressed tablets. The blending process was operated for 70 minutes and was monitored by an in-line NIR probe mounted above the powder leaving the blender. The powder blend was moved to the tablet press by a conveyor belt, in which tablets containing 100 mg ASA were produced. The ASA content of the tablets was measured by the same NIR probe in at-line mode and by off-line HPLC as well.

The in-line results showed low ASA content fluctuation in the powder blend (20.70% ASA, 5.78% RSD) in steady state (Figure 6). The at-line analysis of the tablets was in good agreement with these results (20.18% ASA, 4.70% RSD), and the content uniformity measurements revealed similarly low variation in the steady state, confirmed by HPLC and NIR as well. With the applied throughput ca. 14400 dose units could be produced per day. In conclusion, the end-to-end continuous production of conventional compressed tablets starting from raw materials is proved in this study for the first time. It might be a significant step forward to close the gap between the current industrial practice and the desired future pharmaceutical manufacturing.

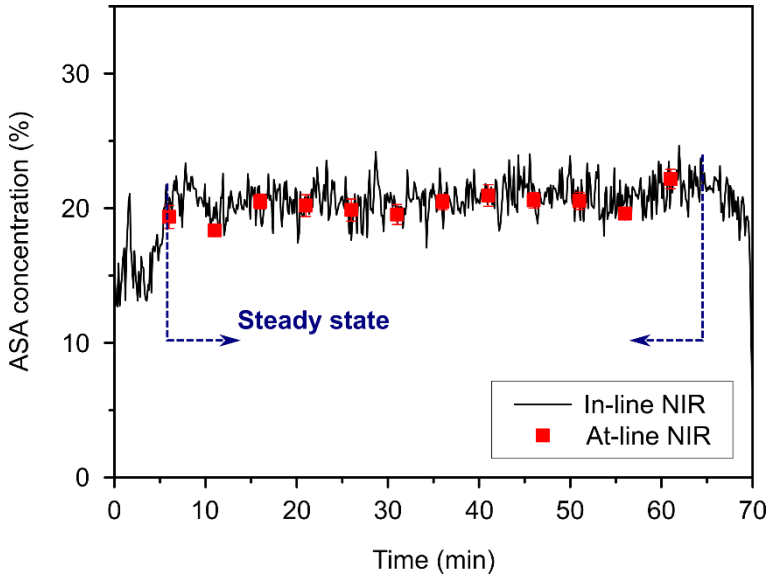

Figure 6. ASA concentration in the powder blend measured by an in-line NIR probe after blending, and the result of at-line NIR analysis of the produced tablets from the steady state.

4 THESIS FINDINGS

1. Acetylsalicylic acid (ASA) was synthesized in continuous flow reactors for the first time. Design of experiment studies were conducted in order to optimize the two synthetic steps: *i.e.* the acetylation of salicylic acid (SA) and the quenching of impurities. By applying the allocated optimal conditions high yield and purity was achieved (>95% ASA and <3% SA). The second, quenching step was optimized both with and without a dissolved polymer excipient, thus the final reaction mixture was ready for direct further processing using either electrospinning or continuous crystallization. [I, XIV, XVI, XVII, XIX]
2. Electrospinning (ES) was applied as an advanced solvent removal tool for the direct processing of a flow reaction mixture for the first time. By applying high voltage on the metal ES spinneret connected to the flow chemistry microreactors, the volatile components evaporated, and the API was embedded into amorphous nanofibers. This way the direct work-up of the reaction mixture was accomplished, and no solid-liquid separation was required before formulation. With appropriate air ventilation the amount of residual solvents could be reduced below the regulatory limits. [I, XIV, XVI, XVII, XIX]
3. We developed and applied an apparatus for the controlled collection of the electrospun product and for the continuous end-to-end production of an orally dissolving web (ODW) formulation. The acetylsalicylic acid-loaded fibers – produced directly from the flow reaction mixture – were collected on the surface of a water-soluble carrier film. The formed double-layered strip was conveyed further to a cutter mechanism and was cut into smaller dosage units ready for patient administration. The good content uniformity and low residual

moisture content of the ODWs was confirmed during longer, 8-hour long operations of the system. [I, XIV, XVI, XVII, XIX]

4. The applicability of the developed continuous system was extended to the production of an ODW formulation containing a poorly water-soluble compound, carvedilol (CAR). ES of CAR-loaded nanofibers was optimized to obtain a stable process. The fibers were collected on the surface of a modified pullulan carrier: citric acid was incorporated into the film to act as pH modifier during dissolution tests. The immediate dissolution and disintegration of the created ODW formulation was confirmed under conditions modelling the oral cavity. The 4-hour long continuous production of CAR-loaded ODWs showed appropriate content uniformity and the residual solvent content of the fibers complied to the regulatory requirements when secondary drying was applied on room temperature. [II]
5. A "Mixed Suspension Mixed Product Removal" (MSMPR) continuous crystallization equipment was directly connected to a Continuous Filtration Carousel (CFC) device for the first time. Stable continuous operation was achieved within the integrated system after the two combined steps were optimized together, and free-flowing crystalline product with excellent quality was obtained at the end of the process. [III, IV, XV]
6. The effect of critical crystallization process parameters on the filtered product quality was determined for the first time in an integrated continuous crystallization-filtration system. We found that only the temperature affected the yield and the particle size of the filtered product, while both residence time and temperature had an impact on the moisture content. The size of the acetylsalicylic acid crystals did not affect the filtration procedure of the used continuous filtration carousel device. The crystals could be dried appropriately to obtain a crystal powder with good flowability, applicable in the following continuous downstream processes. [III, IV, XV]
7. A continuously filtered pharmaceutical material was further processed to continuous blending with microcrystalline cellulose, and to the production of conventional compressed tablets for the first time. The blending efficiency was monitored by an in-line NIR probe. The produced tablets showed very low variation in content uniformity based on at-line NIR and off-line HPLC measurements. Thus, the end-to-end manufacturing of the most widespread compressed tablet dosage form was accomplished for the first time on a proof-of concept level. [IV, XV]

5 APPLICATION OF THE RESULTS

More and more pharmaceutical companies recognize the need to reform the current manufacturing practice and start moving towards continuous technologies. However, the transition is a slow and costly process, as most companies do not have expertise in continuous manufacturing (CM). Typically, one or two steps from the long production line is chosen to develop an alternative of the existing batch process, which takes low risk. However, the real advantage of CM lies in integrated technological steps, with which significant improvements could be accomplished.

In this work several continuous pharmaceutical processes were developed from drug substance to drug product manufacturing. Emphasis was put on the connectability to each other. The interaction of process parameters was evaluated as well. This unprecedented approach towards the development of continuous pharmaceutical processes can facilitate the industrial application of more and more continuous technologies and can contribute to the spread of CM in the pharmaceutical industry.

A significant part of this work was performed in the frame of FIEK project of the National Research, Development and Innovation Office in Hungary. The aim of this project is to conduct research of increased industrial interest, and produce results which can be directly applied by the industrial partners of the collaboration, *i.e.* Richter Gedeon Plc. and Egis Pharmaceuticals Plc.

6 PUBLICATIONS

Publications on which thesis findings are based:

I. A. Balogh, **A. Domokos**, B. Farkas, A. Farkas, Z. Rapi, D. Kiss, Z. Nyiri, Z. Eke, G. Szarka, R. Örkényi, B. Mátravölgyi, F. Faigl, G. Marosi, Zs. K. Nagy, Continuous end-to-end production of solid drug dosage forms: coupling flow synthesis and formulation by electrospinning, *Chemical Engineering Journal*, **350** (2018), 290-299. https://doi.org/10.1016/j.cej.2018.05.188

IF: 8.355 C: 32

II. **A. Domokos**, A. Balogh, D. Dénes, G. Nyerges, Z. Levente, B. Farkas, G. Marosi, Zs. K. Nagy, Continuous manufacturing of orally dissolving webs containing a poorly soluble drug via electrospinning, *European Journal of Pharmaceutical Sciences*, **130** (2019), 91-99. https://doi.org/10.1016/j.ejps.2019.01.026

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III. Y. C. Liu, **A. Domokos**, S. Coleman, P. Firth, Z. K. Nagy, Development of continuous filtration in a novel continuous filtration carousel integrated with continuous crystallization, *Organic Process Research & Development*, **23**, 12 (2019), 2655-2665. https://doi.org/10.1021/acs.oprd.9b00342

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IF: 4.845 C: 0

Related publications:

V. E. Borbás; B. Sinko, O. Tsinman, K. Tsinman; É. Kiserdei, B. Démuth, A. Balogh, B. Bodák, **A. Domokos**, G. Dargó, G. Balogh, Zs. K. Nagy, Investigation and mathematical description of the real driving force of passive transport of drug molecules from supersaturated solutions, *Molecular Pharmaceutics*, **13**, 11 (2016), 3816-3826.

https://doi.org/10.1021/acs.molpharmaceut.6b00613

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VI. A. Balogh, B. Farkas, Á. Pálvölgyi, **A. Domokos**, B. Démuth, G. Marosi, Zs. K. Nagy, Novel alternating current electrospinning of hydroxypropylmethylcellulose acetate succinate (HPMCAS) nanofibers for dissolution enhancement: the importance of solution conductivity, *Journal of Pharmaceutical Sciences*, **106**, 6 (2017), 1634-1643. https://doi.org/10.1016/j.xphs.2017.02.021

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VII. A. Balogh, B. Farkas, **A. Domokos**, A. Farkas, B. Démuth, E. Borbás, B. Nagy, G. Marosi, Zs. K. Nagy, Controlled-release solid dispersions of Eudragit® FS and poorly soluble spironolactone prepared by electrospinning and melt extrusion, *European Polymer Journal*, **95** (2017), 406-417.
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VIII. B. Farkas, A. Balogh, A. Farkas, **A. Domokos**, E. Borbás, G. Marosi, Zs. K. Nagy, Medicated straws based on electrospun solid dispersions, *Periodica Politechnica Chemical Engineering*, **62**, 3 (2018), 310-316.
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X. P. Vass, E. Szabó, **A. Domokos**, E. Hirsch, D. Galata, B. Farkas, B. Démuth, S. K. Anderson, T. Vigh, G. Verreck, G. Marosi, Zs: K. Nagy, Scale-up of electrospinning technology: Applications in the pharmaceutical industry, *WIREs Nanomedicine and Nanobiotechnology*, **12**, 4 (2019), e1611.
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