Continuous end-to-end production of solid drug dosage forms: Coupling flow synthesis and formulation by electrospinning

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HIGHLIGHTS
• Coupling flow synthesis with drug formulation via electrospinning.
• First presentation of the two-step flow synthesis of acetylsalicylic acid.
• Novel electrospun orally dissolving web formulations and their continuous production.
• A unique end-to-end benchtop-scale continuous pharmaceutical manufacturing device.

GRAPHICAL ABSTRACT

End-to-end drug production with electrospinning

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PAT

Abstract

Based on the concept of continuous manufacturing an end-to-end benchtop device was developed unprecedented for the production of solid drug dosage forms by connecting flow synthesis and formulation via electrospinning (ES). Together with the optimized two-step continuous-flow synthesis of acetylsalicylic acid (ASA) a water-soluble polymeric excipient (polyvinylpyrrolidone K30, PVPK30) was introduced. The resulting polymeric solution could be readily electrospun into solid nanofibers with high purity in one single step due to the excellent yet gentle drying effect of ES. The ASA-loaded fibers were electrostatically deposited onto a water-soluble pullulan sheet and the obtained double-layered films were continuously cut into orally dissolving webs (ODWs) as final dosage formulation. The synthesis as well as the dosing of the fibrous films were monitored by Process Analytical Technology (PAT) tools (IR and Raman spectroscopy) with active feedback on product quality. The successful coupling of flow synthesis and fiber formation confirms that ES enables versatile formulation of pharmaceuticals in future continuous production systems.

1. Introduction

Recent trends of pharmaceutical development have focused attention on the paradigm shift from traditional batch production towards continuous manufacturing [1]. The spread of the continuous mindset is also facilitated by leading authorities due to the ease of scale-
up, lower investment and operating costs, and smaller factory footprint compared to batchwise processes [2–4]. Moreover, the advent of modern high-performance PAT devices has allowed real-time monitoring and feedback control of quality in good accordance with the similarly encouraged Quality by Design principles [5,6].

Despite the numerous examples describing continuous pharmaceutical unit operations concerning either drug synthesis [7–9], purification [10–12] or formulation [13], only a handful of attempts have been reported about continuous multi-unit systems. Some of the sequential flow syntheses of active pharmaceutical ingredients (APIs) include artemisinin [14], ibuprofen [15], imatinib [16], oseltamivir [17], pregabalin [18] and prexasertib [19]. However, on the formulation side, besides the attempts to prepare pure liquids of different APIs [20], as far as we know only a few cases are known realizing continuous production of solid dosage forms. In the first case polymeric tablets were heat mold after the last two reaction steps of continuous synthesis of aliskiren hemifumarate by a Novartis-MIT cooperation [21]; nevertheless, heating can be harmful to sensitive APIs and most biologics. The other approaches for the continuous production of film-coated tablets applying PAT for quality assurance are Orkambi® (lumacaftor/ ivacaftor by Vertex), Prezista® (darunavir by Johnson & Johnson) and recently Symdeko® (tezacaftor, ivacaftor by Vertex) [22,23]. These FDA approved formulation plants process the separately produced APIs by continuous blending, tableting and coating [24]. Connecting flow synthesis and formulation of solid dosage forms can be considered rather challenging, a fact recognized also during the latest development of a compact reconfigurable system producing high-purity aqueous liquids of continuously synthesized APIs at the Novartis-MIT center [20]. The main barrier to continuously formulate the API stream into solid dosage forms of greater patient compliance is the several magnitudes higher throughput of the currently available continuous formulation devices required to reach steady state compared to the average output rates of flow reactors.

Electrospinning (ES) is a unique technique capable of producing drug-loaded nanofibers from polymeric solutions under the drawing force of the electrostatic field [25–27]. The rapid yet gentle drying allows the formulation of any kind of API including biopharmaceuticals with controlled release kinetics through the selection of the polymer matrix [28,29]. Furthermore, ES can also be a suitable continuous formulation method of choice when coupling it with flow operations due to its scalable productivity in the range of 0.1–100 g h$^{-1}$ [30,31]. Despite all these considerations, ES has not been applied as a part of a continuous-flow system to process liquid API streams into dry fibers serving as a base to produce solid dosage forms of great therapeutic importance such as tablets, capsules and other formulations.

Thus, in this work we developed an end-to-end continuous model system (CMS) using ES as the key technology to turn the synthesized API solution into a fibrous solid product with the incorporation of a polymer (Fig. 1). Both synthesis and formulation were monitored by PAT tools with chemometric analyses combined with the overall process control. Acetylsalicylic acid (ASA) was selected as the model drug being one of the oldest APIs still marketed; it is used for the treatment of pain, fever, inflammatory diseases, and low-doses of ASA reduce risk of heart attack and stroke [32]. Accordingly, continuous production of a beneficial electrospun orally dissolvable ASA formulation was envisioned to target the treatment of cardiovascular diseases. The design considerations of our benchtop-scale CMS are presented along with the results of detailed product analyses and system performance testing.

**2. Materials and methods**

**2.1. Materials**

Salicylic acid (SA) (Fig. 2a) (> 99.0%), ASA (Fig. 2b) (> 99%), acetic anhydride (Ac$_2$O) (> 99%), polyoxyethylene sorbitan mono-oleat (TWEEN 80), formic acid (95–97%), phosphoric acid (H$_3$PO$_4$) (85 wt%), sulfuric acid (96%), hydrochloric acid (37%) and acidic ion-exchange resin (Amberlite IR-120) were purchased from Sigma Aldrich. Ethyl acetate (EtOAc), methanol (MeOH), acetonitrile (ACN), ethanol (EtOH), acetic acid (AcOH), N,N-dimethylformamide, dimethyl sulfoxide and deuterated methanol (CD$_3$OD) were obtained from Merck. Polyvinylpyrrolidone K30 (PVPK30, Fig. 2c) (average Mw = 40000 Da) was purchased from BASF. Pullulan (Fig. 2d) was a kind gift from Hayashibara Co., Ltd.

**2.2. Flow chemistry experiments**

The continuous synthesis of ASA was carried out in flow reactors constructed with PTFE tubing (1/16″, 0.031″ ID). T-mixers (Supleco, 57661) and fittings compatible with the tubing were purchased from Sigma Aldrich. The reagents and solutions were dosed by Syrris Asia® syringe pumps and a Jasco PU-980 pump. An SSI flow-through backpressure regulator (BPR) (Supleco, 59284) adjusted to 4 bar was used to maintain constant fluid flow conditions.

**2.3. HPLC analysis for purity testing**

Purity of ASA in the synthesized reaction mixtures and solid dosage forms was determined using RP-HPLC (Agilent 1200 series LC System). An isocratic elution of water containing 0.5% phosphoric acid and ACN (40:60 V/V ratio) was performed at a flow rate of 1.5 mL min$^{-1}$ and 25 °C for 7 min. The UV detection wavelength was set to 237 nm. Solutions of ASA at 1 mg mL$^{-1}$ concentration were prepared depending on the composition of the samples. A mixture of ACN, MeOH and phosphoric acid (85%) (92:8:0.5 V/V ratio) was used to dilute, dissolve or extract the ASA samples due to the limited chemical stability of ASA.
and some of the impurities in common solvents [33]. If necessary, the solutions were filtered through PTFE syringe filters (0.45 µm, 25 mm) prior to injection. Samples containing PVPK30 were diluted or dissolved in MeOH due to the precipitation of the polymer with ACN. A 3 µL of sample volume was injected onto a Supelco Inertsil ODS-2 C18 column (5 µm; 250 × 4.6 mm). The amount of the impurities was determined based on the peak areas.

2.4. HPLC-MS measurements

The identification of major impurities in the synthesized reaction mixture was carried out using HPLC-MS. The measurements were performed using an Agilent 1200 liquid chromatography system coupled with an Agilent 6130 single quadrupole mass spectrometer equipped with an ESI ion source (Agilent Technologies, Palo Alto, CA, USA). Analysis was performed at 40 °C on a Supelco Inertsil ODS-2 C18 column (5 µm; 250 × 4.6 mm) with a mobile phase flow rate of 0.6 mL min⁻¹. Composition of eluent A was pure ACN, while eluent B was 0.1 V/V% HCOOH in water. The ratio of eluent A and B was 60:40 V/V%. The injection volume was 3 µL. The chromatographic profile was registered at 237 nm. The operating parameters of the mass selective detector were set as follows: positive ionization mode (70 eV), scan spectra from m/z 120 to 1200, drying gas temperature 300 °C, nitrogen flow rate 121.00 min⁻¹. Spray chamber was preflushed with 0.1% solution of NH₄CO₃ in ACN/water (92:8 V/V ratio).

2.5. NMR measurements

¹H NMR spectra were obtained on a Bruker DRX-500 instrument on 500 MHz at 25 °C, while ¹³C NMR spectra were recorded on a Bruker-300 instrument on 75 MHz at 25 °C. Samples were dissolved in CD₃OD with an ESI ion source (Agilent Technologies, Palo Alto, CA, USA). A HPLC system on 75 MHZ at 25 °C. Samples were dissolved in CD₃OD internal standard and chemical shifts were given in ppm.

2.6. Gel permeation chromatography

Gel permeation chromatography tests were conducted to investigate the chemical changes of PVPK30 during quenching. A HPLC system comprising a Waters S515 HPLC pump, Jetstream 2 Plus column heater and a Jasco RI-4035 Refractive Index Detector was used for the measurements. Prior to analyses the PVPK30 samples were prepared by suspending ca. 0.5 g solid material in 3 mL EtOAc, then dissolving the polymer with 0.5 mL of MeOH. The obtained clear solution was stirred on elevated temperature (80 °C) in order to evaporate the solvents. Thus, the PVPK30 precipitated from the remaining solution rich in EtOAc. Following cooling in ice bath the suspension was vacuum filtered and dried. The PVPK30 samples were dissolved again in N,N-dimethylformamide obtaining an 1 mg mL⁻¹ solution; 200 µL of this stock solution was injected onto Waters Styragel HT 2 and HT4 columns connected in series. The mobile phase consisted of N,N-dimethylformamide containing 0.05 M LiBr. The measurements were performed at 85 °C column temperature and 1 mL min⁻¹ flow rate after 24 h of equilibration. For data analysis PSS WinGPC software was used.

2.7. Electrospinning (ES)

Preliminary ES tests were conducted using an NT-35 high voltage direct current supply (MA2000; Unitronik Ltd, Nagykanizsa, Hungary). The electrical potential applied on the spinneret electrode was varied between 15 and 30 kV. During optimization of ES grounded aluminum plate covered with aluminum foil was used as collector. The distance of the spinneret and the collector was 20 cm. Solutions of the polymeric excipient and the drug were prepared for electrospinning using a magnetic stirrer (600 rpm). The solutions were dosed by a SEP-10S Plus type syringe pump through a needle spinneret (1 mm ID, 2 mm OD) at predetermined flowrate.

For the final version of the CMS an ES unit was developed with the same NT-35 high voltage direct current generator, but the solution was dosed from drug synthesis. Besides, a rotating drum collector was applied with a metal surface made of 1 mm thick aluminum sheet connected to earth. For further details see Sections 3.3 and 3.4.

The ES experiments including those with the CMS were conducted at 25 ± 1 °C and a relative humidity of 50 ± 10%.

2.8. Pullulan film casting

250 mg pullulan and 10 mg Tween 80 was added to 1490 mg purified water and stirred until a clear solution was obtained. Commercial red food coloring (Dr. Oetker, Germany) was added to the solution to improve the observability of the deposition of the white fibers on the film. The solution was spread on a glass surface and cast by a film applicator in predetermined thickness of 30 μm. The smooth pullulan films were dried for 24 h. The final red pullulan films could be readily pulled off from the glass surface by hand. It should be noted that for longer experiments with the CMS not pullulan but a similar strip made of polypropylene was used.

2.9. Scanning electron microscopy (SEM) and fiber diameter analysis

Morphology of the samples was investigated by a JEOL 6380LVa (JEOL, Tokyo, Japan) type scanning electron microscope. Each specimen was fixed by conductive double-sided carbon adhesive tape and sputter-coated with gold prior to the examination. Applied accelerating voltage and working distance were 15–30 kV and 10 mm, respectively. A randomized fiber diameter determination method was used based on SEM imaging as described in our previous work [34], n = 100 measurements were made on each sample.

2.10. Differential scanning calorimetry (DSC)

Differential scanning calorimetry measurements were carried out using a Setaram (Calure, France) DSC 92 apparatus (sample weight: ~10–15 mg, open aluminum pan, nitrogen purge gas). The temperature program consisted of an isothermal period, which lasted for 1 min at 25 °C, with subsequent linear heating from 25 °C to 200 °C at the rate of 10 °C min⁻¹. Purified indium standard was used to calibrate the instrument.

2.11. X-ray powder diffraction (XRPD)

X-ray powder diffraction patterns were recorded by a PANanalytical X’pert Pro MDP X-ray diffractometer (Almelo, The Netherlands) using Cu-Kα radiation (1.542 Å) and Ni filter. The applied voltage was 40 kV while the current was 30 mA. The untreated materials, a physical mixture composition, and the fibrous samples as spun were analyzed for angles 2θ between 4° and 42°.

2.12. In vitro dissolution tests

The in vitro dissolution tests of 30 × 30 mm cut pullulan films covered with different amounts of ASA loaded fibers were carried out by dissolving them in purified water. Layered ODWs corresponding to 1, 5, 12.5, 25 and 50 mg ASA doses were placed in Petri dishes containing 10 mL dissolution media. The dissolution of the ODWs was filmed using a Lenovo P70 camera device. After 10 min the dissolved ASA quantity was confirmed by HPLC measurements using the same method as during purity testing (Section 2.3).

2.13. Residual solvent content determination

The residual solvent content of the electrospun fibers was determined by gas chromatography (GC) in the case of EtOH and EtOAc.
and by HPLC in the case of AcOH.

The determination of EtOH and EtOAc was performed on an Agilent 6890 N GC system combined with a CTC Combi PAL HS autosampler. A 10 m long HP-INNOWax capillary column with 0.25 mm inner diameter and 0.25 μm film thickness with polyethylene glycol stationary phase was used for separation. Helium (purity: 99.999%) was used as carrier gas with a constant flow rate of 1.7 mL min⁻¹. Split injections of 250 μL were made at a split ratio of 50:1. The temperature of the injector was maintained at 250 °C and samples were thermostated at 140 °C for 3 min. For detection an Agilent 5973 inert mass selective detector was used with electron collisional ionization (70 eV). Samples for GC measurements were prepared by dissolving ca. 50 mg fibers in 6 mL dimethyl sulfoxide in 20 mL GC vials.

For the determination of AcOH content a RP-HPLC (Agilent 1200 series LC System) method was developed based on isocratic elution of water containing 0.5 V/V% phosphoric acid and ACN (95:5 V/V ratio). The chromatography tests were performed at a flow rate of 1.5 mL min⁻¹ and 25 °C for 5 min. The UV detection wavelength was set to 210 nm. Samples containing the PVPK30-based fibrous samples were dissolved in purified water due to the precipitation of the polymer in ACN. 20 μL of this solution was injected onto a Supelco Inertsil ODS-2 C18 column (5 μm; 250 × 4.6 mm). The non-eluting compounds such as ASA and SA was periodically washed after 15 injections with a mobile phase of 0.5 V/V% phosphoric acid and ACN (30:70 V/V ratio) and then the column was re-equilibrated for 60 min prior to further analyses. The amount of the AcOH was determined based on the peak area.

2.14. Content uniformity tests (CU)

In order to investigate the consistency of the dosage units content uniformity measurements were carried out. The system was operated in steady state for 8 h, and in each hour 10 cut film samples were dissolved in purified water in volumetric flasks. The deposited ASA dosage on the carrier was measured with HPLC without further dilution using the HPLC method described in Section 2.3.

2.15. FTIR spectroscopy

IR spectra were recorded using a Bruker Alpha FTIR spectrometer equipped with an on-line diamond ATR flow cell and an RT-DLaTGS detector. All spectra were collected in the spectral range of 4000–400 cm⁻¹ with 32 co-added scans at a resolution of 4 cm⁻¹. The spectrometer recorded a full spectrum in every 30 s. The background was acquired using a solvent mixture identical with that used in the acetylation reactor (see Table S8).

2.16. Raman spectroscopy

A Kaiser RamanRxn2® Hybrid analyzer (Kaiser Optical Systems, Ann Arbor, USA) coupled with PhAT (Pharmaceutical Area Testing) probe was utilized in reflection mode to acquire the spectra of the pullulan film covered with ASA-loaded fibers. Prior to analysis, controlled doses of fibers were electrospun on cut films. Each sample was illuminated by a 400 mW, 785 nm Invictus diode laser on 3 different positions, and the reflected Raman photons were collected by the PhAT probe. The diameter of laser spot size was optically expanded to 6 mm and the nominal focus length was 250 mm. Spectra were acquired in the spectral range of 200–1890 cm⁻¹ with a resolution of 4 cm⁻¹. Acquisition time of 30 s was required to achieve desired quality spectra.

3. Results and discussion

3.1. Optimization of the acetylation step of ASA synthesis

To begin with, the optimal parameters and composition of the reaction mixture had to be found for continuous-flow synthesis of ASA. Further processing of the produced API was also taken into consideration during synthesis development. The first step of ASA synthesis was the acetylation of SA with excess Ac₂O. EtOAc was selected as solvent readily dissolving SA (0.138 g mL⁻¹ pure solvent) and being also excellent for ES. Acid catalyst was also required for the fast and complete conversion of SA [35]. Besides many acids tested, such as H₂SO₄, HCl, acidic ion-exchange resin, H₂PO₄ was found to be suitable owing to its high activity and low toxicity.

The aim of the optimization of the acetylation step was to maximize the conversion of SA, minimize process time and impurity content. The effects of the applied amounts of Ac₂O and H₂PO₄, process temperature as well as residence time were explored with Design of Experiment (DoE) studies in batch reactors (Fig. S1). High temperatures (e.g., reflux) and more catalyst (e.g., 0.5 eq.) led to less favorable impurity profiles, while higher excess of Ac₂O (e.g., 10 eq.) did not result in practically better conversion rates. Accordingly, moderately high excess of Ac₂O (5 eq.), lower acid catalyst concentration (0.1 eq.) and 50 °C process temperature were selected for starting parameters of flow experiments.

The impurity profile of the reaction mixture after the acetylation step was investigated using HPLC-MS in order to better understand the chemical background of ASA synthesis (Fig. S2). The two main impurities of acetylation were identified as acetylsalicylic ethanoic anhydride (Impurity A) and acetylsalicylic anhydride (Impurity B). While decomposition of Impurity A to pure ASA seemed to be possible with quenching, Impurity B turned out to be chemically resistant against nucleophiles. These findings were essential during further optimization of acetylation and the following quenching step.

After the batch experiments the optimization was carried out in continuous-flow reactors to achieve high ASA conversion rate and purity. Compared to the use of batch vessels the continuous implementation of ASA synthesis resulted in more homogeneous temperature distribution, allowed easier process monitoring and control. Wider temperature range was also available in pressurized tube reactors. The reactants were mixed and dosed into a capillary tube reactor denoted as R1 (0.031 in. ID, PTFE) immersed into a heated oil bath and combined with a 4 bar BPR at the end. Optimal conditions of 55 °C and 180 min residence time were determined with another two DoE studies (Fig. S3-4) reaching high conversion (> 99%) and a favorable impurity profile (see next section).

3.2. Optimization of the quenching step without or with a polymer

A quenching step was required after acetylation not only to remove the excess Ac₂O but also to convert Impurity A to ASA due to its high relative concentration of ~ 60% in the reaction mixture (Fig. 3a). Different nucleophilic substances were tested as quenching agent. Water appeared at first as a suitable choice, however, aqueous solutions can be processed poorly with ES due to the high specific heat of vaporization. Thus, EtOH was applied instead generating EtOAc and AcOH from Ac₂O while turning Impurity A to pure ASA during quenching. It should be mentioned that the amount of the other major by-product of acetylation, the symmetric ASA anhydride Impurity B remained unchanged under any condition of quenching. Nevertheless, the amount of Impurity B was minimized to < 1% for this reason in the acetylation reaction. The simultaneous deacetylation of ASA back to SA was another hurdle to deal with in the development of quenching.

Our primary approach was the dosing of EtOH (1.3 eq. relative to excess Ac₂O) to the stream of the reaction mixture in flow reactors. Quenching was optimized utilizing further DoE studies to find the highest purity through varying temperature and residence time (Fig. S5). At last, 90 °C temperature and 26 min reaction time were found to be the best for quenching conditions with pure EtOH exceeding 95% ASA purity.

The introduction of a selected polymer (PVPK30) into the liquid
The reaction scheme of the optimized two-step flow synthesis of ASA is concluded in Fig. 4. The attainable high ASA purity of ∼95% also meeting the 3% regulatory limit for SA content evidenced by HPLC (Fig. 3b) and NMR (Fig. S8-9) results was satisfactory enough for formulation without applying any purification in our model system.

3.3. Connecting flow synthesis and electrospinning

There are two ways to connect ES with synthesis. The universal method involves mixing the API with a polymer right after synthesis (or usually a continuous-flow final-product purification) to form a co-solution. Nevertheless, the polymer can also be added earlier into the API stream when assuming no chemical interactions with the reactants. PVPK30 was selected as the polymer for a fast dissolving formulation on account of its great propensity to form co-solvent (EtOH) without chemical alteration in R2 as mentioned earlier thereby avoiding the use of an additional pump.

However, care must be taken with both approaches explained above since adjusting the critical parameters for ES (e.g., polymer concentration, flow rate) greatly affects the overall process design often in an iterative way. For instance, although the formerly explained addition of AcOH as co-solvent during quenching prevented the precipitation of PVPK30 in R2, but the optimal solution composition for the ES is shifted – in our case towards higher polymer concentrations – which might caused precipitation again in the capillary tubes.

Good quality PVPK30-ASA micro- and nanofibers could be obtained using ES with one needle type spinneret after adjusting the polymer concentration in the reaction mixture (Fig. 5). The optimal PVPK30 concentration was determined to be 3.25 g in 10 mL pure solvent based on preliminary experiments (Fig. S10). The dosing rate was fixed at 4 mL h⁻¹ (or 67 μL min⁻¹), the continuously produced polymeric fibers contained approximately 18% (w/w) ASA and possessed an average diameter of 0.97 ± 0.25 μm. The morphology of the fibers did not deteriorate in a wide range of dosing rates (20–120 μL min⁻¹) indicating the robustness of ES for coupling with flow operations (Fig. S11). Above a certain throughput – in our case ∼7 mL h⁻¹ – the excess polymeric solution dripped down from the spinneret instead of fiber formation. Higher throughputs are achievable with the modified versions of ES such as alternating current ES [38] or high speed ES [31]. However, latter cases would require different types of formulation unit design.

The instantaneous conversion of the synthesized API stream into a solid electrospun product was carried out in the ES unit developed and built in-house (Fig. 6a). The drying of the fibers was facilitated with applying active air ventilation in the otherwise closed box. Thus, ES can be considered as a special distillation method to remove solvents. The solvents can be recovered from the purging air, for instance, with the use of a condenser [39].

3.4. Continuous formulation of layered fibrous ODWs

The collection of the fibers was a key challenge as it determines further formulation. For this purpose another special feature of ES was exploited. Controlled deposition could be achieved through the attraction of the fibers towards a collector possessing a suitable wheel geometry as part of the ES unit (Fig. 7). The electrically grounded metallic surface of the wheel was covered with a long wide carrier sheet during ES; the deposited ASA-loaded nanofibers and the carrier film...
formed a double-layered composite structure. Pullulan, a water-soluble polysaccharide (Fig. 2d), was applied to develop a carrier quickly dissolving in the oral cavity. The PVPK30-ASA nanofibers were layered onto the 30 mm wide and ca. 30 μm thick pullulan film. ES combined with electrostatic deposition could be continuously operated to form consistent flat sheets without clogging. Besides the good spinnability of PVPK30 and the use of a less volatile solvent mixture preventing undesired drying at the tip of the spinneret, careful optimization of solution concentration and adjustment of the electrostatic field strength were also essential for a stable operation of ES.

The continuously conveyed ASA-loaded nanofibrous filmstrip was cut into single pieces (see the inset of Fig. 7) by a cutter device integrated into the developed formulation unit (Fig. 6b). Thus, the obtained dosage units can be considered as layered ODWs. ASA doses of 1, 5, 12.5, 25 and 50 mg were prepared with dimensions of 30 × 30 mm after cutting. In addition to factors inherited from the synthesis (i.e., mass flow rate and composition of the fibers) the drug dose can be quickly adjusted for each cut film through varying the parameters of film convection and cutting. Altering convection speed affects the thickness of the fibrous mat while the size of the layered ODWs can be set with changing the time delay between two cuttings. Both mat thickness and the area of the covered surface contributes to the final dosage strength. That feature of the CMS also enables the approach of personalized medicine by being capable to produce tailored dosage units accommodating patient needs.

3.5. Product characterization and CMS testing

The physical state of ASA was also investigated in the nanofibrous product by DSC and XRPD measurements (Fig. 8). Both analytical techniques showed that ASA turned into an amorphous form during ES. The physical mixture of 5% crystalline ASA and PVPK30 served as reference to demonstrate the sensitivity of the methods. The DSC thermogram of the physical mixture clearly indicate the sign of ASA crystallinity as an endothermic melting peak at around 140 °C beside the wide peak of water loss of amorphous PVPK30 below 120 °C. In contrast, the melting peak of ASA is absent on the thermogram of the PVPK30-ASA nanofibers evidencing the amorphous state of the drug.
The most intense characteristic X-ray diffraction peaks of crystalline ASA also appear on the diffractogram of the physical mixture at 20 = 16.3°, 23.8° and 27.7°. These signs of crystallinity could not be detected in the case of the PVPK30-ASA nanofibers in good accordance with the DSC results, only the amorphous humps of the polymer matrix emerge from the scattering background. The ultrafast drying effect of ES presumably froze the fibers into a solid solution where ASA is present molecularly dispersed in the polymer.

Dissolution tests were carried out with different doses of layered PVPK30-ASA nanofibers on pullulan carrier (Figs. 9 and S12). The ODWs were dissolved in 10 mL purified water without additional stirring at 25 °C. Between the range of 1 and 25 mg ASA doses the dissolution of the fibers was instantaneous, the nanofibers disappeared in less than 2–3 s. The dissolution of the red pullulan carrier was not so spectacular but it also disintegrated within 10 s. The dissolution results are in good agreement with the information provided by the solid phase fractionation peaks of crystalline fibers but also to the increased solubility of the amorphous form of ASA.

Residual solvent content measurements were conducted in steady state of the CMS for 4 h. The results revealed satisfactorily low values in the fibrous product (Fig. 10a). The quantities of EtOH, EtOAc and AcOH were below the regulatory limit (5000 ppm) in all cases. The more volatile EtOH and EtOAc solvents with similar boiling points of 77–78 °C were barely present in the fibers, concentrations below 1000 ppm could be determined. Even AcOH with a boiling point of 118 °C could be eliminated using ES from the fibers obtaining around 4000 ppm concentration in the final product.

Repeated content uniformity measurements were conducted for 8 h after the synthesis unit had reached steady state conditions. The settings of the formulation unit (i.e., film speed and cutting frequency) were determined earlier for 5 mg ASA dose. As it can be seen in Fig. 10b the collected layered ODWs showed mean contents close to the original target dose of 5 mg with satisfactorily low fluctuations. In the 1st hour dosage units only with ~4.5 mg ASA were produced due to some deposition of the fibers on other surfaces in the ES box. However, after 2 h fibers deposited mainly on the carrier.

Overall, the CMS was successfully operated for 24 h, i.e., approximately 7 times of the residence time of the whole system including formulation. As it can be seen in Fig. 10c, the purity of ASA in the nanofibers produced from the reaction mixture reached the > 95% level not long after passing the nominal residence time of R1 and R2 combined. The SA content converged below the regulatory limit of 3% complementary with ASA purity. The purity of the ODWs produced by the CMS was comparable to a marketed ASA tablet formulation and both met the regulatory requirements for SA content (Fig. S16).

3.6. Integration of PAT-based control strategies

Real-time monitoring of quality was integrated into the CMS with spectroscopic PAT tools. The CMS was also equipped with PAT-based control loops to ensure quality.

A Bruker Alpha FTIR spectrometer was used with an ATR flow cell to analyze the purity of ASA in the synthesized reaction stream. The flow cell was placed after the BPR and directly before the ES unit. Purity was calculated from the spectra by a quantitative model based on partial least squares (PLS) regression built with different ASA-SA ratios (Fig. 11a) [40]. Following the pretreatment of the IR spectra the relevant spectral regions in terms of the regression were selected by a genetic algorithm (GA). Applying 4 latent variables (LV) on the selected ranges led to an effective PLS model for the commonly experienced high purity reaction mixtures corresponding to the region between 91 and 100% ASA content with low root mean squared of calibration (RMSEC) and root mean squared of cross-validation (RMSECV) values (0.64 and 0.90, respectively). In the case of insufficient purity the high voltage generator turned off automatically to prevent the production of low-grade fibers. The concept of using switching valves to redirect the stream of lower purity into a waste container had to be reconsidered since the drying of the polymeric solution in the stagnant tubing would lead to clogging when switching back.

A Raman probe was applied for the inspection of the fibers on the pullulan strip placed before the cutting mechanism (Fig. 6b). The probe was motorized providing transversal movement of the laser beam patrolling on the surface of the nanofibrous film (Fig. S19a). The Raman
spectra were preprocessed before model building for the fiber quantities. GA was used again for variable selection, the final PLS-GA model used 3 LVs. The indicators of model goodness (RMSEC = 2.09, $R^2_{\text{cal}} = 0.956$) showed that the built model can be suitable for estimating the fiber quantity on the pullulan film (Fig. 11b). If the deposition of the fibers was uneven on the film meaning the cases where certain pullulan areas remained partly or completely uncovered, a bistable slide mechanism redirected the product to the waste bin instead of the approved product container (Fig. S19b).

The details of the chemometric analyses on the FTIR and Raman spectra are given in the Supplementary Information.

4. Conclusions

In this report we presented a novel approach based on ES for the continuous production of a solid dosage form from the synthesis of the API to the final formulation of layered ODWs with integrated PAT quality assurance. The main characteristics of the developed CMS (Fig. 12) are concluded in Table 1. As for productivity, at 5 mg dosage strength $\sim 10^{16}$ doses per day can be reached. Hence, a continuous benchtop device such as the one presented is able to produce considerable amounts of dosage units with ES especially when formulating high-potency APIs.

Besides the optimization of ASA synthesis together with ES for purity and fiber morphology, solid phase analyses were conducted on the nanofibers verifying the amorphous form of the drug. Ultrafast dissolution could be observed with the pullulan-based nanofibrous composites at 1–25 mg ASA dose levels. The CMS was operated for 24 h covering several cycles of the mean residence time ($\sim 3.5$ h); detailed measurements showed excellent stability of drug purity over time in

Fig. 10. Quality attributes of ODWs over time produced by the CMS: (a) residual solvent content, (b) content uniformity, (c) purity (HPLC). The dashed lines indicate either regulatory (SA and residual solvent) or specified process (minimal accepted ASA purity and target dose) limits.

Fig. 11. (a) Comparison between actual and calculated ASA content in the reaction mixtures in the rage of 91–100% (ATR-FTIR, PLS-GA regression). (b) Comparison between actual and calculated weight ratios of PVPK30+18%ASA nanofibers on pullulan film-based layered ODWs (Raman, PLS-GA regression).
The reaction mixture also after purification ES can be a feasible technique in pharmaceutical manufacturing as can be seen in processing the process providing tailored dosage units. Within continuous pharmaceutical manufacturing, FTIR and Raman tools combined with chemometric analyses. Control of both synthesis and formulation was developed using ATR-FTIR and Raman spectroscopy in combination with chemometric analyses.

Our CMS also demonstrates how personalized medicine can be implemented through prompt control of the scaled-down continuous process providing tailored dosage units. Within continuous pharmaceutical manufacturing ES can be a feasible technique in processing the process providing tailored dosage units. Within continuous pharmaceutical manufacturing, FTIR and Raman tools combined with chemometric analyses.

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### Competing interests

Declarations of interest: None.

### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/jcej.2018.05.188.


