Journal of Controlled Release 298 (2019) 120–127

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Continuous alternative to freeze drying: Manufacturing of cyclodextrin-based reconstitution powder from aqueous solution using scaled-up electrospinning

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ARTICLE INFO

Keywords:
Aqueous electrospinning
Voriconazole
Cyclodextrin
Reconstitution injection
Scale up
Continuous

ABSTRACT

The aims of this study were to evaluate electrospinning as a continuous alternative to freeze drying in the production of a reconstitution injection dosage form, and to prove that aqueous electrospinning can be realized with a high production rate at room temperature. High-speed electrospinning with a novel continuous cyclone collection was used to manufacture a formulation of the poorly water-soluble antifungal voriconazole (VOR) with sulfobutylether-β-cyclodextrin (SBE-β-CD). The freeze-dried, marketed product of this drug substance, Vfend® also contains SBE-β-CD as excipient. SBE-β-CD acted as a 'quasi-polymer', and it could be electrospun despite its low molecular mass (2163 Da). According to X-ray diffraction and differential scanning calorimetry, no traces of crystalline VOR were detectable in the fibers. Furthermore, Raman mapping and energy dispersive spectroscopy measurements showed a uniform distribution of amorphous VOR in the fibers. Reconstitution tests carried out with ground fibrous powder showed complete dissolution resulting in a clear solution after 30 s (similarly to Vfend®). The high productivity rate (~240 g/h) achieved using high-speed electrospinning makes this scaled-up, continuous and flexible manufacturing process capable of fulfilling the technological and capacity requirements of the pharmaceutical industry. This work shows that aqueous high-speed electrospinning, being a continuous and high-throughput process, is an economically viable production alternative to freeze drying.

1. Introduction

Parenteral administration, despite its numerous disadvantages (low patient compliance due to pain and discomfort, the need for sterile environment, local adverse reactions etc.), remains the main choice for drug delivery route in emergency situations, in intensive care, in case of low oral bioavailability of the drug, or when the rate of absorption and duration of the effect must be strictly controlled [1]. However, in parenteral solutions, and generally in liquids, most drugs have decreased stability due to the higher reactivity in the liquid phase [2]. This problem can be overcome by using reconstitution injections as this type of formulation combines the advantages of parenteral administration (efficient and immediate systemic delivery) and solid formulation (increased stability in solid form).

Powders for reconstitution are generally prepared by freeze drying because parenteral administration requires fast dissolution in the reconstitution medium, which can be facilitated by the porous structure of freeze-dried cakes. However, lyophilization is a highly energy-intensive batch process with long processing times and high capital as well as high operational expenditures [3]. To reduce the limitations of batch lyophilization, several research groups are working on the development of continuous freeze drying technologies, which are envisioned to reduce the drying time, improve productivity, and provide better control over the quality of the product [4,5]. However, it is estimated that the running cost of continuous freeze drying is still significant as sublimation, vacuum, and condensation, which are responsible for ~95% of the energy consumption of conventional freeze drying, are still part of the continuous lyophilization process [6].

Electrospinning (ES) is considered to be a promising alternative to freeze drying. It is based on the high electric field that enables fiber

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https://doi.org/10.1016/j.jconrel.2019.02.019
Received 14 December 2018; Received in revised form 13 February 2019; Accepted 15 February 2019
Available online 16 February 2019
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formation from viscous polymer solutions [7]. Such a structure can provide fast dissolution owing to the enhanced surface area of the fibers [8]. ES is usually carried out at room temperature, which - combined with the large solution surface area - result in gentle and instant solvent evaporation ($t < 0.1$ s) besides being a continuous process with low energy consumption. ES has been widely used for preparing fibrous drug delivery systems for various application areas e.g. enteral [9,10] and parenteral formulations [11], antibacterial and tissue engineering scaffolds [12], wound dressings [13,14], implants [15], transdermal drug delivery systems [16] and biopharmaceutical formulations [17,18]. Recently, a pharma industry compatible ES device called high-speed electrospinning (HSES) has been developed for pilot-scale production of fibrous amorphous solid dispersions [19]. High-speed electrospinning improves productivity significantly by combining electrostatic [20] and high-speed rotational [21] jet generation and fiber elongation. The technology utilizes a rotating spinneret with orifices that minimizes free liquid surface to avoid solvent evaporation.

In this work, voriconazole (VOR) was applied as the model active pharmaceutical ingredient. VOR is an antifungal drug from the azole family, which is used for the treatment of severe fungal infections (e.g. invasive aspergillosis) occurring in immunocompromised patients [22]. VOR has low aqueous solubility (0.2 mg/mL at pH 3 and 0.6 mg/mL at pH 7), which classifies it to the class II of the Biopharmaceutics Classification System (BCS) [23]. In the marketed, freeze-dried powder for reconstitution of VOR (Vfend®), molecular encapsulation with sulfobutylether-β-cyclodextrin sodium (SBE-β-CD) is applied to increase the VOR solubility in water [24,25]. The freeze drying of VOR with SBE-β-CD results in the amorphization of the drug [26]. A single dose of the marketed product contains 200 mg VOR and 3200 mg SBE-β-CD, and it is intended for reconstitution with 19 mL water to produce a solution containing 10 mg/mL of VOR [27].

SBE-β-CD belongs to the family of cyclodextrins (CDs), which are water-soluble oligosaccharides derived from starch, containing six (α-CD), seven (β-CD) or eight (γ-CD) α-D-glucopyranose units. One of the most appealing characteristics of these cyclic molecules is that they have a relatively hydrophobic central cavity that readily forms a non-covalent host-guest inclusion complex with a lipophilic compound or moiety. The formed complex remains water-soluble due to the hydrophilic outer surface of the hosting CD molecule. This favorable feature can be utilized in pharmaceutical formulations. Nowadays, there are over 60 commercially available pharmaceutical products containing CDs as excipients. In addition, CDs are reported to act as stabilizers for biological drugs like peptides and proteins [28,29]. SBE-β-CD and other cyclodextrins (CDs) have been successfully electrospun recently as CDs are capable of forming polymer-like supramolecular structures via intramolecular interactions. Generally, high CD concentrations are applied to generate strong and large associates (entangled CD molecules) in the solution (therefore, the viscosity will be high as well), which can form fibers [11,30].

The aim of this work was two-fold: to develop a reconstitution injection dosage form consisting of VOR–SBE-β-CD complex prepared by scaled-up electrospinning, and to prove that water-based ES can be realized at room temperature with a high production rate. By this, it could be confirmed that ES is a viable, continuous alternative to freeze-drying, presumably, with significantly lower energy consumption. At the moment, only a handful of examples can be found in literature where aqueous solutions with poorly soluble drugs were spun into fibers [30–35]. Nevertheless, there are usually some limitations and complexity, such as the need to use surfactants (to be able to dissolve the drug) or low productivity. The highest output reported up to now for aqueous pharmaceutical electrospinning was about 20 g/h [17]. In this work, the development of an aqueous electrospinning technology of CDs with high output was attempted, which could potentially serve as a platform technology for the gentle drying of proteins or other sensitive biopharmaceuticals besides poorly soluble drugs.

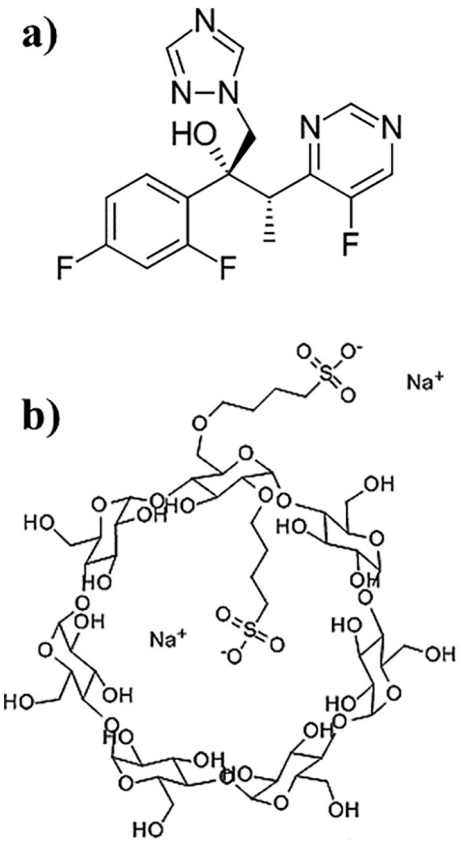

Fig. 1. The structure of a) voriconazole and b) sulfobutylether-β-cyclodextrin (SBE-β-CD) sodium.

2. Materials and methods

2.1. Materials

Voriconazole (Fig. 1. a) was purchased from Sigma-Aldrich (Budapest, Hungary). Vfend® (Pfizer, New York, NY, USA) was obtained from a local pharmacy. SBE-β-CD sodium (Fig. 1. b) (Dexolve™, average degree of substitution = 6.5) was received from Cyclolab Cyclodextrin Research and Development Laboratory Ltd. (Budapest, Hungary). The water used was from a Millipore Milli-Q ultrapure water system.

2.2. Drop electrospinning (DES)

For the placebo optimization experiments, drop electrospinning (DES) was employed. SBE-β-CD (33 to 75 w/w%) was added to purified water and stirred with a magnetic stirrer (600 rpm) at room temperature until complete dissolution (Fig. 2). A drop of the solution was placed on the tip of a metal needle ($d = 5$ mm) attached to high voltage (20 kV). Few milligrams of the products were collected on the collector

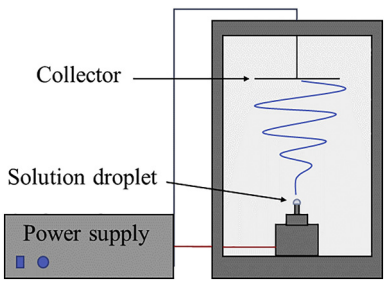

Fig. 2. Schematic drawing of the drop electrospinning (DES) equipment.

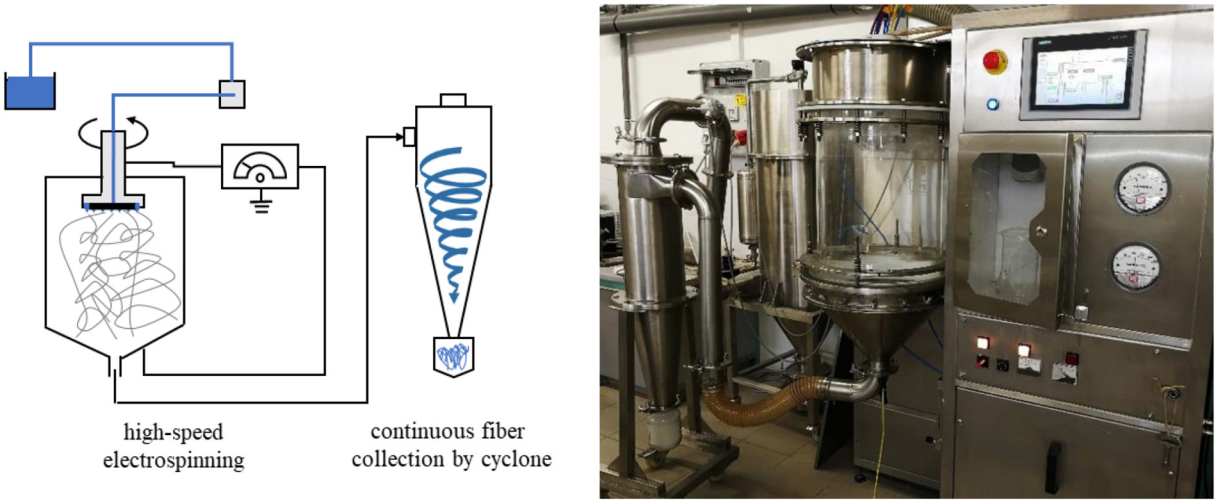

Fig. 3. Schematic drawing and a photo of the continuous high-speed electrospinning (HSES) device with a cyclone collector.

placed above the needle (120 mm distance). Morphology of the product was visually inspected to evaluate product quality (e.g. presence of particles, fibers or a mix of fibers and particles) before microscopical analysis.

2.3. High-speed electrospinning (HSES)

Electrospinning experiments were performed using a HSES setup (Fig. 3) consisting of a stainless steel spinneret (d = 34 mm) connected to a high-speed motor [19]. The spinneret was equipped with orifices (d = 330 μm). For the experiments with VOR, SBE-β-CD (65.9 w/w%) and VOR (4.1 w/w%) were added to purified water and the mixture was stirred with a magnetic stirrer (600 rpm) at room temperature until complete dissolution. The VOR–CD complex solution was fed with a SEP-10 S Plus syringe pump with a flow rate of 150 to 300 mL/h. The rotational speed of the spinneret was fixed at 40,000 rpm. The applied voltage was 40 kV during the experiments (Unitronik Ltd., Nagykanizsa, Hungary). The experiments were performed at ambient temperature (25 °C). The produced fibrous material was collected by a cyclone, which is a novel type of continuous fiber collection technique.

2.4. Viscosity measurements

The viscosity of the solutions was determined using an AR 2000 rotational rheometer (TA Instruments, New Castle, DE, USA) in parallel plate configuration. The upper moving plate of 40 mm diameter and the lower Peltier plate, which adjusted the temperature of the solutions to 25 °C, were made of stainless steel. Viscosity was measured at shear rates linearly increased from 20 to 100 s^{-1}. The reported viscosities are the overall averages of values measured at 5 different shear rates using 2 independent samples (replicates). There were no practically relevant changes in the measured viscosities as a function of shear rate.

2.5. Scanning electron microscopy (SEM) and energy dispersive spectroscopy (EDS)

Morphology of the electrospun samples and Vfend® was investigated by means of a JEOL 6380LVa (JEOL, Tokyo, Japan) type scanning electron microscope. Each specimen was fixed with conductive double-sided carbon adhesive tape and sputter-coated with gold prior to the examination in order to avoid electrostatic charging. The applied accelerating voltage and working distance were set to 15 kV and 10 mm, respectively. Energy dispersive spectrometry (EDS) was used in conjunction with SEM for the mapping of fluorine and sulfur in the samples. (The detection and calculation were based on the peaks identified at 0.677 and 2.307 keV). The detected X-ray radiation was between 4000 and 5000 counts/s, and 10 scans were accumulated.

2.6. Modulated differential scanning calorimetry (DSC)

Modulated differential scanning calorimetry measurements were carried out using a DSC3+ (Mettler Toledo AG, Switzerland) DSC instrument in TOPEM® mode (sample weight: ~5–15 mg, pierced pan, nitrogen flush, 50 mL/min). The equipment uses a stochastic temperature modulation superimposed on the underlying heating rate. The overall heating rate was 1 °C/min, while the pulse height was set to 1 °C (which means that the temperature was modulated by ± 0.5 °C). The pulse width – the frequency of the modulation – was varying randomly between 15 and 30 s. The temperature was increased from 0 °C to 200 °C.

2.7. X-ray powder diffraction (XRPD)

X-ray powder diffraction (XRPD) patterns were recorded with a PANalytical X'Pert Pro MDP X-ray diffractometer (Almelo, The Netherlands) using Cu-Ka radiation (1.542 Å) and Ni filter. Measurements were conducted in a range of 2Θ = 4–44° to determine the crystalline structure of the electrospun samples and the other materials. XRPD measurements were carried out in reflection mode with a step size of 0.0167°. The samples of the electrospun material and Vfend® analyzed were the final drug products i.e. ground electrospun powders and the Vfend® freeze-dried cake (gently pulverized by a spatula before measurement).

2.8. Thermogravimetric analysis (TG)

Thermogravimetric examination of the samples to determine the residual water content was accomplished with a Q5000 TGA instrument (TA Instruments, New Castle, DE, USA) under nitrogen atmosphere. The sample was heated up from 25 to 105 °C at 10 °C/min, and it was kept at 105 °C for 10 min. The applied nitrogen flush was 50 mL/min during the measurement.

2.9. Raman mapping

In order to evaluate the homogeneity of VOR in the fibrous sample and Vfend®, Raman mapping was performed. The Labram-type Raman instrument of Horiba Jobin–Yvon (Kyoto, Japan) coupled with external 532 nm Nd:YAG laser source and Olympus BX-40 optical microscope was employed for spectrum collection. An objective of 50× objective

(laser spot size: ~2 μm) was used in the high-resolution measurements. A 950 groove/mm grating monochromator dispersed the Raman photons, directing them to the CCD detector. The spectral range of 460–1680 cm^{-1} with 3 cm^{-1} resolution was measured in all cases. The maps were collected with 5 μm step size in both directions and consisted of 31 × 31 points. One spectrum acquisition took 30 s and accumulated 2 times in each mapping point. The evaluation was carried out by the classical least squares (CLS) method using the spectra of the reference substances.

2.10. Grinding of the electrospun material

The electrospun material was ground to improve the processability of the fibers collected by the cyclone. A hammer mill (IKA MF10, IKA-WERKE GmbH & Co. KG, Staufen, Germany) was used with a 1.0 mm sieve at 3000 rpm.

2.11. Reconstitution test and concentration measurement

A dissolution test (reconstitution) of the electrospun sample and Vfend® was carried out following the instructions in the Vfend® package insert [27]. 3400 mg ground sample (containing 200 mg VOR) and a physical mixture of 200 mg VOR and 3200 mg SBE-β-CD were weighed into glass vials. 19 mL purified water was added into the vials, which were then shaken vigorously to dissolve powder stuck on the walls as well. In order to monitor the dissolution, pictures were taken at predetermined time intervals using a digital camera.

For the concentration measurements, 1 mL of the solution was filtered through a regenerated cellulose filter with 0.45 μm pores. 40 μL of the filtered solution was filled up to 10 mL. The sampling points were 0.5 and 2 min. An Agilent 8453 UV-VIS spectrophotometer (Hewlett-Packard, Palo Alto, USA) was used to measure the absorbance of dissolved VOR at the wavelength of 256 nm. The concentration could be readily calculated based on the calibration curve of VOR in water.

3. Results and discussion

3.1. Optimization of fiber formation by drop electrospinning

Challenges in process development were anticipated because SBE-β-CD is not an obvious fiber-forming material due to its small molecular mass (2163 Da) and the possible ionic repulsions among its molecules. To determine the suitable SBE-β-CD concentration for fiber formation, a small-scale screening process was carried out using DES. The amount of dissolved SBE-β-CD in the aqueous solution was gradually increased from ~33 w/w% to ~75 w/w% since the concentration of the fiber forming agent is considered to be one of the most critical parameters for ES due to the impact on viscosity and fiber formation [36,37]. Morphology of the prepared samples was investigated by visual inspection and SEM (Fig. 4). Below 67 w/w% concentration, no fiber formation was observed, only particles of the SBE-β-CD solution were collected (presumably, the entanglement of CD molecules is not adequate for forming fibers). Starting from 67 w/w%, particle and fiber formation was noticed, although bead-free fibers were only formed at 71 and 75 w/w% concentration solutions. The presence of beads in the fibrous material is detrimental to the specific surface area and the dissolution rate. Therefore, it is important to select a solution concentration from which bead-free fibers can be produced. As the results show, a wide enough concentration region where stable and robust fiber formation was possible could be identified, and thus, SBE-β-CD acted as a 'quasi-polymer' at high concentrations. Keeping in mind that VOR might also play a role in the fiber formation and may slightly shift the boundaries of the feasible concentration range, 68.8 w/w% aqueous SBE-β-CD solution was chosen for the experiments with VOR.

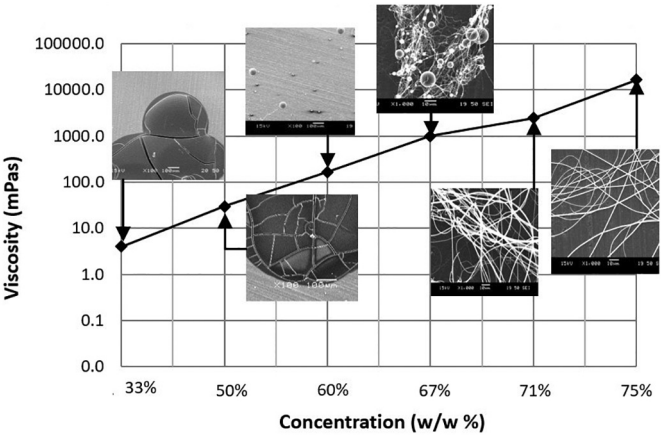

Fig. 4. Optimization of fiber formation.

3.2. High-speed electrospinning (HSES)

Laboratory scaled electrospinning (single needle electrospinning) is incapable of mass production of fibrous material, and therefore, its throughput is far from the needs of commercial pharmaceutical manufacturing. In our experiments, HSES was applied to increase the productivity of the technology.

HSES experiments were carried out using aqueous SBE-β-CD and VOR–SBE-β-CD solutions. When electrospinning from SBE-β-CD without VOR (but keeping the dissolved SBE-β-CD amount the same) particles were formed beside fibers (Fig. 5. a). Fig. 5. b shows the fibrous nature of the produced VOR–SBE-β-CD electrospun material with fiber diameters in the range of approx. 0.5–2 μm. Among the fibers, fewer particles were observable compared to the placebo SBE-β-CD sample. This might suggest that VOR enhances the association (i.e. the entanglement) among the SBE-β-CD molecules and aids the fiber formation. Fragmentation of the fibers is also noticeable, which could be caused by the centrifugal force inside the cyclone resulting in a circular motion of the solid material in the collector bin. It is important to note that all experiments were conducted at room temperature, which makes electrospinning a platform technology that can be employed in case of biopharmaceuticals as well.

The highest feeding rate applied during the experiments was 300 mL/h. Details of this experiment are summarized in Table 1. The total solids concentration in the aqueous solution was 70 w/w% with a mass ratio of 1:16 for VOR:SBE-β-CD. A yield of 88% was achieved with the current settings (material loss was noticed on the walls of the drying chamber), which means that the productivity rate was ~240 g/h. With further process and equipment optimizations (e.g. with additional air knives in the chamber), and during extended productions, it is estimated that the yield of the process could be further increased. Consequently, theoretically, a productivity of ~5 kg/day is achievable with the current HSES setup. This equals an output rate of > 1600 doses/day, which can be further increased by increasing the drying temperature and scaling the spinneret up similarly to rotary atomizers in spray drying [38]. This productivity rate is > 12× higher than the highest aqueous electrospinning production rate reported so far for pharmaceutical application [17]. According to Harrington et al., 2990 people were hospitalized with a primary diagnosis of invasive aspergillosis in 2013 in the USA. If these patients are treated with intravenous Vfend® for 20 days with an average of 3 doses per day, 179,400 doses are required. With our HSES setup (which can still be increased), this amount can be manufactured in < 4 months. Besides this, obviously, downscaling is also possible in order to produce for smaller markets. Therefore, this scaled-up, continuous and flexible manufacturing process seems to be capable of fulfilling the capacity requirements of the pharmaceutical industry.

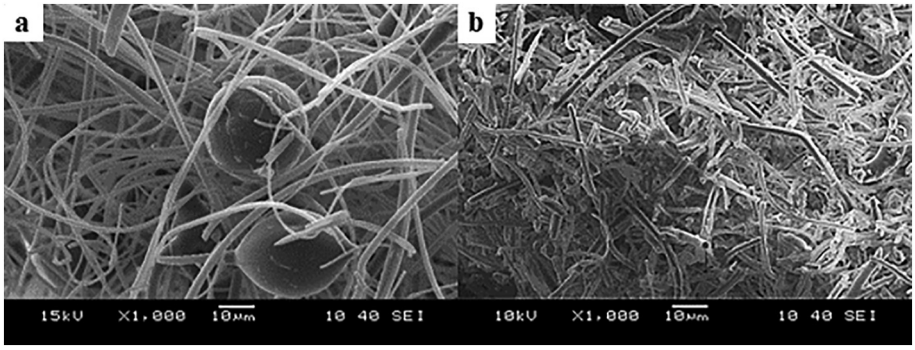

Fig. 5. Scanning electron microscopic images of a) placebo SBE-β-CD fibers; b) VOR–SBE-β-CD complex based fibers.

Table 1
Details of the production of SBE-β-CD + VOR containing fibrous material by HSES.

Dissolved SBE-β-CD + VOR in 100 mL water (g)	Feeding rate (mL/h)	Solution density (g/cm^3)	Yield	Productivity for dried material (g/h)	Productivity for dried VOR (doses/day)	Water content of dried material
220 + 13.75 (70 w/w% total solids content)	300	1.29	88%	240	1600	6.9%

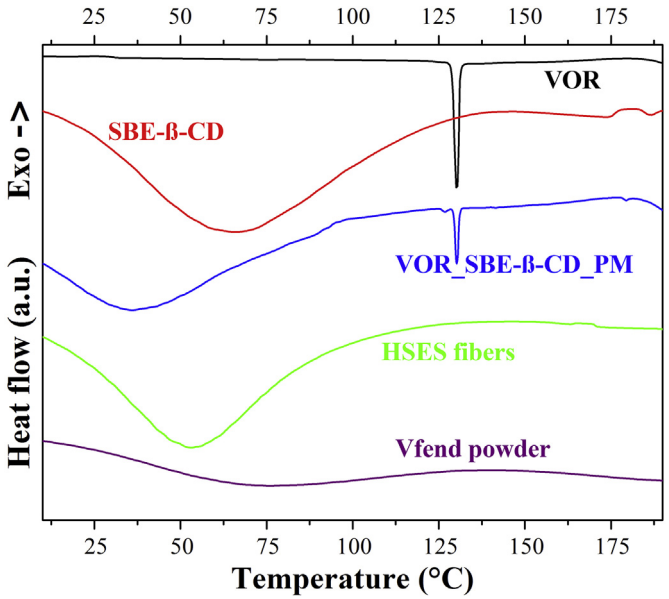

Fig. 6. Differential scanning calorimetry (DSC) thermograms of crystalline VOR, SBE-β-CD, the physical mixture (PM) of VOR and SBE-β-CD, the electrospun VOR–SBE-β-CD complex, and the Vfend® powder.

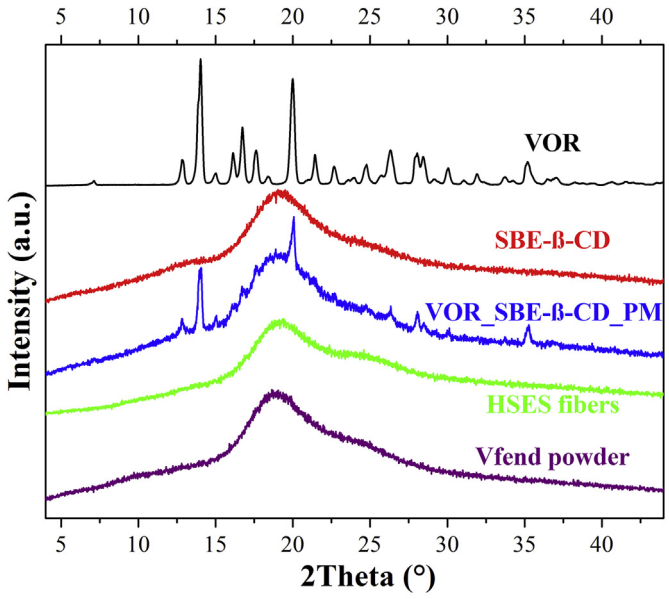

Fig. 7. X-ray powder diffraction (XRPD) patterns of crystalline VOR, SBE-β-CD, the physical mixture (PM) of VOR and SBE-β-CD, the electrospun VOR–SBE-β-CD complex, and the Vfend® powder.

3.3. Differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD)

To investigate the physical state of VOR in the fibrous sample and in Vfend®, DSC and XRPD examinations were carried out. The pure crystalline VOR served as the reference. The DSC thermograms (Fig. 6) of Vfend® and the VOR-SBE-β-CD fibrous material did not show the endothermic melting peak of crystalline VOR around 130 °C, which suggests that VOR is amorphous in both solid formulations. The wide endothermic activity that can be detected in the thermogram of the electrospun sample is related to the water loss of the matrix (in a second heating cycle, this peak does not appear, data not shown). The reversing heat flow did not contain any noticeable glass transition or melting peak (data not shown). No glass transition temperature of the fibrous material (and Vfend®) could be detected by further DSC investigations. This has also been observed previously by other researchers as Zhang et al. could not locate any glass transition temperature of a lyophilized complex of VOR and SBE-β-CD [26]. Possibly, SBE-β-CD and VOR molecules form strong structures that do not show α-relaxation upon heating, while the material decomposes from 245 °C based on our experiment. Glass transition temperatures of actual polymeric derivatives of β-CDs cannot be determined either by conventional methods as they are above the degradation point [39]. The lack of peaks on the XRPD diffractograms (Fig. 7) of Vfend® and the electrospun sample also confirmed the amorphous state of VOR in the two formulations.

3.4. Raman mapping and EDS of the electrospun sample

DSC and XRPD only tell us about the state of the VOR but do not provide exact information about the local concentration of the incorporated drug. Distribution of the amorphous VOR in the fibrous samples was evaluated by EDS and Raman mapping. For accurate

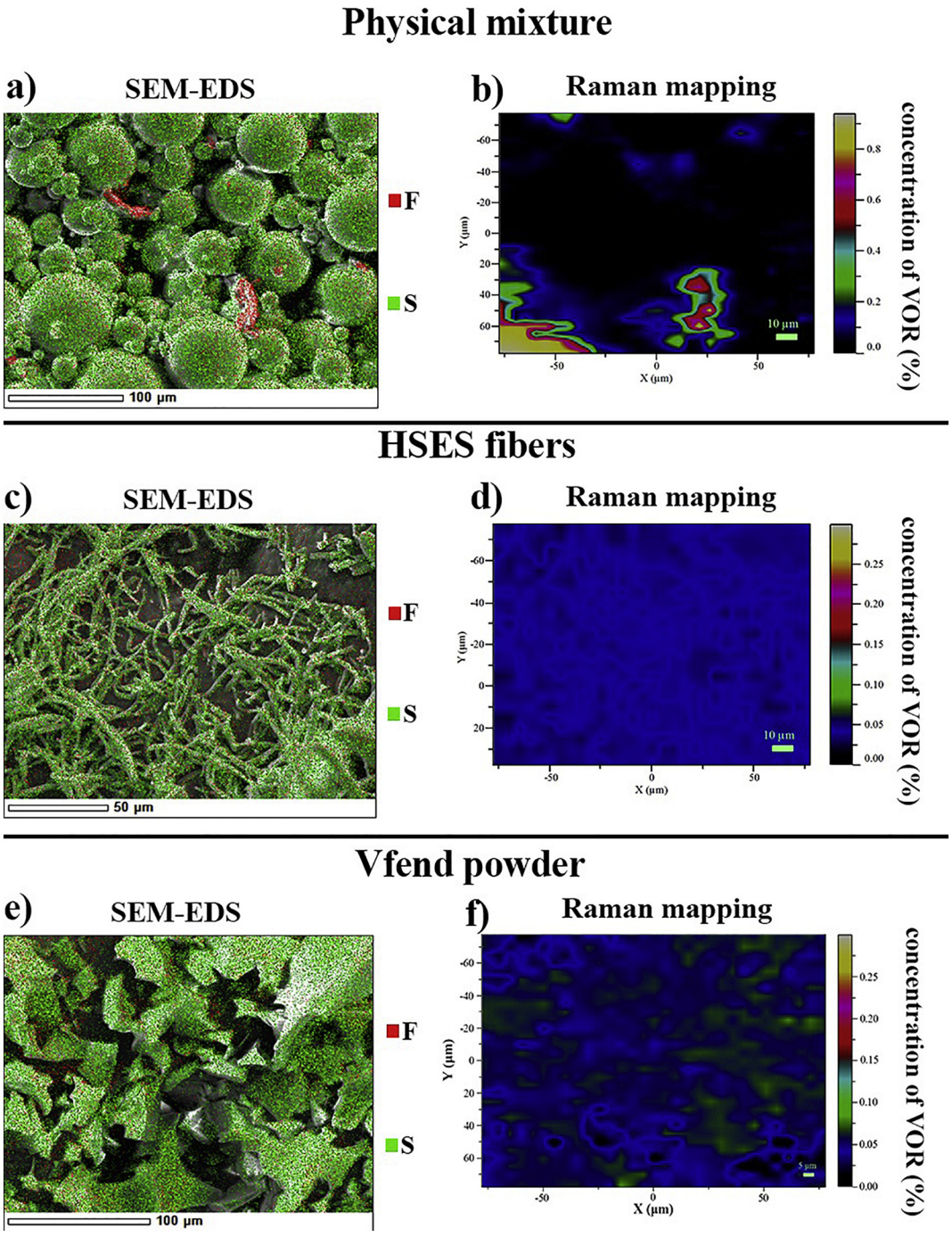

Fig. 8. Homogeneity study of the physical mixture of VOR and SBE-β-CD, the electrospun VOR–SBE-β-CD complex, and the Vfend® powder by SEM-EDS (a, c, e, respectively) and Raman mapping (b, d, f, respectively).

dosing, homogeneity of the VOR in a drug formulation is required. The fibrous material produced by HSES was compared to Vfend® and to the physical mixture of SBE-β-CD and VOR (Fig. 8).

As expected, the Raman chemical map (Fig. 8. b) of the reference physical mixture shows definite areas with high VOR concentrations indicating the uneven distribution of VOR in the mixture on a microscopic level. In contrast, VOR seems to be uniformly distributed in the HSES fibers, as well as in the Vfend® powder according to the maps (Fig. 8. d and f, respectively). However, the modeling error of the CLS evaluation was increased due to the fact that the analysis was performed using the reference spectrum of crystalline VOR (and not the amorphous). Therefore, the chemical mapping was performed with EDS as well. Fig. 8. a), c), and e) show colored elemental maps of the physical mixture, the electrospun material, and the Vfend® powder, respectively. Fluorine and sulfur can be used to differentiate VOR and SBE-β-CD from each other (VOR contains fluorine but not sulfur and SBE-β-CD contains sulfur but not fluorine). The coloring of the EDS maps was performed by following the fluorine (red) and the sulfur (green) signals. It can be seen that the physical mixture contains separate SBE-β-CD and VOR particles whereas the electrospun sample and the Vfend® powder contain SBE-β-CD and VOR evenly distributed. Heterogeneity of VOR cannot be seen either in the fibrous sample or in the Vfend® powder. These examinations imply that the VOR is molecularly dispersed both in the electrospun fibers and the Vfend® powder

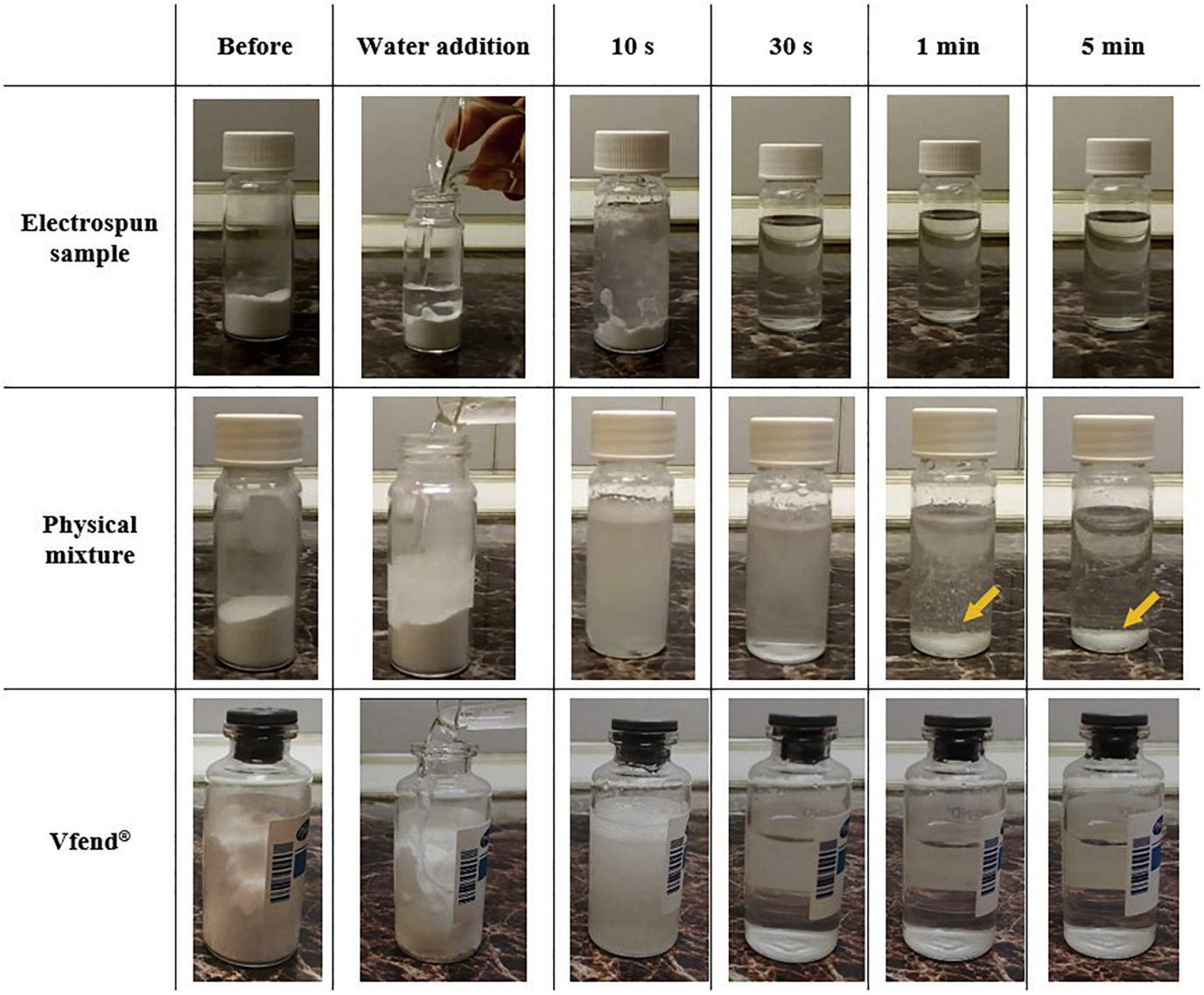

Fig. 9. Images of dissolution test of electrospun VOR–SBE-β-CD complex, the physical mixture, and Vfend®.

Table 2
Results of dissolution rate measurements (n = 3, except for Vfend®, where only 1 sample was measured). 100% equals the VOR concentration of 10 mg/mL.

	30 s	2 min
Electrospun sample	(100.9 ± 2.2)%	(102.4 ± 4.1)%
Physical mixture	(39.1 ± 1.0)%	(53.7 ± 3.0)%
Vfend®	103%	102%

as well.

3.5. Reconstitution test

Following the procedure described on the Vfend® package, the dissolution properties of the prepared electrospun complex were evaluated by adding 19 mL of water to a vial containing 3400 mg of electrospun material (comprising of 3200 mg SBE-β-CD and 200 mg voriconazole). The resulting concentration in the final solution was 10 mg/mL for VOR [27]. Vfend® and the physical mixture of SBE-β-CD and VOR were tested the same way as well to ensure a fair comparison of the different formulations.

The electrospun material could be ground easily by a hammer mill, which increased the previously low bulk density. As it is visible on the recorded images (the vials used in the experiment had the same dimensions), the milled fibers take up significantly less volume than the freeze-dried cake (Fig. 9). After the addition of water, the vials were shaken vigorously to dissolve parts stuck on the wall. The fibrous sample and Vfend® dissolved completely within 30 s (Fig. 9 and Table 2). SBE-β-CD in the physical mixture dissolved nearly instantly due to the good solubility of the cyclodextrin but the crystalline drug (marked with arrows in Fig. 9) persisted for a longer time. The difference between the dissolution rates of the electrospun sample and the physical mixture was confirmed by UV measurements after 30 s and 2 min of dissolution (Table 2). This proves that the enhanced specific surface area of the amorphous fibrous material provides fast dissolution, which makes electrospinning a feasible technology for the preparation of reconstitution injection dosage form.

4. Conclusions

Scaled-up ES was performed from aqueous solutions of VOR–SBE-β-CD complex to demonstrate the feasibility of HSES to produce a fast dissolving reconstitution injection dosage form, which allowed comparison to the marketed freeze-dried VOR formulation (Vfend®). Our

experiments showed that the incorporated VOR was amorphous and homogeneously dispersed in the produced fibers. The reconstitution test of the fibers confirmed the expected fast dissolution characteristics as a clear solution was obtained within 30 s.

The feeding rate of 300 mL/h used gives ~240 g solid product per hour, which is > 12× higher than the maximum reported productivity rate of ES for pharmaceutical application up to now. Therefore, a ~5 kg/day (about 1600 doses/day) production rate is possible with the HSES technology. This scaled-up, continuous and flexible manufacturing process seems to be capable of fulfilling the requirements of the pharmaceutical industry. Our experiments prove that HSES has the potential to replace freeze drying since it is a continuous, high-throughput process of very low energy consumption providing an economically viable production alternative. Furthermore, HSES was performed under ambient conditions, and therefore, it can become a platform technology as biopharmaceuticals can be processed as well.

Acknowledgment

The authors would like to thank Dr. Romána Zelkó and Éva Kiserdei for their help with the experiments. The assistance provided by Dr. János Madarász with the XRPD measurements is also appreciated. This work was supported from grants by National Research, Development and Innovation Office of Hungary (grant numbers: K-112644, PD-128241, KH-124541, and GINOP-2.1.1-15-2015-00541). Support of grant BME FIKP-BIO by Ministry of Human Capacities of Hungary (EMMI) is kindly acknowledged.

Declaration of interest

The authors report no conflict of interest.

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