

Comparison of Electrospun and Extruded Soluplus[®]-Based Solid Dosage Forms of Improved Dissolution

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ABSTRACT: Electrospinning (ES) and extrusion of a poorly water-soluble active pharmaceutical ingredient were used to improve its dissolution, which is a major challenge in the field of pharmaceutical technology. Spironolactone was applied as model drug and recently developed polyvinyl caprolactame–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus[®]) was used as carrier matrix and solubilizer. ES of the polymer matrix from ethanol solution was optimized at first without spironolactone and then the cosolution of the drug and the carrier was used for forming electrospun fibers. It resulted in real solid solution due to its very efficient amorphization effect. On the contrary, a low amount of crystalline spironolactone appeared in the extrudates according to Raman microscopy, X-ray diffraction (XRD), scanning electron microscopy (SEM) and energy-dispersive spectrometry (EDS). Raman microspectrometry had the lowest detection limit of spironolactone crystals compared with XRD and differential scanning calorimetry. Both ES and extrusion techniques resulted in significantly improved dissolution. Electrospun ultrafine fibers increased the dissolution more effectively, owing to the formed solid solution and huge surface. The developed continuous technologies demonstrate great potential to tackle the challenge of inadequate dissolution of poorly water-soluble drugs in several cases. © 2011 Wiley Periodicals, Inc. and the American Pharmacists Association *J Pharm Sci* 101:322–332, 2012

Keywords: electrospinning; improved dissolution rate; nanofibers; extrusion; polymeric drug delivery; solid solution; solid dispersion; Raman microscopy; nanotechnology; oral drug delivery

INTRODUCTION

One of the largest challenges in the field of pharmaceutical technology is the enhancement of drug release from orally taken solid dosage forms, as most recently developed active pharmaceutical ingredients (APIs) are poorly soluble in water.¹ The practices of high-throughput screening method and hit-to-lead optimization increases the ratio of drug candidate failures originating from nonadequate dissolution.^{2–4} This means that a huge amount of capital investment becomes worthless. Most of these drugs are classified as class II (low solubility but high permeability) of the Biopharmaceutical Classification System (BCS).⁵ The rate-limiting step of the absorption of these drugs

in the gastrointestinal tract is the drug dissolution.⁶ It is the formulation that can play a determining role in dissolution and bioavailability of these drugs.

Traditional and nontraditional methods are available in the pharmaceutical technology that can answer the challenges of dissolution of poorly water-soluble drugs.⁷

In recent years, different types of melt extrusion methods (conventional,^{8,9} supercritical,^{10–12} and lipid^{13,14}) have been developed to increase or control the release of the APIs. The technology and applications have been thoroughly reviewed by Breitenbach¹⁵ and Lakshman et al.¹⁶ These researches clearly showed the capability of melt extrusion to tackle the challenge of dissolution in several cases.

In the age of nanotechnology, new approaches became available for improving the dissolution of approved and candidate drug molecules. The applicability of electrospun nanofibers for this purpose is hardly

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known in the pharmaceutical industry, although it can combine several theoretical approaches for accelerating the dissolution and hence increase bioavailability of drugs that are poorly soluble in water:

- The dissolution rate can be improved effectively, according to the Noyes–Whitney equation, by increasing the surface area.¹⁷
- The amorphous form of the drugs generally dissolves faster than the relevant crystalline form because there is no need to overcome the lattice energy.^{18–20}
- The solubility of solid particles increases, according to the Ostwald–Freundlich equation, when the particle size falls and decreases within the “nano” region.^{21–23}
- Dissolution of poorly water-soluble drugs can be enhanced using solid solutions.^{24–26}
- Crystallization of supersaturated solution of poorly water-soluble drugs in the gastrointestinal tract can be hindered by polymer and surfactant content of the fibers.^{27,28}

Electrostatic spinning (electrospinning, ES) is a dynamically developing technology that has been primarily applied in the textile/filtration industry^{29–31} and numerous medical researches have been conducted in the field of wound dressing,³² wound healing,³³ and tissue engineering.^{34,35}

In contrast, ES is just slightly known in pharmaceutical technology because only a few papers are available dealing with the preparation of quickly dissolving nanofibers.^{36–41}

In this work, a relatively new polymeric solubilizer, Soluplus[®], was applied as a polymer matrix for forming solid solutions with a poorly water-soluble drug. Soluplus[®] playing the role of both matrix and active solubilizer (through micelle formation in water) can be considered as a member of the fourth generation of solid dispersions.^{42,43} Improved drug dissolution of several APIs of poor water solubility has been achieved by Soluplus[®] using extrusion techniques⁴³; however, no trial for electrospun fiber formation has been published yet. Thus the optimal conditions for ES had to be determined in the present study. Spironolactone, a synthetic steroid competitive aldosterone antagonist, has been selected as poorly water-soluble model drug.^{44,45}

The aim of this work was to investigate the applicability of extrusion and ES to improve drug dissolution for preparing immediate-release formulations of poorly water-soluble (BCS class II) spironolactone (promoting its bioavailability this way). Thorough characterization was accomplished to examine the physical status of spironolactone in the Soluplus[®] matrix to understand the drug release properties comparing the performance of differ-

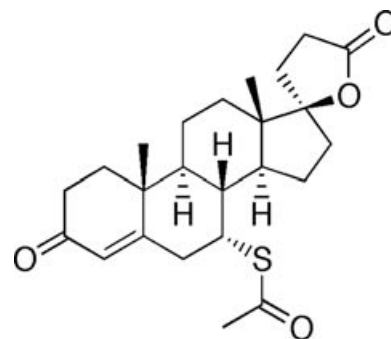


Figure 1. Chemical structure of spironolactone.

ent analytical methods such as differential scanning calorimetry (DSC), X-ray diffraction (XRD), scanning electron microscopy—energy-dispersive spectrometry (SEM–EDS), and Raman microscopy.

MATERIALS AND METHODS

Spironolactone (Fig. 1), a potassium sparing diuretic used as model API of poor water solubility (28 $\mu\text{g/mL}$, BCS II⁴⁵), originated from Sigma–Aldrich (Budapest, Hungary).

Soluplus[®] (Fig. 2), polyvinyl caprolactame–polyvinyl acetate–polyethylene glycol graft copolymer (molecular weight = $\sim 118,000$ Da) was kindly provided by BASF (Ludwigshafen, Germany).

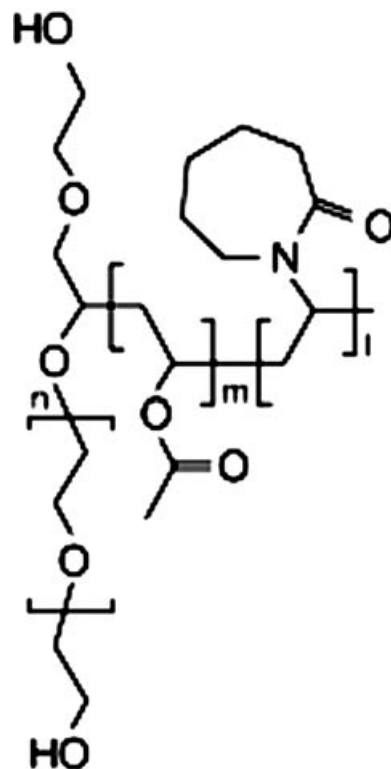


Figure 2. Chemical structure of Soluplus[®].

Table 1. Compositions of the Electrospun Solutions and the Extrudates

Samples Referred as	Ethanol (mL)	Soluplus [®] (g)	Polymer–solvent ratio (w/v%)	Spironolactone (g)
ES Opt 1	8	1.00	12.5	0
ES Opt 2	8	1.25	15.6	0
ES Opt 3	8	1.50	18.8	0
ES Opt 4	8	1.75	21.9	0
ES Opt 5	8	2.00	25.0	0
ES 10%	8	2.00	25.0	0.222
ES 20%	8	2.00	25.0	0.500
EX 10%	0	9.00	–	1.00
EX 20%	0	8.00	–	2.00

Preparation of Solutions for ES

The polymer of required amount was weighted and added into 4 or 8 mL solvent (ethanol) and stirred by a magnetic stirrer (VELP Scientifica, Usmate, Italy) at 600 rpm until the dissolution completed (Table 1). Then the appropriate amount of spironolactone was dissolved in the solution of the polymer (magnetic stirrer, 600 rpm) except in the cases of optimization of polymer concentration (without API) for achieving discrete, thin fibers using ES.

ES Process

The electrostatic spinner used for the experiments was equipped with NT-35 high voltage DC supply (MA2000; Unitronik Ltd, Nagykanizsa, Hungary). The electrical potential applied on the spinneret electrode was adjusted during the experiments between 10 and 35 kV. A grounded aluminum plate covered with aluminum foil was used as collector. The distance of the spinneret and the collector was 15 cm and the experiments were performed at room temperature (25°C). Polymer solutions were dosed by a SEP-10S Plus type syringe pump (Aitecs, Vilnius, Lithuania). The dosing rate was 8 mL/h.

Melt Extrusion

Extruded solid dispersions were prepared by HAAKE MiniLab (Thermo–Haake, Karlsruhe, Germany) system based on a conical twin-screw compounder. A dry premix of API and the polymer was introduced in the hopper of the mini extruder. The temperature and rotation speed were fixed at 120°C and 10 rpm. No recirculation was applied and the residence time was around 5 min. The obtained extrudates were ground before the dissolution tests and were sifted using a sieve (300 µm).

Differential Scanning Calorimetry

Differential scanning calorimetric measurements were carried out using a Setaram (Calure, France) DSC 92 apparatus (sample weight: ~10–15 mg, open pan, nitrogen flush). The temperature program consisted of an isotherm part of 1 min at room temper-

ature and subsequent linear heating from 25°C to 300°C with a rate of 10°C/min.

Raman Microscopy

Raman mapping was carried out using a Horiba Jobin–Yvon LabRAM (Longjumeau, France) system coupled with an external diode laser source (785 nm, 80 mW) and an Olympus BX-40 optical microscope. The samples were compressed into a flat tablet (Camilla OL95; Manfredi, Torino, Italy) and the surface was mapped with an objective of 10× magnification in order to investigate the homogeneity and morphology of the samples. The measured area was approximately 1 × 1 mm in all cases. The component concentrations were estimated with the classical least squares (CLSs) method using the reference spectra of the pure components collected on the same device under the same conditions. Visualized score maps were created with LabSpec 5.41 (Horiba Jobin–Yvon).

X-ray Diffraction

X-ray diffraction patterns of unmilled samples were recorded by a PANalytical (Amelo, the Netherlands) X'pert Pro MDP X-ray diffractometer using Cu-Kα radiation (1.542 Å) and a Ni filter. The applied voltage was 40 kV while the current was 30 mA. The samples were analyzed between 2° and 42° 2θ.

Scanning Electron Microscopy and Energy-Dispersive Spectrometry

Morphology of the samples was investigated by a JEOL 6380LVa (JEOL, Tokyo, Japan) type scanning electron microscope and elemental mapping was also accomplished using the energy-dispersive X-ray detector of the equipment. Each specimen was fixed by conductive double-sided carbon adhesive tape. Applied accelerating voltage and working distance were between 15 and 30 kV and 10 and 12 mm, respectively, and during the elemental mapping, the intensity of the detected X-ray radiation was between 5000 and 12,000 counts/s.

Static Headspace–Gas Chromatography/Mass Spectrometry

The amount of residual solvent in electrospun samples was determined using a static headspace–gas chromatography/mass spectrometry (HS–GC/MS) method. Sample (50 mg) was weighed to a 10 mL vial, and 1 g anhydrous sodium sulfate and 3 mL distilled water were added before climping. The sample was thermostated for 20 min at 80°C and agitated with 600 rpm. Sample (2.5 mL) was collected from the headspace with a 2.5 mL headspace syringe, which was thermostated at 105°C. The sample was injected to a split/splitless injector in split injection mode with a 10:1 split ratio. Injector temperature was set at 180°C. An Agilent 7890 gas chromatograph (Agilent Technologies, Waldbronn, Germany) was used with a RTX-VMS (20 m × 180 μm × 1 μm) column and separation was carried out isothermally at 40°C with a constant 1 mL/min flow of helium 5.0. The temperature of the transfer line, ion source, and quadrupole were set at 250°C, 230°C, and 150°C, respectively. The Agilent 5975C inert XL mass spectrometer (Agilent Technologies) was used in selected ion monitoring mode with target ion 45 and qualifier ions 31 and 46. External standard calibration was used, stock solution was prepared from ethanol 96% (v/v) (Merck, Budapest, Hungary) with distilled water.

In Vitro Dissolution

The dissolution studies were performed by Erweka DT6 dissolution tester (Erweka, Heusenstamm, Germany) using basket method. Prepared samples equivalent to 25 mg spironolactone and pure API were investigated in three parallel tests. The dissolution medium was 900 mL purified water maintained at $37 \pm 0.5^\circ\text{C}$ and stirred at 100 rpm. Samples (5 mL) were taken at predetermined time intervals. The concentration of spironolactone in the filtered samples was analyzed by a Hewlett–Packard 8452A UV-Vis spectrophotometer (Palo Alto, California) and quantified using an Excel-based deconvolution method, which separated the characteristic peak of spironolactone (244 nm) from the overlapping broad absorption peak of Soluplus®. Calibration of the deconvolution method was performed by solutions of appropriate drug–polymer ratios.

RESULTS AND DISCUSSIONS

Optimization of ES and Investigation of the Drug-Loaded Fibers and Extrudates

No information about the applicability of Soluplus® for ES both from solution and melt is available; therefore, optimization of the fiber forming process had to be done at first.

In order to prepare homogeneous, nonbeaded, thin, and discrete Soluplus® fibers, the parameters of the ES were changed systematically. Soluplus® fibers were expected to be formed if sufficient entanglements of the linear polymer can be achieved in solution. The number of entanglements depends on the concentration of the polymer solution. A higher concentration gives a higher chance for fiber formation due to the stronger interlacement of the polymer chains during the elongational flow induced by electrical forces.⁴⁶

Consequently, the adjustment of the concentration of the polymer in the solution is one of the conditions for producing a Soluplus®-based fibrous web. For this purpose, a series of Soluplus®–ethanol solutions were electrospun and the obtained morphologies were examined by a scanning electron microscope (Fig. 3).

At lower concentrations, beaded polymer fibers were obtained. The ratio of beads decreased with increasing polymer concentration, whereas at 25 w/v% Soluplus® concentration, practically bead-free, discrete fibers were formed apart from some very rare thickening (Fig. 3e top left corner). The diameters of these electrospun fibers are 300–900 nm. Thus, it can be concluded that the optimum Soluplus® concentration in ethanol to obtain thin, practically bead-free, discrete fibers is 25 w/v%.

Addition of spironolactone into the solution of Soluplus® does not have a significant effect on the ES process and on the diameter of the fibers. Electrospun spironolactone-loaded fibers were slightly thicker than pure Soluplus® fibers, but the diameters of most of the fibers were still under 1 μm (Fig. 4).

The formed thin electrospun drug-loaded Soluplus® fibers provide huge specific surface areas, which is promising from the aspect of dissolution improvement. Furthermore, the smooth fibers and the lack of visible crystals or particles suggest that the fibers contain amorphous spironolactone. This supposition was reinforced by the fact that the drying of the fibers (evaporation of ethanol) took place extremely rapidly ($<0.1\text{ s}^{47}$), allowing no time for the drug molecules to be arranged in crystalline form. Of course, this supposition needed further evidences, which were acquired in comparison with the samples made by extrusion.

In the case of extruded samples containing 10% or 20% API, the scanning electron microscopic images showed some inhomogeneities on the fractured surfaces (Figure 5 and 6). The number of inhomogeneities in the case of higher drug content (20%) was significantly higher.

For further analyses of these inhomogeneities, elemental mapping was accomplished using the energy-dispersive detector of the scanning electron microscope. As spironolactone contains sulfur (S),

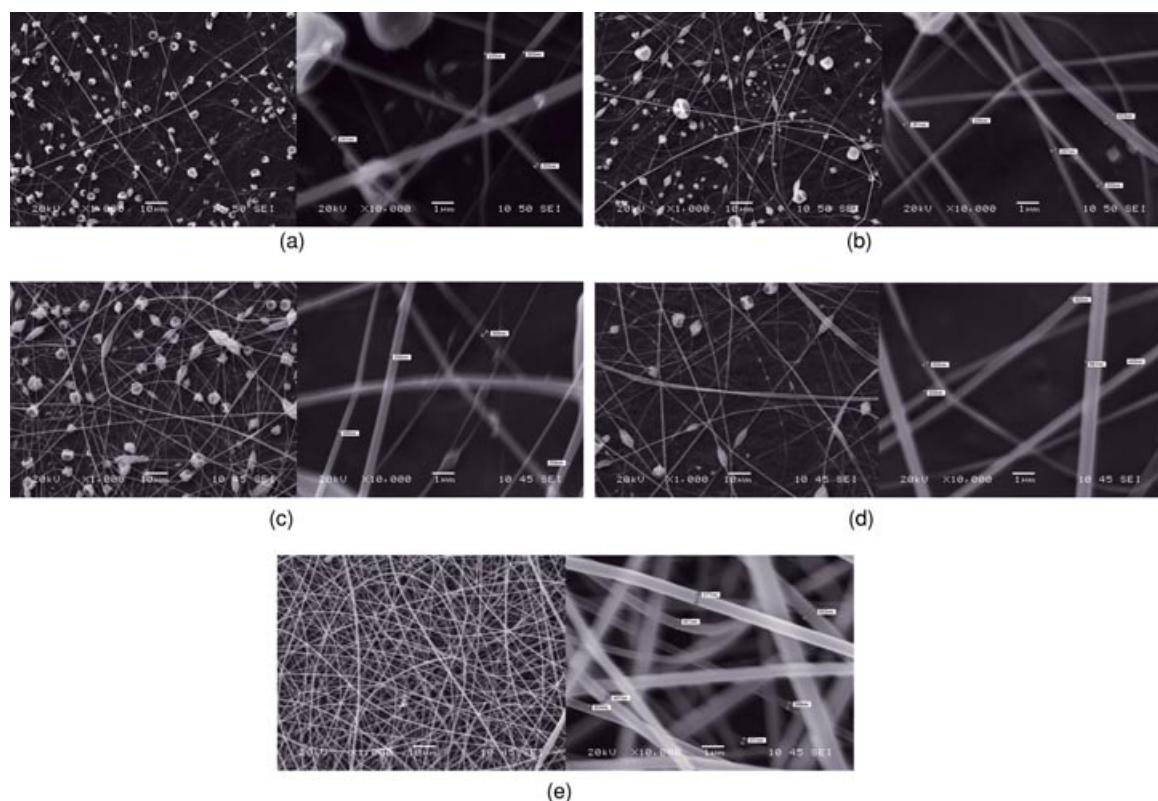


Figure 3. Scanning electron microscopic images of electrospun Soluplus[®] ethanol solutions, magnifications: 1000 $\times$ and 10,000 $\times$. (a) ES OPT 1: 1.00 g Soluplus[®] in 8 mL ethanol (12.5%). (b) ES OPT 2: 1.25 g Soluplus[®] in 8 mL ethanol (15.6%). (c) ES OPT 3: 1.50 g Soluplus[®] in 8 mL ethanol (18.8%). (d) ES OPT 4: 1.75 g Soluplus[®] in 8 mL ethanol (21.9%). (e) ES OPT 5: 2.00 g Soluplus[®] in 8 mL ethanol (25.0%).

being a good candidate for elemental mapping based on characteristic X-ray radiation, it can give valuable information about the distribution of spironolactone. Soluplus[®], containing no S atoms, does not influence this characterization method, thus, S distribution indicates spironolactone distribution (Figure 7 and 8).

Elemental mapping obtained by SEM-EDS shows that the distribution of S is inhomogeneous and increased intensity of characteristic X-ray radiation of S is detected in the environment of the visible inhomogeneities. It suggests that spironolactone aggregates or its residual crystals are present in the extru-

dates. The physical state of spironolactone (whether it is crystalline or amorphous) in these inhomogeneities is, however, not determined by SEM-EDS, thus further characterization was needed.

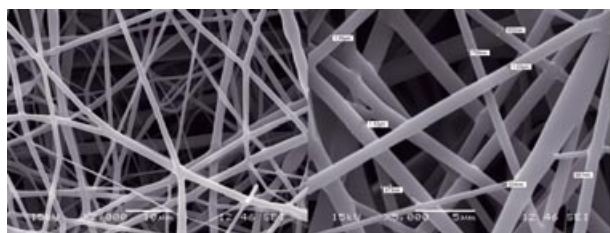


Figure 4. Scanning electron microscopic images of fibers containing Soluplus[®] spironolactone (ES 20%), magnifications: 2000 $\times$ and 5000 $\times$.

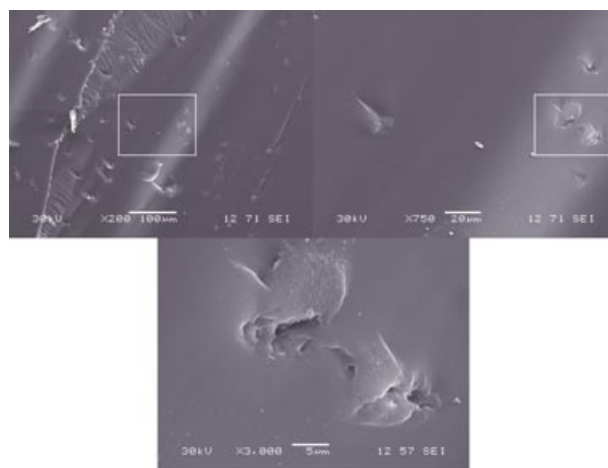


Figure 5. Scanning electron microscopic images of Soluplus[®] spironolactone extrudate (EX 10%), magnifications: 200 $\times$, 750 $\times$, and 3000 $\times$.

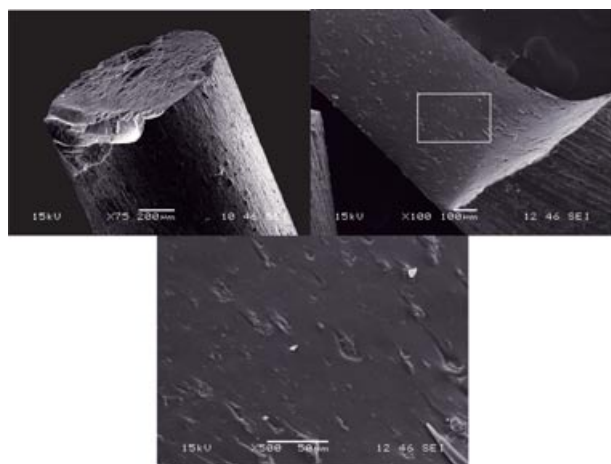


Figure 6. Scanning electron microscopic images of Soluplus® spironolactone extrudate (EX 20%), magnifications: 75 $\times$, 100 $\times$, and 500 $\times$.

Differential Scanning Calorimetry

Differential scanning calorimetry analyses were performed in order to investigate the physical status of the components in the samples. Besides electrospun and extruded samples, reference pure components (Soluplus® and spironolactone) and their physical mixture were examined (Fig. 9).

The relatively sharp melting peak of crystalline spironolactone in its DSC curve appeared at 213°C, whereas the broad glass transition (T_g) of Soluplus® was detected at around 79°C (showing the good extrudability of this polymer at low temperature without using a plasticizer). The melting peak of the drug appeared in the case of physical mixture; conversely, it disappeared in the cases of the extrudates and the

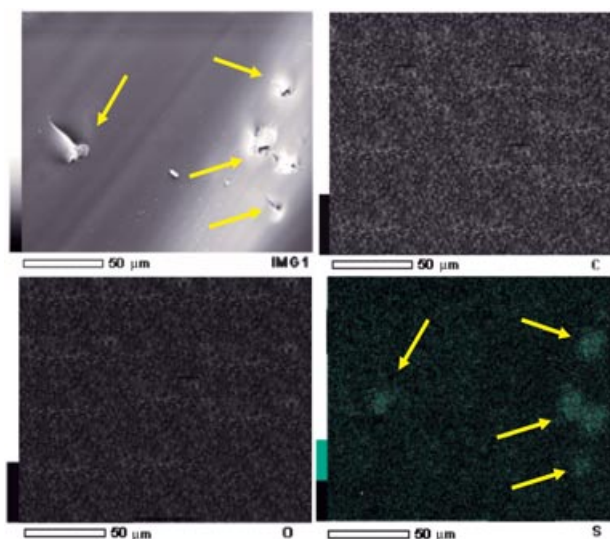


Figure 7. Energy-dispersive elemental mapping of Soluplus® spironolactone extrudate (EX 10%), magnification: 750 $\times$, distribution of C, O, and S atoms.

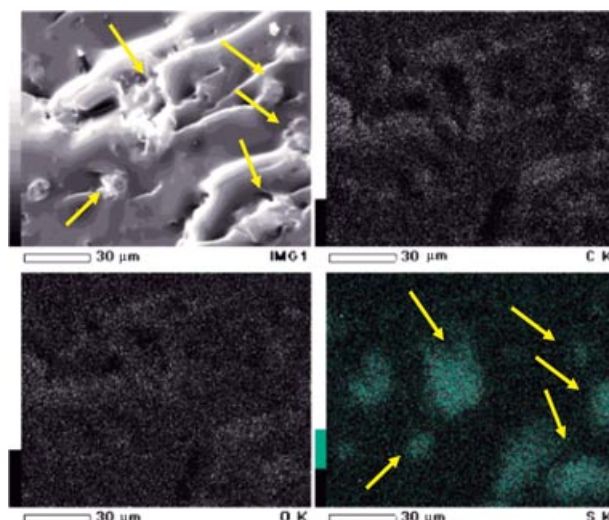


Figure 8. Energy-dispersive elemental mapping of Soluplus® spironolactone extrudate (EX 20%), magnification: 1000 $\times$, distribution of C, O, and S atoms.

electrospun fibers, suggesting the amorphous form of spironolactone in these samples. T_g of the extrudates and electrospun fibers decreased slightly as the interaction between the drug and the polymer released the polymer–polymer interactions. The plasticizing effect of spironolactone allows the segments to move at lower temperatures. According to the T_g values, the interaction between polymer and drug molecules is higher in the cases of electrospun samples (10%: 69°C, 20%: 64°C) than in the extrudates (10%: 76°C,

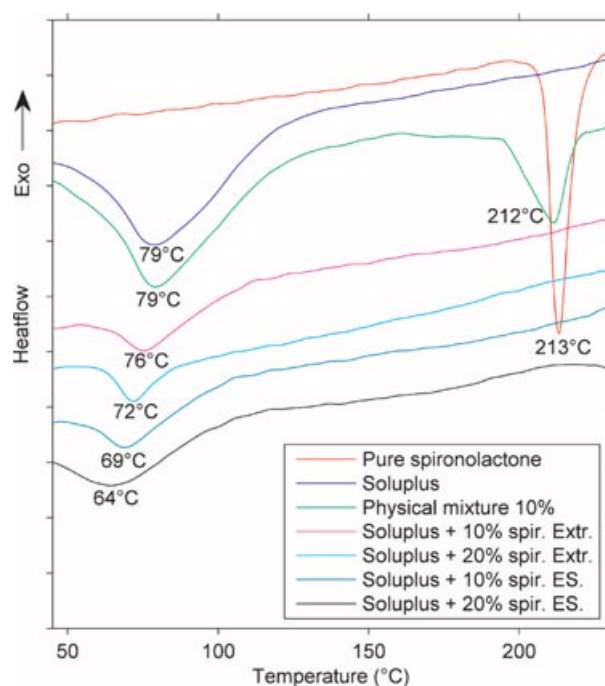


Figure 9. Differential scanning calorimetry curves of pure components, electrospun, and extruded samples.

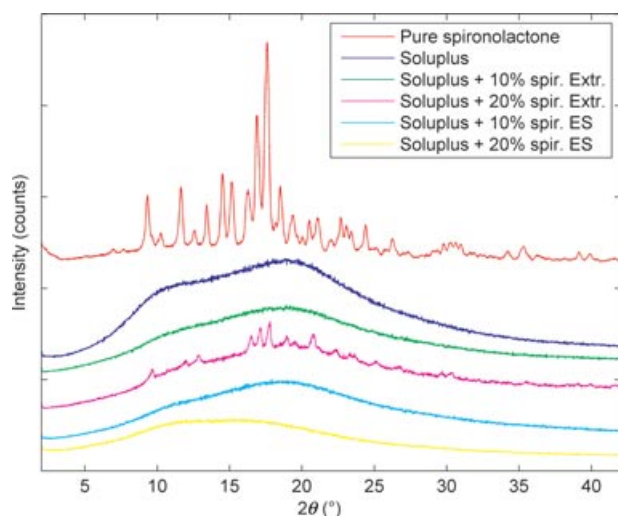


Figure 10. X-ray diffractograms of crystalline spironolactone, pure Soluplus®, electrospun fibers containing 10% and 20% spironolactone, and extrudates containing 10% and 20% spironolactone.

20%: 72°C). The difference, which is in agreement with the SEM and EDS results, suggests that the extrudates were probably not perfect solid solutions. Residual solvent can also decrease the T_g through its plasticizing effect; however, the determined residual solvent content by static HS–GC/MS was less than the detection limit (20 ppm) in the electrospun fibers 2 days after the production and DSC measurements were accomplished more than 2 days after the production. Thus residual ethanol could not have significant effect on the T_g value. Time dependence of the residual solvent content was also examined by HS–GC/MS and the ethanol levels were 520 ppm (± 30 ppm), 85 ppm (± 15 ppm), and less than 20 ppm (detection limit) 2 h, 5 h, 2 days after the production, respectively. These levels are much lower than the authorized maximum limit of ethanol in pharmaceutical products (5000 ppm).

X-ray Diffraction

For further characterization of the morphology of the prepared samples, XRD measurements were carried out and compared with the diffractograms of the pure polymer and the unprocessed spironolactone (Fig. 10).

According to XRD diffractograms, electrospun samples with 10% and 20% drug content proved to be amorphous and the extrudate with 10% drug content was amorphous as well because no peaks, indicating the presence of crystalline phase, could be observed in their diffractograms. However, in the case of the extrudate with 20% spironolactone content, the diffractogram indicates some peaks of the crystalline spironolactone. Morphology of the stored (3 months, 25°C, 40% relative humidity, open container) samples did not change significantly. No crys-

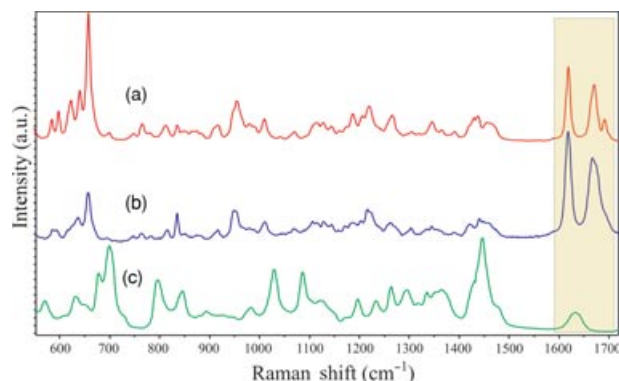


Figure 11. Raman spectra. (a) Crystalline spironolactone, (b) amorphous spironolactone, and (c) pure Soluplus®.

talline phase could be observed in the milled and unmilled extrudates with 10% drug content and in the electrospun samples after 3 months storage based on XRD measurements.

Raman Mapping

Raman mapping analyses were also carried out in order to obtain information about the spatial distribution of the active ingredient in the samples. The quantitative information provided by Raman spectra allows the determination of the homogeneity of the samples.⁴⁸ The Raman spectra show significant changes at the region of 1700 cm^{-1} when spironolactone is in amorphous state, thus the crystal morphology of spironolactone can be investigated as well (Fig. 11).^{45,49} The reference samples were the physical mixture of Soluplus® and spironolactone with the same compositions. The Raman maps show the calculated spectral concentrations of spironolactone between 0 (=0%) and 1 (=100%), which were obtained by CLSs method using the reference spectra of the pure components and different colors illustrating different concentration levels (according to the indicated scale of Fig. 12).

The inhomogeneous distribution of spironolactone in the physical mixtures is well observable on the visualized distribution maps and can also be evaluated by statistical histogram analysis of the calculated spectral concentrations (Table 2). High standard deviation (SD $\sim 10\%$ – 19%) and range between the minimum and maximum values (range $\sim 54\%$ – 78%) clearly demonstrate the inhomogeneous distribution of spironolactone in the physical mixtures. These representative values are considerably lower in the case of the extrudates (SD $\sim 2\%$ – 3% , range $\sim 24\%$ – 28%), which indicate relatively homogeneous distribution of spironolactone compared with prior published¹² relevant results and the visualized Raman maps prove the same. Distribution of spironolactone in the electrospun fibers is extremely homogeneous based on the

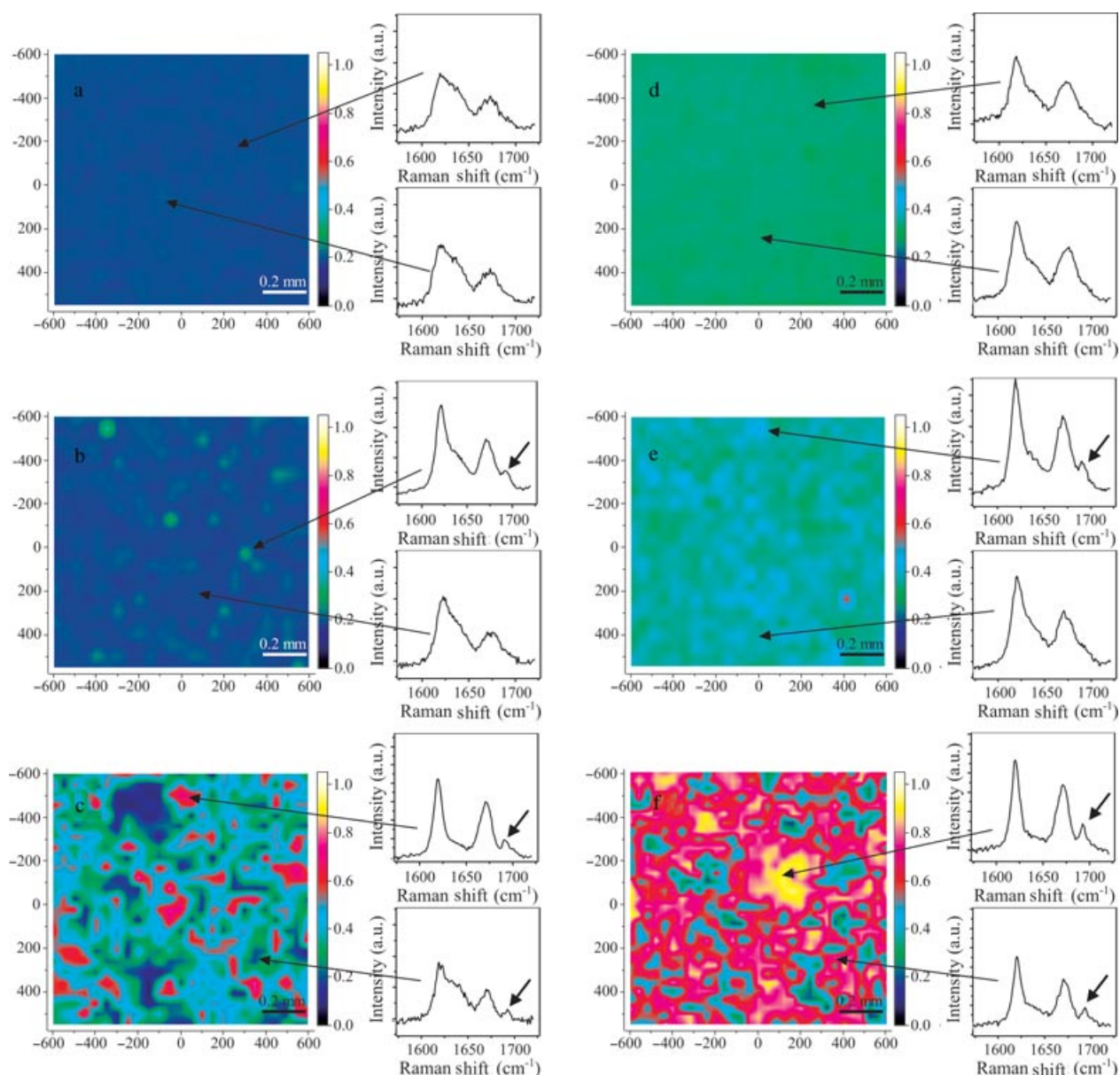


Figure 12. Raman maps of binary systems of Soluplus®–spironolactone with 10% and 20% drug content. (a) Electrospun Soluplus®–spironolactone 10% (ES 10%), (b) extruded Soluplus®–spironolactone 10% (EX 10%), (c) physical mixture of Soluplus®–spironolactone 10%, (d) electrospun Soluplus®–spironolactone 20%, (e) extruded Soluplus®–spironolactone 20%, (f) physical mixture Soluplus®–spironolactone 20%. Two representative spectra with high and low API concentration are shown on each map, peak of crystalline API indicated by an arrow.

Table 2. Results of Statistical Evaluation of Raman Spectral Concentration Maps

Statistical Attribute	10% Spironolactone			20% Spironolactone		
	Electrospun Fibers	Extrudate	Physical Blend	Electrospun Fibers	Extrudate	Physical Blend
Mean	19.82	20.01	18.44	35.79	37.66	36.96
Standard deviation	0.56	2.04	10.47	0.69	3.15	18.60
Minimum observed score	18.34	17.18	1.48	32.93	31.33	3.66
Maximum observed score	23.71	41.37	55.22	39.98	59.79	82.06
Range (maximum–minimum)	5.38	24.20	53.74	7.05	28.45	78.40

visualized Raman maps and the statistical data (SD $\sim 0.5\%$ – 0.7% , range $\sim 5\%$ – 7%). The almost perfect homogeneity of electrospun samples is the result of the extremely fast evaporation (<0.1 s)⁴⁷ of the solvent allowing the formation of a form glassy solid solution with homogeneity similar to the ethanol-based solution.

Besides the valuable information about the distribution of spironolactone, Raman maps provided definite results about the physical state of the spironolactone in each measured point of the sample. Raman peak of crystalline spironolactone at 1690 cm^{-1} assigned to the vibration of double bond between C and O in the thioacetyl group is broadened when spironolactone is in amorphous state and can merge with the baseline, which practically results in the disappearance of this peak.^{45,49} Broadening is due to the various neighborhoods of these double bonds, which perturb the vibration energies of the bonds compared with the molecules in crystalline phase where the neighborhoods of the bonds are the same (owing to the arranged and repetitive structure of spironolactone crystals).

Disappearance of this peak indicates the amorphization of spironolactone (Fig. 11). If this peak is well observable, it means that spironolactone crystals are present. As the peak of the double bond of thioacetyl disappeared, spironolactone molecules are in amorphous state in the electrospun samples (Fig. 12). Raman results confirmed the completely homogeneous and amorphous character of electrospun samples, which proves, in accordance with DSC, SEM, and XRD results, that these electrospun cosolutions of Soluplus® and spironolactone with 10% and 20% drug content form real solid solutions.

The Raman map of extrudate with 20% drug concentration showed spironolactone crystals (appeared as inhomogeneities and aggregates in SEM images in agreement again with the XRD results).

Although XRD and DSC results implied that spironolactone is in amorphous state in the extrudate with 10% drug content, the Raman mapping spectra of this sample demonstrated evidently that there exist a few crystals in the extrudates. Thus, the detection limit of the applied Raman spectrometry method is in this case significantly better than that of the XRD and DSC methods.

The prepared extrudated and electrospun solid formulations were considered promising for dissolution improvement of spironolactone due to the wettability and solubilizing property of Soluplus® and the formed huge surface area in the cases of the electrospun samples.

Figure 13 shows a comparison of dissolution profiles of electrospun samples, extrudates, and unprocessed crystalline spironolactone. In the first few

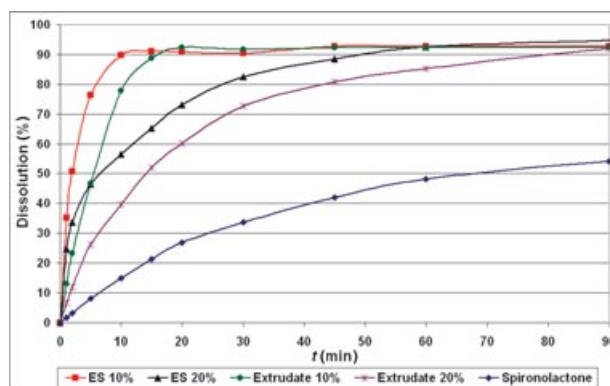


Figure 13. *In vitro* dissolution of spironolactone (dose 25 mg, 900 mL purified water, basket method, 100 rpm, 37°C , $n = 3$), ES 10%: electrospun Soluplus®-based fibers with 10% spironolactone content, ES 20%: electrospun Soluplus®-based fibers with 20% spironolactone content, Extrudate 10%: Soluplus®-based extrudates with 10% spironolactone content, Extrudate 20%: Soluplus®-based extrudates with 20% spironolactone content, Spironolactone: unprocessed crystalline spironolactone (particle sizes $<100\text{ }\mu\text{m}$).

minutes, electrospun samples had the highest dissolution rate due to the huge surface area of the very thin fibers according to the Noyes–Whitney equation and the amorphousness of the drug. The effect of the composition is very well observable as well: a higher polymer ratio increases the dissolution rate independently of the method of sample preparation. The relatively slow dissolution of spironolactone from the samples containing 20% spironolactone (dissolution time: ~ 60 min of electrospun fibres) (dissolution time: ~ 90 min of extrudates) is probably the consequence of the increased hydrophobicity compared with the materials containing 10% spironolactone. Electrospun Soluplus® samples with 10% API content achieving 10 min dissolution time (in contrast to the 53% dissolution of the reference at 90 min) confirms the capability of this technique to provide considerable improvement in the bioavailability of BCS II drugs. The dissolution of the electrospun samples did not change during their storage (3 months, 25°C , 40% relative humidity); however, the dissolution of the extrudates changed slightly. More detailed investigation of the stability of the extrudates is planned to publish together with further optimization of the extrusion process (drug content, residence time, and temperature), which is an ongoing work.

CONCLUSIONS

Considerable dissolution improvement of BCS class II model drug, spironolactone, was achieved by ES or extrusion technology using Soluplus® as drug carrier polymer matrix. ES showed much higher potential

for the amorphization of spironolactone in Soluplus® matrix than the applied extrusion process. The very efficient amorphization effect of ES is due to the ultrafast evaporation of the solvent, which results in solid solution of the drug in the polymer matrix. The residual ethanol content decreased below the detection limit (20 ppm) of static HS–GC/MS method after 2 days, whereas the authorized maximum limit of ethanol in pharmaceutical products is 5000 ppm.

The developed melt extrusion method also has several advantages. It is a robust, solvent free, continuous process with potentially very high throughput. Melt extrusion technology is spreading more and more in pharmaceutical industry. Although the advantages of ES has not been recognized in the pharmaceutical industry yet, owing to the simplicity, efficacy gentleness, and scaling up capability of this technique, an increasing number of applications of ES-based processes is anticipated in the near future in the pharmaceutical industry.

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