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Single Step Assembly of Biomolecule-Loaded Sub-Micron Polysulphone Fibres

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Abstract

Enrichment of chemically resistant hydrophobic polymers with polar biomolecules is relevant to the production of fibre-based drug delivery devices, adsorptive filtration media, as well as fibres for selective molecular recognition of antibodies, enzymes and nucleic acids. Polysulphone (PSU) is an amorphous polymer possessing high-strength, rigidity and excellent thermal stability. The preparation of PSU spinning solutions requires lengthy dissolution times at elevated temperature that tends to degrade commixed polar biomolecules. Using the highly polar metabolite creatinine, as a model system, a variety of co-solvents was evaluated for electrospinning commixed solutions of PSU and creatinine at room temperature. Selection of solvent systems was informed by Hansen solubility parameters. A binary system of N, N-dimethylacetamide (DMAc): methanol (4:1) was not found to be a suitable solvent because of the need for elevated temperature (80°C) to facilitate dissolution, and a binary solvent system of N, N-dimethylformamide (DMF):dimethyl sulfoxide (DMSO) (3:2) resulted in nozzle blockage during spinning. A binary system of DMAc:DMSO (13:7) enabled spinning of PSU with creatinine at ambient temperature and sub-micron fibres substantially free of beads were

produced continuously via electrospinning, yielding fibre diameters in the range 540-890 nm. The presence of creatinine was confirmed by High Performance Liquid Chromatography (HPLC) and fibre morphology was examined by Scanning Electron Microscopy (SEM).

Keywords: Electrospinning, Nanofibres, Polysulphone, Biomolecule, Creatinine

1. Introduction

Sub-micron fibres of high specific surface area with properties enhanced by chemical enrichment of chemically resistant polymers are important for the development of devices for use in regenerative medicine, adsorptive apheresis, blood filtration, as well as in the delivery and release of drugs and biological agents such as proteins.[1-4] For example, in the preparation of alternative molecular recognition membranes, a template molecule is incorporated in the spinning solution, which is later eluted after fibre or membrane production to provide chiral recognition sites. To facilitate production, a co-solvent system is often needed in which both the polymer and biomolecule components could be dissolved. The resultant templated fibres are potentially useful as sorbents or sensors provided rigid, hydrophobic polymers are selected to ensure structural stability of the template cavity.[5, 6] Similarly in the preparation of drug delivery systems, the ability to commix both the fibre forming polymer and the drug in a co-solvent without degradation of the therapeutic compound prior to manufacture is important.

Many hydrophobic, thermoplastic polymers used in medical devices particularly polysulphones (PSU), polyphenylene sulfide (PPS), liquid crystal polymers(LCP), polyethylenimine (PEI), polyamide-imide (PAI), poly(aryl-ether-ether-ketone) (PEEK) have high chemical resistance to solvents, which means spinning solutions containing such polymers are likely to be incompatible with water soluble biomolecules. Chemical resistant polymers with a rigid and highly cross-linked network structures often require lengthy dissolution times at elevated temperature that are likely to degrade biomolecules that need to be present in the solvent.[7] Incorporation of biomolecules in to such polymers without chemical degradation can therefore be highly challenging.

Accordingly, the aim of the present work was to identify suitable co-solvents for spinning of PSU using a model, highly polar water-soluble biomolecule, creatinine ($C_4H_7N_3O$) at room temperature. Creatinine, one of many uremic toxins, is the metabolic product of phosphocreatine produced by muscular activity and is a cyclic derivative of creatine that is soluble in both water and methanol.[8]

PSU is an amorphous polymer that possesses high-strength, rigidity and excellent thermal stability, maintaining these properties over a wide temperature range.[9-11] Previous studies have highlighted the chemical stability of PSU, and poor solubility in supercritical fluids (SCF), butane, dimethyl ether (DME), chlorodifluoromethane, and difluoroethane even at temperatures as high as 200°C and pressures of 2100 bar.[12] Solubility was observed in DME with the addition of 24–65 wt.% tetrahydrofuran

(THF) or N,N-dimethylformamide (DMF), at room temperature/pressure[12] but such a solvent system is likely to denature biomolecules present in a commixture.

Dissolution of PSU requires solutions to be stirred at elevated temperatures between 45 °C to 120 °C.[7, 8, 13] . Wang *et al.*[7] dissolved PSU powder in N,N-dimethylacetamide (DMAc) at 120°C with vigorous stirring to form a homogenous solution with Poly(N-vinyl-2-pyrrolidone) (PVP). Li *et al.*[8] dissolved 25 g PSU pellets in 90 ml DMAc and 10 ml acetone with stirring for 4 hr at 45 ºC.[8] Previous studies producing PSU electrospun webs have frequently used DMF and DMAc as the solvent system,[7, 13, 14] however, dissolution of creatinine is impossible in the solvents that are normally used to dissolve PSU to make an electrospinning solution.

Creatinine is a polar molecule and is known to be soluble in both water and methanol but sparsely soluble in acetone. Thus, one cornerstone of this work was to identify an appropriate co-solvent system for PSU and creatinine that would enable dissolution of both components at near ambient temperature to avoid creatinine degradation and facilitate electrospinning.

2. Material and Methods

2.1 Materials

PSU pellets (Mw: 35,000) were purchased from Aldrich Chemical Co. and Creatinine (99%) was obtained from Acros Organics Co. Dimethyl sulfoxide (DMSO), N,N-dimethyl formamide (DMF), methanol, acetone, N,N-dimethyl acetamide (DMAc) and ethanol were all purchased from Sigma-Aldrich Co. and used without further purification. Di-sodium hydrogen phosphate and citric acid were purchased from Fluka Co.

2.2 Preparation of Polysulfone (PSU) solution

PSU pellets were dried over night at 90°C and were then dissolved in a variety of solvent systems (Table 1).The solvent systems and ratios were selected based on freedom from precipitation during preparation of the spinning solution and the spinnability of the system. Dried PSU pellets were added slowly to the solvent with rapid stirring at room temperature for 20 min. For DMF: methanol (4:1 and 3:2), DMAc: methanol (4:1 and 3:2) and DMAc: methanol: acetone (Table 1), the solutions were refluxed at 80°C until a clear solution was obtained.

Table 1. The solubility of PSU in different solvent systems

Solvent	Ratio (v/v)	PSU concentration (wt. %)	Temperature (°C)	Time (hr)	Result
DMF: methanol	80:20 60:40	10	80	24	Precipitation
DMAc: methanol: acetone	60:20:20 70:20:10	10	80	24	Precipitation
DMAc: methanol	60:40	10	80	12	Precipitation
DMAc: methanol	80:20	10 15 18 22	80	9	Dissolve
DMF: DMSO	60:40	22	Ambient temperature	5	Dissolve
DMAc: DMSO	65:35	22	Ambient temperature	5	Dissolve
DMAc: DMSO	20:80	22	Ambient temperature	24	Dissolve

2.3 Electrospinning

Electrospinning was performed in horizontal alignment with the polymer solution loaded into a 5 ml syringe (Fortuna and Graff) connected to a blunt ended Luer lock metal needle (20 gauge, Sigma-Aldrich). The syringe was mounted in to a syringe pump (KD Scientific) connected to a high voltage power supply (Glassman Inc.). Electrospinning was performed inside a fume cupboard under ambient conditions at a fixed voltage of 25kV and a tip–to–collector distance of 130 mm. The spinning solution feed rate was varied between 0.04 to 0.02 ml min^{-1}. Flat aluminium foil collectors were used throughout.

2.4 Scanning Electron Microscopy (SEM) and image analysis

Samples were sputter coated then imaged with a field emission SEM (Camscan series 4 environmental) to observe fibre morphology and web structure. Mean fibre diameters in the collected webs were determined directly from the SEM images by image analysis (Media Cybernetics, Image Pro-Plus 7) by measuring the diameter of 50 individual fibres. To estimate porosity (*P*) in the webs, binary SEM images (BMP format) were prepared by image thresholding techniques and determined from the mean intensity of the image:

$$P = (1 - \frac{n}{N}) \times 100 \quad \textbf{(Equation 1)}$$

Where, *n* is the number of white pixels and *N* is the total number of pixels in the binary image.[15, 16]

2.5 Pore Size

Pore size characterisation of the as-spun webs was undertaken by capillary flow porometry (PMI model App122 AE). All pore structure characteristics including pore size at the bubble point and pore size distribution were computed from the measured differential pressures and gas flow rates. In the dry sample, the flow rate increases with pressure. In the case of wet samples that are pre-saturated with a liquid of known surface tension (Galwick liquid: surface tension =0.015Nm^{-1}), there is initially no flow

because all the pores are filled with the liquid. At a certain pressure the injection of nitrogen gas empties the largest pore (Bubble point) and gas flow commences through the wet sample. Further increases in pressure progressively empty the smaller pores and the flow rate increases until all the pores are empty and the flow rate through the wet sample is the same as that through the dry sample.

2.6 Molecular Analysis

The presence of creatinine was verified by High Performance Liquid Chromatography (HPLC). The HPLC system comprised of a Kontron HPLC360 auto sampler, HPLC332 UV-vis absorbance detector and HPLC325 pump. The system was controlled via a Dionex UCI-50 Universal Chromatography interface using Chromeleon v.6.80 software. The analytical column was a 150 × 4.6 mm Thermo Scientific BDS Hypersil column packed with 5 micron ODS. The mobile phase comprised25 mM sodium phosphate at pH 3.5 with 0.1% w/v sodium dodecyl sulphate (eluent A) and methanol (eluent B) and a gradient programme was used as follows: 0.0 min 30% B, 6.0 min 70% B, 6.1 min 100% B, 7.9 min 100% B , 8.0 min 30% B , 18.0 min 30% B. The flow rate was 0.8 ml min^{-1}, the injection volume was 20 μL and the eluate was monitored at 254 nm. The expected retention time of creatinine was 4.8 min. Electrospun webs were peeled off the collector and a fixed mass of the sample was added to 50 ml of distilled water and shaken at a constant temperature of 25ºC for 1 hr.

3. Results and Discussion

3.1 Electrospinning of PSU in Polar Binary Solvent Systems

Table 1 summarises the binary and ternary solvent systems. The selection of solvents was informed by previous studies of the solubility of PSU and creatinine[8, 13, 17] and by the Hansen theory of solubility.[18, 19] The solubility parameter (δ) is a numerical value that characterises the relative solvency behaviour of a specific solvent. The concept that solubility is related to the internal energy of solvents and solutes was first introduced by Hildebrand as the square root of the Cohesive Energy Density (CED) of the material. Hansen parameters extended the concept that the total cohesive term and thus the total solubility parameters (δ) of the total Hildebrand value may be divided into the dispersion component (δ_d), polar component (δ_p) and hydrogen bonding component (δ_h) as follows[19]:

$$\delta_t = \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2} \qquad \text{Equation (2)}$$

The SI unit for all Hansen parameters is $MPa^{½}$. Values of δ_d, δ_p, and δ_h at room temperature for a variety of PSU solvents are presented in Table 2. According to Hansen, an approximately spherical area of solubility may be constructed in a three-dimensional coordinate system of δ_d, δ_p, and δ_h. The radius of that sphere, $9.40MPa^{½}$, for PSU, is referred to as the interaction radius (R). A polymer is likely to be soluble in a solvent if the distance between the solvent and the centre of the polymer solubility

sphere ($D_{(s-p)}$) is less than the radius of interaction for the polymer ($D_{(s-p)} < R$).[19] Accordingly, DMAc, acetone, DMF and DMSO would be expected to dissolve PSU, because the distance ($D_{(s-p)}$) is less than the radius of interaction (R) of PSU (Table 2).

Table 2.Solubility parameters of various solvents and Polysulphone (PSU)

	Solubility Parameter ($MPa^{1/2}$)					
Solvent	δ	δ_d	δ_p	δ_h	$D_{(s-p)}$*	R
Dimetylacetamide (DMAc)	22.77	16.80	11.50	10.20	5.50	-
Acetone	19.93	15.50	10.40	7.00	6.29	-
Dimethylformamide (DMF)	24.86	17.40	13.70	11.30	7.09	-
Dimethylsuphoxide (DMSO)	26.70	18.40	16.40	10.20	8.5	-
Ethanol	26.50	15.80	8.80	19.40	13.52	-
Methanol	29.6	15.10	12.30	22.30	17.16	-
Water	47.83	15.60	16.0	42.3	36.55	
Polysulphone (PSU)	21.50	18.50	8.50	7.00	-	9.40

* $D_{(S-P)} = [4(\delta_{dS}-\delta_{dP})^2 + (\delta_{pS}-\delta_{pP})^2 + (\delta_{hS}-\delta_{hP})^2]^{1/2}$

δ_{xs}= *Hansen component parameter for the solvent.*

δ_{xp}= *Hansen component parameter for the polymer.*

Creatinine is highly soluble in water and methanol and among the reported solvents selected for electrospinning of PSU, slightly soluble in DMSO.[8] However, based on Hansen theory, water and methanol are not solvents for PSU (Table 2). The Hansen sphere $(D_{(s-p)})$ of methanol and water are 17.16 and 36.55 $MPa^{1/2}$, respectively, which is not within an appropriate range for the dissolution of PSU. Incorporation of water also decreases the overall evaporation rate during electrospinning.[20] Therefore, methanol, which is a solvent for creatinine, was selected as a component in the preparation of PSU binary and ternary solvent systems [Table 1]. In some cases, addition of methanol altered the solvent ratio leading to precipitation of the PSU, but the binary solvent system of 4:1 DMAc: methanol led to PSU dissolution (Table 1) at 80ºC.The Hansen sphere $(D_{(s-p)})$ of DMAc and DMF are 5.50 and7.09 $MPa^{1/2}$, respectively, which indicates that DMAc is a better solvent for the dissolution of PSU than DMF (Table 2). Furthermore, compared to other solvents (acetone, DMAc and DMF) the distance $(D_{(s-p)})$ of DMSO to the radius of interaction (R) of PSU was not too high, in other words, DMSO, itself was not able to dissolve PSU properly. This was confirmed in preliminary results (not shown herein).As a result, binary and ternary solvent systems of acetone, DMAc, DMF and DMSO were also evaluated to improve the electrospinnability of PSU enriched with creatinine(Table 1). Preparation of PSU solutions in binary solvent systems of DMF: methanol (4:1 and 3:2) were hampered due to precipitation of polymer during the stirring process (Table 1). Based on Hansen

parameters ($D_{(s-p)}<9.40$), the solubility of PSU in DMAc is greater than DMF (Table 2). Therefore, all experiments were conducted using DMAc, methanol and DMSO. The solvent ratios were selected based on previous studies[8, 13, 17, 21] . Precipitation of PSU occurred in the binary solvent system of 3:2 DMAc: methanol even at a low PSU concentration of 10wt. %.Due to the insolubility of PSU in methanol, the ratio of DMAc: methanol was changed from 3:2 to 4:1.

The suitability of a 4:1 DMAc: methanol system was assessed in terms of the freedom from precipitation during preparation of the spinning solution and the spinnability of the resulting solution. Spinnability in this context refers to freedom from needle blockages, consistency of fibre morphology, and freedom from bead and spindle defects in the web. Therefore in the binary system of 4:1 DMAc: methanol, the PSU concentration was varied from 10 to 22 wt. % (Fig. 1 A, B and C). No fibres were obtained at a concentration of 10 wt. % due to a low solution viscosity. As expected, as polymer concentration increased from 15 wt. % to 22wt. %, electrospunmean fibre diameter increased from 600nm to 1.06μm. Morphologically, more uniform fibres free of bead defects were obtained at the highest polymer concentration of 22 wt. %, Fig.1C. Polymer concentration is known to be one of the most effective variables for controlling morphology and diameter[22-27]. While webs containing PSU and creatinine could be successfully produced using a binary solvent system of 4:1 DMAc: methanol (Fig.1C)

dissolution of PSU in binary solvents containing either DMAc or DMF with methanol could not be obtained below 80°C (Table 1).

The limitations of solvent systems containing methanol were addressed by substituting a polar aprotic solvent (DMSO) for methanol. Creatinine is slightly soluble in DMSO and based on the Hansen solubility parameters, the distance for DMSO, $D_{(s\text{-}p)} = 8.5\ MPa^{1/2}$ is less than the radius of interaction (R< 9.40) of PSU (Table 2).DMSO is a polar aprotic solvent that dissolves both polar and non-polar compounds and is miscible with a range of organic solvents including water.[28] Binary solvent systems of DMF: DMSO (3:2) and DMAc: DMSO (13:7) were found to dissolve PSU and creatinine at room temperature. The ratio of DMAc: DMSO (13:7) has been selected based on the non-precipitation of PSU in the solvent system. In the case of DMAc: DMSO (1:4) satisfactory spinning conditions could not be established and continuous electrospinning was hampered due to blockage of the nozzle tip. However, electrospun PSU webs were successfully spun from two binary solvent systems (Table 1), specifically DMF: DMSO (3:2) and DMAc: DMSO (13:7) as indicated in Fig.1 (D and E).

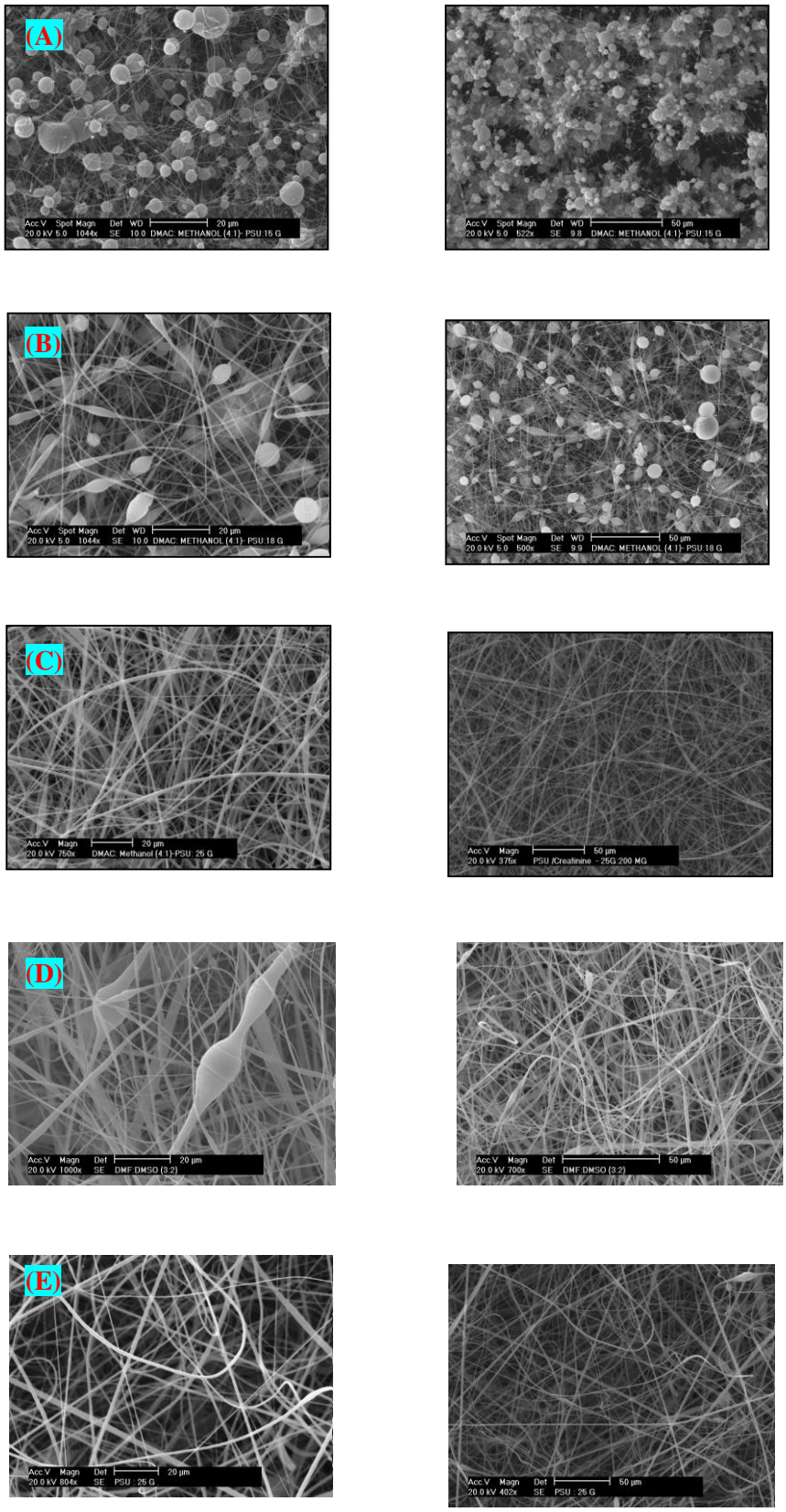

(A)
(B)
(C)
(D)
(E)

Figure 1. SEM micrographs showing the effect of solvent systems and concentration on the structure and morphology of resulting PSU electrospun webs. Mag. 522 X- 1044 X - Electrospinning solvents: (A) PSU 15 wt.%, DMAc: methanol (4:1); (B) PSU 18 wt.%, DMAc: methanol (4:1);(C)PSU 22 wt.%, DMAc: methanol (4:1); (D) PSU 22 wt.%, DMF: DMSO (3:2); (E) PSU 22 wt.%, DMAc: DMSO (13:7).

3.2 Formation of PSU-Creatinine Nanofibrous Membranes using a Binary Solvent System

Both DMF: DMSO (3:2) and DMAc: DMSO (13:7) spinning solutions enabled production of electrospun fibre webs (Fig.1). Electrospinning from DMF: DMSO (3:2) produced a higher mean fibre diameter of 1.1μm (range: 650 nm - 1.90 μm), compared to 630nm (range: 540 nm to 890 nm) for DMAc: DMSO (13:7).Long-term continuous electrospinning of DMF:DMSO (3:2) was partially interrupted by nozzle blockages, whereas DMAc: DMSO (13:7) consistently produced high quality fibres, free from beads and stable spinning conditions at ambient temperature(Fig.1E).

Spinning solutions were prepared of 22 wt. % PSU and 2 wt. % creatinine in DMAc: DMSO (13:7). Solutions were stirred for 5 hr at ambient temperature. Electrospinning was conducted at 25kV, a flow rate of 0.004 $mlmin^{-1}$ and a tip to collector distance of 130 mm. The presence of creatinine in the as-spun PSU nanofibres was confirmed by HPLC.[29] The retention time of creatinine was 4.8 min (Fig.2) and an absorption peak was detected in the sample solution was characteristic of creatinine (Fig.2).

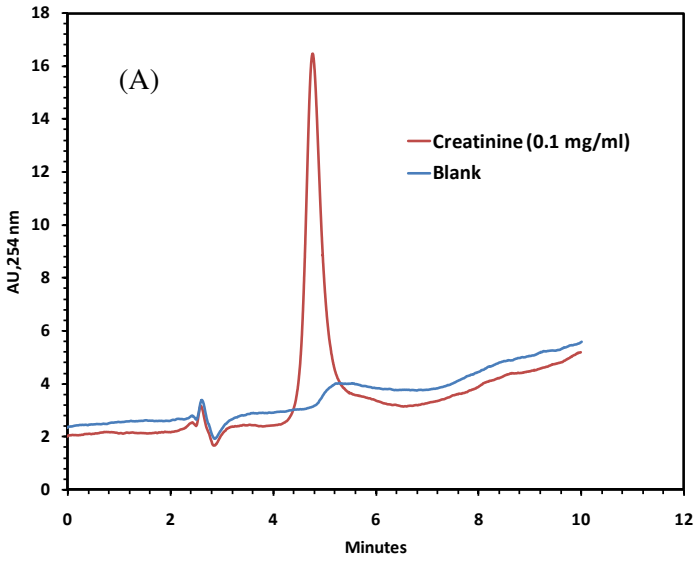


Figure 2. (A) Chromatogram of Creatinine (0.1 mg ml $^{-1}$): Creatinine retention time 4.8 min

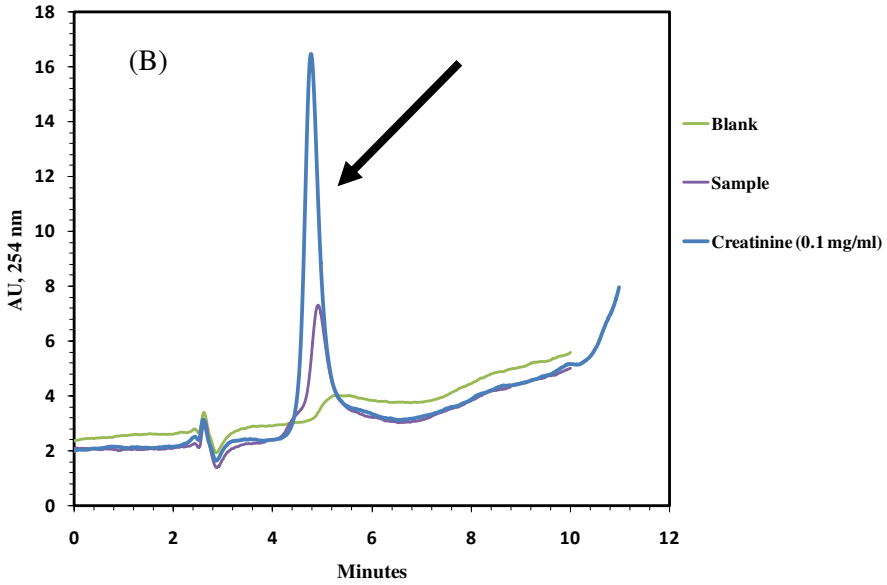


Figure 2. (B) Detection of Creatinine in PSU sub-micron fibres (22 wt.% PSU and 2 wt.% creatinine in DMAc/DMSO (13:7) after washing in 50 ml of distilled water and shaken at a constant temperature of 25ºC for 1 hr. The mobile phase comprised of 25 mM sodium phosphate pH 3.5 with 0.1% w/v sodium dodecyl sulphate (eluent A) and methanol (eluent B). The injection volume was 20 µl and the eluate was monitored at 254 nm. Retention time of Creatinine is 4.8 min.

Successful incorporation of creatinine within the PSU sub-micron fibres was therefore confirmed. SEM micrographs of the PSU-creatinine webs produced from DMAc: DMSO (13:7) are given in Fig.3. The fibres presented cylindrical morphology with diameters in the range 470-870 nm, with a mean of 630 nm.

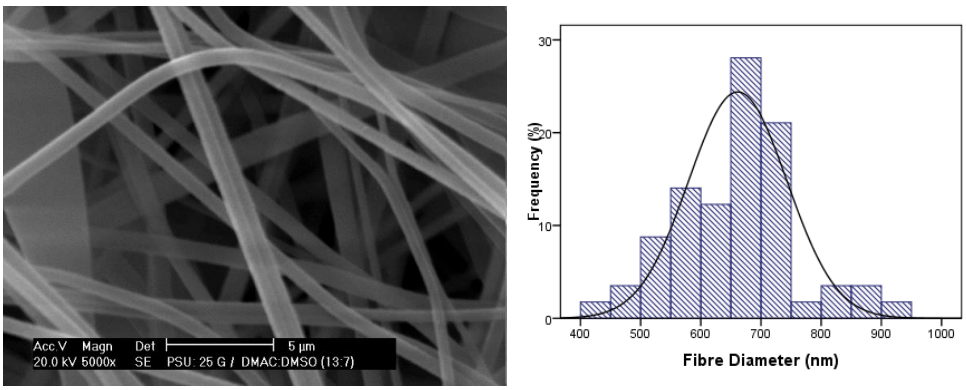


Figure 3. SEM micrographof PSU/Creatinine web produced from DMAc: DMSO (13:7) Binary solvent system. Mean fibre diameter = 630 nm; Mag 5000 X.

The addition of creatinine molecules to the binary solvent solution resulted in no discernible changes in fibre morphology. The wet stability of the as-spun PSU-

creatinine fibres was determined by immersion in distilled water and ethanol for 48 hr. Electrospun webs in the range of 540-890 nm (mean = 630 nm) were carefully peeled off the aluminium collector and immersed in water and ethanol at 25°C. After 48 hr immersion, the samples were removed and dried at room temperature before placing in the SEM sample chamber. No fibre morphology modifications and swelling were observed after extensive washing in water and ethanol for 48 hr (Fig.4). The immersed fibres were mostly of cylindrical morphology and diameters were also in the range of 450-870 nm (mean= 640 nm).

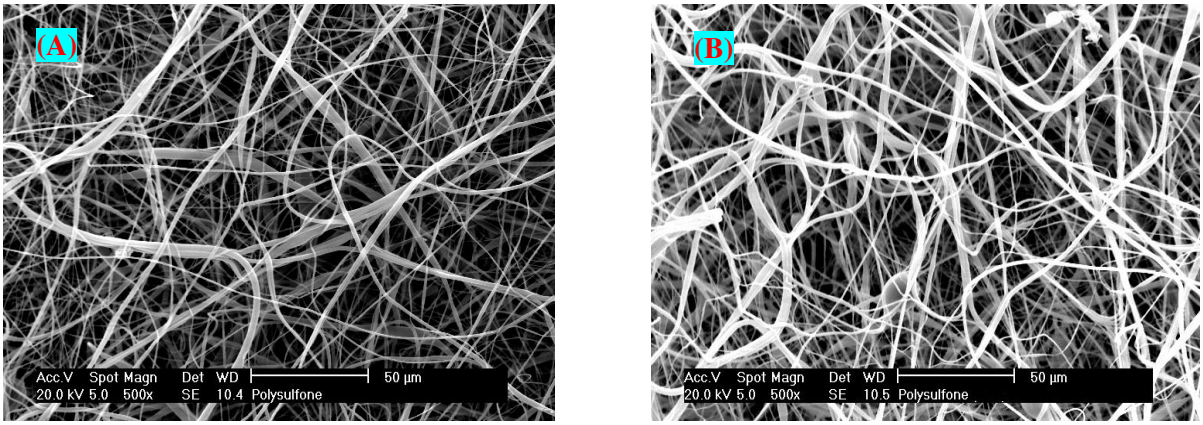


Figure 4. SEM micrograph of PSU-Creatinine Polymer webs produced from DMAc: DMSO (13:7) after 48 hr washing in (A) ethanol and (B) water, Mag. 500 X

3.2 Pore structure of Webs

The porosity of the webs produced from 22 wt. % PSU from different solvents of DMAc: methanol (4:1), DMF: DMSO (3:2) and DMAc: DMSO (13:7) was 64% to 70%. Fig.5 shows typical wet and dry curves obtained by porometry and Table 3 shows the pore size distributions obtained for PSU webs produced from different solvent systems. The wet curve was measured to determine the pore size; the dry curve is needed for the calculation of the mean flow pore size (MFP), smallest pores and the gas permeability. The smallest pore is calculated as the pressure (bar) where the dry curve is closest to the wet curve (Fig.5).

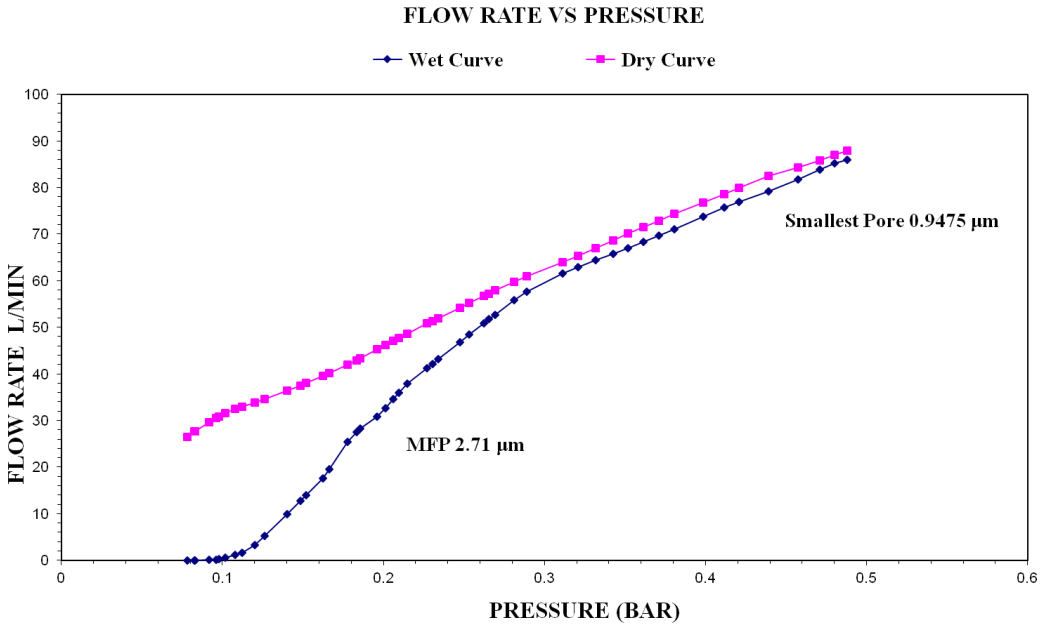
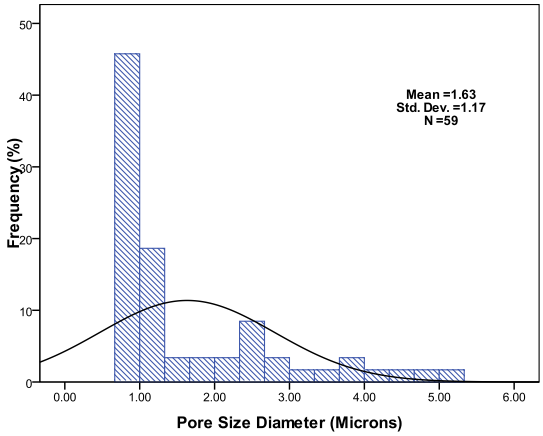
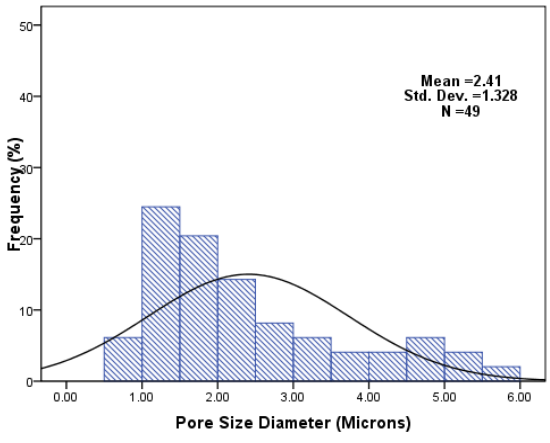


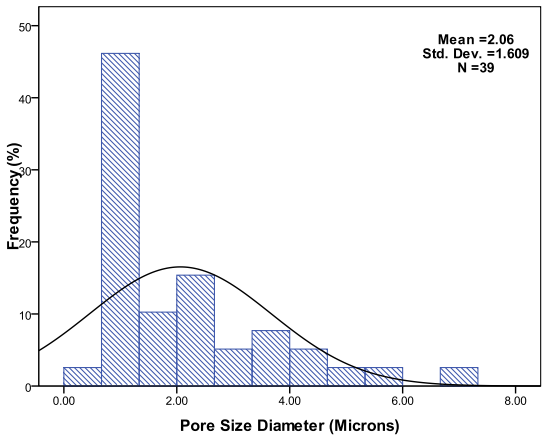
Figure 5. Wet and dry curve of PSU (22 wt %) obtained from capillary flow porometer: DMAc: DMSO (13:7), mean flow pore size (MFP) = 2.71 µm.

The pore structure plays an important role in the filtration behaviour of the web. The largest pore (at bubble point) of 8.8 µm was produced from the binary solvent system of DMF: DMSO (3:2), with the average diameters of fibres 1.1 µm, range: 650 nm -1.90 µm (Table 3). This comparatively large pore size is attributed to the fibre diameter of electrospun nanofibres which potentially affects mean pore size on the sample. The mean pore size increase with increasing fibre diameter,[30] however, the bubble points obtained using the other binary solvents were of the order of 5µm. It has been previously reported that PSU membranes with a bubble point of 4.6 µm were able to

successfully remove 99% of particles of 7 µm-10.8 µm without any permanent fouling.[14]

Table 3. Mean pore size diameter of PSU (22wt. %) webs produced from (A)DMAc: methanol (4:1), (B) DMF:DMSO (3:2) and (C) DMAc: DMSO (13:7)

Sample	Bubble Point (µm)	Mean Pore size Diameter (µm)	Pore Size Distribution
(A)	5.15	1.63	
(B)	8.811	2.41	

(C)	5.80	2.06	

4. Conclusions

The aim of this paper was to find a new solvent system that will allow electrospinning of PSU commixed with a highly polar molecule, creatinine, at near ambient temperature. The binary and ternary solvent systems were selected based on solubility behaviour evaluated using Hansen theory. The addition of methanol to the spinning solution, to increase the solubility of creatinine, altered the solvent ratio leading to precipitation of PSU, except in the binary solvent system of DMAc: methanol (4:1). Bead-free, sub-micron fibres were successfully produced from the binary solvent solution of DMAc: methanol (4:1) by electrospinning with fibre diameters ranging between 600nm-1.05 μm. However, elevated temperature (80°C) was needed to dissolve PSU polymer, which did not provide the ideal solvent system. A co-solvent

system of DMAc:DMSO (13:7) was also found to enable mixing of PSU and creatinine enabling fibres substantially free of structural defects to be produced with diameters in the range 540-890nm. A mixed binary solvent system of DMF: DMSO (3:2) solution was also compatible with PSU: creatinine fibre production but not on a continuous basis due to nozzle blockage. The presence of creatinine in the as-spun PSU fibres produced by the binary solvent system of DMAc: DMSO (13:7) was confirmed by HPLC. No fibre morphology modifications were observed after extensive washing in water and ethanol for 48 hr, which confirmed the wet stability of the as-spun PSU-creatinine fibres.

5. Declaration of conflicting interests

The Author(s) declare(s) that there is no conflict of interest.

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