



Hollow fiber membranes for long-term hemodialysis based on polyethersulfone-SlipSkin™ polymer blends

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ABSTRACT

Hemodialysis (HD) therapy is of vital importance for patients with end stage renal disease (ESRD), when there is no donor organ available for transplantation to replace their malfunctioning kidneys. In contrast to healthy kidneys which work continuously and remove a broad range of toxins, during HD, patients' blood is cleansed three times a week for 4 h and not all uremic toxins are removed. For achieving long-term and/or continuous therapies, including wearable artificial kidneys, one requires membranes with long-term blood compatibility and high fouling resistance. Most membranes currently used in the clinic are made by blending of hydrophobic polymers, such as polysulfone (PSu) or polyethersulfone (PES), with hydrophilic additives, such as polyvinylpyrrolidone (PVP). Studies however, have shown that PVP could leach out from the membranes, especially during prolonged therapy leading to membrane fouling and/or complications to patients.

Here, we develop hollow fibers with no additive leaching, by blending PES with small amounts of SlipSkin™ (SS). The latter, a random copolymer consisting of *N*-vinylpyrrolidone (NVP) and *N*-butylmethacrylate (BMA), has very good blood compatibility. The developed fibers can achieve high removal of a range of uremic toxins (creatinine and protein-bound uremic toxins) combined with excellent fouling resistance.

1. Introduction

A kidney transplantation is the best solution for patients with end stage renal disease (ESRD). However, there are not enough donor kidneys available and these patients are therefore dependent on hemodialysis (HD). In conventional HD therapy, the patients undergo dialysis three times per week for 4 h. The patient is connected to a dialysis machine and the blood is filtrated using a dialyzer, the artificial kidney, a filter that contains up to 15,000 hollow fiber membranes. This therapy can achieve effective removal of small-water soluble toxins (molecular weight, MW < 500 Da) and a small amount of the middle molecules (MW 500–32,000 Da) from the blood of ESRD patients [1–3]. Protein-bound toxins such as hippuric acid (HA) and indoxyl sulfate (IS) are, however, more difficult to remove. The hollow fibers of HD mostly retain serum albumin, the protein that binds HA and IS [4–6].

Recent studies have shown that longer treatment times (e.g. nocturnal dialysis) and/ or continuous HD (e.g. portable/ wearable artificial kidneys) could significantly improve toxin removal and subsequent ESRD patients' survival and quality of life [5–8]. The amount of

toxins present in the intracellular compartment is namely higher than the toxin amount present in the blood plasma and, therefore, more filtration time is necessary for optimal removal [6,8]. Even the removal of protein-bound toxins can be increased by prolonging the dialysis sessions [6,9].

HD requires hollow fibers with high blood compatibility, selectivity and fouling resistance. For producing such membranes, polysulfone (PSu) or polyethersulfone (PES) that are hydrophobic polymers are commonly blended with hydrophilic additives, such as polyvinylpyrrolidone (PVP) [10]. Adsorption of blood proteins onto the fibers, particularly on their surfaces, is minimized due to optimal distribution of hydrophobic and hydrophilic domains on the membrane. Hence, the blood compatibility and fouling resistance of the HD dialyzers is improved [11–14]. Despite having interesting properties such as film-forming properties and good biocompatibility [11,15] that make PVP ostensibly suitable as biomedical membrane material, several studies have shown that PVP could leach from dialyzers during HD [16–21]. For example, Matsuda et al. showed that 10% of the PVP elutes from FDX-15GW filters (polyester-polymer alloy-PVP, Nikkiso) after 4 h

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Table 1
Fabrication conditions of the PES-SS and PES-PVP hollow fiber membranes.

Spinning parameters	PES-SS and PES-PVP fibers
Inner diameter needle of spinneret	0.2 mm
Outer diameter needle of spinneret	–
Inner diameter first orifice of spinneret	0.5 mm
Outer diameter first orifice of spinneret	0.8 mm
Inner diameter second orifice of spinneret	1 mm
Polymer dope pumping speed	1.0 mL min ⁻¹
Bore liquid pumping speed	5.8 mL min ⁻¹
Air gap	10 cm
Pulling wheel speed	18.6 m min ⁻¹

of filtration and shear stress, whereas approximately 20% of PVP leaches out from the dialyzer after 24 h [16]. Namekawa et al. showed that FX-140 filters (PSu-PVP fibers, Fresenius) elute 1 mg m⁻² PVP after 4 h of filtration [21] and 10–30 mg m⁻² PVP elutes from APS-15SA dialyzers (PSu-PVP, Asahi Kasei Medical Co.) and RENAK dialyzers (PSu-PVP, Kawasumi Laboratories) when the filters are flushed with physiological saline [17]. Miyata et al. also showed that 0.5–2 mg m⁻² of PVP elutes from the APS-15SA and RENAK dialyzers after 4 h of filtration [17]. Without a doubt, the elution of PVP from membrane matrices should be avoided, given that it leads to changes in the fibers' structural characteristics and selectivity, decrease of fouling resistance and of the blood compatibility. Moreover, leaching of PVP from the hollow fibers into the blood circulation of an ESRD patient could in time cause its accumulation inside the patient's body and stimulate allergies [15,18,19]. Therefore, alternative ways to prevent PVP loss during HD, including grafting or coating hydrophilic additives on the membranes, have been proposed. For example, Nie et al. [22], grafted heparin-mimicking polymer brushes onto functionalized carbon nanotube-PES composite flat-sheet membranes and He et al. [23] used both graphene oxide and sulfonated polyanion hydrogel thin film to coat the PES membranes. The membranes' blood compatibility and fouling resistance can be improved by these methods, however, coating is not stable and grafting is – because of its extensive chemistry – not easy to implement in the development of hollow fibers for HD dialyzers [15,16,22,24].

Recently, we proposed a simple method for developing blood compatible flat-sheet membranes by blending of PES with small amounts of SlipSkin™ (SS) [25]. The random copolymer SS contains hydrophilic *N*-vinylpyrrolidone (NVP) and hydrophobic *N*-butylmethacrylate (BMA). The high blood compatibility of SS was shown in previous studies [25,26], where extensive blood compatibility experiments following the ISO guideline 10,993: 'Biological evaluation of medical devices, part 4' (including hemolysis, platelet activation and complement activation) were performed with the SS and PES-SS materials. The molecular weight and ratios of hydrophilic and hydrophobic components of a membrane influence among other things membrane pore formation, wetting ability and performance. The effect of molecular weight and different ratios of SS on membrane permeance, selectivity, fouling resistance, blood compatibility and swelling has been investigated in previous studies [25–28]. Those studies showed that SS membranes with a NVP:BMA ratio of 50:50, SS(50:50), showed high fouling resistance, high blood compatibility and the least swelling, compared to for example SS(30:70) or SS(70:30) membranes. In fact, we showed that the flat-sheet PES-SS membranes, containing only 2 wt% of SS, have high blood compatibility and fouling resistance. Higher concentrations of SS in the polymer solution resulted in inhomogeneous PES-SS polymer solutions due to immiscibility issues [25].

Here, we investigate the development of hollow fiber membranes based on this polymer blend of PES and SS(50:50) 2 wt%. We hypothesize that due to the interaction of the random copolymer SS with the PES, the elution of SS during long-term filtration can be minimized and/or avoided. To the best of our knowledge, our study is the first one focusing on the long-term stability of the hydrophilic random copolymer combined to the study of the membrane fouling and uremic toxin

removal. In fact, the spinning conditions are optimized for achieving a PES-SS fiber for long-term filtration with optimal fouling resistance. Finally, the performance of the new fibers concerning fouling resistance and uremic toxin removal is compared to benchmark PES-PVP fibers and commercially available low-flux F8HPS fibers (Fresenius) used in the clinic. The long term performance of the new fiber and the possible leakage of the hydrophilic additive, SS, were compared to the benchmark PES-PVP fibers containing 7 wt% PVP, for which we have already shown that they have optimal performance concerning blood compatibility (see our previous studies [4,29]).

2. Materials and methods

2.1. Materials

For preparing the PES-SS hollow fiber membranes, the same materials were used as in previous flat-sheet membrane study [25] and are summarized here briefly. The polymers SS with NVP:BMA ratio 50:50 (Interface BIOMaterials BV, The Netherlands), PES (ULTRASON, E6020P, BASF, The Netherlands) and PVP (K90, MW ~ 360,000) (Fluka, Sigma-Aldrich, Germany) were dissolved in *N*-methyl-2-pyrrolidone (NMP) (Acros Organics, Belgium). F8HPS fibers were obtained from large, commercial F8HPS dialyzers (Fresenius Medical Care, The Netherlands) and used as reference. All hollow fiber modules were prepared with an effective length of 9.5 cm and an effective surface area of 0.0016 m². Push-in T-connectors (Festo, The Netherlands) and 6 mm polyethylene tubes (Bürkle, Germany) were used to prepare the modules. Two-component Griffon combi fast glue (Klium, The Netherlands) was used to pot the modules. Ultrapure water was used as a non-solvent in the coagulation bath, as bore solution and for transport experiments. This water was prepared using a Milli-Q purification unit (Merck Millipore, Czech Republic). Creatinine (113 Da) and bovine serum albumin (BSA, 60 kDa), both purchased from Sigma-Aldrich (The Netherlands), were dissolved in a phosphate-buffered saline (PBS) solution (pH 7.45, Gibco, United Kingdom). Hippuric acid (HA, 179 Da, relatively low protein-bound ~30% [30]) and indoxyl sulfate (IS, 213 Da, highly protein-bound ~90% [30]), both purchased from Sigma-Aldrich (The Netherlands), were dissolved in human blood plasma from healthy donors (Sanquin, The Netherlands; ethical guidelines were applied). A home-made dialysate solution (pH = 7.4), following the protocol of Geremia et al. [31], was prepared by dissolving 2 mM KCl, 140 mM NaCl, 1.5 mM CaCl₂, 0.25 mM MgCl₂, 35 mM NaHCO₃ (Sigma-Aldrich, Germany) and 5.5 mM glucose (Life Technologies Europe BV, The Netherlands) in ultrapure water. The concentration of HA and IS in human plasma and dialysate solution were analyzed using reverse-phase high-performance liquid chromatography (RP-HPLC). For this, three eluents were used: eluent A (50 mM ammonium formate buffer and 10% methanol, HPLC-grade, pH = 3), eluent B (50 mM ammonium formate buffer and 90% methanol, HPLC-grade, pH = 3) and eluent C (acetonitrile, HPLC-grade), all purchased from Sigma-Aldrich (The Netherlands).

2.2. Hollow fiber preparation

The polymer dope for the preparation of PES-SS hollow fiber membranes was prepared by blending 15 wt% PES and 2 wt% of SS to obtain a homogeneous solution [25]. Hollow fiber PES-PVP membranes were fabricated from 15 wt% PES and 7 wt% PVP dissolved in NMP and used as reference. The PES-SS and PES-PVP solutions were subsequently mixed on a roller bank at room temperature, filtered using a Bekipor ST AL3 15 µm filter (Bekaert, Belgium), transferred into stainless steel syringes and degassed overnight before hollow fiber preparation. The PES-SS and PES-PVP hollow fibers were prepared by dry-wet spinning via immersion-precipitation. Both the polymer dope and the bore liquid (ultrapure water) were pumped through a spinneret (see Table 1 for spinneret dimensions) using high-pressure syringe pumps. The extruded

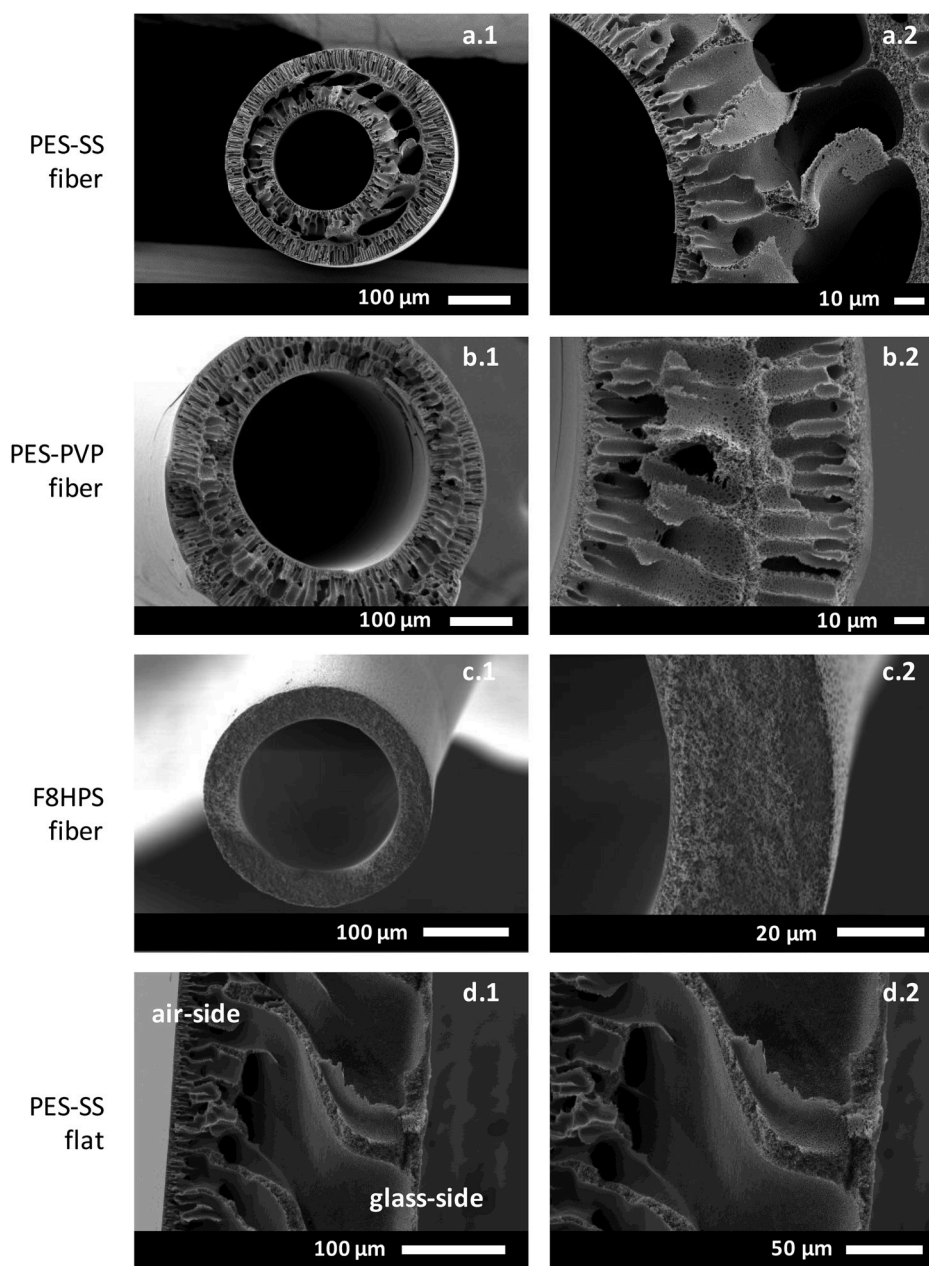


Fig. 1. SEM images of hollow fiber membranes PES-SS (a), PES-PVP (b) F8HPS (Fresenius) (c) and flat-sheet PES-SS membrane (d) [25]. Images show cross-sections with size bars of 100 μm (1) and 10 μm (2), except for image c.2 and d.2 where the size bars indicate 20 μm and 50 μm , respectively.

Table 2

Dimensions of the PES-SS, PES-PVP and F8HPS hollow fiber membranes.

	PES-SS	PES-PVP	F8HPS
Inner diameter (μm)	167 ± 5	316 ± 8	191 ± 9
Outer diameter (μm)	364 ± 8	517 ± 10	268 ± 12
Wall thickness (μm)	97 ± 17	99 ± 18	39 ± 1

fibers were immersed in a non-solvent ultrapure water coagulation bath after an air gap of 10 cm and the fibers were formed by phase separation. Three (pulley) wheels inside the coagulation bath and a collecting wheel were used to continuously guide, pick up and collect the fibers. All spinning parameters are listed in Table 1. Immediately after the spinning, the hollow fibers were rinsed and washed extensively with fresh ultrapure water and, finally, the fibers were stored in ultrapure water.

2.3. Hollow fiber characterization

2.3.1. Scanning electron microscopy (SEM)

SEM (Jeol JSM-IT 100 LV, InTouchScope™ software) was used to examine the PES-SS, PES-PVP and commercial F8HPS hollow fibers' structures. All fibers were dried overnight in air and at room temperature. Then, the dried fibers were broken cryogenically in liquid nitrogen, placed in SEM cross-section holders and coated with gold (Cressington 108 auto-sputter coater). For all cases at least 3 different hollow fiber membrane pieces were examined.

2.3.2. Membrane UF coefficient

To determine the ultrafiltration (UF) coefficient of the hollow fibers ($n = 12$), the two ends of the potted membrane modules were cut open first. Then, a similar protocol that was used for determining the UF coefficient of the flat-sheet PES-SS membranes was used [25]: (1) For 30

Table 3

Transport properties of the PES-SS, PES-PVP and F8HPS hollow fiber membranes and of the flat-sheet PES-SS membranes of previous study [25].

	PES-SS hollow fiber	PES-PVP hollow fiber	F8HPS hollow fiber	PES-SS [25] flat membrane
UF coefficient (mL h ⁻¹ m ⁻² mmHg ⁻¹)	10 ± 2	3 ± 0.1	10 ± 4	75
Retention index, R _i (-)	0.99 ± 0.02	0.97 ± 0.02	0.97 ± 0.01	0.70
Flux recovery ratio, FRR (%)	90 ± 17	96 ± 2	79 ± 4	82
Total flux decline ratio, DR _t (%)	9 ± 7	6 ± 2	34 ± 3	13
Creatinine removal after 4 h (mg m ⁻²)	4120 ± 435	-	3657 ± 257	-
Hippuric acid removal after 4 h (mg m ⁻²)	638 ± 53	-	1011 ± 26	-
Indoxyl sulfate removal after 4 h (mg m ⁻²)	74 ± 19	-	75 ± 12	-

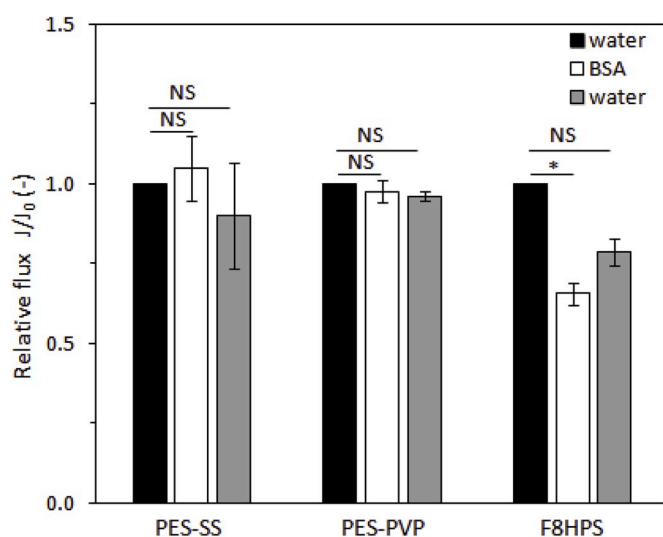


Fig. 2. Fouling resistance experiments with PES-SS, PES-PVP and F8HPS hollow fiber membranes, using BSA protein (TMP = 750 mmHg). The relative flux was calculated via subsequent water, BSA in PBS solution, and water transport experiments. The error bars show standard deviation (n = 3).

min, the modules were wetted and pre-pressurized using ultrapure water, in dead-end setting, at transmembrane pressure (TMP) of 1500 mmHg. (2) After that, the TMP was decreased to 375 mmHg and increased again to 750, 1125 and 1500 mmHg to measure the amount of permeated water during 30 min of each TMP. (3) Finally, a graph was made by plotting the resulting flux (mL h⁻¹ m⁻²) versus TMP (mmHg). The slope of this graph, then, represents the UF coefficient (mL h⁻¹ m⁻² mmHg⁻¹) of the fiber. It is important to note that the UF coefficient of the tested hollow fiber membrane modules was first determined prior to performing fouling resistance experiments, long-term filtration tests and experiments with uremic toxins (see later sections).

2.3.3. Protein retention and membrane fouling

In our previous study, we showed that PES-SS flat-sheet membranes have high fouling resistance to proteins and middle-size molecules [25]. The anti-fouling properties of the PES-SS, PES-PVP and F8HPS hollow fiber membranes were determined in similar manner in this study too (n = 3): (1) After wetting and pre-compacting the fibers, the flux, J_{w,1} (L

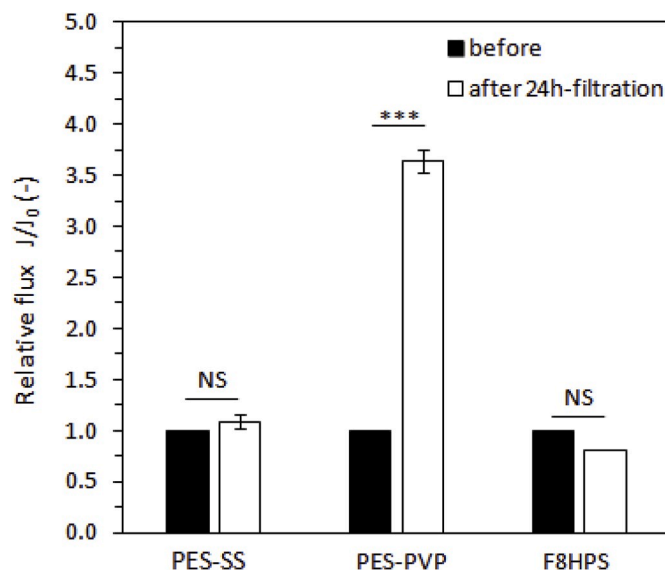


Fig. 3. Effect of long-term filtration on the water transport properties of PES-SS, PES-PVP and F8HPS hollow fiber membranes. The water flux of the fibers was measured, in dead-end setting, before (J₀) and after 24 h-filtration (J). The error bars show standard deviation (n = 3).

h⁻¹ m⁻²) of the water through the fibers at a TMP of 750 mmHg for 1 h was determined. (2) Then, the module was emptied and a protein solution, BSA in PBS solution (1 mg mL⁻¹, pH = 7, 300-rpm) was pushed through the fibers (TMP of 750 mmHg) for 1 h and the protein solutions' flux (J_{BSA}) was determined. (3) Finally, the hollow fiber modules were washed with ultrapure water and the clean water flux (J_{w,2}) was determined in the same way as in step 1. The following formulas were used to calculate the hollow fibers' fouling resistance:

$$\text{flux recovery ratio (FRR)} = \frac{J_{w,2}}{J_{w,1}} \cdot 100\% \quad (1)$$

$$\text{total flux decline ratio (DR}_t) = \left(1 - \frac{J_{BSA}}{J_{w,1}}\right) \cdot 100\% \quad (2)$$

The fouling resistance of the fibers is high, when the fibers' FRR is high and DR_t is low. The BSA protein retention index (R_i) of the hollow fibers was also determined in the same way as the sieving coefficient of previous study [25]. After completion of the BSA transport measurements, the BSA concentration of 2 mL permeate (C_{permeate} in mg mL⁻¹) and retentate (C_{retentate} in mg mL⁻¹) solution samples were determined using UV-spectrophotometry (Varian, Cary 300 Scan UV-visible spectrophotometer) at 280 nm. The following equation was used to determine the fibers' R_i:

$$R_i = 1 - \frac{C_{\text{permeate}}}{C_{\text{retentate}}} \quad (3)$$

The fibers retain all BSA proteins when the R_i is 1 and when all proteins go through the fiber walls the R_i is 0.

2.3.4. Long-term filtration

Hydrophilic additive elution can be investigated in various ways. Here, changes in the fibers' characteristics after long-term filtration were investigated by determining the membrane UF coefficient and by performing surface characterization experiments.

First, the influence of long-term filtration on the hollow fibers water transport was investigated. For this, the membrane modules were connected to a cross-flow set-up (Convergence, The Netherlands) [4] and ultrapure water was pumped through the fibers at 5 mL min⁻¹ – to obtain a TMP of 0 mmHg and perform the experiments in diffusion mode – for 24 h at room temperature (24 h-filtration experiments). The water

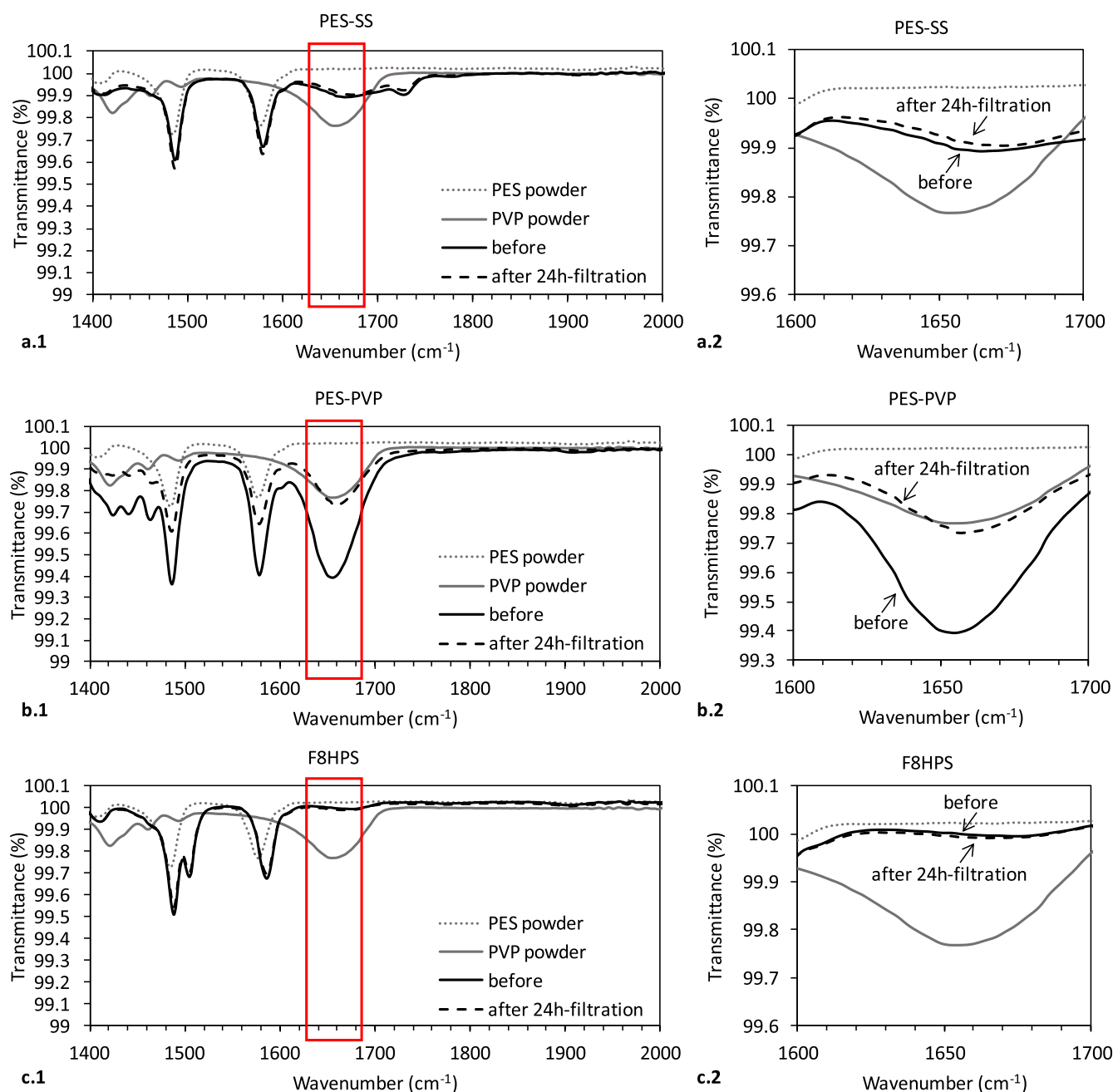


Fig. 4. ATR-FTIR spectra: effect of long-term filtration on the presence of the hydrophilic additives of PES-SS (a), PES-PVP (b) and F8HPS (c) hollow fiber membranes. The carbonyl group is depicted by the red box in (1) and a zoom-in of this peak is presented in (2). The black lines (—) of the ATR-FTIR spectra represent the PES-SS, PES-PVP and F8HPS fibers before and the dotted black lines (---) represent the fibers after 24 h-filtration, respectively. The spectra of PES powder (grey lines —) and PVP powder (grey dotted lines ...) are also presented as reference. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

flux of the modules was determined before and after these long-term experiments, using the same conditions as were used to determine the UF coefficient and the relative flux was calculated. Then, the modules of the long-term filtration tests were disassembled, and the fibers were dried in air, at room temperature. The surfaces of the dried fibers before and after 24 h-filtration were investigated using attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR) and X-ray photoelectron spectroscopy (XPS). For ATR-FTIR (Spectrum Two, PerkinElmer and Spectrum Quant software), all scans were performed on various parts of the membrane surface ($n = 3$), at a resolution of 4 cm^{-1} and at room temperature. A Quantera SXM set-up (Physical

Electronics) at 4 e^{-8} torr, Compass software for XPS control and Multipak v.9.8.0.19 software for data reduction were used for XPS analysis of the dried PES-SS, PES-PVP and F8HPS samples ($n = 3$). On the XPS spectra, the peak intensities of the fibers after 24 h-filtration are shifted by 32,000 (a.u.), to be able to discriminate between the fibers before and after long-term filtration.

2.3.5. Uremic toxin removal

The membrane modules were connected to the cross-flow set-up (Convergence, The Netherlands) [4]. To perform the experiments in diffusion mode (TMP is 0 mmHg), the flow rates of the feed and dialysate

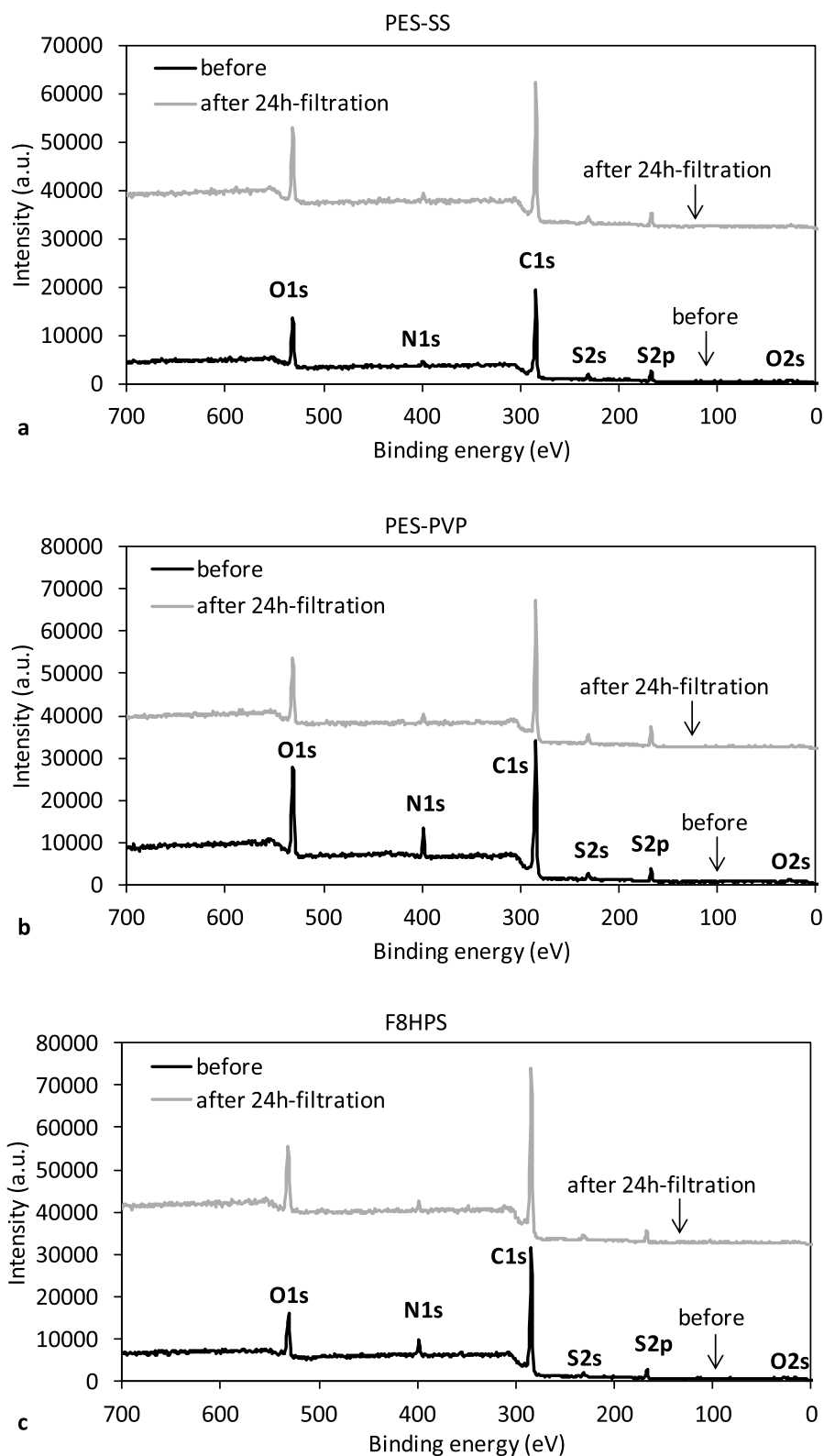


Fig. 5. XPS spectra: effect of long-term filtration on the presence of the hydrophilic additives of PES-SS (a), PES-PVP (b) and F8HPS (c) hollow fiber membranes. The black and grey lines present the elemental analysis of the PES-SS, PES-PVP and F8HPS fibers before and after 24 h-filtration, respectively.

solutions were set to 1 mL min^{-1} and 20 mL min^{-1} , respectively. For the creatinine model solution cross-flow experiments, 50 mL of creatinine dissolved in PBS solution (100 mg L^{-1} , close to the mean uremic creatinine concentration [3]) was used as feed solution and was pumped

through the fiber lumen. A 50 mL PBS solution was used as dialysate solution and was pumped through the module housing in counter current direction [4,29]. The creatinine transport experiments were performed for 4 h and to quantify the creatinine removal, 1 mL samples of

Table 4

XPS element percentages of the PES-SS, PES-PVP and F8HPS hollow fiber membranes.

Element percentage	before	after 24 h- filtration	before	after 24 h- filtration	before	after 24 h- filtration
	PES-SS	PES-SS	PES-PVP	PES-PVP	F8HPS	F8HPS
C (%)	72.0	73.7	69.7	75.1	78.6	78.8
N (%)	3.0	3.4	6.0	3.1	5.2	2.5
O (%)	21.9	20.3	22.1	18.0	14.4	16.6
S (%)	3.1	2.6	2.2	3.8	1.8	2.1
N/S	0.97	1.3	2.7	0.82	2.9	1.2

both the feed and dialysate solution were taken before the start of the experiment and after 1, 2, 3 and 4 h from the start of the experiment. To determine the samples' creatinine concentration, a UV-spectrophotometer (Varian, Cary 300 Scan UV-visible spectrophotometer) at 230 nm was used. The mass balance was monitored, and the toxin removal was calculated by the concentrations of creatinine found in the dialysate solution. Finally, the creatinine removal was expressed in mg m^{-2} .

For the protein-bound toxin cross-flow experiments, 50 mL of human plasma spiked with 110 mg L^{-1} HA and 40 mg L^{-1} IS (both close to the mean uremic HA and IS concentrations [3]) and 100 mL of home-made dialysate solution were used as feed and dialysate solution, respectively. The protein-bound toxin removal experiments were performed for 4 h and to quantify the HA and IS removal, samples of both the feed and dialysate solution were taken before the start of the experiment (3 mL), after 30 min (2 mL) and after 1, 2, 3 and 4 h from the start of the experiment (2 mL). A RP-HPLC set-up (JASCO, Japan) was used to determine the samples' HA and IS concentrations. For this, all samples were first diluted $4\times$ with ultrapure water, then de-proteinized via heat treatment (95°C) for 30 min and afterwards filtered using a 10 kDa filter (Ultracel-10, 0.5 mL sample volume, Merck). UV (245 nm) and fluorescence ($\lambda_{\text{ex}} = 272 \text{ nm}$, $\lambda_{\text{em}} = 374 \text{ nm}$) detection were used to determine the concentrations of HA and IS, respectively [31]. The mass balance was monitored, and the toxin removal was calculated by the concentrations of HA and IS found in the dialysate solution. Finally, the removal of HA and IS was expressed in mg m^{-2} . Furthermore, a NanoDrop-1000 spectrophotometer (Fisher Scientific) and NanoDrop-1000 software V3.8.1 were used to determine the total protein concentrations (at 280 nm) of the plasma and dialysate samples at the start, after 30 min and after 1, 2, 3 and 4 h from the start of the protein-bound toxin experiments. For this, all plasma samples were first diluted $40\times$ with ultrapure water.

2.3.6. Statistics

ANOVA and post-Tuckey ($p < 0.05$) and independent samples *t*-test ($p < 0.05$) tests of GraphPad PRISM (software package version 5.00) were used to calculate statistical difference and compare the results of the different fiber types.

3. Results and discussion

3.1. Membrane characterization

Fig. 1 presents the cross-section SEM images of the hollow fiber PES-SS, PES-PVP and F8HPS membranes and the flat-sheet PES-SS membranes of previous study (for comparison) [25]. The PES-SS and PES-PVP fibers (see Fig. 1a and b, respectively) have asymmetric pore structure, in contrast to the F8HPS fibers (Fig. 1c) that have rather symmetric and spongy pore structure. Finger-like pores are present on the outer walls of both the PES-SS and PES-PVP fibers. In the center of the fibers' walls, macrovoids are observed for the PES-SS fibers and large pores for the PES-PVP fibers.

The structure of the PES-SS fibers resembles that of the PES-SS flat-sheet membranes of previous study [25] (Fig. 1a and d, respectively). The finger-like pores on the air-side of the PES-SS flat-sheet membranes are also present on both the inner and outer walls of the PES-SS fibers (and on the PES-PVP fibers). These finger-like pores are the result of the fast solvent/non-solvent exchange during the phase inversion fabrication process. The glass-side of the flat-sheet PES-SS membranes was not directly exposed to the non-solvent during membrane formation, while the inner and outer walls of the PES-SS fibers (and PES-PVP fibers) were immediately exposed to the non-solvent bore solution and water vapor of the air gap, respectively. In spite of the macrovoids present, the mechanical properties of the PES-SS fibers are quite good, and they can be handled easily. Moreover, the inner diameter of the PES-SS fibers is small ($167 \pm 5 \mu\text{m}$) and similar to the inner diameter of the F8HPS and of others currently used in HD dialyzers for clinical practice [1,4]. However, the outer diameter and wall thickness of both the PES-SS and PES-PVP fibers is a bit larger than that of the commercial F8HPS fibers (see Table 2).

3.2. Membrane transport properties

3.2.1. Membrane UF coefficient

The PES-SS, like the PES-PVP and F8HPS fibers, can be categorized as low-flux membranes [1,30], see Table 3. The PES-SS fibers' UF coefficient is $10 \pm 2 \text{ mL h}^{-1} \text{ m}^{-2} \text{ mmHg}^{-1}$ (measured at the TMP range of 375–1500 mmHg) and is similar to the commercial F8HPS fibers ($10 \pm 4 \text{ mL h}^{-1} \text{ m}^{-2} \text{ mmHg}^{-1}$). Moreover, the change of configuration – from flat-sheet PES-SS membrane (of previous study [25]) to hollow fiber PES-SS membrane – decreased the UF coefficient significantly from $\sim 75 \text{ mL h}^{-1} \text{ m}^{-2} \text{ mmHg}^{-1}$ to $\sim 10 \text{ mL h}^{-1} \text{ m}^{-2} \text{ mmHg}^{-1}$, respectively (Table 3). The PES-SS fibers' lower UF coefficient could be explained by the smaller, finger-like pores that are present both on the inside and the outside of the fibers. In contrast, the flat-sheet PES-SS membranes showed on the membranes' air-sides a dense selective layer and finger-like pores, while on the glass-side larger macrovoids were present [25].

3.2.2. Protein retention and membrane fouling

The HD membranes should not leak human serum albumin, since this is a plasma protein with vital functions. Human serum albumin regulates, for example, the plasma colloid osmotic pressure between the blood and other tissues and it is an important transporter because of its exceptional binding capacity to small molecules such as toxins [32]. Table 3 shows the albumin retention indices of the PES-SS, PES-PVP and F8HPS fibers and of the flat-sheet PES-SS membranes of previous study [25]. All fibers retain albumin: PES-SS fibers ($R_i \sim 0.99$), PES-PVP fibers ($R_i \sim 0.97$) and F8HPS fibers ($R_i \sim 0.97$). Moreover, the protein retention of the PES-SS fibers increased in comparison to that of the PES-SS flat-sheet membranes (from $\sim 70\%$ of albumin retained to $\sim 99\%$ of albumin retained, respectively, Table 3). This could be attributed to the denser structure of the PES-SS fibers.

For an optimal performance during blood filtration, the hollow fiber membranes should also have good protein fouling resistance. In this study, the hollow fibers' fouling resistance was investigated by measuring the transport of water and of the protein BSA through our hollow fibers and by calculating the FRR and DR_t . Fig. 2 shows the change in relative flux of the PES-SS, PES-PVP and F8HPS fibers for the subsequent water, BSA protein and water experiments. For the PES-SS and PES-PVP modules, there seems to be low fiber-protein interaction, since there is no significant difference between the water and protein flux as well as no difference between the water flux prior and after the protein filtration (see Fig. 2). However, the significant difference between the first water flux and BSA protein flux presented for the F8HPS fibers (Fig. 2), indicates protein-fiber interaction there.

The low protein fouling of the PES-SS and PES-PVP fibers, in contrast to the F8HPS fibers, is also reflected in the FRR and DR_t values (see

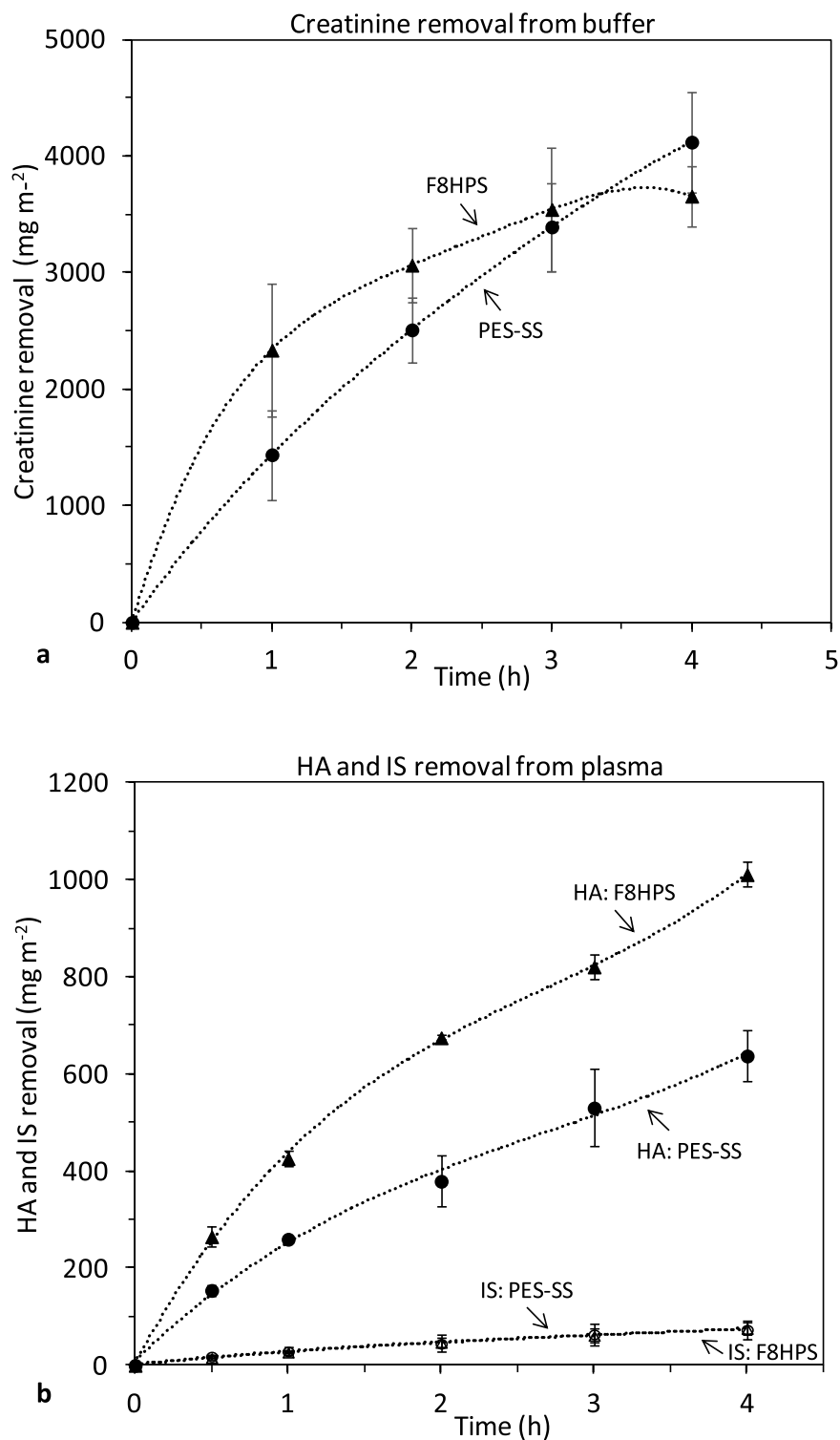


Fig. 6. Uremic toxin removal by PES-SS and F8HPS fibers. (a) Creatinine removal (mg m^{-2}) from buffer by PES-SS (●) and F8HPS (▲) fibers. (b) Protein-bound toxin removal (mg m^{-2}) from human plasma by PES-SS (hippuric acid (HA) ●, indoxyl sulfate (IS) ○) and F8HPS fibers (HA ▲, IS △). Error bars indicate standard deviations ($n = 3$). The lines are plotted to guide the eye.

Table 3). Here, high fouling resistance is expressed in a high FRR and low DR_t . The PES-SS and PES-PVP fibers have high flux recovery ratios (FRR is $90 \pm 17\%$ and $96 \pm 2\%$, respectively) and low total flux decline ratios (DR_t is $9 \pm 7\%$ and $6 \pm 2\%$, respectively). The high fouling resistance of the PES-SS hollow fiber membranes could be attributed to

the presence of the hydrophilic NVP block of SS on the selective layer and inside the pores of the PES-SS hollow fibers, that is anchored by the hydrophobic block of SS (BMA) into the membrane matrix [26,33]. These results of the PES-SS fibers are consistent with the results reported earlier for the PES-SS flat membranes; the latter also having low fouling

(the FRR even increased for the PES-SS fibers compared to the flat-sheet membranes from ~82% to ~90%, respectively and the DR_t decreased from ~13% to ~9%, respectively, Table 3) and excellent blood compatibility [25]. It is important to note that this excellent fouling resistance was obtained even when using the “worst case scenario” concerning filtration; dead-end filtration mode and high TMP of 750 mmHg. We anticipate that when using the PES-SS fibers during HD with cross flow filtration mode and low TMP (75 mmHg) the fouling resistance will also be excellent. When comparing to other studies developing low fouling membranes, our results for the PES-SS fibers are also very good. For example, Abidin et al. [34], developed low-flux and high-flux multi-walled carbon nanotubes-PES-PVP hollow fibers with similar BSA retention (R_t 's in the range of 88–97%) but much lower FRR (49% for low-flux fiber and 81% for high-flux fiber) than our PES-SS fibers. Furthermore, the PES-heparin-mimicking polyurethane blend fibers reported by Ma et al. [35] also had quite high BSA FRR (92%), but their DR_t (~23%) was much higher than that of our PES-SS fibers (9%).

3.3. Long-term filtration

3.3.1. Influence on membrane transport

From the results so far, we can conclude that the PES-SS hollow fiber membranes have very good fouling resistance comparable to commercial fibers. However, since other studies have shown that hydrophilic additives, that ensure important properties such as good fouling resistance, can leach from the fiber's membrane matrix during dialysis [16, 21], we also investigate whether the SS leaches out of the membrane during longer term filtration. In fact, after measuring the clean water flux of all membranes (PES-SS, PES-PVP and F8HPS), we performed a long-term (24 h) diffusion mode experiment (TMP = 0) using pure water. The water flux of the modules was determined before and after the long-term experiments, using the same conditions as those used to determine the UF coefficient. Naturally, hydrophilic additive elution from the hollow fibers during this long-term filtration is undesirable because it can lead to change of both the membrane transport properties and fouling resistance. Fig. 3 shows the results for all membranes. For the PES-SS and F8HPS fibers there is no change of pure water flux before or after long-term filtration. However, the water flux of the PES-PVP fibers after 24 h-filtration increases significantly indicating elution of PVP and increase of membrane's porosity and/or membrane's pore size. To investigate further the changes of the membrane structure there we performed systematic studies of all membranes using ATR-FTIR and XPS.

3.3.2. Influence on membranes' surface chemistry

Fig. 4 and Fig. 5 present respectively the ATR-FTIR and XPS results of the PES-SS, PES-PVP and F8HPS fibers before and after 24 h of water filtration. For the ATR-FTIR spectra, attention should be focused on the characteristic peak of the carbonyl groups of NVP/PVP around 1680 cm^{-1} . In the XPS spectra, the presence of NVP/PVP is indicated by the peak intensity of the element nitrogen (binding energy of ~400 eV). Furthermore, in the ATR-FTIR spectra the fibers before water filtration are indicated with a black line, whereas after 24 h water filtration the fibers are indicated with a black, dashed line. The spectra of PES powder (grey lines) and PVP powder (grey dotted lines) are also presented as reference. Fig. 4a shows there is no significant change of the spectra around 1680 cm^{-1} for the PES-SS fibers before and after 24 h-filtration [25,36] indicating that the NVP component of SS is still present in the membrane matrix of the PES-SS fibers after long-term filtration. However, Fig. 4b shows a significant decrease in peak intensity of the carbonyl group for the PES-PVP fibers after 24 h-filtration compared to the peak intensity of the PES-PVP fibers before filtration, indicating an elution of PVP after the 24 h-filtration, consistent to our findings presented in Fig. 3. For the F8HPS fibers, there is no peak at 1680 cm^{-1} (see Fig. 4c) suggesting that no PVP is used as an additive there.

The results of the XPS analysis confirm the findings obtained by the

ATR-FTIR for the PES-SS and PES-PVP fibers. In fact, there is no difference between the XPS results for the PES-SS fibers before and after 24 h-filtration (Fig. 5a, Table 4), however, there is a significant difference between the nitrogen intensities of the PES-PVP fibers (Fig. 5b, Table 4). Besides, the N/S ratio of the PES-PVP membranes after 24 h-filtration is approximately 70% lower compared to the PES-PVP membranes before the long-term filtration. Interestingly, there is also a significant decrease in nitrogen percentage and peak intensity after long-term filtration for the F8HPS fibers (see Fig. 5c and Table 4) which is probably due to release of another additive than PVP. Nevertheless, this does not lead to changes of the transport properties of these membranes (see Fig. 3).

It is clear that long-term filtration has no impact on the flux of the PES-SS fibers and our hypothesis that the strong interaction between the BMA (hydrophobic component of random copolymer SS) with the PES would avoid leaching is correct. In contrast, for the PES-PVP fibers, PVP is dissolved in water and leaches out of the membrane leading to changes in the membrane filtration performance. This is consistent to the results reported by others using commercial dialyzers [16,17,21]. For the APS-15SA, RENAK and FX-140 dialyzers PVP elution up to 2 mg m^{-2} after 4 h has been reported [17,21], whereas for the FDX-15GW filters, 20% of the PVP was eluted after 24 h of use, because of filtration and shear stress [16]. It was also reported that the fibers' surface hardness was increased as well as the adsorption of human serum albumin, due to the elution of PVP from these commercial dialyzers [21].

3.4. Removal of uremic toxins

In this section, we present the results of the removal of uremic toxins by the PES-SS and F8HPS membranes which have similar UF coefficients. We investigated first the removal of creatinine from a buffer solution (to compare to earlier studies) and the removal of two protein-bound toxins from human plasma. The removal of the latter is crucial for avoiding progression of kidney disease, minimizing the chance of cardiovascular events and decreasing patient mortality [6,36]. Here, we investigated the removal of one rather low protein-bound (~30%) toxin; hippuric acid (HA) and one highly protein-bound (~90%) toxin; indoxyl sulfate (IS). Fig. 6 presents the results.

In general, the removal of creatinine is higher than the removal of protein-bound toxins. Creatinine is a water-soluble toxin and, in contrast to the toxins HA and IS, is not bound to albumin. Fig. 6a presents the kinetics of the removal of creatinine by the membranes from a buffer solution and Table 3 presents the total removal after 4 h. Our results show that there is no significant difference between the creatinine removal by the PES-SS and F8HPS hollow fibers. This was to be expected, since creatinine is a small water-soluble toxin and the UF coefficients of both fibers are quite similar. Assuming the *in vivo* creatinine removal of PES-SS fibers is similar to their removal capacity measured here and taking into account a daily production of the toxin creatinine of approximately 1800 mg [37], a dialysis module of 0.44 m^2 of PES-SS fibers is needed. This is a realistic surface area, because HD modules usually have an effective surface area of 0.4–2.6 m^2 [38]. Fig. 6b compares the removal of IS and HA by the PES-SS and F8HPS membranes. It is clear that the removal of HA by both membranes is higher than the removal of IS due to its higher concentration in the plasma (110 mg L^{-1} HA versus 40 mg L^{-1} IS) and its lower protein binding (30% for HA versus 90% for IS) in agreement with other studies [31,37]. Furthermore, there is no significant difference between the IS removal by the PES-SS and F8HPS membranes (Fig. 6b and Table 3) as expected due to their similar UF coefficients. Interestingly, the removal of HA by the F8HPS fibers is much higher (1.5 times) in comparison to the PES-SS fibers despite having the same UF coefficient. This could be due to higher interaction and higher adsorption of the proteins and of HA on the surface of the F8HPS membrane. In fact, detailed estimation of the mass balance of HA and of the total protein (amount missing from the blood plasma versus the amount transported to the dialysate) shows that 1.4× more proteins are absorbed on the F8HPS fibers in comparison to

PES-SS fibers whereas in both cases, proteins are not transported to the dialysate.

These findings are consistent to the BSA tests (see section 3.2.2) where we also found higher membrane-protein interaction for the F8HPS than the PES-SS membranes leading to lower fouling resistance (see Fig. 2 and Table 3 for FRR and DR_p), for the F8HPS membranes.

Finally, comparison of the removal of HA and IS by the PES-SS fibers to other studies where commercial dialyzers were used in a clinical setting, suggests that our PES-SS hollow fiber membranes have quite good potential for application in the clinic. For example, the HA removal of the PES-SS fibers is higher than the HA removal by the low-flux filter Sureflux-150 L (Nissho Nipro, HA removal after 4.5 h: 571 mg m⁻² [39]), the high-flux filter Sureflux-150FH (Nissho Nipro, HA removal after 4.5 h: 531 mg m⁻² [39]) and the high-flux dialyzer FX80 (Fresenius, HA removal after 4 h: 346 mg m⁻² [9]). Furthermore, the IS removal of the PES-SS fibers is higher than the IS removal of the Sureflux-150FH filter (IS removal after 4.5 h: 69 mg m⁻² [39]) and in the same range as the Sureflux-150 L filter (IS removal after 4.5 h: 77 mg m⁻² [39]) and FX80 filter (IS removal after 4 h: 82 mg m⁻² [9]).

4. Conclusions and outlook

In this work, new PES-SS hollow fibers were developed and tested. The PES-SS hollow fibers show no elution of the hydrophilic additive after 24 h water filtration. Despite using rather small amounts of SS (2 wt%), the membranes have optimal distribution of hydrophilic/hydrophobic domains ensuring good fouling resistance and very good uremic toxin removal in comparison to benchmark membranes. Importantly, the removal of protein-bound toxins by the PES-SS fibers is based on removal of the free-fraction, rather than adsorption of the proteins (and consequently removal of the protein-bound fraction) as the benchmark membranes did. The protein adsorption on the benchmark membrane might be the reason of the rather nonlinear removal of toxins in time. In contrast, for the PES-SS fibers, the uremic toxin removal seems to increase linearly with time. The focus of future work will therefore be on PES-SS fiber module upscaling and long-term tests *in vitro* with full blood as well as *in vivo* with small and large animals.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- C. Ronco, W.R. Clark, Haemodialysis membranes, *Nat. Rev. Nephrol.* 14 (2018) 394–410.
- D.F. Stamatialis, B.J. Papenburg, M. Gironés, S. Saiful, S.N.M. Bettahalli, S. Schmitmeier, M. Wessling, Medical applications of membranes: drug delivery, artificial organs and tissue engineering, *J. Membr. Sci.* 308 (2008) 1–34.
- R. Vanholder, R. De Smet, G. Glorieux, A. Argilés, U. Baurmeister, P. Brunet, W. Clark, G. Cohen, P.P. De Deyn, R. Deppisch, B. Descamps-Latscha, T. Henle, A. Jörres, H.D. Lemke, Z.A. Massy, J. Passlick-Deetjen, M. Rodriguez, B. Stegmayr, P. Stenvinkel, C. Tetta, C. Wanner, W. Zidek, Review on uremic toxins: classification, concentration, and interindividual variability, *Kidney Int.* 63 (2003) 1934–1943.
- D. Pavlenko, E. Van Geffen, M.J. Van Steenberghe, G. Glorieux, R. Vanholder, K.G. F. Gerritsen, D. Stamatialis, New low-flux mixed matrix membranes that offer superior removal of protein-bound toxins from human plasma, *Sci. Rep.* 6 (2016).
- A.W. Martinez, N.S. Recht, T.H. Hostetter, T.W. Meyer, Removal of P-cresol sulfate by hemodialysis, *J. Am. Soc. Nephrol.* 16 (2005) 3430–3436.
- S. Eloit, D. Schneditz, T. Cornelis, W. Van Biesen, G. Glorieux, A. Dhondt, J. Kooman, R.J.P.O. Vanholder, Protein-bound uremic toxin profiling as a tool to optimize hemodialysis, *PLoS One* 11 (2016), e0147159.
- A. Davenport, V. Gura, C. Ronco, M. Beizai, C. Ezon, E.J.T.L. Rambod, A wearable haemodialysis device for patients with end-stage renal failure: a pilot study, *Lancet* 370 (2007) 2005–2010.
- A. Davenport, Portable and wearable dialysis devices for the treatment of patients with end-stage kidney failure: wishful thinking or just over the horizon? *Pediatr. Nephrol.* 30 (2015) 2053–2060.
- T. Cornelis, S. Eloit, R. Vanholder, G. Glorieux, F.M. Van Der Sande, J.L. Scheijns, K.M. Leunissen, J.P. Kooman, C.G. Schalkwijk, Protein-bound uraemic toxins, dicarbonyl stress and advanced glycation end products in conventional and extended haemodialysis and haemodiafiltration, *Nephrol. Dial. Transplant.* 30 (2015) 1395–1402.
- H. Susanto, M. Ulbricht, Characteristics, performance and stability of polyethersulfone ultrafiltration membranes prepared by phase separation method using different macromolecular additives, *J. Membr. Sci.* 327 (2009) 125–135.
- M. Teodorescu, M. Bercea, Poly(vinylpyrrolidone) – a versatile polymer for biomedical and beyond medical applications, *Polym. Plast. Technol. Eng.* 54 (2015) 923–943.
- Y. Koga, H. Fujieda, H. Meguro, Y. Ueno, T. Aoki, K. Miwa, M. Kainoh, Biocompatibility of polysulfone hemodialysis membranes and its mechanisms: involvement of fibrinogen and its integrin receptors in activation of platelets and neutrophils, *Artif. Organs* 42 (2018) E246–E258.
- Y. Su, C. Li, W. Zhao, Q. Shi, H. Wang, Z. Jiang, S. Zhu, Modification of polyethersulfone ultrafiltration membranes with phosphorylcholine copolymer can remarkably improve the antifouling and permeation properties, *J. Membr. Sci.* 322 (2008) 171–177.
- S. Nie, J. Xue, Y. Lu, Y. Liu, D. Wang, S. Sun, F. Ran, C. Zhao, Improved blood compatibility of polyethersulfone membrane with a hydrophilic and anionic surface, *Colloids Surf. B Biointerfaces* 100 (2012) 116–125.
- X. Liu, Y. Xu, Z. Wu, H. Chen, Poly (N-vinylpyrrolidone)-modified surfaces for biomedical applications, *Macromol. Biosci.* 13 (2013) 147–154.
- M. Matsuda, M. Sato, H. Sakata, T. Ogawa, K.I. Yamamoto, T. Yakushiji, M. Fukuda, T. Miyasaka, K. Sakai, Effects of fluid flow on elution of hydrophilic modifier from dialysis membrane surfaces, *J. Artif. Organs* 11 (2008) 148–155.
- M. Miyata, S. Konishi, Y. Shimamoto, A. Kamada, K. Umimoto, Influence of sterilization and storage period on elution of polyvinylpyrrolidone from wet-type polysulfone membrane dialyzers, *Am. Soc. Artif. Intern. Organs J.* 61 (2015) 468–473.
- K. Namekawa, A. Kaneko, K. Sakai, S. Kunikata, M. Matsuda, Longer storage of dialyzers increases elution of poly(N-vinyl-2-pyrrolidone) from polysulfone-group dialysis membranes, *J. Artif. Organs* 14 (2011) 52–57.
- S. Konishi, A. Fukunaga, H. Yamashita, M. Miyata, M. Usami, Eluted substances from hemodialysis membranes elicit positive skin prick tests in bioincompatible patients, *Artif. Organs* 39 (2015) 343–351.
- L.S. Wan, Z.K. Xu, Z.G. Wang, Leaching of PVP from polyacrylonitrile/PVP blending membranes: a comparative study of asymmetric and dense membranes, *J. Polym. Sci. B Polym. Phys.* 44 (2006) 1490–1498.
- K. Namekawa, M. Matsuda, M. Fukuda, A. Kaneko, K. Sakai, Poly (N-vinyl-2-pyrrolidone) elution from polysulfone dialysis membranes by varying solvent and wall shear stress, *J. Artif. Organs* 15 (2012) 185–192.
- S. Nie, L. Ma, Y. Xia, C. He, J. Deng, L. Wang, C. Cheng, S. Sun, C. Zhao, Novel heparin-mimicking polymer brush grafted carbon nanotube/PES composite membranes for safe and efficient blood purification, *J. Membr. Sci.* 475 (2015) 455–468.
- C. He, Z.-Q. Shi, C. Cheng, H.-Q. Lu, M. Zhou, S.-D. Sun, C.-S. Zhao, Graphene oxide and sulfonated polyanion co-doped hydrogel films for dual-layered membranes with superior hemocompatibility and antibacterial activity, *Biomater. Sci.* 4 (2016) 1431–1440.
- N. Nady, M.C. Franssen, H. Zuilhof, M.S.M. Eldin, R. Boom, K. Schroen, Modification methods for poly (arylsulfone) membranes: a mini-review focusing on surface modification, *Desalination* 275 (2011) 1–9.
- O. ter Beek, D. Pavlenko, M. Suck, S. Helfrich, L. Bolhuis-Versteeg, D. Snisarenko, C. Causserand, P. Bacchin, P. Aimar, R. van Oerle, R. Wetzels, P. Verhezen, Y. Henskens, D. Stamatialis, New membranes based on polyethersulfone – SlipSkin™ polymer blends with low fouling and high blood compatibility, *Separ. Purif. Technol.* 225 (2019) 60–73.
- M. Tjink, J. Janssen, M. Timmer, J. Austen, Y. Aldenhoff, J. Kooman, L. Koole, J. Damoiseaux, R. Van Oerle, Y. Henskens, D. Stamatialis, Development of novel membranes for blood purification therapies based on copolymers of N-vinylpyrrolidone and n-butylmethacrylate, *J. Mater. Chem. B* 1 (2013) 6066–6077.
- H.H.L. Hanssen, G.M.R. Wetzels, A. Benzina, F.H. Van Der Veen, T. Lindhout, L. H. Koole, Metallic wires with an adherent lubricious and blood-compatible polymeric coating and their use in the manufacture of novel slippery-when-wet guidewires: possible applications related to controlled local drug delivery, *J. Biomed. Mater. Res.* 48 (1999) 820–828.
- R.T. Pijls, H.H.L. Hanssen, R.M.M.A. Nuijts, L.H. Koole, Flexible coils with a drug-releasing hydrophilic coating: a new platform for controlled delivery of drugs to the eye? *Bio Med. Mater. Eng.* 14 (2004) 383–393.
- M.S. Tjink, M. Wester, J. Sun, A. Saris, L.A. Bolhuis-Versteeg, S. Saiful, J.A. Joles, Z. Borneman, M. Wessling, D.F. Stamatialis, A novel approach for blood purification: mixed-matrix membranes combining diffusion and adsorption in one step, *Acta Biomater.* 8 (2012) 2279–2287.
- S. Eloit, Experimental and Numerical Modeling of Dialysis, Ghent University, 2004.

- [31] I. Geremia, R. Bansal, D. Stamatialis, In vitro assessment of mixed matrix hemodialysis membrane for achieving endotoxin-free dialysate combined with high removal of uremic toxins from human plasma, *Acta Biomater.* 90 (2019) 100–111.
- [32] G. Rabbani, S.N. Ahn, Structure, enzymatic activities, glycation and therapeutic potential of human serum albumin: a natural cargo, *Int. J. Biol. Macromol.* 123 (2019) 979–990.
- [33] Y. Liu, Y. Su, X. Zhao, Y. Li, R. Zhang, Z. Jiang, Improved antifouling properties of polyethersulfone membrane by blending the amphiphilic surface modifier with crosslinked hydrophobic segments, *J. Membr. Sci.* 486 (2015) 195–206.
- [34] M.N.Z. Abidin, P.S. Goh, A.F. Ismail, M.H.D. Othman, H. Hasbullah, N. Said, S.H.S. A. Kadir, F. Kamal, M.S. Abdullah, B.C. Ng, The Effect of PCA-g-MWCNTs loading on the performance of PES/MWCNTs hemodialysis membrane, *Chem. Eng. Trans.* 56 (2017) 1609–1614.
- [35] L. Ma, B. Su, C. Cheng, Z. Yin, H. Qin, J. Zhao, S. Sun, C. Zhao, Toward highly blood compatible hemodialysis membranes via blending with heparin-mimicking polyurethane: study in vitro and in vivo, *J. Membr. Sci.* 470 (2014) 90–101.
- [36] G. Lesaffer, R. De Smet, N. Lameire, A. Dhondt, P. Duym, R. Vanholder, Intradialytic removal of protein-bound uraemic toxins: role of solute characteristics and of dialyser membrane, *Nephrol. Dial. Transplant.* 15 (2000) 50–57.
- [37] M.S. Tjink, M. Wester, G. Glorieux, K.G. Gerritsen, J. Sun, P.C. Swart, Z. Borneman, M. Wessling, R. Vanholder, J.A. Joles, Mixed matrix hollow fiber membranes for removal of protein-bound toxins from human plasma, *Biomaterials* 34 (2013) 7819–7828.
- [38] G. Catapano, J. Vienken, Biomedical applications of membranes, in: N.N. Li, A. G. Fane, W.S. Ho, T. Matsuura (Eds.), *Advanced Membrane Technology and Applications*, 2008, pp. 489–517.
- [39] R. De Smet, A. Dhondt, S. Eloit, F. Galli, M.A. Waterloos, R. Vanholder, Effect of the super-flux cellulose triacetate dialyser membrane on the removal of non-protein-bound and protein-bound uraemic solutes, *Nephrol. Dial. Transplant.* 22 (2007) 2006–2012.