Green Chemistry

Green membrane manufacture for peptide separations
DooLi Kim, Octavio R Salazar and Suzana Pereina Nunes

Nanstructured polymeric membranes are key tools in biomedical applications such as hemodialysis, protein separations, and purification heavily count on nanostructured polymeric membranes. For industrial membrane manufacture, an important step is the casting of polymer solutions. Polysulfone (PSU) and polyethersulfone (PES) are among the most successful polymers in this field. However, despite of the success of membrane technology, membrane manufacture itself is now under scrutiny. Solution casting uses relatively harmful solvents, such as dimethylformamide, N-methyl pyrroliodone, and dimethyl acetamide. These solvents are now included in the Registration, Evaluation, Authorization, and Restriction of chemicals (REACH) of the European Chemicals Agency (EACH), with perspectives to be banned in the near future and not be applicable anymore for membrane industrial fabrication, at least in Europe. It has been recently reported that the membrane manufacture industry produces 50 billion liters of wastewater containing toxic solvents per year. Finding green alternatives for membrane manufacture is urgently needed. This is the main motivation of this work. We report here a process in which PES is fully dissolved in an ionic liquid, without addition of any other organic solvent. Ionic liquids are considered green solvents from the perspective of enabling processes with no generation of harmful volatile organic chemicals (VOC), even if aspects related to the synthesis, life cycle and toxicity in wastewater of some of them have been seen as less environmentally friendly than mostly claimed. For a sustainable membrane fabrication, ionic liquids should be recycled. The role of ionic liquids in membrane technology has been limited and considered mostly in a different way. The membrane research using ionic liquids takes advantage of their ion conductivity, for instance in fuel cells, or their preferential interaction with CO₂ for gas separation. A successful strategy is the use of ionic liquid supported in porous membranes (SIMMs) as medium for gas CO₂ or SO₂ separation from other gases. Ionic liquids have been also polymerized as membrane material for gas separation. These applications rely on the fact that polymers hardly dissolved in ionic liquids. Few examples of polymer dissolution in ionic liquids have been previously reported. Therefore, ionic liquids have been seldom used for membrane fabrication. The few reports used cellulose in [EMIM]OAc, cellulose acetate in [EMIM]SCN and [BMIM]SCN, mixture of polybenzimidazole and polyimide in [EMIM]OAc, and polyimide in [EMIM]OAc. Ionic liquids have been additionally used in combination with other solvents.

1. Introduction

Biomedical separations, food processing, water desalination, and purification heavily count on nanostructured polymeric membranes. For industrial membrane manufacture, an important step is the casting of polymer solutions. Polysulfone (PSU) and polyethersulfone (PES) are among the most successful polymers in this field. However, despite of the success of membrane technology, membrane manufacture itself is now under scrutiny. Solution casting uses relatively harmful solvents, such as dimethylformamide, N-methyl pyrroliodone, and dimethyl acetamide. These solvents are now included in the Registration, Evaluation, Authorization, and Restriction of chemicals (REACH) of the European Chemicals Agency (EACH), with perspectives to be banned in the near future and not be applicable anymore for membrane industrial fabrication, at least in Europe. It has been recently reported that the membrane manufacture industry produces 50 billion liters of wastewater containing toxic solvents per year. Finding green alternatives for membrane manufacture is urgently needed. This is the main motivation of this work. We report here a process in which PES is fully dissolved in an ionic liquid, without addition of any other organic solvent. Ionic liquids are considered green solvents from the perspective of enabling processes with no generation of harmful volatile organic chemicals (VOC), even if aspects related to the synthesis, life cycle and toxicity in wastewater of some of them have been seen as less environmentally friendly than mostly claimed. For a sustainable membrane fabrication, ionic liquids should be recycled. The role of ionic liquids in membrane technology has been limited and considered mostly in a different way. The membrane research using ionic liquids takes advantage of their ion conductivity, for instance in fuel cells, or their preferential interaction with CO₂ for gas separation. A successful strategy is the use of ionic liquid supported in porous membranes (SIMMs) as medium for gas CO₂ or SO₂ separation from other gases. Ionic liquids have been also polymerized as membrane material for gas separation. These applications rely on the fact that polymers hardly dissolved in ionic liquids. Few examples of polymer dissolution in ionic liquids have been previously reported. Therefore, ionic liquids have been seldom used for membrane fabrication. The few reports used cellulose in [EMIM]OAc, cellulose acetate in [EMIM]SCN and [BMIM]SCN, mixture of polybenzimidazole and polyimide in [EMIM]OAc, and polyimide in [EMIM]OAc. Ionic liquids have been additionally used in combination with other solvents.

2. Methods

Materials
Polyethersulfone (PES, Ultrason®, average Mn = 75,000), 1-ethyl-3-methylimidazolium diethylphosphate ([EMIM]DEP, ≥ 98.0 %), dimethyl formamide (DMF, ≥ 99.8 %), dimethyl acetamide (DMAc, ≥
99.5 %) and N-methyl-2-pyrrolidone (NMP, ≥ 99.0 %) were supplied by Sigma-Aldrich. The polymer and the ionic liquid’s structures are shown in Scheme 1. Polyethylene glycol (PEG) and polyethyleneoxide (PEO) (Sigma-Aldrich), with molecular weights 300; 1,500; 6,000; 10,000; 35,000; 100,000; and 600,000 g mol\(^{-1}\), were used for solute rejection evaluation and determination of the molecular weight cut-off (MWCO). Bovine serum albumin (BSA) and 1,4-Dithiothreitol (DTT), ammonium bicarbonate and trifluoroacetic acid were also obtained from Sigma Aldrich. Iodoacetamide was obtained from GE Healthcare. Sequencing-grade modified trypsin was supplied by Promega. Acetonitrile was purchased from Fisher-Scientific.

Solution thermodynamics

The Hansen solubility parameter (\(\delta\)) for the ionic liquids [EMIM]DEP and [EMIM]OAc were determined by using the HSPIP software (4th edition 4.1.07)\(^{31}\). The total solubility parameter is given by equation 1:

\[
\delta^2 = \delta_m^2 + \delta_r^2 + \delta_h^2
\]

where \(\delta_m\) is the contribution due to the van der Waals interactions, \(\delta_r\) is relative to polar cohesive forces and \(\delta_h\) is due to hydrogen bonds. Miscibility tests were performed in 44 solvents with known solubility parameters to evaluate the \(\delta\) values for the ionic liquid. The phase diagram of a specific polymer/solvent solution can be theoretically estimated by calculating the Gibbs free energy of mixing, \(\Delta G_m\), based on \(\delta\) and \(\Delta G_m\) should be negative if only one phase is present with the polymer fully dissolved. \(\Delta G_m\) can be calculated\(^{26,32}\) with equation 2:

\[
\frac{\Delta G_m}{N_A} = kT \left[ \chi \phi_1 \phi_2 + \frac{a_1}{X_1} \ln \phi_1 + \frac{a_2}{X_2} \ln \phi_2 \right]
\]

where \(\chi\) is the Flory-Huggins parameter. \(\chi\) can be estimated from the difference between the total Hansen solubility parameters of the polymer and ionic liquid, determined as mentioned above. \(k\) is the Boltzmann constant; \(N_A\) is the Avogadro number; \(\phi_1\) and \(\phi_2\) are the volume factions of solvent and polymer, respectively; \(X_1\) and \(X_2\) are the corresponding number of segments of each component. From \(\Delta G_m\) values, the system compositions with the highest miscibility can be delimited, as conducted by other systems\(^{35}\).

Phase diagrams for PES/solvent/water ternary systems were estimated by measuring the cloud points for each solution with addition of water. The experiments were conducted at room temperature. PES solutions of various concentrations were prepared in different solvents. Water was added to each solution until it became turbid. The detected cloud points for a specific PES/solvent/water system delineate the binodal curve, which denotes the boundary between the stable (one phase) region and the meta-stable region of the phase diagram.

The coil size distribution of PES in each solvent was measured by dynamic light scattering (Zetasizer, Malvern). 0.1 wt% PES solutions in [EMIM]DEP, NMP, DMAc, and DMF were prepared and filtered through membranes with 0.45 mm pores before analysis. The experiments were done using He-Ne laser with wavelength 633 nm.

Solution kinetics

The kinetics of the phase separation, when different casting solutions are immersed in water, was evaluated by transmittance measurement using a Cary 5000 UV-Vis-NIR, Agilent, equipment. 16 wt% PES solutions in [EMIM]DEP, NMP, DMAc, and DMF were cast on a glass plate forming a 150μm-thick layer, which was immersed in a glass cuvette containing water. Changes of transmittance, starting from the moment of immersion in water until reaching a constant value, were monitored as a function of time at 600 nm\(^{22}\).

Values of relative light transmittance (\(T_r\)) were calculated by equation 3.

\[
T_r = \left( \frac{T - T_{\min}}{T_{\max} - T_{\min}} \right) \times 100 \%
\]

where, \(T\) is transmittance at a given time; \(T_{\min}\) is the minimum transmittance; and \(T_{\max}\) is the maximum measured transmittance. The rheological properties of polymer solutions were evaluated in an AR1500ex Rheometer (TA Instruments) at different temperatures at 1 Hz and 10 % oscillation strain. The viscosity of each polymer solution was measured at 10 s\(^{-1}\) shear rate.

Membrane preparation

Four binary solutions were prepared with PES in [EMIM]DEP. The following PES concentrations were chosen: 8, 12, 14, and 16 wt% PES. Additionally, 16 wt% PES solutions were prepared in NMP, DMAc and DMF. PES was dissolved in the ionic liquid at 90 °C and in NMP, DMAc, and DMF at 60 °C, stirring for a day. The polymer solutions were cast on a glass plate using a doctor blade with 150 μm gap and immersed into a deionized water bath to induce phase inversion and pore formation.

Membrane characterizations

The membrane morphology was observed on FEI Quanta 200, 600, and Nova Nano Field Emission Scanning Electron Microscopes (FESEM). To avoid pore collapse, the membranes were freeze-dried. For the cross-section, freeze-dried membranes were fractured in liquid nitrogen and then sputter coated with iridium.

Water permeance and rejection of neutral solutes (PEG) were measured under 2 bar in a dead-end filtration cell, calculated with the following equations:
The trypsin: proteinolute (PEG and PEO) diameter was calculated using the Stokes radius equation, where \( a = 16.73 \times 10^{-10} \text{M}^{0.557} \) for PEG and \( a = 10.44 \times 10^{-10} \text{M}^{0.587} \) for PEO, with \( a \) being the Stokes radius (in cm) and \( M \) the molecular weight of PEG and PEO (g mole\(^{-1}\)). The rejections were plotted as a function of the Stokes diameters (\( d = 2a \)) corresponding to each molecular weight.

### Protein digestion and peptide analyses

Bovine serum albumin (BSA) (Sigma-Aldrich) was digested into peptides and their rejection was evaluated in membrane filtration experiments, using a dead-end filtration cell. In summary, 500 µg of BSA dissolved in 8 M Urea Tris-HCl pH 8.5 were reduced by the addition of 10 mM DTT and incubated for 1 hour at 37 °C. Proteins were alkylated by the addition of 40 mM iodoacetic acid and incubated in the dark for 1 hour at 37 °C. 10 mM DTT were added to the sample, which was then incubated in the dark for another 15 minutes. The sample was diluted 10 times in 50 mM ammonium bicarbonate at pH 8.5 to reduce urea concentration to < 1 M. To digest the proteins, trypsin was added in a 1:50 (trypsin: protein) ratio and incubated overnight at 37 °C. The digestion was stopped by the addition of trifluoroacetic acid to a final concentration of 2 %. The sample was cleaned via reverse phase purification with Sep-Pak C18 cartridges (Waters), dried in a speedvac, re-suspended in 50 µl of 3 % acetonitrile 0.1 % trifluoroacetic acid in MQ water and used as feed. The peptide concentration was measured with Nanodrop at 280 nm wavelength.

To measure the rejection of the peptides, feed solutions containing 40 µg of peptides were filtrated by the membranes fabricated from PES/[EMIM][DEP] solutions using a sterilized Amicon cell (Millipore) under 2 bar. Feed and permeates were weighed, dried in a speedvac, and resuspended in 30 µl of 3 % acetonitrile (Fisher-Scientific) 0.1 % trifluoroacetic acid in MQ water. 2 µl per sample (feed and permeate) were loaded into the LC/MS (Ultimate 3000 UPPLC/Q-Exactive, Thermo Scientific) with an Acclaim PepMap RSLC 75 µm x 15 cm nanoViper column. Peak files were compared against UniProt database through MASCOT. MASCOT search results were combined and analyzed with Scaffold. Spectral counts from Scaffold were used to calculate the BSA peptide rejection (%) for each membrane as function of the peptides identified in the feed solution.

### Ionic liquid recovery

The waste containing a mixture of [EMIM][DEP] and water from the coagulant bath, after fabricating membranes was treated to recycle [EMIM][DEP]. Few steps were carried out to increase the concentration of [EMIM][DEP]. First, the water was evaporated in rotavapor (Buchi, Rotavapor R-215) at 90 °C (heating); 5 °C (cooling); 80 rpm (rotating speed), under 250 mbar (vacuum) for 2 hrs. In a second step the solution was submitted to vacuum at 130 °C. Third, magnesium sulfate (MgSO\(_4\)) was added to the solution to capture the remaining water and then centrifuged. The recycled ionic liquid concentration was quantified in all steps by refractometry (AR2008 Digital Abbe Refractometer, KRÜSS) using a calibration curve in all steps.

## 3. Results and discussion

### Solution thermodynamics

The Hansen solubility parameter (δ) of the ionic liquids [EMIM][DEP] and [EMIM][OAc] was estimated with the HSPiP software based on miscibility tests between the ionic liquids and 44 solvents (Table S1). The δ value for PES was previously reported by Hansen. The estimated differences between values for PES and ionic liquids, (δPES - δ[EMIM]DEP) and (δPES - δ[EMIM]OAc), were 4.9 and 8.7, respectively, indicating that [EMIM][DEP] is indeed a better solvent for PES than [EMIM][OAc]. |δPSU - δ[EMIM]DEP| is 5.4. This difference is already large enough to disfavor solubilization. From δ values for PES, [EMIM][DEP], [EMIM][OAc] and other solvents, the Flory-Huggins parameters, \( \chi_{PES/EMIM}^{DEP} \), \( \chi_{PES/EMIM}^{OAc} \), \( \chi_{PES/DEP} \), \( \chi_{PES/OAc} \), and \( \chi_{DEP/OAc} \), were calculated and applied to obtain a \( \Delta G_m \) for different concentrations. Figure 1 compares \( \Delta G_m \) values for different systems at 25 °C and 90 °C. \( \Delta G_m \) for PES/[EMIM][DEP] is positive in all range of concentrations, but it is lower than for PES/[EMIM][OAc] and for PSU/[EMIM][DEP]. The values for PES in NMP, DMAc, and DMF are negative. For non-charged organic solvents, \( \Delta G_m \) can be calculated from δ and \( \chi \) values, which mainly take into consideration interaction contributions of van der Waals forces, polarity, and hydrogen bonds. The \( \Delta G_m \) estimation in the case of ionic liquids is a relatively rough approximation, since additional strong coulombic interactions are not taken into account and ionic liquids are more complex systems than ordinary organic solvents. But the relative values shown in Figure 1 are a good indication of the quality of different solvents for PES and PSU. By comparing Figures 1a and b, the effect of temperature on the solubility of PES in ionic liquids can be seen. \( \Delta G_m \) decreases as the temperature is increased from 25 °C to 90 °C, a clear indication that the solubility is higher at higher temperatures.

Figure 2 shows the phase diagrams for different PES/solvent/water systems obtained by measuring their cloud
points. The 2 phases region increases in the following order of PES/NMP < PES/DMAc < PES/DMF ≤ [EMIM]DEP. The estimated $\Delta G_m$ for 16 wt% PES solutions increases in the same sequence. An indication of the solvent quality for a specific polymer is given also by the size of the coil in a diluted solution measured by DLS. The values of coil size for 0.1 wt% PES solutions in NMP, DMAc, and DMF are 17, 15, and 13 nm, respectively (Table 1). A better polymer-solvent interaction leads to coil expansion, which is consistent with the sequence of $\Delta G_m$ values measured for higher polymer concentration. The coil size in [EMIM]DEP was 15 nm, which is in the same range as in DMAc and even larger than in DMF.

Solution kinetics

The membrane morphology is highly influenced by the solution thermodynamics and by the kinetics of phase separation. The kinetics was investigated for 16 wt% PES solutions, by measuring the transmittance reduction when the solution is immersed in water. The results are shown in Figure 3. The phase separation kinetics for solutions in NMP, DMAc and DMF is very similar, with abrupt turbidity increase in the first 10 s, after immersion in water. For solutions in [EMIM]DEP, the turbidity increase is slower. This could be a consequence of higher solution viscosity, which delays the water-solvent exchange. The curves delineated by the cloud points (Figure 2) can be considered coincident with the binodal curve separating the stable (one phase) region of the phase diagram and the metastable region. The metastable region is separated from the instable (2 phases) region by spinodal curves. If the water-solvent exchange is fast, the solution will be quenched into the 2 phases region and phase separation will follow the spinodal decomposition mechanism, starting with continuous oscillations of concentration. If the water-solvent exchange is slow, the system might stay relatively long in the metastable region, between binodal and spinodal curves. This might be favored in PES/[EMIM]DEP solutions immersed in water, while spinodal decomposition might prevail in other solvents.

Independently of the phase separation mechanism, after entering the 2-phases region the system will separate in a dilute phase which gives rise to the pores and a continuous matrix with high polymer concentration. When the concentration of this phase is high enough, the mobility of the phase separated systems is so low that the morphology is immobilized, kinetically trapped.

Figure 1. (a) $\Delta G_m$ estimated for PES and PSU solutions in different solvents and polymer concentrations at 25 ºC and (b) at 90 ºC.

Figure 2. Phase diagram measured by cloud point test at 25 ºC.
Table 1. Coil diameters (Z-average) and polydispersity measured by DLS for 0.1 wt% PES solutions in different solvents; calculated Rg and c* values.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Diameter Z-Average(nm)</th>
<th>PDI</th>
<th>Rg(nm)</th>
<th>C*(wt%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMP</td>
<td>17.3 ± 0.2</td>
<td>0.18</td>
<td>6.6</td>
<td>10.0</td>
</tr>
<tr>
<td>DMAc</td>
<td>15.7 ± 0.2</td>
<td>0.19</td>
<td>6.0</td>
<td>15.4</td>
</tr>
<tr>
<td>DMF</td>
<td>13.3 ± 0.3</td>
<td>0.18</td>
<td>5.1</td>
<td>22.6</td>
</tr>
<tr>
<td>[EMIM]DEP</td>
<td>15.3 ± 0.3</td>
<td>0.23</td>
<td>6.0</td>
<td>15.4</td>
</tr>
</tbody>
</table>

Figure 3. Relative light transmittance, Tr, (600 nm wavelength) of 16 wt% PES solutions in different solvents cast as a 150 μm-thick layer as a function of time, after immersion in water.

As long as the viscosity of the concentrated phase is still low enough, the morphology evolves, the dilute phase changes in size and form, giving rise to larger pores before further water-solvent exchange proceeds and the system solidifies. In addition to the microporous morphology guided by phase separation, membranes frequently have large finger-like cavities, which are highly influenced by solution viscosity and will be discussed later.

**Solution rheology**

The viscosity of 16 wt% PES solutions in the different solvents and in different concentrations for solutions in [EMIM]DEP was investigated as a function of temperature; the results are shown in Figure 4a. The viscosity of 16 wt% PES solutions in [EMIM]DEP is up to 500-fold higher than in other solvents (NMP, DMAc or DMF) at room temperature (25 ºC). An abrupt decrease is observed as the temperature increases. The viscosity values become similar as the temperature approaches 70 ºC. The influence of concentration is directly related to the extent of entanglement between coils. Above the scaling critical concentration (c*) the coils begin to entangle, entering the semi-diluted regime (Figure 4b, inset). c* can be estimated from values of the radius of gyration, Rg, using equation 8:

\[
c* = \frac{M}{2\pi N_A R_g^3}
\]

where M is the polymer molecular weight.

Figure 4. (a) Viscosity at shear rate 10 s⁻¹ as a function of temperature for PES/[EMIM]DEP solutions with different concentrations; the red curve corresponds to 16 wt% PES solutions in DMF, NMP or DMF, which are practically coincident at this scale; (b) Storage modulus G’ at 1 Hz and oscillation strain 10 % as a function of temperature for 8-16 wt% PES/[EMIM]DEP and 16 wt% PES/DMF solutions; curves for 16 wt% PES in NMP and DMAc coincide with that in DMF; inset: representation of polymer coils in solutions with concentrations below and above c*; (c) G’/G” ratios as a function of temperature measured at 1 Hz and oscillation strain 10 % for PES/[EMIM]DEP solutions with temperature range, the viscosity has a strong dependence on different concentrations and 16 wt% PES solutions in NMP, DMF, and DMAc.
The z-average diameters in Table 1, obtained by DLS, are a measure of the hydrodynamic diameters ($D_n = 2R_g$) of the polymer coils in different solvents. In theta solvents, $R_g = 0.77 R_h$, where $R_h$ is the hydrodynamic radius. Therefore, $c^*$, for PES/[EMIM]DEP, could be estimated as being around 15.4 wt% (Table 1). Figure 4b shows how the values of the storage modulus $G'$ changes as a function of temperature for solutions with different PES concentration in [EMIM]DEP. $G'$ is a measure of elasticity. The absolute values of $G'$ are higher for the 16 wt% PES solution than for 8 wt%. 16 wt% is above $c^*$. 8 wt % is far below $c^*$ and therefore with poor entanglement between coils. The ratio between the loss modulus $G''$ and $G'$, as a function of temperature, is shown in Figure 4c. It indicates the solution capacity to dissipate energy, behaving more like a liquid and less like a gel at high ratios. $G''/G'$ is particularly high for 16 wt% PES solutions in NMP and decreases in this sequence: NMP > DMAc > DMF > [EMIM]DEP ($G''/G' = 193, 105, 79, 2$, respectively at 25 °C). The gel character of PES solutions in [EMIM]DEP is therefore higher than in other solvents. As the temperature increases, the $G''/G'$ ratios for different solvents become more similar. 16 wt% PES solutions in NMP are also above $c^*$ (estimated as 10 wt% for PES in NMP in Table 1). However, NMP is a better solvent for PES than [EMIM]DEP with lower $\Delta G_m$. NMP acts as plasticizer, reducing the friction between polymer-polymer segments. This leads to low viscosity (Figure 4a) and low elasticity.

Membranes were prepared from 16 wt% PES solutions in different solvents and different concentrations in [EMIM]DEP. Their morphologies were investigated by field emission scanning electron microscopy (FESEM) and shown in Figure 5. Membranes prepared from 16 wt % casting solutions in NMP, DMAc, and DMF have finger-like porous structures. Membranes cast from solutions in [EMIM]DEP are sponge-like, regardless of the polymer concentration (from 8 to 16 wt%, Figure 5 and 15), different than in other solvents. Pores could be hardly observed (Figure 2S), even at high magnification when [EMIM]DEP was used as solvent. This morphology is favoured by the high viscosity of the casting solution (20-550 Pa s, as seen in Figure 4a), which promotes a slow phase separation. When the water-ionic liquid exchange takes place, after immersion in the coagulation bath, the system might long remain metastable. Phases diluted in polymer do not evolve to form large pores. The ionic liquid diffuses into the bath and water comes into the polymer concentrated layer immobilizing the morphology as seen in the final membrane. With other solvents the solution viscosity is lower than 10 Pa s. Phase separation is fast (see Figure 3). By immersion in water the system is quenched into the 2-phases region of the phase diagram, which favours spinodal decomposition to form the pores. Pores might predominate, in opposite of casting solutions in other solvents. Moreover, high viscosity hinders the formation of finger-like cavities or macrovoids in solutions with ionic liquid. Macrovoids are caused by the abrupt intrusion of water into the solution layer, promoted by local instabilities of interface tension at the border between polymer solution and water. Low viscosity facilitates the uncontrolled water invasion. 42,44 Macrovoids are seen in Figure 5 for membranes prepared from solutions in NMP, DMAc and DMF, which have much lower viscosity than those in ionic liquid.

Membrane performance

The water permeances of the nanoporous membranes cast from PES/[EMIM]DEP solutions were measured and compared with membranes cast from solutions in NMP, DMAc and DMF. Although the pores of membranes fabricated from PES/[EMIM]DEP are smaller, their water permeance is higher than that of membranes cast from solutions in the other solvents, as shown in Figure 6a. The water permeances of the membranes fabricated from 16 wt%, 14 wt%, 12 wt%, and 8 wt% PES solutions in [EMIM]DEP were 20, 30, 65, and 140 L m⁻² h⁻¹ bar⁻¹. Comparing the membranes prepared with the same PES concentration (16 wt%) in different solvents, the permeances of those cast from solutions in [EMIM]DEP were 2 times higher than in NMP, 6-fold higher than in DMAc, and 20-fold higher than in DMF. The membranes cast from PES/[EMIM]DEP solutions had nanosized pores. As shown in Figure 6b and Table 25, the MWCO of membranes cast from 8, 12, 14, and 16 wt% PES solutions were 30, 5, 1.3, and 1.25 kg mol⁻¹, respectively. These values correspond to 5.2, 1.9, 0.9, and 0.88 nm solutes sizes respectively, as estimated using the Stokes radius equations 6 and 7. For comparison, membranes prepared from 16 wt% PES in NMP, DMAc and DMF are able to reject only larger solutes with the following sizes: 5.3, 5.1 and 5.5 nm. The pore size distribution estimated for different membranes is shown in Figure 6c, confirming that membranes prepared under comparable conditions using [EMIM]DEP had smaller pore sizes than when using NMP, DMAc or DMF.

Figure 5. FESEM images of membrane cross-sections: membranes prepared from 16 wt% PES solutions in [EMIM] DEP, NMP, DMAc, and DMF.
Figure 6. (a) Water permeance as a function of time, measured for membranes prepared from PES/[EMIM]DEP solutions with different polymer concentrations and 16 wt% PES solutions in NMP, DMF, and DMAc; (b) PEG (and PEO) rejections for the same membranes tested in Fig. 6a (data in Table 2S); (c) estimated pore size distributions.

The MWCO’s of the membranes prepared in this work were compared with PES membranes previously reported in the literature. The MWCO-permeation trade-off plot is shown in Figure 7a. The MWCO-permeation trade-off plot of the membranes fabricated in this study (in red) and membranes previously reported in the literature (Table 3S) are shown in Figure 7a. The membranes prepared from PES/[EMIM]DEP solutions are able to reject smaller solutes (1,250 g mol\(^{-1}\)) than most other membranes, while keeping superior water permeance. As a whole in the range of MWCO below 70 kg mol\(^{-1}\) only one literature data on permeance (187 L m\(^{-2}\) h\(^{-1}\) bar\(^{-1}\)) is reported higher than in our case (for MWCO 10 kg mol\(^{-1}\)) which resulted from optimization by non-solvent addition in the dope solution, using a short air gap.

Figure 7. (a) MWCO-permeation trade-off plot of the membranes fabricated in this study (in red) and membranes previously reported in the literature (Table 3S) and (b) BSA peptides rejection versus peptides molecular weight, measured with membranes cast from PES/[EMIM]DEP solutions with different polymer concentrations.

Peptides separation
The membranes cast from PES/[EMIM]DEP were applied in the separation of peptides with molecular weights ranging from 800 to 3,500 g mol\(^{-1}\). After peptide analyses by proteomics, the rejections were calculated. The peptide rejection for each membrane can be found in Figure 7b. All BSA peptides larger than 1,150 g mol\(^{-1}\) were rejected more than 95% by the membrane cast from 16 wt% PES in [EMIM]DEP with MWCO 1,250 g mol\(^{-1}\) (estimated with PEG). Peptides with molecular
weight larger than 2000 g mol⁻¹ were rejected almost 100 %. In the case of the membrane from 14 wt% PES, 95 % rejection of peptides with molecular weight 1,450 g mol⁻¹ and 100 % rejection of peptides with size over 2,050 g mol⁻¹ were measured. Membranes from 12 wt% and 8 wt% of PES had MWCO’s of 5,000 and 30,000 g mol⁻¹, respectively, and were able to reject even peptides slightly smaller than their measured MWCO’s. As a whole, their rejection of smaller peptides was lower than for membranes from 14 and 16 wt% PES. The membrane separation of charged solutes can be affected by size exclusion and Donnan exclusion effects. In nanofiltration (NF) membranes, the size exclusion effect is however predominant; Donnan exclusion effects are predominant in the separation of peptides with ultrafiltration (UF) membranes⁵⁹. Membranes from 16 wt% and 14 wt% have MWCO’s of 1,250 and 1,300 g mol⁻¹. Separation by size exclusion might be the preferential mechanism in this case. However, membranes from 12 wt% and 8 wt% solutions have pores in the range of ultrafiltration and, might be more affected by Donnan exclusion effects. This might be one of the reasons why some peptides, which are smaller than the pre-estimated MWCO, could be rejected.

Recovery of [EMIM]DEP
We evaluated the possibility of recovery of ionic liquid from the membrane fabrication bath. The concentration of [EMIM]DEP in the all recovery steps is shown in Figure 8. The starting concentration of [EMIM]DEP in the waste solution was of 1.4 %. The solution was first concentrated by rotary evaporation, leading to the [EMIM]DEP concentration of 87.4 %. The additions of vacuum and heat increased the concentration to 95.5%. MgSO₄ was used to absorb the remaining water, leading to a final concentration of 99.6%.

Figure 8. Concentration of [EMIM]DEP at different steps of [EMIM]DEP recovery.

4. Conclusion
We identified an ionic liquid that is able to completely dissolve PES. We propose the PES/[EMIM]DEP system for membrane manufacture by solution casting and immersion in water. The new process is fully absent of volatile solvents and therefore constitutes a new route for PES membrane manufacture. The process is environmentally friendly and healthier than classical membrane manufactures currently implemented in the industry, as long as a further step of ionic liquid recovery from the water bath could be provided. The proposed casting solution uses only chemicals accepted as non-hazardous and attend any criteria to keep the process out, for instance of the REACH list of concerned chemicals. The method guarantees the continuity of production of PES membranes even if future environmental policies would ban the currently used solvents, such as NMP, DMF, and DMAc, from industrial production. We evaluated the thermodynamic conditions and the kinetics of phase separation for the new system. ΔG° is positive, when estimated taking into account solubility parameters, but low enough to promote a homogeneous solution, while higher values were calculated for PSU/[EMIM]DEP. The viscosity and G’ are higher than for PES solutions in NMP, DMF and DMAc. The values are highly dependent of concentration in the range of 8 to 16 wt%, which is relevant for membrane fabrication. Nanoporous sponge-like membranes with unusually fine structure were obtained. By controlling the polymer concentration, membranes with MWCO’s of 30, 5, 1.3, and 1,250 g mol⁻¹ were obtained with high water permeance. The membranes were applied in the separation of a peptide mixture with molecular weights in the range of 800 to 3,500 g mol⁻¹, which could be effectively separated. Now concerning recycling, the ionic liquid could be recovered from the membrane fabrication bath, by simple steps, based on evaporation. The new manufacturing process is not only environmentally advantageous, but leads to PES membranes with performance characteristics that were previously not available.

Acknowledgements
The research reported in this publication was sponsored by King Abdullah University of Science and Technology (KAUST).

Supporting Information
Rejections of PEG, morphological characterization, and membrane rejection properties compared to the literature.

References