Research Paper

Effect of Polymer Loading on Membrane Properties and Uremic Toxins Removal for Hemodialysis Application

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Article info

Keywords

Highlights

- The lower weight percentage loading of PES was studied to remove urea and p-cresol.
- Percentage of PES was significant on morphology, properties and toxins removal.
- The sample solution was conditioned to the real sample.
- Urea and p-cresol removal for 14 wt.% of PES loading was 80.90% and 36.85% for 4h.

Graphical abstract

Abstract

The adequacy of uremic toxins removal via hemodialysis treatment is essential for every kidney failure patient. To obtain hemodialysis adequacy, the effects of main polymer were investigated. The hollow fiber membranes were produced by using dry/wet spinning process from dope solution comprising PES as the main polymer, 3% poly(vinyl pyrrolidone) (PVP) in 1-methyl-2-pyrrolidone (NMP) at 40-cm air gap. PES loadings of 14, 16, and 18 wt.% were studied. The membrane morphology was characterized by using a scanning electron microscope (SEM) and the membrane properties were measured by using contact angle measurement (WCA). Membrane performance was evaluated by pure water flux (PWF), retention to bovine serum albumin (BSA), p-cresol and urea removal (URR) by using cross-flow permeation system. SEM analysis showed the asymmetric finger-like structure obtained for each polymer loading. The dense skin layer in the inner surface had thickened, followed by the increasing polymer weight loading. The 14 wt.% PES loading had a better pore size (116 nm) and porosity (74%). The WCA showed that the hollow fiber membranes studied were hydrophilic, and the utilization of 14 wt.% PES loading obtained better PWF (108.58 Lm^{-2}h^{-1}). However, this result had an impact on the impairment of BSA retention. The BSA retention for 14 wt.% PES loadings was 88.23%. The URR and p-cresol removal for 14 wt.% PES loading was higher (80.90% and 36.85% for 4 h, respectively) compared to others. As a conclusion, the percentage weight loading for polymer was a significant influence for morphology, membrane properties, and uremic toxins removal.

1. Introduction

Kidney is one of the important organs needed to carry out human body functions. Its main role in the body is to clean body fluid from organic acids and metabolic waste by a series of urine production stage that covers water and toxin clearance. Patients with kidney failure are immediately required to obtain treatment from the doctor. It refers to the incapability of the kidney to perform their essential tasks: eliminating waste products of body metabolism, such as urea, creatinine and excess water, apart from maintaining balanced electrolytes in body and other substances by removing excess sodium [1]. It is commonly due to certain conditions, such as diseases (e.g., diabetes, hypertension) and those injured with septic or systemic inflammatory
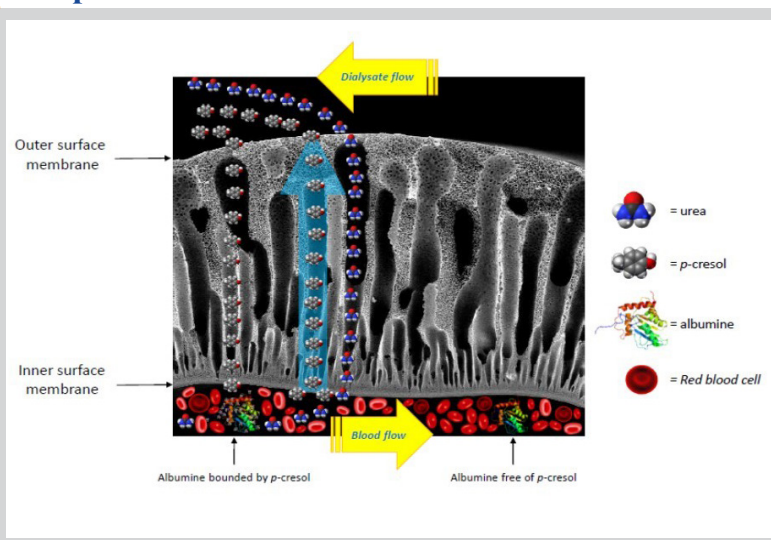
response syndrome (SIRS). Kidney failure can be detected through some signs such as pallor leuconychia, pulmonary edema, raised blood pressure, peripheral edema, and pleural effusion with symptoms such as tiredness, loin pain, anorexia, itching, nausea, vomiting and hematuria [2]. Generally, peritoneal dialysis, kidney transplant or hemodialysis (HD) can be opted as clinical treatment for kidney failure patients. By considering the cost and frequency of infection occurred during treatment, a widely used clinical treatment widely is HD using dialysis membrane. Through this treatment, the water-soluble uremic toxins such as urea and creatinine, middle molecular weight uremic toxins such as β_2-microglobuline, and protein-bounded uremic toxins such as *p*-cresol and phenol can be removed [3]. The HD membrane eliminates metabolites or wastes from the blood of kidney failure patients via an artificial kidney through dialysis principle called hemodialysis membrane. Hemodialysis treatment is not intended for healing the patient, but to prolong the life of patient in acute and chronic conditions.

Polyethersulfone (PES) is one of most commonly materials used to produce HD membrane besides cellulose triacetate, polysulfone, polyamide, polyacrylonitrile, and polymethylmethacrylate [4]. Some of the advantages of PES are its good oxidative, thermal stability, chemical properties, and mechanical properties [5]. Those materials have to fulfill the main requirements for HD membrane in terms of having biocompatibility and an excellent trait for uremic toxins removal. The definition of biocompatibility in HD membranes is referred to the insufficiency of reaction by body affected of the membrane. In HD, the biocompatibility called hemocompatibility refers to the properties that the membrane has to fulfill in terms of reduced coagulation, platelet adhesion, protein adsorption, and hemolysis [6,7]. Blood and membrane surfaces will be in contact during a HD process, causing a biological effect that leads to adverse effect on the patient health and membrane performance. Some cases that occur during the HD process while the blood is in contact with an incompatible membrane are an infection, cardiopulmonary disease, malignancy, and malnutrition [8]. The coagulation of protein in the blood is perhaps the most common while the blood is in contact in the bioincompatibility membrane. Meanwhile, the effect on membrane performance decreases the membrane quality as a result of blockage of membrane surface (pore) by the protein blood.

To meet the eligibility requirements in uremic toxins removal, the membrane produced has to be asymmetric and thin in size. The cellulosic-based membrane has a thin wall, which has a good impact on the diffusion process. On the other hand, an original synthetic membrane such as polysulfone has a very thick wall, which leads to the poor performance in diffusion process. Therefore, PES was developed and named as a modern synthetic membrane with good permeability and thinner walls. This material has proven to involve diffusion and convection to be employed simultaneously [9].

HD membrane is derived from polymeric materials. The main principle of the membrane is filtration. Membrane separation technology is more effective and efficient. That is because the membrane separation has the advantage of flexibility, requires little energy, does not alter the molecular structure of a substance separated, can be operated at room temperature, and does not require additional chemical substances during the separation process [10]. The dialysis membrane must possess a selective transport property that is able to withstand larger species and skip the smaller species through the membrane.

The criteria of a dialysis membrane include high solute permeability, high water permeability, and a balance between solute and water permeability, mechanical strength when wet, biocompatibility, and low in cost. The HD membranes become wet through contact with blood, where they will change in inner diameter, thickness or length, and they must have excellent mechanical strength. The best membranes applied into HD are membranes that have a large pore area, are strong, readily stretched, thin, and lightweight [11].

Blending on polymer interpreted a physical mixture that is not bonded covalently by accumulating the properties of different polymers into a single membrane [12]. This technique is most widely used in the development of HD membrane modifications, as its specifications were to increase the hydrophilicity and biocompatibility of synthetic membrane dialyzer. However, problems regarding material leaching during HD process and biocompatibility of material added are very important to consider. Therefore, this study will explore the minimal percentage loading of polymer used. Increasing the hydrophilicity of the membrane will help through the addition of poly(vinyl pyrrolidone) (PVP). PVP was used to improve the porosity, uremic solute removal, and biocompatibility performance of the main polymer. The favorable channel- and finger-like structures were obtained with lower PVP (below than 4 wt.%). This led to greater solvent and nonsolvent exchange rate obtained [13].

Some parameters on dry-wet spinning parameters process and composition of dope solution greatly affect the thickness and thinness of the

hollow fiber (HF) membrane produced. The effect of air gap distance of the membrane spun, collector drum speed, dope extrusion rate, and bore fluid flow rate has been studied by Mansur et al. [14]. It was stated that the extra small and thin membrane can be obtained by increasing the air gap, thus affecting the flux and BSA retention performance. The perfectly asymmetric structure for membrane can be obtained when the bore fluid and dope extrusion rate were set in a ratio of 1:1. Meanwhile, a composition of dope solution such as main polymer (PES), poly(vinyl pyrrolidone) (PVP) as additive, and 1-methyl-2-pyrrolidone (NMP) as solvent, was also studied in order to obtain the desired hollow fiber size.

In the present study, the weight percentage (wt.%) loading of PES was optimized to obtain the best morphology and properties for urea removal that was representative of the water-soluble uremic toxins and *p*-cresol removal as representative of the protein bounded uremic toxins. The weight percentage loading less than 20 wt.% was chosen to obtain a thin membrane. Furthermore, the adequacy of uremic toxins removal could be achieved. It also considered of capability the membrane to clean and remove protein-bounded uremic toxins (*p*-cresol). Based on the hypothesis, with a low polymer weight percentage loading, it is possible to produce membranes with better pore size, better percentage porosity, and thinner in size in order to clean more of the protein-bounded uremic toxins. The 14, 16, and 18 wt.% of PES were studied using 3 wt.% PVP for the fabrication of hollow fiber membrane using dry/wet phase inversion spinning.

The BSA solution was used as solvent for the *p*-cresol in this study. It is known that *p*-cresol is bounded by protein in the blood. Furthermore, this study tried to utilize BSA solution in order to close the test solution to the actual or real condition of a real sample. Normally, researchers would use pure water as a solvent for the uremic toxins tested. This study is intended to inhibit any inhibitor parameter during the removal process. Moreover, the results obtained from this study will not differ much from the application with that on a real sample.

2. Materials and methods

2.1. Materials

The PES (Radel A-300 Resin) as main material was obtained from Solvay Advanced Polymer (USA). Additive PVP-K90 (MW=360.000 g/mol) as pore forming agent and hydrophilicity as well as biocompatibility booster and also bovine serum albumin (BSA) in purity more than 98% were purchased from Sigma-Aldrich. Solvent NMP analysis grade (purity 99.5%; MW=99.1 g/mol) was obtained from Acros Organics. Meanwhile the Urea 99%, para-(dimethylamino)benzaldehyde (DMAB) 98%, ethyl alcohol 96% and hydrochloric acid (HCl) 37% were purchased from Sigma Aldrich.

2.2. Experimental

2.2.1. Hollow fiber membrane fabrication

Hollow fiber membranes were spun by using dry/wet spinning machine as shown in Figure 1. PES was dried in a oven at 60°C for 5 h to remove absorbed water prior to use. Homogenous dope solutions were made from PES and PVP dissolved in NMP solvent. The composition of dope solutions was varied by changing the PES percentage (14, 16, and 18 wt.%). PVP concentration was fixed for 3 wt.%. The mixture of PES, PVP, and NMP were put into dissolving bootle at 50°C under constant mechanical stirring for 24 h to make the dope mixture dissolve completely. The homogenous dope solution was then degassed for 4 h to get rid of the bubbles. The fresh dope solution was inserted to dope reservoir. The air gap was set for 40 cm. By pressured using nitrogen gas, the dope solution go passed through to the spinneret (orifice diameter size for inner and outer is 0.4/0.8 mm). The dope solutions were spun at dope extrusion rate (DER) of 1 mL/min. While the distilled water as a bore fluid was set the flow rate of 1 mL/min. Then dope solution and bore fluid were then fall and go inside to the water in coagulant bath. The spun hollow fibers were collected by drum collector at the speed of 10 m/min. Spinning process was done at room temperature (29°C). After spinning process finished, the fabricated hollow fibers were stored under tap water for 3 days to removed residual NMP. At the end, the fabricated hollow fibers were kept in 10 wt.% glycerol for 1 day to prevent membrane structure collapse.

2.3. Characterizations

2.3.1. Scanning electron microscopy (SEM)

The structural morphology of the HF membrane outer surface view and

cross sectional view were observed by tabletop SEM (Model: TM3000 Hitachi High Technologies America, USA). The cross section samples were prepared under liquid nitrogen. The samples then attached to an aluminum specimen stab with double surface carbon tape prior to sputtering with gold using SC7620 'Mini' sputter coater/glow discharge system (Quorum Technologies, UK).

2.3.2. Porosity and pore size

Membrane porosity (ε) was measured by dry-wet weight method. The membrane was equilibrated in water for 5 h. The weights of wet membrane, dry membrane, and the volume of HF membrane was measured. The membrane porosity was calculated by Eq.1 [15].

$$\varepsilon = \frac{M_1 - M_2}{V . \delta_{water}} \tag{1}$$

where, M_1 and M_2 are the weights of wet and dry membrane (gram), respectively. V is the volume of HF membrane (cm^3) and δ_{water} is the density of pure water (g/cm^3). Then the pore size was calculated by Guerout-Elford-Ferry equation (Eq. 2) [15].

$$r_m = \sqrt{\frac{(2.9 - 1.75\varepsilon) x \, 8\eta \iota Q}{\varepsilon x A x \Delta P}} \tag{2}$$

where, η is water viscosity at 25°C, ι is membrane thickness (m), Q is permeate water per unit time (m^3/s), A is effective area of membrane (m^2), and ΔP is operational pressure (Pascal). Pore diameters of HF membrane are calculated by multiplying r_m by 2.

2.3. Contact angle measurement

The hydrophilicity of HF membranes produced weremeasured by using the sessile drop method Goniometer (System OCA; Dataphysic, USA). A small drop 0.3 μL of pure water dropped on the surface membrane using a syringe with 1 μL/s of dosing rate. The micro syringe and needle need to be dirt free and dry prior to filled up. Ten measurements were taken for each strand then calculate for the average contact angle value.

2.4. Membrane properties

2.4.1. Pure water flux and BSA rejection

The water flux was measured to evaluate the performance of HF membrane. The water flux of the HF membranes fabricated were calculated using Eq.3 and tested by using cross-flow permeation system.

$$J_W = \frac{V}{Axt} \tag{3}$$

where J_W is the water flux of HF membrane (L.m^{-2}.h^{-1}), V is the volume of permeate (L), A is the effective surface area (m^2), and t is the permeation time (h). While the BSA rejection as represent of protein rejection was calculated using Eq. 4.

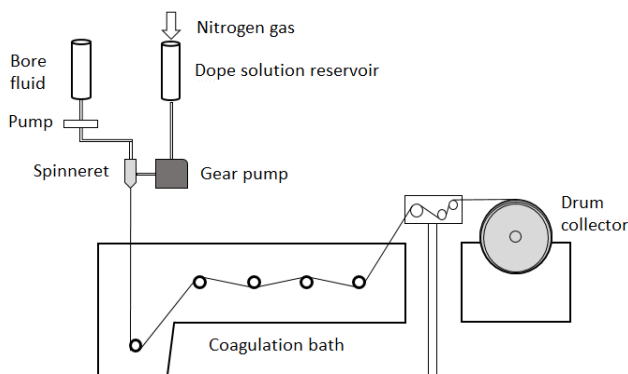$$R(\%) = \left(1 - \frac{C_p}{C_f}\right) x \, 100\% \tag{4}$$

where C_p and C_f are the BSA concentration of the permeate and feed respectively. The BSA concentration was analyzed by using UV-Vis spectrophotometer (DR 5000) under wavelength 280 nm. An thousand ppm of BSA was used as feed concentration.The cross-flow permeation system was used to measured the PWF, BSA rejection, and urea removal can be seen in the Figure 2.

Based on the Figure 2, the feed solution is come in from one edge of hollow fiber membrane and retentate come out at the other edge. While, the permeate solution is coming out from pores in the surface of hollow fiber membrane.

2.4.2. Urea and p-cresol analysis

The qualitative and quantitative analysis of urea used an Ehrlich's ragent (DMAB). The DMAB as spectrophotometric reagent coupled with ethyl alcohol and HCl to produce complex agent. The DMAB together urea at ambient temperature was producing a chromogen that emits a yellow-green colorthat can be detected under UV Vis spectrophotometer (as seen on Figure 3). The complex agent was prepared by dissolving 1.6 gram of DMAB in small amount of ethyl alcohol, 10 mL of concentrated HCl is added subsequently and volume was made up to 100 mL using ethyl alcohol [16]. Then 2 mL of urea mixed with 2 mL of complex agent and measured at 420 nm by using UV Vis spectrophotometer. While the p-cresol was measured at 283 nm by using UV Vis spectrophotometer. The 50 μg/mL of p-cresol was used as feed solution by adding 100 μg/mL of BSA to representing the presence of proteins during performance test. It is due to the presence of p-cresol always binding to proteins, like red blood cell and albumin.
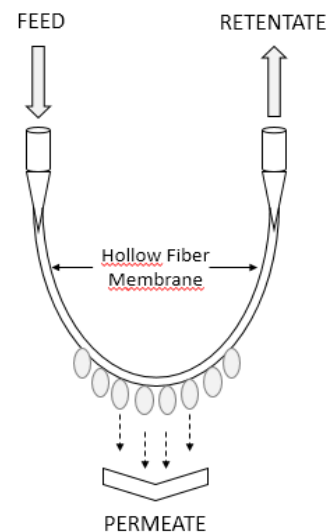
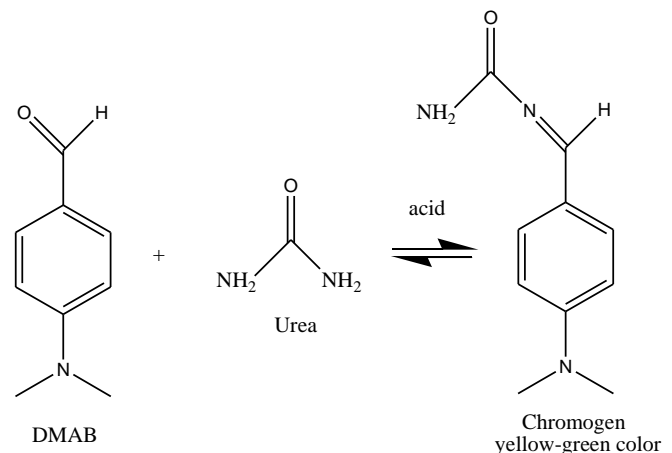**Fig. 2.** Schematic experimental set up of cross cross flow single hollow fiber membrane.

Fig. 1. The schematic diagram of HF spinning.

Fig. 3. Sheme of DMAB-urea reaction.

2.4.3. Urea and p-cresol removal

The cross-flow HF permeation system (Figure 2) was used to measure the urea and *p*-cresol removal. Removal mechanism is through a decreasing concentration flowing from the feed to the permeate through the pores of HF membrane. The calculation of removal (*%*) was using Eq.5.

$$Removal\ (\%) = \frac{C_p}{C_f}\ x\ 100 \qquad (5)$$

with C_p and C_f are concentration of urea or *p*-cresol in permeate and feed respectively.

3. Results and discussion

3.1. Effect of polymer loading on membrane morphology

The fabrication of HF membrane using dry/wet phase inversion spinning for each percentage of PES has been successfully fabricated. The morphology of membranes studied can be seen in Figure 4. From the cross-sectional view, the porous structure and finger-like void structure from inner to outer edge of membranes studied are almost similar for the varied polymer concentration. All of the membranes contained macrovoids structure. The 14 wt.% PES loading had larger finger-like macrovoids. It is due to its lower polymer concentration that caused the non-solvent diffusion rate to be faster than the solvent into polymer-poor phase [17].

On the other hand, the thicker dense skin layer in the innermost surface exhibited higher polymer concentration. There was thicker size of the outer diameter, inner diameter, and wall thickness of membranes with higher polymer concentration. Those phenomena occur due to the viscosity of dope solutions that was increased by increasing polymer concentration [11]. These phenomena had a bad impact on the PWF and solute removal, but neither had any (impact) to the BSA rejection. The dense structure helps in retaining the albumin and red blood cells to cross through the membrane, however, the thicker dense part at the innermost layer was unfavorable for the uremic toxin removal. The thicker dense skin layer on inner surface was due to the demixing of solvent and non-solvent during phase inversion, which was time consuming compared with the lower polymer concentration that can take place spontaneously [17].

The viscosity of the dope solution was measured by using the Cole-Parmer® viscometer. Viscosities of 14, 16, and 18 wt.% polymer loadings were 2003.9, 2414.3, and 2860.2 centipoise (cP), respectively. From the outer surface view, the pore size of the HF membrane can be observed (Table 1). Based on the images obtained from SEM, the smaller pore size (116 nm) and higher percentage porosity (74%) were achieved by the 14 wt.% loading of PES. This achievement is better compared with other weight percentage loadings. It may cause 14 wt.% weight loading of PES to have a smaller viscosity. Thus, it impacts the pore formation during spinning process. The higher weight percentage loading of PES produces higher viscosity [18]. The greater the viscosity, the greater the pore size is, making it inhomogenous, as seen in the 16 wt.% and 18 wt.% weight loadings of PES. Generally, the pore size and porosity affects the performance of permeability and uremic toxin removal, especially for water-soluble uremic toxins such as urea, creatinine, and uric acid [19].

3.2. Effect of polymer loading on membrane transport properties

Excess water in the body is one of the symptoms of kidney failure disease that needs to be treated using hemodialysis treatment. Excess water has harmful effects by contributing to difficulty in breathing, high blood pressure, heart problem, discomfort, and swelling or edema. By cleansing the water overload in the blood, the water-soluble uremic toxins can be removed automatically. Therefore, water flux measurement is required for testing on developing HD membranes. Synthetic polymers such as polysulfone (PSf) and PES, which are commonly used as basic polymer in HD membrane, are known to have high hydrophobicity. To support the physical properties of PES, PVP was used as additives to enhance the hydrophilicity. The PVP is also able to increase the membrane porosity [20].

Table 1
Characteristics of membranes studied.

Polymer loading (wt.%)	Viscosity (cP)	Average Pore size (nm)	Porosity (%)	Outer/ inner diameter size (µm)	Dense skin layer (nm)
14	2003.9	116	74	446/ 227	436
16	2414.3	420	48	543/ 332	610
18	2860.2	331	37	639/ 394	1,700

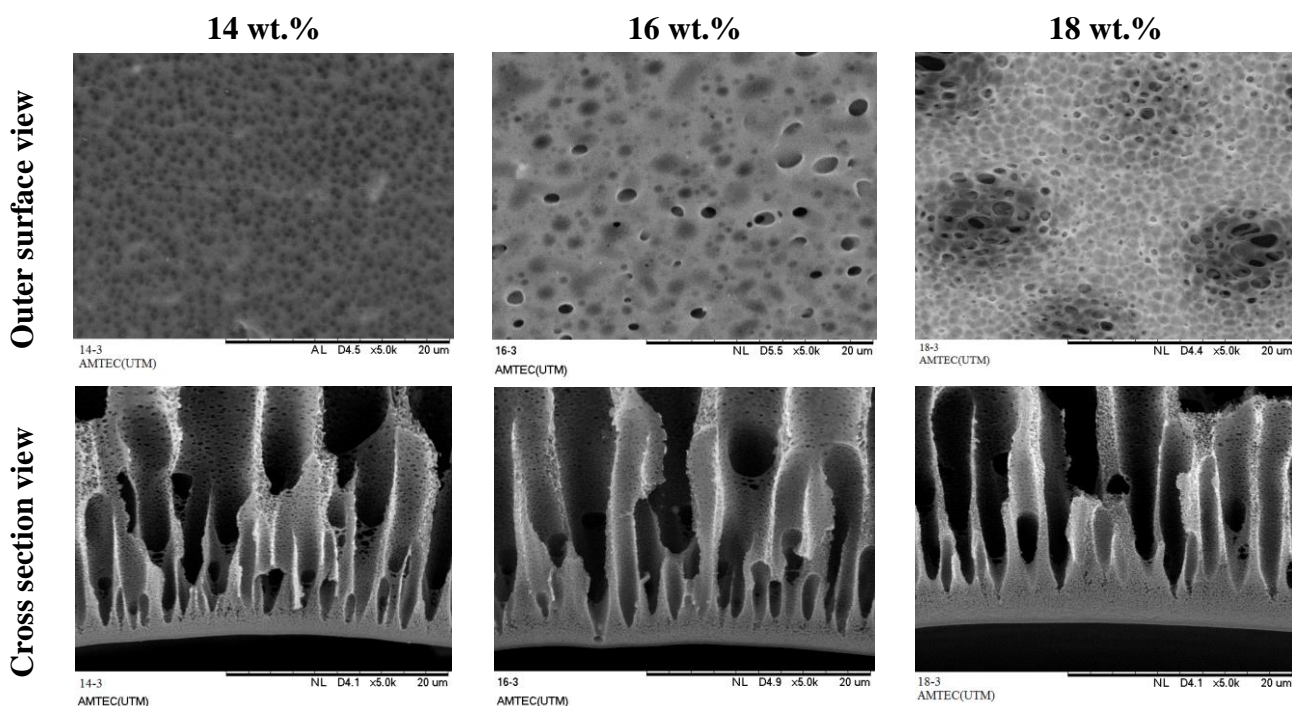|	14 wt.%	16 wt.%	18 wt.%

Fig. 4. Scanning electron microscopy images for varying polymer loading.

The HF membranes produced in this study had low water contact angle (65.58, 78.67, and 79.31 for 14, 16, and 18 wt.% PES loadings, respectively), which indicates hydrophilic membrane (Figure 5a). These properties have a great impact on pure water flux and protein rejection. The highest value of PWF was achieved by the 14 wt.% PES loading, which was 108.58 Lm^{-2}h^{-1} (Figure 5b). This is attributed to its lower surface hydrophilicity. However, its BSA rejection was smaller compared with other polymer loadings. The best value of BSA rejection in this study was achieved by 18 wt.% PES loading (Figure 5b). This may be due to the higher dense layer formed in the inner surface, which restrained the BSA movement across the HF membrane [21].

3.3. Effect of polymer loading on urea and p-cresol removal

Urea and *p*-cresol have a slightly similar molecular weight. The molecular weight of urea is 60.056 g/mol and *p*-cresol is 108.14 g/mol. Basically, the uremic toxins are easy to remove by using polymeric HF membranes. However, *p*-cresol is classified as protein-bounded uremic toxins, which is difficult to be removed by polymeric HF membranes through diffusion process. In this study, there was an attempt to remove *p*-cresol via PES-based membrane combined with PVP and NMP as additive and solvent, respectively.

Based on the Figure 6, it is shown that urea had been removed to 80.90% by 14 wt.% PES loading for 4 h through the cross-flow permeation system. The best URR for varied polymer loading study was 14 wt.%. This is because the 14 wt.% PES loading of the HF membrane has a great hydrophilicity compared to others. The more hydrophilic the membrane is, the easier the water and uremic toxins can be dissolved and exit from the lumen of the HF membrane. The great porosity also supports the removal of uremic toxins during the dialysis process [22]. All membranes studied had a gradually increased URR following the test permeation time starting from 1 to 4 h.

Different from the results obtained for urea removal, *p*-cresol removal in BSA solution has a lower percentage of removal by using cross-flow permeation system. The higher percentage of removal of *p*-cresol in the BSA solution was 36.85% obtained by the 14 wt.% PES loading (Figure 7). The 18 wt.% PES loading had a lower removal of *p*-cresol due to its thicker dense layer compared with other loadings. Since the *p*-cresol dissolved in the BSA solution, it bound with the BSA via Van der Waals' type interaction [23]. Therefore, the *p*-cresol was not easily removed although it had a small molecular weight due to the protein-binding [24].

4. Conclusions

The porous asymmetric and finger-like void structure from the inner to outer edge of membranes studied had been successfully fabricated by varied polymer loadings (14, 16, and 18 wt.%). The hydrophilic membrane was achieved for all polymer loadings by using PVP as an additive. The lower WCA achieved had a good impact on the water flux performance but not for BSA rejection. The HF membrane using 14 wt.% of PES loading could obtained PWF 108.58 Lm^{-2}h^{-1}. However, the BSA rejection was smaller (88.23%) compared with the 18 wt.% PES loading (90.49%). For the uremic toxins removal, the 14 wt.% of PES loading had a better removal of urea as representative of the water-soluble uremic toxin, and *p*-cresol removal as representative of the protein-bounded uremic toxin, compared with other percentage loadings. The urea was very easily removed compared with *p*-cresol even though it had a smaller molecular weight. The effect of interaction between the toxins and proteins really impacted the uremic toxin removal during dialysis. The membrane performances such as water flux, protein retention, and uremic toxins clearance during treatment must be in the main consideration criteria.
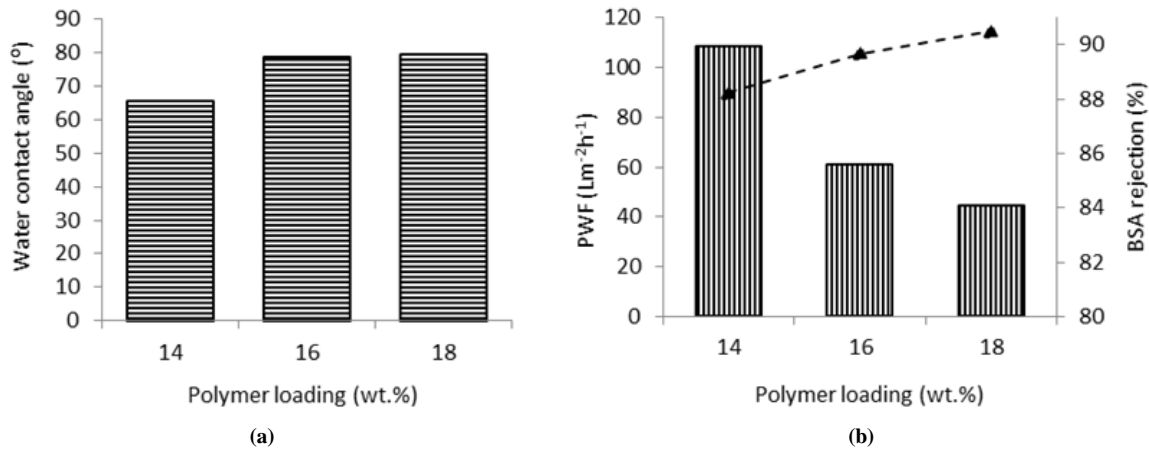
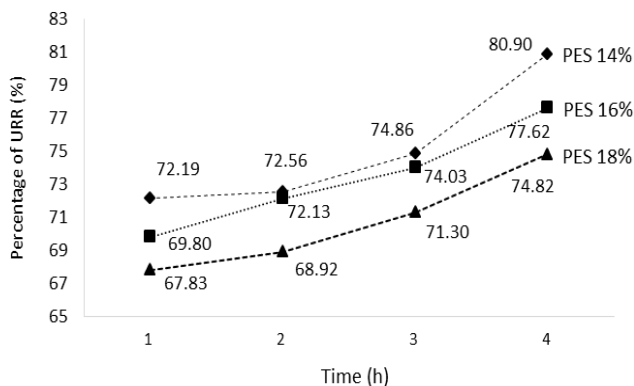**Fig. 5.** Profile of (a) WCA, (b) PWF and BSA rejection for membranes studied.
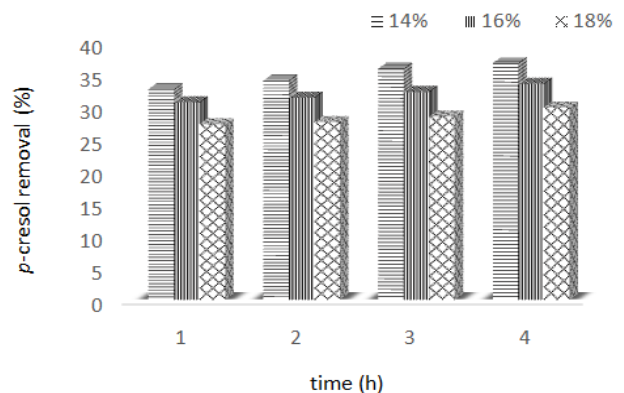
Fig. 6. Urea removal for membranes studied.

Fig. 7. *p*-Cresol removal for membranes studied.

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