WILEY | Hindawi

Research Article

Manufacturing and Separation Characteristics of Hemodialysis Membranes to Improve Toxin Removal Rate

Gyeong Tae Lee and **Young Ki Hong**

Department of Biomedical Materials, Konyang University, 158 Gwanjeodong-ro, Seo-gu, Daejeon, Republic of Korea

Correspondence should be addressed to Young Ki Hong; ymhong@konyang.ac.kr

With the recently growing interest in health care, hemodialysis is being performed not only to treat patients with renal disease but also to improve blood circulation. At present, filters used for hemodialysis are manufactured only in certain countries, and all other countries must rely on imports. In this study, polyethersulfone (PES), which has excellent blood compatibility, was used as the main material to develop hemodialysis membranes for hemodialysis filters, and these hemodialysis membranes were prepared by adding a hydrophilic polymer, polyvinylpyrrolidone (PVP), and varying the type of nonsolvent during the manufacturing process to improve the toxin removal rate and biocompatibility. The addition of PVP was confirmed through attenuated total reflection Fourier transform infrared (ATR-FTIR), and the structure of the membranes depending on the nonsolvent was analyzed through scanning electron microscopy (SEM) and atomic force microscopy (AFM) images. The contact angle results indicated that the hydrophilicity of the membrane surface was improved as the concentration of PVP increased. The results of the toxin filtration efficiency experiment using urea, creatinine, and bovine serum albumin (BSA) confirmed removal rates of 58.8% and 56.87%, respectively, and a protein loss of less than 8%. Also, cell viability was over 90% at the PVP concentration of 2% or higher. A preliminary study was conducted on the improvement of toxin filtration efficiency and the development potential of these hemodialysis membranes with excellent biocompatibility.

1. Introduction

The kidney is an essential organ, which removes excess moisture from the body and toxins from the blood. In the case of renal disease patients, the kidney cannot perform its role owing to abnormalities in the glomerulus of the kidney, and renal replacement therapies such as kidney transplantation, peritoneal dialysis, and hemodialysis are implemented [1, 2]. The most common among these therapies is hemodialysis, which is an extracorporeal method of exchanging blood and dialysate through a semipermeable hydrolysis membrane to remove toxins and excess moisture by means of the diffusion derived from concentration differences [3, 4]. In addition to renal disease patients, hemodialysis is also being performed to improve blood circulation and discharge wastes from the blood as the general public's interest in health care increases with the emergence of a super-aged society. In hemodialysis, the membrane separation process and dissolution-diffusion act in combination, and the membrane separation process using the hemodialysis membrane performs selective separation according to the difference in molecular weight. The membrane separation process removes metabolites of medium molecular weight or less and excess water in the body, and low molecular weight metabolites such as urea and creatinine dissolve and diffuse depending on the concentration. Such a hemodialysis membrane is the most important part of a hemodialysis filter and appears in various structures depending on the material and manufacturing method of the hemodialysis membrane. The structure of the hemodialysis membrane is related to the removal rate of toxins such as urea and creatinine, and since the hemodialysis membrane comes into direct contact with blood, not only membrane selectivity and stain resistance but also biocompatibility is required. Currently, hemodialysis filters are manufactured only in some countries such as the United

States, Japan, and Europe, and in countries other than the manufacturing countries, the actual situation is that all of them depend on imports.

Polyethersulfone (PES) is a material with oxidation, thermal, and hydrolysis stabilities and chemical resistance, as well as excellent mechanical strength and film formation properties [5, 6]. It is used for membrane separation in various fields such as biomedicine, water purification, food processing, plasma separation, and hemodialysis. PES can control the molecular weight cut-off (MWCO), allowing selective separation of various components present in the blood such as toxins, moisture, and proteins when used in hemodialysis membranes [7]. However, as PES is hydrophobic, proteins can be adsorbed onto the surface of hemodialysis membranes in contact with the blood, which degrades the performance of the membranes and causes blood clots [8–10]. Numerous studies have been conducted on the use of PES membranes as hemodialysis membranes. The methods of reforming PEM membranes include coating, blending, physical surface treatment, and surface grafting [11–13]. Among them, the blending method of hydrophilizing the membrane surface by blending a hydrophilic polymer is the simplest and widely used method. Polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP) are typically used as hydrophilic polymers [14, 15]. PVP is a nonionic water-soluble polymer, which is attracting significant attention as an additive for its physiological inactivity, excellent chemical stability, and biocompatibility [16, 17].

These PES membranes are generally manufactured by phase inversion methods, including nonsolvent-induced phase inversion, vapor-induced phase inversion, and heat-induced phase inversion. The nonsolvent-induced phase inversion method is the most frequently used as the process is simple and less costly [18, 19]. In the nonsolvent-induced phase inversion method, a homogeneous polymer solution is prepared by dissolving a polymer in a solvent, followed by precipitation in a nonsolvent to induce phase inversion. The polymer solution precipitated in the nonsolvent undergoes a gelation process, and liquid–liquid exchange subsequently occurs due to diffusion between the solvent and the nonsolvent, forming a porous membrane. The size, structure, and porosity of the pores in the prepared polymer membrane are affected by the precipitation rate of the polymer or the liquid–liquid exchange rate of the nonsolvent and solvent [20, 21]. These rates can be adjusted under various conditions, such as the composition of the polymer solution, viscosity, type of additive, type of nonsolvent, temperature, and coagulation condition.

In this study, five groups of PES-based hemodialysis membranes were prepared by adding a hydrophilic polymer, PVP, at various concentrations using different types of nonsolvents to improve the toxin removal rate of hemodialysis membranes. The toxin removal rate of the prepared hemodialysis membranes was evaluated using urea, creatinine, and BSA. In addition, a preliminary study was conducted on the currently stalled domestic development of hemodialysis membranes by assessing their structural properties and biological stability, comprehensive biocompatibility, and functionality.

TABLE 1: Composition of polymer solution.

Membrane no.	PES (wt%)	Solvent (wt%)	PVP (wt%)	Nonsolvent
PESVP0-1		82	0	
PESVP1-1	18	81	1	D·W
PESVP2-1		80	2	
PESVP3-1		79	3	
PESVP0-2		82	0	
PESVP1-2	18	81	1	4°C D·W
PESVP2-2		80	2	
PESVP3-2		79	3	
PESVP0-3		82	0	
PESVP1-3	18	81	1	50°C D·W
PESVP2-3		80	2	
PESVP3-3		79	3	
PESVP0-4		82	0	
PESVP1-4	18	81	1	EtOH
PESVP2-4		80	2	
PESVP3-4		79	3	
PESVP0-5		82	0	
PESVP1-5	18	81	1	MeOH
PESVP2-5		80	2	
PESVP3-5		79	3	

2. Materials and Methods

2.1. Materials.
PES with an average molecular weight of 5,800 was purchased from Goodfellow and used as a membrane-forming polymer. N, N-Dimethylacetamide (DMAc, 99.5%) was purchased from Samchun as a solvent to prepare membranes. PVP was purchased from Sigma-Aldrich and used as an additive. Urea (Wako), creatinine (Junsei), and BSA (Research and Diagnostic Technology) were used to constitute artificial blood, and dialysate was prepared based on the actual dialysate composition, including sodium chloride (NaCl, Duksan), calcium chloride (CaCl$_2$, Daejung), sodium acetate (CH$_3$COONa, Daejung), magnesium chloride (MgCl$_2$, Samchun), and potassium chloride (KCl, Samchun). Ethyl alcohol (EtOH, 99.5%) and methyl alcohol (MeOH, 99.5%) were purchased from Samchun and used as nonsolvents. To analyze the concentrations of BSA, urea, and creatinine, a BSA asset kit was purchased from Thermo Scientific, and urea and creatinine asset kits were purchased from Cell Biolabs.

2.2. Preparation of PESVP Membranes.
PESVP membranes were prepared by the nonsolvent-induced phase inversion method. The 18 wt% PES solution was prepared by stirring it at room temperature for 24 h. The membranes were divided into five groups depending on the type and temperature of nonsolvent, and the concentration of the additive was also varied. The PESVP membranes were named by designating the middle number of the membrane according to the concentration of the PVP additive and the last
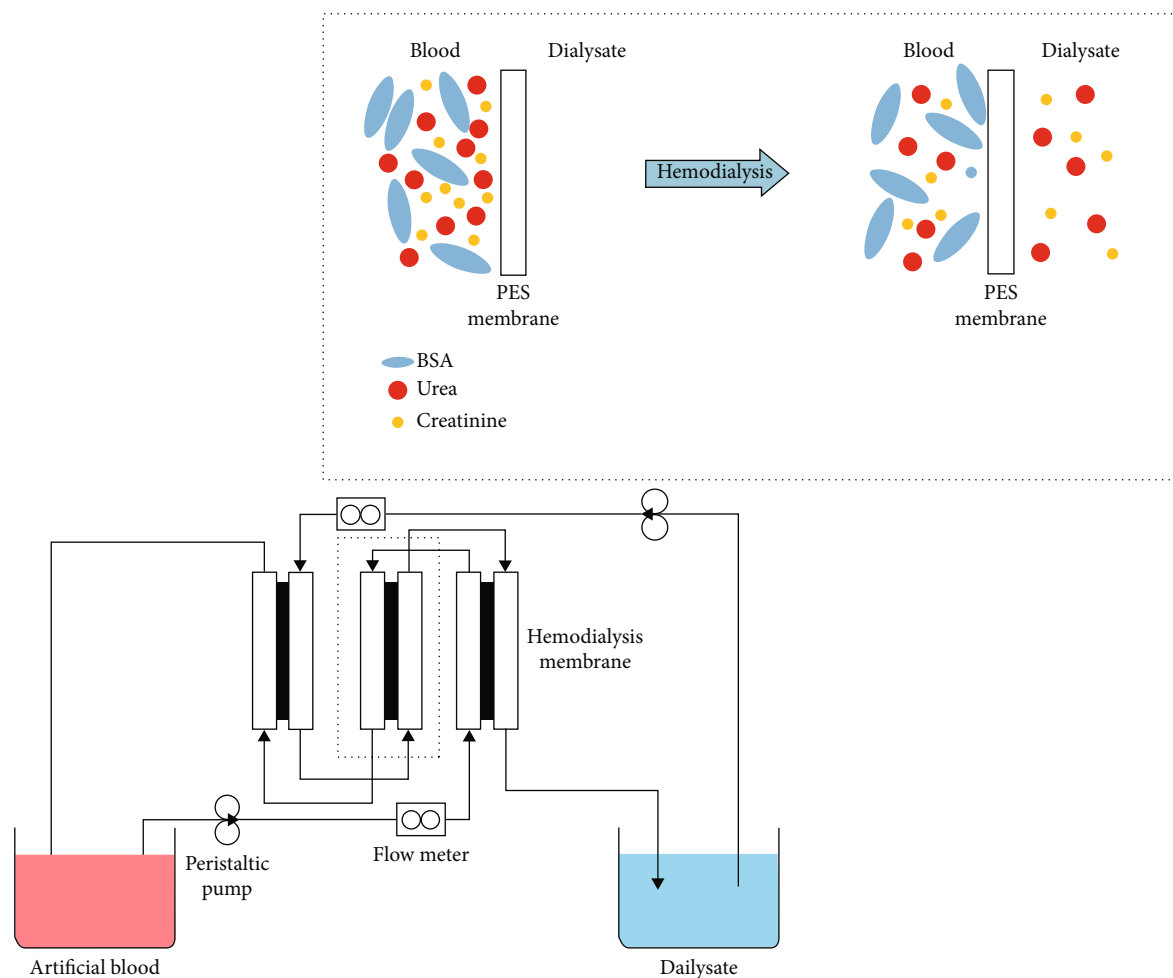
Figure 1: Schematic diagram of multimembrane dialysis system.

number according to the type and temperature of nonsolvent (D·W:1, 4°C D·W:2, 50°C D·W:3, EtOH:4, MeOH:5). Table 1 presents the composition of the polymer solution. The air bubbles remaining in the prepared polymer solution were removed through ultrasonic treatment. The solution with air bubbles removed was cast on a glass plate to a thickness of 150 μm using a casting knife. The cast solution was immersed in a coagulation bath containing the nonsolvent. The residual solvent was removed from the solvent for 24 h, which was then washed with distilled water before proceeding with the experiment.

2.3. Analysis of PESVP Membrane Properties. The surface chemical properties of the PESVP membranes prepared by the nonsolvent-induced phase inversion method were analyzed by measuring the attenuated total reflection Fourier transform infrared (ATR-FTIR, Cary 630, Agilent Technologies) in the range of 4000 cm^{-1} to 400 cm^{-1}. The morphology and microstructure of the PESVP membranes were examined through scanning electron microscopy (SEM, JSM-6335F, JEOL). The prepared PESVP membranes were frozen in liquid nitrogen and cut in pieces. In addition, through atomic force microscopy (AFM, SPM-9700, Shimadzu), the 3D shape of the PESVP membranes and the roughness of

Table 2: Composition of artificial blood and dialysate.

Artificial blood (g/l)		Dialysate (g/l)	
Urea	1	NaCl	202.5
		KCl	6.5
Creatinine	0.1	CaCl$_2$	9
		MgCl$_2$	5.3
BSA	1	CH$_3$COONa	28.6

the membrane surface area (10 μm × 10 μm) were analyzed in terms of the roughness average (Ra) and root mean square (RMS). The PESVP membrane samples were cut into 1 cm × 1 cm pieces for AFM.

2.4. Analysis of Surface Hydrophilicity. The surface hydrophilicity of the PESVP membranes was evaluated by measuring the water contact angle with a contact angle meter (Phoenix 10, Surface Electro Optics). A water droplet was placed on the membrane surface, and the contact angle
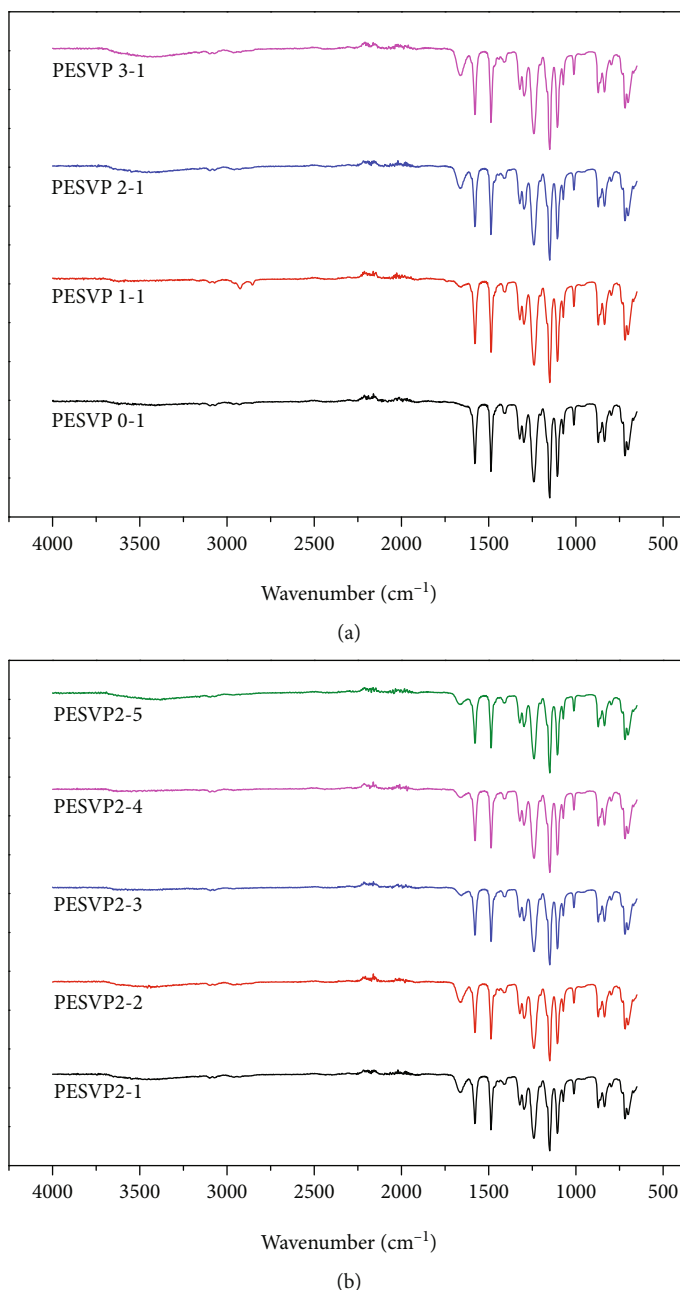
(a)

(b)

FIGURE 2: ATR-FTIR spectra of the different PESVP membranes: (a) effect of PVP concentration; (b) effect of nonsolvent type.

was measured using a monitor and the SurfaceWare9 program.

2.5. Analysis of Mechanical Properties. The mechanical properties of the prepared PESVP membranes were evaluated by measuring the thickness of the membranes and performing tensile strength tests. The tensile strength of the PESVP membranes was measured depending on the additive concentration and the type of nonsolvent using the Universal Testing Machine (UTM, AGS-X STD, Shimadzu). Samples were prepared in the size of $76.2 \, \text{mm} \times 25.4 \, \text{mm}$, and the cross-head speed was set at $25.4 \, \text{mm/min}$.

2.6. Evaluation of Toxin Filtration Efficiency. A dialysis simulation was performed to evaluate the toxin filtration efficiency of the PESVP membranes. Figure 1 shows the schematic of the dialysis simulation experiment. Artificial blood was prepared using urea and creatinine as toxins and BSA as a plasma protein. The dialysate was prepared using NaCl, KCl, $CaCl_2$, $MgCl_2$, and CH_3COONa. Table 2 provides the compositions of the artificial blood and dialysate. The prepared dialysate and artificial blood were allowed to flow at a constant flow rate in opposite directions with a PESVP membrane placed between the two. The flow rate of the artificial blood was set at 200 ml/min, and that of
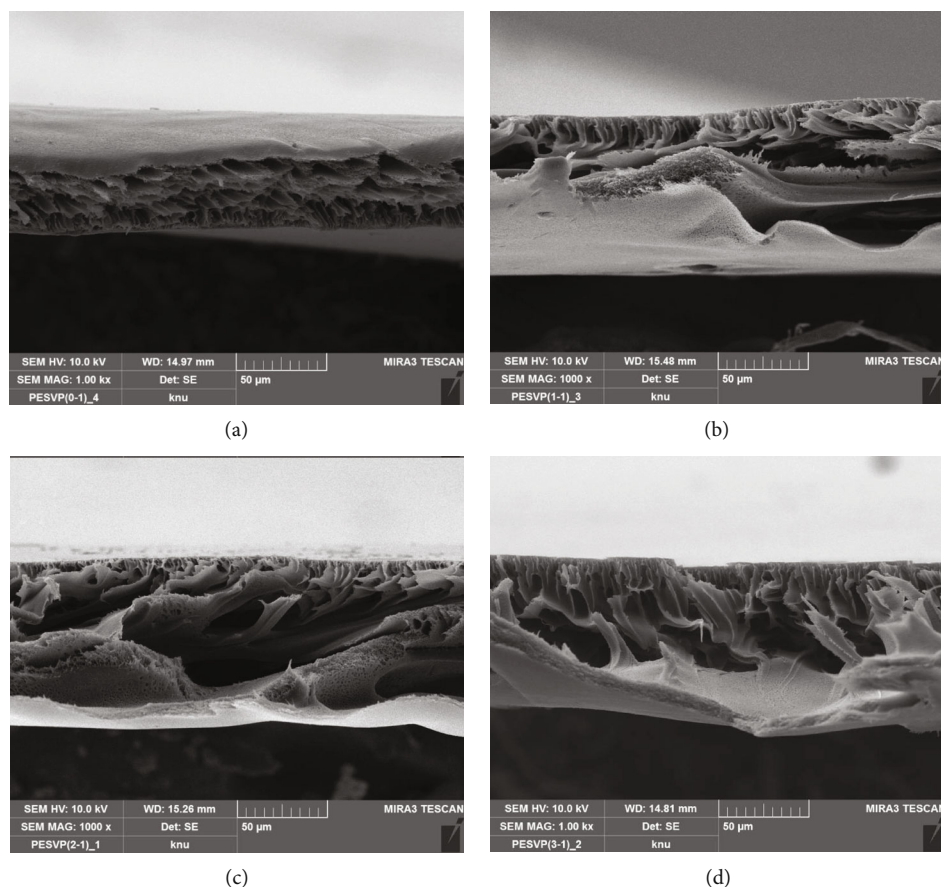
(a)

(b)

(c)

(d)

FIGURE 3: SEM image of PESVP membranes cross-section: (a) PESVP0-1; (b) PESVP1-1; (c) PESVP2-1; (d) PESVP3-1.

the dialysate was set at 100 ml/min. The experiment was conducted such that 87 cm^2 of the PESVP membrane area was in contact with the artificial blood and dialysate. The dialysis simulation was performed for a total of 2 h while collecting samples of the artificial blood every 30 min. The filtration efficiency was measured through a quantitative analysis of urea and creatinine in the collected artificial blood using an enzyme-linked immunosorbent assay (ELISA, SpectraMax ABS Plus, Molecular devices), and the extent of plasma protein loss was examined through a quantitative analysis of BSA.

2.7. Evaluation of Cytotoxicity. The cytotoxicity of the prepared PESVP membranes was evaluated and quantified through an MTT analysis using human umbilical vein endothelial cells (HUVECs). HUVECs were cultured at 37°C and 5% CO_2 using a culture medium and were seeded on the PESVP membranes at a concentration of 2×10^3 cells/well. Mitochondrial dehydrogenases of living cells convert the MTT reagent into formazan crystals, which produce blue or purple colors as they dissolve in ethanol. Therefore, the level of cell metabolism can be determined by the amount of formazan crystals dissolved in ethanol. The amount of formazan dissolved in ethanol was measured at 492 nm using ELISA. Cells cultured in the membranes for 2, 4, and

6 days were used for the MTT analysis, and the cell viability was calculated as follows:

$$\text{Cell viability} = \frac{\text{Sample Absorbance}}{\text{Control Absorbance}} \times 100. \qquad (1)$$

3. Results and Discussion

3.1. Characterization of PESVP Membranes. ATR-FTIR was used to characterize the chemical structure of the PESVP membranes. Figure 2(a) shows the ATR-FTIR analysis results at various concentrations of the PVP additive, and Figure 2(b) shows the structural analysis results of the membranes depending on the nonsolvent. All PESVP membrane samples demonstrated peaks at 1480 cm^{-1} and 1580 cm^{-1} owing to the C=C stretching vibration of the benzene ring. The peak associated with the phenyl group was observed at 1240 cm^{-1}, and the peaks at 1150 cm^{-1} and 1100 cm^{-1} confirmed the presence of the sulfone group. As shown in Figure 2(a), PESVP1-1, PESVP2-1, and PESVP3-1, which contained PVP, exhibited a new peak. The new peak observed at 1677 cm^{-1} was associated with the C=O of PVP, confirming the addition of PVP to the PES membranes [22, 23]. As shown in Figure 2(b), the peak of PES was also observed, indicating that there was no change in the
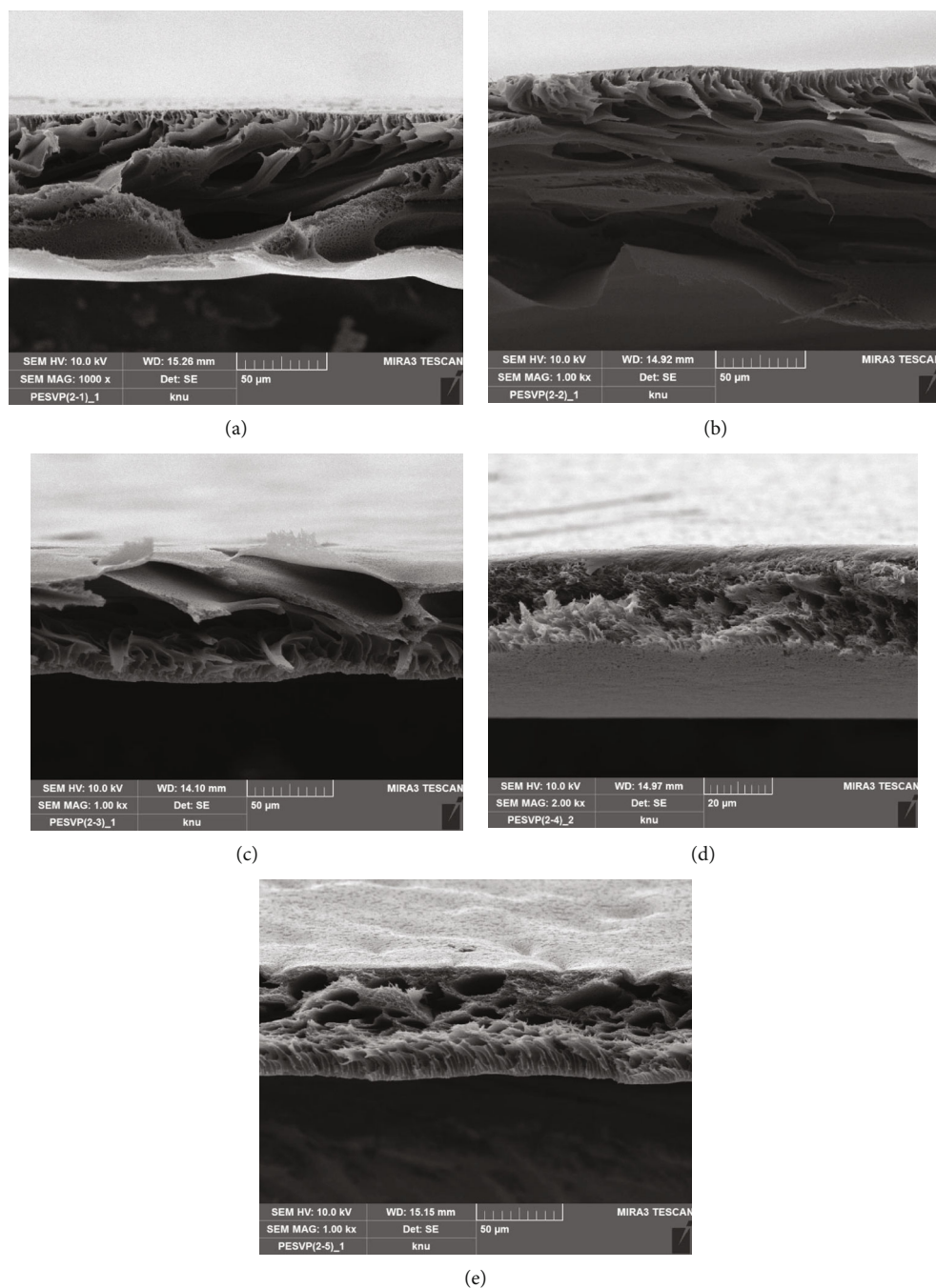
(a)

(b)

(c)

(d)

(e)

FIGURE 4: SEM image of PESVP membranes cross-section: (a) PESVP2-1; (b) PESVP2-2; (c) PESVP2-3; (d) PESVP2-4; (e) PESVP2-5.

chemical structure of the PESVP membranes with the type and temperature of nonsolvent.

3.2. Microstructure of PESVP Membranes. The performance of hemodialysis membranes is significantly affected by the shape of the membranes. To improve the performance of membranes, such as selectivity and transmittance, it is necessary to understand their formation process and structure. In addition, as the physical and chemical properties of the membranes are affected by the microstructure, their cross-section was observed using SEM. Figure 3 shows cross-sectional SEM images of the PESVP membranes

with varying concentrations of the PVP additive, where (a) PESVP0-1, (b) PESVP1-1, (c) PESVP2-1, and (d) PESVP3-1 are cross-sectional images of the PESVP membranes added with PVP at concentrations of 0%, 1%, 2%, and 3%, respectively. All the PESVP membranes presented an asymmetric structure consisting of a thin and dense upper layer and a porous lower layer with a finger-like structure supporting the upper layer [24, 25]. The upper layer allows the removal and permeation of solutes, whereas the porous lower layer provides mechanical support to the membrane. As the PVP concentration increased, the pores of the finger-like structure of the lower layer grew in size, exhibiting
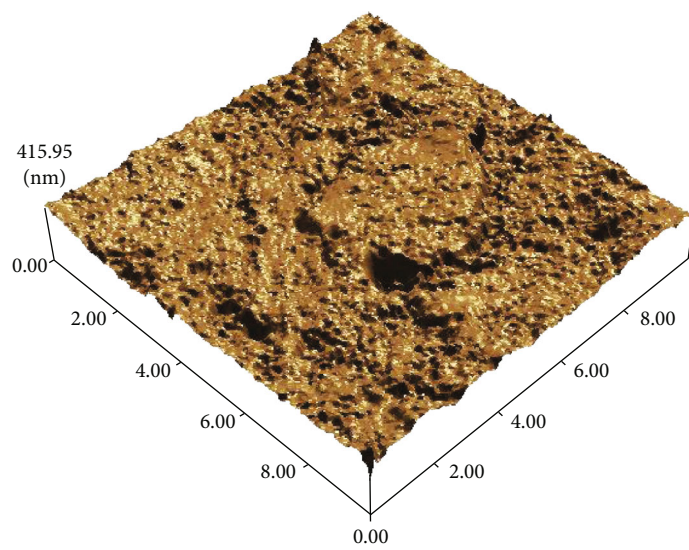
(a)
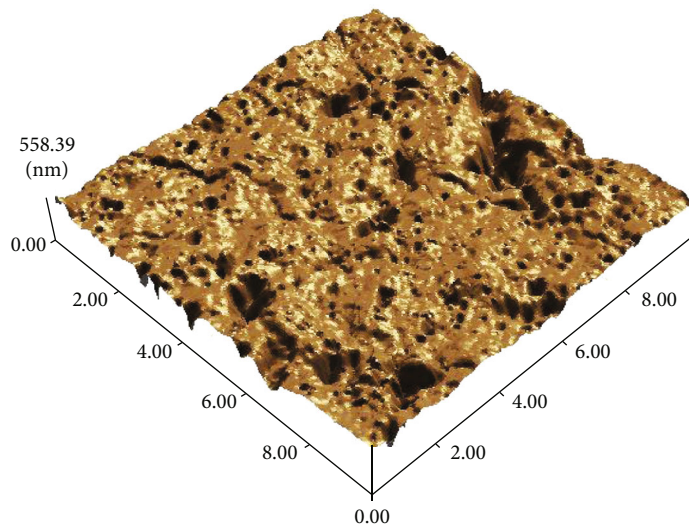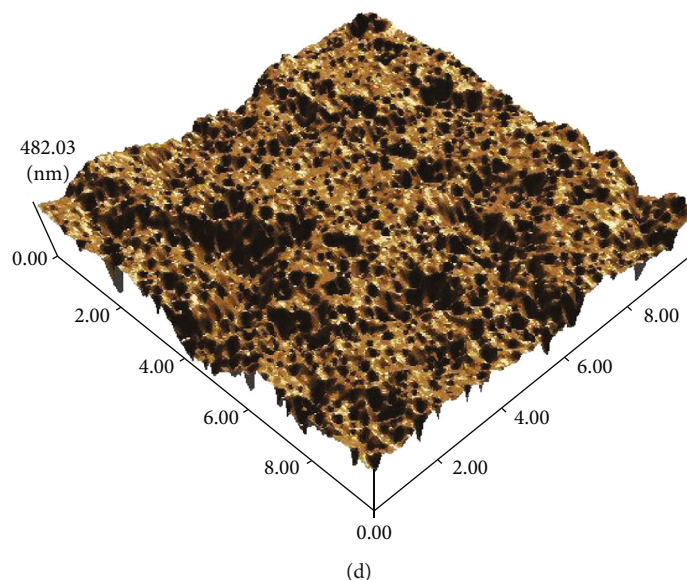

(b)
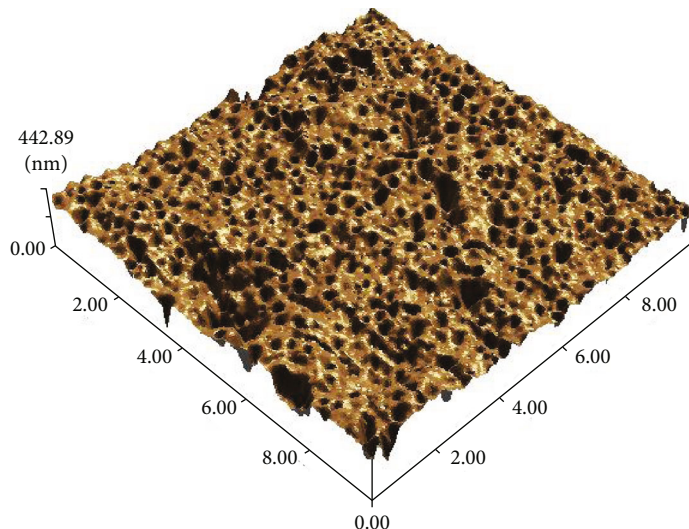
(c)

Figure 5: Continued.

(d)

FIGURE 5: AFM surface topography image PESVP membranes: (a) PESVP0-1; (b) PESVP1-1; (c) PESVP2-1; (d) PESVP3-1.

an irregular shape. Macropores were also observed with numerous micropores formed on the surface of these macropores. The increase in the PVP concentration improves the viscosity of the cast solution, which results in the formation of micropores as the exchange time between the solvent and nonsolvent increases. This affects the ultrafiltration performance of the membranes.

Figure 4 shows the cross-sectional SEM images of the PESVP membranes prepared with different types of nonsolvent during the manufacturing process. The membrane structure depends on the liquid–liquid exchange rate during the formation process, which is affected by the affinity between the nonsolvent and the solvent. The finger-like structure is formed when liquid–liquid exchange occurs at a high rate due to high affinity between the nonsolvent and solvent, whereas the sponge structure is formed when liquid–liquid exchange occurs at a low rate due to low affinity [26–28]. (a) PESVP2-1, (b) PESVP2-2, (c) PESVP2-3, (d) PESVP2-4, and (e) PESVP2-5 are PESVP membranes prepared with PVP at a concentration of 2% while using D·W, 4°C D·W, 55°C D·W, EtOH, and MeOH as nonsolvents, respectively. (a), (b), and (c), prepared by varying the temperature with D·W used as a nonsolvent, exhibited an asymmetrical, finger-like structure with a dense upper layer, which confirmed that the temperature of the nonsolvent did not affect the structure of PESVP membranes. Unlike the PESVP membranes exhibiting a finger-like structure with D·W used as a nonsolvent, (d) and (e) with EtOH and MeOH used as nonsolvents exhibited a sponge structure.

3.3. Surface Roughness of PESVP Membranes. The surface roughness is one of the important parameters of hemodialysis membranes and affects the interaction between the surface, proteins, and cells. When the surface roughness is high, proteins adhere to the membrane surface, which not

only hinders the permeability of the membrane but also requires high pressure [29, 30]. The lower the surface roughness is, the less the adhesion of cells, thereby improving the biocompatibility of the membrane. AFM analysis was performed in a noncontact mode to measure the surface roughness of the PESVP membranes, and Figures 5 and 6 show the 3D images. The average roughness, Ra, refers to the relative average value of the surface. While this value cannot be absolute, all AFM analyses were performed using an identical cantilever within the same range to determine Ra and RMS of the PESVP membranes prepared under different conditions, as presented in Table 3. Figure 5 shows 3D AFM images of the PESVP membrane surfaces with varying concentrations of the additive PVP. (a) PESVP0-1, (b) PESVP1-1, (c) PESVP2-1, and (d) PESVP3-1 are 3D images of the surface of the PESVP membranes containing PVP at concentrations of 0%, 1%, 2%, and 3%, respectively. The Ra value of PESVP0-1 with 0% of additive was found to be 26.36 nm, and as the additive concentration increased, the Ra value tended to increase with PESVP1-1 at 27.5 nm, PESVP2-1 at 29.78 nm, and PESVP3-1 at 33.43 nm. The RMS value also increased from 33.55 nm to 35.33, 38.09, and 42.17 nm, indicating that the value improved with the increasing additive concentration, in a manner similar to the Ra value. This is consistent with the increase in surface roughness with the formation of macropores on the surface. Given that the differences in the Ra value compared to that of PESVP0-1 were 1.14, 3.42, and 7.07 nm, respectively, there was no significant variance in surface roughness. In Figure 6, (a) PESVP2-1, (b) PESVP2-2, (c) PESVP2-3, (d) PESVP2-4, and (e) PESVP2-5 are the 3D surface AFM images of the PESVP membranes prepared by adding PVP at a concentration of 2% and using D·W, 4°C D·W, 55°C D·W, EtOH, and MeOH as nonsolvents, respectively. The Ra value of PESVP2-1 with D·W used as a nonsolvent was 29.78 nm. Depending on the nonsolvent, the Ra values of
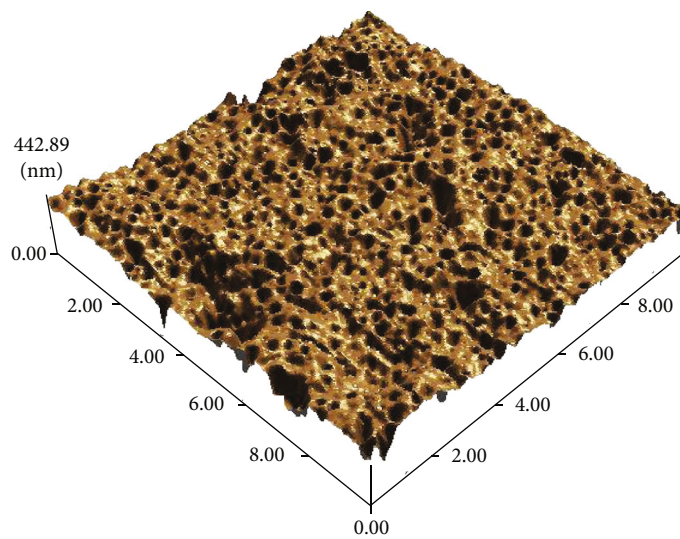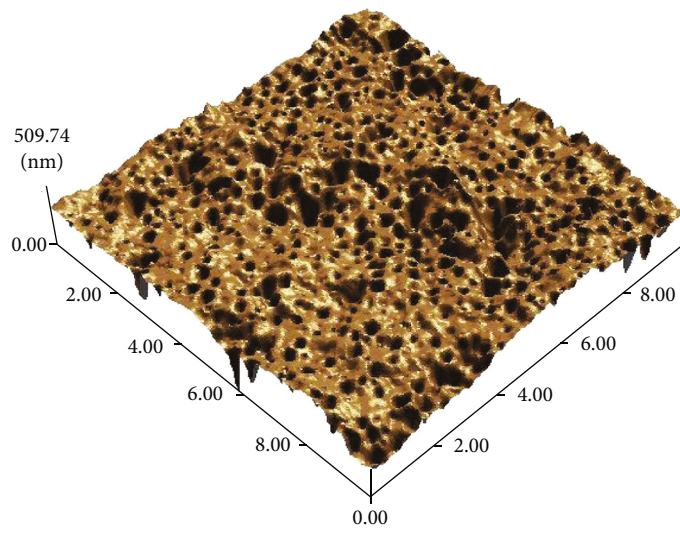
(a)
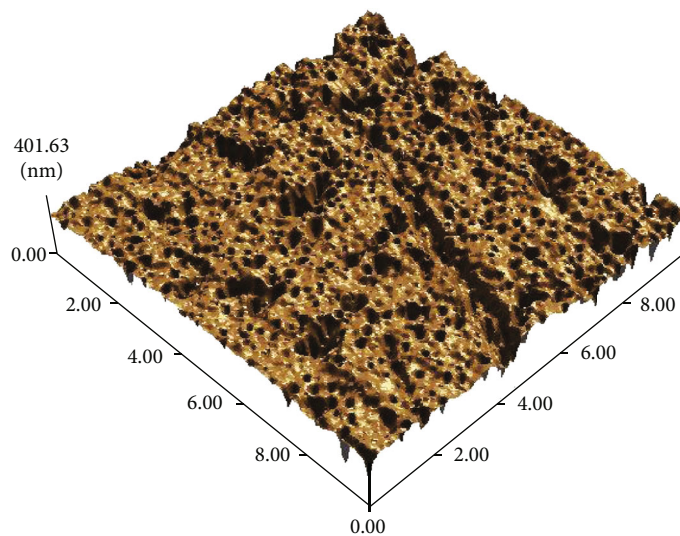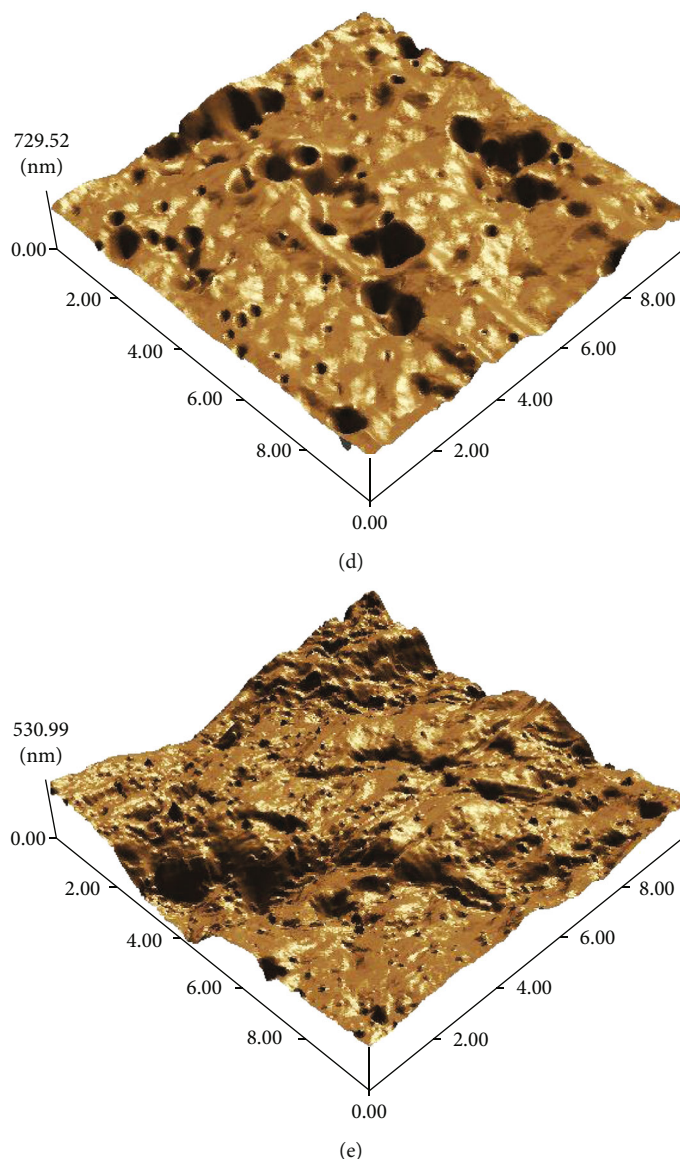

(b)

(c)

FIGURE 6: Continued.

(d)

(e)

FIGURE 6: AFM surface topography image PESVP membranes: (a) PESVP2-1; (b) PESVP2-2; (c) PESVP2-3; (d) PESVP2-4; (e) PESVP2-5.

PESVP2-2, PESVP2-3, PESVP2-4, and PESVP2-5 were 35.03, 43.09, 44.52, and 41.84 nm, respectively. In a similar manner to the Ra values, the RMS values also indicated that the surface roughness increased when D·W was not used.

3.4. Evaluation of Hydrophilicity of PESVP Membranes. Hydrophilicity is one of the important factors in hemodialysis membranes. Hydrophilicity improves the permeability and biocompatibility of the membrane by suppressing the adhesion of proteins or platelets [31–33]. The static contact angle was measured to evaluate the hydrophilicity of the PESVP membranes. The measurement of contact angles is a simple method of evaluating the wettability of the membrane surface, which provides information on the interfacial energy between the surface and the liquid. Figure 7 shows the static contact angle measurements of the prepared PESVP membranes. The contact angle of PESVP0-1 with no added PVP was 55.47°, and those of PESVP1-1, PESVP2-1, and PESVP3-1 were 32.98°, 32.7°, and 30.61°, respectively, which confirmed that the membrane hydrophilicity increased with the PVP concentration. This is attributed to the change in the chemical composition as the concentration of PVP, a hydrophilic polymer, increases. The contact angle of the PESVP membranes prepared by fixing the PVP concentration at 2% and varying the type of nonsolvent was the smallest for PESVP2-1 and PESVP2-2, for which D·W and 4°C D·W were used, at 32.7° and 33.17°, respectively. The contact angles of PESVP2-3, PESVP2-4, and PESVP2-5, in which 55°C D·W, EtOH, and MeOH were used, were 34.85°, 37.85°, and 40.22°, respectively. This trend is similar to the surface roughness, and it is believed that the hydrophilicity of the membranes is influenced by the chemical composition as well as the physical roughness of the surface [34, 35].

TABLE 3: Surface roughness results of PESVP membranes.

(a)

	PESVP0-1	PESVP1-1	PESVP2-1	PESVP3-1
Ra (nm)	26.36	27.50	29.78	33.43
RMS (nm)	33.55	35.33	38.09	42.17

(b)

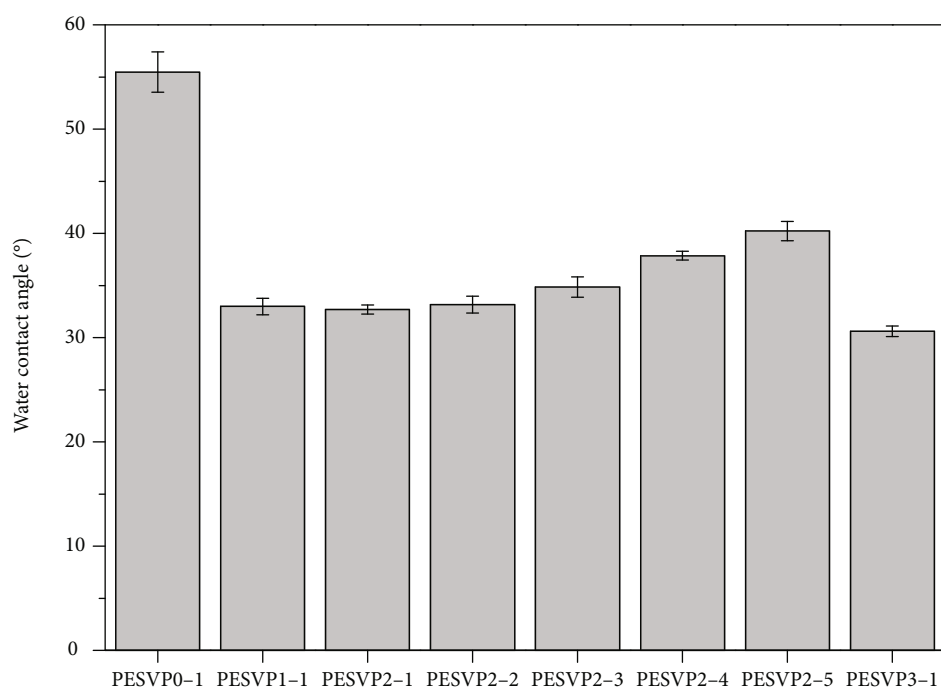|	PESVP2-1	PESVP2-2	PESVP2-3	PESVP2-4	PESVP2-5
Ra (nm)	29.78	35.03	43.09	44.52	41.84
RMS (nm)	38.09	46.96	59.12	56.86	56.17

FIGURE 7: Water contact angle results of PESVP membranes.

3.5. Evaluation of Mechanical Properties of PESVP Membranes. The mechanical properties are an important aspect in the actual application of the membranes as hemodialysis membranes. The mechanical properties of PESVP membranes were evaluated through tensile tests, and given that membranes maintain a wet state during hemodialysis, tensile strength was measured both in the dry and wet states. Figure 8(a) shows the tensile strength test results with various concentrations of the PVP additive, and Figure 8(b) shows the tensile strength test results of the PESVP membranes with different nonsolvents. The tensile strength of PESVP0-1 in a dry state with no added PVP was 6.17 MPa. As the PVP concentration increased, the tensile strength decreased to 2.7, 2.6, and 2 MPa. The tensile strength test in the wet state also confirmed that the tensile strength decreased from 5.82 MPa to 2.51, 2.58, and 1.96 MPa. It is believed that, as the PVP concentration increases, the finger-like internal structure increases in diameter, creating macropores and decreasing the tensile strength. In the tensile strength test of the PESVP membranes under various nonsolvent conditions, the tensile strength in the dry state when using the D·W, 4°C D·W, and 55°C D·W nonsolvents was 2.61, 2.75, and 2.93 MPa, respectively, which did not vary from the tensile strength test results in the wet state. For the PESVP membranes prepared using EtOH and MeOH as nonsolvents, the tensile strength was significantly improved to 4.17 and 7.7 MPa. It is considered that a finger-like structure is formed with D·W used as a nonsolvent at various temperatures, whereas a sponge structure is formed with EtOH and MeOH used as nonsolvents, resulting in higher tensile strength.

3.6. Evaluation of Toxin Filtration Efficiency of PESVP Membranes. The hemodialysis membrane should remove
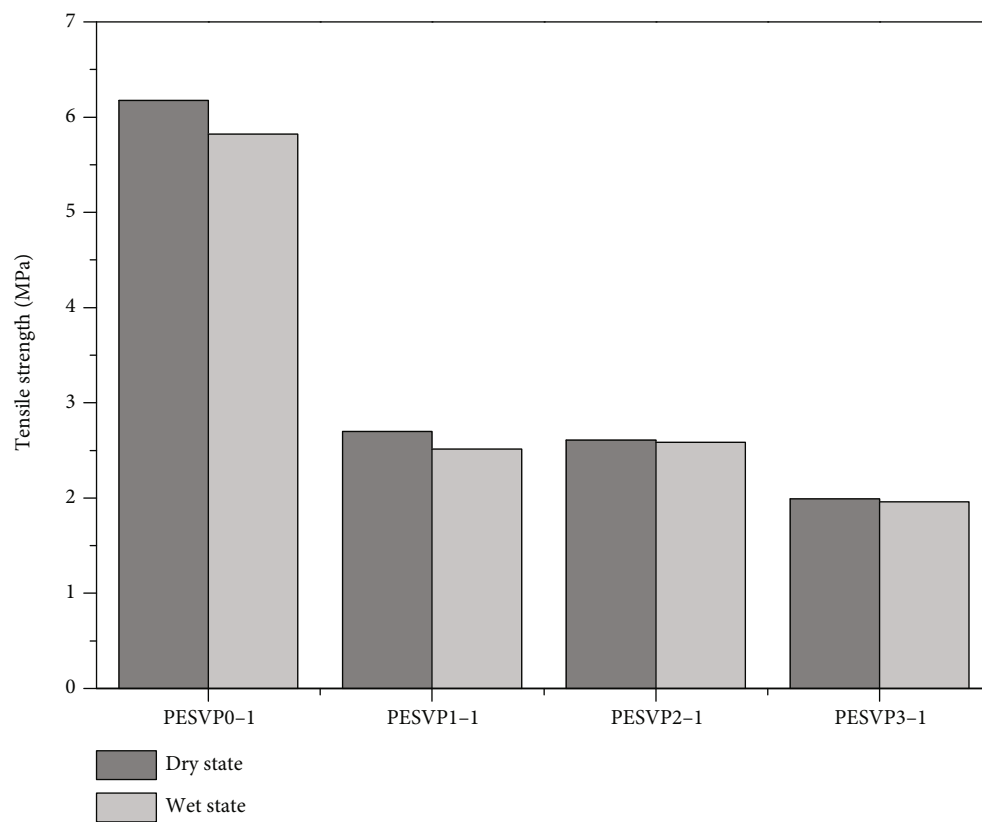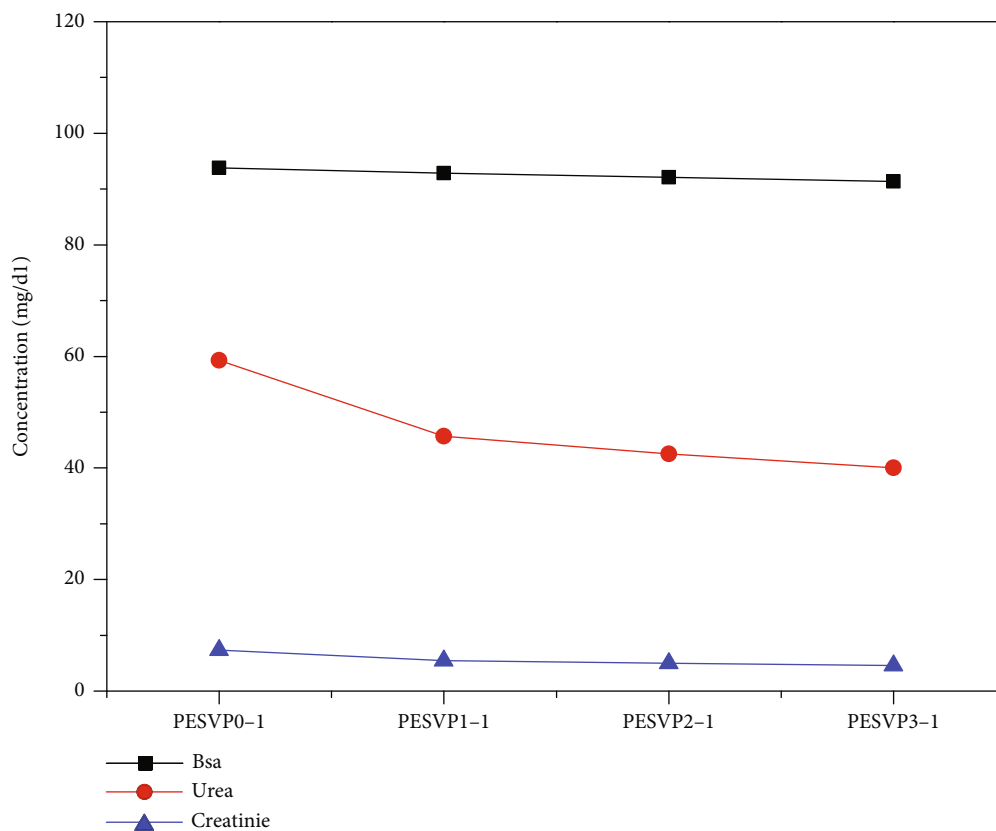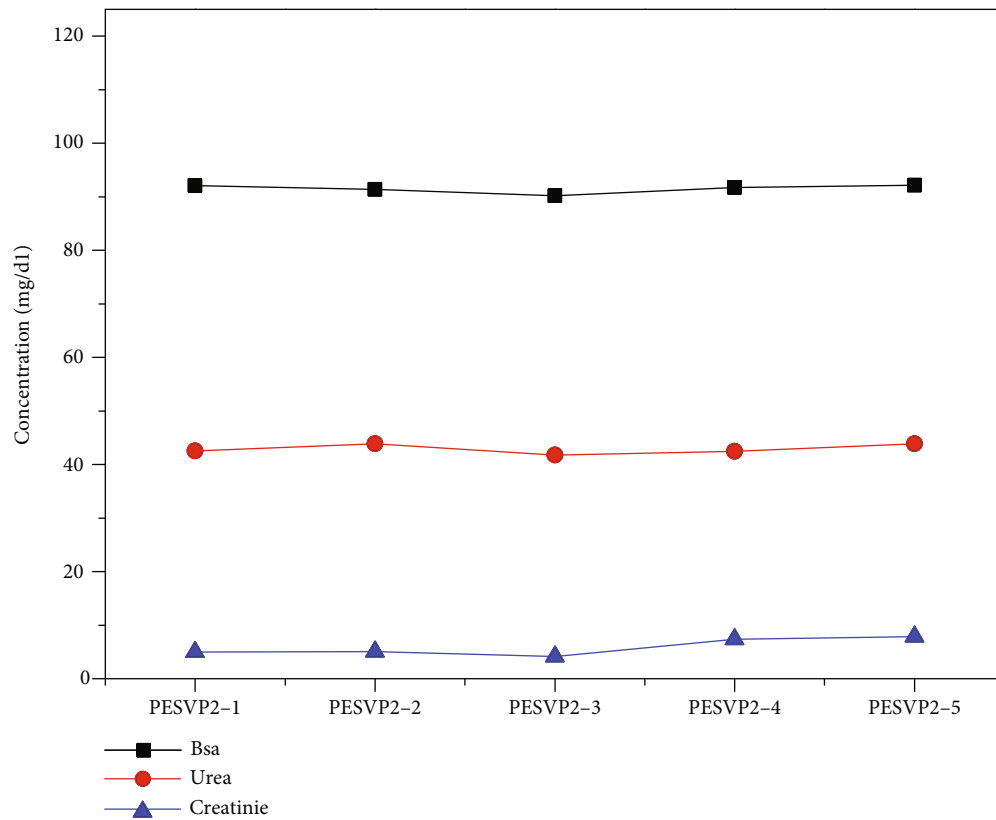
(a)
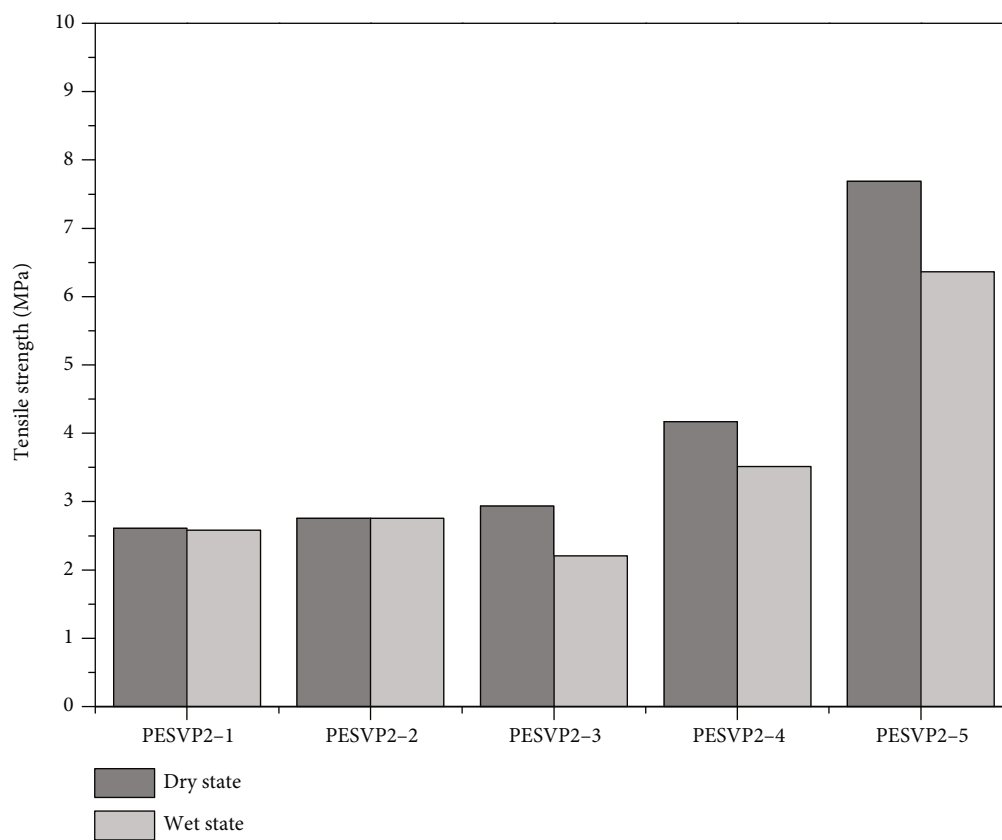
(b)

FIGURE 8: Mechanical property results of PESVP membranes: (a) effect of PVP concentration; (b) effect of nonsolvent type.

(a)

(b)

FIGURE 9: Test results of filtration efficiency of toxin substances in PESVP membranes.

TABLE 4: Urea, creatinine, and BSA removal rate of PESVP membranes.

(a)

	Urea			Creatinine			BSA		
	$C_{\text{feed urea}}\,(mg/dl)$	$C_{\text{permeate urea}}\,(mg/dl)$	$R(\%)$	$C_{\text{feed creatinine}}\,(mg/dl)$	$C_{\text{permeate creatinine}}\,(mg/dl)$	$R(\%)$	$C_{\text{feed BSA}}\,(mg/dl)$	$C_{\text{permeate BSA}}\,(mg/dl)$	$R(\%)$
PESVP0-1	97.49	59.31	39.16	9.86	7.33	25.73	98.53	93.77	4.83
PESVP1-1	98.16	45.71	53.44	9.77	5.43	44.45	98.32	92.88	5.53
PESVP2-1	98.55	42.55	56.83	9.83	4.96	49.54	97.69	92.08	5.74
PESVP3-1	97.31	40.01	58.88	9.82	4.59	53.26	98.19	91.34	6.98

(b)

|	Urea			Creatinine			BSA		
	$C_{\text{feed urea}}\,(mg/dl)$	$C_{\text{permeate urea}}\,(mg/dl)$	$R(\%)$	$C_{\text{feed creatinine}}\,(mg/dl)$	$C_{\text{permeate creatinine}}\,(mg/dl)$	$R(\%)$	$C_{\text{feed BSA}}\,(mg/dl)$	$C_{\text{feed BSA}}\,(mg/dl)$	$R(\%)$
PESVP2-1	98.55	42.55	56.83	9.83	4.96	49.54	97.69	92.08	5.74
PESVP2-2	97.19	43.84	54.9	9.73	5.04	48.24	98.37	91.36	7.13
PESVP2-3	98.19	41.76	57.47	9.62	4.148	56.87	96.99	90.15	7.05
PESVP2-4	98.11	42.48	56.7	9.77	7.359	24.67	96.32	91.74	4.75
PESVP2-5	97.39	43.84	54.98	9.81	7.841	20.1	97.17	92.17	5.15
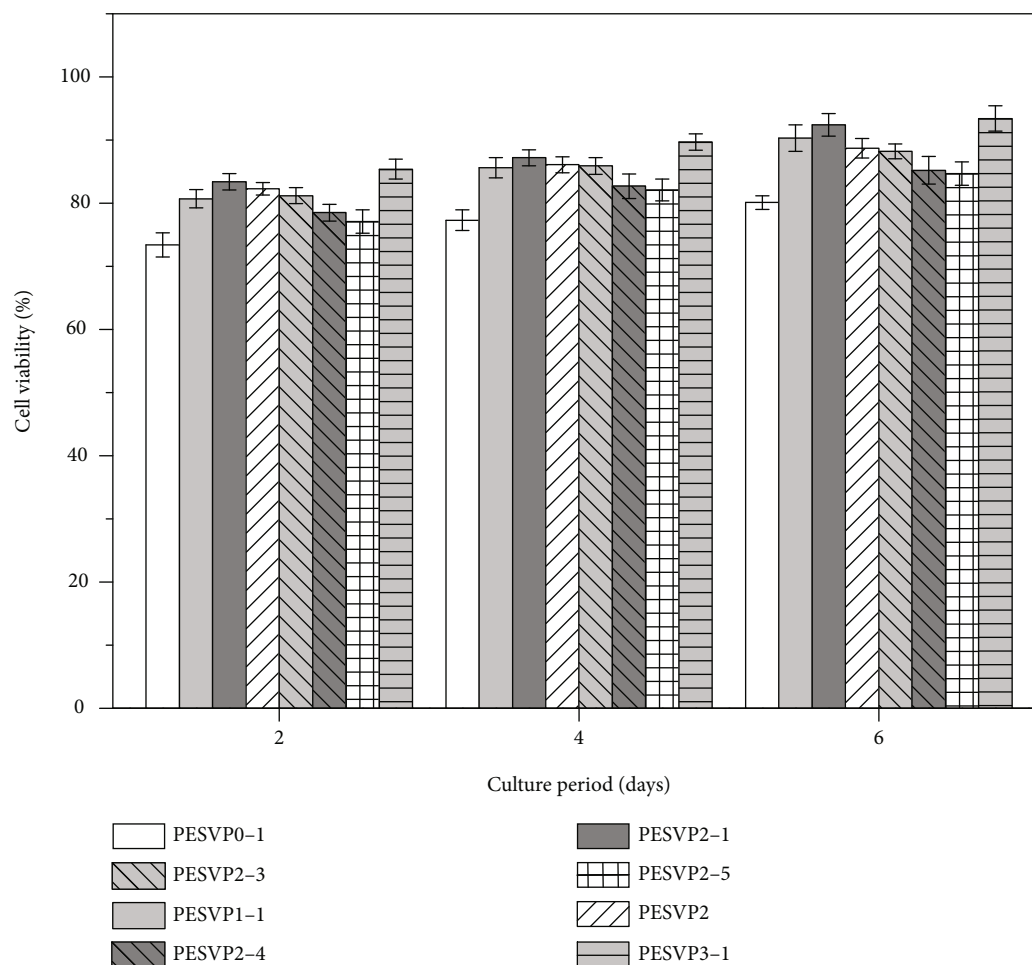
FIGURE 10: Viability of cells on the PESVP membranes measured by MTT assay.

TABLE 5: Comparison of the performance of different PES hemodialysis membranes.

	Surface roughness (nm)	Water contact angle (°)	Tensile strength (MPa)	Rejection of BSA (%)	Cytocompatibility		Citation
					Cell	MTT assay	
PESVP	44.52	37.85	7.7	95.3	HUVECs	Higher	This work
PES-T/D-S	26.6	37	—	~97.1	—	—	[39]
TMPES	24	65.9 ± 2.51	—	95.14	HK-2	Higher	[40]
TiO2/PES	—	59.6 ± 1.4	4.22 ± 0.27	~99.9	—	—	[41]
PES/PES-zwitterionic	15.1	37.8	—	98.3	—	—	[17]
PES/GMA/PAA-AMPS	—	43.2	—	~99	—	—	[42]
Heparin-PVA/PANTFNC	32.1 ± 5.2	62.8 ± 1.2	—	94.5	HUVECs	Higher	[43]

small and middle toxin molecules in the blood during hemodialysis while minimizing the loss of proteins [36]. Therefore, a dialysis simulation experiment was performed as a method for evaluating the performance of the prepared PESVP membranes as hemodialysis membranes. Artificial blood was prepared using urea and creatinine as toxins and BSA as a plasma protein, and dialysate was prepared based on the composition of the dialysate actually used in hemodialysis [37, 38]. Figure 9 shows the results of the toxin filtration efficiency test of the PESVP membranes, and Table 4 presents the concentration before and after dialysis and the filtration efficiency of BSA, urea, and creatinine. Figure 9(a) shows the results of the toxin filtration efficiency test depending on the concentration of the PVP additive. For the PESVP membrane with no added PVP, the residual amounts of urea and creatinine were 59.309 and 7.325 mg/dl, respectively, achieving filtration efficiencies of approximately 39.16% and 25.73%. For PESVP3-1 with the

highest concentration of PVP, the residual amounts of urea and creatinine were 40.012 and 4.589 mg/dl, respectively, achieving filtration efficiencies of 58.88% and 53.26%. In addition, 4.83% of the protein, BSA, was lost in PESVP0-1, while 6.98% was lost in PESVP3-1. This demonstrated that the increase in additive concentration improved the toxin filtration efficiency and increased the loss of protein, but the differences were insignificant. It is believed that, while the filtration performance and the loss of protein increase as the PESVP membrane forms macropores, and the finger-like structure grows in size, the hydrophilicity of the membrane provided by the hydrophilic polymer, PVP, reduces the loss of protein caused by protein absorption, resulting in no significant differences.

Figure 9(b) shows the results from the toxin filtration efficiency test of the PESVP membranes under various nonsolvent conditions. Based on the test results, the residual amounts of urea and creatinine in PESVP2-1 with D·W used as a nonsolvent were 42.548 and 4.962 mg/dl, respectively, exhibiting filtration efficiencies of 56.82% and 47.65%. The filtration efficiency results were similar for PESVP2-2 and PESVP2-3 with 4°C D·W and 55°C D·W used as nonsolvents. Meanwhile, in PESVP2-4 with EtOH used as a nonsolvent and PESVP2-5 with MeOH used as a nonsolvent, the residual amounts of urea were 42.4826 and 43.8439 mg/dl or 56.7% and 54.98% in filtration efficiency, respectively. These results were similar to those of PESVP2-1, PESVP2-2, and PESVP2-3, but the filtration efficiency for creatinine, which had a larger molecular weight than urea, was lower at 24.67% and 20.1%. In the case of proteins, PESVP2-1, PESVP2-4, and PESVP2-5 exhibited a loss of 5.74%, 4.75%, and 5.15%, respectively. This implies that, unlike PESVP2-1, PESVP2-2, and PESVP2-3 with a finger-like structure, PESVP2-4 and PESVP2-5 have a sponge structure and do not exhibit noticeable differences in filtration efficiency for urea with a molecular weight of 60.1 Da, while the filtration efficiency was significantly reduced for creatinine with a molecular weight of 113.1 Da. Additionally, the loss of protein varied by up to 2.38%. While the extent of protein losses is smaller in the sponge structure than in the finger-like structure, more proteins are adsorbed on the membrane surface when the surface is rougher. Therefore, based on the surface roughness in the AFM measurement results, the rougher the surface, the more proteins are absorbed on the membrane surface, resulting in insignificant differences.

3.7. Cytocompatibility of PESVP Membranes. Biocompatibility is important for medical devices used in applications involving direct contact with blood, such as hemodialysis membranes. The cytocompatibility of the prepared PESVP membranes was evaluated based on HUVECs as the model, and cell vitality was examined through MTT analysis, as shown in Figure 10. The cell viability in PESVP0-1 without PVP was 73.4% after 2 days, 80.7% in PESVP1-1, 83.4% in PESVP2-1, and 85.4% in PESVP3-1. Additionally, as the concentration of PVP increased, the cell viability also increased to 80.1%, 90.3%, 92.4%, and 93.4%, respectively, after 6 days. This indicates that the addition of PVP, a

hydrophilic polymer, to PES with hydrophobic properties increases the hydrophilicity of the surface and cell viability, which is consistent with the results of the contact angle experiment of the PESVP membranes. In addition, depending on the type of nonsolvent, the cell viability was found to be 92.4%, 88.7%, 88.2%, 85.2%, and 84.7%. Among the prepared PESVP membranes, PESVP2-1 and PESVP 3-1 showed the highest cell viability of over 90%, and all the PESVP membranes exhibited a cell viability of over 70%. Therefore, it can be concluded that the membranes are non-cytotoxic and can be utilized as hemodialysis membranes.

3.8. Comparison of Research on the Latest Hemodialysis Membranes. In order to evaluate the results of this paper, the performance of various hemodialysis membranes such as surface roughness, contact angle, tensile strength, protein removal rate, and cell compatibility is summarized in Table 5. PESVP membranes produced through the addition of hydrophilic polymers and changes in nonsolvent to improve toxin removal rates showed excellent hydrophilicity, high tensile strength, and improved cell compatibility. PES has excellent mechanical strength and film forming ability but has hydrophobic properties, causes efficiency decrease and thrombus formation due to adsorption of blood proteins, and is partially modified for use as a hemodialysis membrane. Much research has been done on solving the above problems with coating, blending, surface physical treatment, and surface graphing methods. There is also a need to develop a PES membrane that is easy to remove not only low molecular weight toxin substances such as urea and creatinine but also medium molecular weight toxin substances.

4. Conclusions

In this study, PES-based membranes were prepared by adding a hydrophilic polymer, PVP, to improve the toxin removal efficiency of hemodialysis membranes. The properties of the membranes prepared with different nonsolvents during the manufacturing process were also analyzed. The SEM analysis demonstrated that the increase in the PVP concentration led to the formation of macropores. Depending on the type of nonsolvent, a finger-like structure was formed when D·W was used, while a sponge structure was formed when EtOH or MeOh was used. In the tensile strength test, the tensile strength decreased as the PVP concentration increased, whereas the membranes with a sponge structure exhibited high tensile strength. The addition of PVP, a hydrophilic polymer, increased the hydrophilicity of the membrane surface, thereby suppressing the precipitation of proteins, and the cell viability was significantly improved from 80.1% in PESVP0-1 without PVP to 93.4%. In the simulation experiment using urea and creatinine as toxins, the maximum removal rate was 58.8% for urea and 56.87% for creatinine, and the loss of protein was less than 8%. These results serve as a preliminary study on the currently stalled domestic development of hemodialysis membranes by confirming the biocompatibility and functionality of PESVP membranes as hemodialysis membranes.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

References

[1] I. Ledebo and C. Ronco, "The best dialysis therapy? Results from an international survey among nephrology professionals," *NDT Plus*, vol. 1, no. 6, pp. 403–408, 2008.

[2] M. T. Sultan, B. M. Moon, J. W. Yang et al., "Recirculating peritoneal dialysis system using urease-fixed silk fibroin membrane filter with spherical carbonaceous adsorbent," *Materials Science and Engineering: C*, vol. 97, pp. 55–66, 2019.

[3] N. C. V. Melo, R. M. A. Moyses, R. M. Elias, and M. C. M. Castro, "Reprocessing high-flux polysulfone dialyzers does not negatively impact solute removal in short-daily online hemodiafiltration," *Hemodialysis International*, vol. 18, no. 2, pp. 473–480, 2014.

[4] R. Sinnakirouchenan and J. L. Holley, "Peritoneal dialysis versus hemodialysis: risks, benefits, and access issues," *Advances in Chronic Kidney Disease*, vol. 18, no. 6, pp. 428–432, 2011.

[5] R. Lu, C. Zhang, M. Piatkovsky, M. Ulbricht, M. Herzberg, and T. H. Nguyen, "Improvement of virus removal using ultrafiltration membranes modified with grafted zwitterionic polymer hydrogels," *Water Research*, vol. 116, pp. 86–94, 2017.

[6] C. Cheng, S. Sun, and C. Zhao, "Progress in heparin and heparin-like/mimicking polymer-functionalized biomedical membranes," *Journal of Materials Chemistry B*, vol. 2, no. 44, pp. 7649–7672, 2014.

[7] L. Ma, H. Qin, C. Cheng et al., "Mussel-inspired self-coating at macro-interface with improved biocompatibility and bioactivity via dopamine grafted heparin-like polymers and heparin," *Journal of Materials Chemistry B*, vol. 2, no. 4, pp. 363–375, 2014.

[8] B. Qian, J. Li, Q. Wei, P. Bai, B. Fang, and C. Zhao, "Preparation and characterization of pH-sensitive polyethersulfone hollow fiber membrane for flux control," *Journal of Membrane Science*, vol. 344, no. 1-2, pp. 297–303, 2009.

[9] J. Zhao, X. Zhao, Z. Jiang et al., "Biomimetic and bioinspired membranes: preparation and application," *Progress in Polymer Science*, vol. 39, no. 9, pp. 1668–1720, 2014.

[10] L. Wang, M. He, T. Gong et al., "Introducing multiple biofunctional groups on the poly (ether sulfone) membrane substrate to fabricate an effective antithrombotic bio-interface," *Biomaterials Science*, vol. 5, no. 12, pp. 2416–2426, 2017.

[11] J. Jiang, L. Zhu, L. Zhu, B. Zhu, and Y. Xu, "Surface characteristics of a self-polymerized dopamine coating deposited on hydrophobic polymer films," *Langmuir*, vol. 27, no. 23, pp. 14180–14187, 2011.

[12] B. Fang, Q. Ling, W. Zhao et al., "Modification of polyethersulfone membrane by grafting bovine serum albumin on the surface of polyethersulfone/poly(acrylonitrile-co-acrylic acid) blended membrane," *Journal of Membrane Science*, vol. 329, no. 1-2, pp. 46–55, 2009.

[13] A. Razmjou, J. Mansouri, and V. Chen, "The effects of mechanical and chemical modification of TiO$_2$ nanoparticles on the surface chemistry, structure and fouling performance of PES ultrafiltration membranes," *Journal of Membrane Science*, vol. 378, no. 1-2, pp. 73–84, 2011.

[14] B. Van der Bruggen, "Chemical modification of polyethersulfone nanofiltration membranes: a review," *Journal of Applied Polymer Science*, vol. 114, no. 1, pp. 630–642, 2009.

[15] C. Zhao, J. Xue, F. Ran, and S. Sun, "Modification of polyethersulfone membranes - a review of methods," *Progress in Materials Science*, vol. 58, no. 1, pp. 76–150, 2013.

[16] J. Jiang, L. Zhu, L. Zhu, H. Zhang, B. Zhu, and Y. Xu, "Antifouling and antimicrobial polymer membranes based on bioinspired polydopamine and strong hydrogen-bonded poly (N-vinyl pyrrolidone)," *ACS Applied Materials & Interfaces*, vol. 5, no. 24, pp. 12895–12904, 2013.

[17] J. Wang, M. Qiu, and C. He, "A zwitterionic polymer/PES membrane for enhanced antifouling performance and promoting hemocompatibility," *Journal of Membrane Science*, vol. 606, article 118119, 2020.

[18] N. Li, A. G. Fane, W. W. Ho, and T. Matsuura, *Advanced membrane technology and applications*, John Wiley & Sons, 2011.

[19] R. W. Baker, "Membrane technology," *Encyclopedia of Polymer Science and Technology*, vol. 3, 2002.

[20] G. R. Guillen, Y. Pan, M. Li, and E. M. V. Hoek, "Preparation and characterization of membranes formed by nonsolvent induced phase separation: a review," *Industrial & Engineering Chemistry Research*, vol. 50, no. 7, pp. 3798–3817, 2011.

[21] Z. Wang and J. Ma, "The role of nonsolvent in-diffusion velocity in determining polymeric membrane morphology," *Desalination*, vol. 286, pp. 69–79, 2012.

[22] L. Li, Z. Yin, F. Li, T. Xiang, Y. Chen, and C. Zhao, "Preparation and characterization of poly(acrylonitrile-acrylic acid-N-vinyl pyrrolidinone) terpolymer blended polyethersulfone membranes," *Journal of Membrane Science*, vol. 349, no. 1-2, pp. 56–64, 2010.

[23] W. Zhao, J. Huang, B. Fang et al., "Modification of polyethersulfone membrane by blending semi-interpenetrating network polymeric nanoparticles," *Journal of Membrane Science*, vol. 369, no. 1-2, pp. 258–266, 2011.

[24] J. T. Lai, D. Filla, and R. Shea, "Functional polymers from novel carboxyl-terminated trithiocarbonates as highly efficient RAFT agents," *Macromolecules*, vol. 35, no. 18, pp. 6754–6756, 2002.

[25] S. Nie, J. Xue, Y. Lu et al., "Improved blood compatibility of polyethersulfone membrane with a hydrophilic and anionic surface," *Colloids and Surfaces B: Biointerfaces*, vol. 100, pp. 116–125, 2012.

[26] L. Zhu, F. Liu, X. Yu, and L. Xue, "Poly (lactic acid) hemodialysis membranes with poly (lactic acid)-block-poly (2-hydroxyethyl methacrylate) copolymer as additive: preparation, characterization, and performance," *ACS Applied Materials & Interfaces*, vol. 7, no. 32, pp. 17748–17755, 2015.

[27] M. Irfan, A. Idris, N. M. Yusof, N. F. M. Khairuddin, and H. Akhmal, "Surface modification and performance enhancement of nano-hybrid f-MWCNT/PVP90/PES hemodialysis membranes," *Journal of Membrane Science*, vol. 467, pp. 73–84, 2014.

[28] A. Gao, F. Liu, and L. Xue, "Preparation and evaluation of heparin-immobilized poly (lactic acid) (PLA) membrane for hemodialysis," *Journal of Membrane Science*, vol. 452, pp. 390–399, 2014.

[29] T. Wang, Y.-q. Wang, Y.-l. Su, and Z.-y. Jiang, "Improved protein-adsorption-resistant property of PES/SPC blend membrane by adjustment of coagulation bath composition," *Colloids and Surfaces B: Biointerfaces*, vol. 46, no. 4, pp. 233–239, 2005.

[30] L.-P. Zhu, X.-X. Zhang, L. Xu, C.-H. du, B.-K. Zhu, and Y.-Y. Xu, "Improved protein-adsorption resistance of polyethersulfone membranes via surface segregation of ultrahigh molecular weight poly (styrene-alt-maleic anhydride)," *Colloids and Surfaces B: Biointerfaces*, vol. 57, no. 2, pp. 189–197, 2007.

[31] H. Wang, J. Li, F. Liu et al., "Enhanced hemocompatibility of flat and hollow fiber membranes via a heparin free surface crosslinking strategy," *Reactive and Functional Polymers*, vol. 124, pp. 104–114, 2018.

[32] W.-B. Tsai, J. M. Grunkemeier, C. D. McFarland, and T. A. Horbett, "Platelet adhesion to polystyrene-based surfaces preadsorbed with plasmas selectively depleted in fibrinogen, fibronectin, vitronectin, or von Willebrand's factor," *Journal of Biomedical Materials Research*, vol. 60, no. 3, pp. 348–359, 2002.

[33] W.-B. Tsai, Q. Shi, J. M. Grunkemeier, C. McFarland, and T. A. Horbett, "Platelet adhesion to radiofrequency glow-discharge-deposited fluorocarbon polymers preadsorbed with selectively depleted plasmas show the primary role of fibrinogen," *Journal of Biomaterials Science, Polymer Edition*, vol. 15, no. 7, pp. 817–840, 2004.

[34] M. He, Q. Wang, R. Wang, Y. Xie, W. Zhao, and C. Zhao, "Design of antibacterial poly (ether sulfone) membranes via covalently attaching hydrogel thin layers loaded with Ag nanoparticles," *ACS Applied Materials & Interfaces*, vol. 9, no. 19, pp. 15962–15974, 2017.

[35] X. Yu, L. Shen, Y. Zhu et al., "High performance thin-film nanofibrous composite hemodialysis membranes with efficient middle-molecule uremic toxin removal," *Journal of Membrane Science*, vol. 523, pp. 173–184, 2017.

[36] X. Yu, Y. Zhu, C. Cheng, T. Zhang, X. Wang, and B. S. Hsiao, "Novel thin-film nanofibrous composite membranes containing directional toxin transport nanochannels for efficient and safe hemodialysis application," *Journal of Membrane Science*, vol. 582, pp. 151–163, 2019.

[37] G. Lesaffer, R. de Smet, N. Lameire, A. Dhondt, P. Duym, and R. Vanholder, "Intradialytic removal of protein-bound uraemic toxins: role of solute characteristics and of dialyser membrane," *Nephrology Dialysis Transplantation*, vol. 15, no. 1, pp. 50–57, 2000.

[38] E. Salimi, A. Ghaee, A. F. Ismail, and M. Karimi, "Anti-thrombogenicity and permeability of polyethersulfone hollow fiber membrane with sulfonated alginate toward blood purification," *International Journal of Biological Macromolecules*, vol. 116, pp. 364–377, 2018.

[39] Z. Zhang, Y. Zhao, X. Luo, S. Feng, and L. Wu, "Preparation of a heparin-like functionalized tannic acid-coated polyethersulfone ultrafiltration membrane for hemodialysis by a simple surface modification method," *Applied Surface Science*, vol. 572, article 151440, 2022.

[40] X. Fu, T. Lei, S.-j. Li, Y.-f. Liu, J. Peng, and J.-p. Ning, "Construction of novel antiplatelet modified polyethersulfone membrane and study into its blood compatibility," *Materials Science and Engineering C*, no. article 112659, 2022.

[41] C.-C. Chang, K. G. Beltsios, J.-D. Lin, and L.-P. Cheng, "Nano-titania/polyethersulfone composite ultrafiltration membranes with optimized antifouling capacity," *Journal of the Taiwan Institute of Chemical Engineers*, vol. 113, pp. 325–331, 2020.

[42] H. Ji, H. Xu, L. Jin et al., "Surface engineering of low-fouling and hemocompatible polyethersulfone membranes via in-situ ring-opening reaction," *Journal of Membrane Science*, vol. 581, pp. 373–382, 2019.

[43] X. Yu, Y. Zhu, T. Zhang et al., "Heparinized thin-film composite membranes with sub-micron ridge structure for efficient hemodialysis," *Journal of Membrane Science*, vol. 599, article 117706, 2020.