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Research Article

Bioinspired Polyethersulfone Membrane Design via Blending with Functional Polyurethane

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Polyurethanes (PUs) are currently considered to be biocompatible materials but limited by a low resistance to thrombus. We therefore design a heparin-like PU (HLPU) to modify polyethersulfone (PES) membranes approaching integrated antifouling and antithrombotic properties by bioinspiration of heparin structure. Poly(vinyl pyrrolidone)-HLPU (PVP-HLPU) was synthesized via reversible addition-fragmentation chain transfer polymerization of VP using PU as a macroinitiator and then sulfonated by concentrated H_2SO_4. FTIR and NMR results demonstrated the successful synthesis of PVP-HLPU. By incorporation of PVP-HLPU, the cross-sectional structure of PES composite membranes altered from finger-like structure to sponge-like structure resulting in tunable permeability. The increased hydrophilicity verified by water contact angles benefited both the permeability and antifouling property. As a consequence, the composite membranes showed good blood compatibility, including decreased protein adsorption, suppressed platelet adhesion, lowered thrombin-antithrombin III generation, reduced complement activation, and prolonged clotting times. Interestingly, the PVP-capped HLPU showed better blood compatibility compared to polyethyleneglycol-capped and citric acid-capped HLPUs. The results demonstrated the enhanced antifouling and antithrombotic properties of PES hemodialysis membranes by the introduction of functional HLPUs. Also, the proposed method may forward the fabrication of hemocompatible membranes via bioinspired surface design.

1. Introduction

Polyurethanes (PUs) are currently facing growing applications in biomedical fields such as bone regeneration [1], near-infrared imaging [2], shape memory [3], anti-inflammatory platform [4], cancer gene therapy [5], controlled drug delivery [6], tissue engineering [7], and nervous system repair [8], due to the main advantage of their flexible chemical structure. Simple alterations of stoichiometry and/or monomers during the synthesis of PUs can produce various materials ranging from elastic thermoplastic polymers to rigid thermoset ones [9]. Besides these, a facile modification of pendent groups of PU can result in a broad spectrum of properties ranging from removing toxin bilirubin to antibacterial properties [10]. However, a limitation of low resistance to thrombi is still associated with these biomaterials that restricted their uses as blood-contacting materials.

Heparin is a highly acidic, polyanionic, and dispersive linear polysaccharide [11]. The bearing of highly negative charged groups (sulfate and carboxylate groups) and the acceptably hydrophilic structure facilitate its anticoagulant property, leading to a wide use in clinical practice. Therefore, numerous approaches have been developed to prepare heparin-immobilized PUs for potential biomedical applications with improved biocompatibility and anticoagulant activity [12], enhanced antiadhesive and antibacterial properties [13], inhibited protein and platelet adhesion [14], enhanced viability of transplanted hepatocytes and inducing angiogenesis [15], and so on. In an earlier study, blood-contacting PU films were prepared by alternatively immersing PU films in human serum albumin and heparin solutions [16]. However, the physically coated heparin onto PUs is not stable with the ionic interaction between human serum albumin (HSA) and heparin. Thereafter, researches turn

the direction towards covalently immobilization of heparin onto PUs. Tan et al. covalently linked heparin onto PU surfaces by the reaction between the amino group from pregrafted polyethylenimine and the carboxyl group from heparin, which significantly improved the hydrophilicity and hemocompatibility of the materials [12]. However, fabricating a heparin-like structure in PU polymer chains is rarely targeted. Herein, we aim to design novel heparin-like PU (HLPU) for the modification of polyethersulfone (PES) membrane by a simple blending method, which may be used for the fabrication of hollow dialysis membranes.

PES has become one of widely used polymers, due to its good oxidative, thermal and hydrolytic stabilities, and good mechanical and film-forming properties [17, 18]. However, the anticoagulant and antifouling properties of PES are not ideal so far. Therefore, our recent study focused on the functionalization of PES dialysis membranes by HLPUs. The heparin-like polyurethanes contained $–SO_3H$, –COOH, and –OH groups, which were fabricated to modify the anticoagulate property of PES membranes by a blending method [19]. In order to endow PES membrane with both anticoagulant and antifouling properties, herein, poly(vinyl pyrrolidone) (PVP) is employed as an end-capped groups in HLPU. The resultant PVP-HLPU was then blended with PES. The water contact angle, antifouling property, and hemocompatibility for the membranes were performed. In addition, the effect of the end-capped groups on the properties of modified PES membranes was studied.

2. Experimental

2.1. Materials. Polyethersulfone (PES, Ultrason E6020P) was purchased from BASF chemical company (Germany). *N*-Vinyl-pyrrolidone (VP; 99%) was purchased from Alfa Aesar. Diphenyl-methane-diisocyanate (MDI; 98%) and dimethylolpropionic acid (DMPA; 98%) were obtained from Aladdin (China). MDI, DMAP, VP, and DMAc were distilled under reduced pressure prior to use. *N*,*N*-dimethylacetamide (DMAc; 98%) was obtained from Chengdu Kelong Company (China). Bovine serum albumin (BSA) and bovine serum fibrinogen (FBG) were purchased from Sigma (USA). All the other chemicals were obtained from Chengdu Kelong Inc., China.

2.2. Synthesis and Characterization of PVP-HLPU. PU was firstly synthesized. Typically, 0.060 mol MDI was dissolved in 200 mL DMAc with stirring under N_2, followed by adding 0.062 mol DMPA. After completely dissolving the monomers, the reaction was performed in airtight equipment at 70°C for 4 h under N_2. The reaction pathway is presented in Scheme 1. The crude product was purified by methanol and hot deionized (DI) water, respectively, to remove the residues. The obtained PU was dried completely at 40°C in a vacuum oven over 3 days.

Then, PU RAFT agent was synthesized. Typically, 1.74 g chain transfer agent (CTA), 1.18 g EDC, and 0.83 g HOBT were dissolved in 200 mL DMAc with continuous stirring at nitrogen atmosphere. After the activation for 1 h, 18 g PU was added to above-mentioned solution and kept the reaction at room temperature for 24 h. The product was purified with methanol and hot DI water, respectively, to guarantee a full removal of the impurities. The obtained product (macro-RAFT agent) was dried completely at 30°C in a vacuum oven until reaching constant weight.

Table 1: The compositions of modified PES membranes.

Sample code	PES (wt.%)	PVP-HLPU (wt.%)	DMAc (wt.%)
M-0	18	0	72
M-2	18	2	70
M-4	18	4	68
M-6	18	6	66
M-8	18	8	64

Polymerization of VP into the polymer chain of PU was carried out in a sealed tube. Briefly, 2.49 g of VP, 1 g of the macro-RAFT agent, and 0.02 g of AIBN were added to a Schlenk flask followed by the addition of DMAc. After three cycles of freeze-pump-thaw, the reaction mixture was allowed to warm to 80°C under a nitrogen atmosphere, and the polymerization was carried out for 10.5 h. After dialysis against DI water for couple of days, the product was freezing-dried resulting in white powders and termed as PVP-PU.

The obtained PVP-PU was sulfonated by concentrated H_2SO_4 with a mass ratio of 1 : 10. After stirring at room temperature in the H_2SO_4 for 10 h, the PVP-HLPU was purified with DI water for couple of times to remove the residue H_2SO_4. The HLPU powder was dried at 30°C for 72 h. A Fourier transform infrared spectroscope (FTIR) and a BRUKER spectrometer were used to characterize PVP-HLPU polymer.

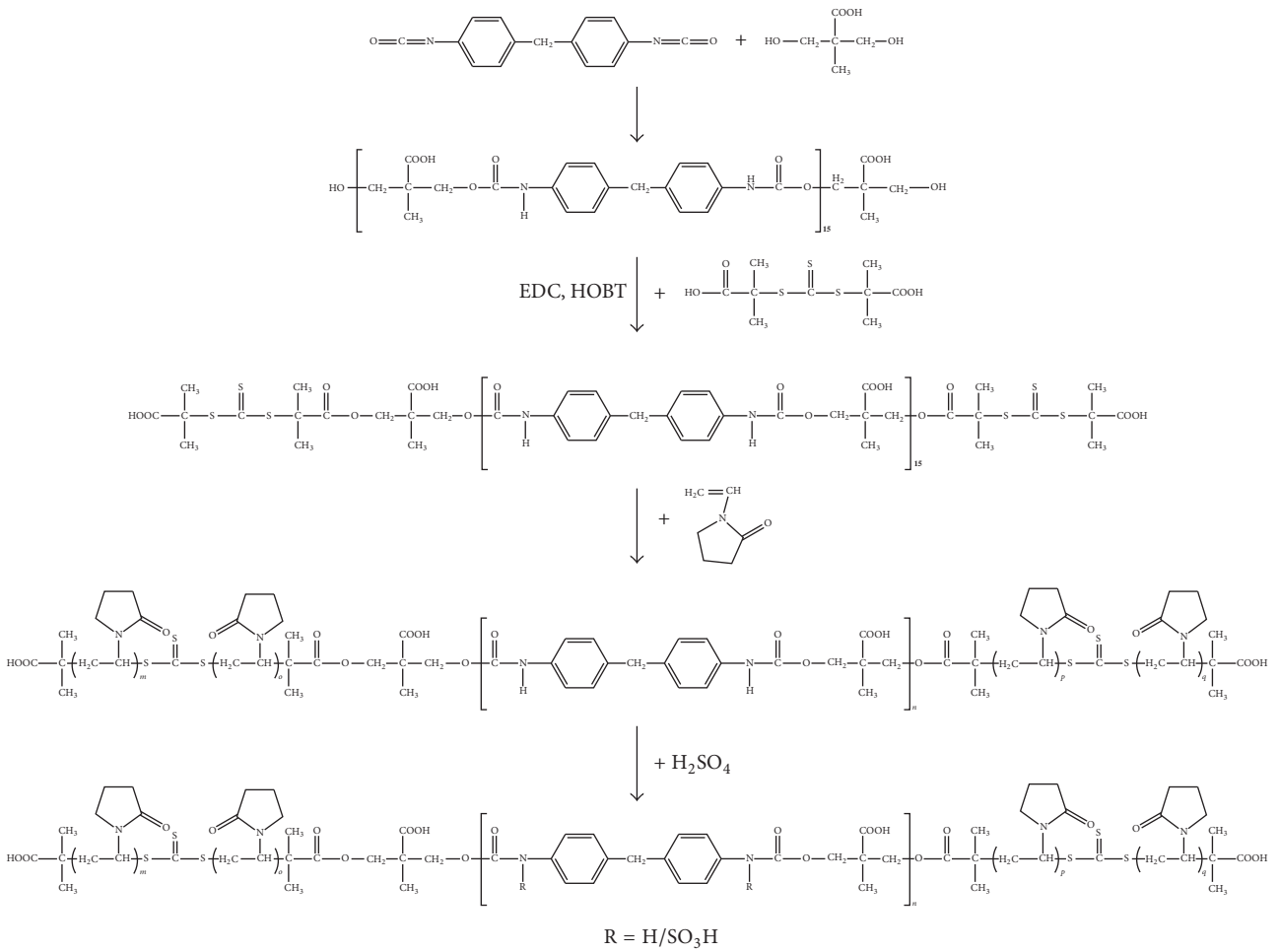
2.3. Preparation and Characterization of Membranes. The membranes were prepared by a liquid-liquid phase-inversion technique as described in our earlier studies [20]. The modified membranes with different mass percentages of the PVP-HLPU are shown in Table 1.

A scanning electron microscope (FE-SEM, JSM-7500F, JEOL, Japan) was used to characterize the cross section morphology of the membranes.

The hydrophilicity of the membranes was characterized by a contact angle goniometer (OCA20, Dataphysics, Germany) equipped with video capture. At least five measurements were averaged to reach a reliable value.

2.4. Antifouling Property of Membranes. The characterization of the antifouling property of membranes were provided in S1 (see Supporting Material available online at https://doi.org/10.1155/2017/2158124).

2.5. Blood Compatibility of Membranes. The protein adsorption behavior of PES membranes was carried out according to our previous study [10]. The protein adsorption, platelet adhesion, clotting times (activated partial thromboplastin times (APTTs) and thrombin times (TTs)), platelet activation (Human Platelet Factor 4 (PF4)), coagulation activation (thrombin-antithrombin III complex (TAT)), and complement activation (C3a and C5a) of PES membranes were



Scheme 1: Synthesis of PVP-HLPU.

carried out, and the details were provided in S2 (see Supplementary Material).

3. Results and Discussion

3.1. Synthesis and Characterization of HLPU. The FTIR spectra for the PVP-PU and PVP-HLPU are shown in Figure 1. It was observed that the peaks at 3310 cm^{-1} and 3391 cm^{-1} were the characteristic stretching vibration peaks of the N–H of the isocyanate [19] in the PVP-PU and PVP-HLPU, respectively. After the sulfonation, the peak intensity at 3310 cm^{-1} decreased, which indicated the successful sulfonation of PVP-PU. The peaks at 2914 cm^{-1} and 2908 cm^{-1} were attributed to the $-CH_3$ of the CTA in the PVP-PU and PVP-HLPU, respectively, while the peaks at 1732 and 1736 cm^{-1} were attributed to the –C=O in the carboxyl group of the isocyanate in both the PVP-PU and PVP-HLPU. The characteristic stretching vibration peak of cyclanone in VP was observed at 1662 cm^{-1}. Besides, the characteristic peak of S=O of the sulfonic group in PVP-HLPU should be between 1600 and 1750 cm^{-1}, which was covered by the characteristic peak of C=O.

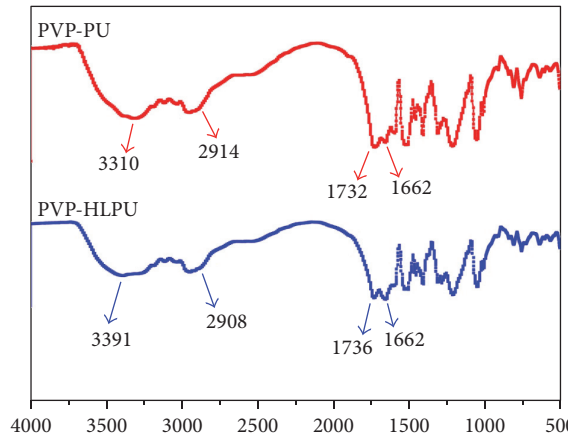


Figure 1: FTIR spectra of PVP-PU and PVP-HLPU.

The NMR spectra for the PVP-PU and PVP-HLPU are presented in Figure 2. The synthesized PVP-PU was verified by the signals at a (δ = 9.59 ppm, N–H), b and c (δ = 7–7.5 ppm, Ar–H), d (δ = 4.22 ppm, $-CH_2-$ in DMPA), e

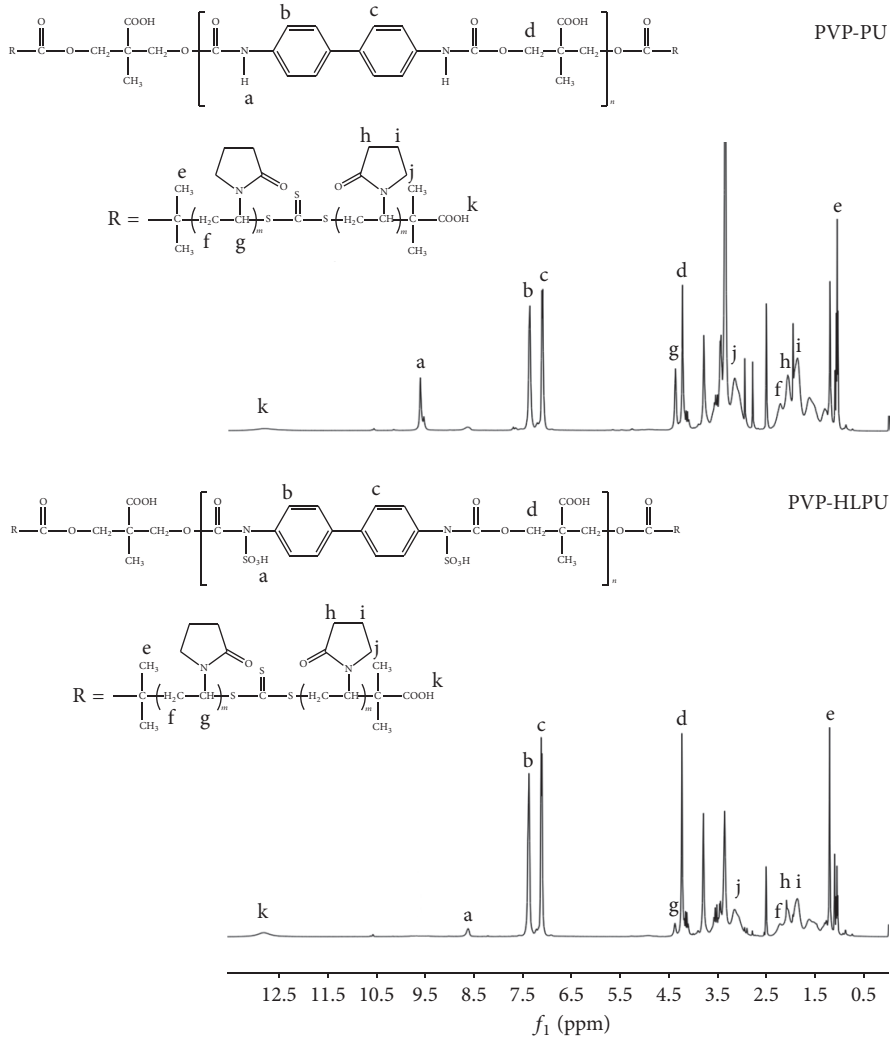


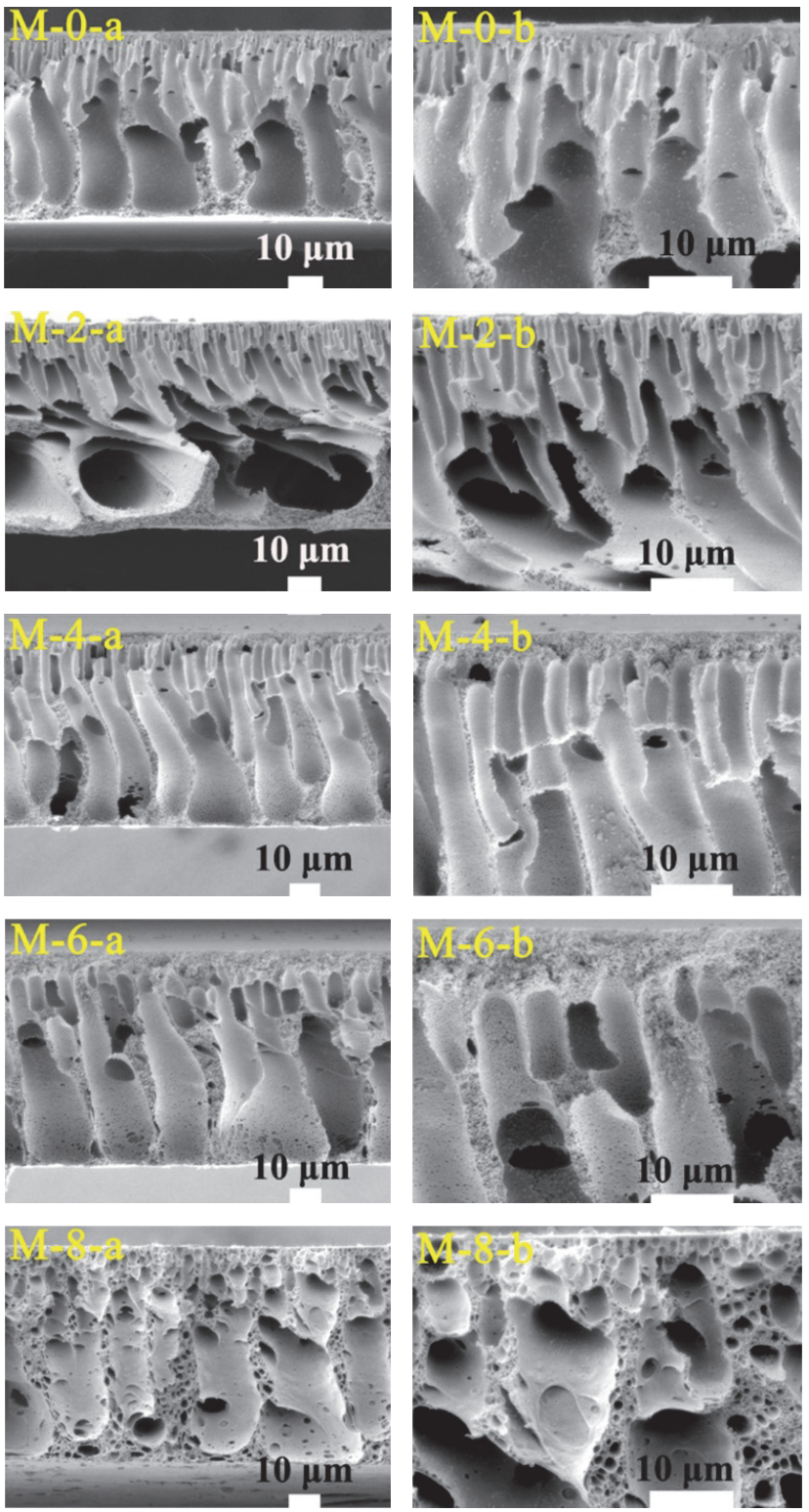
Figure 2: The ^{1}H NMR of PVP-PU and PVP-HLPU.

(δ = 1.21 ppm, $-CH_3$ of the CTA), f ($-CH_2-$ on the PVP backbone), g (C–H on the PVP backbone), h, i, and j (the $-CH_2-$ of the cyclanone in VP), and k (–COOH of the PVP-PU). Compared to the NMR spectrum for the PVP-PU, the signal at δ = 9.59 ppm (N–H) of the NMR spectrum for the PVP-HLPU almost disappeared, which was replaced with an intensified signal at δ = 8.53 ppm due to the sulfonic group in PVP-HLPU).

3.2. Morphologies and Hydrophilicity of PES Membranes. Figure 3 shows the SEM images for the cross section of the membranes. It was observed that the cross section structure of the membranes showed two dense layers and an interlayer. Interestingly, the pores of the modified membranes changed gradually from finger-like structure to sponge-like structure with the addition of the PVP-HLPU, when compared to the membrane M-0. Especially when the PVP-HLPU content reached 8 wt.% (M-8), the finger-like pores almost disappeared and the cross-sectional structure nearly changed to sponge-like structure. Furthermore, the sponge-like pore size increased gradually with the PVP-HLPU content changing from 2 wt.% to 8 wt.%; the reason might be that the hydrophilic PVP-HLPU migrated to the membrane surfaces and the pore surfaces during the phase separation process of the membrane preparation [17].

3.3. Antifouling Property of Membranes. To investigate the antifouling property of the membranes, BSA ultrafiltration was carried out, and the data are shown in Figure 4. The PBS fluxes of all the modified membranes were higher than that of the pristine PES membrane. For the modified membranes, the PBS flux increased with increasing the HLPU amount, which might be resulted from the changed membrane structure and the increased surface hydrophilicity (as shown in Figure 3 and Table 2). It was reported that the viscosity of the casting solution would be changed after blending the amphiphilic PU, which had great effect on the phase separation during membrane formation [21].

Meanwhile, a slight reduction in the PBS solution was observed with time as shown in Figure 4. The fluxes of



(a) (b)

Figure 3: SEM images of the cross sections of different PES membranes. Magnification: (a) 1000x; and (b) 2500x.

Table 2: Water contact angle and permeability of PES membranes.

Sample code	Copolymer (wt. %)	Water contact angle (°)	Water flux (mL/h×m^2×mmHg)	Flux recovery ratio (%)
M-0	0.0	76.8 ± 2.2	30.6	40.8
M-2	2.0	65.8 ± 1.9	90.0	81.7
M-4	4.0	58.2 ± 1.5	113.6	84.7
M-6	6.0	51.3 ± 1.8	133.5	88.2
M-8	8.0	46.7 ± 2.5	155.1	92.0

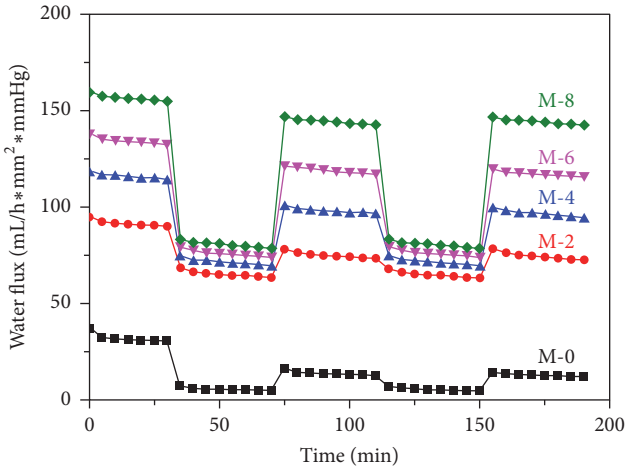


Figure 4: Time-dependent fluxes of the PES and modified membranes. PBS solution: 0–30 min, 80–110 min, and 160–190 min; BSA solution: 40–70 min and 120–150 min.

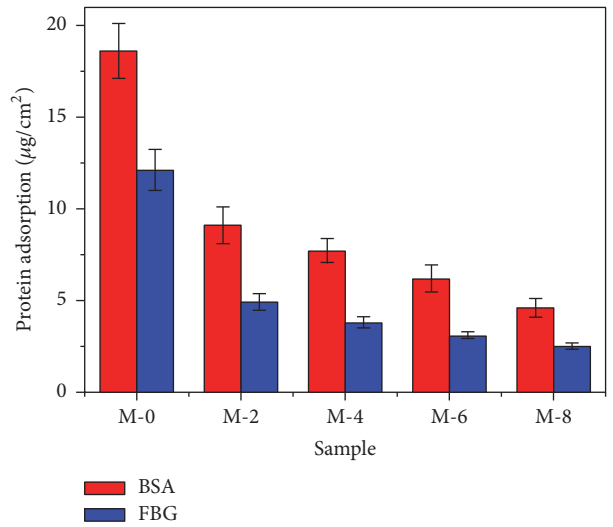


Figure 5: The protein adsorbed amount for the pure PES membrane and the composite membranes.

the membranes decreased dramatically when the filtration solution changed from PBS to BSA solution. This might be due to BSA molecules deposition/adsorption on the membrane surfaces and/or in the membrane pore surfaces [22].

The decline in flux under constant pressure was caused by two reasons: concentration polarization and membrane fouling [23]. As a result, several cycles of filtration and flux recovery ratios were tested to determine the main reason for the flux decline of the membranes. The composite membranes were washed with PBS solution for 10 min after 60 min of protein ultrafiltration. Afterward, the PBS solution fluxes were carried out once again. It could be observed in Figure 4 that the fluxes for all the modified membranes recovered in a larger extent compared to the pristine PES membrane after rinsing in DI water for 30 min. It indicated that the fluxes of the modified membranes were much easier to be recovered and thus showed better antifouling property.

In addition, flux recovery ratios (F_{RR}) were used to judge the antifouling property [24]. The better antifouling property of the membrane is reflected by higher F_{RR} values. As shown in Table 2, all F_{RR} values for the modified membranes were over 80%, which are higher than that (40.8%) of the pristine PES one. In addition, F_{RR} increased gradually with increasing blended amounts of HLPU. It indicated that the composite membranes showed good antifouling property after the addition of HLPU.

3.4. Blood Compatibility of Membranes

3.4.1. Protein Adsorption. Protein adsorption on biomaterial surfaces is always considered as the first step of many undesired bioreactions and bioresponses [25]. Protein adsorption is affected by numerous factors, such as hydrophilicity/hydrophobicity, surface charge, surface topology, interactions between the adsorbed molecules, the composition of the protein solution, and the surface chemistry [26]. The modified membranes after blending with hydrophilic additives exhibited decreased protein adsorption and enhanced biocompatibility [22]. Otherwise, plasma protein adsorbed on material surface had great influence on platelet adhesion and activation [27]. Thus, protein adsorption was firstly tested to investigate the blood compatibility of the membranes.

The adsorption of BSA and FBG of the membranes was studied in vitro, and the results are presented in Figure 5. As expected, all the modified membranes exhibited decreased protein adsorption amounts compared to the pristine PES membrane (M-0). The BSA adsorption and FBG adsorption for the pristine PES membrane were 18.5 μg/cm^2 and 11.8 μg/cm^2, respectively. As for the modified membranes, the protein adsorption amounts decreased with increasing the blended HLPU content. In particular, when the PVP-HLPU content was 8 wt.%, the BSA and FBG adsorption of the membrane (M-8) decreased dramatically to 4.9 μg/cm^2 and 2.4 μg/cm^2, respectively. It might be caused by the

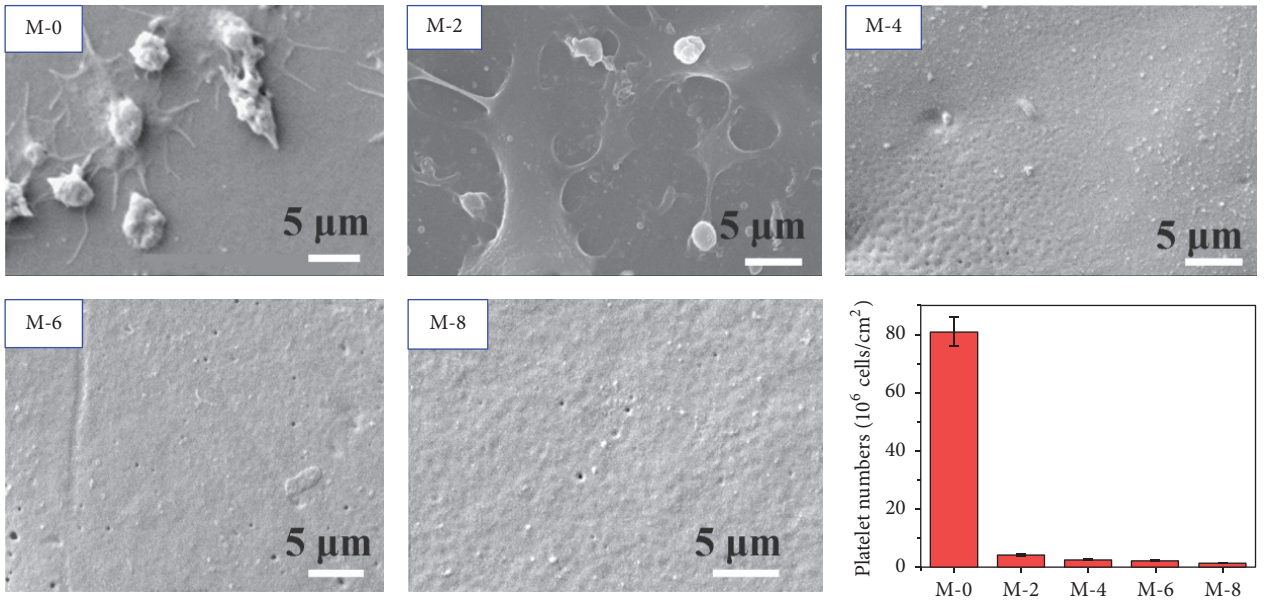


Figure 6: SEM micrographs of platelets adhered on the membrane surface.

increased hydrophilicity and electrostatic repulsion of the negative charge of the modified membrane surface. The enhanced protein antifouling properties improved the blood compatibility of the modified membranes.

3.4.2. Platelet Adhesion. Platelet adhesion on the surface of biomaterials is also critical to evaluate hemocompatibility. Once a foreign material contacts with blood, inducing of adsorbing proteins in blood, platelet adhesion and platelet activation cannot be avoided, then forming thrombus [28].

The results of platelet adhesion onto PES membranes are presented in Figure 6. It could be observed that the amount of adhering platelets decreased sharply with increasing the PVP-HLPU amounts in the modified membranes. When the PVP-HLPU content reached above 6 wt.% (M-6 and M-8), there was almost no platelet adhesion on the modified membranes. Meanwhile, the adhered platelets on the surface of modified membranes showed rounded shape, and almost no pseudopodium and deformation were observed on the surface of the modified membrane. However, an aggregation of the adhered platelets on the original PES membrane were deformed with extended pseudopodia. It was due to the improved hydrophilicity and the relatively low protein adsorption on the modified membranes. It indicated that the hemocompatibility of the PVP-HLPU modified membranes was improved.

3.4.3. Clotting Times (APTT and TT). The activated partial thromboplastin time (APTT) and thrombin time (TT) are also used to characterize the anticoagulant properties of the membranes. We measured the APTTs and TTs for the membranes to investigate the anticoagulation activity of the membranes, and the results are presented in Figure 7.

Both the APTTs and TTs increased sharply with increasing the blended PVP-HLPU amounts. When the blended

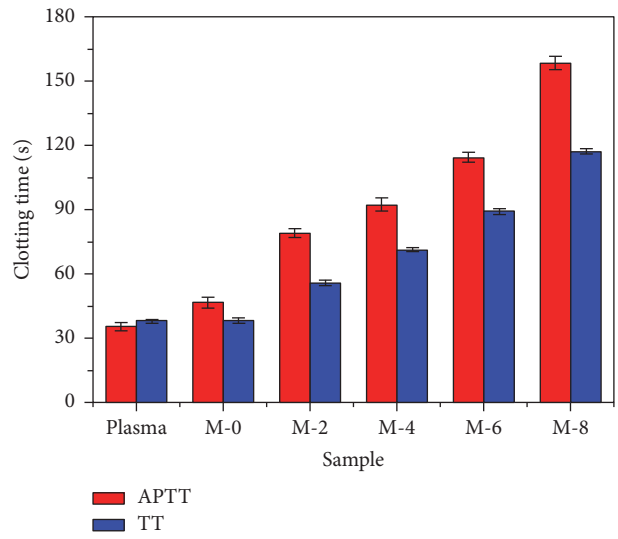


Figure 7: Clotting time results for all the membranes. Values are expressed as means ± SD ($n = 3$).

amounts of PVP-HLPU reached 8 wt.%, both the APTT and TT of the membrane M-8 were over three times longer than the APTT and TT of the membrane M-0. The increase of clotting time was much higher than those reported in other studies [29]. The excellent anticoagulant property was caused by the heparin-mimicking structure of HLPU, the enhanced hydrophilicity, and antifouling properties. Therefore, the clotting time tests indicated the anticoagulant properties of the PVP-HLPU modified membranes were improved.

3.4.4. Platelet Activation and Thrombin Generation. Contact activation of the coagulation system is crucial to induce blood coagulation. Platelet activation could result in platelet

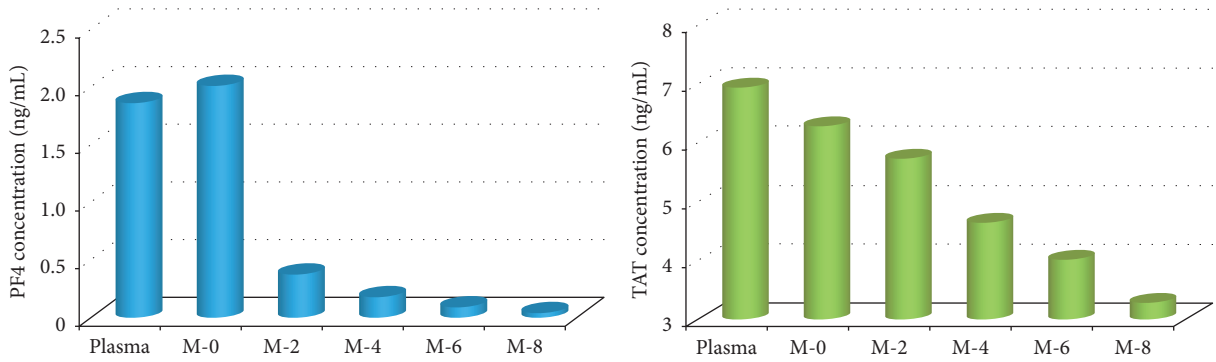


Figure 8: Platelet factor 4 (PF4) and thrombin-antithrombin III (TAT III) complex concentrations for the membranes.

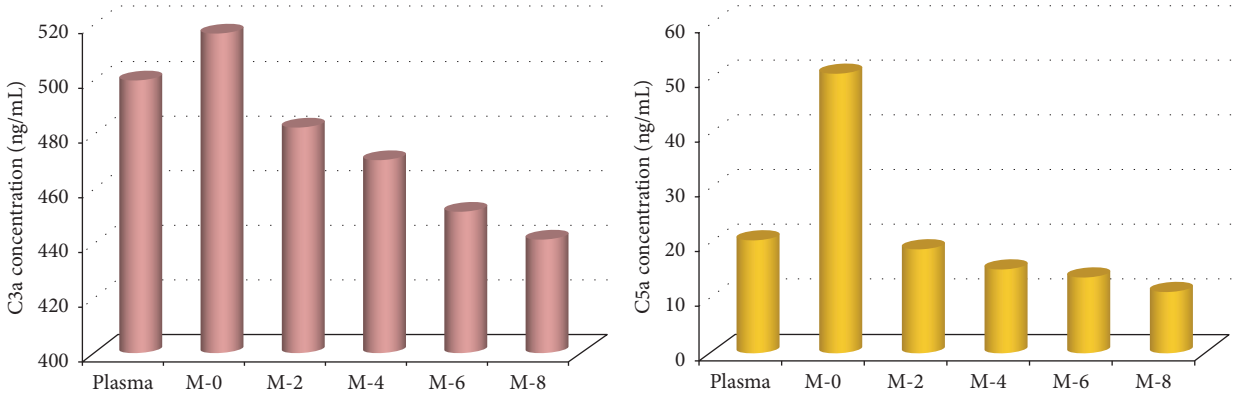


Figure 9: C3a and C5a concentrations for the membranes.

aggregation and activate the coagulation cascade system. Platelets interact with coagulation factors, while formed thrombin is a potent platelet-activating agonist [30]. The activated platelets could result in forming platelet factor 4 (PF4), while the formed thrombin could couple with antithrombin III to generate thrombin-antithrombin III (TAT) complexes [31]. Therefore, the concentrations of PF4 and TAT complexes could reflect the contact activation level, and the results are presented in Figure 8.

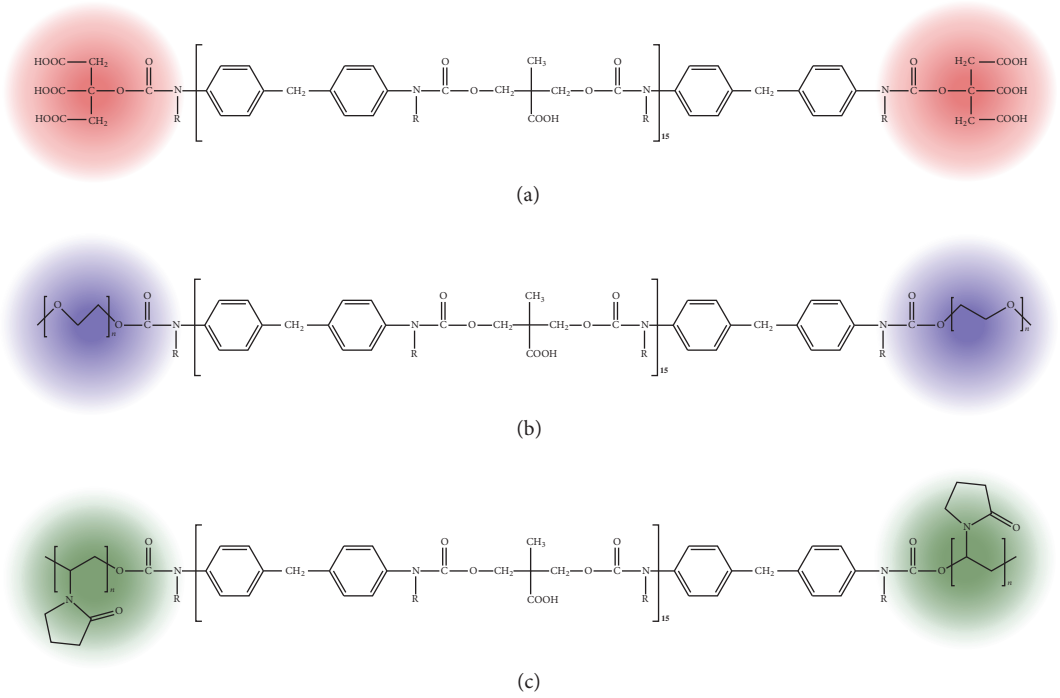
Both the PF4 and TAT complexes concentrations for the modified membranes decreased dramatically compared to the pristine PES membrane (M-0) or the plasma, which indicated that the modified membranes would not induce the activation of platelet and coagulation cascade. Thus, the modified membranes showed excellent blood compatibility after introducing the PVP-HLPU.

3.4.5. Complement Activation. Human complement system is also important in the body's defense mechanisms against infection and "nonself" elements [32]. After contacting the blood, the complement activation reflects the hemocompatibility of materials. After complement activation, followed by C3a, C4a, and C5a release, which are anaphylatoxins [33]. In current study, activation of C3a and C5a was tested to evaluate the complement activation of the modified membranes, and the results are presented in Figure 9.

Both the C3a and the C5a concentrations in plasma increased after the membrane M-0 contacted with the plasma. However, for the modified membranes, the C3a and the C5a concentrations in plasma decreased to a certain extent. In addition, their concentrations decreased with increasing the amount of PVP-HLPU additive. The results indicated that the modified membranes showed suppressed complement activation after introducing the PVP-HLPU.

3.4.6. Comparison of End-Capped Hydrophilic Segments. In order to study the influence of the HLPUs with different end-capped hydrophilic segments on membrane performances, CA- and PEG-capped HLPUs were also synthesized and used for the modification of PES membranes. The molecular structures of the HLPUs are illustrated in Scheme 2.

In the study, 8 wt.% of CA-, PEG-, and PVP-capped HLPUs were blended with 18 wt.% of PES, and the membranes were fabricated by a phase-inversion method and termed as M-CA-HLPU, M-PEG-HLPU, and M-PVP-HLPU, respectively. Pure PES membrane was also prepared as the reference and named as M-PES. The properties of PES membranes are listed in Table 3. The hydrophilicity, water flux, and F_{RR} of modified PES membranes increased after blending functional HLPUs. The PES composite membranes with PEG-capped HLPU exhibited lowest protein adsorption compared with those with other functional HLPUs. PVP-capped HLPU could endow PES membranes (M-PVP-HLPU) with the best blood compatibility, which was demonstrated by the highest APTT and TT and the lowest platelet activation, TAT generation, and complement activation.



(a)

(b)

(c)

Scheme 2: Molecular structures of HLPUs with different end-capped segments.

Table 3: Systematical comparison of different HLPUs modified membranes.

Testing Name	Plasma	M-PES	M-CA-HLPU	M-PEG-HLPU	M-PVP-HLPU
Contact angle (°)	/	81.5	54.3	51.2	46.7
Water flux (mL/h∗m^2∗mmHg)	/	30.6	165.2	175.5	155.1
F_{RR} (%)	/	40.8	95.3	95.3	92.0
BSA adsorption (μg/cm^2)	/	18.6	3.8	3.3	4.6
FBG adsorption (μg/cm^2)	/	12.1	2.7	1.6	2.5
APTT (s)	35.5	46.8	136.2	100.2	158.7
TT (s)	37.9	38.5	108.7	88.5	117.5
PF4 concentration (ng/mL)	1.86	2.01	0.06	1.05	0.04
TAT concentration (ng/mL)	6.95	6.29	5.05	4.86	3.29
C3a concentration (ng/mL)	499.7	516.8	482.5	456.1	441.6
C5a concentration (ng/mL)	20.6	51.1	16.9	13.9	11.2

4. Conclusion

In this study, a heparin-like poly(vinyl pyrrolidone)-capped polyurethane (PVP-HLPU) was designed by reversible addition-fragmentation chain transfer polymerization combined with a sulfonation. The obtained PVP-HLPU could be directly blended with PES matrix to prepare membranes. The modified membranes showed excellent hemocompatibility and excellent protein antifouling properties compared with pristine PES membrane. In a conclusion, it is an effective system to evaluate the blood compatibility of the membranes by combination of APTT, TT, and platelet adhesion and so on. That is not to say that there is no drawback by use of these three methods. Other methods such as complement activation, hemolysis test could also be employed to characterize the blood compatibility of polymeric materials. Nonetheless, our results indicated that the PVP-HLPU modified membranes had great potential to be used in blood purification.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

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