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Surface characteristics and hemocompatibility of PAN/PVDF blend membranes

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Polyacrylonitrile (PAN) was blended with polyvinylidine fluoride (PVDF) at various ratios and made into membranes. The hemocompatibility of the resulting membranes was evaluated based on human plasma proteins adsorption, platelet adhesion, thrombus formation, and blood coagulation time. The PAN/PVDF blends exhibited partial miscibility according to the inward shifting of their two glass transition temperatures. The microstructures of blend membranes examined using atomic force microscopy (AFM) indicated that the roughness increased with the PVDF content, and the phase separation was too severe to form a membrane when the PVDF content was more than 30%. The water contact angle of PAN/PVDF blend membranes increased with the PVDF content. By blending with 20 wt% apolar PVDF the adsorption of blood proteins could be reduced, and hence the platelet adhesion and thrombus formation was also reduced. However, when the PVDF content was 30 wt%, severe thrombogenicity was observed due probably to the more porous structure of blend membrane. These results demonstrated that the hemocompatibility would be improved for PAN/PVDF blend membranes with appropriate hydrophilicity and roughness.

KEYWORDS: polyacrylonitrile; polyvinylidine fluoride; blends; miscibility; membranes

INTRODUCTION

Hemodialysis is an important clinical procedure for the removal of toxic biological metabolites in patients with end-stage renal disease.[1] Polyacrylonitrile (PAN) hollow fiber membranes are widely used as hemodialyzers that can remove low to middle molecules as a high-flux dialysis therapy. However, the inherent thrombogenicity of PAN remains a problem and limits its application.[2]

Blending is frequently used in order to change the properties of polymeric materials.[3,4] And shows good potential for application in various fields such as semiconductor, electronics and biomaterials. Recently, much effort has been focused on the development, manufacturing and application of biocompatible materials.[5,6] In the literature, hollow fibers of PAN blended with a small amount of polyvinylidine fluoride (PVDF) have been reported by Yin *et al*.[7] The results show that PAN and PVDF are partially miscible, and that the spinnability of PAN is greatly improved and the hollow fiber membranes possess much higher flux than pure PAN membrane while maintaining a high retention ratio. PVDF has higher mechanical strength than PAN, and can resist attrition, acid- and alkali-attack, and radiation (UV and γ-rays). In addition, PVDF is one of the materials for making artificial blood vessels.[8] Thus, PVDF can reduce protein adsorption and platelet adhesion onto its surface and hence is a good thrombus-resisting material.[9]

In our previous studies,[10,11] we have reported that heparin-immobilized surface of PAN membrane can suppress the adsorption of human plasma proteins and adhesion of platelets, hence effectively improving the hemocompatibility. In addition, the blending morphology and permeation of PAN/PVDF blend membranes have also been studied. As a continuation of our earlier efforts to modify the properties of PAN, in this present work, we evaluate the blend membranes of PAN/PVDF in terms of morphology and dynamic mechanical properties. Additionally, we also evaluate the hemocompatibility of blend membranes with different PVDF content based on protein adsorption, platelet adhesion, blood coagulating time, and thrombus formation. We hope the results of this preliminary study can not only contribute to improve the hemocompatibility of PAN membrane by blending modification, but also apply the membranes to blood-contacting devices.

EXPERIMENTAL

Materials

PAN and PVDF were purchased from Aldrich, USA. *N,N*-Dimethylformamide (DMF) was purchased from Acros, USA. Anticoagulant citrate dextrose (ACD) human blood and plasma were obtained from the Blood Center in Taiwan.

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Fabrication of PAN/PVDF blend membrane

The membranes were prepared by the phase inversion method.[11] The casting polymer solutions were prepared by dissolving polymer chips in DMF at various ratios of PAN and PVDF. The total polymer content was 20 wt%. Afterwards, the polymer solution was cast onto a glass plate to form a flat membrane by immersing in de-ionized (DI) water at 25°C. The resulting membranes were rinsed with DI water for 12 hr, and then were dried under vacuum for 6 hr. The PAN/PVDF (90/10, 80/20, 70/30 wt%) blend membranes were designed as PAN91, PAN82 and PAN73, respectively.

Characterization analysis

The surface morphology was examined using atomic force microscopy (AFM) (MMAFM-2, Digital Instrument, Santa Barbara, CA) and scanning electron microscopy (SEM) (Oxford S360, Cambridge, UK, JEOL JSM-6310). The mechanical properties were determined using dynamic mechanical analyzsis (DMA, DMA7e, Perkin–Elmer, USA) from 173 to 423 K at a heating rate of 5 K/min.

Hydrophilicity measurement

The hydrophilicity of the surface was evaluated based on the dynamic water contact angle of the membrane measured using a contact angle goniometer (DSA 100, Krüss GmbH, Hamburg, Germany).[12] Each value was averaged from six measurements.

Blood coagulation time[10]

To obtain platelet-rich plasma (PRP), the ACD human blood was centrifuged at 100*g* for 20 min at 4°C to separate the blood corpuscles. Subsequently, portions of PRP were further centrifuged at 2000*g* for 20 min at 4°C to obtain the platelet-poor plasma (PPP). A sample membrane ($1 \times 1\ cm^2$) was put into 0.5 ml PPP and was incubated at 37°C for 1 hr. The activated partial thrombin time (APTT), prothrombin time (PT), and fibrinogen time (FT) of reacted PPP were determined using an automated blood coagulation analyzer (CA-50, Sysmex Corp., Kobe, Japan). The control was measured against the glass tube without a polymer sample.

Protein adsorption

A piece of membrane of $1 \times 1\ cm^2$ was immersed in 5 ml of PPP solution (total protein: 6 g/dl) and shaken at 100 rpm and 37°C for 2 hr, respectively. The membrane was gently taken out and rinsed five times with phosphate-buffered saline (PBS). Then the membrane was placed in a glass bottle with 1 wt% aqueous solution of sodium dodecyl sulfate (SDS) and shaken for 60 min at room temperature to remove the protein adsorbed on the surface. A protein analysis kit (MicroBCA protein assay reagent kit, Pierce, Rockford, IL, USA) was used to determine the concentration of the total proteins in the SDS solution.[5] Ishihara *et al.*[5] proved that the protein adsorped onto the polymer could be completely desorbed in SDS solution. The albumin (Alb) and fibrinogen (FN) amounts were determined by bio-analyzer (SAAB 1000, Italy) and blood coagulation analyzer (CA-50, Sysmex Corp., Kobe, Japan), respectively.

Evaluation of platelet adhesion

The determination of platelet adhesion was described in our precious studies.[10] Briefly, rinsed samples ($1 \times 1\ cm^2$) were placed into the wells of 24-well culture plates in contact with 1.5 ml of human PRP and were incubated at 37°C for 30, 60 and 120 min. PBS (6 ml) was then added to the PRP and stood for l min to stop further platelet adhesion. The platelet-adhered membrane was soaked into 10 ml Triton-100 solution at 37°C for 30 min and the platelet-adhered number was determined by the lactate dehydrogenase (LDH) method[13] using a kit form purchased CARO, Germany.

Thrombus formation

Thrombus formation test procedure was described in our previous studies.[10,11] Briefly, the samples were rinsed with doubly-distilled water and placed into the wells of 24-well culture plates in contact with 1.5 ml of human whole blood without anticoagulant and were incubated at 37°C for 30, 60 and 120 min, and then the samples were washed five times with PBS. The samples were then dehydrated with graded ethanol and dried by the critical-point procedure. The degree of thrombosis (DT) of the membrane is defined as follows:

$$DT = \frac{W_t - W_{dry}}{W_{dry}}$$

where W_{dry} and W_t are the dry membrane weights after incubated for time and the initial membrane, respectively.

RESULTS AND DISCUSSION

Morphology of PAN/PVDF blend membranes

In our previous study,[11] we found that with increasing PVDF content, the hydraulic permeability (L_p) of the blend membranes increased while the rejection ratio ($R\%$) decreased. In the present work, AFM topographic images further displayed the microstructures on the surface of blend membranes, as shown in Fig. 1. The blend membranes exhibited larger domains and rougher surfaces than those of pure PAN and PVDF membranes. Table 1 lists the roughness parameters in both height mode and phase mode. The height mode roughness of pure PVDF ($Rq = 31.4$ nm) was higher than that of PAN (12.7 nm) and PAN91 (16.0 nm) and was close to that of PAN82 (32.6 nm). Furthermore, pure PAN and PVDF had a denser surface without obvious pores, whereas for blend membranes, the pore size became larger and irregular with the increase of the PVDF content, as described by our previous study.[11] We believe the different surface and structure morphology will result in the different hemocompatibility of PAN/PVDF blend membranes.

DMA measurement of blends

Dynamic mechanical properties of PAN/PVDF blend membranes were evaluated by DMA measurements to observe the relationship between Tan δ and temperature, as shown in Fig. 2. It is well known that the glass transition temperature (T_g) of a polymer is one of the most important criteria for the miscibility of components.[14] The definition for miscible

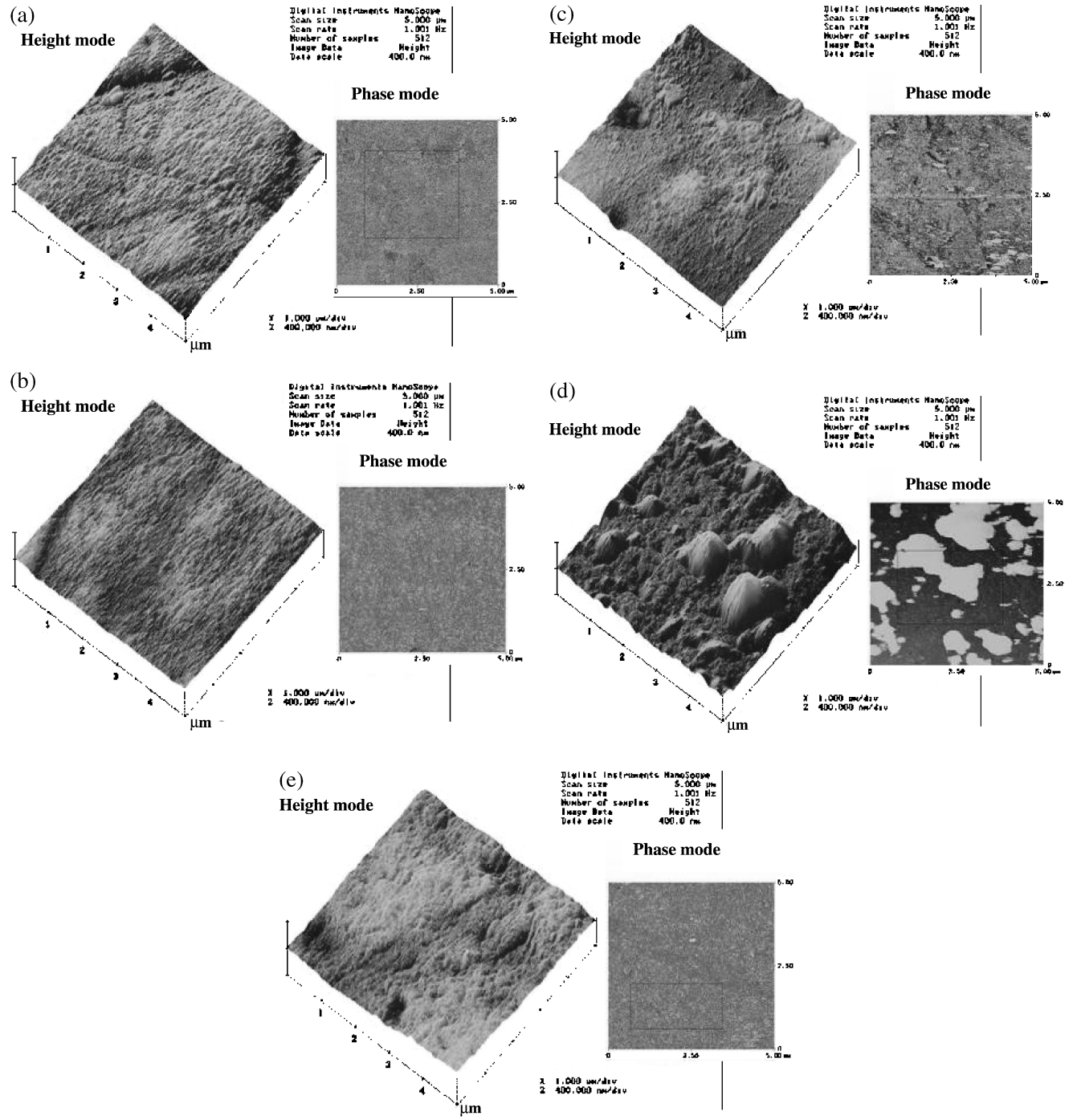

Figure 1. AFM topographic images including height mode and phase mode for: (a) the pure PAN membrane; (b) PAN91; (c) PAN82; (d) PAN73; (e) pure PVDF.

Table 1. Values of height mode roughness and phase mode roughness obtained from AFM

Membrane type	Height mode roughness, root mean square, Rq (nm)	Phase mode roughness, root mean square, Rq (°)
PAN	12.661	10.067
PAN91	15.950	11.286
PAN82	32.582	19.346
PAN73	69.200	32.371
PVDF	31.414	13.039

and partially miscible blends has been well established. If the two components of a binary blend are miscible in the amorphous phase, only one T_g intermediate between those of the two component polymers will be detected. The immiscibility of two polymers is demonstrated by the retention of the T_g values of both individual components. If two components are only partially miscible, the T_g values of each component phase are shifted toward each other because of some degree of molecular mixing at the interface between the two polymeric phases; it is usually composition-dependent. The result

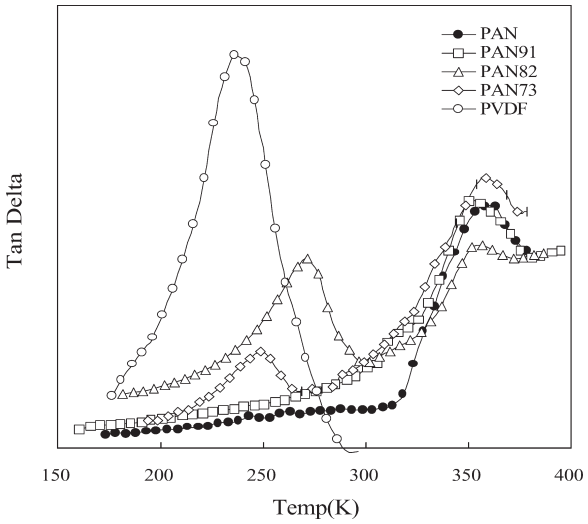

Figure 2. DMA thermograms of PAN, PVDF and blend membranes.

of DMA indicated that the tan δ peaks of these PAN/PVDF blends exhibit two T_g values. Table 2 shows that the T_g value of pure PVDF and PAN membranes were 237 and 361 K, respectively. Although the T_g value of PAN82 membrane showed partial-misciblility with two characteristic peaks of 275 and 355 K, these two peaks were closer to each other than pure PAN and PVDF. However, the peaks of PAN73, 249 and 358 K, were nearly the same with PAN and PVDF alone. This suggests that the blend membranes with more than 30% PVDF would be more heterogeneous and show phase separation. Blend T_g is given by Tang *et al.*:[15,16]

$$\frac{1}{T_g} = \frac{w_1}{T_{g1}} + \frac{w_2}{T_{g2}}$$

where w_i is the weight fraction of component i in the blend (1 and 2 represent PAN and PVDF, respectively). However, the theoretical T_g values of blend membranes in Table 2 can not correlate well with the experimental data. The composition of conjugated phase is further calculated as follows:[16,17]

$$W_2' = \frac{T_{g2}(T_{g1} - T_g)}{T_g'(T_{g1} - T_{g2})}$$

$$W_1'' = \frac{T_{g1}(T_g'' - T_{g2})}{T_g''(T_{g1} - T_{g2})}$$

where, W_i is the weight fraction of component i in the blend (1 and 2 designate PAN and PVDF, respectively), T_g' and T_g'' represented the T_g values of pure PAN and PVDF, respectively, and W_i', W_i'' are the weight fraction in PAN-rich and PVDF-rich phase. The compositions of the conjugated phase were calculated by the W_2', W_1'' values which are the weights in PVDF-rich and PAN-rich, respectively.

The compositions of the conjugated phases were calculated using the T_g values from the tan δ peaks in Table 2. The results are also listed in Table 2. As an example, for PAN82, the solubility of PAN in PVDF-rich phase (40.2 wt%) is much greater than that of PVDF in PAN-rich phase (3.2 wt%). The solubility of the two polymers decreased with the increase in the PVDF content. The results imply that the phase separation became greater with increasing PVDF content. Partial miscibility was observed for samples with less than 20 wt% PVDF, whereas immiscibility was observed for those samples with more than 30 wt% PVDF.

Hydrophilicity

Figure 3 shows that the contact angles of PAN/PVDF membranes increase with PVDF content. This indicates that the PVDF addition reduces the wettability of the PAN membrane. However, the contact angles of these blend membranes decreased with the increase of time duration. In addition, the decrease in the contact angle of PAN73 membrane was steeper than those of other blend membranes. Although PAN73 was the most hydrophobic among these blend membranes, the increase in pore size or porosity resulted in higher water permeation as reported in our previous work.[11]

Protein adsorption

Plasma adsorption is the key factor for evaluating the hemocompatibility when blood contacts artificial surfaces. Figure 4 shows that the adsorption of total plasma protein decreased with the increase of PVDF content, except that of PAN73. Pure PVDF membrane exhibited the minimum protein adsorption, as compared with blends and pure PAN. This suggests that the more hydrophobic surfaces will suppress the protein adsorption. The apolar structure $-CF_2-CH_2-$ of PVDF exhibits extremely low affinity to bind or adsorb protein molecules. However, the polar CN group of PAN adsorbs more proteins via hydrogen bonding. Although more hydrophobic, PAN73 membrane however caused more protein adsorption than PAN82 membrane. This is due to larger pore size and higher surface roughness of the PAN73 membrane. These pores can entrap proteins to the inner structure of membranes. Nevertheless, the protein adsorption of pure PAN and PAN91 membranes were more than that of PAN73. Furthermore, Table 3 shows that the membrane surfaces adsorbed more Alb than FN. It was

Table 2. Glass transition temperature of blends obtained from tan δ peaks and conjugate of blend

		PVDF-rich phase		PAN-rich phase	
Membrane type	PVDF content (wt%)	T_g' (K)	w_1'	T_g'' (K)	w_2''
PAN	0	—	—	361	0.000
PAN91	10	310	0.686	350	0.060
PAN82	20	275	0.402	355	0.032
PAN73	30	249	0.140	358	0.016
PVDF	100	237	0.000	—	—

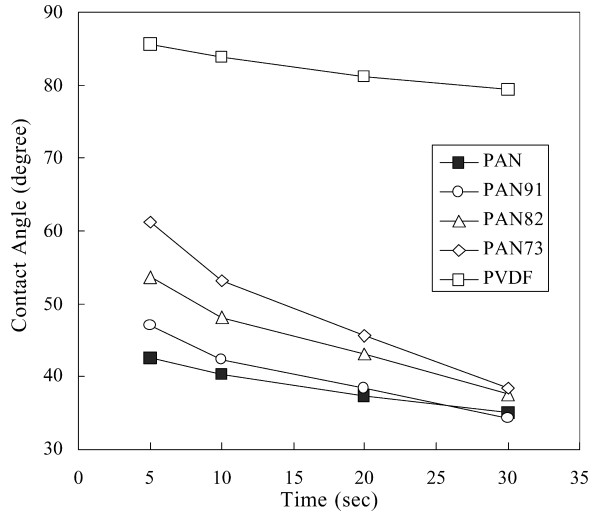

Figure 3. Measurement of contact angle of PAN/PVDF blend membranes versus time ($n = 6$).

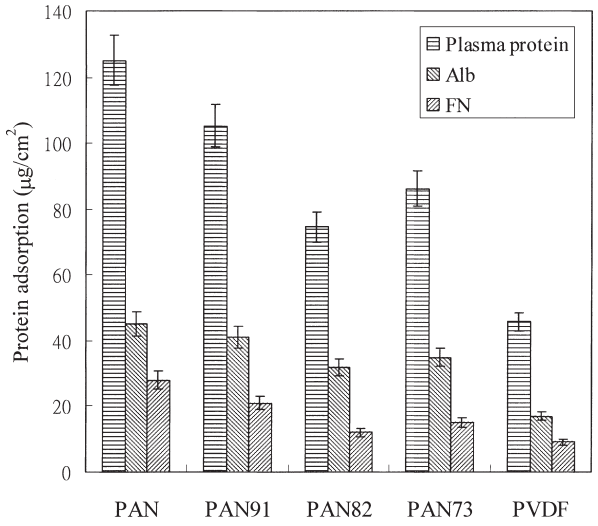

Figure 4. Comparison of protein adsorption of PAN/PVDF blend membranes at 37°C for 2 hr incubation ($n = 3$).

probably due to the smaller molecular size of Alb (Alb/FN: 65000/340000) and higher steric hindrance for FN.[17]

Human plasma has at least 200 kinds of proteins with different molecular weights and properties,[18] including both platelet adhesion promoting proteins, such as FN, von Willebrand factor (vWF), and fibronectin, and platelet adhesion inhibiting proteins, such as Alb, immunoglobulin G (IgG) and high molecular weight kininegen (HMWK), etc. Comparing the protein adsorption between pure PAN and pure PVDF, the adsorbed protein amounts onto PAN82 were 74.6, 32.4 and 19 μg/cm^2 for total plasma protein, Alb and FN,

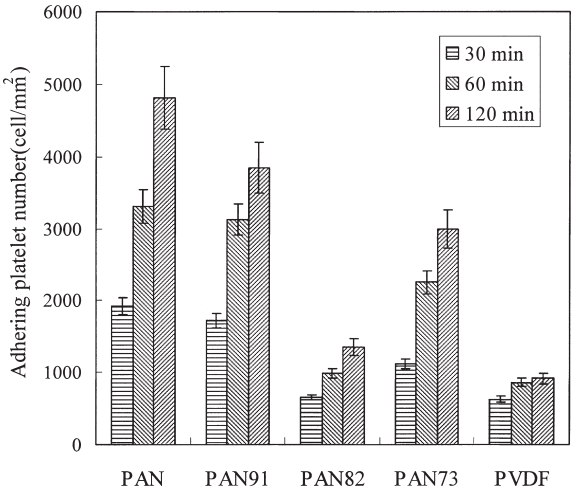

Figure 5. Comparison of platelet adhesion of PAN/PVDF blend membranes after 30, 60 and 120 min incubation ($n = 3$).

respectively. This suggests that the addition of PVDF can reduce the protein adsorption, and that the decrease of FN is steeper than that of Alb. The results were consistent with the report of Hu and Tsai.[19] They reported that the acid hydrolysis of PAN yielded amide and acid groups, resulted in more polar surface, and more adsorption of bovine serum albumin (BSA).

Platelet adhesion

The platelets adhered to the blend membranes were counted by LDH assay. As shown in Fig. 5, the platelet adhesion on PVDF and PAN82 membranes changed little after 30 min, while the adhesion on PAN and PAN91 increased significantly with time. The number of adhering platelets on PAN membrane after 2 hr (4810 cells/mm^2) was the highest, whereas that on PVDF membrane surface (911 cells/mm^2) was the lowest. Among these blend membranes, PAN82 exhibited the highest platelet adhesion resistance.

The platelet activation and adhesion depend on the characteristics of artificial surface and protein adsorption.[20] Initially, when blood flows through the artificial surfaces, the plasma proteins such as Alb, IgG and FN are adsorbed on the surface, which depends on the characteristics of the polymers themselves. Generally speaking, the polymers such as PAN, polysulfone (PSF) and poly(methyl methacrylate) (PMMA) are less attractive to proteins than cellulosic materials.[21] Platelets are extremely sensitive cells that may respond to minimal stimulation. Activation causes platelets to become sticky and change in shape to irregular spheres with spiny pseudopods, accompanied by internal contraction and extrusion of the storage granule contents into the extracellular

Table 3. Average values of protein adsorption on the blend membrane after 1 hr-incubation ($n = 3$)

Membrane type	Plasma protein (μg/cm^2)	Alb (μg/cm^2)	FN (μg/cm^2)	Alb/FN
PAN	125.1 ± 3.9	45.2 ± 2.9	28.4 ± 1.9	1.61
PAN91	105.3 ± 3.8	41.8 ± 2.5	21.8 ± 1.5	1.95
PAN82	74.6 ± 2.4	32.4 ± 2.3	12.7 ± 1.5	2.67
PAN73	86.3 ± 2.3	35.1 ± 1.9	15.4 ± 1.2	2.33
PVDF	45.8 ± 2.1	19.8 ± 1.7	7.6 ± 1.1	2.71

environment. These secreted platelet products stimulate other platelets, cause irreversible platelet aggregation, and lead to the formation of fused platelet plugs. Subsequently, the platelets release some materials such as adenosine diphosphate (ADP), adenosine triphosphate (ATP), serotonin and platelet factor 4 (PF4), beta-thromboglobulin (βTG), FN, vWF and fibronectin, and then activated arachidonic acid to produce thromboxane A2 (TXA2). Then ADP and TXA2 induce more platelet aggregation on the surface and result in more plugs. Followed by, Hagemen factor (factor XII) which is activated to induce the intrinsic pathway, meanwhile, the white blood cells release thromboplastin to induce the extrinsic pathway and common pathway. Finally, the system leads to the formation of thrombin, a non-soluble fibrin network, or, thrombus.[22]

Dion *et al.*[23] proposed that the Alb/FN ratio was an important index when assessing the adhesion of platelets to artificial surfaces. The higher the ratio is, the lower the number of adhering platelets. The Alb/FN ratio obtained in this work is listed in Table 3. The highest Alb/FN ratio (2.71) was observed on PVDF membrane, and that of PAN82 (2.67) was the highest in these blend membranes. Lee and Lee[20] have studied the degree of platelet adhesion on wettability gradient surfaces of low density polyethylene (PE) sheets in the absence and presence of plasma protein. It was observed that platelet adhesion in the presence of plasma proteins decreased gradually with the increasing surface wettability. However, plasma protein adsorption on a wettability-gradient surface increased with the increasing surface wettability in the absence of plasma protein. More plasma protein adsorption on the hydrophilic surface caused less platelet adhesion, probably due to platelet adhesion inhibiting proteins, such as high-molecular-weight kininogen, which preferably adsorbs onto the surface by the so-called Vroman effect. Although both the presence of plasma proteins and surface wettability play important roles for platelet adhesion and activation, the porous and surface roughness should also be taken into consideration. The surface of PAN/PVDF blend membranes was rougher than PAN membrane, as shown in Fig. 1. Additionally, the surface with higher PVDF content was rougher. The adhesion of plasma proteins on the PAN/PVDF blend membranes decreased with the increase of PVDF content, except for PAN73 membrane. The higher Alb/FN ratio appeared in that of PAN82. The result shows that PAN82 membrane would adsorb the more platelet inhibiting protein such as Alb onto the surface, thus causing less platelet adhesion.

Blood coagulation

The blood coagulation cascade includes intrinsic pathway, extrinsic pathway, and common pathway. APTT and PT are used to examine mainly the extrinsic and intrinsic pathway, respectively. FT and thrombin time (TT) are used as a measure of the time for transferring FN and thrombin into non-soluble thrombus, respectively. Table 4 shows that the clotting times of PAN, PVDF, and blend membranes are nearly the same as the human plasma (the negative control). This implies that all of these membranes cannot induce the coagulation pathways. Because these coagulation time tests were all carried out using PPP, thus platelets should play the crucial role in the initial clotting procedure. Therefore, the testing of thrombus formation on the membranes was performed using whole blood without anticoagulant. The trend of the thrombus formation, as shown in Fig. 6, is similar to that of the platelet adhesion in Fig. 5. PVDF membrane caused the lowest thrombus formation, whereas PAN had the highest. In addition, PAN82 membrane caused least thrombus formation among the blend membranes. This suggests that the factors suppressing protein adsorption and platelet adhesion onto membranes can also curtail the thrombus formation.

Table 4. The coagulation time of PAN/PVDF blend membranes evaluated by APTT, PT, FT, and TT ($n = 3$)

Membrane type	APTT (sec)	PT (sec)	FT (sec)	TT (sec)
Negative control	36.5 ± 1.1	12.5 ± 1.2	12.4 ± 0.5	40.1 ± 1.3
PAN	37.7 ± 1.7	12.3 ± 0.8	11.9 ± 0.4	39.3 ± 1.0
PAN91	36.9 ± 0.9	12.4 ± 0.7	12.3 ± 1.1	39.8 ± 0.5
PAN82	38.5 ± 0.8	12.4 ± 0.9	12.6 ± 0.7	40.5 ± 0.7
PAN73	39.6 ± 1.2	12.6 ± 1.0	12.7 ± 0.4	41.2 ± 1.2
PVDF	42.1 ± 1.3	13.1 ± 0.4	13.5 ± 0.8	42.3 ± 1.3

CONCLUSIONS

By blending PVDF into PAN, the protein adsorption, platelet adhesion, and thrombus formation on PAN membrane surfaces can be reduced. The hydrophilicity decreased with the increase of PVDF content. The results from DMA and AFM revealed that severe phase separation occurred in the blend membrane with 30% PVDF. However, the protein adsorption, platelet adhesion, and thrombus formation was the least for the blend with 20% PVDF instead of the blend with 30% PVDF. This can be attributed to the higher roughness of the latter. Overall results demonstrated that blending with 20% PVDF showed more improvement in the *in vitro* hemocompatibility of PAN membranes. Based on this preliminary study, the PAN/PVDF blend hollow fiber dialyzers have

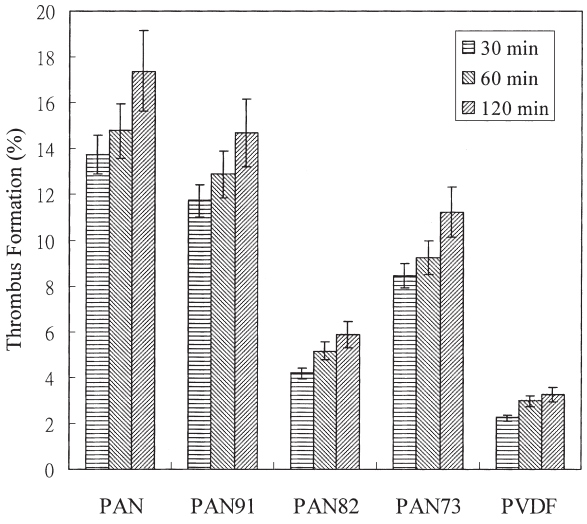

Figure 6. Comparison of thrombus formation ratio of PAN/PVDF blend membranes after 30, 60 and 120 min incubation ($n = 3$).

been fabricated and the evaluation of hemodialyzer is now in progress in this group.

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