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Polyethersulfone Hollow Fiber Membranes for Hemodialysis

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1. Introduction

Polyethersulfone (PES) is one of the most important polymeric materials and is widely used in separation fields. PES and PES-based membranes show outstanding oxidative, thermal and hydrolytic stability as well as good mechanical and film-forming properties. PES membranes could endure many kinds of sterilized methods, including epoxy ethane gas, steam, and γ-ray. Furthermore, PES-based membranes show high permeability for low molecular weight proteins when used as hemodialysis membranes. Thus, PES membranes are also widely employed in biomedical fields such as artificial organs and medical devices used for blood purification, e.g., hemodialysis, hemodiafiltration, hemofiltration, plasmapheresis and plasma collection (Zhao et al., 2001; Tullis, et al., 2002; Samtleben et al., 2003; Werner et al., 1995), especially in recent years.

However, when contacting with blood, proteins will be rapidly adsorbed onto the surface of PES membrane and the adsorbed protein layer may lead to further undesirable results, such as platelet adhesion, aggregation and coagulation. As a consequence, the blood compatibility of PES membrane is not adequate, and injections of anti-coagulants are needed during its clinical application (Liu et al., 2009).

The main disadvantage is related to the relatively hydrophobic character of PES membrane. And many studies have concluded that membrane fouling (as caused by protein adsorption) is directly related to hydrophobicity as reviewed by Van der Bruggen (Van der Bruggen, 2009) and Khulbe et al. (Khulbe et al., 2010), although the opposite has also been reported (Yu et al., 2008). Membrane fouling is mainly caused by adsorption of nonpolar solutes, hydrophobic particles or bacteria (Van der Bruggen, 2009; Koh et al., 2005). It is a serious problem in membrane filtration, resulting in a higher energy demand, shorter membrane lifetime, and unpredictable separation performance (Agenson & Urase, 2007). Thus, PES hollow fiber membranes used in hemodialysis are usually modified by hydrophilic polymers.

For the modification of PES membranes, there are three approaches: (1) bulk modification of PES material, and then to prepare modified membrane; (2) surface modification of prepared PES membrane; and (3) blending, which can also be regarded as a surface modification. The modification procedures allow finding a compromise between the hydrophobicity and hydrophilicity, and localize the hydrophilic material specifically in the membrane pores, where they have a positive effect on flux and fouling reduction, and on the membrane

surface to improve blood compatibility. However, not all the methods are suitable for the modification of PES hemodialysis membranes.

For hemodialysis membranes, safety and efficiency should be evaluated firstly in vitro before clinical application, and simulation solutions are used. Through the experiments in vitro, many results, which are useful for clinical applications, could be obtained, including protein adsorption, platelet adhesion, ultrafiltration (UF) coefficient, and solute clearances (such as for urea, creatinine, and phosphate, and so on). For high-flux hemodialysis membranes, the clearance of β_2-microglobin should be investigated. When the membranes are applied for patients, the safety and efficiency are also very important.

In the present chapter, preparation and characterization of PES hemodialysis hollow fiber membranes are discussed firstly, and then the safety and efficiency in vitro and in vivo are discussed.

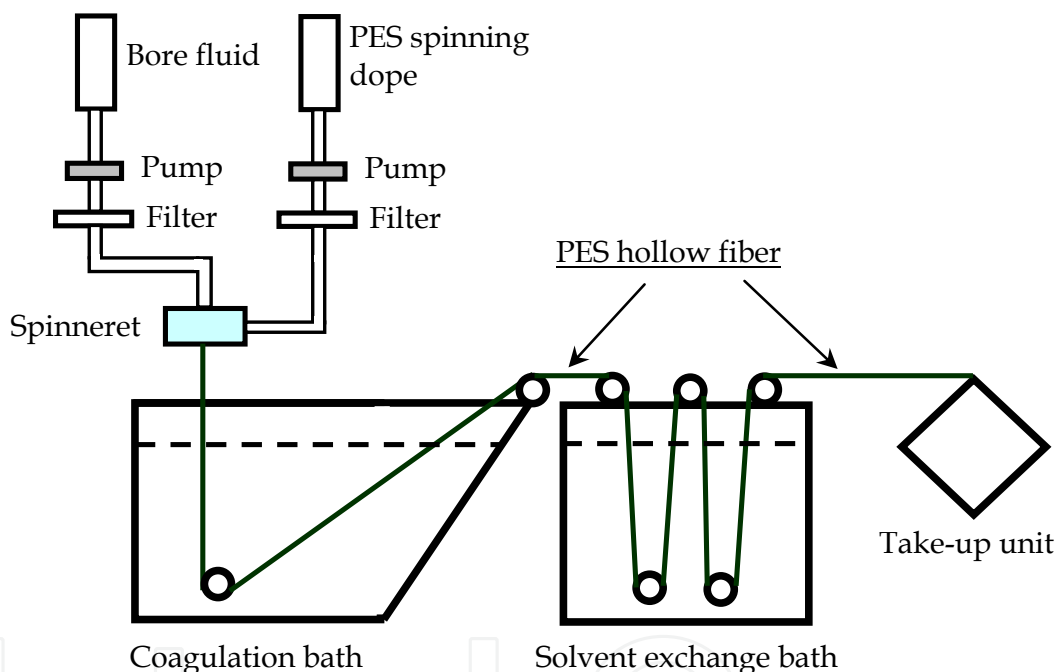## 2. Preparation and modification of polyethersulfone hollow fiber membranes

Fig. 1. PES hollow fiber spinning line

PES hollow fiber membranes for hemodialysis are usually spun by dry-wet spinning technique based on liquid-liquid phase separation method, see Figure 1. The cross-section view of the PES hollow fiber membrane is shown in Figure 2. After post-treatment, PES hollow fiber hemodialyzer is prepared by using polyurethane resin as the potting material. However, the blood compatibility of the PES membrane is not adequate, and injections of anticoagulants are needed during hemodialysis. Thus, all the PES membranes used for hemodialysis are not the pristine PES membranes. As a hydrophilic additive and a membrane forming agent, poly (vinyl pyrrolidone) (PVP) is most widely used for the modification of PES membranes by blending. Many other methods can also be used for modifying PES membranes. The aim of the modification is to improve the biocompatibility and protein antifouling property of the membranes, thus different sections are separated based on the methods and the modification objective.
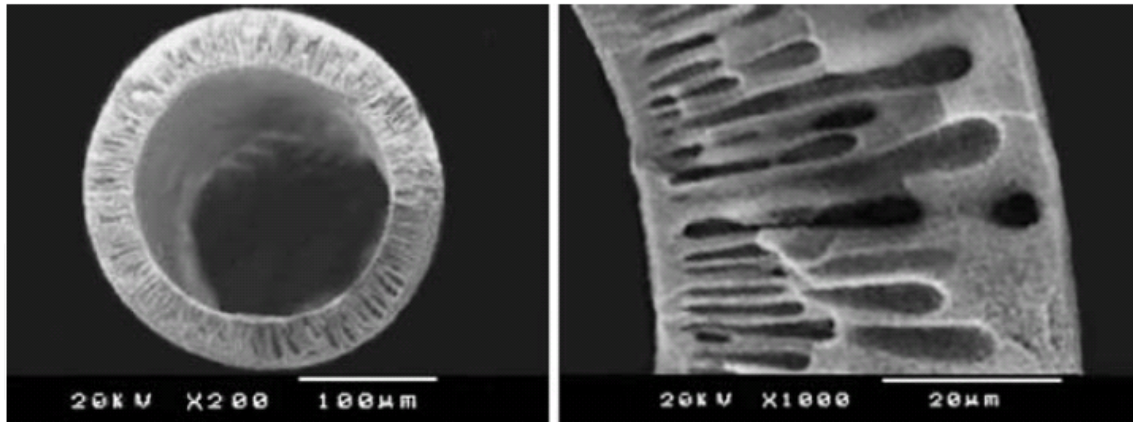
Fig. 2. SEM images of PES hollow fiber membrane (From reference, Su et al., 2008)

2.1 Blending

Blending is the simplest and most widely used method to modify PES membranes both for flat-sheet and hollow fiber membranes, though sometimes the results might be not very well. By directly blending with hydrophilic polymers, such as polyvinylpyrrolidone (PVP) (Barzin et al., 2004; Mosqueda-Jimenez et al., 2006; Su BH, et al., 2008; Wang et al., 2009) and polyethyleneglycol (PEG) (Wang et al., 2006), PES membranes are easy to be modified; here PVP and PEG also are also used as pore-forming agents. The hydrophilicity of the membranes increased, the antifouling property and blood compatibility are also increased (Su BH, et al., 2008; Wang et al., 2006). However, the elution of the blended hydrophilic polymer is unavoidable. Thus, amphiphilic copolymers are synthesized recently and used for blending with PES to prepare membranes (Zhu et al.; 2008a, 2008b; Zhao et al., 2008; Peng et al., 2009). For hemodialysis membranes, the objective of blending is to improve the membrane hydrophilicity, biocompatibility, and other properties, such as protein antifouling property.

2.1.1 Improve biocompatibility

In our recent study (Su BH, et al., 2008), larger molecular weight PVP was used to blend with PES to prepare hollow fiber hemodialysis membrane, and the performance was evaluated in vitro and in vivo. The biocompatibility profiles of the membranes showed slight neutropenia and platelet adhesion at the initial stage of the hemodialysis. The clearance and the reduction ratio after the hemodialysis of small molecules (urea, creatinine, phosphate) for the PES membrane were higher in vitro than that in vivo.

Barzin et al. (Barzin et al., 2004) prepared two kinds of PES hollow fiber membranes for hemodialysis by blending two ratios of PES to PVP (PES/PVP = 18/3 and 18/6 by weight). It was observed that the water flux of the hollow fiber increased significantly when heat-treated in water, while decreased when heat-treated in air. On the other hand, the molecular weight cutoff of the hollow fiber increased slightly when heat-treated in water, while decreased drastically when heat-treated in air. SEM images also showed that the surface morphology of the membranes was different before and after heat-treatment. The performance data of the hollow fiber heated in air at 150 °C was found to be the most appropriate for hemodialysis application. It was also found that the hollow fiber membrane prepared from the blend ratio of PES/PVP = 18/3 showed slightly higher flux than that

prepared from a solution with PES/PVP ratio of 18/6. Of course, PVP could also be used to modify PES hollow fiber membranes for hemofiltration (Yang et al., 2009). Gholami et al. (Gholami et al.; 2003) found that the hollow fiber membranes shrank by heat treatment, as evidenced by a decrease in flux and an increase in solute separation, although there was no visible change in the hollow-fiber dimension. However, for flat-sheet PES membranes, the membrane surface altered, and surface parameters (such as surface roughness) have been changed after non-contact heating (microwave irradiation) (Mansourpanah et al., 2009).

Erlenkotter and coworkers (Erlenkotter et al, 2008) evaluated the dialysis membrane hemocompatibility. In order to compare different polymers used in the manufacturing of dialysis membranes, a set of the following hemocompatibility parameters was assessed and assembled to an overall score: generation of complement factor 5a, thrombin-antithrombin III-complex, release of platelet factor 4, generation and release of elastase from polymorphonuclear granulocytes, and platelet count. By blending polyarylate with PES, the membrane hemocompatibility improved. They also provided a score model to facilitate the selection of membrane polymers with an appropriate hemocompatibility pattern for dialysis therapy.

2.1.2 Improve antifouling property

Membrane fouling is still a crucial problem for hollow fiber membrane. When fouling takes place on membrane surfaces, it causes flux decline, leading to an increase in production cost due to increased energy demand. Qin et al. (Qin et al., 2004) selected solvent-resistant hollow-fiber UF membranes by measurement of fiber swelling and treatability studies on spent solvent cleaning rinse. The results indicated that the membranes made of both cellulose acetate (CA) and polyacrylonitrile (PAN) materials could tolerate the solvent present and were suitable or treating the spent solvent rinses, whereas PES and PSF membranes were not suitable. The CA membrane had the lowest fouling tendency when treating the spent solvent rinse. Nakatsuka et al. (Nakatsuka et al., 1996) also found that the permeate flux for the hydrophilic CA membranes was much higher than that of the hydrophobic PES membrane, a phenomenon which was explained by membrane fouling due to the adsorption of substances in raw water on and in the pores of the membranes. Xu et al. (Xu et al., 2009) observed that the fouling layer grew faster on the inside surface of the PES hollow fiber at a lower flow rate than that at a higher flow rate due to the lower shear stress. These results suggested that PES hollow fiber membrane should be modified to improve antifouling property by increasing hydrophilicity.

Arahman et al. (Arahman et al., 2009) modified PES hollow-fiber membrane by blending with hydrophilic surfactant Tetronic 1307. The fouling of the PES membrane with blending Tetronic 1307 was lower than that of the original PES membrane in the case of BSA filtration. A functional terpolymer of poly (methyl methacrylate–acrylic acid–vinyl pyrrolidone) (PMMA-AA-VP) was synthesized via free radical solution polymerization using DMAC as the solvent in our recent study (Zou et al., 2010). The terpolymer can be directly blended with PES using the solvent to prepare modified PES hollow fiber membrane. The hydrophilicity of the blended membranes increased, and the membranes showed good protein antifouling property. The antifouling property is always expressed as the time-dependent flux during the ultrafiltration process (PBS solution and BSA solution alternatively switched), as shown in Figure 3.
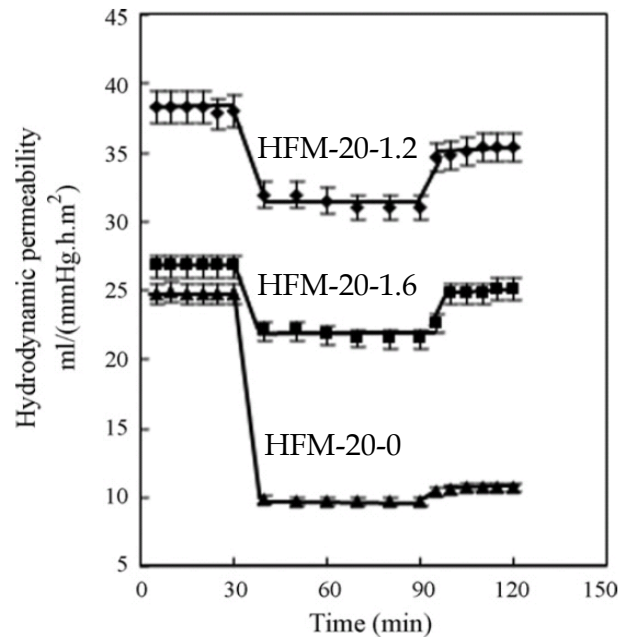
Fig. 3. Time-dependent flux of PMMA-AA-VP modified PES membranes during the ultrafiltration process.
For the membranes: HFM-20-1.2 (The amounts of PES and the terpolymer are 20 and 1.2 wt.%, respectively); HFM-20-1.6 (The amounts of PES and the terpolymer are 20 and 1.6 wt.%, respectively); HFM-20-0 (20wt.% PES).
PBS solution: 0–30 and 95–120 min; BSA solution: 40–90 min. n=3.
(From reference, Zou et al., 2010)

2.2 Other methods
Many other methods can also be used for the modification of PES hollow fiber, the following reviewed the methods. Though not all of them are discussed for hemodialysis membranes, some of the methods can be used for the modification of PES hemodialysis membranes.

2.2.1 Surface-coating
Torto and coworkers (Torto et al., 2004) provided a method for the in situ modification of hollow fiber membranes used as sampling units for microdialysis probes. The method consisted of adsorption-coating of high-molecular-weight PEI onto membranes, already fitted on microdialysis probes. Modification of membranes was designed to specifically explore the so-called Andrade effects and thus enhance the interaction of membranes with enzyme. Such a procedure can be modified and employed to either promote or reduce membrane-protein interaction for hollow fibers used as microdialysis sampling units or other similar membrane applications.

2.2.2 Photo-induced surface grafting
To modify PES membranes, photochemical surface technique is attractive, and has several advantages. Mild reaction conditions and low temperature may be applied; and high selectivity is possible by choosing the reactive groups or monomers and respective excitation wavelength; and it can be easily incorporated into the end stages of a

manufacturing process (Zhao et al., 2003). However, the method is always applied to modify flat-sheet membrane; it is difficult to modify hollow fiber membranes, especially to modify the internal surface of hollow fiber membrane.

Few studies focused on the modification of PES hollow fiber membranes by photo-induced grafting method, since it is difficult to apply irradiation on internal surface of hollow fiber membrane. Bequet and coworkers (Bequet et al., 2002) developed a way to prepare nanofiltration hollow fiber from ultrafiltration membranes, consisting of in-line external modification of the skin of a polysulfone (PSF) ultrafiltration hollow fiber by grafting AA under UV irradiation. The continuous photo-grafting set-up is shown in Figure 4. As shown in the figure, the modification is applied on the outer surface of the hollow fiber membrane. As mentioned above, AA and MA could be grafted on the surfaces of PES membranes by the photochemical method. It should be noticed that due to the present of carboxyl groups, these modified membranes showed pH-sensitivity.
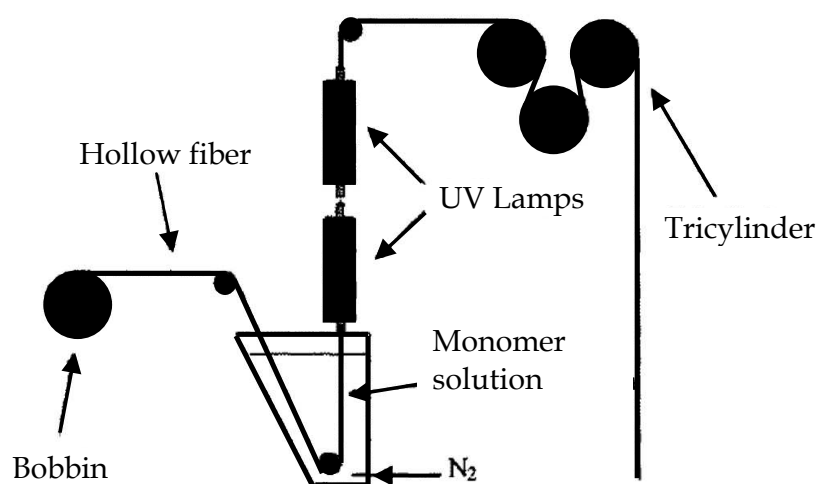
Fig. 4. Schema for the experimental continuous photo-grafting set-up.
(From reference, Bequet et al., 2002)

Shen et al. (Shen et al., 2005) modified the inner-surface of PSF hollow fiber UF membranes by using gas-initiation under UV and liquid-polymerization, which aimed to adjust the diameter of the pores in the membranes. Benzophenone (BP) was in a gaseous condition as photo-initiator, AM as graft monomer, the polyacrylamide (PAM) chain was grafted on the surface of the membranes. After the membrane surface being modified, the water flux and retention altered, and thus it could be seen that the diameter of the pores in the membrane was altered. Of course, the method could also be used to produce the PES hollow fiber membrane with small pore size.

Goma-Bilongo and co-workers (Goma-Bilongo et al., 2006) developed a numerical model to represent the process by which hollow-fiber membranes could undergo continuous surface modification by UV photo-grafting, which was the same as reported by Bequet (Bequet et al., 2002). The model took into account the coupled effects of radiation, mass transfer with polymerization reaction and heat transfer with evaporation. Then, they modified PSF hollow fiber membranes using sodium p-styrene sulfonate (NaSS) as a vinyl monomer, for treatment of anionic dye solutions (Akbari et al., 2007). However, till now, no report for the modification of PES hollow fiber membranes was found.

Hollow fiber scaffolds that compartmentalize axonal processes from their cell bodies can enable neuronal cultures with directed neurite outgrowth within a three-dimensional (3-D) space for controlling neuronal cell networking in vitro. Controllable 3-D neuronal networks in vitro could provide tools for studying neurobiological events. In order to create such a scaffold, PES micro-porous hollow fibers were ablated with a KrF excimer laser to generate specifically designed channels for directing neurite outgrowth into the luminal compartments of the fibers. These hollow fiber scaffolds can potentially be used in combination with perfusion and oxygenation hollow fiber membrane sets to construct a hollow fiber-based 3-D bioreactor for controlling and studying in vitro neuronal networking in three dimensions between compartmentalized cultures (Brayfield et al., 2008).

2.2.3 Plasma treatment and plasma-induced grafting polymerization

The same as other methods mentioned above, few study was reported on the modification of PES hollow fiber membranes by plasma treatment or plasma-induced grafting method. Only one study on the modification of PES hollow fibres by O2 plasma treatment (Batsch et al., 2005) was reported. After about one month of stable operation, the membrane samples were taken and also cleaned with chemical solutions, and the fouling could be prevented by the modification.

2.2.4 Thermal-induced grafting and immobilization

Thermal induced graft polymerization is a facile way to modify PES membranes. The method always uses chemical initiator or cleavage agent. Furthermore, many kinds of biomolecules, such as enzyme, protein and amino acid, could be covalently immobilized onto PES membranes by a simple chemical reaction.

Kroll et al. (Kroll et al., 2007) chemically modified commercially available PES and PSF hollow fiber membranes by reacting terminal hydroxyl groups with ethylene glycol diglycidyl ether (EGDGE) to produce terminal epoxy groups. For increasing loading capacity hydroxyethyl cellulose polymers were bound to the epoxy groups. Second epoxidation produced final polymers containing reactive epoxy groups on the hollow fiber surface. From this modified PES and PSF, respectively, a wide variety of N-containing reagents (e.g. iminodiacetic acid (IDA)) can be bound to the epoxy groups. The different reactions were proved by acid orange II assay and phenol sulfuric assay. The chelating IDA-membranes were complexed with different divalent metal ions (Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+}). Immobilized metal ion affinity PES hollow fiber membranes were used for purification of a recombinant protein (GFP-His) from Escherichia coli, which carried a polyhistidine sequence.

3. Biocompatibility and separation performance of the membrane in vitro

The biocompatibility and separation performance of PES-based hemodialysis membranes in vitro are discussed. Protein adsorption on material surface is a common phenomenon during thrombogenic formation. Thus, the amount of protein adsorbed on the PES membrane is considered to be one of the important factors in evaluating the blood compatibility of the membrane. The adhesion of platelets to blood-contacting medical devices is a key event in thrombus formation on material surface. Thus, protein adsorption and platelet adhesion on PES membrane surface are studied. In addition, the clearance and

the reduction ratio of small molecules (urea, creatinine, phosphate) during hemodialysis for the PES membrane in vitro are investigated.

3.1 Protein adsorption and platelet adhesion
3.1.1 Experimental

3.1.1.1 Protein adsorption

The protein adsorption experiments were made with BSA and FNG solutions. The concentrations of BSA and FNG were 4.0 g/dl and 0.3 g/dl in phosphate buffered saline (PBS, pH=7.4), respectively. The membrane with an area (for hollow fiber, it's the total surface areas of inside surface and outer surface) of 1 cm² was incubated in distilled water for 24 h, washed 3 times with PBS solution, and then immersed in the protein solution for 2 h. After protein adsorption, the membranes were carefully rinsed 3 times with PBS solution and then rinsed with distilled water. The adsorbed proteins were quantitatively eluted with 1.0 ml 2% SDS solution for 6 h. The amount of protein in the SDS solution was quantified by protein analysis (Micro BCA protein assay reagent kit).

3.1.1.2 Platelet adhesion

The platelet adhesion experiments were carried out using platelet-rich plasma (PRP). Healthy human fresh blood was collected using vacuum tubes (7 ml, Venoject II, Terumo, Co.), containing citrate/phosphate/dextrose/adenine-1 mixture solution (CPDA-1) as an anticoagulant (anticoagulant to blood ratio, 1:7). The blood was centrifuged at 1000 rpm for 10 min to obtain platelet-rich plasma (PRP) or at 2800 rpm for 15 min to obtain platelet-poor plasma (PPP). The fresh PRP sample was used for the platelet adsorption experiments.

The PES membranes (1×1 cm² each piece, always flat-sheet membranes) were immersed in PBS solution and equilibrated at 37 °C for 1 h. The PBS solution was removed and then 1ml of fresh PRP was introduced. The membranes were incubated with PRP at 37 °C for 2 h. PRP was decanted off and the membranes were rinsed 3 times with PBS solution. Finally, the membranes were treated with 2.5 wt% glutaraldehyde in saline for 2 days at 4 °C. The samples were washed with PBS solution, subjected to a drying process by passing them through a series of graded alcohol-saline solutions (0%, 25%, 50%, 75% and 100%) and then dried at room temperature. The dried membranes after gold coating were examined using a S-2500C scanning electron microscope (SEM, Hitachi, Japan). The number of adhering platelets on the membranes was calculated from four SEM pictures at a 500 magnification from different places on the same membranes. These procedures were performed on each membrane using four independent membranes (totally n=16), and the number was finally averaged to obtain reliable data.

3.1.2 Results and discussion

3.1.2.1 Protein adsorption

Non-specific protein adsorption is a dominant factor for membrane fouling. When membrane is used for blood purification, protein adsorption is the first stage of the interactions of membrane and blood, which may lead to further undesirable results. Protein adsorption has some relationship with the blood compatibility. There are many factors which affect the interaction between membrane surface and protein, such as surface charged

character, surface free energy and topological structure, solution environment (e.g. pH, ionic strength), and protein characters (Leng et al., 2003; Okpalugo et al., 2004). The hydrophilic/hydrophobic character of membrane material plays a relatively important role in the interaction between protein and membrane. Since hydrophilic surface preferentially adsorbs water rather than solutes, many researchers have followed the idea of increasing the hydrophilicity of a membrane material with the goal of reducing protein fouling and/or protein adsorption (Mockel et al., 1999). Herein, the surfaces of the PES and some typical modified PES membranes (Copolymer of poly (acrylonitrile-co-acrylic acid), PAN-AA, modified PES membranes with the ratios of the copolymer to PES of 0/16, 0.4/16 and 0.6/16, respectively; and BSA grafted membranes following the copolymer/PES blended membranes) were studied in relation to the adsorption of BSA and FNG in vitro, data are shown in Fig. 5.

3.1.2.2 Platelet adhesion

The adhesion of platelets to blood-contacting medical devices is a key event in thrombus formation on material surface. After the platelet adhesion and activation, a series of actions could produce the thrombins which led further coagulant. Therefore, in vitro platelet adhesion assay could reflect the blood compatibility of material surface. To study the platelet adhesion, the morphology of the adhering platelet and the amounts of platelet adhesion on the membrane surfaces are always investigated through scanning electron microscopy (SEM).

Figure 6 shows the typical morphology of the platelets adhering to the PES and modified PES membranes. Herein, the membranes were modified by blending sulfonated PES and a terpolymer of poly (acrylonitrile-acrylic acid-N-vinyl pyrrolidinone) (P(AN-AA-VP)). To prepare the membranes, PES, SPES and P(AN-AA-VP) were dissolved in solvent NMP. The solution was vigorously stirred until clear homogeneous solution was obtained. The concentration of all the solute was 16 wt. %. In the experiment, different kinds of membranes were prepared by changing the ratios of PES, SPES and P(AN-AA-VP) in the casting solutions, and the ratios of PES, SPES and P(AN-AA-VP) were 16:0:0, 15:0:1, 14:0:2, 10:6:0,10:5:1, 10:4:2, respectively. After vacuum degassing, the casting solutions were prepared into membranes by spin-coating coupled with a liquid-liquid phase separation technique at room temperature. The obtained membranes were washed with distilled water thoroughly to remove the residual solvent, which were confirmed by UV scanning. All the prepared membranes were in a uniform thickness of about 60~70 µm, and the membranes were termed M-16-0-0, M-15-0-1, M-14-0-2, M-10-6-0, M-10-5-1, and M-10-4-2, respectively.

As shown in Figure 6, when compared the pictures in the same amplification multiple, it was observed that a large amount of platelets were adhered and aggregated on the PES membrane surface and the platelets formed circular or "pan-cake" shape, which suggested that the platelets were activated and already retracted the pseudopods. However, for the modified membranes, very sparse platelets were found; and the platelet expressed a rounded morphology with nearly no pseudopodium and deformation.

Figure 7 shows the amounts of the adhering platelets on the membranes from platelet-rich plasma. It could be observed that much lower number of the adhering platelets on the modified membranes compared with the PES membrane. Furthermore, the platelet
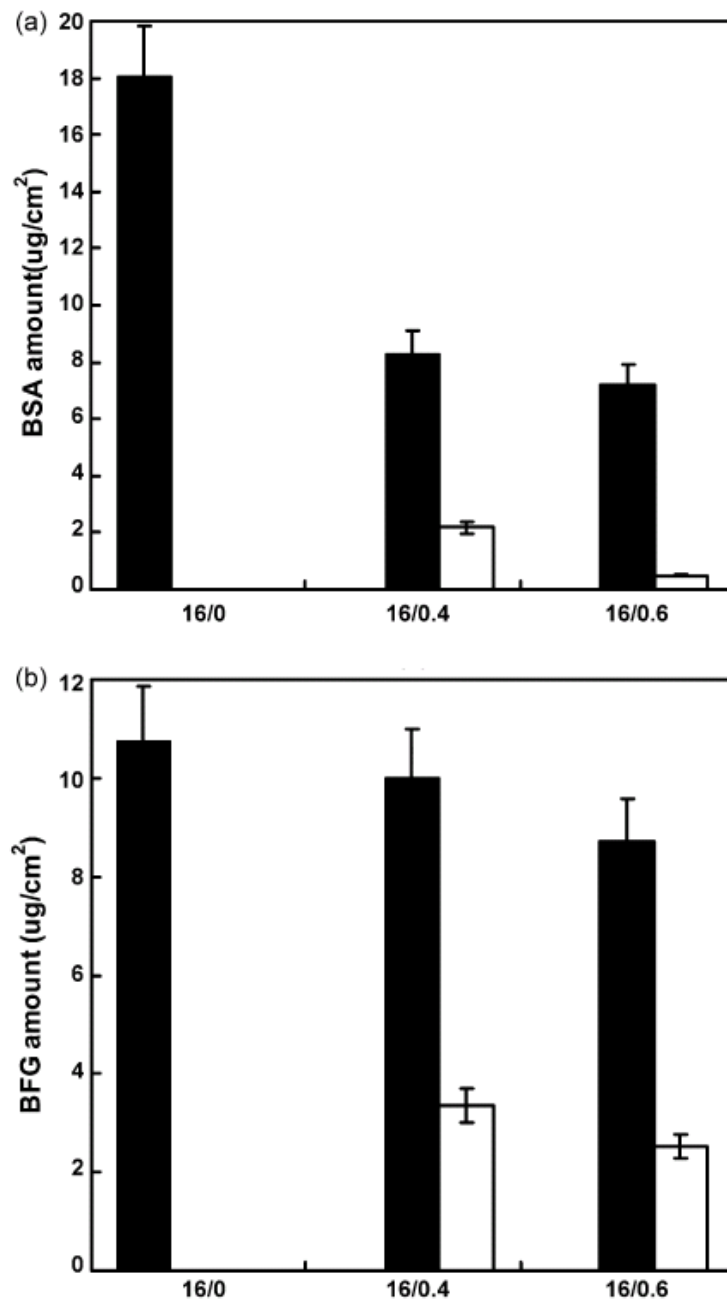
Fig. 5. (a). BSA adsorption on the membrane surfaces with the blending ratios of PES to PANAA as 16/0.2, 16/0.4, 16/0.6. (■) For the blended membranes; (□) for the BSA grafted membranes (each point represents the means±S.D. of three independent measurements.). (b) BFG adsorption on the membrane surfaces with the blending ratios of PES to PANAA as 16/0.2, 16/0.4, 16/0.6. (■) For the blended membranes; (□) for the BSA grafted membranes (each point represents the means±S.D. of three independent measurements.).
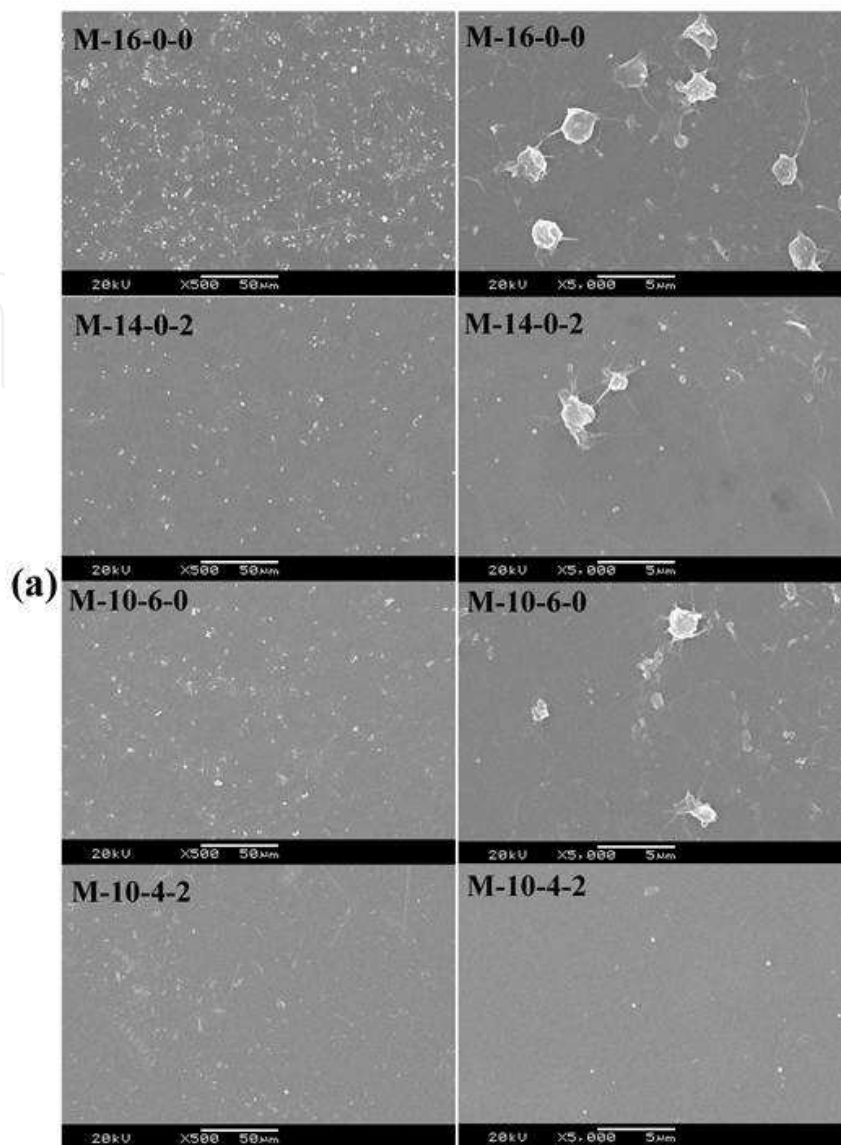(From reference, Fang et al., 2009)

Fig. 6. Scanning electron micrographs of the platelets adhering to the membranes.

adhesion on the terpolymer modified membranes decreased with the increase of the content of the terpolymer P(AN-AA-VP). These results were consistent with those obtained from the protein adsorption, which demonstrated that the platelet adhesion had some relation with the carboxylic groups which were supplied by P(AN-AA-VP). It could also be observed that the platelet adhesion of the SPES modified membrane was significantly depressed, which was attributed to the sulfonic acid group provided by SPES.

Han et al. (Han et al., 1996) suggested that the sulfonic acid groups exhibited high adsorption of albumin and low adsorption of FBG, which might improve the blood compatibility. Thus, the platelet adhesion demonstrated the enhanced blood compatibility of SPES modified membrane. Furthermore, as the ratios of P(AN-AA-VP) to SPES changing, the different amounts of the platelet adhesion could be obtained, and no adhering platelet was found on the surface of the modified membrane M-10-4-2. The reduction of the platelet adhesion on the modified membranes was considered to be the introduction of the sulfonic acid and carboxylic groups which were supplied by SPES and P(AN-AA-VP), respectively.

The platelet adhesion results were consistent with FBG adsorption. It is well known that FBG adsorption from plasma onto a material surface might promote the adhesion of the platelets because it had the ability to bind specifically to the platelet membrane glycoprotein, GP IIb-IIIa (Phillips et al., 1988). Thus, the observed decreasing amounts of platelet adhesion might be attributed to the increased hydrophilicity, and decreased FBG adsorption. These results indicated that the surface heparin-like PES membranes modified by SPES and P(AN-AA-VP) had good blood compatibility for using as blood contacting devices.
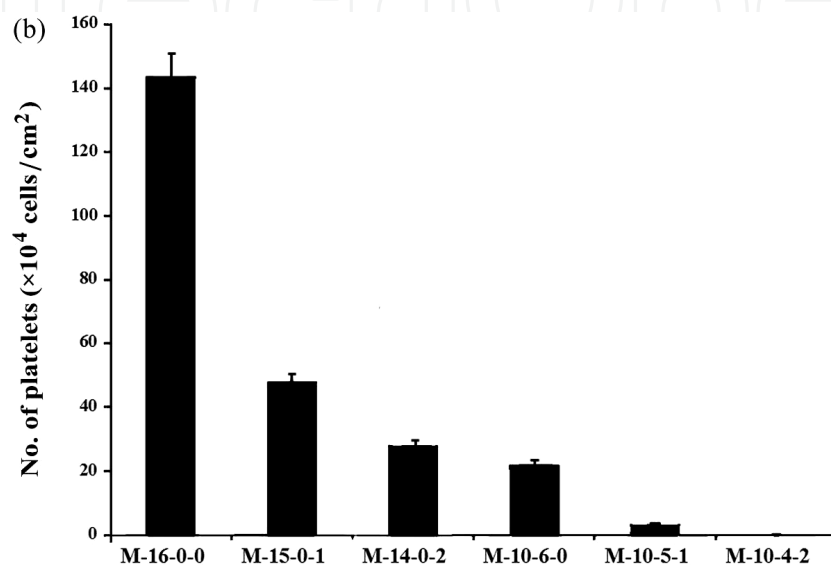
Fig. 7. The number of the adhering platelets on the membranes

3.2 Ultrafiltration and solute clearances
3.2.1 Experimental

3.2.1.1 Hemodialysis using a simulation solution

The test solutions were prepared according to the international standard ISO 8637. The molar concentrations of urea, creatinine and phosphate in the simulation solution were 15mmol/l, 500μmol/l and 1mmol/l, respectively. The test procedure was accordant to the procedure in ISO 8637. The ultrafiltration coefficient was calculated as the unit ml/mmHg.h. The clearance (K) of small molecules (urea, creatinine, phosphate) were established by sampling from the inlet and outlet segments of the extracorporeal circuit 1 h after the initiation of the treatment, and was calculated using the following formula.

$$K = \left(\frac{C_{BI} - C_{BO}}{C_{BI}} \right) Q_{BI} + \frac{C_{BO}}{C_{BI}} Q_F$$

where C_{BI} is the solute concentration in the blood (here is the simulation solution); I and O refer to the inlet and the outlet to the device, respectively; Q_{BI} is the blood flow rate at the dialyser inlet; Q_F is the filtration rate.

Urea was determined by a reagent Kit for Urea Determination (Diethyl-Monoxime, Beijing chemical regent factory, China); creatinine was quantified by the absorption at 235nm using an UV-VIS spectraphotometer U-200A (Hitachi Co., Ltd., Tokyo, Japan) through a standard

curve. Phosphate was determined using the molybdate blue method: phosphate reacts with ammonium molybdate and is then reduced by stannous chloride to form a blue complex, and then measured at 670nm with the UV-VIS spectraphotometer U-200A.

3.2.1.2 Hemodialysis using swine blood in vitro

Fresh swine blood was collected using a glass tank, containing citrate/phosphate/dextrose/adenine-1 mixture solution (CPDA-1) as an anticoagulant (anticoagulant to blood ratio, 1:7). The dialysis procedure was the same as the section **3.2.1.1**, and the solute clearance was calculated using the same formula as described in the section 2.2. The concentrations of urea, creatinine and phosphate were determined using an Auto Biochemistry Analyzer 7170A (Hitachi Co., Ltd., Tokyo, Japan)

3.2.2 Results and discussion

Table 1 summarizes the clearance data and the reduction ratio after the dialysis for small molecules in vitro. It was clearly that the clearances and the reduction ratios for all the solutes were larger using the simulated solution than that for blood. The removal of small molecules during dialysis is governed by hydrodynamic conditions within the dialyser rather than membrane structure since the major resistance to transport from the blood into the dialysis fluid lies not in the membrane but boundary layers adjacent to the membrane. Thus, the data of clearance and the reduction ratio (Table 1) for the simulated solution were higher than that for the blood due to the proteins in the blood, which may induce concentration polarization.

Hemolysis ratio was determined for the swine blood in vitro and for the goat blood in vivo. Data showed that there was only a slightly hemodialysis phenomena (about 1.7%) in vitro.

	Clearance (ml/min)			Reduction ratio (%)	
	Urea	creatinine	phosphate	Urea	creatinine
Simulated solution	174.0±6.0	169.0±5.0	170.0±6.0	94.3±3.8	92.4±4.1
Blood in vitro	157.5±7.4	143.6±6.8	144.5±7.2	71.2±3.9	69.9±4.0
Blood in vivo	153.6±9.4	141.6±8.2	142.5±7.3	69.2±4.5	68.9±5.2

Data are expressed as the means±SD, n =3

Table 1. Small molecular clearance at a blood (or simulated solution) flow rate of 180 ml/min and dialysate flow rate of 500 ml/min

4. Performance evaluation in vivo

The biocompatibility and separation performance of PES-based hemodialysis membranes in vivo are also discussed. Animal experiments are carried out to evaluate the PES hollow fiber membranes firstly, and goat was selected as the experimental animal. Experiments were performed to evaluate the solute clearance and the blood compatibility. The blood compatibility and performance of the PES-based high-flux hemodialysis membrane in hemodialyzation were also clinically evaluated, and compared with those of two conventional high-flux membranes, polysulfone (PSF) and polyamide (PA) membranes. The PES and PSF membranes showed similar blood compatibility and solute clearance, and the blood compatibility for PES and PSF might be better than that of the PA membrane.

4.1 Evaluation by animal experiments
4.1.1 Experimental

4.1.1.1 Hemodialysis procedure

Adult hybrid goats (about 20 kg) were used in the experiment. All the animals underwent local anesthesia with 1.0% procaine hydrochloride by injection into the neck muscle. The hair on the neck was cleared away carefully. The animal was laid on its back and fixed on the experimental table.

Extracorporeal circuits were primed with 500ml normal saline solution to remove the bubbles in the circuits and in the dialyzer, then primed with 500ml saline solution containing 10000 IU heparin. 150mg urea and 50mg creatinine were injected to the animal blood before the treatment. At the initiation of the treatment goats received a loading dose (3000 IU) of heparin, and followed by continuous infusion (3000 IU/h). The infusion was terminated at 30 min prior to the end of the dialysis.

4.1.1.2 Solute transport

Extracorporeal circuits with left–right neck intravenous cannulation were created on the animal using B. Braun blood tubing lines for hemodialysis. The clearance (K) of small molecules (urea, creatinine, phosphate) were established by sampling from the inlet and outlet segments of the extracorporeal circuit 1 h after the initiation of the treatment, and was calculated using the formula described in section 3.2. The fluid removal ratio during these measurements was maintained at (3 ml/min).

Removal of β_2-microglobulin was established from the changes in plasma β_2-microglobulin levels during the treatment at different time intervals (30, 60, 120, 180 and 240mins). Plasma β_2-microglobulin levels were determined using a commercially produced ELISA assay (Cambridge Life Sciences, Cambridge, UK).

Electrolyte levels were determined before and after hemodialysis. K^+, Na^+ and Cl^- were determined using electrolyte analyzer (NOVA CRT-4, US), and Ca^{2+} was determined using an Auto Biochemistry Analyzer 7170A (Hitachi Co., Ltd., Tokyo, Japan).

4.1.1.3 Biocompatibility

The levels of urea, creatinine, phosphate, total proteins, albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were determined using an Auto Biochemistry Analyzer 7170A (Hitachi Co., Ltd., Tokyo, Japan).

Blood cells including red blood cell (RBC) and white blood cell (WBC), and blood components including hemoglobin (HGB) and platelet were determined using a blood cell analyzer (BC-3000peus, Shenzhen Mairui Biomedical Device Co. Ltd., China). Blood gas was determined using a blood gas analyzer (CORNing 238, US).

For complement and WBC activation investigation, various membranes were used from different companies, Cuprophane (Nephross, Netherlands), Cellulose acetate (Nissho, Japan), Hemophane (Ningbo-Yatai, China), Polysulfone (PSF, Fresenius, Germany). Polycarbonate (PC) was obtained from BASF Co. Ltd., and the PC membrane was prepared in our Lab. Complement C_3 activation was determined in vitro by enzymelinked immunosorbent assays (ELISA) (Zwirner et al., 1995). For comparing the results, activation for Cuprophane membrane was used as control.

4.1.2 Results and discussion

4.1.2.1 Solute transport

Table 1 also summarizes the clearance data and the reduction ratio after the dialysis for small molecules in vivo. Changes in β_2-microglobulin during the dialysis for the goats are plotted in Figure 8. The reduction ratio was about 50% after the treatment for 4hrs.

The ultrafiltration coefficient was obtained by the hemodialysis process using the simulated solution with a value of 81ml/h.mmHg, from which we could conclude that the PES membrane was a high-flux hemodialysis membrane.

The PES membrane was able to reduce the plasma burden of β_2-microglobulin during the treatment, as shown in Figure 8. The data were analyzed by consideration of actual values and the percentage reductions achieved. The reduction ratio was about 50% after the treatment for 4 hrs; this value is comparable to that for PSF membrane and polyflux (Hoenich & Katopodis, 2002).

As shown in table 1, the reduction ratio for the β_2-microglobulin was smaller than that for the urea and creatinine due to the higher molecular weight (p<0.05). The alteration of β_2-microglobulin in plasma levels may not simply be a result of trans-membrane transport; the adsorption to the membrane may also play a role in the observed plasma changes (Hoenich & Katopodis, 2002). For the removal of β_2-microglobulin, cellulose derived membrane is impermeable to β_2-microglobulin due to its dense symmetrical structure which does not permit the easy diffusion or convection of proteins through the membrane, while polyacrylonitrile (PAN), polysulfone and polymethylmethacrylate (PMMA) membrane could be used (Moachona et al., 2002). The PMMA membrane could also adsorb β_2-microglobulin. To remove β_2-microglobulin more efficiently from plasma, hemodialysis membranes must therefore not simply be considered as filters of low-molecular-weight metabolites but should be equally assessed for their capacity to eliminate potentially deleterious low-molecular-weight plasma proteins. For the PES membrane, β_2-microglobulin adsorption is not an important mechanism of removal. The large solute removal by the membrane is mainly caused by the asymmetric structure and the higher ultra-filtration coefficient, which was presumably caused by the larger pore size and the hydrophilicity of the membrane.
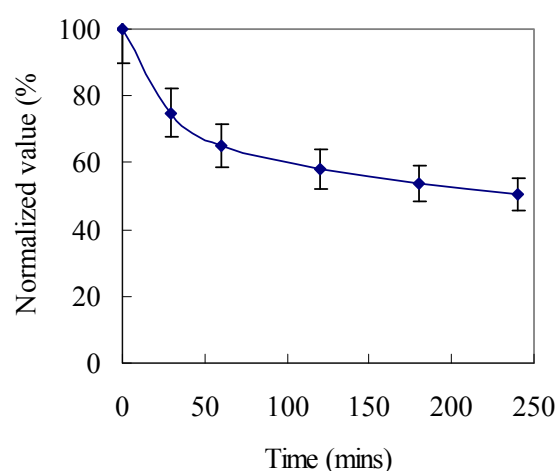

Fig. 8. Changes in β_2-microglobulin during the dialysis. Data are expressed as the means±SD, n =3 (From reference, Su et al., 2008)

Table 2 shows the electrolyte values in the goat blood before and after the dialysis process. Among the these ions, only the K^+ exhibited statistically significant decreases after the dialysis, whereas Na^+, Cl^- and Ca^{2+} did not change. As shown in the table, only the K^+ exhibited statistically significant decreases during the dialysis ($p<0.05$), whereas Na^+, Cl^- and Ca^{2+} did not change ($p>0.05$). The electrolyte balance could be adjusted by the dialysis fluid, and the accurate K^+ values are critically important for the management of patients with little or no residual kidney function (Barry 2003; Morgera et al., 2005).

	pre-dialysis	post-dialysis
K^+(mmol/L)	3.71±0.37	2.98±0.17
Na^+(mmol/L)	144.0±3.8	142.8±1.8
Cl^-(mmol/L)	105.1±4.1	101.0±1.2
Ca^{2+}(mmol/L)	2.12±0.16	2.02±0.11

* Data are expressed as the means±SD, n =3

Table 2. Electrolyte values pre- and post-dialysis

4.1.2.2 Biocompatibility

Figure 9 summarizes the changes in the goat blood observed during the dialysis in respect of white cells (WBC) and platelets. Both white blood cell and platelet counts have been normalized to pretreatment levels and expressed as a percentage of these values. A small decline in both was noted at the first 30 minutes, which returned to the initial levels after about 2 h. These phenomena have been reported frequently in hemodialysis, hemofiltration, and plasma separation.
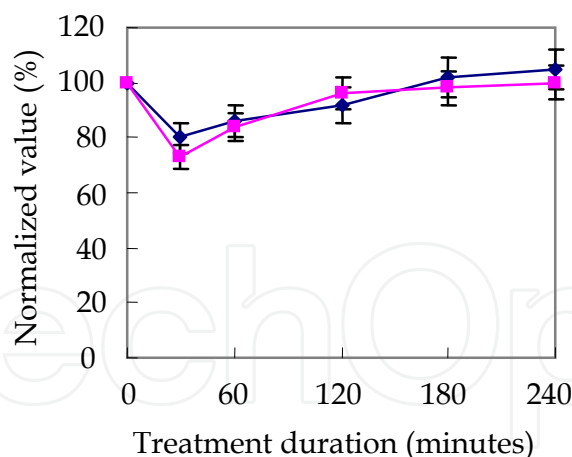

Fig. 9. Changes in WBC and platelet during the dialysis in vivo ♦ Platelet; ■ WBC; Data are expressed as the means±SD, n =3 (From reference, Su et al., 2008)

The complement and WBC activation for various membranes were investigated after contacting to blood for 1h. The data showed the correlation between the complement and WBC activation. We also found that the concentration of C3a increased rapidly at the beginning of the contact between the blood and the PES membrane and remained constant after 90 min, which was consistent with the decrease of white blood cells (Zhao et al., 2001). The decrease of WBC is caused by complement activation; the activation of complement

system results in release of anaphylatoxins into the circulation which have potent physiological effects, thus complement activation has been the most widely used parameter to evaluate hemocompatibility.

Hemolysis ratio was determined for the swine blood in vitro and for the goat blood in vivo. Data showed that there was only a slightly hemolysis phenomena (about 1.7%) in vitro, while the hemolysis ratio was zero in vivo (The absorption value for (+) is 0.832, but for the sample is 0).

The red blood cell (RBC) and hemoglobin (RGB) levels were also determined during the dialysis. The RBC level was $(2.04\pm0.12)\times1012/L$ and $(1.96\pm0.10)\times1012/L$ respectively before and after the hemodialysis. And the HGB level was 115.0 ± 8.0g/L and 110.5 ± 8.0g/L before and after the hemodialysis, respectively.

Biochemistry for the blood was analyzed before and after the hemodialysis, and the data were summarized in Table 3. Only the alkaline phosphatase (ALP) level increased. And the others, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP) and plasma albumin (ALB) were slightly decreased. The blood gas was also analyzed as shown in Table 4. The data showed no statistically change during the dialysis. The urine solution was also analyzed before and after the hemodialysis; the pH value, urine protein and urine glucose had no change before and after the hemodialysis. The concentrations of urobilinogen were 3.5mmol/L and 3.7mmol/L before and after the hemodialysis, respectively.

Red blood cells (RBC) and hemoglobins (HGB) levels decreased slightly after the treatment, and both of the reduction ratios were about 5%. Slightly decreases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP) and plasma albumin (ALB) were also observed. The reduction ratios for all of them ranged 3-10%, which were presumably caused by the dilution of the blood by normal saline solution infused after the hemodialysis process. ALP is produced primarily in the liver and in bone, and the result for ALP indicts that the PES membrane has no effect on the liver.

	pre-dialysis	post-dialysis
ALT(IU/L)	29.0±3.0	26.5±1.5
AST(IU/L)	189.5±9.5	173.0±15.5
ALP(IU/L)	284.0±33.0	266.0±13.0
TP(g/L)	70.2±1.4	63.8±1.8
ALB(g/L)	29.2±0.4	27.6±0.4

* Data are expressed as the means±SD, n =3

Table 3. Data for biochemistry analysis pre- and post-dialysis

	pre-dialysis	post-dialysis
pH	7.43±0.0	7.47±0.02
PCO$_2$(Kpa)	4.5±0.7	4.3±0.1
PO$_2$ (Kpa)	9.7±0.4	9.2±0.3
HCO$_3$(mmol/L)	24.5±2.4	25.6±1.5

* Data are expressed as the means±SD, n =3

Table 4. Blood gas values pre- and post-dialysis

4.1.3 Summary

The PES hollow fiber hemodialysis membrane could effectively remove water and waste products, not only small molecular weight solute such as urea and creatinine, but also "middle" molecular solute as β_2-microglobulin. Slight neutropenia and platelet adhesion were observed at the initial stage of the hemodialysis and no significant differences were found in electrolyte, blood gas and blood biochemistry before and after the treatment. The results also suggested that the PES membrane hemodialyzer could be used for clinical application.

4.2 Clinical evaluation
4.2.1 Experimental

4.2.1.1 Hemodialysis procedure

Three groups of hemodialysis patients with mature functioning arteriovenous fistula participated in this study. Their mean age was 48 ± 12 yr, and they had been receiving dialysis treatments for 35 ± 14 months with an average frequency of 3 times per wk. For each patient, Hct was determined at the beginning of the hemodialysis session.

Standard midweek hemodialysis sessions were analyzed, and bicarbonate dialysate was used. The dialysate contained 140 mmol/L sodium, 2 mmol/L potassium, 108 mmol/L chloride, 1.50 mmol/L calcium, 0.5 mmol/L magnesium and 32 mmol/L bicarbonate. The blood flow was 200 ml/min and the dialysate flow was 500 ml/min. Three kinds of dialyzers (PES, polysulfone (PSF), and polyamide (PA)) were used for the three groups of patients, respectively.

4.2.1.2 Calculation of solute clearance

The levels of urea, creatinine, phosphate, total proteins, albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were determined using an Auto Biochemistry Analyzer 7170A (Hitachi Co., Ltd., Tokyo, Japan).

The removal of β_2-microglobulin was established by the changes in plasma level during the treatment at different time intervals (30, 60, 120, 180 and 240mins). Plasma β_2-microglobulin levels were determined using a commercially produced ELISA assay (Cambridge Life Sciences, Cambridge, UK).

Electrolyte levels were determined before and after hemodialysis. The levels of K+, Na+ and Cl- were determined using electrolyte analyzer (NOVA CRT-4, US), and Ca2+ was determined using an Auto Biochemistry Analyzer 7170A (Hitachi Co., Ltd., Tokyo, Japan).

4.2.1.3 Evaluation of blood compatibility

In order to investigate the complement and immunoglobin activation, complement C3, C4 and immunoglobin G, A, M and E were determined by enzyme-linked immunosorbent assays (ELISA)

Blood cells including red blood cell (RBC) and white blood cell (WBC), and blood components including hemoglobin (HGB) and platelet were determined using a blood cell analyzer (BC-3000peus, Shenzhen Mairui Biomedical Device Co. Ltd., China). Blood gas was determined by a blood gas analyzer (CORNing 238, US).

4.2.1.4 Statistical analysis

The software of SPSS 13.0 was used for statistical analysis. The deviation between the three groups was calculated by analysis of one-factor variance (ANOVA), and the deviation

between samples in one group was calculated by Student-Newman-Keuls (q-test). All the data are shown by mean values and standard deviations (m±s), p<0.05 is considered to have statistical difference.

4.2.2 Results and discussion

All the patients participated in the whole study period. The vital signs were stable with no adverse events during the dialysis, and there were no abnormal findings in laboratory security parameters. During the dialysis by PA membrane dialyzer, some clots were found after 175 minutes in the extracorporeal blood circuit of a male patient who was on a repeated bolus fraxiparine anticoagulation regimen (6000 IU in total), but the patient still finished the treatment. This was the only adverse event during the whole study. All of patients who were treated by PES, PA or PSF membrane dialyzers were performed without provoking any adverse symptoms, such as headache or hypotension.

4.2.2.1 Solute clearance

The clearance of small molecular and middle molecular toxins was expressed as the solute reduction ratio (RR) after 4 hours hemodialysis, and could be calculated by: RR (%) = (1-(post-solute concentration/pre-solute concentration))×100%. The blood flow was controlled at 200 ml/min and the dialysate flow was 500 ml/min. Figure 10 shows the RRs of urea, creatinine and β_2-microglobulin for the three kinds of hollow fiber dialyzers. As shown in the figure, large amount of the toxins were removed after the hemodialysis. The RRs of urea for PES, PA and PSF membranes were 61.2%, 63% and 62.3%, respectively. The RRs of creatinine were 51.3%, 54.5% and 54.7%, respectively. Meanwhile, the RRs of β_2-microglobulin were 60.8%, 51.3% and 57.7%, respectively. The RRs of urea and creatinine for the PES membrane were slightly smaller than that for the PA and PSF membranes, but no statistical difference. However, the RRs of β_2-microglobulin for the PES membrane were slightly larger than that for the PA and PSF membranes. It proved that the PES, PA and PSF hollow fiber hemodialysis membranes could effectively remove waste products including not only small molecular weight solutes such as urea and creatinine but also "middle" molecular solutes as β_2-microglobulin.

To increase the removal of large molecular solutes, the rates of diffusion and convection should be increased, and the membrane pore size and porosity should be increased. Pore size limitations arise from the concern over potential loss of blood proteins such as albumin. Given that dialysis patients are generally malnourished, and the relative risk of death of dialysis patients increases as the serum albumin concentration decreases, it is desirable to minimize the albumin loss to the dialysate. Furthermore, small albumin losses may be clinically insignificant to the patient, but may lead to practical problems in the dialysis clinic, such as the foam formation in the dialysate drains. An ideal dialysis membrane should have a uniform pore size large enough to allow the passage of β_2-microglobulin but small enough to retain albumin (66,000 daltons). Unfortunately, methods currently used to produce dialysis membranes resulted in a non-uniform pore size distribution. In the phase inversion membrane production process, polymer is dissolved in a solvent and then exposed to a non-solvent as it is extruded through an annular die. The breadth of the distribution produced by the phase inversion process resulted from the finite rate of molecular diffusion through the viscous polymer solution during the membrane coagulation phase (Qian et al., 2009). While previous membrane improvements have resulted from reducing the viscosity of the polymer solution, it is unlikely that the breadth of the pore size

distribution can be significantly reduced by further modification of the phase inversion process. Given a fixed breadth of the pore size distribution, the requirement for albumin retention limited not only the maximum pore size but also the mean pore size. As a result, the sieving coefficient of β_2-microglobulin is generally 0.6 or less in order to maintain the albumin sieving coefficient at 0.01 or less. The PES membrane may be adequate to this requirement (Kim & Kim, 2005).
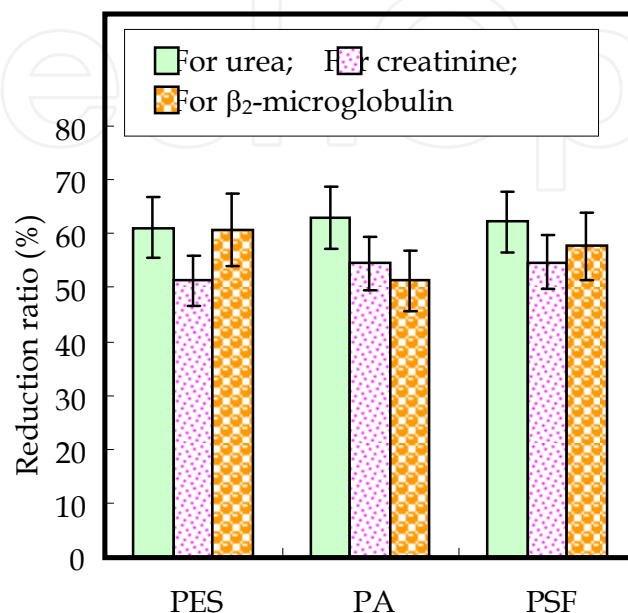

Fig. 10. Reduction ratios of small molecules urea and creatinine, as well as middle molecules β_2-microglobulin after four hours hemodialysis at a blood flow rate of 200 ml/min and dialysate flow rate of 500 ml/min. Data are expressed as the means±SD, n =3

4.2.2.2 Biocompatibility

Figure 11 shows the white cell (WBC) changes in the patient bloods during the dialysis for the three kinds of membranes. The blood cell counts have been normalized to pre-treatment levels and expressed as a percentage of these values. A small decline was noted at the first 30 minutes for all the membranes, and returned to the initial levels after about 1 h, and no significant difference was observed among the three membranes. The changes in platelet, complement factor C3, and complement C4 during the hemodialysis process for the three membranes were also investigated, and similar results were obtained as the change in WBC (Data not shown).

Retrospective analyses have shown that hemodialysis with synthetic dialysis membranes is associated with improved patient survival in ESRD (Kim & Kim, 2005). This observation was mainly attributed to membrane biocompatibility. Synthetic membranes are generally regarded as to be highly biocompatible, since they lead to low complement activation and leucopenia, which are the two classical parameters to characterizing biocompatibility in dialysis (Hakim et al., 1996). However, several other systems become altered during blood–membrane interaction. Among them are the coagulation system and imbalances of the oxidative and anti–oxidative system (Krieter et al., 2007; Klingel et al., 2004).

A slightly decrease in outlet leukocyte counts was observed for the three dialyzers, and significant difference was observed among them, as shown in Figure 11. The decrease of

white blood cells was caused by complement activation, thus similar results were obtained in the changes of complement factor C3 and complement C4 during the hemodialysis process. When comparing PES, PA and PSF membranes, these change showed no significant difference, which indicated that the blood compatibility might be the same, though different membrane materials were used.
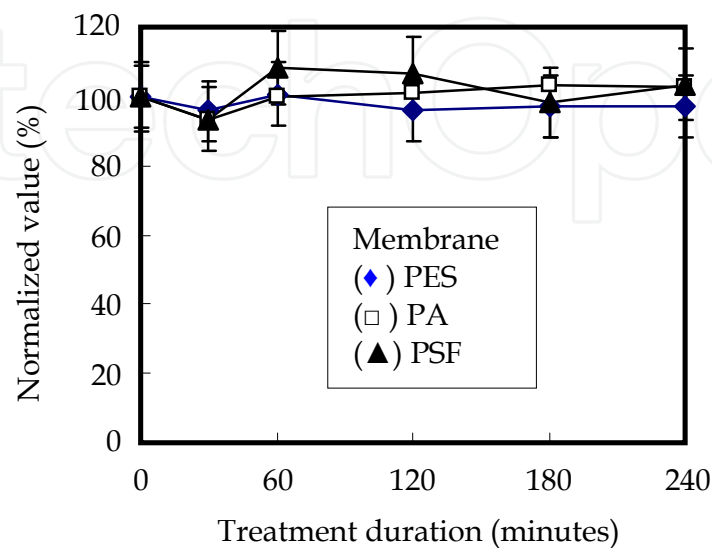

Fig. 11. Changes in WBC during the dialysis in vivo. Data are expressed as the means±SD, n =3

The concentration of albumin (ALB) and immunoglobin (GLB) slightly increased after 4 h hemodialysis, and no significant difference among the three membranes. Total protein adsorption of the membranes was also determined, and the amounts for PES, PA and PSF membranes were 12.2, 10.2, and 11.9 g/cm², respectively.

Total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels were measured after 4 h hemodialysis, and compared with the initial levels for the three kinds of membranes, as shown in Figure 12. There are no significant differences in the changes of TBIL, DBIL, ALT, and AST for the PES and PSF membranes, and both the TBIL and DBIL levels increased compared to the initial levels. However, for the PA membrane, the TBIL, and AST levels decreased obviously.

In Figure 12, slightly changes in total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were also observed. The change ratios for all of them ranged 3-10%. There are no significant differences in the changes of TBIL, DBIL, ALT, and AST for the PES and PSF membranes, and both the TBIL and DBIL levels increased compared to the initial levels, which were presumably caused by the dilution of the blood by normal saline solution infused or pachemia after the hemodialysis process. However, for the PA membrane, the TBIL, and AST levels decreased obviously. TBIL, DBIL, ALT and AST are produced primarily in the liver; all of them are lipophilic and hydrophobic. The dialyzer permits diffusive clearance of non-protein-bound, water soluble uraemic solutes, such as urea and creatinine. The corollary is that the substances are tightly protein-bound and present in small quantities in the aqueous phase, or are lipophilic and removed by HD in negligible amounts, if at all. The results indicted that the PES and PSF membrane had no effect on the liver, and might have possibly higher hydrophilicity than PA membrane.
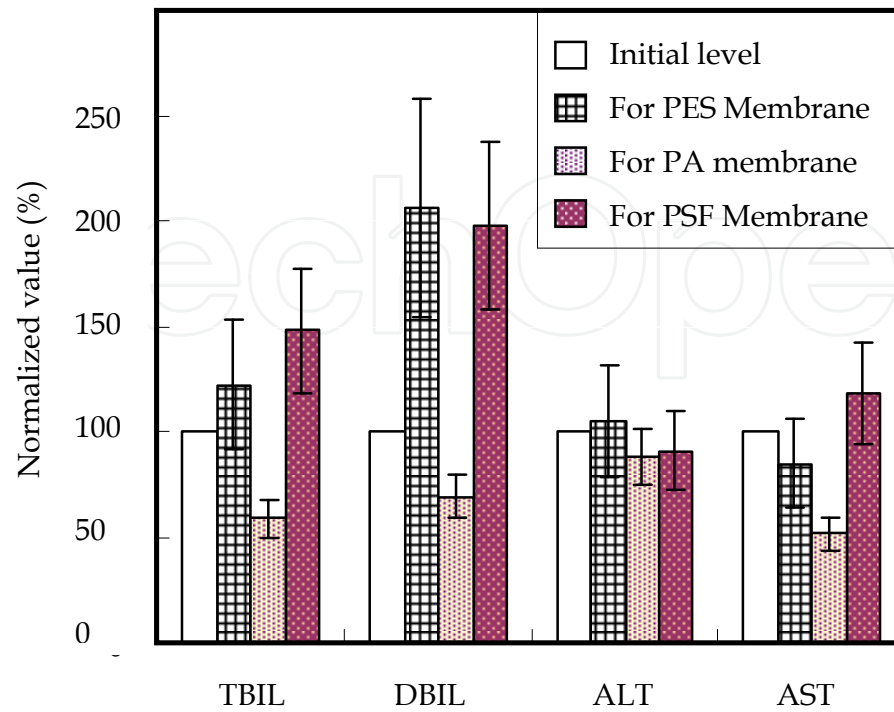
Fig. 12. *Total* bilirubin (TBIL), *direct* bilirubin (DBIL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) level changes after 4 h hemodialysis. Data are expressed as the means±SD, n =3

We speculated that the high-flux dialysis membrane might possibly let some biocompatibility markers enter dialysis solution so that the plasma levels of these markers could provide biased information. The plasma levels of biocompatibility markers may have also been influenced by adsorption to the membrane surface (Benz et al., 2007; Gotz et al., 2008). The adsorption to the membrane was not determined in our study. However, the protein adsorption capacity was investigated, and no difference was observed. On the basis of our results, we concluded that the designed modifications of the new high-flux PES dialyzer resultED in its higher middle molecule clearance efficacy, and had an effect on thrombogenicity as assessed by platelet behavior and fibrinolysis. Although coagulation system judged by one of the evaluated parameters was slightly higher compared with the other dialyzers, it was still within the biocompatible dialyzer range. In terms of complement activation and changes in leukocyte count, the new dialyzer is also comparable with the other biocompatible dialyzers. Besides the thrombogenicity, complement activation, and WBC count changes, other issues must be considered when evaluating bio(in)compatibility (Krieter et al., 2007; Klingel et al., 2004)

One further aspect merits consideration is that the PES membrane dialyzer series exhibits a higher permeability and thus, cytokine-inducing substances, possibly present in the dialysis fluid, might gain access to the blood stream through internal filtration (backfiltration). Therefore, investigations on the pyrogen permeability of PES membranes have been performed to the studies on the inflammatory response of the membrane. In the study, the dialysate compartment was deliberately contaminated with purified lipopolysaccharides (LPS) from Escherichia coli, as well as with LPS derived from Stenotrophomonas (Sten)

maltophilia. No significant generation of interleukin 1 (IL-1), IL-6 or tumor necrosis factor (TNF) was found in the blood compartment for the PES dialyzer and Fresenius PSF series of dialyzers as compared with sterile controls. However, significant induction of IL-1, IL-6, and TNF was observed for the highly permeable polysulfone membrane DIAPES, suggesting that not all of the polysulfone membranes were alike with regard to their pyrogen permeability due to the different modification methods. The PES, PA, and PSF dialyzers offered important safety features with regard to a possible contamination of the dialysis fluid (Wang et al., 1996; Schiffl & Lang, 2010).

4.2.3 Summary

The PES hollow fiber membrane hemodialyzer was effective and safe in the therapy for uremic patients. The PES hollow fiber hemodialysis membrane could effectively remove water and waste products including not only small molecular weight solutes such as urea and creatinine but also "middle" molecular solute as β_2-microglobulin. Slight neutropenia and platelet adhesion were observed at the initial stage of the hemodialysis and no significant difference was found in electrolyte or blood biochemistry before or after the treatment. The data indicated that the performances of PES, PSF and PA hemodialyzers in the clinical setting were comparable and the PES hemodialyzer might be better than the others. The results indicated that PES hollow fiber membrane had a potentially wide application for hemodialysis.

5. Conclusions

Polyethersulfone (PES) is one of the most important polymeric materials and is widely used in separation fields. PES and PES-based membranes show outstanding oxidative, thermal and hydrolytic stability as well as good mechanical and film-forming properties. Furthermore, PES-based membranes show high permeability for low molecular weight proteins when used as hemodialysis membranes. However, the blood compatibility of the PES membrane is not adequate, and injections of anti-coagulants are needed during its clinical application.

Thus, all the PES membranes used for hemodialysis are not the pristine PES membranes, and most widely used modification method for hemodialysis PES membranes is blending. Poly (vinyl pyrrolidone) (PVP) is the most widely used for the modification of PES membranes by blending, and PVP also acts used as a hydrophilic additive and a membrane forming agent. Surface-coating and grafting methods can also be used for the modification of PES hollow fiber membranes. All the modifications are based on the premise that the materials used in the modification give inherently more hydrophilicity and adsorb less protein than the underlying substrate.

Protein adsorption on material surface is a common phenomenon during thrombogenic formation. Thus, the amount of protein adsorbed on the PES membrane is considered to be one of the important factors in evaluating the blood compatibility. The adhesion of platelets to blood-contacting medical devices is a key event in thrombus formation on material surface. The clearances and the reduction ratios of small molecules (urea, creatinine, phosphate) for the PES membrane after the hemodialysis in vitro were larger than those in vivo. Animal experiments and clinical experiments indicated that the PES-based high-flux hemodialysis membrane had good blood compatibility, and could effectively remove "middle" molecular solute as β_2-microglobulin.

The blood compatibility and performance in hemodialyzation were compared with two conventional high-flux membranes, polysulfone (PSF) and polyamide (PA) membranes. The PES and PSF membranes showed similar blood compatibility and solute clearance, and the blood compatibility for PES and PSF might be better than the PA membrane.

In conclusion, PES-based hollow fiber membranes have good blood compatibility and solute clearance, and the PES hollow fiber membrane hemodialyzer might be a good commercial product in the future.

6. Acknowledgment

7. References

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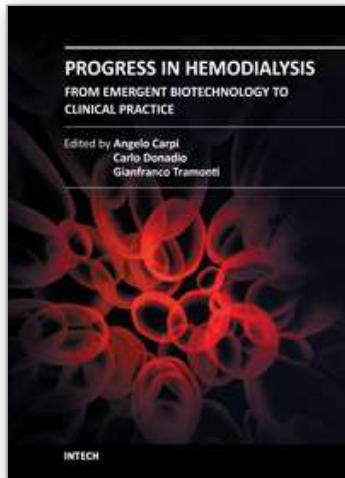
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