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High efficient protocol for the modification of polyethersulfone membranes with anticoagulant and antifouling properties via in situ cross-linked copolymerization

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ABSTRACT

In this paper, we provide a highly efficient, convenient and universal protocol for blood-compatible modification of polyethersulfone (PES) membranes via in situ cross-linked copolymerization of 2-hydroxyethl methacrylate (HEMA) and acrylic acid (AA) in PES solutions. Static water contact angle, protein adsorption, platelet adhesion, and clotting time of the modified PES membranes are systematically studied, and the results indicate that the modified membranes show improved hydrophilicity, good blood anticoagulant and antifouling properties after introducing HEMA and AA. Meanwhile, the modified membranes perform low contact activation and complement activation when they come in contact with blood. The effect of the HEMA/AA ratios on the blood compatibility is also investigated to identify the different roles played by HEMA and AA in the modification; the HEMA could more effectively enhance the membrane antifouling property, while the AA could more effectively improve the anticoagulant property. The results indicated that the blood-compatible PES membranes prepared via the in situ cross-linked copolymerization had potential to be used in the field of blood purification.

1. Introduction

Good blood compatibility (especially anticoagulant property and antifouling property) is highly desired for the materials and artificial devices which directly come in contact with blood. To improve blood compatibility, it is effective to introduce hydrophilic and/or blood-compatible groups in the materials [1–5]. During the past decades, carboxyl group (–COOH) and hydroxyl group (–OH) have been widely used for the design and preparation of materials with good blood compatibility [2,4,6–8]. It has been reported that carboxyl groups in materials could bind calcium ions (Ca^{2+}) in blood, resulting in the improvement of anticoagulant property [9]; while hydroxyl-rich materials show excellent hydrophilicity and protein antifouling property, which might help to inhibit thrombus formation [1,7,10–12].

In previous researches, carboxyl and/or hydroxyl groups have been applied to blood-compatible modification of membranes via surface grafting, coating and blending methods [12–17]. Among membrane matrix materials, polyethersulfone (PES) is famous for its outstanding oxidative, thermal and hydrolytic stability as well as good mechanical and film-forming properties [18], and PES membranes have been widely employed in biomedical fields such as artificial organs and medical devices used for blood purification (hemodialysis, hemodiafiltration, hemofiltration, plasmapheresis and plasma collection) [19–21]. However, the blood compatibility of PES membranes is not ideal [22], and modification is needed.

Recent studies revealed that functional groups could be enriched on PES membrane surface using surface modification methods, such as surface grafting and coating [14,23,24]; and the modified membranes showed obviously improved blood compatibility. Yu et al. [25] grafted polyzwitterions onto polyamide by click chemistry and nucleophilic substitution on nitrogen, and the prepared polyamide membranes exhibited excellent antifouling capability. Xiang et al. [23] grafted poly (N-vinylpyrrolidone) onto PES membrane surface by surface-initiated atom transfer radical polymerization, and the modified membranes showed improved blood compatibility. Ma et al. [14] prepared modified PES membranes with high blood compatibility via surface self-coating of dopamine grafted heparin-like polymer (HepLP, poly (sodium 4-vinylbenzenesulfonate)-co-poly (sodium methacrylate)) (DA-g-HepLP) and dopamine grafted heparin (DA-g-Hep). Ni et al. [26] synthesized a novel random terpolymer

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poly (methylacryloxyethydimethyl benzyl ammonium chloride-r-acryl-amide-r-2-hydroxyethyl methacrylate) (P(MDBAC-r-Am-r-HEMA)) and used it as a coating material on polyamide thin film composite (TFC) reverse osmosis (RO) membrane, the antifouling performance of the prepared membrane was improved. The modification by grafting could be the most stable among all the current methods because the grafted layer is covalently tethered on the membrane material, but the modification process is complex. Surface coating is convenient but may be less stable, especially for long-term filtration application. Thus the applications of surface grafting and coating may be limited for the surface modification of membranes, and a more efficient approach is highly desired.

Compared with surface grafting and coating, direct blending is easier and more convenient, and has been widely used to improve the blood compatibility of membranes [27–32]. In our previous studies, a series of random copolymers were synthesized and used for preparing blood-compatible PES membranes [16,33–35]. Li et al. [36] synthesized copolymers poly (acrylonitrile–acrylic acid–N-vinyl pyrrolidinone) (p(AN–AA–VP)) via free radical solution polymerization to modify PES membranes, and the modified membranes showed improved hydrophilicity and protein antifouling property. However, only 1.6 wt% of the p(AN–AA–VP) was blended into the casting solution due to the poor miscibility between the copolymer and PES matrix. Zou et al. [35] synthesized poly (methyl methacrylate–acrylic acid–vinyl pyrrolidone) (p(MMA–AA–VP)) for the modification of PES membranes, and similar results were obtained. The low introduced amount of the functional copolymers led to poor modified efficiency and then limited the application of the direct blending method. On the other hand, block copolymers were also applied to the blood-compatible modification of PES membranes, and the blended amount of the copolymers and modification efficiency were obviously improved [4,5,37,38]. Nie et al. [4] synthesized triblock copolymer poly (styrene-co-acrylic acid)-b-poly (vinyl pyrrolidone)-b-poly (styrene-co-acrylic acid) (p(St-co-AA)-b-PVP-b-p(St-co-AA)) to improve the blood compatibility of PES membranes. The introduced amount was as high as 5 wt%, and the modified membranes showed good blood compatibility. However, compared with random copolymers, block copolymers were difficult to be synthesized and purified (atom transfer radical polymerization (ATRP) and reversible addition-fragmentation chain transfer (RAFT) polymerization are usually used for synthesizing block copolymers), which might limit the practical application of the block copolymers.

The in situ polymerization is easy and effective for the modification of polymeric materials and has been widely applied to design functional materials in the fields of fuel cells and water treatment [39–44]; however, it has almost never been used for preparing blood-compatible materials. In the present study, AA and HEMA, which had been applied for the modification of PES membranes separately [45–48], were used to endow PES membranes with combined anticoagulant and antifouling properties. As shown in Scheme 1, in the casting solution, the molecule chains of PES and p(HEMA–AA) were intertwined together, which might result in a high blending amount of the functional polymer and in a good stability of the modified membranes. In the study, a series of p(HEMA–AA) modified PES membranes were prepared via in situ cross-linked copolymerization, and the hydrophilicity, blood anticoagulation property and protein antifouling property of the prepared membranes were investigated.

2. Experimental

2.1. Materials

Polyethersulfone (PES, Ultrason E6020P, No. 25608-63-3) was purchased from BASF Chemical Co. (Germany). 2-Hydroxyethyl methacrylate (HEMA) ($C_6H_{10}O_3$, 98%, CAS No. 868-77-9) and acrylic acid (AA) ($C_3H_4O_2$, AR, CAS No. 79-10-7) were purchased from Aladdin Chemistry Co. Ltd., and purified through an aluminum oxide column to remove the inhibitors before use. N-Methyl-2-pyrrolidinone (NMP) (C_5H_9NO, AR, CAS No. 872-50-4) was purchased from Chengdu Kelong Inc. (Chengdu, China), and used as solvent. Azo-bis- isobutryonitrile (AIBN) ($C_8H_{12}N_4$, AR, CAS No. 78-67-1) was purchased from Chengdu Kelong Inc. (Chengdu, China), and was used as an initiator. N, N′-Methylenebisacryl amide (MBA) ($C_7H_{10}N_2O_2$, $\geq$99%, CAS No. 110-26-9) was purchased from Aladdin Chemistry Co. Ltd., and used as a cross-linking agent. Bovine serum albumin (BSA) and bovine serum fibrinogen (BFG) were obtained from Sigma Chemical Co. Micro BCA™ Protein Assay Reagent kit was purchased from PIERCE Inc. Activated partial thromboplastin time (APTT) reagent, calcium chloride reagent for APTT test, Owren's Veronal Buffer, and Factor XII-deficient plasma were purchased from Siemens Co. Ltd. All the other chemicals (AR) were obtained from Chengdu Kelong Inc. (Chengdu, China), and were used without further purification. Deionized water was obtained from a pure water production system and used throughout the experiments.

2.2. Preparation of modified PES membranes

PES casting solutions were prepared via in situ cross-linked copolymerization of HEMA and AA in PES solutions. PES was dissolved in NMP at 80 °C, then a mixture composed of HEMA, AA, MBA and AIBN was added into the PES solution (the feed compositions are shown in Table 1). After bubbling nitrogen for 30 min, cross-linked copolymerization was carried out at 80 °C for 5 h under a nitrogen atmosphere with mechanical stirring (200 rpm); the solution was then exposed in air at room temperature to terminate the polymerization. For the M-0 and M-1-1 samples, clear and homogeneous casting solutions were obtained, and slightly turbid casting solutions were obtained for the other samples.

In this study, spin coating coupled with a phase inversion technique was used to prepare the membranes [49]. After degassing with a vacuum pump, the casting solution was spin coated on glass surfaces (the glasses were pretreated with freshly prepared Piranha solution. *Caution! Piranha solution, which contains concentrated sulfuric acid and hydrogen peroxide with volume ratio of* 7:3, *is an extremely strong oxidant and should be handled only with the proper equipment*), then immersed into deionized water, and then the membranes were prepared via the liquid–liquid phase separation technique. The membrane thickness was controlled to be about 70 μm. In order to eliminate the effect of residual solvent, the prepared membranes were washed by deionized water several times and stored in deionized water for two weeks before use.

2.3. Membrane characterization

To investigate the surface compositions of the membranes, attenuated total reflection-Fourier transform infrared (ATR-FTIR) spectra were obtained on a Nicolet-560 spectrophotometer (Nicol, US) between 4000 cm^{-1} and 1000 cm^{-1}, with a resolution of 4 cm^{-1}. All the membranes were dried in a vacuum freeze drier for 10 h before the characterization.

The morphology of the cross-section views for the membranes was observed using a scanning electron microscopy (SEM) (JSM-7500F, JEOL, Japan). Before the observation, the membranes were quenched and fractured in liquid nitrogen, attached to the sample supports and coated with gold layers.

The hydrophilicity/hydrophobicity of the membranes was investigated on the basis of contact angle measurement, using a contact