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Hemocompatibility and film stability improvement of crosslinkable MPC copolymer coated polypropylene hollow fiber membrane

Yan-Bing Wang [a], Ming Gong [a,b], Shan Yang [a,c], Kenichi Nakashima [d], Yong-Kuan Gong [a,*]

[a] Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, College of Chemistry and Materials Science, Northwest University, Xi'an 710069, Shaanxi, PR China
[b] School of Chemistry and Chemical Engineering, Xian University of Science and Technology, Xi'an 710054, Shaanxi, PR China
[c] College of Chemistry and Life Science,Weinan Normal University, Weinan 714000, Shaanxi, PR China
[d] Department of Chemistry, Faculty of Science and Engineering, Saga University, 1 Honjo-machi, Saga 840-8502, Japan

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ABSTRACT

Hollow fiber membranes (HFMs) based artificial lungs require a large blood-contacting membrane surface area to provide adequate gas exchange. However, such a large surface presents significant challenges to hemocompatibility. For improving the hemocompatibility, amphiphilic and cell outer membrane mimetic 2-methacryloyloxyethyl phosphorylcholine (MPC) copolymers containing 3-(Trimethoxysilyl)propyl methacrylate (TSMA) and/or n-butyl methacrylate (BMA) units, poly(MPC-co-BMA-co-TSMA) (PMBT) and poly(MPC-co-BMA) (PMB) were coated on a commercial polypropylene (PP) HFM. Dynamic contact angle, ATR-FTIR and XPS results showed that both the PMB and PMBT phospholipid polymer coatings are stable in water, but only the crosslinked PMBT coating can resist the dissolution by ethanol or SDS aqueous solution. Protein adsorption, platelet adhesion and whole blood contact experiments showed significant improvement in hemocompatibility after being coated with the PMBT. Moreover, oxygenation experiments indicated that the blood compatible coating could resist blood permeance and did not hinder the gas exchange. Overall these findings revealed improved hemocompatibility which can be realized through crosslinkable phospholipid polymer coating, enabling more stable and more biocompatible HFMs respiratory assist devices.

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1. Introduction

Most artificial lung devices (oxygenators) used today are composed of bundles of hollow fiber membranes (HFMs). The HFMs made from polymeric materials such as polypropylene (PP) and polysulfone (PSF) are routinely employed to oxygenate blood by direct contact between blood and oxygen gas. However, continuous contact of large area of the synthetic polymer with whole blood causes protein adsorption and platelet adhesion, which will further lead to formation of thrombus and decrease of gas permeability [1]. A routine method of reducing the formation of thrombus is systemic heparinization. The addition of heparin can effectively suppress blood coagulation, but, it can produce hemorrhagic complications in patients at high risk of bleeding [2]. At the same time, the addition of heparin cannot reduce the adsorption of protein on the HFMs [3].

Although a wide variety of surface modification techniques has been evaluated to reduce the thrombogenicity of blood-contacting biomaterials, there have been relatively few reports specifically focused on the HFMs utilized in artificial lung applications. Covalently immobilized carbonic anhydrase onto the surface of PP-HFMs and siloxane-grafted PP-HFMs by a plasma polymerization process with 1,3,3,7-tetramethyhydrocyclosiloxane have shown reduced thrombogenesis relative to unmodified fibers [4–6]. These covalent modification techniques are effective for small samples to achieve good adhesion between coating and substrate and to generate coatings that present excellent thermal and chemical resistance.

Another approach to improve the biocompatibility of HFMs is to coat with 2-methacryloyloxyethyl phosphorylcholine (MPC) copolymers, new materials which are recognized as mimicking the red blood cell outer membrane, have been shown to possess excellent hemocompatibility, and suppress biological reactions by inhibiting undesirable interactions with biomolecules and cells [7,8]. Nakabayashi et al. coated poly(MPC-co-dodecylmethacrylate) (PMD) onto polyethylene (PE) porous membrane [9]. The permeability of oxygen gas through the PMD/PE porous membrane was the same as the original PE porous membrane when the MPC unit in PMD was more than 0.20 mol fraction. This membrane showed great blood compatibility and was regarded useful as a

* Corresponding author. Tel.: +86 298 830 2109; fax: +86 298 830 2604.
E-mail addresses: gongyk@163.com, gongyk@nwu.edu.cn (Y.-K. Gong).

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novel oxygenator membrane. Ishihara et al. reported the modification of cellulose acetate (CA) HFMs by blending or coating poly (MPC-co-Butylmethacrylate) (PMB). The phospholipid polymer PMB modified CA-HFMs showed improved performance in solute and water permeability, suggesting great potential for developing a high performance hemocompatible plasmapheresis and hemofilter device [10,11]. On the other hand, the amphiphilic phospholipid polymers might dissolve in an aqueous environment, especially in the complicated and flowing blood environment [12–14]. To increase the coating stability of MPC polymers, crosslinkable trimethoxysilyl methacrylate (TSMA) unit has been introduced to MPC polymers. The dip-coated films onto glass, stainless steel, and chitosan surfaces can form stable and blood compatible coatings after crosslinking treatment [13–15].

Herein, we report a simple and mass productive dip-coating strategy for fabricating more hemocompatible and more stable phospholipid copolymer coated PP-HFM. The coating properties of poly(MPC-co-BMA-co-TSMA) (PMBT) and poly(MPC-co-BMA) (PMB) were evaluated by comparison. As expected, both the PMB and PMBT phospholipid polymer coatings are stable in water and more hemocompatible than the bare PP-HFM, but only the crosslinked PMBT coating can resist the dissolution by ethanol or SDS aqueous solution. Moreover, the stable and hemocompatible PMBT coating did not hinder the gas permeability.

2. Experimental

2.1. Materials

2-Methacryloyloxyethyl phosphorylcholine (MPC) was synthesized according to the method reported by Ishihara et al. [16]. N-butyl methacrylate (BMA) was distilled under reduced pressure. 3-(Trimethoxysilyl)propyl methacrylate (TSMA) was purchased from Aldrich Chemical Co. Tetrahydrofuran (THF) was distilled over calcium hydride (CaH_2). Diethyl ether was dried over Na metal and distilled prior to use. Methanol and ethanol were distilled over Mg metal. 2, 2′-Azoisobutyronitrile (AIBN) was recrystallized from methanol and dried in vacuum. Nitrogen (high purity) was dried through concentrated sulfuric acid. Bovine serum albumin (BSA) and bovine plasma fibrinogen (Fg) were purchased from Sigma-Aldrich and used as supplied. Platelet-rich plasma (PRP) was prepared using fresh blood provided by a healthy donor according to a previously reported method [17]. Polypropylene hollow fiber membrane (thickness 50 μm, inner diameter 300 μm) and oxygenator were supplied by Xi'an Xi Jian Medical Supplies Co., Ltd. Whole blood was obtained from a bovine with a normal body temperature, no physical signs of disease, including diarrhea orrhinorrhea. The blood was collected in 500 mL blood bags containing sodium citrate. All other materials and reagents were analytical grade and were used without further purification unless otherwise indicated.

2.2. Synthesis of PMB and PMBT copolymers

Chemical structures of PMBT and PMB copolymers are shown in Fig. 1. The PMBT was synthesized by conventional free-radical polymerization according to the following process named "monomer-starved" method [18]. N_2 was bubbled into the reaction flask containing solvent ethanol for 30 min to eliminate oxygen and then heating the flask to 75 °C. 1/3 Volume of the AIBN initiator THF solution was added into the reaction flask. Then desired amounts of MPC, BMA, and TSMA dissolved in ethanol were mixed with the other 2/3 AIBN/THF solution. The mixed solution was dropped into the reaction flask for 1–2 h with constant pressure addition funnels, after that, the N_2 flow was stopped and the reactor was sealed. Polymerization was performed at 75 °C for 24 h. After cooling the reactor, the content was poured into a large excess of diethyl ether to eliminate the remaining monomer and precipitate the polymer. Then the precipitated polymer was dissolved in ethanol and precipitated with diethyl ether again. Finally, the polymer was dissolved in methanol to form a concentrated solution for long-term preservation. Similarly, PMB was synthesized and purified by the same procedure as PMBT. The composition in the PMBT and PMB polymers was determined by ^{1}H NMR (INOVA-400, Varian, USA) spectral measurements.

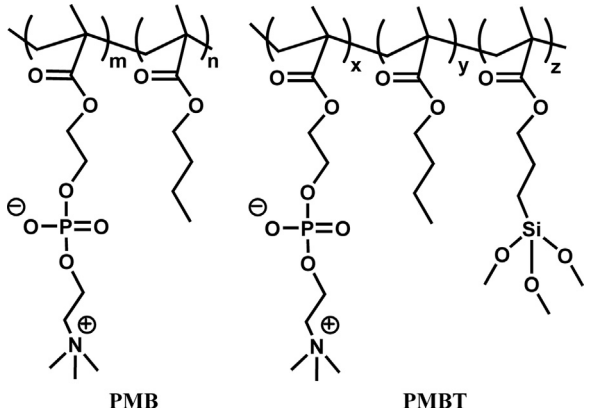

Fig. 1. Chemical structures of PMB and PMBT (m:n=52.6:47.4; x:y:z=43.3:46.9:9.8).

2.3. PP-HFM surface coating

Commercial PP hollow fiber membrane (PP-HFM) was cut into 2.0 cm × 1.0 cm size, cleaned with ethanol under sonication for 30 min, thoroughly rinsed with deionized water and dried in vacuum at 30 °C for 24 h. PMBT and PMB copolymers were dissolved in a mixed solvent of methanol:water=90:10 (v/v). The clean HFM was immersed into the freshly prepared PMBT or PMB solution with different concentrations at room temperature for different periods (10 s, 30 s, 1 min, 5 min and 2 h). Then the PP-HFMs were removed from the solution and the coated PMBT film was crosslinked in the atmosphere of 10% (v/v%) triethylamine aqueous solution for at least 3 days. Finally the dip-coated and/or crosslinked phospholipid polymer surface was thoroughly rinsed with deionized water and dried at 30 °C under vacuum.

The PP-HFMs assembled in artificial lung devices (oxygenators) were also coated with the 1 mg/mL PMBT solution. Three-hundred milliliter of the polymer solution was injected into the hard-shelled jacket from the blood inlet, left for 10 min and then removed from the jacket. Then, the vapor of 10% (v/v%) triethylamine aqueous solution was pumped into the jacket via the blood inlet, sealed for 3 days to crosslink the coated PMBT. Finally, the PMBT coated PP-HFM oxygenator was thoroughly washed with deionized water and dried at 30 °C under vacuum.

2.4. Dynamic contact angle (DCA) measurements

The water contact angle of the bare and the phospoholipid copolymer coated PP-HFM surfaces was measured by the Wilhelmy plate method using a DCAT 21 tensiometer (DataPhysics Instruments GmbH). The method was described in detail in our previous report [14]. Before and after the dynamic contact angle measurements, the surface tension of the probe liquid-deionized water (Direct-Q3 UV Millipore system, 18.2 MΩ, France) was recorded with the DCAT 21. In each case, a minimum of three specimens was analyzed to ensure reproducibility.

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