Journal of Membrane Science 476 (2015) 234–242

Contents lists available at ScienceDirect

Journal of Membrane Science

journal homepage: www.elsevier.com/locate/memsci

Ionic-strength-sensitive polyethersulfone membrane with improved anti-fouling property modified by zwitterionic polymer *via in situ* cross-linked polymerization

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ARTICLE INFO

Article history:
Received 7 January 2014
Received in revised form
10 October 2014
Accepted 23 November 2014
Available online 2 December 2014

Keywords:
Zwitterionic polymer
In situ cross-linked polymerization
Ionic-strength-sensitive
Anti-fouling
Blood compatibility

ABSTRACT

A new method to prepare ionic-strength-sensitive membrane with improved anti-fouling property and blood compatibility is developed *via in situ* cross-linked polymerization of sulfobetaine methacrylate (SBMA) in polyethersulfone (PES) solution and a liquid–liquid phase separation technique. The modified membrane is characterized by attenuated total reflectance-Fourier transform infrared spectra (ATR-FTIR), X-ray photoelectron spectroscopy (XPS), ^{1}H NMR measurements, thermogravimetric analysis (TGA), scanning electron microscopy (SEM), and water contact angle (WCA) measurement. The membrane with high PSBMA content shows obvious ionic-strength-sensitive property and ionic-strength reversibility, which are expressed by the fluxes of salt solutions. Meanwhile, with the increase of the PSBMA content in the membrane, the anti-fouling property and blood compatibility are considerably improved.

1. Introduction

Polymeric materials are widely used in blood-contacting devices, such as cellulose acetate (CA), polyacrylonitrile (PAN), polyvinyl alcohol (PVA), polysulfone (PSf) and polyethersulfone (PES) [1–3]. PES is not only a popular material due to its thermal stability, mechanical strength and chemical inertness, but also one of the few biomaterials that can withstand all sterilization techniques (steam, ethylene oxide, gamma radiation) [4]. However, the anti-fouling property and blood compatibility of PES membrane are not ideal, and the modification is desired.

Recently, zwitterionic polymers are widely used to prepare materials with good anti-fouling property and biocompatibility [5–7]. In general, zwitterionic polymers are mainly introduced into materials by means of blending method [8,9] and covalently grafting method, including surface-initiated atom transfer radical polymerization (SI-ATRP) [10–13], O_2 plasma surface grafting [14] and atmospheric plasma-induced surface copolymerization [15], and so on. Meanwhile, zwitterionic polymer based hydrogels were also fabricated with different kinds of crosslinking agents [7,16–18]. These zwitterionic polymer modified materials showed obvious antimicrobial property, anti-fouling property and biocompatibility [7,12]. It was also reported that zwitterionic polymers, whether in linear or cross-linked forms display "anti-polyelectrolyte" behavior [19], and the presence of salt might break the intrachain and intragroup association of the poly(sulfobetaines) and give rise to chain expansion [20]. Thus, we deduce that zwitterionic polymer modified membrane might be ionic-strength-sensitive to salt solutions, and the membrane might also show improved anti-fouling property and blood compatibility. To the best of our knowledge, no study has been reported on ionic-strength-sensitive PES membrane modified with zwitterionic polymer.

To improve the biocompatibility of PES membrane, many methods including blending method and grafting method have been employed to improve the hydrophilicity by introducing charged groups onto the membrane surface [4]. Though the blending method is the simplest method, the elution of hydrophilic functional polymers is unavoidable. In our recent studies [21–25], we synthesized many amphiphilic copolymers using hydrophilic functional monomers such as acrylic acid (AA) or maleic anhydride (MA) and hydrophobic monomers such as methyl methacrylate (MMA), styrene (St) or acrylonitrile (AN) to avoid the elution. Though the elution problem was solved, the miscibility of the copolymers and PES in the common solvent was poor. Recently, *in situ* free radical polymerization was applied to fabricate modified poly(vinylidene fluoride) (PVDF) membrane with

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http://dx.doi.org/10.1016/j.memsci.2014.11.045
0376-7388/

improved anti-fouling property and mechanical behavior, which was different from the simple blending method [26–28]. The phase separation mechanism during the precipitation process and the crystalline structure of the membrane had been studied. However, the amounts of 2-hydroxyethyl methacrylate (HEMA) or polyethylene glycol monomethyl ether methyl methacrylate (PEGMA) in the membranes were not quantitative and the structure might be unstable, since no crosslinking agent was used in the polymerization, and the elution of the water-soluble polymer might be occurred.

In this study, we aim to prepare ionic-strength-sensitive PES membrane using zwitterionic polymer poly(sulfobetaine methacrylate) (PSBMA) through *in situ* cross-linked free radical polymerization. PES was firstly dissolved in dimethyl sulfoxide (DMSO) to get a homogeneous solution. Then, monomer sulfobetaine methacrylate (SBMA), initiator 2,2′-azobis(2-methylpropionitrile) (AIBN) and crosslinking agent N,N′-methylenebisacrylamide (MBA) were added into the above solution under nitrogen atmosphere. After reaction, the obtained solution was directly used as casting solution to prepare membranes by a liquid–liquid phase separation technique. The ultrafiltration experiments for pure water, BSA solution and salt solutions (NaCl, $CaCl_2$ and $FeCl_3$ solutions) were used to investigate the anti-fouling property and the ionic-strength-sensitive property. Furthermore, the blood compatibility, including protein adsorption, platelet adhesion, activated partial thromboplastin time (APTT) and thrombin time (TT)) of the modified membranes was also evaluated.

2. Materials and methods

2.1. Materials

Commercial polyethersulfone (PES, Ultrason E6020P) was purchased from BASF. The monomer sulfobetaine methacrylate (SBMA) was synthesized according to our previous reported procedures [10]. 2,2′-Azobis(2-methylpropionitrile) (AIBN, 98%, Aladdin) was purified by recrystallization. Dimethyl sulfoxide (DMSO, 99.8%, Aladdin), N,N′-methylenebisacrylamide (MBA, 99%, Aladdin), sodium chloride (NaCl, 99%, Kelong), calcium chloride ($CaCl_2$, 99%, Kelong), and ferric chloride ($FeCl_3$, 99%, Kelong) were used as received. Bovine serum albumin (BSA, fraction V) and bovine serum fibrinogen (BFG) were obtained from Sigma Chemical Co. Micro BCA™ protein assay reagent kits were the products of PIERCE. APTT and TT reagent kits were purchased from SIEMENS. Deionized water was used throughout the studies.

2.2. Membrane preparation

A typical procedure for the synthesis of poly(sulfobetaine methacrylate) (PSBMA) in PES solution *via in situ* cross-liked polymerization was as follows: The total weight of the reaction system was 100 g. 16 g PES (16 wt% of the total solution) was firstly dissolved in 60 g DMSO to get a homogeneous solution. Then a mixture of expectant amounts of SBMA (2 g, 4 g or 6 g), AIBN (2 mol% with respect to SBMA), MBA (2 mol% with respect to SBMA) and DMSO was added into the PES solution under nitrogen atmosphere. The polymerization was carried out at 75 °C with vigorous stirring for 24 h and then cooled to room temperature. After being vacuum degassed, the solution was prepared into membranes by spin casting coupled with a liquid–liquid phase separation technique at room temperature [29]. The membranes were rinsed with deionized water thoroughly to remove the residual solvent. All the prepared PES/PSBMA membranes were in a uniform thickness of about 55 ± 3 μm. The membrane which was prepared by the solution with 2 wt% SBMA was named M-2%; and so did the others. For comparison, pristine PES membrane without PSBMA was also fabricated using the same procedure, and named M-0.

2.3. Characterization

Attenuated total reflection-Fourier transform infrared (ATR-FTIR) spectra were obtained by using a Fourier-transform infrared spectrometer (Nicolet 560, America). Each spectrum was collected at a resolution of 4 cm^{-1} and the reflectance spectra were scanned over the range of 675–4000 cm^{-1}. Surface element analysis of the samples was characterized using a Kratos AXIS ULTRA^{DLD} XPS Instrument, employing Al Kα excitation radiation. ^1H NMR measurements were recorded on a Bruker AVII-400 MHz spectrometer (Bruker Co., Germany). Thermogravimetric analysis (TGA) was performed on a TG209F1 TG instrument (Netzsch, Germany) at a heating rate of 10 °C/min and nitrogen atmosphere. The cross section morphology of the membranes was characterized by using JSM-7500F field-emission scanning microscope (SEM) (JEOL, Japan) with the voltage of 5 kV.

2.4. Wettability measurements

The hydrophilicity of the membrane surface was characterized on the basis of contact angle measurement. The dynamic contact angles (DCAs) were measured and calculated on a contact angle goniometer (Dataphysics OCA20, Germany) equipped with a video capture at ambient temperature. One drop of water (3 μL) was dropped onto the surface of the membrane with an automatic piston syringe and photographed. The contact angles at every three minutes were determined from these images by using the professional calculation software.

2.5. Ultrafiltration experiments

Ultrafiltration of membrane was measured by using the apparatus as described in our previous study [30]. A dead-end ultrafiltration (UF) cell was used with an effective membrane area of 13.8 cm^2. The test membrane was pre-compacted at the pressure of 0.1 MPa by deionized water for 30 min in order to get steady filtration, and then the flux was measured at the pressure of 0.05 MPa. All the flux measurements were conducted at room temperature.

2.5.1. Ultrafiltration of pure water

The pure water flux of the membrane was determined by collecting the solution after getting steady, and was calculated by using the following equation:

$$Flux = \frac{V}{SPt} \tag{1}$$

where V (mL) is the volume of the permeated solution; S (m^2) is the effective membrane area; P (mmHg) is the pressure applied to the membrane and t (h) is the time for collecting permeated solution.

2.5.2. Ultrafiltration of BSA solution

For the ultrafiltration experiments, bovine serum albumin (BSA) was dissolved in isotonic phosphate-buffered saline solution (PBS, pH 7.4) with a concentration of 1.0 mg/mL. The flux was calculated by Eq. (1) and the BSA rejection ratio (R) was defined as follows:

$$R(\%) = \left(1 - \frac{C_p}{C_b}\right) \times 100 \tag{2}$$

where C_p and C_b (mg/mL) are the BSA concentrations of the permeated and bulk solutions, respectively, which are measured by an UV–vis spectrophotometer (UV-1750, Shimadzu, Japan) at the wavelength of 278 nm.

After protein filtration, the membrane was cleaned with deionized water; then, the PBS flux of the cleaned membrane was measured again and the flux recovery ratio (F_{RR}) was calculated using the