Carbohydrate Polymers 95 (2013) 64–71

Contents lists available at SciVerse ScienceDirect

Carbohydrate Polymers

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

Blood compatibility of polyethersulfone membrane by blending a sulfated derivative of chitosan

Jimin Xue, Weifeng Zhao, Shengqiang Nie, Shudong Sun*, Changsheng Zhao

College of Polymer Science and Engineering, State Key Laboratory of Polymer Materials Engineering, Sichuan University, Chengdu 610065, People's Republic of China

ARTICLE INFO

Article history:
Received 1 August 2012
Received in revised form 4 February 2013
Accepted 15 February 2013
Available online xxx

Keywords:
Chitosan
Polyethersulfone
Blood compatibility

ABSTRACT

In this study, a novel sulfated derivative of chitosan, which could be dissolved in many common organic solvents, is conveniently synthesized for the modification of polyethersulfone (PES) membrane. Elemental analysis, FTIR, ^{1}H NMR and X-ray diffraction diagrams (XRD) are used to demonstrate the introduction of functional groups. Owing to the solubility in organic solvents, the sulfated derivative of chitosan could be directly blended with PES in organic solvent to prepare membrane by means of a liquid–liquid phase separation technique. The modified membrane showed lower protein (bovine serum albumin (BSA) and bovine serum fibrinogen (BFG)) adsorption and suppressed platelet adhesion. Moreover, the activated partial thromboplastin time (APTT) for the modified membrane was enhanced as high as 60% compared to pure PES membrane. The lower protein adsorption, suppressed platelet adhesion and increased APTT confirmed that the blood compatibility of the modified PES membrane by the sulfated derivative of chitosan was significantly improved.

1. Introduction

In order to achieve a further controlled modification reaction of chitosan or to obtain some modification reactions in homogeneous conditions smoothly, phthaloylation reaction was carried out (Kurita, Ikeda, Yoshida, Shimojoh, & Harata, 2002; Nishimura, Kohgo, Kurita, & Kuzuhara, 1991), since the product of phthaloylated chitosan was a particularly convenient organosoluble precursor for efficient modifications.

The sulfated chitosan is one kind of the most important products of different modifications of chitosan due to the numerous applications, such as post-treatment of wastewater, anticoagulant, adipogenesis inhibition and antibacterial (Chaudhari & Murthy, 2011; Huang, Du, Zheng, Liu, & Fan, 2004; Karadeniz, Karagozlu, Pyun, & Kim, 2011; Muzzarelli et al., 1984). It is noteworthy that the structure of sulfated derivatives of chitosan is similar to that of heparin, a natural blood anticoagulant. Several studies about the anticoagulant activity of sulfated chitosan had been reported (Muzzarelli & Giacomelli, 1987; Vikhoreva et al., 2005; Vongchan, Sajomsang, Subyen, & Kongtawelert, 2002; Yang et al., 2012), however, few of these sulfated derivatives of chitosan were organosoluble, which are likely to restrict the applications in some specific areas.

In order to expand the applications of the sulfated derivatives of chitosan and obtain an improved blood compatible material, a novel organosoluble sulfated derivative of chitosan was synthesized for the modification of PES membrane in this study. As one of the most important polymeric materials, PES is widely used in separation fields and biomedical fields such as artificial organs and medical devices used for blood purification (Samtleben, Dengler, Reinhardt, Nothdurft, & Lemke, 2003; Zhao & Li, 2001); however, the blood compatibility of PES membrane was not adequate. Ran et al. (2011) modified PES membrane by blending an amphiphilic triblock co-polymer, Sperling, Houska, Brynda, Streller, and Werner (2006) coated albumin–heparin multilayer coatings on PES membrane by layer-by-layer technique, and Fang et al. (2009) grafted bovine serum albumin onto the surface of PES/poly (acrylonitrile-co-acrylic acid) blended membrane to improve the blood compatibility. It is well accepted that blending is the simplest way to modify PES membranes compared with other methods, and thus widely used in industrial fields.

In the present study, a novel sulfated derivative of chitosan was synthesized through a simple method. Then, the sulfated derivative of chitosan was used as a macromolecular additive for direct blending with PES to prepare modified PES membranes by a phase inversion technique, and the surface properties (surface compositions and water contact angles), blood compatibility (protein adsorption, platelet adhesion and clotting time)

* Corresponding author. Tel.: +86 28 85400453; fax: +86 28 85405402.
E-mail addresses: stephen9988@126.com (S. Sun), zhaochsh70@163.com, zhaochsh70@scu.edu.cn (C. Zhao).

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http://dx.doi.org/10.1016/j.carbpol.2013.02.033

and the ultrafiltration property of the modified membranes were investigated.

2. Experimental

2.1. Materials

PES (Ultrason E6020P) was obtained from BASF, Germany. *N*,*N*-Dimethylacetamide (DMAc) (AR, 99.0 wt.%) and *N*,*N*-dimethylformamide (DMF) (99.0 wt.%) were purchased from Chengdu Kelong Inc. (China), which were purified with vacuum distillation over CaH_2, and used as the solvents. Bovine serum albumin (BSA) and bovine fibrinogen (BFG) were obtained from Sigma Chemical Company. Chitosan (C) (M_w: 60 kDa; DD: 90%; the deacetylation degree (DD) of chitosan samples was determined by alkalimetry) was obtained from Shanghai Bio Science & Technology Corp. (China). *O*-Phthalic anhydride was purchased from Chengdu Kelong Inc. (China). Spectra/Por Dialysis membrane (MWCO 8000–14,000) was purchased from Chengdu Kebite Biotechnologies Co. Ltd. (China). All the other chemicals (analytical grade) were obtained from Chengdu Kelong Inc. (China), and were used without further purification.

2.2. Synthesis and characterization of the derivative of chitosan

2.2.1. Synthesis of phthaloylated chitosan and sulfonated phthaloylated chitosan derivatives

O-Phthalic anhydride (3.6 g) and chitosan (2 g) were dissolved in 40 mL of mixed solvent (DMF/water, 97/3, v/v), and the reaction was performed at 120 °C under nitrogen atmosphere with stirring for 5 h. Then, the resulting mixture was cooled to room-temperature and diluted with DMF (20 °C); After that, the solution was centrifugated at 8000 rpm for 10 min to remove the insolubles, the supernatant solution was collected and dialyzed against ethanol for 72 h, and then against double distilled water for 72 h; the resulting suspension was freeze-dried. Then organic soluble chitosan (OC) was obtained. In order to investigate the effect of the phthaloylation on the degree of sulfation, the reaction was also conducted in DMF without water, and the product was marked as OC1.

Chlorosulfonic acid, the most commonly used sulfating reagent, was adopted to synthesize the sulfated derivative of chitosan. Chlorosulfonic acid (20 mL) was added dropwise into DMF (20 mL) with stirring at 0 °C under N_2 atmosphere and kept agitating for 1 h; then a solution of OC (0.5 g) and DMF (20 mL) was added. The mixture was reacted under N_2 atmosphere for 24 h at 20 °C. The crude solution was neutralized with 20 wt.% NaOH solution to pH = 7, and dialyzed against double distilled water; then the resulting suspension was freeze-dried, and the final powder was named as SOC. Moreover, SOC1 was synthesized from the OC1 in the same way.

The reaction pathway is shown in Fig. 1.

2.2.2. Characterization

The FTIR spectra were recorded with KBr pellets on a Nicolet-560 spectrophotometer (USA). 32 scans at a resolution of 4 cm^{-1} were averaged and referenced against air.

^1H NMR (400 MHz) spectra were recorded on a Bruker AVII-400MHz spectrometer (Bruker Co., Germany), using tetramethylsilane (TMS) as the internal standard in DMSO-d_6 at room temperature.

Elemental analysis, which is based on the determination of carbon (C), hydrogen (H), nitrogen (N) and sulfur (S), was performed using a CARLO ERBA 1106 elemental analyzer (Italy), with a carrier gas (He, at a flow rate of 100 mL min^{-1}) at a combustion temperature of 1000 °C using the solid samples.

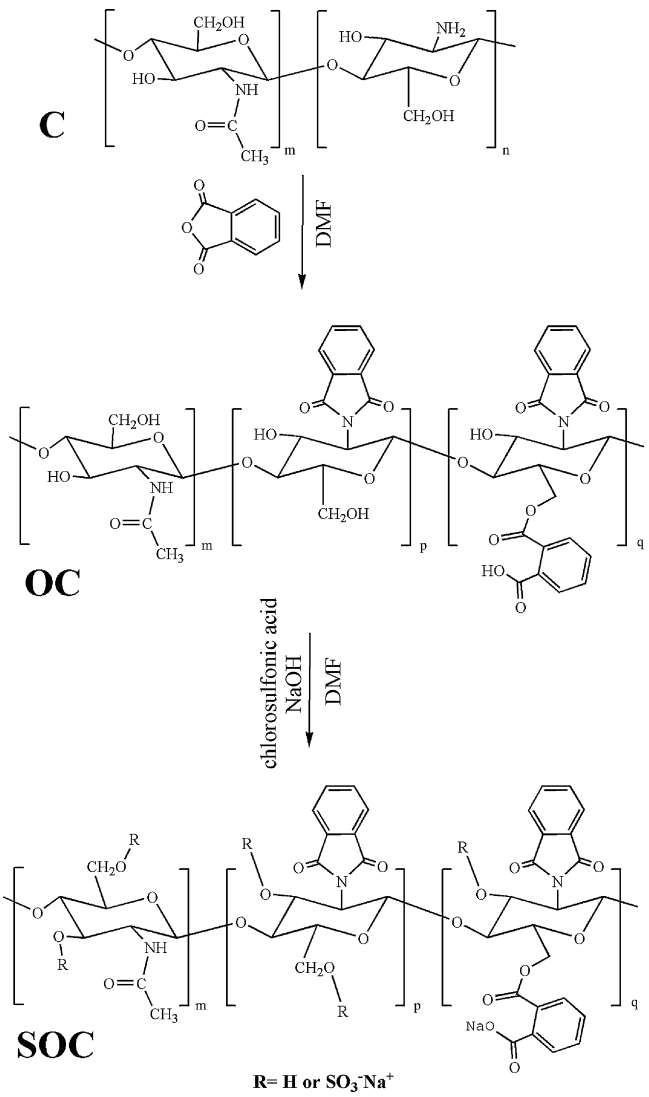

Fig. 1. Mechanism of the synthesis of the sulfated derivative of chitosan (SOC).

X-ray diffraction diagrams were obtained by the powder method with the use of Ni-filered Cu Kα radiation with an X'Pert Pro MPD instrument (Philips, Holland).

2.3. Preparation and characterization of modified membranes

The modified membranes were prepared by a phase inversion technique. PES and the synthesized derivatives of chitosan were dissolved in DMAc by vigorous stirring. In the study, the concentration of PES was kept at 16 wt.%, and the weight percentage of SOC or OC in the casting solutions was varied. The content of SOC/OC in the casting solutions was 0, 1, 2, and 4 wt.% 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 as the method mentioned in the literature (Matsuyama, Nishiguchi, & Kitamura, 2000). The membranes were thoroughly rinsed with distilled water to remove the residual solvent. The prepared membranes with PES/SOC ratios of 16/0, 16/1, 16/2, and 16/4 (wt.%) were termed M0, M1, M2, and M4; the membranes with PES/OC (as control samples) ratios of 16/1, 16/2, and 16/4 (wt.%) were termed P1, P2, and P4, respectively (compositions are shown in supplementary Table S1).

Attenuated total reflection-Fourier transform infrared spectra (ATR-FTIR) for the surfaces of membranes were obtained by a