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Enhanced hemocompatibility of flat and hollow fiber membranes via a heparin free surface crosslinking strategy

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ABSTRACT

Insufficient hemocompatibility is challenging for current dialysis membranes. The current modification methods have some limitations in effectiveness, practicality and cost. Herein, we develop a heparin-free crosslinking approach to enhance the hemocompatibility of both the flat (polylactide) and hollow fiber (polysulfone) membranes with heparin-mimicking surface. Poly (triethoxyvinylsilane-*N*-vinyl-2-pyrrolidone) (P (VTES-VP)) is first introduced to the membrane surface to improve the hydrophilicity, which is facilitated to the adsorption and further crosslinking of poly (triethoxyvinylsilane-Acrylic acid-Sodium 4-vinylbenzenssulfonate) (P(VTES-AA-SSNa)). The mixture of *N*, *N*-dimethylacetamide (DMAc) and water was modulated for good solubility, swelling and adsorption of precopolymer. The chemical structure of the heparin-mimicking membrane was confirmed by attenuated total reflectance Fourier transform infrared spectra (FTIR-ATR), X-ray photoelectron spectroscopy (XPS), weight measurement and scanning electron microscopy (SEM). The hydrophilicity was improved by the heparin-mimicking surface. Moreover, the heparin-mimicking membranes presents higher platelet resistance, prolonged coagulation time (APTT for ~180.1 s), decreased Plasma fibrinogen (FIB for ~122 mg/dL), and suppressed complement activation. More importantly, the heparin-free crosslinking approach can be utilized to significantly enhance the hemocompatibility of commercial PSF hollow fiber membranes, indicating its potential application in heparin free dialyzers.

1. Introduction

Dialysis membranes play an important role in artificial kidneys, which can remove excess water, biological metabolites, endotoxins, and harmful micro molecules from the blood of chronic kidney disease patients [1,2]. The ideal hemodialysis membranes require good hemocompatibility, certain permeability, precise selectivity and performance stability [3]. Poly sulfone (PSF) and polyether sulfone (PES) membranes have been widely used in clinical dialysis [4–6]. However, the long term hemocompatibility remains the biggest challenge. A more biocompatible surface is desired for the current membranes. Poly (lactic acid) hemodialysis membranes have attracted enormous attention recently as an environment friendly material [7]. However, the intrinsic hydrophobicity will cause dialysis complication and blood coagulation when long-term dialysis through the membranes [1]. Typically, continuous administration of heparin is used to prevent dialyzer and circuit clotting [8]. But, it has many adverse effects: bleeding in cases of injury, prolonged and laborious compression of the needle puncture of fistulas, pruritic allergic reactions, and heparin-induced thrombocytopenia [9,10]. Therefore, versatile approaches have been extensively explored to improve the hemocompatibility of the dialysis membranes for the purpose of decreasing or avoiding the heparin usage in hemodialysis [11–14].

In particular, biomolecules e.g. heparin or hirudin can be utilized to modify polymeric membranes which showed improved hemocompatibility due to the bioactivity [12,13,15,16]. However, the high cost of coating or grafting process influences its scalable application in clinic [17]. In addition, the frequent utilization of heparin still cannot avoid the heparin-induced thrombocytopenia [18]. A dramatic loss of bioactivity and degradation in vivo occurs in biological systems due to the covalent or non-covalent bindings with blood components, which results in the lack of stability and durability. Therefore, some anticlotting candidates were synthesized for membrane modification, which are considered as heparin-mimicking polymers [19–21]. The molecule

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designing principle is mainly based on the anticoagulant mechanism that the anticoagulation activity of heparin comes from the carboxyl and sulfonic groups on the macromolecular backbone [22–25]. According to this theory, many heparin-mimicking polymers have been synthesized via free radical polymerization [12,22,26–28]. Blending the heparin-mimicking polymer into the casting solution is an effective method to improve the anticoagulation property [28]. But, it would change the phase inversion process and consequently influence the porous structure and dialysis performances. A more efficient and feasible way is desirable to modify the membrane without influencing the microstructure. Functional polymers, such as poly (vinylpyrrolidone) (PVP) or polyethylene glycol (PEG), can be immobilized on membrane surfaces via a cross-linking treatment [2,29–31]. The precopolymer comprising hydrophilic segments and silane coupling agent was first synthesized and then introduced to the membrane through the swelling, adsorption and crosslinking. The crosslinking of the segment VTES (vinyltriethoxysilane) can be controlled by the solvent-water interaction and the hydrothermal treatment.

In the study, a heparin-free crosslinking strategy was developed. The PLA membrane was first modified by P(VTES-VP) to produce a hydrophilic surface, which is crucial to reduce the adsorption of protein. The protein anti-fouling surface prevents the platelet attachment via the bonding between platelet glycoprotein IIa/IIIa receptors and proteins [32–34]. Subsequently, the hydrophilic membrane was modified by an anionic copolymer P(VTES-AA-SSNa) to generate a heparin-mimicking surface. Therefore, a hydrophilic heparin-mimicking was constructed to improve the hemocompatibility. The hydrophilic precopolymer P (VTES-VP) and anionic precopolymer P(VTES-AA-SSNa) was synthesized via a free radial polymerization respectively as schemed in Fig. 1. The formation of hydrophilic layer benefits the adsorption of the anionic copolymer P(VTES-AA-SSNa) through the hydrogen boning interaction. The hemocompatibility was explored by wettability, platelet adhesion, complement activation (C3a, C5a), activated partial thromboplastin time (APTT), Plasma fibrinogen (FIB), thrombin time (TT) and prothrombin time (PT). The antifouling property of the membranes was investigated by the ultrafiltration of BSA solution [28]. The surface crosslinking strategy was implemented on commercial PSf hollow fibers. The resultant membrane showed significantly enhanced hemocompatibility.

2. Experimental

2.1. Materials

Polylactide (PLA, 2003D) was bought from Natural Works. Polyethylene oxide (PEO, Mw 2000), 1-methyl-2-pyrrolidinone (NMP, AR > 99.0%), 1-vinyl-2-pyrrolidone (NVP, AR > 99.0%), Sodium 4-vinylbenzenssulfonate (SSNa, 90%), acrylic acid (AA 99%) and 2, 2-azobis (2-methylpropionitrile) (AIBN, Mw 164.21) were purchased from Aladdin and used without further purification. Vinyltriethoxysilane (VTES, Mw 190.31) and triethyl phosphate (TEP, Mw 182.15) were purchased from Sinopharm Chemical Reagent Co., Ltd. The solvent *N*, *N*-dimethylacetamide (DMAc) was distilled under reduced pressure with calcium hydride (CaH_2) to remove the water. Platelet-rich plasma (PRP) and platelet-poor plasma (PPP) was provided by Ningbo Blood Center, China. The APTT, PT, TT and FIB Kit were purchased from Shanghai Sun Biotech Co., Ltd. PUN-2048A coagulation analyzer was purchased from Beijing perlong New Technology Co., Ltd. Bovine serum albumin (BSA) and NaCl were purchased from Aladdin. C3a and C5a ELISA kits were purchased from Cusbio Biotech Co., Ltd., China. The hollow fiber hemodialyzer (PSF) was purchased from Langsheng Co., Ltd., China.

2.2. Preparation of heparin-mimicking PLA membranes

6.0 g PEO and 18.0 g PLA [7] were dissolved into 76.0 g NMP with stirring speed of 230 rpm for 24 h at 80 °C. After removing air bubbles, the casting solution was casted onto a clean non-woven fabric with a knife's width of 200 μm and then solidified in the water bath at 25 °C. For further modification and characterization, the produced pristine

significantly enhanced hemocompatibility.

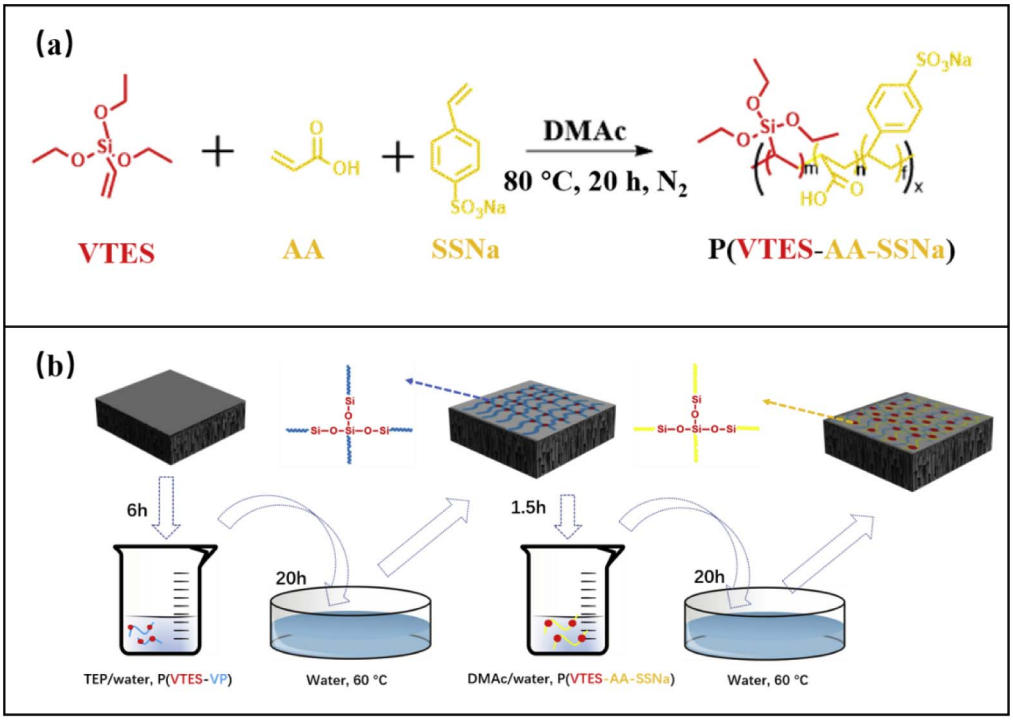

Fig. 1. (a) The synthetic routes of anionic P (VTES-AA-SSNa); (b) The heparin free surface crosslinking process.