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β -Cyclodextrin modified PES hollow fiber membrane, a new strategy for bilirubin separation

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ABSTRACT

The aim of this study was to synthesis and evaluates the capability of modified polyethersulfone (PES) hollow fiber membrane for bilirubin separation from patients' blood. Cyclodextrin (CD) was grafted on the membrane surface via ester bond between hydroxyl groups in CD and sulfonate functional groups on the membrane surface. Surface modification not only improved the membrane hydrophilicity, but also inhibited bovine serum albumin (BSA) and platelets adhesion on the surface. Moreover, the modified membrane could adsorb bilirubin up to 51 mg/g membrane. In conclusion, the proposed system could be a promising candidate to be used instead of resins in hemoperfusion column.

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1. Introduction

Bilirubin (BR) is an oxidative metabolite of heme, which is usually conjugated with glucuronic acid to form a water-soluble complex. Hyper-bilirubinemia happens as a result of high concentration of free bilirubin in blood, which can damage brain cells [1]. Different procedures such as phototherapy, hemodialysis and hemoperfusion were followed to separate free (unconjugated) bilirubin from patients' blood. Among these treatments, hemoperfusion was recognized as an effective and reasonable treatment in which blood is circulated through a column containing appropriate adsorbents to remove excessive unconjugated BR. Different kinds of adsorbents were employed to separate free BR from plasma [2–4]. One of the common adsorbent, which is widely used to separate toxins, was active charcoal. But, due to its poor biocompatibility, it needed to be coated with a biocompatible polymer which consequently could affect adsorption efficiency [5]. Also, anion exchange resins like Dowex I [6] that contain amine groups were good candidates for BR adsorption. However, due to the release of metallic ions during exchange process and influencing the balance of electrolytes in plasma, these resins could not be applicable in hemoperfusion.

In recent years, some researchers focused on employing porous membrane adsorbents in hemoperfusion column instead of particles due to their high mass-transfer efficiency [7,8]. Different

strategies were applied to modify the membranes surface and enhance BR removal [9,10].

Cyclodextrins (CDs) are commercially available cyclic oligopolysaccharides composed of several glucose units. CD molecules structure composed of a hydrophobic cavity surrounded by a hydrophilic outer shell, which enable them to form inclusion complexes with many hydrophobic compounds. CDs were immobilized on polymeric supports and demonstrated to have inclusion ability to adsorb bilirubin [11,12]. Due to the size of β -CD cavity (6–6.5 Å), the pyrrole rings of bilirubin can be accommodated into the cavity [13]. In this study, capability of immobilized β -CD on the PES hollow fiber membrane for bilirubin separation was evaluated. Polyethersulfone was chosen as the membrane material due to its mechanical, thermal and chemical stability [14]. In order to form a covalent bond between β -CD and the membrane surface, sulfonated polyether ether ketone (SPEEK) was synthesized and mixed with PES to form hollow fiber membrane by using the phase inversion technique. Membrane characteristics as well as blood compatibility were studied. The BR adsorption capacity of the modified membrane was also investigated through static adsorption experiment.

2. Experimental

2.1. Materials

Polyethersulfone (PES, Veradel[®] A-301) and β -CD were supplied by Solvay Advanced Polymers (USA) and Merck respectively.

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Polyvinylpyrrolidone (PVP, k90), N-methylpyrrolidinone (NMP), and poly (etherether ketone) (PEEK) were obtained from Fluka and Victrex USA, Inc. respectively.

2.2. Preparation of hollow fiber membrane

PES/SPEEK hollow fiber membranes were fabricated according to our previous publication [15]. The cleaned hollow fiber membrane was soaked in a solution of 10 wt% β -CD for 24 h. CD molecules was immobilized on the membrane surface due to the formation of ester bond between CD and available sulfonate groups on the surface. The surface characteristics of the Hollow fiber membranes were characterized by FTIR (Nicolet-Magna 560 IR

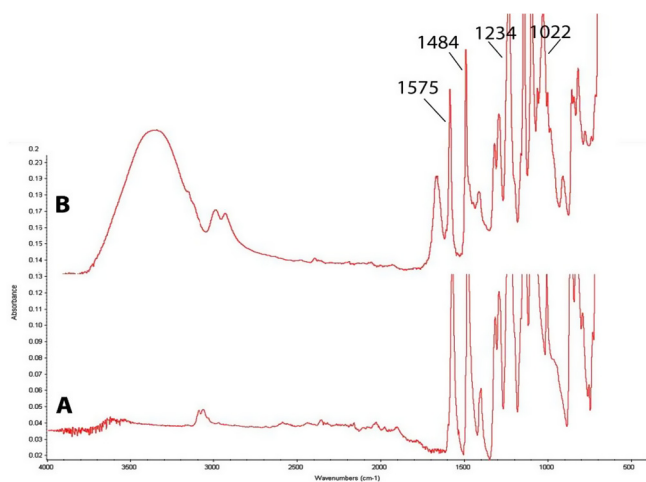


Fig. 1. ATR-IR spectra of (A) pristine PES membrane (B) CD-coated PES membrane.

spectrometer) and contact angle measurement instrument. Morphology of the prepared membranes were observed by SEM microscope (TM3000, HITACHI, Japan) and hemocompatibility was investigated via protein adsorption and platelet adhesion assays.

2.3. Preparation of BR solution

Considering that BR solubility in water is low [16], therefore, NaOH solution (2.5 mL, 0.1 M) was used as the medium to dissolve BR. In order to preserve the pH value of the prepared alkaline suspension [9], phosphate buffer (10 mL, 0.2 M) was mixed with the solution under moderate swirling to obtain a BR buffered solution. Then, 50 mL deionized water was employed to dilute the solution and the final pH was 7.5. The achieved solution was used as stock solution in BR adsorption tests.

2.4. Batch experiments of bilirubin adsorption

Small piece of membrane (15 mg) was soaked in 10 mL bilirubin buffered solution in a covered cuvette. An aluminum foil was used to cover the cuvette to protect the solution from light exposure. The sample was shaken and adsorption capacity of membrane was evaluated in various conditions such as adsorption time and BR initial concentration. The amounts of the adsorbed bilirubin have been measured by using Eq. (1).

$$q = \frac{C_i - C_f}{m} V_s \quad (1)$$

Where q is the quantity of adsorbed bilirubin onto unit mass of the membrane (mg/g); C_i and C_f are the bilirubin concentrations in the initial and in the final solution after adsorption, respectively (mg/l); V is the volume of the bilirubin solution; and m is the mass of the membrane (g). The concentration of unbound bilirubin in the solution was detected by HITACHI 7060 automated analyzer.

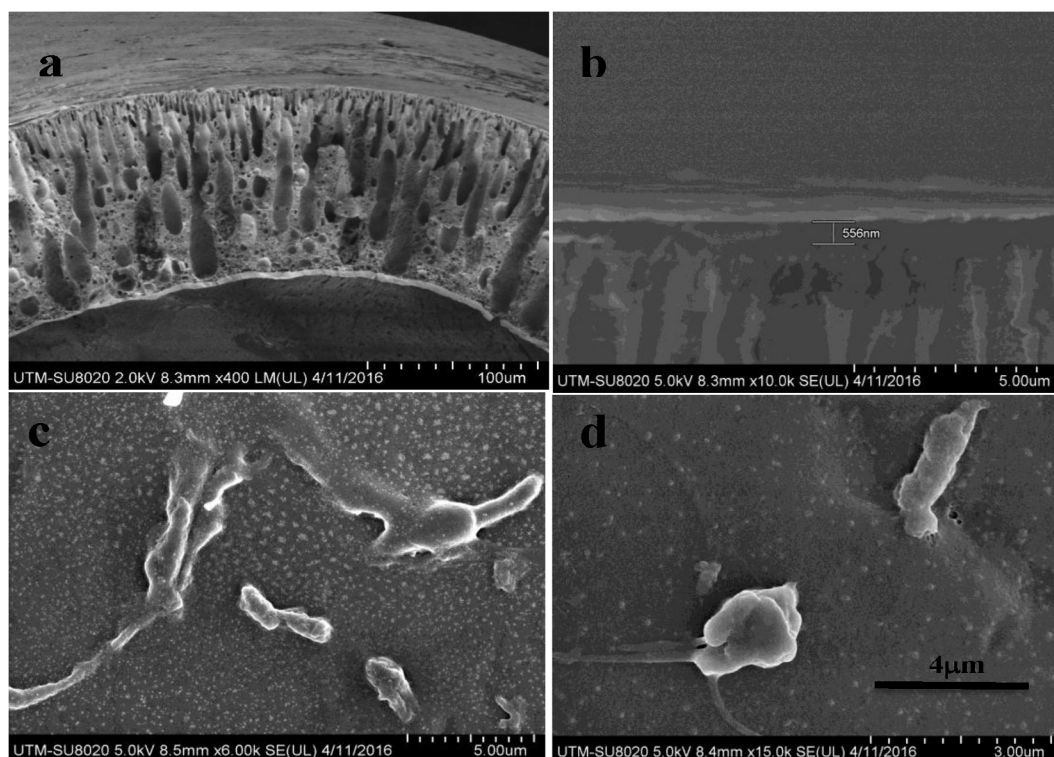


Fig. 2. FESEM images of (a) pristine PES membrane cross section, (b) modified PES membrane cross section, (c) adhered platelets on the pristine PES membrane surface and (d) adhered platelets on the modified PES membrane.

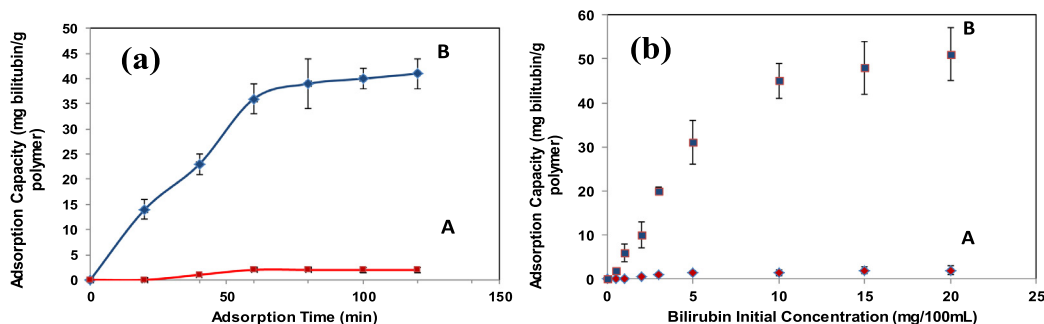


Fig. 3. Effect of (a) time and (b) bilirubin initial concentration, on bilirubin adsorption capacity.

3. Results and discussion

As shown in Fig. 1, IR spectra of the modified membrane exhibited special peak at 3329 cm^{-1} due to the existence of high quantity of OH groups on the membrane surface, which indicate presence of the β -CD molecule, and other CD characteristic peaks were overlapped with PES spectrum. Most of the other peaks on the modified membrane are similar to the pristine.

FESEM images indicated the formation of a thin homogenous layer (556 nm) on the membrane surface after coating procedure (Fig. 2b), which could be assigned to the presence of CD molecules. Additionally, high concentration of OH groups of the CD structures could improve the hydrophilicity of the membrane surface and reduce the contact angle from around 48° to 24° .

Fig. 3a represented the equilibrium adsorption curve within 2 h of incubation. It could be observed that the adsorption rate was faster at the beginning, gradually achieved to equilibrium after around 1 h which means that all the available cyclodextrin cavities on the membrane surface were occupied by bilirubin molecules.

Adsorption of bilirubin at initial concentration of 10 mg/100 mL on the pristine membrane was not remarkable and only about 0.65 mg/g was obtained, but adsorption capacity of the modified membrane was much higher and could reach up to 39.7 mg/g.

As depicted in Fig. 3b, by increasing the initial concentration of bilirubin, amount of the adsorbed bilirubin increased as a result of raising the driving force. In this research, the highest achieved capacity for separation of bilirubin was around 51 mg bilirubin/g membrane, which was quite comparable with most of the novel affinity membranes as presented in Table 1.

Covering the PES membrane surface with β -CD molecules, which improved the interaction of water molecules with the membrane and enhanced the surface hydrophilicity restricted the interaction of proteins and platelets with the membrane surface. Amount of the adsorbed albumin on the surface was reduced from $8\text{ }\mu\text{g}/\text{cm}^2$ to around $5\text{ }\mu\text{g}/\text{cm}^2$ upon surface modification. Moreover,

number of adhered platelets decreased from 3×10^5 to 10^5 cell/ cm^2 after coating procedure, as depicted in (Fig. 2c and d).

4. Conclusions

Coating of PES hollow fiber membrane with β -CD could formed a dense homogenous layer on the surface and improved the membrane hydrophilicity. CD molecules not only could serve as an appropriate ligand for bilirubin separation, but also could improve the membrane surface blood compatibility. The proposed modified hollow fiber membrane could be a high potential candidate to be employed in hemodialysis system as hemoperfusion column.

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Table 1

Comparison of the utmost capacities of membranes for BR adsorption ($q_{BR, m}$).

Matrix	Ligand	Adsorption capacity (mg/g membrane)	References
Alumina	Lysine	32.4	[9]
Nylon	Polylysine	32.4	[17]
PTFE	Cibacron Blue F3GA	63.4	[10]
PHEMA-GMA ^a	PEI ^c	29.7	[18]
EVA ^b	BSA	25	[19]
PES	β -CD	51	This work

^a PHEMA-GMA, poly(hydroxyethylmethacrylate-co-glycidylmethacrylate).

^b EVA, ethylene vinyl alcohol.

^c PEI, poly ethyleneimine.

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