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Original article

Fabrication and evaluation of molecularly imprinted regenerated cellulose composite membranes *via* atom transfer radical polymerization

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ABSTRACT

A simple and effective method for surface molecularly imprinted composite membranes (MICMs) for artemisinin (Ars) based on regenerated cellulose membranes was first prepared through surface-initiated atom transfer radical polymerization (ATRP), and the as-prepared MICMs were then evaluated as adsorbents for selective recognition and separation of Ars molecules. Batch rebinding studies were conducted to determine the specific adsorption equilibrium, kinetics and selective permeation performance. The adsorption capacity of MICMs toward Ars by the Langmuir isotherm model was 2.008 mg g^{-1}, which was nearly 5.0 times higher than non-molecularly imprinted composite membranes (NICMs). The kinetic property of MICMs was well-fitted by the *pseudo*-second-order rate equation. The selective permeation experiments were successfully investigated to prove the excellent selective permeation performance for Ars than the competitive analog (artemether).

1. Introduction

Artemisinin (Ars), a sesquiterpene lactone featuring an endoperoxide bond, is a high-performance antimalarial drug which is found in the interior of trichome glands located superficially on the leaves of *Artemisia annua* L., and is mainly extracted for use as a herbal medicine [1,2]. It has an excellent prospect for development with very important scientific value. Because of its unique structure and antimalarial mechanism, Ars has shown excellent antimalarial efficacy with low toxicity and thus is recommended as an antimalarial drug by World Health Organization (WHO) [3]. Unfortunately, it is not without complications in treating malaria only by herbal infusions due to high variability of the Ars extract from the leaves, which could compromise the efficient recovery of the patient and lead to the development of resistance of the plasmodium for the drug. However, with the rapid increase of market demand, the traditional extraction method is a time-consuming and multistep process in which a large percentage of the Ars is lost at each of these stages reducing yield and thus increasing the cost of the product [4,5]. Therefore, since the administration of Ars in tablet format is essential, it is necessary to find a more effective extraction and purification method.

Molecular imprinting technology (MIT), as one of the most promising methodologies producing molecule-specific recognition sites in synthetic molecular imprinting polymers (MIPs), has already demonstrated its potential for separation and analytical applications and the development of limited applications in different fields [6–8]. Recently, significant attention has been paid to the surface molecular imprinting technique (SMIT) based on the surface modification of polymeric membranes. The combination of the MIT and the membrane technique has provided membrane-specific selectivity and permeation for the separation of target analytes [9–11]. Molecular imprinting layer can be formed on the surface of the porous membrane with optimized flux *via* an interfacial polymerization technique. Herein, the imprinted membrane technique can not only overcome disadvantages, but also can endow the imprinted membrane with robust and self-supporting properties [12]. Among the many membranes successfully used in membrane separation technology, the affinity or adsorptive membranes, which have functional groups on the membrane surface, has been experiencing an increasing growth in applications, such as in biomedical, biochemical and environmental fields [13,14]. It has been reported that the conventional adsorptive membranes were usually prepared by surface modification [15–17].

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Recently, regenerated cellulose (RC) membranes have found extensive commercial applications in membrane separation processes, because of their relatively low cost, good compatibility with biological compounds and their remarkable hydrophilic properties [18]. It is worth noting that utilizing abundant plant cellulose as a source material can not only reduce loss of limited petroleum resources, but also protect the environment. Among the various membrane surface modification methods, surface-initiated atom transfer radical polymerization (ATRP) is a relatively new method [19]. Thus, the hydroxyl groups can be used in surface-initiated polymerization on RC membranes to achieve the immobilization of the ATRP initiator on membrane surface. In comparison with other grafting methods, ATRP offers some advantages: the initiator is anchored on the membrane surface in advance, and the initiated polymerization of the monomers only happens on the surface. Also, the end of the molecular chain is still active after grafting, which can also initiate other monomers to polymerize.

In this article, molecular imprinting composite membranes (MICMs) for Ars onto the surface of RC membranes *via* ATRP method was first prepared by using acrylamide (AM) as monomer, Ars as template, and ethylene glycol dimethacrylate (EGDMA) as cross-linker, respectively. The characterization, adsorption capacity, kinetics and selectivity of the MICMs were investigated in detail. The MICMs for Ars show high adsorption capacity and good selectivity for Ars.

2. Experimental

Regenerated cellulose (RC) membranes (average pore diameter of 0.45 μm, 25 mm in diameter, 100 μm thick) were purchased from Sartorius. Artemisinin (Ars, 98%), anhydrous tetrahydrofuran (THF, 99.9%), acrylamide (AM, 99.9%), ethylene glycol dimethacrylate (EDGMA, 98%), 2-bromoisobutyryl bromide (2-BIB), *N*,*N*,*N*′,*N*″,*N*″-pentamethyl diethylenetriamine (PMDETA, 99%) and acetic acid (AR) were supplied by Aldrich-reagent (Shanghai). Triethylamine (TEA, AR), ethanol (AR) and methanol (AR) were obtained from Sinopharm Chemical Reagent Co., Ltd. (Shanghai). CuBr was washed with dilute hydrochloric acid and acetone repeatedly, and then dried under vacuum. HPLC grade water was obtained from Sigma–Aldrich. All of the above reagents were analytical grade or better. Doubly distilled water was used for preparing all aqueous solutions and cleaning processes. The ATRP initiator could be immobilized on the surface of the RC membranes by reaction with the hydroxyl groups of the membranes. Because of the emergence of nitrogen element from the EGDMA and AM, the imprinting membranes could also be further analyzed by using XPS. Analysis was carried out with an ESCALAB 250 spectrometer using a monochromatic Al Kα X-ray source. The morphology of the MICMs was observed by using the scanning electron microscope (SEM, JSM-6360LV, JEOL, Japan).

A piece of RC membrane which was pre-wetted in methanol to remove resin and was then washed with doubly distilled water and triethylamine (1.0 mL), were added to anhydrous THF (30 mL) in a three-neck round-bottom flask (100 mL). After the reaction mixture was degasses three times with high-purity nitrogen for 20 min, 2-BIB (1.0 mL) was added dropwise to start the reaction for 2.0 h in an ice bath. The mixture was vibrated at 25 °C for 12 h under the protection of nitrogen to obtain RC membrane@initiator. The membrane was then removed from the reaction mixture and washed thoroughly with THF and then HPLC water.

Ars (1.0 mmol) and AM (4.0 mmol) were dissolved in 50 mL ethanol in a 250 mL flask in accordance with the proportion of 1:4. After ultrasonic treatment for 30 min, the mixed system was incubated for 24 h to allow Ars molecules and AM molecules to form stable complexes. And then 20 mmol of EDGMA, a piece of membrane with anchored initiator, was added to the above complex system. Before polymerization, the flask was flushed with nitrogen for 30 min, then 0.1 mmol of CuBr and 0.2 mmol of PMDETA were added to the flask under the protection of nitrogen. The time of the ATRP process was 12 h with the reaction carried out at 50 °C. The membranes were then extracted with ethanol/acetic acid (9:1, v/v) in a Soxhlet apparatus to remove non-grafted polymer, residual initiator and the template. As the control, non-imprinted composite membranes (NICMs) were prepared simultaneously without adding the template molecules. After drying, the membranes were weighted again and the degree of graft modification (DG) was calculated from mass differences. The variations of DG values for preparations repeated in triplicate were $\leq$10%.

3. Results and discussion

This study focused on the application of ATRP in the preparation of Ars-imprinted RC membranes. Fig. 1 illustrates the synthesis routes of MICMs. Firstly, for the surface-initiated ATRP of molecular imprinted polymerization on the RC membranes, 2-BIB, triethylamine and membranes were added into anhydrous THF. The reaction between 2-BIB and the hydroxyl groups on the membrane surface was run for 12 h. Subsequently, AM was adopted to be functional monomer based on the consideration that the amido group of AM and the lactone group of Ars could provide multiple hydrogen-binding sits. In this work, the mol ratio of template and monomer was chosen 1:4, and EGDMA, as a cross-linking agent, was chosen to participate in the polymerization reaction. The polymerization was induced by the initiating radicals, which were stemmed from the reaction between an alkyl halide (2-BIB) and a transition metal complex (Cu^{+}/PMDETA) in its lower oxidation state. The equilibrium between the dormant species (alkyl halides) and active species (radicals) can be quickly established soon after the initiation of polymerization, which is crucial for the achievement of the controlled polymerization. Moreover, the ATRP time of 12 h at 50 °C was used for the preparation of the MICMs.

There was no obvious difference between MICMs and NICMs. The DG values for the MICMs and NICMs are 145 mg g^{-1} and 136 mg g^{-1}, respectively, indicating the presence of a polymer layer. Fig. 2a shows an XPS wide-spectrum for an initiator-functionalized membrane. The spectra around 70 eV (top right insert of Fig. 2a) were recorded as Br3d spectra, indicating that the initiator had been anchored on the membrane surface. Fig. 2b is the XPS wide-spectrum for Ars imprinted membranes. The spectra around 400 eV were recorded as N1s spectra (top right insert of Fig. 2b), pointing out that the polymerization had been carried out due to the existence of N1s from the cross-linker (EGDMA) and functional monomer (AM). The atomic compositions of raw, functionalized membranes and MICMs are given in Table 1.

Membrane morphology was examined by SEM. From the cross-sectional images (Fig. 3a and b), it is apparent that MICMs had the same asymmetric structure as RC membrane, demonstrating the robust RC membrane substrate made the imprint composite membrane stable and self-supported. The introduction of imprinted layer onto the membrane surface not only created imprinted sites as a result of surface chemistry change, but also altered the surface morphology of the membrane. It was evident that the surface of the Ars imprinted membrane was covered by a thin, imprinted layer after the polymerization process compared with the raw RC membrane (Fig. 3c and d).

To evaluate the adsorption capacity of the MICMs for Ars and the equilibrium constants, the adsorption isotherm experiments were performed at the different Ars concentrations ranging from 5.0 mg L^{-1} to 25 mg L^{-1}. A high-performance liquid