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Effects of membrane surface chemistry on fouling investigated using self-assembled monolayers

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ABSTRACT

Fouling is one of the key factors limiting the application of membrane processes. Recent studies have demonstrated that membrane fouling can be reduced by various surface modification techniques. However, the surface modification methods currently available often result in simultaneous changes in other membrane properties (e.g. reduction in pore size, damage to the base membrane, spatial non-uniformity in the degree of modification). These complications pose a challenge to quantitatively identify the key features in the surface modification that are needed to reduce fouling.

Here a controlled surface modification technique without altering other membrane properties was applied to identify the surface chemistry required for developing fouling resistant membranes. We use self-assembled monolayers with various terminal functional groups including acid, alcohol, alkane, and tri(ethylene glycol) on silver membranes to investigate the effects of membrane surface chemistry on protein fouling. This method allows uniform coating of the internal pore structure with a monolayer of the modifier.

The flux decline of the tri(ethylene glycol) terminated SAMs modified membrane is significantly reduced compared to the native membrane during bovine serum albumin (BSA) filtration. Other SAMs modified membranes also showed some minor effects on reducing the rate of flux decline. These results demonstrate a new approach to modify membrane surface chemistry for fouling investigation.

1. Introduction

Membrane processes are widely used in the pharmaceutical and biotechnology industries for sterile filtration, buffer exchange, or purification of proteins. One of the major problems in the use of membranes for bioprocessing is membrane fouling caused by specific interactions between the membrane and proteins. The aggregated protein in the process stream generated by shear or contact with a nonbiocompatible surface causes a decay in filtrate flux and an alteration in membrane selectivity. These problems progress throughout the filtration and eventually require cleaning or replacement of the membrane [1].

Previous studies have demonstrated that fouling can be reduced by membrane surface modification. Membrane surfaces are often modified to increase surface hydrophilicity to minimize protein adsorption [2–8]. Numerous surface modification methods have been reported to enhance membrane fouling resistance. Some common methods for surface modifications include: (i) adsorption, grafting, or crosslinking of a modifier on the membrane surface and (ii) chemical or physical post treatment (e.g., hydrolysis or gas plasma treatment). The interpretation of membrane performance based on data obtained with different modifiers is often complicated by the simultaneous variation in other membrane properties such as damage to the base membrane and non-uniformity in the degree of modification. Crosslinking and chain scission to the base membrane can occur during photo induced grafting [9]. Grafted or adsorbed polymer chains often block the internal pores of the membrane and significantly reduces membrane permeability [2–8]. Membrane permeability is reduced most significant when long polymer chains are attached onto the membrane [10–12]. Existing techniques also nonuniformly modify the surface chemistry of internal pore structures due to absorption of radiation as one moves into the membrane structure. The grafted chain density and chain length is often affected by a variety of factors such as radiation wavelength and addition of chain transfer agent [13]. Thus, identifying the key features in the modification that contribute to the reduced fouling in modified membranes remains a challenge.

Here we demonstrate a new approach to examine the effects of membrane surface chemistry on fouling by modifying the membrane surface with self-assembled monolayers. Alkanethiolates spontaneously adsorb onto metal surface and self-assemble into a semi-crystalline monolayer. SAMs have been widely used in study-

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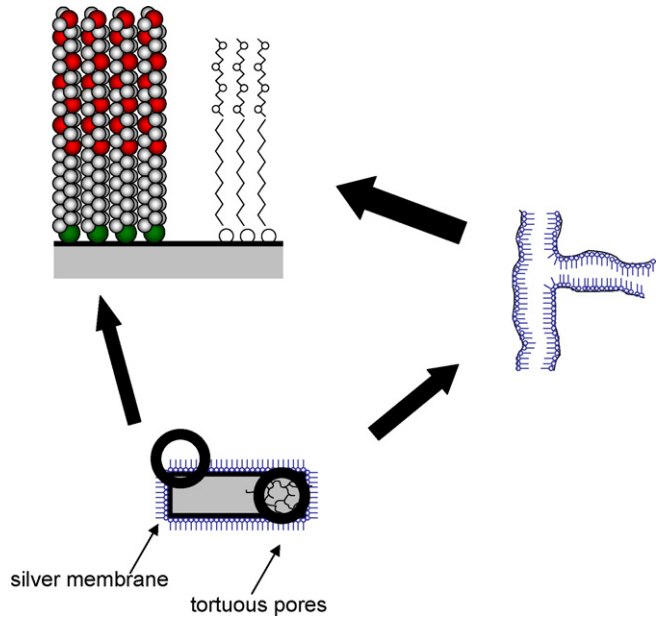

Fig. 1. Schematic of self-assembled monolayers on the surface and internal pore structures of the membrane.

ing the biocompatibility of materials [14], in the development of biosensors, and in cell biology [15–17]. The long term stability, high packing density, and controllable surface functionality of self-assembled monolayers (SAMs) makes them suitable for studying the effects of surface chemistry on protein fouling. SAMs can form on the membrane surface and inside the membrane pore structures as shown in Fig. 1. The thickness of SAMs formed is on the order of 2 nm and has minimal effects on the size and structure of membrane pores.

Polyethylene glycol (PEG) has been widely used as a modifier to coat the surface of biomaterials to prevent adhesion of biomolecules and improve the biocompatibility of materials. The resistance of PEG to the adsorption of proteins is due to its hydrophilicity, molecular conformation [18–20], and tightly bound water on the oligo(ethylene glycol) moieties [21]. Previous studies have successfully grafted PEGs onto polymer membranes using low temperature plasma [22] and UV [4] and demonstrated its potential to reduce protein fouling. However, the degree of grafting using this technique is varied with different chemical modifiers. Here, we modify the silver membrane by attaching SAMs with various terminal groups such as alcohol, acid, alkane, and tri(ethylene glycols). Flux decline during bovine serum albumin (BSA) filtration is recorded to investigate the role of surface chemistry on protein fouling.

2. Materials and methods

2.1. Materials

All experiments were performed with 25-mm diameter silver membranes with pore size rating of 0.45 μm (Product number AG45 025 50, Millipore, Billerica, MA). 1-Undecanethiol, 11-mercaptoundecanoic acid, and 11-mercapto-1-undecanol were obtained from Sigma–Aldrich (St. Louis, MO). (1-Mercaptoundec-11-yl)tri(ethylene glycol) were synthesized with a three-step synthesis starting with 11-bromoundec-1-ene [23]. A general strategy for the conversion of a haloalkene to an oligo(ethylene glycol)-terminated alkanethiol is shown in Fig. 2. Briefly, in the first step, 10 equiv. of oligo(ethylene glycol) is treated with a slight excess of 50% aqueous sodium hydroxide. The mixture is heated to 100 °C under argon while being stirred. After 30 min, 1 equiv. of an 11-haloundec-1-ene is added. The mixture is stirred at 100 °C under argon for 24 h. The reaction takes place as a phase transfer reaction (Gibson, 1979). After the first step in the reaction scheme the product is an oligo(ethylene glycol)-terminated alkene. To transform the alkene to a thiol is a two-step procedure: first, the alkene is photochemically reacted with thiolacetic acid to form a thioacetate. In order to prevent oxidation of the thiol to the disulfide, methanolysis is carried out using sodium methoxide in methanol and then neutralizing the reaction mixture. Once the thiol is formed, it can be stored under argon in a freezer for up to 3 months before appreciable disulfide formation occurs.

2.2. Membrane modification with self-assembled monolayers

Silver membranes were cleaned prior to use by soaking the membrane in a concentrated sodium hydroxide solution for 10 min to remove any oxide layer. The membrane was then rinsed with water followed by ethanol and dried in a stream of argon gas. To form self-assembled monolayers on the silver membranes, a 2 mmol of the desired alkanethiol was dissolved in 500 mL of absolute ethanol (Aaper Alcohol and Chemical Company, Shelbyville, KY). A silver membrane was placed in a 25 mm diameter ultrafiltration cell (Amicon model 8010) connected to a solution reservoir filled with 500-mL of the alkanethiol solution. The pressure was set at 10 psi to force 250 mL of the alkanethiol solution to pass though the membrane. The pressure was then decreased to 1.5 psi and the remaining solution was allowed to pass though the membrane. The membrane was carefully removed from the stirred-cell holder and dried completely using argon and minimized exposure to oxygen. The modified membranes exhibited a color change and a distinctive thiol smell. The membranes before and after modifications were imaged using Hitachi FEG SEM and Oxford energy dispersive X-ray spectroscopy analysis (EDS).

2.3. Filtration experiments

Phosphate-buffered saline solution (PBS) consisting of 0.03 M KH_2PO_4, 0.03 M $Na_2HPO_4{\cdot}7H_2O$, and 0.03 M NaOH was prepared by dissolving pre-weighed quantities of the appropriate salts (Sigma, St. Louis, MO) in the desired volume of water obtained from a Millipore Milli-Q Biocel A10 system (Millipore, Billerica, MA) with resistivity greater than 18 MΩ cm. The PBS was then vacuum-filtered through a 0.1-μm pore size Supor® membrane (Gelman Science, Inc., Ann Arbor, MI) to remove any large particulates. Finally, the solution pH was measured to within 0.01 pH units using an Oakton® Acorn™ pH 6 meter (Fisher Scientific, Pittsburg, PA) and adjusted to 7.4 by addition of NaOH if necessary.

Prior to protein filtration, the hydraulic permeability of the modified membranes were quantified by measuring the flux of PBS solution (J) through the membrane as a function of transmembrane pressure drop (ΔP) and evaluated by

$$L_p = \frac{\mu J}{\Delta P} \quad (1)$$

Filtration experiments were conducted using bovine serum albumin (BSA, Sigma catalog number A7906) as a model protein. BSA (2 g/L) was dissolved without stirring in PBS. All BSA solution was used within 8 h of preparation. After the hydraulic permeability measurement, the stirred cell and the reservoir were emptied and filled with BSA solution. The height of the reservoir was set to provide a hydrostatic pressure of 2 psi. For the first 40 min of the filtration experiment, flux measurements were made every 2 min by timed collection using a digital balance. From 40 min to 120 min, flux measurements were carried out every 5 min.