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Regular Article

A versatile approach towards multi-functional surfaces via covalently attaching hydrogel thin layers

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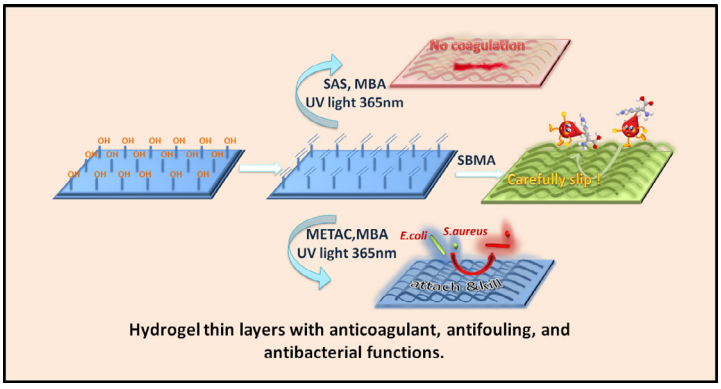
GRAPHICAL ABSTRACT



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ABSTRACT

In this study, a robust and straightforward method to covalently attach multi-functional hydrogel thin layers onto substrates was provided. In our strategy, double bonds were firstly introduced onto substrates to provide anchoring points for hydrogel layers, and then hydrogel thin layers were prepared via surface cross-linking copolymerization of the immobilized double bonds with functional monomers. Sulfobetaine methacrylate (SBMA), sodium allysulfonate (SAS), and methyl acryloyloxygen ethyl trimethyl ammonium chloride (METAC) were selected as functional monomers to form hydrogel layers onto polyether sulfone (PES) membrane surfaces, respectively. The thickness of the formed hydrogel layers could be controlled, and the layers showed excellent long-term stability. The PSBMA hydrogel layer exhibited superior antifouling property demonstrated by undetectable protein adsorption and excellent bacteria resistant property; after attaching PSAS hydrogel layer, the membrane showed incoagulable surface property when contacting with blood confirmed by the activated partial thromboplastin time (APTT) value exceeding 600 s; while, the PMETAC hydrogel thin layer could effectively kill attached bacteria. The proposed method provides a new platform to directly modify material surfaces with desired properties, and thus has great potential to be widely used in designing materials for blood purification, drug delivery, wound dressing, and intelligent biosensors.

1. Introduction

Many polymers, such as polyether sulfone (PES) [1], poly(ethylene terephthalate) (PET) [2], poly(lactic acid) (PLA), polytetrafluoroethylene (PTFE) [3], cellulose acetate (CA) [4], polyvinyl chloride

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(PVC), and polyurethane (PU) [5], have been widely used in biomedical fields such as blood purification [6], vascular graft [7], biosensor [8], guided tissue regeneration membrane [9], and would dressing [10]. However, the original properties of these materials, such as antifouling property, blood compatibility, and antibacterial property are unideal for some specific applications. Thus, various techniques have been developed to enhance their surface properties and/or endow them with multi-function, such as surface plasma treatment [11], surface grafting [12], surface coating [13], and physical blending [14,15]. However, some inherent drawbacks of these techniques have been recognized: (i) for surface plasma treatment and surface grafting, the modification efficiency is sometimes restricted by the insufficient introduced functional groups and their non-uniform distribution [16]; (ii) for surface coating, the long-term stability is the main drawback due to the weak force between the functional polymer and substrate [17]; (iii) for physical blending, the immiscibility between the functional polymer and substrate may limit its application.

Addressing the above mentioned issues, much attention has been emphasized on physically or chemically attaching hydrogel thin layers onto substrates to improve the surface properties [18–20]. Bulk hydrogels have been widely used in many fields, such as contact lenses, drug delivery systems, biochips, biosensors, for their outstanding biocompatibility and resemblance to biological tissues [21–23]. Chemically attaching 3D porous hydrogel thin layers onto substrates can not only take the advantage of the hydrogel layers to enhance the surface properties, but also offset the poor mechanical strength of the hydrogel thin layers. Compared with conventional surface modification methods, chemically attaching hydrogel thin layers onto substrates presented several highlights [24]: (i) the long-term stability was reliable because the hydrogel layers were bonded onto substrates via multiple anchoring points [25]; (ii) the modification efficiency was guaranteed by the sufficient functional groups [26]; (iii) many bioactive agents can be easily loaded into the hydrogel layers to confer the substrates with multi-function [27–29].

Obviously, the key process for stably attaching hydrogel layers onto substrates is to create sufficient anchoring sites for the hydrogel layers, and many methods have been developed. For example, Zhang et al. immobilized isopropyl thioxanthone semi-pinacol (ITXSP) dormant groups onto polycaprolactone (PCL) film surface as anchoring sites of hydrogel layer [30]. Yuk et al. introduced double bonds onto various solid surfaces as anchoring sites by the reaction of silane 3-(trimethoxysilyl) propyl methacrylate and the surface hydroxyl groups [31]. Chollet and Yang both immobilized 3-mercaptopropyl trimethoxysilane onto substrates to introduce —SH groups as anchoring sites, and then hydrogel layers were grafted through thiol-ene click chemistry [19,32]. Zhao et al. synthesised PES-*b*-PHEDMA block copolymer to introduce hydroxyl groups onto PES membrane surface by blending, and then double bonds were grafted onto the surface as anchoring sites by the reaction of methacryloyl chloride and the introduced hydroxyl groups [33]. Boere et al. introduced methacrylate groups as the side groups of poly(hydroxymethylglycolide-co-ε-caprolactone), and then blended with PCL to provide double bonds as anchoring sites for hydrogel layer [34]. In our previous studies, *in situ* cross-linking polymerization was employed to fabricate PES composite membranes with various properties [35,36]. We proposed that sufficient hydroxyl groups would be introduced onto PES membrane surfaces via *in situ* cross-linking polymerization of HEMA, and then provide anchoring sites for fabricating hydrogel thin layers.

In this study, PES was selected as model substrate, while sulfobetaine methacrylate (SBMA), sodium allysulfonate (SAS), and methyl acryloyloxygen ethyl trimethyl ammonium chloride (METAC) were selected as model functional monomers to endow PES membrane with antifouling, anticoagulant, and antibacterial properties, respectively. In order to provide anchoring sites for hydrogel layers, hydroxyl groups were firstly introduced onto PES membrane surface via *in situ* crosslinking polymerization of HEMA followed with a phase invasion technique, and then double bonds were introduced via the reaction of the hydroxyl groups and acryloyl chloride. At last, the hydrogel layers were formed and simultaneously attached onto the surfaces by cross-linking copolymerization of the introduced double bonds with the monomers at 365 nm UV light. The chemical compositions, surface morphology, and hydrophilicity of the attached hydrogel thin layers were characterized by attenuated total reflectance/Fourier transform infrared spectroscopy (ATR/FTIR), scanning electron microscopy (SEM), atomic force microscope (AFM), and water contact angle measurement. The stability of the attached hydrogel layers was evaluated, and the influence of monomer concentrations on hydrogel layer thickness was also investigated. Meanwhile, the antifouling, anticoagulant, and antibacterial properties were evaluated by protein adsorption, clotting times, and bacteria activity.

2. Materials and methods

2.1. Materials

Commercial polyethersulfone (PES, Ultrason E6020P) was purchased from BASF. 2-Hydroxyethyl methacrylate (HEMA) (98%, CAS No. 868-77-9), sodium allysulfonate (SAS) (99%, CAS No. 2495-39-8), 2-ketoglutaric acid (99%, CAS No. 328-50-7), lysozyme (LYS), methyl acryloyloxygen ethyl trimethyl ammonium chloride (METAC), and N,N′-methylenebisacrylamide (MBA) (99%, CAS No. 110-26-9) were purchased from Aladdin Chemistry Co. Ltd. Sulfobetaine methacrylate (SBMA) was synthesized according to our previous reported procedures [37]. N-methyl-2-pyrrolidinone (NMP) (AR, CAS No. 872-50-4) and azo-bis-isobutryonitrile (AIBN) ($C_8H_{12}N_4$, AR, CAS No. 78-67-1) were purchased from Chengdu Kelong Inc. (Chengdu, China), and used as received. Thiethylamine (98%, CAS No. 121-44-8) and acryloyl chloride (99%, CAS No. 814-68-6) were purchased from Best-reagent Inc. Bovine serum albumin (BSA) and bovine serum fibrinogen (FBG) were obtained from Sigma Chemical Co. Ltd. Micro BCA™ Protein Assay Reagent kit was purchased from PIERCE Inc. Activated partial thromboplastin time (APTT) reagent, thrombin time (TT) reagent, Owren's Veronal Buffer, and Factor XII-deficient plasma were purchased from SIEMENS Co. Ltd. Deionized water was used throughout the experiments.

2.2. Membrane preparation

Firstly, hydroxyl groups were introduced onto PES membrane surface via *in situ* cross-linking polymerization of HEMA in PES solution, followed by spin coating coupled with a phase inversion technique. A typical procedure was as following: 9.6 g PES (16 wt.% of the total solution) was dissolved in 40 g NMP to get a homogeneous solution; then a mixture of HEMA (1.8 g, 3 wt.% of the total solution), AIBN (1 mol% with respect to HEMA), MBA (1.5 mol% with respect to HEMA) and NMP was added into the PES solution. Cross-linking polymerization was carried out at 70 °C for 5 h under nitrogen atmosphere with mechanical stirring (300 rpm). The solution was then exposed in air at room temperature to terminate the polymerization. After degassing the air in the solution, the casting solution was spin coated on a glass surface, and then immersed into deionized water. The prepared membrane was washed by deionized water for several times and stored in deionized water for one week before use, and termed as PES-OH.

To obtain double bond enriched PES membrane, fifty pieces of dry PES-OH membranes with the area of 1×1 cm^2 for each piece were immersed into 50 mL diethyl ether solutions with 4 mL