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Full Length Article

Fabrication of robust biomimetic coating by integrated physisorption/chemical crosslinking technique

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ABSTRACT

Intrinsic hydrophobicity of polymeric biomedical devices generally causes adverse complications (i.e. thrombosis formation). In this study, biomimetic surface modification is conducted on different hydrophobic substrates (PP, PET and PTFE) by physisorption and subsequent UV induced chemical crosslinking of a ternary methacrylate copolymer bearing phosphorylcholine (PC), cholesteryl (Chol) and azidophenyl (Az) side groups, poly (MPC-*co*-CMA-*co*-AzMA) (PMCA). X-ray photoelectron spectrophotometer (XPS), atomic force microscopy (AFM) and water contact angle (WCA) measurements are used to monitor the changes in chemical composition, morphology and wetting behavior of the polymeric substrate surfaces before and after surface modification. The protein adsorption and platelet adhesion experiments are also performed to assess its antifouling properties. The results show that the synergistic contribution of physical anchor of Chol groups and chemical crosslinking of Az moieties leads to the formation of a highly crosslinked cell outer membrane mimetic coating with relatively uniform and dense nano-granular surface textures. The resultant PMCA modified surface exhibits greatly enhanced hydrophilicity due to the enrichment of hydrophilic phosphorylcholine moieties on the outer layer of PMCA coating. Particularly, compared with poly(MPC-*co*-CMA) (PMC) and poly(MPC-*co*-AzMA) (PMA) coatings, PMCA coating possesses good surface stability and interfacial adhesion performance. It provides the polymeric substrates with significantly improved antifouling property. The amounts of proteins and platelets adsorbed or adhered on PMCA modified surfaces could be reduced by at least 85% and 97% after incubation for 48 h, respectively. It offers a facile way to fabricate robust antifouling surface for the improvement of the biocompatibility of polymeric biomedical devices.

1. Introduction

Polymeric biomaterials are widely used for implantable medical devices because of their unique physical properties and bulk mechanical performance, including polypropylene (PP), fluoropolymers (PTFE), poly(ethylene terephthalate) (PET), etc. [1–3]. Unfortunately, when these intrinsically hydrophobic surfaces come into contact with blood, the non-specific adsorption of plasma proteins occurs immediately, which in turn influences the activation of the platelet adhesion and further induction of thrombus formation, resulting in a dramatic decrease of device efficacy and safety [4–7]. The extent of such unfavorable interactions at the interfaces of blood–implant is predominantly correlated with the surface properties of polymer-based implants, i.e. surface hydrophilicity and surface charges [3–9]. Therefore, surface modification of polymeric biomaterials has been of intense interest.

Phosphorylcholine (PC) as a highly hydrophilic zwitterion moiety is enriched in the outer surface of the erythrocyte bilayer in the cell membrane [10]. It offers the exceptional antifouling performance to the cell membrane in the bloodstream [11]. Numerous researches have shown that the creation of cell outer membrane mimetic coatings on the surfaces of biomaterials could be used as an effective strategy to suppress the undesirable blood–implant interactions and improve the biocompatibility, owing to the charge neutrality and rapid hydration capacity of the modified surfaces [4,7,12–31].

Chemical grafting of PC-containing polymers is very popular in the development of robust cell outer membrane biomimetic coatings on polymeric biomaterials, since the polymer chains are tethered on the substrate surfaces through covalent bonding [13,15–22]. However, when PC-containing polymers are grafted to a surface, the steric

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hindrance effect usually limits the grafting density, which plays a crucial role in antifouling performance [16,18a,19,20]. Compared to the "grafting to" method, surface initiated polymerization (SIP) often involves the growth of polymer brushes from the initiators immobilized on the surfaces and allows the formation of polymer brushes with higher density and thickness, leading to a better antifouling performance [15,17,18b]. But the immobilization of initiators on polymeric surfaces is very challenging, especially for the inert polymers such as polyethylene (PE), polyprolylene (PP) and poly(tetrafluoroethylene) (PTFE), which often requires harsh and complex activating steps, such as different plasma treatments, ozone oxidation, UV irradiation, oxidative hydrolysis with NaOH/$KMnO_4$ or H_2SO_4/$KMnO_4$, exposure in aqueous LiOH followed by successive reduction of $NaBH_4$ and diisobutylaluminium hydride, etc. [26]. Therefore, a facile and universal approach is desirable for surface modification of inert polymeric biomaterials to achieve a dense and robust biomimetic antifouling coating similar to that prepared by SIP technique.

In this study, taking advantage of strong hydrophobicity nature of cholesteryl (Chol) moieties and well-known nitrene C—H insertion chemistry correlated to azidophenyl (Az) moieties, a ternary methacrylate-based phospholipid copolymer (PMCA) is designed and synthesized through conventional free radical polymerization of 2-methacryloyloxyethyl phosphorylcholine (MPC), cholesteryl methacrylate (CMA) and 2-methacryloyloxyethyl-4-azidobenzoate (AzMA). A simple drop-coating/UV irradiation process is then employed to facilitate the formation of dense and robust cell outer membrane mimetic coating on PP surface (Scheme 1). During the coating formation, strong hydrophobic interactions between Chol moieties and substrate, physisorption among the pendent Chol (and Az) moieties far from the substrate surfaces, and photo-induced intra-/inter-layer crosslinking *via* inserting Az-derived nitrene into the neighboring C-H bonds, are all proposed to take place. The synergistic effect of physisorption anchoring of Chol moieties and chemical crosslinking of Az moieties on coating uniformity, thickness and stability is investigated, with poly(MPC-*co*-AzMA) (PMA) and poly(MPC-*co*-CMA) (PMC) coatings as control. The universality of physisorption and chemical crosslinking of PMCA on other polymeric substrates (i.e. PET and PTFE) is also explored. The *in vitro* cytotoxicity of the obtained biomimetic coating against mouse fibroblasts cell L929 is performed with MTT assay. The protein adsorption and platelet adhesion experiments are employed to evaluate antifouling properties. Moreover, it is also expected to provide an alternative choice for biomimetic surface modification of hydrophobic polymeric biomaterials by avoiding the usage of pre-activation steps and the polymers with complex synthesis procedure or high humidity sensitivity (i.e. silanes) [25,28].

2. Experiment

2.1. Materials

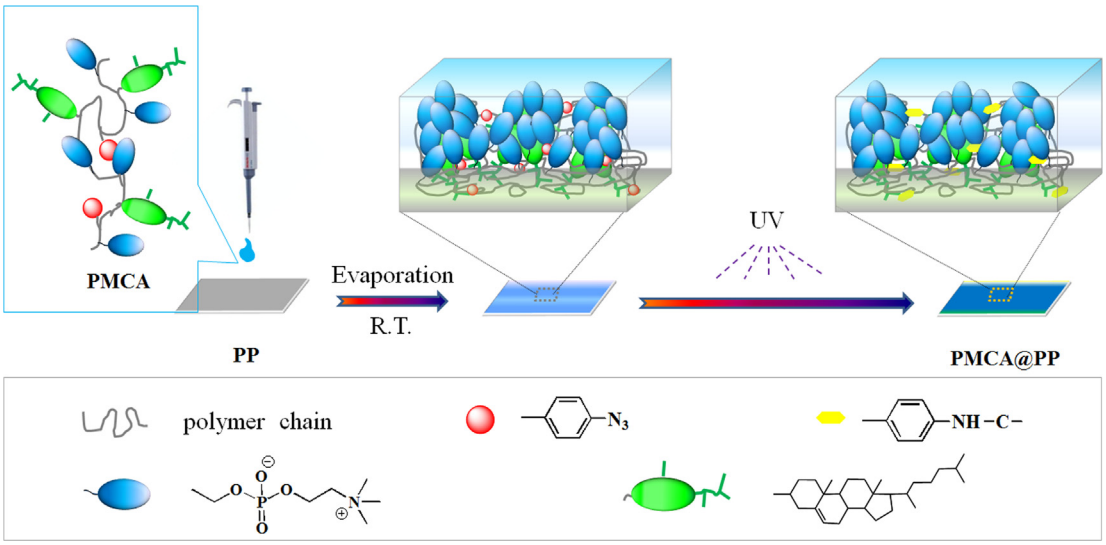
2-Methacryloyloxyethyl phosphorylcholine (MPC), cholesteryl methacrylate (CMA) and 2-methacryloyloxyethyl-4-azidobenzoate (AzMA) were all prepared by previously reported protocols [32,33] (Supporting information, Section S2.1). 2,2-Azobisisobutyronitrile (AIBN, Adamas., China) was used as initiator. Polypropylene (PP), poly(ethylene terephthalate) (PET) and poly(tetrafluoroethylene) (PTFE) plates with thickness of about 0.3 mm were purchased from Zhejiang Hongtai Plastic Products Co., Ltd (China). Deionized water was prepared using a Nanopure diamond filtration system and had a resistivity of 18 MΩ/cm. All the other chemicals were analytical reagents and used as received without further purification unless otherwise addressed.

2.2. Synthesis of poly(MPC-co-CMA-co-AzMA) (PMCA)

Poly(MPC-*co*-CMA-*co*-AzMA) (PMCA) was synthesized *via* conventional free-radical copolymerization of MPC, CMA and AzMA with AIBN as initiator. Briefly, a designed molar ratios of MPC, CMA and AzMA (50:30:20, mol%) were dissolved in a mixed solvent of ethanol (C_2H_5OH) and chloroform ($CHCl_3$) (1:1. v:v) (10 folds of total milimole of monomers). 1.0 wt% of AIBN (with respect to total weight of the monomers) was dissolved in 6 mL of tetrahydrofuran (THF). Then, another 10% of mixed solvent (with respect to the total amount of solvent) and 2 mL of AIBN solution were introduced to a three-necked flask equipped with condenser, thermometer and dropping funnel. Under stirring, the flask was heated to 70 °C after purging with nitrogen for 30 min. The mixture of monomer solution and 4 mL AIBN solution was subsequently added at 70 °C during 3–4 h under N_2. The copolymerization was further performed for about 24 h at 70 °C. The formed polymer was purified by dialysis against the mixed solvent (C_2H_5OH:$CHCl_3$), ethanol and deionized water, successively, until the conductivity of dialysis solution was consistent with deionized water. The molecular weight cut-off value of the dialysis membrane was 6–8 kDa. PMCA was finally achieved as white powders after lyophilization using FD-1A-50 freeze drier (Beijing Boyikang Laboratory Instruments Co. Ltd., China) at −50 °C for 48 h.

Poly(MPC-*co*-AzMA) (PMA) and poly(MPC-*co*-CMA) (PMC) were synthesized with the same procedure and used as control.

The chemical structures of PMCA, PMA and PMC were shown in



Scheme 1. Fabrication of dense and biomimetic coating through physisorption/UV irradiation process.