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Zwitterionic fibrous polypropylene assembled with amphiphatic carboxybetaine copolymers for hemocompatible blood filtration ☆

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ABSTRACT

The present study serves three main functions. First, it presents a novel random copolymer, made of octadecyl acrylate hydrophobic blocks and 2-(dimethylamino)ethyl methacrylate hydrophilic groups, and it zwitterionic form. Second, random copolymer and zwitterionic random copolymer, OmDn and Z-OmDn, are used to modify polypropylene membranes by evaporation coating. Our investigations unveil that this method leads to sufficiently stable self-assembling provided a minimum number of hydrophobic repeat units of 77, which also corresponds to a hydrophobic degree of 74%. Third, antifouling and hemocompatible properties of membranes are thoroughly investigated using all types of blood cells separately, as well as challenging membranes against whole blood in static and dynamic conditions. Membranes modified with zwitterionic copolymer containing 26% of zwitterionic groups are shown to be highly antifouling and hemocompatible, for a coating density as low as 0.2 mg/cm^2. Their application in a specially designed blood filtration module enabled to almost totally inhibit blood cells interactions with membrane material, as well as to importantly reduce platelet activation in the permeate (2.5-fold reduction).

Statement of Significance

The design of new zwitterionic copolymer material is proposed and demonstrated in this study. It was showed that hydrophobicoctadecyl acrylate segments can be introduced in the zwitterioniccarboxybetaine polymer chain with a well-controlled random sequence. Stable, efficient, and effective surface zwitterionization of hydrophobic polypropylene are obtained via *grafting onto* approach by evaporation-induced self-assembling coating. In the perspective of potential application, hemocompatible blood filtration was demonstrated with the excellent results of non-activated platelets obtained.

Summary of Impacts

Design: New zwitterionicmaterial, amphiphatic carboxybetaine copolymers.
Development: Evaporation-induced self-assembling grafting.
Application: Hemocompatible blood filtration.

1. Introduction

Design of antifouling materials is essential in a number of research fields including (i) the development of protective coatings for boats [1–3], (ii) dentistry [4], (iii) membrane engineering [5,7], or (iv) blood contacting devices, since the adhesion of blood cells mediates a number of biological responses eventually leading to

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clotting and so, biofouling and death of cells [8–10]. Therefore, fouling of materials is a major concern in numerous research fields, so that the development of antifouling polymers has grown in importance over the past 15 years.

The essential properties of ideal antifouling material have been presented in the early 2000's by Whiteside groups, and different classes of materials meet these requirements [11]. The most popular one is that constituted by PEGylated materials, with which several approaches exist to modify a polymer surface [12–16]. One can either use (i) surface modification processes [17], (ii) self-assembling process (coating) [18], or (iii) *in situ* modification [19]. The first methods are expensive and difficult to scale-up, but fairly well-controlled at lab scale. The second approach is readily carried out, inexpensive, but lack of stability may arise. Finally, the third approach suffers from lack of knowledge of the potential effect of PEGylated polymer on matrix structuring during elaboration.

The second important class of antifouling materials is that composed of zwitterionic and pseudo-zwitterionic polymers [20–24]. They have become more popular than PEGylated derivatives which may self-oxidized, leading to partial degradation and loss of their nonfouling power. Zwitterionic materials contain electropositive and electronegative sites on the same chain while pseudo-zwitterionic materials, also termed mixed-charge, arise from the combination of an electropositive side chain and an electronegative one on the skeleton of the polymer. Either types of polymers are usually grafted onto or grafted from a surface.

Both types of materials – PEG/zwitterionic and pseudo-zwitterionic – have been successfully applied in the design of antifouling membranes [6,7,19,25–28]. In general, the focus is laid on the evaluation of the resistance to protein adhesion or bacterial attachment as well as on the antifouling properties in dynamic conditions, often during the filtration of bovine-serum-albumin or bacterial solutions [25,29,30]. In other words, water filtration is on target. In comparison, much less work and investigations have been performed on the evaluation of biofouling by human cells including blood cells or skin cells. Yet mechanisms at play during fouling by these cells are pretty similar to biofouling by bacteria, so that deeper investigation should be conducted in this direction to shed light on the potential application of these membranes as scaffold for tissue engineering, wound dressings or materials for blood contacting devices and hemodialysers. Recently, we presented a novel PEG-derivative employed in the *in situ* modification of PVDF membranes, prepared by vapor-induced phase separation (VIPS) process [31]. Membranes were shown to resist both the adsorption of proteins and bacteria found in waters, as well as proteins and human cells found in blood, therefore demonstrating the general antifouling properties of such materials and wide potential range of application. In addition, we have worked on the self-assembling of poly(propylene oxide)-block-poly (sulfobetaine methacrylate) (PPO-*b*-PSBMA) zwitterionic molecules onto polyvinylidene fluoride membranes, and showed that zwitterionic materials could be extremely efficient to make PVDF membranes highly hemocompatible [32]. Polypropylene (PP) is another important membrane material and some recent studies have highlighted its potential as a blood compatible matrix [33–37]. However, their number is marginal, probably because of the difficulty to modify PP. Hou et al. focused on the design of superhydrophobic PP membranes by the so-called Erbil's method proved their hemocompatibility by challenging them with whole blood and platelets [33]. Later, Zhao et al. modified PP microfiltration membranes, grafting [3-(methacryloylamino)propyl]-dimethyl(3-sulfopropyl) ammonium hydroxide by plasma treatment and UV induced grafting polymerization and revealed that modified membranes presented improved platelet resistance [34]. More recently, Li et al. presented a series of work on the modification by γ-ray co-irradiation of polypropylene non-woven fabrics [35,36]. Grafting of N-vinyl-2-pyrrolidone or of both N-vinyl-2-pyrrolidone and sodium styrenesulfonate also led to improved blood compatibility of matrices. Last but not least, Zhang et al. also recently improved the hemocompatibility of PP non-woven fabrics using poly(acrylic acid) polymer and a combination of O_2 plasma treatment and UV-irradiation [37]. These fabrics also showed reduced platelet adhesion and delay of blood clotting time. Therefore, some reference studies exist on the design of hemocompatible PP matrix (mostly non-woven). However, all processes used (γ-ray irradiation, plasma treatment, UV-radiation) are definitely not economically-worthwhile and only controllable at small scale. In addition, researchers have usually concluded on the improved hemocompatibility of their engineered surface by carrying out one kind of blood cell attachment (usually platelets). However blood contains numerous cells and deeper investigations, using red blood cells and white blood cells as potential foulant, should be conducted to conclude on hemocompatibility. Also, only one study, to the best of our knowledge, makes use of a zwitterionic polymer to modify PP membrane for the design of blood compatible membranes [34] but the process is a chemical-surface modification (plasma treatment and UV-irradiation) and blood compatibility tests incomplete.

Therefore, a lot still needs to be done regarding the design of novel zwitterionic materials, their use for surface modification of PP membrane by a facile method, and the assessment of hemocompatibility of such membranes using all types of blood cells as potential foulant. All these uninvestigated directions were the starting point of the present research. We begin this paper with the presentation of the synthesis of a novel random copolymer, OmDn, arising from the combination of octadecyl acrylate hydrophobic blocks and 2-(dimethylamino)ethyl methacrylate hydrophilic groups. Using 3-iodopropionic acid as a reactant leads to its zwitterionic form named Z-OmDn. All the steps of this reaction are well controlled, including the last step leading to the carboxybetaine-derivative. The choice of ODA was based on its long alkyl chain, very likely to interact with polypropylene membrane via hydrophobic–hydrophobic interactions as recently reported in our study on the synthesis of random copolymer made of poly(4-vinylpyrrolidone) and ODA for membrane modification [38]. As sulfobetaine-derivatives, phosphobetaine-derivatives or mixed-charge moieties currently focus most of the attention of researchers designing zwitterionic molecules for nonfouling, the random copolymer used in the present study has never been reported, to the best of our knowledge. Copolymers are then used to modify PP membranes by solvent evaporation. We then get insights into the antifouling properties and hemocompatibility of surface-modified membranes, and discuss the effect of amphiphaticity on the efficiency of zwitterionization reaction as well as on the antibiofouling properties. Finally, we applied our new system in blood filtration and showed that for a particular composition of the copolymer and a certain coating density, the amphipathic copolymer minimized blood cell interactions with membrane material and final platelet activation in the permeate.

2. Materials and methods

2.1. Materials

Octadecyl acrylate (ODA), 2-(dimethylamino)ethyl methacrylate (DMAEMA) and 3-iodopropionic acid (IPA) were purchased from Aldrich (USA). Azobisisobutyronitrile (AIBN) was purchased from Showa (Japan). Chloroform-d, tetrahydrofuran (THF) and toluene, bought from Aldrich, were used as solvent for polymer synthesis or polymer analysis, without further purification. PP membranes were purchased from Millipore, USA. Phosphate

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