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Probing structure–antifouling activity relationships of polyacrylamides and polyacrylates

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ABSTRACT

We have synthesized two different polyacrylamide polymers with amide groups (polySBAA and polyHEAA) and two corresponding polyacrylate polymers without amide groups (polySBMA and polyHEA), with particular attention to the evaluation of the effect of amide group on the hydration and antifouling ability of these systems using both computational and experimental approaches. The influence of polymer architectures of brushes, hydrogels, and nanogels, prepared by different polymerization methods, on antifouling performance is also studied. SPR and ELISA data reveal that all polymers exhibit excellent antifouling ability to repel proteins from undiluted human blood serum/plasma, and such antifouling ability can be further enhanced by presenting amide groups in polySBAA and polyHEAA as compared to polySBMA and polyHEA. The antifouling performance is positively correlated with the hydration properties. Simulations confirm that four polymers indeed have different hydration characteristics, while all presenting a strong hydration overall. Integration of amide group with pendant hydroxyl or sulfobetaine group in polymer backbones is found to increase their surface hydration of polymer chains and thus to improve their antifouling ability. Importantly, we present a proof-of-concept experiment to synthesize polySBAA nanogels, which show a switchable property between antifouling and pH-responsive functions driven by acid–base conditions, while still maintaining high stability in undiluted fetal bovine serum and minimal toxicity to cultured cells. This work provides important structural insights into how very subtle structural changes in polymers can yield great improvement in biological activity, specifically the inclusion of amide group in polymer backbone/sidechain enables to obtain antifouling materials with better performance for biomedical applications.

1. Introduction

Biofouling is defined as the spontaneous accumulation of undesirable proteins, cells, bacteria, and microorganisms on artificial surfaces of medical implants [1–3], drug delivery carriers [4,5], biosensors [6], and ship hulls [7–12]. In most cases, once biofouling occurs, it will irreversibly impair not only the function of biomedical devices through blood clot formation, tissue fibrosis, thrombosis coagulation, and bacterial infection, but also the performance of many industrial applications of nano/microfiltration, membrane separation, pipe corrosion, and ship navigation through biofilm formation. Many polymeric materials including poly(ethylene glycol) (PEG) [13–19], poly(2-hydroxyethyl methacrylate) (polyHEMA) [20], poly(hydroxypropyl methacrylate) (polyHPMA) [21], tetraglyme [6], dextran [22], mannitol [23], glycerol dendron [24], poly(sulfobetaine methacrylate) (polySBMA) [25–27], poly(carboxybetaine methacrylate) (polyCBMA) [28–30], and poly(2-methacryloyloxyethyl phosphorylcholine) (polyMPC) [31–34] have been developed to resist protein adsorption, cell/bacterial adhesion, and biofilm formation. Although these antifouling polymeric materials have different chemical and structural characteristics (e.g. chemical structure, hydrophobicity, charge distribution, geometrical properties, molecular conformation/architecture/sequence/weight, etc.) in both monomeric and polymeric forms, they all possess certain degrees of antifouling capabilities in different biological media. However, the exact structural–property relationship of these antifouling

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materials still remains unclear, which leads to difficulties in fundamental understanding of the role of chemical and structural characteristics in antifouling properties and in practical design of new antifouling biomaterials.

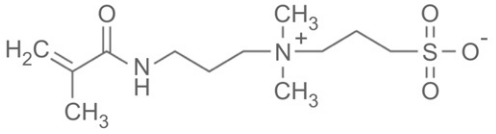
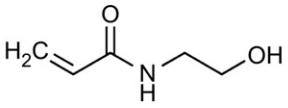
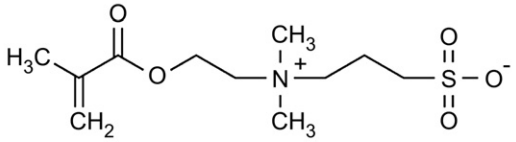
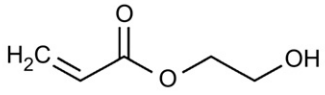
Several mechanisms have been proposed to interpret the resistance of materials to protein adsorption and microorganism attachment on the surface. Considering the fact that all existing antifouling materials contain either hydrophilic or zwitterionic moieties, the "water barrier" theory [14,35,36] suggests that a tightly bound water layer formed around the materials provides a physical and energetic barrier to prevent biomolecule adsorption on the surface. Expulsion of water molecules from the interfacial region between polymers and proteins requires strong surface–protein interactions to compensate solvent entropy loss for protein adsorption. Such tightly bound hydration layer at the polymer interface can be achieved differently, i.e. hydrophilic polymers achieve surface hydration via hydrogen bonds, while zwitterionic polymers achieve hydration via ionic solvation. Due to flexible nature of polymer chains, the "steric repulsion" resulting from the compression of polymer chains as proteins approach the surface is also proposed to be responsible for prevention of protein adsorption [37]. Moreover, adsorption kinetic models highlight the importance of surface density of grafted polymers to resist protein adsorption, presumably because high surface coverage through increased polymer density reduces possible binding sites for protein adsorption on the supporting substrate, resulting in protein resistance [38]. In addition, polymer conformation and architecture were also found to be a key factor to control protein adsorption [39–42]. Despite of different antifouling mechanisms, it is not likely that a single mechanism is solely responsible for the onset of antifouling events, but rather a combination of many. More importantly, underlying intermolecular interactions among proteins, materials, and solvent at atomic level that are not well understood are the key determinant for the macroscopic antifouling performance of the materials. Thus, fundamental understanding of molecular interactions between materials and their surroundings is equally important for rational design of biomaterials.

Recent studies from our and other works have shown that under optimal conditions, both zwitterionic polyCBAA and hydrophilic polyHEAA can achieve similar "zero" protein adsorption from undiluted human blood plasma and serum [28,43]. From a molecular structural point of view, although both CBAA and HEAA monomers have major structural differences in molecular size, surface hydrophobicity, and partial charge distributions, they both possess a common structural motif of an amide group in the backbone. The incorporation of the amide group into the hydroxyl group of HEAA or the carboxybetaine group of CBAA is expected to promote the formation of a hydration layer. In this study, we aim to elucidate the structure–antifouling activity relationship of polyacrylamide and polyacrylate with and without amide groups using combined experimental and computational approaches. The hydration and antifouling abilities in vitro of four different polymers of polySBAA and polyHEAA with amide groups and polySBMA and polyHEA without amide groups (Scheme 1) in polymer brush and hydrogel forms (Scheme 2) was characterized. Additionally, we synthesized polySBAA-based nanoparticles to test the control-release of R6G drugs upon pH-responsive changes by taking advantage of its integrated superlow fouling ability and zwitterionic nature (Scheme 3).

2. Materials and methods

2.1. Materials

[3-(Methacryloylamino)propyl]dimethyl(3-sulfopropyl)ammonium hydroxide (SBAA, 96%), [2-(methacryloyloxy)ethyl]dimethyl-(3-sulfopropyl)ammonium hydroxide (SBMA, 97%), *N*-hydroxyethyl acrylamide (HEAA, 97%), 2-hydroxyethyl acrylate (HEA, 96%), 2-(methacryloyloxy) ethyl trimethyl ammonium (TM, 80 wt.% in H_2O), 2,2′-bipyridyl (BPY, 99%), copper(I) bromide (99.999%), copper(I) chlorine (99.999%), *N*,*N*′-methylene-bis-acrylamide (MBAA), 2-hydroxy-4′-(2-hydroxyethoxy)-2-methylpropiophenone (98%), Span 80 (sorbitan monooleate), Tween 80

Monomer		Molecular Structure
Acrylamide	SBAA	
	HEAA	
Acrylate	SBMA	
	HEA	

Scheme 1. Molecular structures of four monomers used in this work.