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Review

Applications of zwitterionic polymers

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ABSTRACT

Zwitterionic polymers are characterized with equal anion and cation groups on the molecular chains, which make them highly hydrophilic and antifouling. They can resist nonspecific protein adsorption, bacterial adhesion, and biofilm formation. Therefore, they have great potential to be applied in a wide range of biological and medical related fields, such as antifouling coatings of biomedical implants, blood contacted sensor and drug delivery in vivo, separation membrane and marine coatings. The review mainly focuses on the progress of those applications of zwitterionic polymers on the molecular level. Problems existed in these applications are also discussed and the development of in future is prospected.

1. Introduction

Biofouling, such as nonspecific protein adsorption, microorganism adhesion, and biofilm formation, is of the most important phenomena and a huge problem from biosensors, implanted medical devices, drug delivery systems, separation membrane to enormous ship hulls. It causes many problems like haemolysis, thrombosis, anticoagulation-related haemorrhage, immune responses, infection, and tissue overgrowth in implanted devices [1,2]. Biofouling can also increase the voyage resistance by 60% and decreases the voyage rate by 10%. One of the crucial factors affecting fouling is the surface properties because they determine the interaction between fouling substance and the surface.

To address the fouling problem, various hydrophilic polymers, including poly(vinyl alcohol), poly(*N*-vinylpyrrolidone), poly(2-oxazoline) and poly(ethylene glycol) (PEG), and zwitterionic polymers, have been developed to construct the hydrophilic surface, and these polymers can evidently reduce the biofouling on the surface. It should be noted that PEG is a biocompatible polymer and it becomes a gold standard for unfouling polymers [3] because of its high hydrophilicity, non-toxicity, and anti-protein-fouling [4]. However, PEG has poor stability as PEG macromolecular chains can rapidly autoxidize and degrade during storage and handling at room temperature, especially by transition metal ions, which exists in most biological related solution [5–7]. The autoxidation mechanism is a free radical mechanism initiated by minor amounts of free radicals present or catalyzed by metal salts, e.g. copper sulfate [8]. Peroxides and hydroperoxides are the primary oxidation products followed by formation of carbonyl compounds, including ethoxylated formats, formaldehyde, ethoxylated aldehydes, and acetaldehyde, as secondary oxidation products [7,9,10]. It is shown that oligo(ethylene glycol)-terminated SAMs decompose within a week at 45 °C or after 1 month at 20 °C [11], and the decomposition is greatly accelerated by the direct contact between ethylene glycol segments and a catalyst (e.g., gold), oxygen and higher temperatures [12]. PEG brushes lost their antifouling capacity when the temperature rises to 35 °C [13]. Furthermore, it is frequently reported that PEG induced antibodies after repeated injection and PEGylation reduces the bioactivity of conjugated therapeutic proteins, antibodies, and enzymes [14,15]. In addition, PEG cannot be metabolized naturally. These drawbacks greatly limit the application of PEG. Therefore, it is urgently to seek alternative non-fouling material other than PEG.

Zwitterionic polymers are just perfect alternatives for PEG. As compared with amphiphilicity of PEG, zwitterionic polymers are super hydrophilic due to the presence of abundant ions and subsequent strong hydration layer.

Zwitterionic polymers refer to a family of materials that have the same number of cations and anions along their polymer chains. Typical cations are quaternized ammonium, and zwitterionic groups can be classified into sulfobetaine (SB), carboxybetaine (CB), phosphorylcholine (PC) according to anions. Specially, zwitterionic group is SB when anions are sulfonates, CB when anions are carboxylates, and PC when anions are phosphonates. Hydrophilicity of anionic groups decreases with increasing acidity in the order: $-COO-$ > $(RO)_2-P(=O)O^-$ > $-SO_3^-$ [16]. SB based polymers are most promising to be

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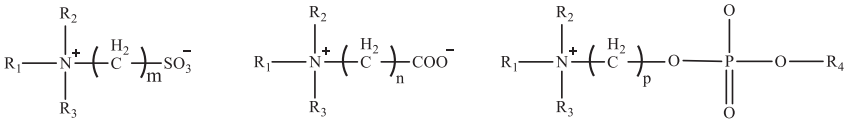
industrialized because it is easy to prepare SB monomers, and some of them are commercially available. CB-based materials have attracted great interests for their advantages over other zwitterionic materials, including their super antifouling properties [17], good biocompatibility [18] and functionability. PC based polymers also have excellent bio and blood compatibilities, but their high production cost hinders its wide application.

As compared with other moieties with no charges, these materials are characterized with both high dipole moments and highly charged groups [19]. Due to the presence of so many cations and anions on the macromolecular chains, zwitterionic polymers are super hydrophilicity, while other polymers such as PEG are amphiphilic with both hydrophilic and hydrophobic properties [3]. It is reported that CB based zwitterions have better unfouling properties than PEG, and their self-assembled micelles have greater stability than PEG analogs during lyophilization [20,21]. The superior antifouling properties of zwitterionic materials in complicated environment were derived from their strong interaction with water via ionic salvation, while the antifouling capacity of PEG was dependent on hydrogen bond with water [22].

Besides their excellent antifouling capacity, zwitterionic materials have various other merits such as ease of functionalization and design flexibility [23]. It has many choices of zwitterions to be chosen from. Especially, as far as PCB is concerned, it can be functionalized by the −COOH groups through the 1-ethyl-3-(3-dimethylamino) propyl carbodiimide (EDC) and *N*-hydroxysuccinimide (NHS) chemistry. Moreover, PCB have many derivatives and their polymer backbones can be (meth)acrylate or (meth)acrylamide [24]. There are various choices of substitution groups of quaternary ammonium, and number (n) of carbon spacers between carboxylate and quaternary ammonium groups [24–26]. Thus, zwitterionic materials have a wide variety of applications in antifouling blood contacted sensors, drug delivery, etc. Besides these biomedical applications, they are also very useful in chemical separation membrane and marine coating.



SB CB PC

Just as any other functional polymers, zwitterionic polymers can be synthesized by two different approaches: (1) direct polymerization of zwitterionic monomers or (2) post zwitterionization of reactive polymers. Evidently, polymerization from zwitterionic monomers is the most straightforward strategy to obtain zwitterionic polymers, and can achieve polymers with 100% zwitterion functionality. Most frequently, they are prepared by free radical polymerization [27]. But it's difficult to synthesize well-defined polymers or polymers with complex architectures (e.g., block copolymers and star copolymers) through free radical polymerization. Controlled radical polymerization, such as atom transfer radical polymerization and particularly the reversible addition fragmentation transfer method, is a convenient strategy to obtain polybetaines with defined end groups and molecular weight, and block and star copolymers [28–30]. As compared with direct polymerization, post zwitterionation is easy to perform and it is allowed to prepare reactive polymers with adjustable chemical structures. But the steric hindrance from neighboring group can have some adverse effects on reaction kinetics and yield can seldom be 100%.

This review will be focus on development and progress of the applications of zwitterionic polymers, such as PSB, PCB and PPC, in biomedicine, separation membrane and marine coating. Examples of the methods to construct the antifouling surfaces or nanoparticles for these applications will be given and discussed from molecular level. Problems existed in these applications are also discussed and their future is also prospected.

2. Applications

Due to their favorable unfouling capacities, zwitterionic materials have numerous applications, including biosensors, drug delivery, cell preservation, as well as chemical separation and marine coatings.

2.1. Blood contacted sensor

2.1.1. Application of PSB in blood contacted sensor

PEG and poly(sulfobetaine methacrylate) (PSBMA) were used to modify the surface of the nanostructured portable imaging SPR chip and the unfouling properties have been compared [31]. The zwitterionic polymer surface showed the best antifouling properties. Well-controllable electrochemically mediated atom transfer radical polymerization (eATRP) was very useful to prepare ultrathin PSBMA layers on electrode surfaces and minimize the biofouling impact on the implantable neutral electrodes [32,33]. The resulting polymer brush coatings repel over 99% nonspecific protein adsorption and long-time stability, which is favorable for the application of sensors. The sensitivity of the evaluated sensor was maintained at 94% after 15 days. The overall sensitivity drift was 7% higher than that of the polyurethane-coated ones and commercially available glucose biosensors.

Although PSB brushes have been successfully employed to construct anti-fouling surfaces for biosensors as discussed above, their biosensing application has been largely restrained due to the intrinsic lack of functional groups [34]. So far, three ways are employed to introduce functional groups to PSB brushes.

The first one is copolymerization with nonzwitterionic monomers with functional groups. Wen et al. introduce the epoxide functional group into SB copolymer by copolymerizating of sulfobetaine methacrylate (SBMA) with nonzwitterionic glycidyl methacrylate. The resulting copolymer was grafted onto surface-enhanced Raman scattering (SERS) substrate through covalent bond by the reaction between the epoxide group on the copolymer and the −SH group on SERS substrate surface [35]. Malachite green (MG) was easily trapped on copolymer-grafted Ag nanocube and enhanced the SERS signals. The drawback is that the introduction of (10 or 50%) nonzwitterionic epoxide units diminished the antifouling performance.

Zuilhof et al. develop another approach by postmodification of fully zwitterionic sulfobetaine brushes through top exchange reactions of the remaining terminal halogen substituent after ATRP [36,37]. The problem of this approach is that it is only applicable to relatively thin brushes (20–25 nm) since the end groups in thicker brushes are buried inside the brush [38], and unavailable for functionalization. Another shortcoming of this method is that number of introduced functional groups is very limited.

To overcome the limitations outlined above, Zuilhof et al. develop a new method that allows for efficient three dimensional polymer brush functionalization without compromising the zwitterionic character and antifouling properties. They synthesized a novel SB-based zwitterionic monomer equipped with a clickable azide moiety [39].