Biomaterials 33 (2012) 8928–8933

Contents lists available at SciVerse ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Synchronizing nonfouling and antimicrobial properties in a zwitterionic hydrogel

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ARTICLE INFO

Article history:
Received 28 July 2012
Accepted 9 September 2012
Available online 20 September 2012

Keywords:
Nonfouling
Antimicrobial
Switchable polymer
Zwitterionic

ABSTRACT

In this work, we report a new approach to integrate antimicrobial and nonfouling properties into a single platform without compromising each other. To achieve this, a zwitterionic hydrogel is conjugated with an antimicrobial agent as a leaving group in a way that maintains the zwitterionic form of the hydrogel before, during and after drug release, preventing bacteria surface adhesion and bulk proliferation simultaneously. The antibacterial salicylate anion contributes the negative charge to the initial zwitterionic state and is released through the ester linkage hydrolysis. The hydrogel then switches to its final zwitterionic state with the carboxylate as its new negatively charged group. We prove that this hydrogel can reach one-salicylate-per-monomer drug loading while still retaining the nonfouling property at protein and bacteria levels. It was also shown that its drug release profile was dictated by the hydrolysis rate of the monomer, making it possible to control and tailor the release rate of small hydrophilic drugs from the highly hydrated nonfouling polymer matrix.

1. Introduction

Bacterial surface adhesion and subsequent colonization have been among the major issues for many biomedical applications, causing device failure as well as tissue infections [1–3]. Traditionally, two common approaches exist to combat such threats. The first approach utilizes antimicrobial agents, particularly quaternary ammonium compounds and small molecular weight antibiotics, to actively kill the bacteria [4–6]. The second approach uses nonfouling coatings such as poly (ethylene glycol) (PEG) and zwitterionic materials to fend off bacteria from adhering onto the surface [7–9]. Despite their popularity, each has its own significant drawbacks. One major concern for the "attacking" approach is the surface accumulation of dead microorganisms blocking antibiotic functional groups, whereas the key problem associated with "defending" approach lies in its incapability to inhibit bacterial proliferation both on surface and in bulk. Many efforts have been made to combine these two features into a single system. The direct immobilization of an antimicrobial agent onto a nonfouling polymer background, though straightforward, usually compromises one property in the pursuit of the other [10]. An alternative route is to prepare switchable polymers that undergo separate stages of functionality. In recent years, we have reported three such approaches capable of switching between the cationic antimicrobial form and the zwitterionic nonfouling form of the material through reversible lactonization, ester hydrolysis, and ester hydrolysis coupled with an antimicrobial counter ion [11–13]. However, in all three cases, it inevitably involves a positively charged state at the bactericidal stage of their action. Such cationic states are subject to severe biofouling, making them unsuitable for many applications in complex media. A generic strategy that can help address this dilemma is hence needed, but, unfortunately, rarely reported. Ideally, a material or surface shall be able to carry a certain biological function (e.g. antimicrobial activity) with minimal interference to its nonfouling property. We envision that a good way to accomplish this is to create a polymer–drug complex, whose conjugate form as well as the unconjugated polymer itself are zwitterionic and nonfouling, thus achieving effective bacteria surface resistance and bulk growth inhibition simultaneously.

Herein, we demonstrate this concept through the design, synthesis and characterization of a new polymer that will meet this criterion and provide the capabilities aforementioned. In this system, poly (2-(2-((2-(methacryloyloxy) ethyl) dimethylammonio) acetoxy) benzoate) (PCBSA) polymers consist of an antimicrobial leaving group salicylic acid (SA) conjugated to a carboxyl betaine (CB) zwitterionic unit through a hydrolyzable ester linkage (Fig. 1a) [14]. This drug conjugate enjoys a high drug loading capacity unattainable via post-polymerization modification and a controllable drug release rate. More importantly, this resulting functional polymer maintains its zwitterionic state and nonfouling property both before and after the SA release, keeping the surface free from

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http://dx.doi.org/10.1016/j.biomaterials.2012.09.011