Stimuli-Responsive and Tunable-Bioadhesive Hydrogels of Nonionic Poly(N-isopropyl acrylamide) Containing Zwitterionic Polysulfobetaine

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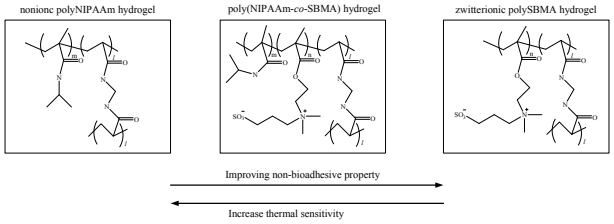
Introduction: This work describes a novel thermoresponsive and tunable-bioadhesive hydrogel of nonionic *N*-isopropylacrylamide (NIPAAm) containing zwitterionic sulfobetaine methacrylate (SBMA) to highly regulate the adsorption of plasma proteins, the adhesion of human platelets and cells, and the attachment of bacteria. Nonionic hydrogels of polyNIPAAm, zwitterionic hydrogels of polySBMA, and three nonionic-zwitterionic hydrogels of poly(NIPAAm-*co*-SBMA) having different monomer ratios of SBMA and NIPAAm were prepared. The effect of temperature on the swelling behavior and hydrophilicity of these hydrogels were discussed in aqueous solution in detail. This study also demonstrates the adsorption of plasma proteins and platelets onto these hydrogel surfaces from human blood plasma, and the bioadhesive activity of the prepared hydrogels by the tests of cell adhesion and bacteria attachment.

Methods: Nonionic hydrogels of polyNIPAAm (S#0), zwitterionic hydrogels of polySBMA (S#100), and three co-polymeric hydrogels of poly(NIPAAm-*co*-SBMA) (S#20, S#50, and S#70) were prepared from various monomer compositions between NIPAAm and SBMA using free radical copolymerization incorprating crosslinking reaction, as shown in Scheme 1.



Scheme 1. Chemical structure of the polyNIPAAm, poly(NIPAAm-*co*-SBMA), and polySBMA hydrogels

To determine the soluble–insoluble phase transition at LCST of poly(NIPAAm-*co*-SBMA) hydrogels without crosslinking, the optical absorbance of dilute uncross-linked gel solution was measured using a UV-visible spectrophotometer with precise temperature control from 25°C to 70°C. An enzyme-linked immunosorbent assay (ELISA) using monoclonal antibodies was used to measure different plasma protein adsorption on the prepared hydrogel surfaces. The attachment of blood platelets and the spreading of H68 cells were observed only on hydrogel surfaces using SEM and optical microscope. Two bacterial species, *Staphylococcus epidermidis* and *Escherichia coli*, were used to investigate the bacterial adhesion behavior on the surface of poly(NIPAAm-*co*-SBMA) hydrogels.

Results: We have found that the balance of hydrophobic or electrostatic intra and intermolecular interactions between polymer segments in poly(NIPAAm-*co*-SBMA) hydrogels dominated by the portion of polyNIPAAm or polySBMA decide stimuli-responsive swelling characteristics, which depend strongly on the temperature and ionic strength. It is worth emphasizing that appropriate control of nonionic and zwitterionic molar mass ratios leads to poly(NIPAAm-*co*-SBMA) hydrogels containing polySBMA at 31 mol % that exhibit the balanced swollen behavior with water molecules, which is independent of the ionic strength over a wide range of concentrations of NaCl from 0.1 to 2.5 M at physiological temperature, as shown in Figure 1. The excellent performance of poly(NIPAAm-*co*-SBMA) and polySBMA hydrogels in dramatically reducing the accumulation of *S. epidermidis* is due to their ability to resist nonspecific protein adsorption and bacterial adhesion, as shown in Figure 2.

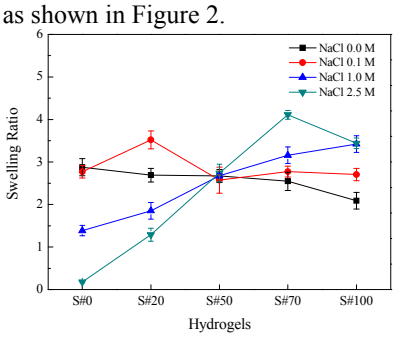


Figure 1. Swelling properties of chemical hydrogels in the presence of salt ions (NaCl)

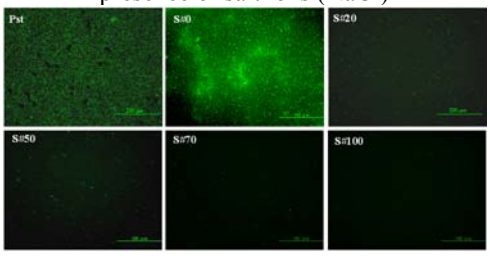


Figure 2. Reprehensive fluorescence microscopy graphs of *S. epidermidis* attachment on various gel surfaces at 24 h.

Conclusions: In this work, a controllable-thermoresponsive and tunable-bioadhesive hydrogel was obtained in the cross-linked chemical networks with a regulated ratio of nonionic polyNIPAAm and zwitterionic polySBMA. From the ELISA test and contact angle measurement, it is revealed that the hydrated-promoting effect on gel surface is associated with the nonfouling characteristics for resisting nonspecific protein adsorption. It was found that poly(NIPAAm-*co*-SBMA) hydrogels can be used to control the attachment or detachment of cells on the surfaces using the switchable temperature transition between 25°C and 37°C. This study suggests that the co-polymeric hydrogels from nonionic polyNIPAAm incorporating zwitterionic polySBMA is a potential stimuli-responsive biomaterial to provide a tunable bioadhesive functions for use in a wide range of general biomedical applications.