Functional Nanogel Coatings as Antifouling and Antibacterial Surfaces

Keskin, Damla

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SUMMARY

Nowadays, many people use biomedical implants such as voice prosthesis, hip and breast implants, and urinary catheters, which are significantly impacting the quality of life of patients. During the implantation of a biomaterial into the body, bacteria can attach to the surface, which eventually creates an infection on the implant and causes its malfunction as well as a great danger for the life of the patient. In this project, the aim was to overcome the great challenge of bacteria-driven infections in the current state of the biomedical implants by developing a broadly applicable surface coating. **Chapter I** of this thesis provides a brief introduction to biofilm formation and biomaterial-associated infections. A specific focus lies on the unique properties of nanogels and the preparation and applications of nanogel coatings in the biomedical field. The infection problem is highly challenging for medical implants; therefore, inhibiting the initial bacteria attachment on the surface is vital to combat the biomaterial-associated infections.

Chapter II gives an overview of different methods for preventing initial bacterial adhesion and growth on biomedical implant surfaces. The implementation of nanotechnology to develop efficient antimicrobial systems has a significant impact on the prospects of the biomedical field. Nanogels are soft polymeric particles with an internally cross-linked structure, which behave as hydrogels and can be reversibly hydrated/dehydrated (swollen/shrunken) by the dispersing solvent and external stimuli. Their excellent properties, such as biocompatibility, colloidal stability, high water content, desirable mechanical properties, tunable chemical functionalities, and interior gel-like network for the incorporation of biomolecules, make them fascinating in the field of biological/biomedical applications. In this chapter, various approaches will be discussed and compared to the newly developed nanogel technology in terms of efficiency and applicability for determining their potential role in combating infections in the biomedical area, including implant-associated infections.

The mechanical properties of coatings and their influence on the substrate characteristics play an important role in modulating the coating parameters for a desired biomedical application. **In Chapter III**, macro-sized hydrogel coatings have been created on the polydimethylsiloxane (PDMS) surfaces via UV mediated free radical polymerization using benzophenone as an initiator. PDMS is a silicone elastomer-based material that is used in various applications, including coatings, tubing, microfluidics, and medical implants. PDMS has been modified with hydrogel coatings to prevent fouling, which was done through UV-mediated free radical polymerization using benzophenone. We have investigated the properties of hydrogel coatings and their influence on the bulk properties of PDMS under various preparation conditions, such as the type and concentration of monomers and UV treatment time. Acrylate-based monomers were used to perform free radical polymerization on PDMS surfaces under various reaction conditions. This approach provided insights into the relationship between the hydrogel coating and bulk properties of PDMS. Altering the UV polymerization time and the monomer concentration resulted in different morphologies

with different roughness and thickness of the hydrogel coating, as well as differences in the bulk material stiffness. The surface morphology of the coated PDMS was characterized by AFM. The cross-section and thickness of the coatings were examined using scanning electron microscopy coupled with energy-dispersive X-ray spectroscopy. The dependence of coating development on the monomer type and concentration used was evaluated by surface hydrophilicity, as measured by water contact angle. Elongation-until-break analysis revealed that specific reaction conditions affected the bulk properties and made the coated PDMS brittle. Therefore, boundary conditions have been identified to enable high-quality hydrogel coating formation without affecting the bulk properties of the material. Acrylate-based monomers such as N-isopropylacrylamide, hydroxyethyl methacrylate, and acrylamide were covalently bonded onto the surface under various reaction conditions.

We proved in the previous chapter that creating a hydrogel coating without affecting the bulk material integrity is crucial. Taking this issue into account, in **Chapter IV,** we designed hydrogel coatings consisting of nanogels which are not influencing the bulk material properties. Bacterial infection is a severe problem, especially when associated with biomedical applications. In **Chapter IV,** it has been effectively demonstrated that poly-N-isopropylmethacrylamide based microgel coatings prevent bacterial adhesion. The coating preparation via a spraying approach proved to be simple and cost and time efficient, creating a homogeneous dense microgel monolayer. In particular, the influence of cross-linking density, microgel size, and coating thickness was investigated on the initial bacterial adhesion. Adhesion of *Staphylococcus aureus* ATCC 12600 was imaged using a parallel plate flow chamber setup, which gave insights into the number of the total bacteria adhering per unit area onto the surface and the initial bacterial deposition rates. All microgel coatings successfully yielded more than 98% reduction in bacterial adhesion. Bacterial adhesion depends both on the cross-linking density/stiffness of the microgels and the thickness of the microgel coating. Bacterial adhesion decreased when a lower cross-linking density was used at equal coating thickness and at equal cross-linking density with a thicker microgel coating. The highest reduction in the number of bacterial adhesion was achieved with the microgel that produced the thickest coating (h = 602 nm) and had the lowest cross-linking density. The results provided in this chapter indicate that microgel coatings serve as an interesting and easily applicable approach and that they can be fine-tuned by manipulating the microgel layer thickness and stiffness. Besides, the coatings were shown to be stable under experimental conditions as the nanogel layer was still present after the flow experiments. Hence, we successfully evaluated the influence of these parameters and gained new insight to enhance the non-fouling surface characteristics for biomedical implants.

Based on the platform developed in **Chapter IV**, we investigated in **Chapter V** the antifouling nanogel coatings combined with quaternary-ammonium-compounds (QACs) and Triclosan incorporation to include bacteria-killing properties. Multifunctional nanogel coatings provide a promising antimicrobial strategy against biomedical implant-associated infections. Nanogels can create a hydrated surface layer to promote antifouling properties effectively. Further modification of nanogels with QACs potentiated antimicrobial activity owing to their positive charges along with the presence of a membrane-intercalating alkyl chain. This chapter effectively demonstrated that poly(N-isopropylacrylamide-co-N-[3(dimethylamino)propyl]methacrylamide) (P(NIPAM-*co*-DMAPMA)-based nanogel coatings possessed antifouling behavior against *S. aureus* ATCC 12600, a Gram-positive bacterium. Through the tertiary amine in the DMAPMA comonomer, nanogels were quaternized with a 1-bromo-dodecane chain via an N-alkylation reaction. The alkylation introduced the antibacterial activity due to the bacterial membrane binding and the intercalating ability of the aliphatic QAC. Subsequently, the quaternized nanogels enabled the formation of intraparticle hydrophobic domains because of intraparticle hydrophobic interactions of the aliphatic chains allowing for Triclosan incorporation. The coating with Triclosan-loaded nanogels showed a killing efficacy of up to 99.99% of adhering bacteria on the surface compared to non-quaternized nanogel coatings while still possessing an antifouling activity. This powerful multifunctional coating for combating biomaterial-associated infection is envisioned to impact the design approaches for future clinically applied coatings greatly. Taken together, these results not only confirmed that surface-coated nanogels offer an exciting approach to prevent bacteria adhesion on the surface but also demonstrated the possibility to achieve Triclosan encapsulation into the nanogel within a coating for a powerful antibacterial effect. To this end, the coatings, which have both bacteria-repelling and bacteria-killing properties, were developed based on nanogel chemistry. We engineered antifouling nanogel coatings so that initial bacterial adhesion is prevented on the implant; moreover, with chemical modification of the nanogels, the coating also demonstrated bacterial killing properties. The innovative nanogel coatings are envisioned to diminish infection risk significantly.

In **Chapter VI**, the general discussion is given, and the findings of this thesis are highlighted concerning the different chapters and ongoing research. Current understanding and future perspectives toward developing multifunctional surface coatings with multifunctional nanogels are discussed.