Stimuli-responsive polymeric composites for advanced controllable biomaterials

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SUMMARY

Nowadays, polymers have become an integral part in the field of biomaterials. The use of polymeric matrices in the field of biomedicine is extensive and reaches from nanomedicine and drug delivery systems to tissue engineering, and medical implants. Especially the past decades, research has shown the tremendous possibilities of finetuning the chemical and physical properties of polymers making polymeric systems highly versatile. It ultimately, allows for designing the desired features depending on their intended use. Synthesizing stimuli responsive polymers allows the material to respond to environmental changes by undergoing conformational changes. This is particularly important for future applications in precision medicine, where the adaptability of biomedical materials is crucial to address complex healthcare challenges. **Chapter I** gives a brief introduction to polymers used for biomedical applications. A specific focus lies in the possibilities of integrating various stimuli responses inside polymeric matrices, namely physical, chemical, and biochemical stimuli.

Chapter II gives an extensive overview of the possibilities of inducing chemical reactions by applying ultrasound. This newly emerging field, called sonochemistry, offers tremendous possibilities while working under mild conditions. Exposing chemical reactions to acoustic waves leads to the acceleration of reaction rates, changes physical properties, and enables the alteration of reaction paths. Sonochemistry has found many applications in industry, reaching from food production, pharmaceutics, cosmetics, and environmental remediation. The overview given in this chapter focusses on the intriguing possibilities of using ultrasound in industry, particularly in the field of biomedicine. We show that echogenic applications in biomedical engineering reaches from improved ultrasonic imaging with the help of ultrasound contrast agents, to sonodynamic therapy, and drug delivery systems based on microbubbles.

Based on the insights gained from **Chapter II**, we developed a diacetylene-stabilized microbubble (diacMB), which is responsive to medical ultrasound. The findings are presented in **Chapter III**. A 10,12-pentacodiynoic acid (PCDA) stabilized oil-in-water emulsion, and the subsequent covalent crosslinking of diacetylene bonds, led to stable microdroplet formation. These very stable microdroplets were able to withstand differential centrifugation, allowing the collection of a monodisperse emulsion. Subsequent lyophilization enabled the integration of diacMBs in various polymeric matrices, reaching

from pHEMA coatings to polyacrylamide hydrogels. The latter showed significant improvement of the echogenic visualization when compared to its control group, which consisted of the same chemical composition of the polymeric matrix without the integration of diacMBs. While diacMBs embedded in a polyacrylamide hydrogel did not show triggered disassembly even at high Mechanical Index, diacMBs suspended in water started to rupture at a Mechanical Index of 0.75. The developed system shows promising echogenic behavior and serves as a foundation for future experiments to validate its potential as a future theranostic platform.

Based on the intriguing possibilities of stabilized emulsions, **Chapter IV** focused on dynamically crosslinked microstructures based on nanogel stabilized Pickering emulsions. N-Isopropylacrylamide (NIPAM) nanogels were functionalized with either amine or ketone groups. The ketone-functionalized nanogels were suspended in an organic phase, while the amine-functionalized nanogels were suspended in water. Emulsification of the immiscible phases led to dynamically covalently crosslinked microstructures through the formation of imine bonds between the amine- and ketone-functionalized nanogels. The resulting physiochemical properties of the microstructure showed pH-triggerable responsive behavior, where low and high pH led to the diffusion of the microstructure, while slightly acidic conditions maintained stable matrices. Using nanogels as surface stabilizers for Pickering emulsions is advantageous, as the synthesis of nanogels shows high control over the size, temperature responsive behavior, and their chemical functionalization. It ultimately enables to fine-tune the resulting properties of the microstructure, making this system promising for a wide range of applications.

In **Chapter V** we continued our research on dual-responsive NIPAM-based systems. By homogenously incorporating ferromagnetic particles through free radical polymerization within the NIPAM network, we fabricated a thermo- and magnetic responsive soft robot. This robot shows excellent control over both stimuli, allowing for complex locomotion, such as pick-and-place and release maneuvers of objects using independent triggers. First, the robot is magnetically actuated in a gripping state, and subsequent increase in temperature, transitions the robot from a swollen to a collapsed state, ultimately allowing the robot to maintain in a secured configuration without magnetic actuation. The increase in temperature enables the robot to be locked in the gripping state, while performing secondary movements via magnetic actuation. Ultimately, the object can be released at the target location by decreasing the temperature, where the polymeric network transitions back

to its swollen state. This dual responsive soft robot could be particularly useful for biomedical applications where controlled and programmable responses are crucial, as is the case for minimally invasive surgeries.

Chapter VI highlights the findings of this thesis and provides a general discussion of the previous chapters. Future perspectives are provided on how stimuli-responsive polymers can enhance the shift from standardized to precision medicine to provide customized medical solutions.