Abstract

This doctoral thesis focuses on the design, synthesis, and characterization of novel polymer materials responsive to physical and chemical stimuli. The presented findings will serve mainly for improving polymer-based drug-delivery systems (DDSs) and will help in advancing the development of future theranostics – materials combining therapeutic and diagnostic qualities into a single system. The emphasis is put on the bottom-up approach – design and synthesis of new small molecules, including light- and/or redox-responsive compounds, using light- and redox-responsive monomers for creating well-defined responsive polymers through controlled polymerizations, as well as controlling the exact monomer composition along polymer chains to achieve improved drug loading in micelle-like DDSs.

Pyrazinacenes are a specific type of heteroacenes formed from linearly-fused 1,4-pyrazine units. Pyrazinacenes are redox-active, strongly colored, fluorescent compounds that could be potentially used for designing new upconverting materials (*i.e.* conversion of lower energy photons to a higher energy photon) and their complexes with ruthenium could intercalate into DNA in a similar manner as the well-studied DNA probe/photoswitch $[Ru(bpy)_2dppz]^{2+}$. In this work, a novel and scalable one-pot synthesis of phenanthroline-fused pyrazinacenes from relatively inexpensive starting materials is described. The phenanthroline moiety was employed to form pyrazinacene complexes with Ru^{2+} ions and a straightforward *N*-alkylation strategy was developed for future conjugation of pyrazinacene upconversion materials with polymers.

In pursuit of light-responsive micelle-like DDSs, we have studied a model amphiphilic block copolymer based on poly[(2-nitrobenzyl)acrylate] (PNBA). UV-irradiation of the hydrophobic PNBA block led to its photodecomposition to poly(acrylic acid) resulting in polymer hydrophilization and micelle disassembly. We have described the first controlled polymerization of (2-nitrobenzyl)acrylate (NBA) using single-electron transfer living radical polymerization (SET-LRP) leading to polymers with narrow dispersity. We have successfully used the SET-LRP to prepare poly(ethylene oxide)-*block*-PNBA block copolymers, that formed micelle-like particles in aqueous environment and readily disassembled upon UV-irradiation. These block copolymers could serve as a model light-responsive excretable micellar DDSs.

We further moved to responsive fluorinated polymer systems of two different polymer classes – poly[(*N*-(alkyl)acrylamides] and poly(2-oxazolines) (POx). The described fluorinated polymers were designed as potential theranostic materials applicable for stimuli-responsive DDSs traceable *in vivo* by ^{19}F magnetic resonance imaging (^{19}F MRI). The studied thermo-/pH-responsive polymers based on poly[*N*-(2,2-difluoroethyl)acrylamide] (PDFEA)

have demonstrated both excellent biocompatibility and highly favorable ^{19}F MRI imaging properties. Furthermore, we have successfully prepared thermo-/redox-responsive micelle-like PDFEA copolymer systems by incorporating ferrocene (Fc) moieties into the PDFEA thermoresponsive/hydrophobic block. The nanoparticles of such polymers disassembled in oxidative environment due to hydrophilization through formation of positively charged ferrocenium moieties (Fc^+). However, in the ferrocene-modified PDFEA polymers there was no significant change in ^{19}F MRI signal upon oxidation, and, therefore, ^{19}F MRI cannot be used for probing the redox state of similar DDSs.

To enable redox sensing, we have designed and synthesized two novel fluorinated ferrocene derivatives bearing an amino group, that was employed for amide coupling with the pending carboxyl groups of poly{[2-methyl-2-oxazoline]-*block*-[2-methyl-2-oxazoline-*stat*-2-(2-carboxyethyl)-2-oxazoline]} polymer. The copolymers decorated with fluorinated Fc moieties formed nanoparticles that disassemble upon oxidation through formation of Fc^+ and converting the diamagnetic fluorinated Fc moieties into paramagnetic Fc^+ changed the relaxation times and chemical shifts of the ^{19}F nuclei distinguishable by ^{19}F MRI.

This thesis also presents a synthesis of novel 2-aryl-2-oxazoline monomers and a first direct comparison of analogous amphiphilic gradient and block polyoxazolines containing 2-aryl-2-oxazoline monomers. DDSs with gradient polyoxazoline copolymers exhibited improved drug loading capacity and higher hydration/mobility of the micelle core (potentially favorable for ^{19}F MRI imaging and the design of new theranostic materials).

In summary, this doctoral thesis advances polymer materials designed to respond to physical and chemical stimuli, while focusing on polymer-based DDSs. Key achievements include the straightforward synthesis of new conjugable pyrazinacenes showing promise as materials for upconversion; the development of the first controlled polymerization of NBA and synthesis of PNBA-based copolymers that disassemble under UV light; and the introduction of pH-, thermo-, and redox-responsive fluorinated polymers for ^{19}F MRI imaging. Novel fluorinated ferrocene derivatives were employed to create redox-responsive polymer sensor systems traceable by ^{19}F MRI. New 2-aryl-2-oxazoline monomers were synthesized and superior properties of their gradient copolymers for DDSs were demonstrated. This work provides valuable insights and methodologies for future improvements in responsive polymer systems.

Keywords: Pyrazinacenes, poly[(2-nitrobenzyl)acrylate], light-responsive, poly[*N*-(2,2-difluoroethyl)acrylamide], ^{19}F MRI, thermoresponsive, ferrocene, redox-responsive, poly(2-alkyl-2-oxazoline), poly(2-aryl-2-oxazoline), drug-delivery systems.