Role of Synthetic and Dimensional Synthetic Organic Chemistry in Block Copolymer Micelle Nanosensor Engineering

This thesis investigated the role of amphiphilic triblock copolymer micelle nanomaterials in nanosensors, with emphasis on the synthesis of micelle particle sensors. The thesis is focused on the role of synthetic and dimensional synthetic organic chemistry in amphiphilic triblock core-shell-corona micelle based ratiometric fluorescence pH nanosensor fabrications. Two synthetic strategies such as post micelle modification and mixed micellisation (co-micellisation) were employed for pH nanosensor synthesis.

In the post micelle modification strategy, dimensional synthetic modifications on polymer micelles were performed. The structural potential of amphiphilic functional triblock copolymer selfassembly to provide regioselective functionalization and cross-linking was the key factor for this approach. Initially, functional amphiphilic triblock copolymers (functional unimers) were prepared by synthesis based on isolated macroinitiator ATRP of protected functional monomers. Selfassembly of these functional unimers in water resulted in functional core-shell-corona micelles. The functional micelles were stabilized by covalent cross-linking at the distinct functional shell or core domains of the micelle. The cross-linked micelles were converted into ratiometric pH nanosensors by conjugating pH sensitive and reference fluorophores at the shell region. The amphiphilic triblock copolymers, PEG-b-PAEMA-b-PS, PEG-b-PAEMA-b-PES and PEG-b-PAEMA-b-PCMA, were used for the preparation of functional micelles. Shell cross-linking on PEG-b-PAEMA-b-PS micelles was performed by amidation reactions between the amino groups of PAEMA blocks using a di-carboxylic acid cross-linker. Also a dendritic cross-linker based click chemistry was used to stabilize the PEG-b-PAEMA-b-PES micelle having click readied PES core. In another study, UV radiation was used to induce non-reversible and reversible photo core crosslinking of core-shell-corona functional micelles were also investigated. A PEG-b-PAEMA-b-PES micelle core was photo cross-linked by UV induced oxidative coupling between alkyne groups present at the micelle core. In a different system, reversible photo dimerization of coumarin was used to construct reversibly photo core cross-linked PEG-b-PAEMA-b-PCMA micelle. By conjugating pH sensitive and reference fluorophores at the shell regions of the shell and core crosslinked micelles, pH nanosensors were synthesized with sensitivity ranges that were appropriate for pH measurements in living cells. The sensitivity ranges of the nanosensors were simply altered by changing the fluorophores conjugated to the shell region. Nanosensors having targeting capabilities were synthesized by mixed micellisation or cemicellisation strategy. In this approach, the amphiphilic triblock copolymers synthesized by ATRP were further modified, and conjugated with targeting ligands and fluorophores. The co-micellisation of this functionalized amphiphilic triblock copolymers resulted in functionalized mixed micelle nanosensors. Post polymer modifications were easier to implement and quantify than post micelle modifications; hence the co-micellisation strategy provided more precise knowledge about the composition of the nanosensor.

Targeted non-cross-linked and targeted cross-linked ratiometric pH nanosensors were prepared by mixed micellisation or a co-micellisation strategy. Fluorophores and octaarginine conjugated amphiphilic triblock copolymers were synthesized by post-polymer modifications of PEG-b-PHEMA-b-PMMA and NH₂-PEG-b-PHEMA-b-PMMA. Co-micellisation of these functionalized triblocks resulted in octaarginine surface functionalized mixed micelle pH nanosensors. Similarly, a cross-linked cyclic RGD peptide targeted mixed micelle nanosensor was also prepared. The cyclic RGD peptide (cRGDfK) and fluorophores were conjugated to the amphiphilic triblock copolymers, NH₂-PEG-b-PAzEMA-b-PMMA and PEG-b-PAzEMA-b-PMMA. Mixed micellisation of these functionalized unimers followed by dendritic click shell cross-linking resulted in a stable cRGDfK targeted mixed micelle pH nanosensor.

Thus, the engineerability of triblock core-shell-corona micelle was utilized for the synthesis of ratiometric pH nanosensor having desired pH sensitivity ranges.