Dynamic and Stimuli-Responsive Hydrogel Systems for Controlled Release of Proteins

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Background and hypothesis

Hydrogels have been extensively used as biomaterials for controlled release applications due to their biocompatibility and tunable networks. Stimuli-responsive, or smart, hydrogels are of interest due to their potential for localized release based upon local stimuli such as pH. In addition to smart materials, dynamic hydrogels have been utilized to obtain unique release profiles such as biphasic release curves. We hypothesized that by leveraging dynamic and stimuli-responsive click chemistry we can fabricate hydrogels with unique and controlled release profiles.

Project Methods

A new reversible addition fragmentation chain transfer (RAFT) polymer known as PADO, was synthesized bearing a ketone functional group allowing for crosslinking with hydrazide bearing motifs to form a pH labile acylhydrazone bond. In addition, polyethylene glycol (PEG) based hydrogels have been extensively used in controlled release applications due to their biocompatibility and antifouling properties. Previously, we have developed a novel conjugation technique for functionalizing norbornene onto hydroxyl-terminated PEG through a cyclic desymmetrization reaction with carbic anhydride. The new polymer, $PEGNB_{CA}$, was further conjugated with dopamine via amide conjugation to form $PEGNB_{D}$. Mass loss and protein release analysis were conducted for PADO and $PEGNB_{D}$ hydrogels, respectively.

Results

Mass loss studies confirmed that PADO hydrogel degraded faster at mildly acidic pH of 6 compared to physiological pH of 7.4. In addition, the rapid hydrolysis of $PEGNB_{D}$ crosslinked via inverse electron demand Diels-Alder reaction demonstrated higher protein release compared to conventional PEGNB hydrogels, which are hydrolytically resistant.

Conclusion/Impact

The sensitivity to degradation PADO hydrogels in an acidic environment~~,~~ and the hydrolytically sensitive $PEGNB_{D}$ hydrogels, can be utilized for targeted therapeutic release. For example, the pH-sensitive hydrogel system can be utilized for therapeutic release into an acidic neoplasm while having minimal release in neutral pH tissues.