Reducing-environment Sensitive Hydrogels For Controlled Drug Delivery

Prathamesh M. Kharkar,[1] April M. Kloxin,[1,2] and Kristi L. Kiick[1,3]

[1] Materials Science and Engineering, University of Delaware, Newark, DE
[2] Chemical and Biomolecular Engineering, University of Delaware, Newark, DE
[3] Biomedical Engineering, University of Delaware, Newark, DE

Statement of Purpose

Controlled drug release for improved efficacy and reduced toxicity remains a challenge in the treatment of disease, including skin cancer. Injectable hydrogels allow efficient encapsulation of cargo molecules and are promising for local, controlled drug administration in a minimally invasive way via the incorporation of responsive chemistries.[1] Here, injectable poly(ethylene glycol)(PEG)-based hydrogels have been synthesized with succinimide thioether linkages that undergo retro and exchange reactions in the presence of a glutathione (GSH) reducing environment, which is present in carcinoma tissues (ca. 0.5 – 10 mM). The rate of hydrogel degradation was tuned by thiol selection (pK_a and hydrophobicity) and network connectivity, and release of a model cargo molecule (BSA) was studied. These results demonstrate the ability to tune the rate of degradation and cargo release by chemistry selection and the promise of these materials for the treatment of cancer.

Methods

4-arm PEG was functionalized with 3-mercaptopropanoic acid (MP) and 4-mercaptophenylacetic acid (MPA).[2] Hydrogels were prepared by mixing separate polymer solutions (5 wt%) of PEG-4SH (non-degradable control), PEG-4MP (one degradable group, D1) or PEG-4MPA (two degradable groups, D2) with maleimide functionalized PEG (PEG-2MI) in a truncated syringe mold. Hydrogel gelation and final storage modulus was characterized using rheometry (1% strain, 6 rad s^{-1} angular frequency, linear viscoelastic regime). Further, the hydrogel was suspended in phosphate buffered saline (PBS) with GSH at varying concentration (0, 0.01, and 10 mM), and degradation was monitored using swelling ratio measurements and rheometry. Fluorescently-labeled Bovine Serum Albumin (BSA) was used as a model cargo molecule and encapsulated within the network during hydrogel formation. The release of BSA from control, D1, and D2 hydrogels was monitored using fluorometry under reducing microenvironment (10 mM GSH).

Results

Hydrogels containing different degradable functional groups were synthesized to enable microenvironment controlled protein release. Owing to the presence of ester linkages, MP-based hydrogels undergo ester hydrolysis, whereas the MPA-based hydrogels undergo ester hydrolysis and exchange & retro reactions. PEG-4SH-based hydrogels served as a non-degradable control owing to lack of any degradable functional groups. Gel formation varied from >20 sec (D2) to ~40 sec (Control and D1), which correlated with the Michael donor reactivity. However, the final storage moduli of all hydrogel compositions post gelation were approximately 2.3 kPa irrespective of the identity of mercaptoacid functionalized PEG. Under *in vitro* reducing microenvironment conditions (10 mM GSH), control (Fig. 1) and D1 hydrogel (data not shown) did not exhibit significant changes in their storage moduli; in contrast, D2 hydrogel exhibited first order degradation kinetics ($k = 9 \times 10^{-4}$ min^{-1}) with a reverse gelation point observed at approximately day 4, which can be attributed to retro and exchange reactions. The release of BSA from D2 hydrogels correlated with the degradation profile, and complete cargo release occurred around the reverse gel point at 5700 minutes.

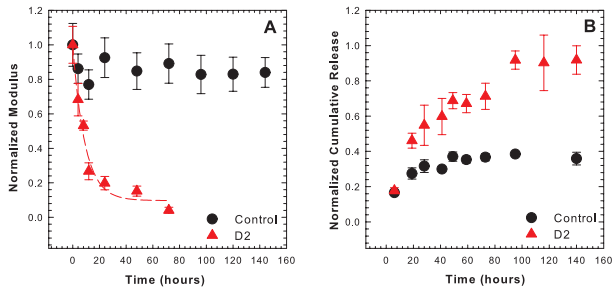

Fig. 1. GSH-responsive hydrogels. A. Degradation of the hydrogel was monitored by the decrease in storage modulus. **B.** Release of encapsulated BSA was monitored using fluorescence spectrometry. Significant differences in release kinetics correlate with the degradation profile of D2 hydrogel, which can be attributed to retro and exchange reactions.

Conclusions

Reducing microenvironment sensitive PEG hydrogels have been successfully synthesized using a Michael-type addition reaction. D2 hydrogels exhibited faster degradation kinetics owing to retro and exchange reactions. The ability to tune the release of cargo molecules using selective functional groups opens an exciting avenue for controlled drug delivery for cancer treatment.

References

1. Kharkar PK. Chem Soc Rev. 2013; 42:7335-7372
2. Baldwin AD. Poly Chem. 2013; 4:133-143.