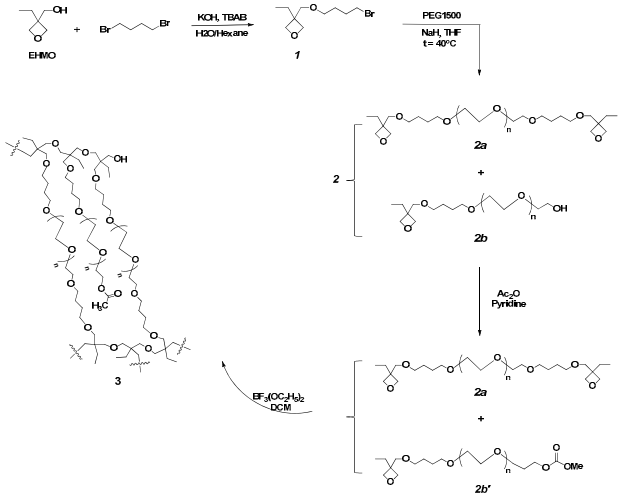
Novel Polyoxetane Hydrogel for Drug Delivery

Olga Yu. Zolotarskaya[1], Kenneth J. Wynne[2], and Hu Yang[1,3]
[1]Department of Biomedical Engineering, [2]Department of Chemical and Life Science Engineering, [3]Massey Cancer Center, Virginia Commonwealth University, Richmond, Virginia 23284

Statement of Purpose: Oxetanes have been recognized as an essential element in many drugs and play a pivotal role in facilitating desirable pharmacokinetic properties. Oxetanes can also be utilized as monomers to synthesize linear or branched polymers via ring-opening polymerization (ROP) (JA Burkhard *et al.*, Angew. Chem. Int. Ed. 2010, 49, 9052). The purpose of the work presented herein is to synthesize novel cross-linked polyoxetane hydrogel and investigate its potential for drug delivery.

Methods: *Synthesis.* As illustrated in Scheme 1, 3-Ethyl 3-(hydroxymethyl) oxetane is modified with 1,4-dibromobutane and coupled with polyethylene glycol (Mn=1500 $gmol^{-1}$) via its terminal hydroxyl groups. Following acetylation, a cross-linked polyoxetane hydrogel network forms in the presence of boron trifluoride diethyl etherate. The obtained hydrogel was then washed and dried.



Scheme 1. *Synthesis route of cross-linked polyoxetane.*

Characterization: ^{1}H NMR was used to characterize structure of intermediates and polyoxetane. SEM was applied to examine morphology of the network. TGA and DSC were applied to examine thermal properties of the hydrogel. Polyoxetane hydrogel swelling and degradation behaviors were examined in pH 7.4 PBS at 37ºC. FITC-dextran was used a model compound, and its *in vitro* release from the hydrogel was studied. *In vitro* cytotoxicity of the hydrogel to fibroblasts was assessed using the MTT assay.

Results: We had success synthesizing PEG bisoxetane macromonomer (Fig.1). To avoid undesired reaction of free hydroxyl groups with Lewis acid during ring opening polymerization, unmodified hydroxyls were acetylated. PEG bisoxetane then undergoes ring-opening polymerization to form a hydrogel network. The TGA thermogram (not shown) shows that the hydrogel (dehydrated) begins to degrade at 233ºC. DSC data shows that melting temperature (Tm) of the cross-linked polymer is 5 ºC higher than that of the macromonomer. But its crystallization temperature is 1 ºC lower than that of the macromonomer (Fig. 2).

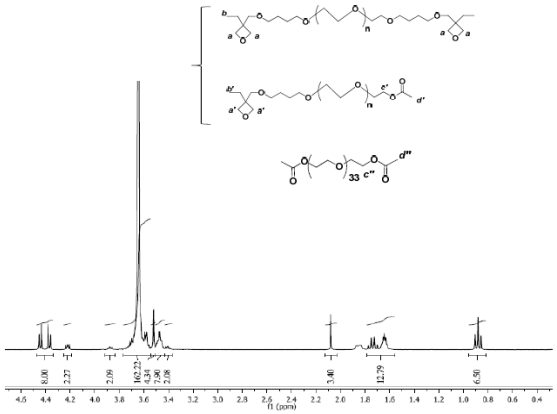


Fig. 1. *^{1}H-NMR spectrum of PEG bisoxetane.*

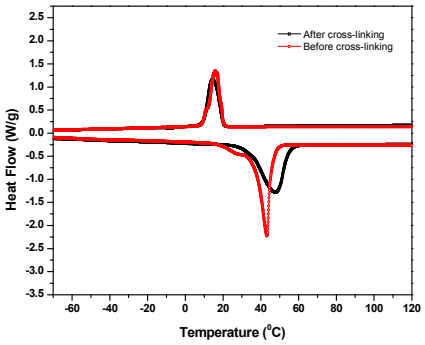


Fig. 2. *DSC analysis of PEG bisoxetane and cross-linked hydrogel.*

FITC-dextran was slowly released over a period of 24 h (Fig. 3). Cross-linked polyoxetane has improved cytocompatibility at high concentrations (Fig. 4).

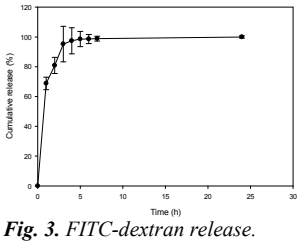


Fig. 3. *FITC-dextran release.*

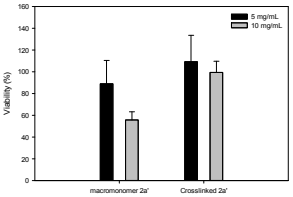


Fig. 4. *In vitro cytotoxicity assay*

Conclusions: We successfully synthesized and characterized novel polyoxetane hydrogel and assessed its potential for drug delivery. Our future work will be oriented toward wound dressing development based on this novel hydrogel.