Lactose functionalized polyurethanes/polyesterurethanes as biomaterials

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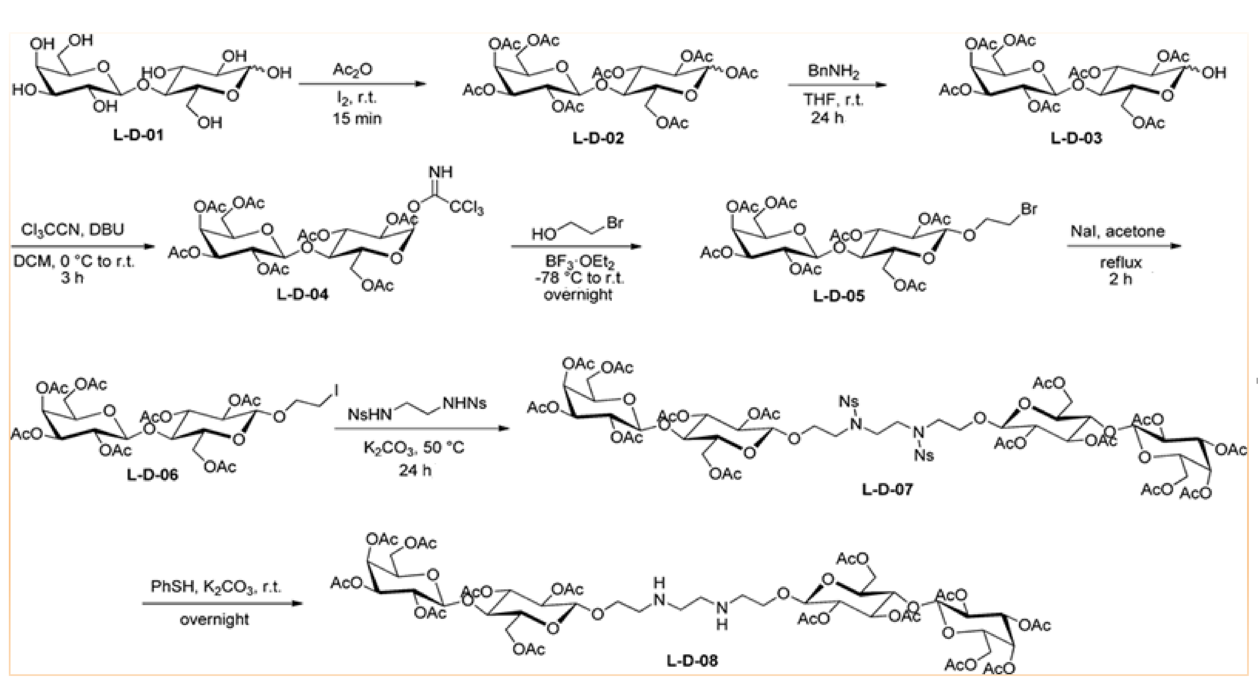
Shape memory polymers (SMPs) are a class of responsive polymers that have attracted attention in designing biomedical devices because of their potential to improve minimally invasive surgeries. Use of porous SMPs in vascular grafts has been proposed because porosity aids in transfer of fluids through the graft and growth of vascular tissue. However, porosity also allows blood to leak through grafts so preclotting the materials is necessary. Here hydrogels have been synthesized from acrylic acid and N-hydroxyethyl acrylamide and coated around a porous SMP produced from lactose functionalized polyurea-urethanes. The biocompatibility of the polymers used to prepare the cross-linked shape memory material is demonstrated using an in vitro cell assay. As expected, the hydrogel coating enhanced fluid uptake abilities without hindering the shape memory properties. These results indicate that hydrogels can be used in porous SMP materials without inhibiting the shape recovery of the material. Aside from the obvious advantage of having a shape memory polymer, polyurethanes were used in this work because they are widely used in biomedical applications due to their toughness, durability, flexibility, and biocompatibility. The polyurethanes prepared from lactose diamine have been shown to have excellent blood compatibility. However, synthesis of the carbohydrate containing polyurethanes requires lengthy and complicated procedures. This inspired our group to look for alternative and more efficient routes for bringing carbohydrates and polyurethanes together as biomaterials. Specifically, thiol-ene click chemistry between a lactose thiol and polyurethanes containing pendant allyl groups. Polyurethanes were also copolymerized with poly(caprolactone)-diol (PCL-diol) to impart biodegradability on the material, a common requirement of biomaterials.

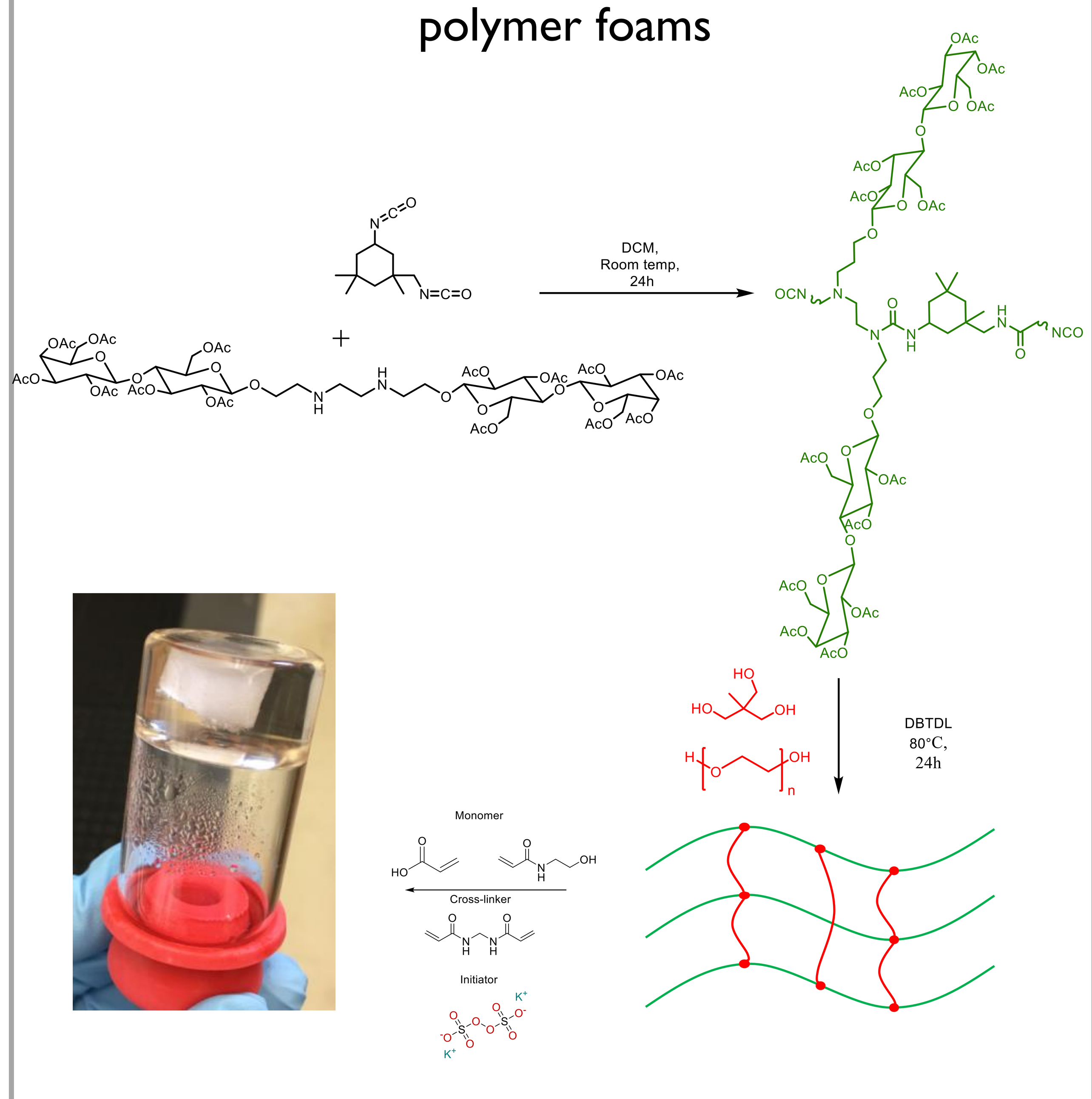
Hypothesis

Lactose containing polyurethanes will be biocompatible shape memory polymers. Incorporating hydrogels into the shape memory network will enhance fluid uptake without disrupting the shape memory process. Subsequently, cross-linking of lactose containing polyurethanes with polycaprolactone will afford a biodegradable shape memory material with a larger scope of applications.

Current method

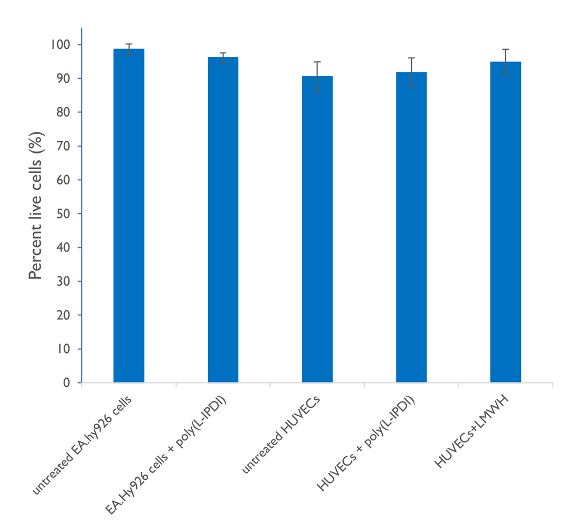


Synthesis of polyurethane/urea shape memory polymer foams

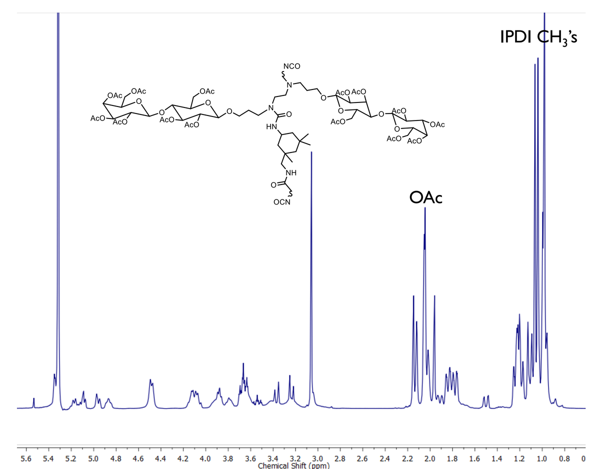


The pre-polymer was characterized by [1]H NMR and assayed in cell viability studies. The cross-linked foam was placed in a hydrogel solution and the hydrogel polymerized around and inside the pores of the foam. Hydrogel coated foams were characterized for their swelling ratios and shape memory properties.

Pre-polymer characterization

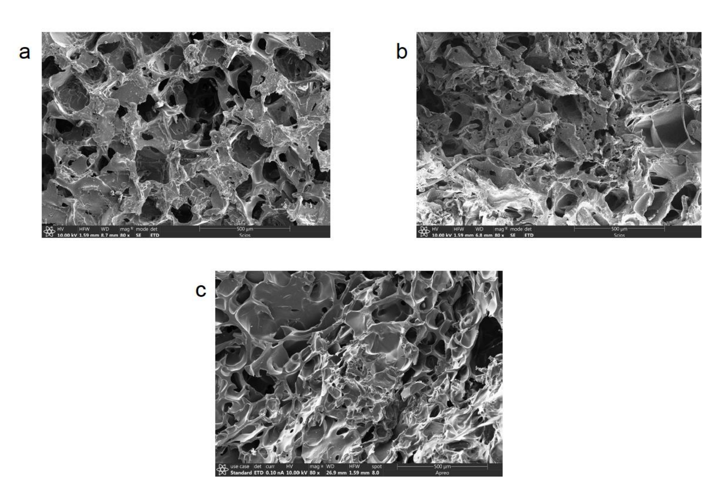


Live/Dead cell assay for EA.hy926 cells and HUVECs with poly(L-IPDI) or without (untreated). Also shown is data for the HUVECs treated with a low molecular weight heparin

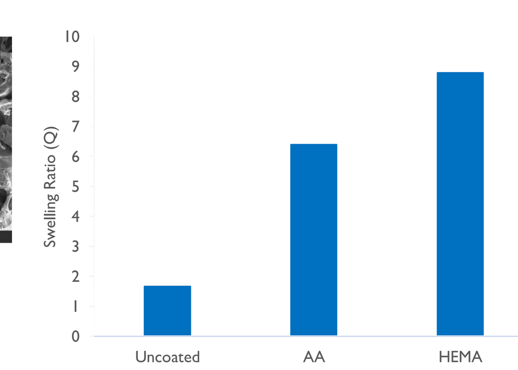


[1]H NMR spectrum of LD-IPDI isocyanate terminated prepolymer

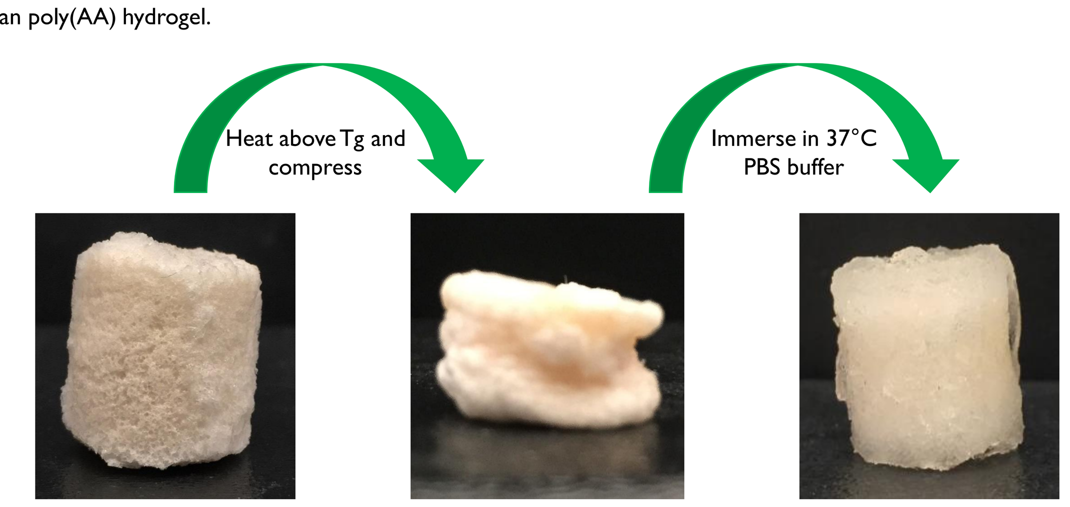
Shape memory foam characterization



SEM images showing (a) the uncoated SMP foam, (b) the SMP foam coated with a poly(HEAAm) hydrogel, and (c) the SMP foam coated with an poly(AA) hydrogel.



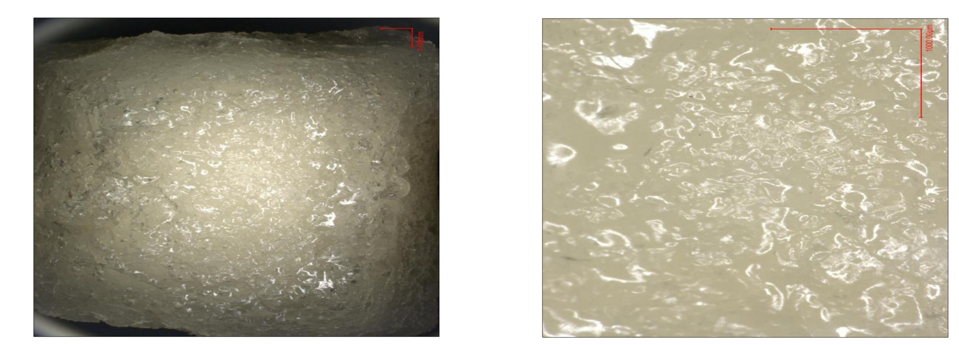
Swelling ratios of the hydrogel-foam composites consisting of poly(HEAAm), poly(AA), and the uncoated shape memory foam.



Hold stress and let cool

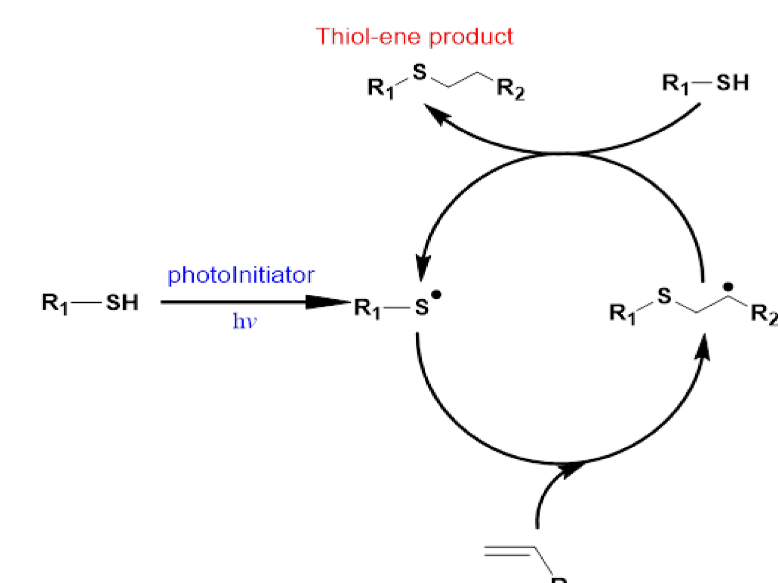
Hydrogel in composite	$R_r(1)$ %	$R_r(2)$ %	$R_r(3)$ %
polyHEAAm	77	87	140
polyAA	89	95	112
Uncoated	98	95	95

Shape recovery evaluations of SMP foams composited with hydrogels based on AA and HPMA with three successive cycles in in 37°C PBS buffer, the last cycle lasting overnight. The values are an average of two.



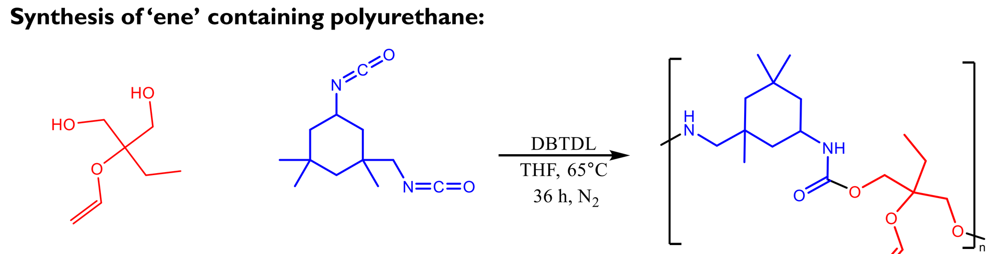
Microscope images of SMP foam coated with a poly(HEAAm) hydrogel and swollen with DI water at (top image) 20x and (bottom image) 1000x magnification.

New method using Thiol-ene chemistry



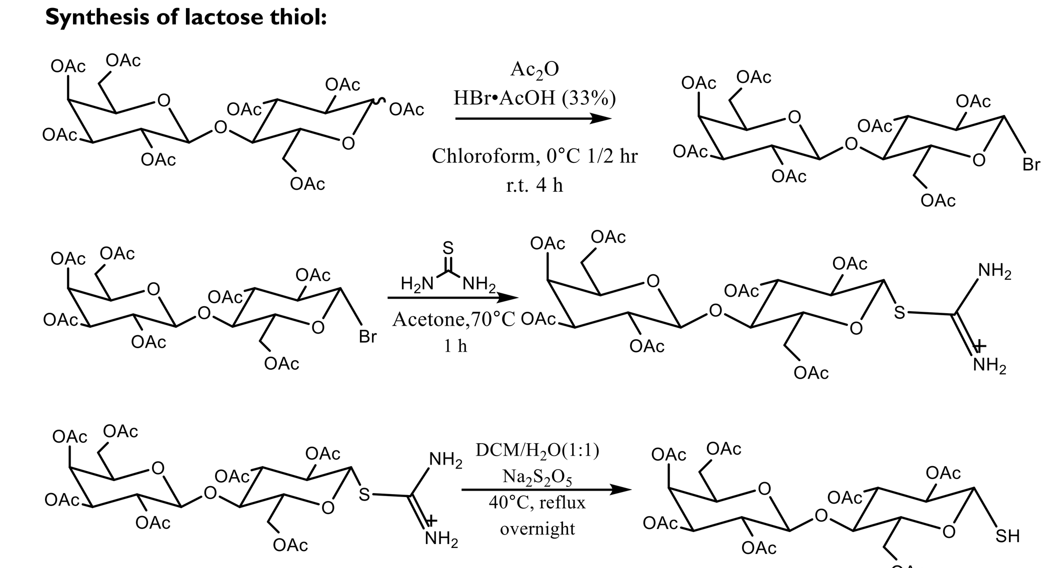
Materials synthesis

Synthesis of 'ene' containing polyurethane:



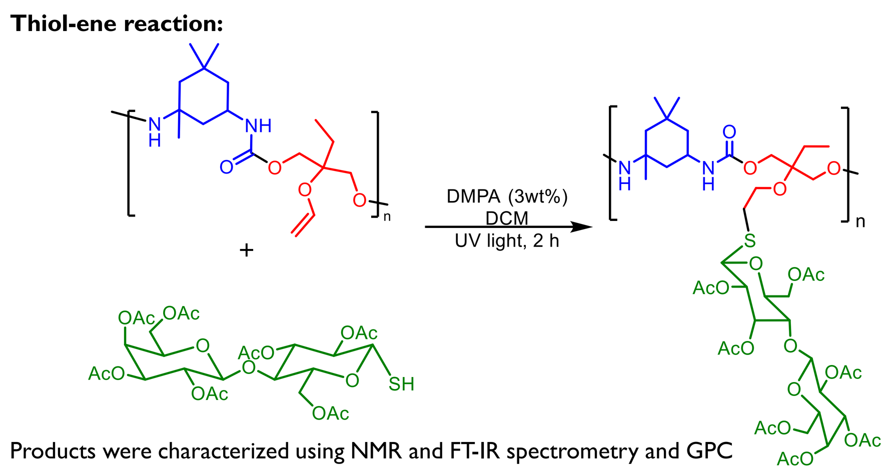
Products were characterized using NMR and FT-IR spectrometry and GPC

Synthesis of lactose thiol:



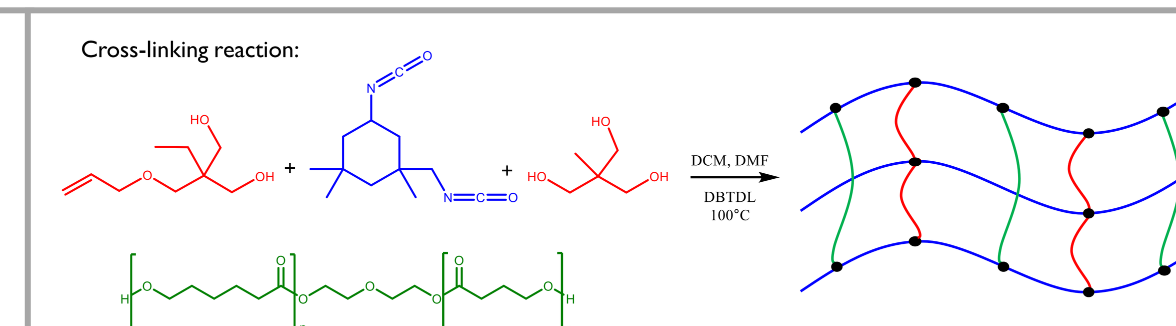
Products were characterized using NMR, FT-IR, and MS spectrometry

Thiol-ene reaction:



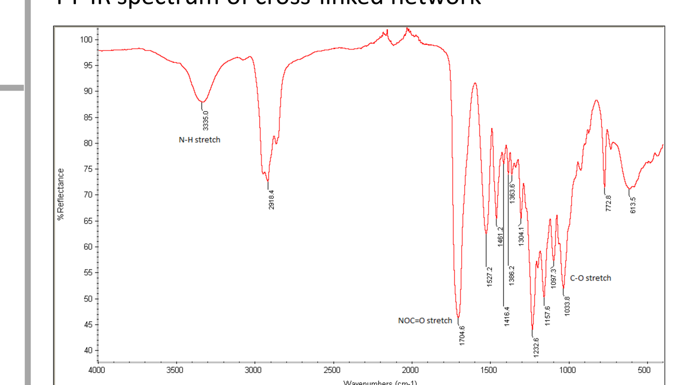
Products were characterized using NMR and FT-IR spectrometry and GPC

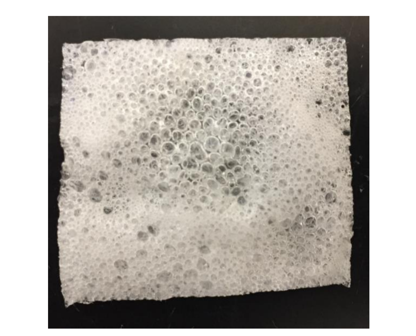
Cross-linking reaction:

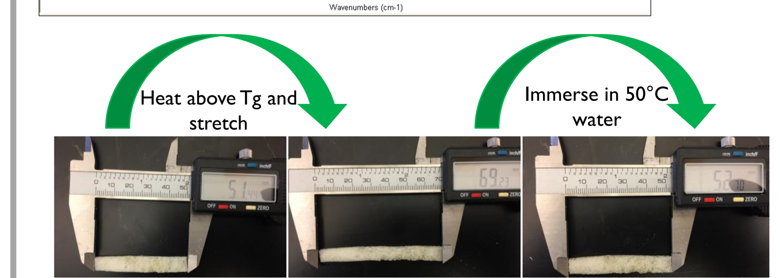


Cross-linked materials were characterized using FT-IR spectroscopy. Their shape memory properties were observed by heating the material above the switching temperature.

FT-IR spectrum of cross-linked network







Hold stress and let cool

Shape memory cycle	1	2	3
R_r	99	99	97
$F_{(t)}$	82	97	92

Conclusions

- PolyHEAAm- and polyAA-based hydrogels were successfully incorporated into SMP foams
- The SMP foam hydrogel composites showed enhancement of fluid uptake
- The shape memory properties were repeatable
- Demonstrates the feasibility of a hydrogel-coated SMP composite that can maintain advantages of hydrogel and SMP systems for potential use as vascular grafts
- Step growth polymerization of IPDI and TMPAE yields polyurethanes with pendant allyl groups that can be functionalized with lactose through thiol-ene chemistry
- The materials can be cross-linked with PCL-diol to create shape memory polymers with a low switching temperature

Future Work

- Optimize shape memory properties by controlling amount of hard and soft segments in the cross-linked network
- Characterize new polyesterurethanes for their thermal, mechanical, and shape memory properties
- Sulfate the surface of cross-linked materials and perform platelet adhesion assays to examine blood compatibility
- Perform cell culture studies on linear lactose containing polyesterurethanes to examine the biocompatibility of the linear polymer in an *in vitro* environment

Acknowledgments

Department of Chemistry, University of Cincinnati.