Mix-and-Match Design of Poly(oligoethylene glycol methacrylate) Hydrogels Using Different Thermoresponsive Precursors

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Introduction

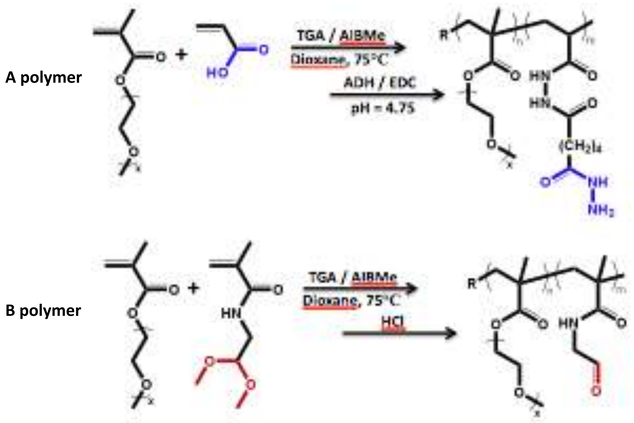
Injectable hydrogels are an interesting area of research for biomedical applications. They are advantageous due to their biocompatible, biodegradable, and non-invasive properties.

ADVANTAGES	CURRENT CHALLENGES
Selective permeation to desired chemicals in/out of matrix	Increasing tunability of polymer scaffold
High hydrophilicity offers low protein adsorption	Controlling scaffold-cell interactions
Mechanical and structural properties can mimic natural ECM	Limiting immune response triggering *in vivo*
	Minimally invasive administration

The purpose of this study was to determine the characteristic differences between homogeneous poly(oligoethylene glycol methacrylate) (POEGMA) hydrogels and how mixing the precursors in defined ratios (i.e. heterogeneous hydrogels) would influence the macroscopic and microscopic hydrogel properties. In this way, we hoped to be able to design a polymeric hydrogel platform that was tunable, allowing for use in specific materials, medical, and drug delivery applications.

Experimental

Preparation of POEGMA Precursors



The LCST of the POEGMA precursors can be controlled by the length of the oligoethylene glycol side chain. In this case, the "short chain" was defined as x = 2 ($M(EO)_2MA$) whereas the "long chain" was defined as y = 8-9 (OEGMA). Functionalization was carried out by an ADH/EDC reaction for the A polymer and by acid deprotection for the B polymer.

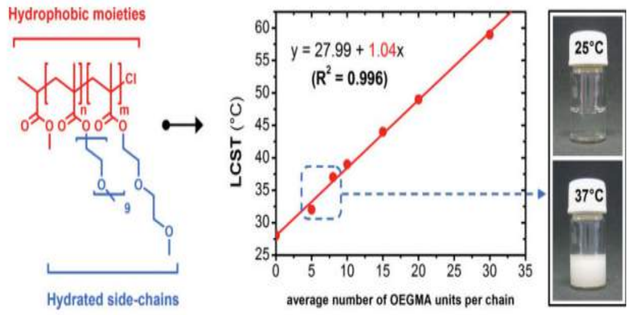
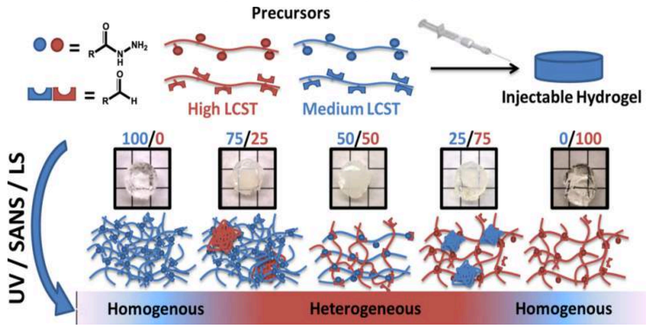


Image taken from: Lutz, J. F. (2008). Journal of Polymer Science Part A: Polymer Chemistry, 46(11), 3459-3470.

Experimental

Preparation of Hydrogels



When the A and B polymer precursors are mixed together, the hydrazide and aldehyde functional groups form a covalent hydrazone bond, effectively cross-linking the network. For this study, the high and medium LCST precursors were mixed in the defined ratios shown above to produce a hydrogel series.

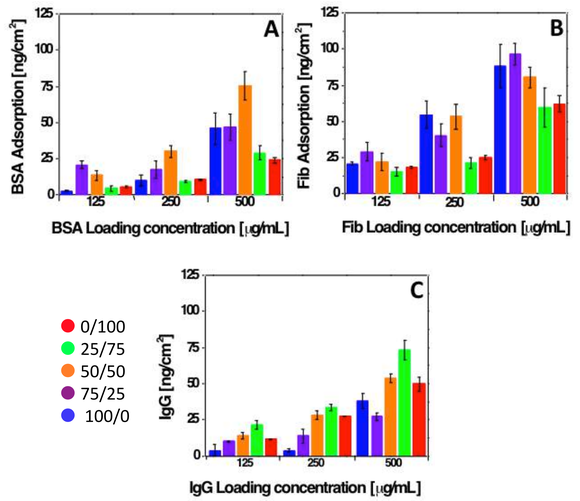
Results

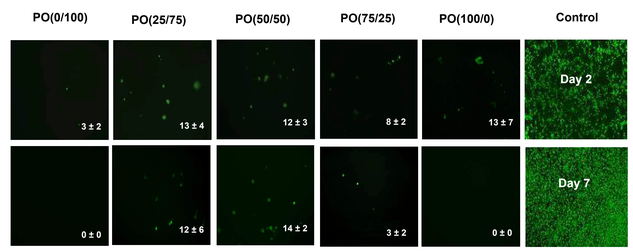
Macroscopic Properties

While there is no visible transition temperature (LCST) for the 0/100 hydrogel, each of the other gels in the series exhibit a visible transition – around 32°C for 100/0 (this is its known VPTT) and lower for the mixed hydrogels. This indicates that the network in the heterogeneous hydrogels collapses much faster, possibly due to the phase separated domains within the network. For the mechanical and swelling kinetics data, there is an obvious linear trend in the property changes. As the amount of high LCST precursor increases, the strength of the hydrogel decreases and the network can take on an increasing amount of water over time. This can be related to the VPTT and LCST values for the hydrogels and incorporated POEGMA precursors. As the hydrogel network collapses, more water is expelled and vice versa.

Results

Microscopic Properties





Intermediate ratio mixtures seemed to absorb a higher amount of protein – this may be due to the presence of the small domains, causing the hydrogel surface to be more heterogeneous and allowing more protein to adsorb. However, when these results are compared to those for other materials, like poly(ethylene glycol), the amount of protein adsorbed is still relatively low. When the hydrogel series was cultured with 3T3 mouse fibroblasts, the results reflected those for protein adsorption. Minimal cells adhered to the homogeneous hydrogels, while only some adhered to the heterogeneous samples. Therefore, the biological properties were not greatly affected and still mimic the stealth PEG-like properties, limiting non-specific adhesion. In all cases, the phase separated domains lead to non-linear property changes.

Conclusions

Based on the results collected, it was determined that the macroscopic properties are linearly influenced by the precursor incorporation. While the microstructure of the hydrogels does not completely govern the bulk properties, it does contribute in a small capacity. On the other hand, microstructure does control the biological properties of these hydrogels. Both the macroscopic and microscopic properties can be tuned based on the amount of long and short chain precursors. This leads to domain formation, causing heterogeneity throughout the hydrogels by increasing their hydrophobicity, but allows for a modular approach to hydrogel design.

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