Injectable and Degradable, Hydrophobically Modified Poly(Oligoethylene glycol methacrylate) Hydrogels with Decoupled Physicochemical and Biological Properties

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Introduction

Poly(ethylene glycol) (PEG)-based hydrogels are attractive biomaterials for drug delivery applications due to their hydrophilic, non-cytotoxic and non-immunogenic properties. However, the use of linear PEG is limited as it is difficult to chemically modify these polymers to allow for chemical versatility due to the limited number of reactive end groups present[1]. We recently reported on *in situ*-gelling PEG-analogue hydrogels based on poly(oligoethylene glycol methacrylate) (POEGMA) based on rapid gelation of hydrazide and aldehyde-functionalized POEGMA oligomers upon mixing. This approach overcomes many of the challenges of conventional PEG-based hydrogels while maintaining the favourable properties of PEG[2]; furthermore, by tuning the length of the oligo(ethylene glycol) side chains[3], both PEG-mimetic and thermoresponsive hydrogels can be formed[4]. However, such materials continue to suffer from two primary drawbacks from an applications perspective: (1) the highly hydrophilic nature of PEG and POEGMA limits their potential for hydrophobic drug binding and delivery and (2) the cross-link density and the degradation time of the existing hydrazone cross-linked hydrogels cannot be decoupled, making customization of hydrogels with defined mechanics and degradation time challenging.

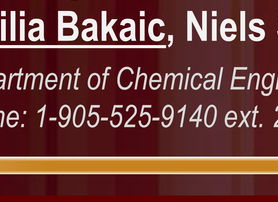
To address this challenge, we have developed hydrogels generated based on crosslinked hydrazide and aldehyde-functionalized copolymers of OEGMA and oligo(lactic acid) methacrylate (OLA). The OLA side chains in such a polymer represent degradable hydrophobic residues that can address both of the key stated limitations of PEG/POEGMA-based hydrogels: (1) self-association of OLA residues enables the formation of hydrophobic nanodomains that can facilitate significantly enhanced protein and hydrophobic drug binding relative to POEGMA alone and (2) OLA self-association creates physical cross-links (via hydrophobic interactions) that can compete with and/or supplement covalent hydrazone cross-link formation, with the balance between the two chemistries enabling decoupling of gel mechanics and gel degradation.

Experimental

Oligo(D,L-lactide) modified poly(oligoethylene glycol methacrylate)

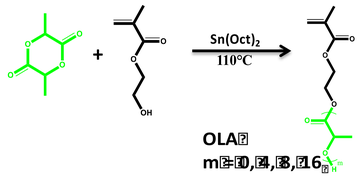
- Hydrazide-functionalized poly(OEGMA-OLA) copolymers ($PO_xOLA_{m\text{-}z}$) were prepared by free radical chain transfer copolymerization of OEGMA, OLA, and acrylic acid, followed by carbodiimide-mediated coupling of an excess of adipic acid dihydrazide.
- OEGMA monomer mixtures of 10% *n*=2/90% *n*=8-9 (PO_{10}) or 100% *n*=8-9 (PO_{100}), where *n* is the number of ethylene glycol repeat units in the OEGMA monomer, were used, the former of which creates a thermoresponsive gel (mimicking poly(N-isopropylacrylamide)) and the latter of which has no thermal phase transition temperature (mimicking PEG).

POEGMA

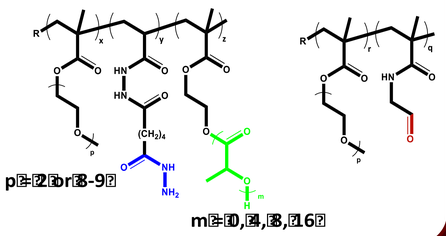


PEG chain length:
$M(EO)_2MA$: **x = 2 (short chain)**
$OEGMA_{475}$: **y = 8-9 (long chain)**

- Copolymerization of oligo (lactic acid)-hydroxyethyl methacrylate (OLA-HEMA) with POEGMA leads to hydrophobic domain formation in the resultant hydrogel network[3].

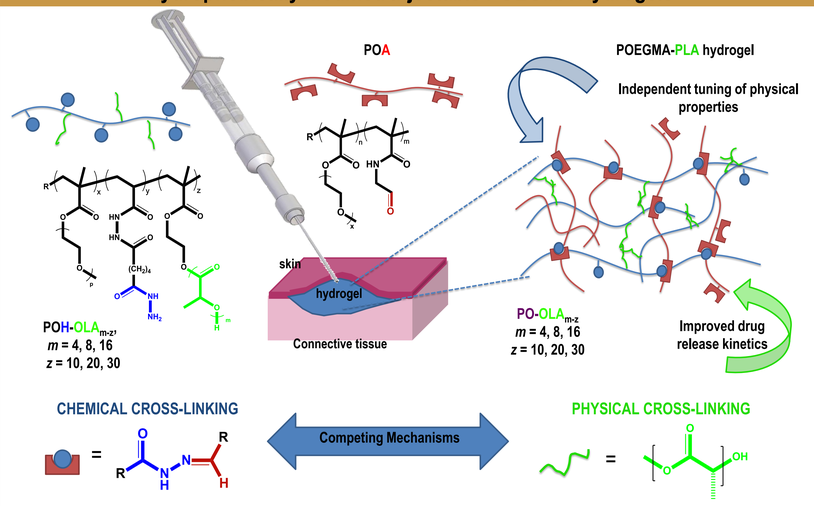


- Similarly, OLA monomers containing *m*=4, *m*=8, or *m*=16 lactic acid repeat units were prepared and copolymerized at overall monomer ratios ranging from z=0-20 mol% to vary the hydrophobic driving force for POLA self-assembly. Cross-linking was performed using aldehyde-functionalized POEGMA polymers with the same OEGMA monomer ratio.
- Copolymers were evaluated by ^{1}H-NMR, conductometric titration, and gel permeation chromatography.



Results

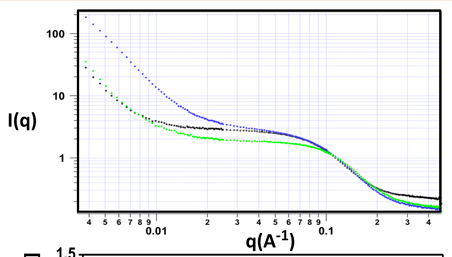
Hydrophobically Modified Injectable POEGMA Hydrogels

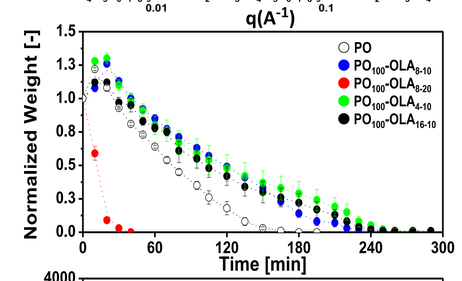


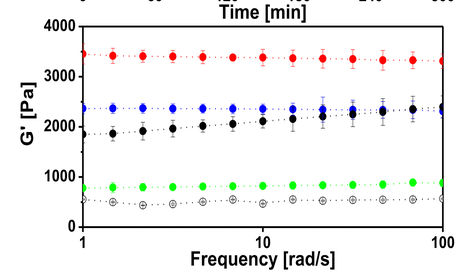
- Hydrazide and aldehyde-functionalized polymer precursor solutions are co-injected using a double barrel syringe into rubber moulds to form 0.9 cm^3 gels.
- A combination of chemical and physical crosslinking present

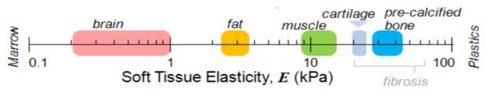
Physiochemical Properties of PO-OLA Hydrogels

- Small angle neutron scattering confirms OLA self association, with scattering intensities increasing with larger OLA monomer concentrations within the polymer.
- Hydrogels prepared using oligomers containing longer oligo(lactic acid) side chains or higher concentration OLA monomer concentrations (→ higher physical crosslinking) undergo faster degradation under acidic conditions (50mM HCl) relative to PO_{100} gels.
- Comparatively, increasing the concentration of OLA monomer in the gels increases the mechanical properties substantially.
- Higher physical cross-link densities (via OLA self-association) compete with the formation of the more stable hydrazone covalent bonds, creating a new mechanism to decouple gel mechanics and degradability.
- By varying the mol % functionalization (y) and precursor concentration, a range of mechanical properties can be achieved that directly mimic native tissue elasticities.



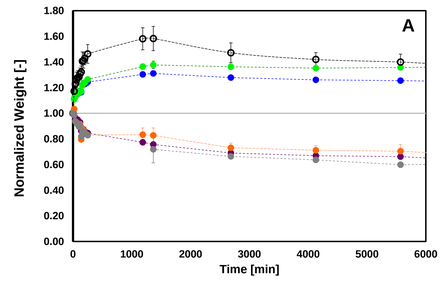


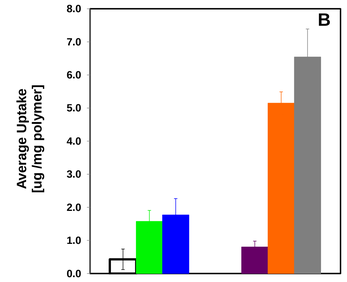


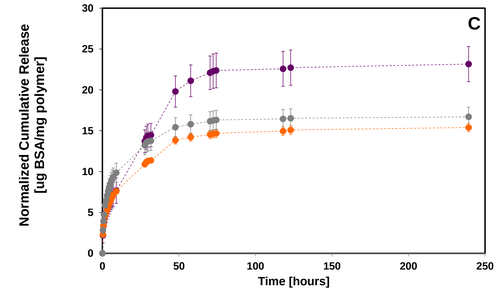


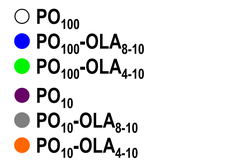
Results

Application Properties of PO-OLA Hydrogels









- PO_{100}OLA polymers self-assembled but did not show lower critical solution temperature (LCST) behavior
- PO_{10}OLA polymers all showed distinct LCSTs that were decreased with higher OLA loadings.
- Volume phase transition temperature behavior and the swelling kinetics of the resulting hydrogels were not significantly affected by the incorporation of OLA.
- Protein adsorption is significantly increased as more OLA (higher z) of longer chain lengths (higher *m*) is incorporated into the gels, with thermoresponsive PO_{10}OLA gels further enhancing protein uptake.
- Incorporation of OLA residues decreases the rate and total amount of BSA release in PO_{10}OLA gels → increased hydrophobic domain formation provides higher affinity BSA binding sites.

Conclusions

- Hydrophobically modified POEGMA hydrogels offer significant potential to both decouple otherwise dependent gel properties due to their competing mechanisms of gelation (for tissue engineering applications) and tune both the uptake and release of hydrophobic (or hydrophobic-binding) drug cargoes (for controlled release applications)
- Tunability of gel properties by the varying side chain length of OEG and/or OLA monomers provides a flexible synthetic system without compromising gel degradability

Acknowledgements and References

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