Guest-Host Assembly of Shear-Thinning Hyaluronic Acid Hydrogels

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Statement of Purpose: Injectable hydrogels continue to gain interest as scaffolds for biomolecule delivery and tissue engineering due to their minimally-invasive delivery.[1] Shear-thinning hydrogels afford direct injection or catheter delivery without potential premature gel formation and delivery failure or the use of triggers such as chemical initiators or heat. However, many shear-thinning hydrogels require long reassembly times or exhibit rapid erosion.[2] Thus, we developed shear-thinning hyaluronic acid (HA) hydrogels that rapidly reassemble, have tunable mechanical properties, and erode slowly for the sustained release of biomolecules. The hydrogel is based on the guest-host interactions of adamantane-modified HA (Ad-HA) and β-cyclodextrin-modified HA (CD-HA). Mixing results in a hydrogel composed of non-covalent dynamic bonds with properties dependent on crosslink density through macromer concentration, modification, or the ratio of guest and host functional groups. The hydrogels show potential as a minimally-invasive injectable material for cell and drug delivery.

Methods: To obtain hydrogel precursors capable of forming a hydrogel upon mixing, two separate macromers were synthesized. Briefly, the tetrabutylammonium salt of HA (HA-TBA) was modified by coupling of 1-adamantane acetic acid via BOC2O/DMAP mediated esterification to yield Ad-HA. The percent of HA repeat units modified were varied from 20%-50% as denoted by the component subscript (ex: Ad_{20}-HA for 20% modification). Separately, β-cyclodextrin was bound to a 1,6-hexanediamine linker as previously described[3] and reacted with HA-TBA through BOP mediated amidation to yield CD_{20}-HA. The interaction of macromers with the complementary guest or host was confirmed by ^{1}H NMR. Continuous flow experiments and oscillatory rheology (AR2000) were used to characterize the physical properties of the hydrogel network including shear-thinning behavior, reassembly time, storage and loss moduli, and bulk relaxation time.

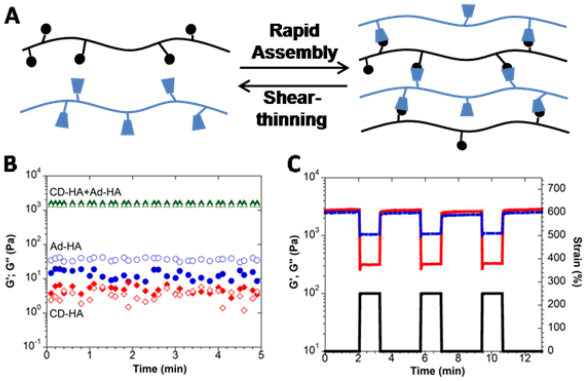

Figure 1. (A) Schematic of dynamic crosslink formation. (B) Oscillatory time sweeps of individual macromers and hydrogel formed at 5wt%; storage modulus (filled symbols) and loss modulus (empty symbols) at 10 Hz, 1.0% strain. (C) Storage (red) and loss modulus (blue) of hydrogel (AD_{20}-HA+CD_{20}-HA, 7.5wt%) under cyclic deformation of 0.5 and 250% strain at 10Hz (black).

Results: Individual macromers are viscous solutions, as confirmed by oscillatory rheology. A drastic increase in moduli and formation of a pseudoplastic hydrogel is observed upon mixing (Fig. 1B). Under continuous flow conditions (shear rate=0-0.5 s^{-1}), materials exhibit shear-thinning behavior, and higher strain rates show evidence of shear-banding behavior (data not shown). Oscillation of the applied strain demonstrates transition to a liquid state at high-strain and near immediate recovery (<1 s) at onset of low-strain conditions (Fig. 1C). This behavior will allow for facile delivery of the material through syringe or catheter systems with rapid reassembly.

Modulation of the guest to host group ratio confirms interaction in a 1:1 fashion through convergence of mechanical properties on a maxima (data not shown). Variation in crosslink density by change in the macromer concentration results in an increase in the storage and loss moduli as well as the relaxation time (Fig. 2A,C). Variation in crosslink density by increasing Ad-HA modification results in a more drastic increase in relaxation time, though moduli plateau at high Ad-HA modifications (Fig. 2B,D). These data illustrate the ease of tunability for the HA hydrogel system mechanics for widespread use.

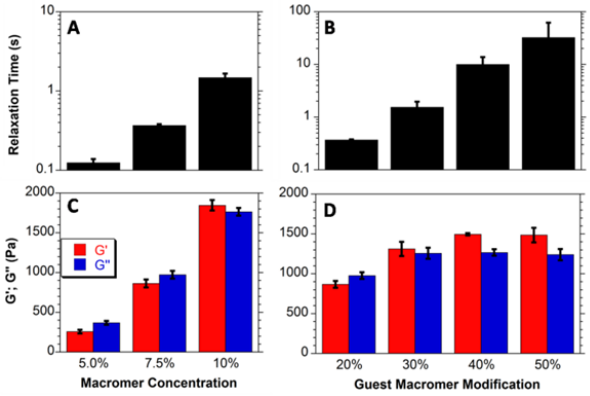

Figure 2. Macromer concentration and guest macromer modification effects on bulk relaxation time (A, B) and the storage and loss moduli at 1.0 Hz, 1.0% strain (C, D).

Conclusions: In the context of an injectable system, results demonstrate the ability of the materials developed to form a pseudoplastic hydrogel upon mixing, flow for injection delivery, and recover near-instantaneously at the target site without potentially detrimental chemical reactions. Furthermore, the mechanical properties of the hydrogel network are tunable through the density of dynamic crosslinks formed by the pendant guest and host functional groups. Ongoing work includes demonstrating the effect of the network topology on erosion and concurrent biomolecule release, as well as implementing towards specific biomedical applications (e.g., after infarction) where injectable hydrogels are needed.

References: [1]Kretlow JD, et al. Advanced Drug Delivery Reviews. 2007:59:263-73. [2]Guvendiren M, et al. Soft Materials. 2012:8:260-72. [3]Kaya E, Et al. Journal of Polymer Science Part A, 2009:48:581-92.