Development of Multifunctional Shear-thinning Guest-host Assembled Colloidal Hydrogels

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Statement of Purpose: Colloidal hydrogel systems, created by crosslinking hydrophilic particles, show great potential for use in biomaterial and drug delivery applications.[1,2] We recently used reversible guest-host chemistry between β-cyclodextrin (CD) and adamantane (Ad) to design self-assembling and shear-thinning hydrogels that were easily injected into tissues.[3] Here, we applied this guest-host chemistry as an inter-particle crosslinking mechanism of hyaluronic acid (HA) based microgel particles (Fig.1A), to introduce shear-thinning and self-assembling properties to a colloidal hydrogel. Furthermore, we explored the modularity of this system by developing colloidal hydrogels assembled with multiple particle populations with individual erosion and drug release properties.

Methods: HA (75kDa) was modified with Ad and either methacrylates (AdMeHA) or norbornenes (AdNorHA). AdNorHA or AdMeHA precursor solutions were formed into droplets using a microfluidic system, and photocrosslinked under UV with I2959 initiator to form AdMeHA microgels or I2959 with a dithiol crosslinker (DTT or MMP cleavable peptide: GCNSGGRMSMPVSNCG) for AdNorHA microgels.[4] Colloidal hydrogels were formed by combining hydrated microgels and CD modified HA (CD-HA). Rheology was performed on self-assembled colloidal hydrogels using a stress-controlled rheometer. Multi-particle colloidal hydrogels were assayed for drug release and degradation by incubation at 37 °C in calcium supplemented PBS containing 0 or 100 U/mL Type II collagenase and measured for fluorescein-dextran (FITC-Dex) or HA.

Results: AdMeHA and AdNorHA particles were successfully synthesized via microfluidic techniques (Fig. 1B) and assembled into colloidal hydrogels by mixing with CD-HA (Fig.1C). The hydrogels retained distinct regions of particles and the CD-HA polymer. Time sweeps showed that both gel groups had similar mechanics and were significantly higher ($p < 0.01$) than controls with no CD (AdMeHA particles with unmodified HA) or with no Ad (MeHA particles with CD-HA) at 1 and 10Hz frequencies (Fig.1D). Thus, both guest-host components were needed for assembly. The application of high strain (500%) and return to low strain (1%) was used to illustrate shear-thinning and rapid self-healing properties of guest-host colloidal hydrogels (Fig.1E), which will permit injectability. Colloidal hydrogels were also formed from two distinct particle populations with varied properties, one made with AdMeHA designed to be stable and another from AdNorHA with protease cleavable crosslinks and encapsulating FITC-Dex (Fig.2A). FITC-Dex release (Fig.2B) and degradation (Fig.2C) were significantly higher with collagenase treatment, illustrating the tuning of bulk properties through design of the microgels crosslinking. Distinct release profiles could be obtained by entrapping different drugs in particles with varying erosion behavior.

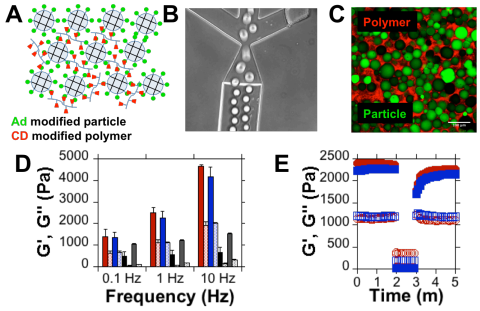

Figure 1. Schematic representation of colloidal hydrogels (A). Microgel droplet generation on microfluidic device (B). Confocal image of colloidal hydrogel, (C, scale=100 μm). G' (solid) and G" (shaded) for AdMeHA colloidal hydrogels (red), AdNorHA colloidal hydrogels (blue), controls without CD (black) and controls without Ad (grey) (D). High (500%) and low (1%) strain recovery profiles for AdMeHA (red) and AdNorHA (blue) colloidal hydrogels (E).

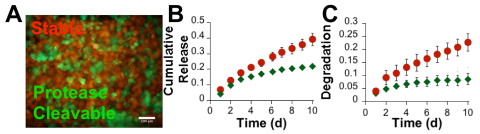

Figure 2. Fluorescence image of dual-particle (stable: red, protease degradable: green) colloidal hydrogels (A, scale=100 um). FITC-Dex release (B) or uronic acid release (C) from dual-particle colloidal hydrogels in 0 U/mL (green) or 100 U/mL (red) collagenase.

Conclusions: Guest-host chemistry between Ad and CD provides a useful inter-particle crosslinking mechanism for assembling self-healing colloidal hydrogels that could be injected into tissues. Furthermore, intra-particle crosslinking chemistry can be varied, while maintaining hydrogels with similar mechanics, to develop multi-functional hydrogels. This property permits the assembly of hydrogels with various compartments, where independent release profiles are possible (e.g., from stable and protease cleavable particles). These findings are significant, as they provide a platform technology leveraging molecular self-assembly to construct modular micro-scale components into a macro-scale hydrogel network. Highly structured materials such as these are important in implementing multi-functional therapies towards complex pathologies such as myocardial infarction.

References: 1. Griffin DR. Nat Mater. 2015; 14:737-744 2. Appel EA. Nat Commun. 2015; 6:6295 3. Rodell CB. Biomacromolecules. 2013;14: 4125-34. 4. Jeong HH. Lab Chip. 2015; 15: 4387

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