Ultrastiff nanocomposite hydrogels for biomedical applications

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Hydrogels are highly hydrated three-dimensional polymeric network that mimics native tissue microenvironment. However, the utility of hydrogels is severely hampered by its limited mechanical stiffness and toughness. Ranges of chemical and physical mechanisms are proposed to engineere mechanically stiff and tough polymeric network; for example a covalent crosslinking gelatin hydrogel have stiffness between 3-30kPa. A range of nanoparticles is incorporated within the hydrogel network to enhance to mechanical stiffness by 2-5 folds. But most of these modifications render the formation of brittle hydrogels. Here, we report covalently reinforced ultrastiff hydrogels from methacrylated gelatin (GelMA) and (poly-ethylene glycol)-diacid functionalized magnetic nanoparticles (MNPs).

Methods: We synthesized oleic acid functionalized magnetic nanoparticles using high temperature decomposition of iron oleate complex in presence of oleic acid at 325 °C. The reaction time governs the ultimate size of nanoparticles and MNPs with 4, 8 and 12nm are synthesized. The oleic acid coated MNPs are transferred into aqueous media by surface modification with PEG-diacid (M_W ~ 600) using EDC-NHS chemistry. These surface functionalized MNPs were mixed in 5% GelMA solution (80% acrylation degree) to obtain chemically crosslinked GelMA-Fe_3O_4 hydrogels. We have synthesized three sizes of MNPs: 4, 8 and 12 nm and varied the concentration of MNPs from 0.01 to 0.5 µg. Different wt% of GelMa was 5% to 15% also used used to prepare discs shaped gels for physical, structural and chemical characterization. In vitro cell studied are performed using human bone marrow derived stem cells.

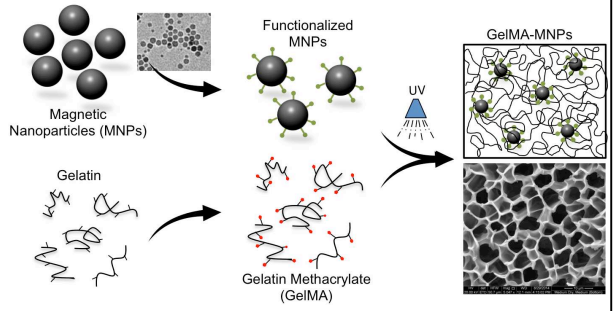

Figure 1: Schematic illustration of MNPs interaction with GelMA matrix. Representative TEM image indicates the spherical shape and size of 8 nm MNPs.

Results: A remarkable increase in the compression modulus of GelMA was observed due to increase in MNPs size and concentration. The addition of small amount of MNPs (0.0005%) to GelMA (5%) results in more than a 10-fold increase in mechanical stiffness and a 20-fold increase in toughness. For example, the toughness of the GelMA was improved from 20 to more than 300 kJ/m^3 due to the addition 0.5 µg/mL concentration of 12 nm MNPs. The increase in mechanical stiffness of nanocomposites indicates a strong covalent interaction between the free amine groups available on GelMA backbone with the PEG-diacid group available on MNPs (size approx. 8 nm) as determined by infrared, nuclear magnetic resonance and X-ray photoelectron spectroscopy. The mechanical stiffness of nanoengineered hydrogel can be easily tailored to 1MPa by fine-tuning the size of MNPs (4, 8 and 12 nm) and the ratio of GelMA to MNPs. Moreover the nanoengineered hydrogels are highly elastomeric and can sustain more than 90% compressive strain without any plastic deformation. Bone marrow dereived stem cells readily attach and proliferation on all the nanocomposite surfaces. We are also in process of evaluate the effect of chemical reinforcement on cell shape in 3D microenvironment. Overall, we showed that hydrogels made from surface functionalized MNPs could be used chemically reinforce hydrogel network for biomedical applications

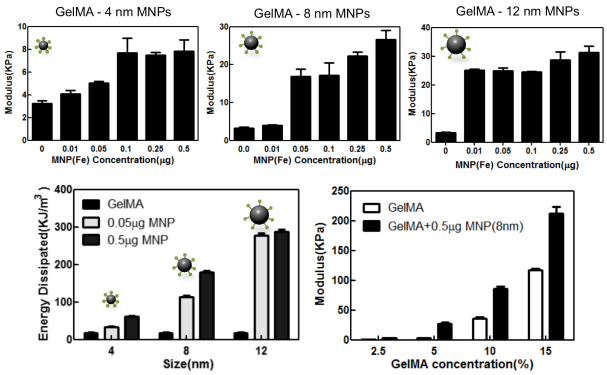

Figure 2: The addition of MNPs with different diameters (4, 8 and 12 nm) to GelMA results in significant increase in mechanical stiffness. The energy required to 90% compressive deformation is listed in bottom left graph. The addition of small amount of MNPs showed more than 20 fold increase in toughness. Thee modulus for diffrent GelMa concentrations (2.5, 5, 10 and 15 wt%) loaded with 8nm MNPs is shown in bottom right graph.

Conclusions: Hydrogel with high stiff can be obtained via chemical reinforcement of MNPs that can results in 10-fold increase in mechanical stiffness and a 20-fold increase in toughness. Moreover the nanoengineered hydrogels are highly elastomeric and can sustain more than 90% compressive strain without fracture. These nanoengineered hydrogel can be used to engineer mechanically stiff network for biomedical applications including tissue-engineered scaffolds, drug delivery vehicles, bioactuators and sensors.