Temperature-sensitive Hydrogels with SiO_2-Au Nanoshells for Controlled Protein Delivery

Malavosklish Bikram[1], Andre M. Gobin[1], Rachel E. Whitmire[1], Scott R. Sershen[1], and Jennifer L. West[1]
[1]Department of Bioengineering, Rice University, 6100 Main, Houston, TX, USA 77005.

Introduction: In the field of drug delivery, modulated release of a therapeutic agent in response to physiological requirements remains a hurdle that needs to be overcome. To this end, there have been many systems designed to respond to stimuli in the local environment including ultrasound, electric fields, and mechanical forces.[1] In certain diseases e.g. diabetes mellitus, only a low level of drug is required for therapeutic efficacy. Thus, to obtain the controlled release of proteins we have developed a composite hydrogel material composed of the temperature-sensitive copolymer *N*-isopropylacrylamide (NIPAAm)-*co*-acrylamide (AAm) and silica-gold (SiO_2-Au) nanoshells. NIPAAm-*co*-AAm hydrogels have a lower critical solution temperature (LCST) that is slightly above physiological temperature. Nanoshells such as SiO_2-Au strongly absorb near-IR light that does not affect tissue with the result that heat is generated. The heat facilitates collapse of the hydrogel above its LCST thereby releasing the embedded drug.

Methods: Stock concentrations of NIPAAm and AAm (1.75 M) were used to prepare hydrogels at a 95/5 molar ratio respectively. MBAAm was used as a crosslinker at 1/750 (crosslinker/monomer) ratio. Briefly, 15 mL of NIPAAm and AAm were added to a round-bottom flask to which 50 µL of 10 % (w/v) APS and 10 µL TEMED were added with stirring. Two concentrations of nanoshells (2.0×10^9 and 4.0×10^9 particles/mL) were then added to the solution with stirring. The reaction solution was then poured into glass molds and cured at 30 ºC for 2 h. Circular disks were then cut out with a cork borer and dried in a vacuum oven. Control hydrogels were prepared as outlined without nanoshells. The reversibility of the temperature induced collapse of the NIPAAm-co-AAm hydrogels only was determined by adding disks to 5 mL 0.05 M tris buffer, pH 7.4 that was allowed to swell overnight. The wet weigh was recorded and then disks were moved to a 50°C water bath and the weight at various time points were recorded. The disks were then moved to room temperature and the weights of the disks were determined as a function of time. The disks were left overnight and the weight at 50ºC and at room temperature was again determined as outlined above. The deswelling ratio (DSR) vs. time was plotted. The photothermal behavior of the hydrogel-nanoshell composites was determined with various concentrations of nanoshells at three different fluences – 1.2, 1.4, and 1.6 W/cm^2. The hydrogels containing nanoshells were allowed to swell as previously described. Each disk was then irradiated along its vertical axis with a continuous wave diode laser for 10 min intervals at the end of which the disks were weighted. The laser was then turned off and the weight of the each disk was recorded as a function of time.

Results/Discussion: The temperature-induced collapse of the NIPAAm-co-AAm hydrogels only was shown to be reversible up to 3 d in which the hydrogels collapsed to a DSR of ~14.4 ± 1.16 % in 3 h. The photothermal collapse of the nanoshells-composite hydrogels showed a dependence on both nanoshell concentration as well as fluence of the laser (Figures 1, 2, and 3).

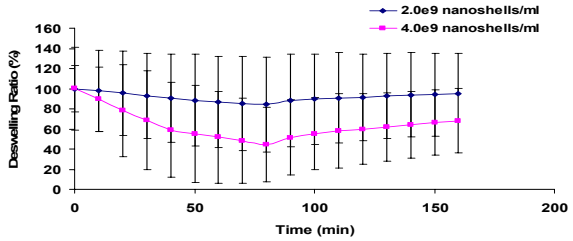

Figure 1 Photothermal behavior of nanoshell-composite hydrogels with concentrations of 2.0e9 and 4.0e9 nanoshells/mL during and after irradiation at 808 nm (1.2 W/cm^2). Control hydrogels only showed no collapse. Data represent mean ± SD (N=3).

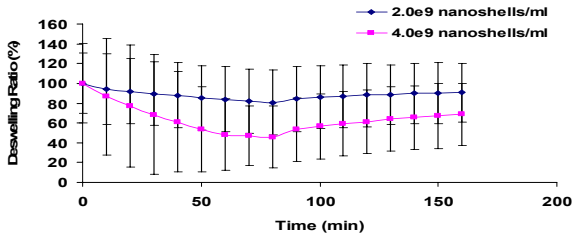

Figure 2 Photothermal behavior of nanoshell-composite hydrogels with concentrations of 2.0e9 and 4.0e9 nanoshells/mL during and after irradiation at 808 nm (1.4 W/cm^2). Control hydrogels only showed no collapse. Data represent mean ± SD (N=3).

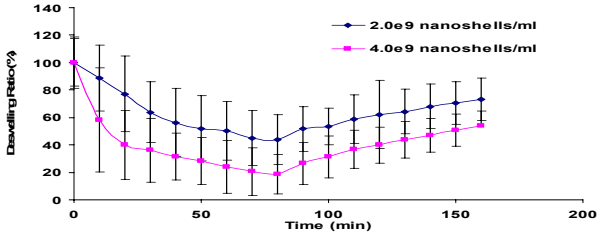

Figure 3 Photothermal behavior of nanoshell-composite hydrogels with concentrations of 2.0e9 and 4.0e9 nanoshells/mL during and after irradiation at 808 nm (1.6 W/cm^2). Control hydrogels only showed no collapse. Data represents mean ± SD (N=3).

The data revealed that the higher nanoshell concentration of 4.0×10^9 particles/mL at the highest fluence of 1.6 W/cm^2 produced the lowest DSR of 18.6 ± 14.5 % compared with 45.8 ± 31.0 % and 44.4 ± 37.0 % for fluences at 1.2 and 1.4 W/cm^2 respectively.

Conclusions: Photothermal modulation of hydrogel collapse represents a promising strategy to the successful delivery of therapeutic proteins and drugs. This data indicates that the hydrogels can be modified by many parameters e.g. nanoshell concentration in order to obtain a desired drug release profile that is suitable to the disease model. Future studies will be focused on the release profiles of protein-loaded hydrogels for the treatment of diabetes.

References: 1. Sershen S. and West J. (2002) *Advanced Drug Delivery Reviews*. **54**, 1225-1235.