Hydrogel-Nanoshell Composite Materials for Therapeutic Delivery

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Statement of Purpose: Controlled release systems have been highly investigated to limit the off-site toxicities of chemotherapeutic regimens. This work aims to improve upon existing methods by creating an injectable delivery system that controls drug release to occur only at the site of malignant tissue. This system consists of two novel material components. A thermally responsive poly[n-isopropylacrylamide-co-acrylamide] (NIPAAm-co-AAm) hydrogel material acts to encapsulate the drug, leading to increased serum stability and decreased exposure to off-site tissues. In addition, embedded gold-silica nanoshells act as a triggering mechanism to release the therapeutic payload only at the site of malignant tissue.
Thermally responsive hydrogels go through a physical property transition at their lower critical solution temperature (LCST). When heated above the LCST, the material collapses, expelling large amounts of water and absorbed molecules. This phase change can be optically triggered exposing the embedded gold-silica nanoshells to near-infrared (NIR) light, as these particles rapidly transfer NIR light into heat through the surface plasmon resonance phenomena. When these composites are exposed to NIR light, which can penetrate biological tissue, a rapid temperature increase, hydrogel collapse, and drug expulsion will occur. This work investigates delivery of two different cancer therapeutics (doxorubicin and a 21 base pair DNA duplex mimicking siRNA) from bulk constructs of this composite material, as well as advances the development of the material as injectable-sized particles.

Methods: Poly(NIPAAm-co-AAm) hydrogels were synthesized via free radical polymerization of a prepolymer solution (95:5 molar ratio of NIPAAm:AAm with a 1:750 ratio of the crosslinker methylenebisacrylamide to the monomers) and $8 \cdot 10^9$ nanoshells/mL gold-silica nanoshells (bulk hydrogels) or $1.5 \cdot 10^{10}$ nanoshells/ml (nanoscale hydrogels). Ammonium persulfate (APS) and tetramethylethylenediamine (TEMED) were added to initiate polymerization. Bulk hydrogels were cured between two glass slides with a spacer of 1.5 mm, while nanoscale hydrogels were cured in gelatin templates containing 500 nm cylindrical wells. In studies of the bulk hydrogel composites, the LCST of the hydrogels was determined by incubating gels in a water bath at increasing temperatures and weighing to analyze deswelling behavior. For release studies, hydrogels were swollen in a solution of either doxorubicin or DNA duplexes. Temperature was then altered by either incubation at 50 ^{o}C or exposure to an 808 nm laser at 8 W/cm^2. Samples of buffer solution were taken at various time points and analyzed via UV-Vis spectroscopy for drug content. Nanoscale hydrogel composite particles were analyzed using TEM, 2-photon microscopy, and hyperspectral microscopy. Thermal collapse of particles was analyzed by taking DLS measurements at 25 ^{o}C, 50 ^{o}C, and after exposure to an NIR laser (808 nm, 4 W/cm^2, 5 min).

Results: The LCST of bulk poly(NIPAAm-co-AAm) hydrogels was determined to be from 39-45 ^{o}C, or slightly above physiologic temperature. Collapse of the hydrogel-nanoshells composites is seen to follow both incubation at 50 ^{o}C and irradiation with the NIR laser. Doxorubicin and dsDNA delivery from irradiated bulk hydrogels containing nanoshells is significantly higher than controls at all times t>0 (Fig. 1A). Analysis by TEM indicates that the composite particles consist of nanoshells surrounded by a thin polymer coating (Fig. 1B), whereas bare nanoshells do not display this coating (Fig. 1C). Nanoscale hydrogel composites deswell in response to both increased temperature and NIR irradiation, indicating these composite particles display the same thermal properties as previously investigated bulk material.

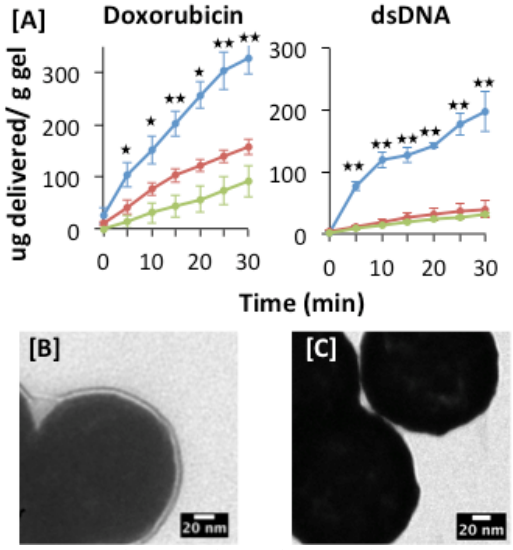

Figure 1. [A] Release of doxorubicin and dsDNA from bulk composite gels. Gels with nanoshells exposed to an NIR laser (blue) delivered significantly more drug than gels exposed to the laser without nanoshells (red) or gels left a room temperature (green; *p<0.05, **p<0.01). [B] TEM image of hydrogel-nanoshell composite particles. [C] TEM image of bare nanoshells.

Conclusions: Burst release various cancer therapeutics can be triggered by NIR irradiation of nanoshell containing poly(NIPAAm-co-AAm) hydrogels. This material can be synthesized into nanoscale, injectable particles which maintain the same thermal properties as the bulk hydrogels. Ultimately, this material could be used as an injectable delivery platform as follows. Drug-loaded particles would be injected intravenously, would passively accumulate in tumor tissue due to the enhanced permeation and retention (EPR) effect, at which time an external NIR laser would be applied to trigger drug release directly at the tumor site.