Pulsatile Drug Delivery from Poly(NIPAAm-co-AAm)- Gold Nanoshell Composites

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Statement of Purpose: Pulsatile drug delivery systems allow for tight spatial and temporal control, which is advantageous in delivery of chemotherapeutic agents for which exposure to healthy tissue should be minimized to increase efficacy and decrease side effects. As example, poly(NIPAAm-co-AAm) hydrogels can be loaded with macromolecules and tuned to have a lower critical solution temperature (LCST) slightly above that of physiologic temperature. When these gels are raised to above their LCST, they expel water along with any absorbed drug molecules in a burst release fashion[1]. We demonstrate that this delivery can be triggered by near-infrared (NIR) irradiation of gold-silica nanoshells in a composite hydrogel system.

Methods: **Nanoshell Synthesis**: Gold-silica nanoshells were synthesized by previously described methods[2]. **Hydrogel Synthesis**: Poly(NIPAAm-co-AAm) hydrogels were synthesized using a 95:5 molar ratio of NIPAAm:AAm and a 1:750 ratio of crosslinker MBAAm to monomers. Gold-silica nanoshells ($4 \cdot 10^9$ nanoshells/mL) were added to the monomer/crosslinker solution and Ar gas was bubbled through for 20 min to minimize dissolved O_2 content. Ammonium persulfate (APS) and tetramethylethylenediamine (TEMED) were added to initiate free radical polymerization of the hydrogels. The gels were poured between two glass slides separated by a 1.6 mm Teflon spacer and cured under vacuum for 2 h at 30°C. Individual gels were then punched out using a 6 mm diameter cork borer. **Drug Release Studies**: Dried gels were swollen in a drug containing solution and then transferred to TRIS buffer. Temperature was altered by either incubation in a water bath or exposure of nanoshell composite gels to NIR light. Aliquots of buffer solution were taken at certain time points and drug concentration was measured via UV-Vis spectroscopy. Drugs analyzed in this study include model drug methylene blue (MW=374) and the chemotherapeutic doxorubicin (MW=580). In addition, release of proteins was analyzed using the BCA protein assay.

Results: Reversible deswelling of poly(NIPAAm-co-AAm)-nanoshell composite hydrogels follows both incubation at 50°C and laser irradiation at 808 nm. Following NIR irradiation, there is a burst release of low MW drugs, such as methylene blue or doxorubicin, from nanoshell composite hydrogels that were exposed to NIR light. When using larger drugs, such as the proteins insulin (MW=5800) or lysozyme (MW=14700), this effect is more pronounced.

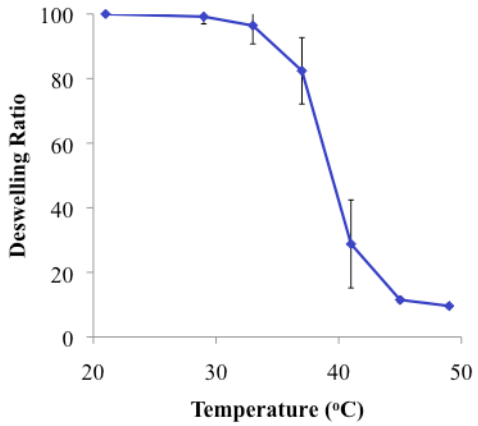

Figure 1. **LCST Determination**. Deswelling of NIPAAm-co-AAm hydrogels as a function of temperature. These hydrogels tend to collapse from 39-45°C.
(Deswelling Ratio = $Weight_{temp}$/ $Weight_{temp=21C}$)

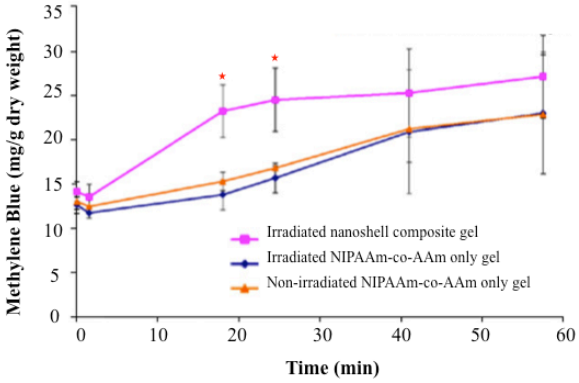

Figure 2. Drug Release in Response to NIR Irradiation. Release of model drug methylene blue (MW= 374). Gels were irradiated with an 808 nm laser at 1.3 W/cm^3 for 60 min. At initial times points (t=18 and 24.5 min) there is a significant increase in methylene blue released in irradiated nanoshell composite gels ($p<0.05$).

Conclusions: Poly(NIPAAm-co-AAm)-gold silica nanoshell composite hydrogels have an LCST above physiologic temperature. Deswelling of the gels occurs with exposure to NIR light and results in a burst release of absorbed drug molecules, making it a promising platform for controlled drug delivery.

References:

[1] Sershen SR *et al.* Journal of Biomedical Materials Research Part A 2000; 51(3):293-298.
[2] Oldenburg SJ *et al.* Chem Phys Lett. 1998; 288: 243-247.