Integration of Thermally Responsive Nanosphere Hydrogels with Gold Nanoparticles for Intelligent Therapeutic Applications

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Statement of Purpose: Research in the field of biomaterials and drug delivery is moving toward individually tailored intelligent therapeutic systems which are capable of responding to and correcting undesirable conditions, on a molecular level, within the body. The intelligent therapeutic nanocomposite systems presented here are composed of a metal nanoparticle core, surrounded by a temperature-responsive interpenetrating polymer network (IPN) layer, which encapsulates desired molecules or compounds, and exhibits a sharp positive swelling transition, which is ideal for drug delivery applications. The metal nanoparticle core of these systems can be tuned to absorb visible to near infrared (530 – 1200 nm) wavelengths of light depending on either the core to shell thickness in metal nanoshells or the diameter in solid metal nanoparticles. This absorbed light energy is then converted to heat and transmitted locally to the surrounding IPN layer, which triggers the swelling of this temperature-response polymer layer and hence the release of any encapsulated agents.

Methods: The integration of gold nanoparticles inside of polymer nanospheres was achieved using a two step sequential IPN synthesis method. First, gold nanoparticles were synthesized using standard methods (1,2) and encapsulated inside of polyacrylamide nanoparticles by *in situ* inverse emulsion polymerization with the gold nanoparticles located in the aqueous monomer droplet phase. A typical inverse emulsion solution consisted of an 81% hexane continuous phase, with a 13% surfactant phase (sodium bis(2-ethylhexyl) sulfosuccinate and Brij 30 in a 2:1 ratio), and a 6% aqueous phase. The remaining portion of the aqueous phase was then split into two separate premixes containing each containing 11.7% monomer, 4% crosslinker (N,N'-methylenebisacrylamide), 5.3% initiator (ammonium persulfate), and 79% deionized distilled water by weight. The only difference in these two premixes was that one contained only acrylamide monomer and the other only acrylic acid monomer. In the first step of the sequential IPN synthesis method the acrylamide only aqueous premix was added to the same 3-neck round bottom flask already containing the hexane, gold particles, and emulsifiers. This mixture was then purged with nitrogen gas for 30 minutes to remove oxygen, after which the polymerization was initiated with the injection of N,N,N',N'-tetramethylethylenediamine (TEMED) (0.3 ml) and allowed to react for two hours at room temperature. After two hours the reaction was cooled to 0˚C and opened to the atmosphere to terminate the reaction. The second step of the IPN synthesis was then carried out by the addition of the acrylic acid only premix to the reaction vessel followed again by purging and the addition of TEMED. The final IPN polymer-gold nanocomposites were then purified and collected using reduced pressure to remove the hexane solvent phase and centrifugation in ethanol to precipitate out the particles.

Results / Discussion: The size and relative shape of synthesized gold nanoparticles were examined using a JOEL 2010F transmission electron microscope (TEM). The composition of these particles was also confirmed using an Oxford INCA energy dispersive spectroscopy (EDS) detector with a probe spot size of 0.5 nm attached to the JOEL 2010F TEM. These techniques confirmed that the synthesized gold nanoparticles were roughly spherical in shape with an average diameter of ~50 nm for the solid gold spheres and ~600 nm for the gold nanoshells. The swelling behavior of the IPN hydrogel nanoparticles was examined using a Brookhaven ZetaPlus dynamic light scattering (DLS) instrument operating at a 90˚ scattering angle with a 635 nm diode laser source. The IPN nanoparticles exhibited a sharp positive sigmoidal swelling response with temperature at around 40 ± 5 ˚C with a linear swelling ratio increase of greater than four times the collapsed particle diameter (~ 300 nm). The size, morphology, and composition of the final IPN polymer-gold nanocomposites were examined using a Philips EM 208 TEM operating at 100kV and a LEO 1530 field emission scanning electron microscope (FE-SEM) operating at 10kv with attached Oxford INCA EDS detector. These techniques confirmed that the final morphology of the polymer-gold nanocomposites is spherical with an overall particle diameter of roughly 300 nm. EDS and TEM analysis also confirmed the successful integration of gold nanoparticles inside of IPN hydrogel nanospheres.

Conclusions: This paper illustrates the successful synthesis of a thermally responsive IPN polymer-gold nanocomposite system. TEM and EDS analysis confirm the successful synthesis and incorporation of solid gold nanoparticles inside of IPN nanospheres. DLS analysis also confirms that these IPN nanospheres exhibit a positive and sharp sigmoidal swelling response with increases in temperature. Therefore the swelling and hence therapeutic release of these systems can be controlled externally using non-invasive laser heating of the gold nanoparticle cores of these systems making them an externally triggered intelligent therapeutic system. DLS studies of the laser induced swelling and therapeutic release properties of these novel thermally responsive polymer-gold nanocomposites will be the focus of future work.

References: (1) Goodman, S.L., G.M. Hodges, L.K. Trejdosiewicz, and D.C. Livingston, "Colloidal Gold Markers And Probes For Routine Application In Microscopy." *J. Microsc.-Oxf.*, **123**, 201-213, 1981. (2) Oldenburg, S.J., R.D. Averitt, S.L. Westcott, and N.J. Halas, "Nanoengineering of optical resonances." *Chem. Phys. Lett.*, **288**, 243-247, 1998.