Temperature-Sensitive Polymer-Gold Nanocomposites for Externally Controlled Therapeutic Systems

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Introduction: The goal of the proposed therapeutic system is to provide a means to externally trigger the release of an encapsulated agent at a desired time and location. Temporal and spatially controlled delivery of therapeutics via the composite nanoparticles will greatly increase the quality of life of patients by lowering overall systemic doses, decreasing side effects, and extending the release time of effective dose concentrations allowing fewer administrations.

The intelligent therapeutic nanocomposite systems presented here are composed of a metal nanoparticle core, surrounded by a temperature-responsive polymer layer, which encapsulates desired molecules or compounds, and exhibits a sharp swelling transition. The metal nanoparticle core, either gold nanoshells or nanorods, of these systems can be tuned to absorb visible to near infrared wavelengths of light depending on either the core to shell thickness in metal nanoshells or the aspect ratio of solid gold nanorods. Maximum absorption in the near-infrared region is desired, because light in this region is physiologically noninvasive and penetrates deeply. This absorbed light energy is then converted to heat and transmitted locally to the surrounding thermally sensitive polymer layer, which triggers a swelling response in aqueous soluitions, and hence the triggered release of any encapsulated agents. Specifically, these systems would exhibit a negative swelling transition upon heating, where the particle quickly "squeezes" out an encapsulated therapeutic.

Methods: Thermally-responsive nanogels based on N-isopropylacrylamide have been synthesized via aqueous dispersion polymerization. N-isopropylacrylamide, N,N-methylenebisacrylamide crosslinker, and sodium dodecyl sulfate were added to water in a round bottom flask. The flask was purged for 30 minutes with nitrogen to displace the oxygen in the flask. The flask was submerged in a 70ºC bath and the temperature allowed to equilibrate. Since the resultant polymer network has a lower critical solution temperature (LCST) around 32ºC the growing macroradicals are hydrophobic and nucleate to form particles in the aqueous environment. A solution of ammonium persulfate was injected into the flask to initiate the reaction.

Additionally, temperature-sensitive nanoparticles have been synthesized of copolymers of N-isopropyl acrylamide with more hydrophilic monomers including acrylamide and acrylic acid. Copolymers with a 95/5 molar ratio of N-isopropylacrylamide to acrylamide or acrylic acid were synthesized using the same procedure described above.

A solution of gold nanorods has been incorporated in the various polymerizations to form gold-polymer nanocomposites

Results / Discussion: The temperature influenced swelling behavior of the nanoparticles was examined using dynamic light scattering. Particle diameters below the LCST were roughly 200-300 nm in diameter at 25ºC in water depending on the specific monomer composition. Particle size was measured at 2ºC intervals between 10 and 60ºC. Upon an increase in temperature the particles exhibit a negative sigmoidal swelling curve with swelling transition temperatures ranging from 32 to 40ºC. Copolymers incorporating acrylamide or acrylic acid demonstrate LCST behavior at the high end of this range which is desirable for use in vivo where the LCST needs to exceed physiological temperature.

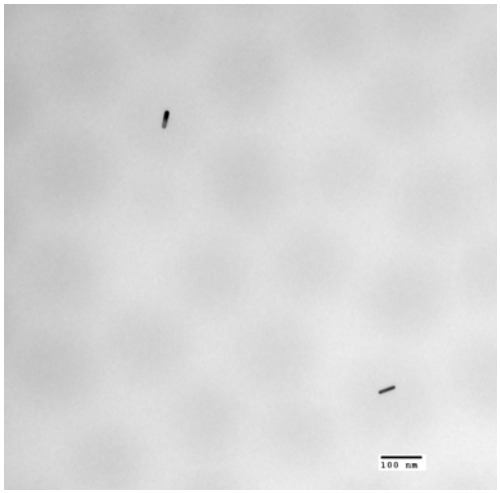

Figure 1. Representative TEM micrograph of gold-polymer nanocomposites.

The gold-polymer composites were examined using transmission electron microscopy (TEM). The nanocomposie particles were deposited on carbon coated copper grids from aqueous solution following plasma cleaning. Micrographs confirm uniform particle formation with diameters under 300nm and incorporation of 40nm long gold nanorods within the polymer layer in approximately 10% of particles.

Conclusions: TEM analysis confirmed formation of gold-polymer nanocomposites by the incorporation of gold nanorods inside of thermally responsive polymer nanogels. The temperature-responsive behavior of the particles was demonstrated by particle sizing over the relevant temperature range using dynamic light scattering. As a result, these systems show promise as an externally triggered system where non-invasive light could be used to heat the particles triggering therapeutic release. Future work focuses on optimizing nanocomposite formation and demonstrating the light-induced release of encapsulated agents from the novel therapeutic systems.