Nanoparticulate Gold-Polymer Systems for Externally-Controlled Delivery

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Statement of Purpose: Externally controlled systems are therapeutic devices that can be triggered to release an encapsulated agent at a desired time and location, by external means. Specifically, the systems we are developing consist of metal-polymer nanocomposite materials with a metal core and a surrounding temperature-sensitive polymer layer that can be triggered to release encapsulated therapeutics upon exposure to an external light source.

The metal nanoparticle component of these systems, gold nanorods, can be tuned to absorb near infrared wavelengths of light. Maximum absorption in the near-infrared region is desired, because light in this region is physiologically noninvasive and penetrates most deeply. This absorbed light energy is converted to heat and transmitted locally to the surrounding thermally sensitive polymer layer, which triggers a swelling response in aqueous solutions, and subsequent triggered release of any encapsulated agents.

An additional benefit of the incorporation of gold in the system is that it can act as a contrast agent for certain medical imaging techniques including photoacoustic imaging. Photoacoustic imaging uses a NIR nanopulsed laser and an ultrasound transducer. The gold nanorods absorb light in the NIR region and undergo thermoelastic expansion in response to the pulsed laser light. This pulsed expansion produces ultrasonic waves that can be detected by the transducer. The detected pattern can be used to reconstruct an image of the area of interest and confirm the presence of the composite particles at the desired release target.

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 as a stabilizer were reacted in aqueous environment at 70ºC. 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. This class of particles is capable of entrapping a therapeutic in the swollen state and upon heating through the LCST a negative swelling transition occurs squeezing out entrapped molecules.

Additionally, temperature-sensitive nanoparticles have been synthesized using copolymers of N-isopropyl acrylamide and more hydrophilic monomers including acrylamide or acrylic acid to shift the LCST to temperatures greater than physiologic temperature.

A solution of gold nanorods has been incorporated in the various polymerizations to form gold-polymer nanocomposites. Nanocomposites have been formed both by synthesizing the polymer layer outward from the gold core and by attaching gold nanorods to polymer nanoparticles following polymerization.

Swelling behavior has been characterized using dynamic light scattering. Electron microscopy techniques have been used to study nanoparticle size and polydispersity, polymer morphology, and composite formation. Loading and release of a model therapeutic from nanoparticulate systems have been measured to demonstrate the potential use of the systems for externally-controlled delivery.

Results: The gold-polymer composites were examined using transmission electron microscopy (TEM). Micrographs confirm uniform particle formation with typical diameters between 300 and 500 nm and incorporation or attachment of 40nm gold nanorods.

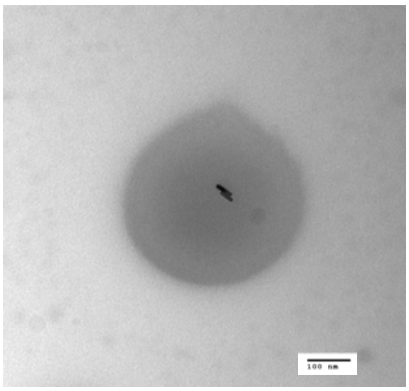

Figure 1. TEM micrograph of gold-polymer composite particle. Gold nanorods have been incorporated within the crosslinked polymer nanoparticle.

The temperature influenced swelling behavior of the polymer nanoparticles was examined using dynamic light scattering. 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

Particle loading capacity and release behavior has been studied using a model therapeutic, FITC-Dextran. Loading studies were performed in phosphate buffered saline (PBS) and percent loading quantifying using a fluorescence microplate reader. Release from loaded nanoparticles was similarly quantified in PBS at 37ºC, at 50ºC, and in pulsatile temperature change studies.

Conclusions: TEM analysis confirmed formation of gold-polymer nanocomposites by the incorporation or attachment of gold nanorods to polymer nanoparticles. The temperature-responsive behavior of the particles was demonstrated by particle sizing over the relevant temperature range using dynamic light scattering. Loading and release of a model therapeeutic has been demonstrated. As a result, these systems show promise as an externally triggered system. Future work focuses on optimizing nanocomposite formation, demonstrating the light-induced release of encapsulated agents from the novel therapeutic systems, and using photoacoustic imaging techniques to demonstrate theranostic use.