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ScienceDirect
Journal of Controlled Release 123 (2007) 219–227
journal of controlled release
www.elsevier.com/locate/jconrel

Temperature-sensitive hydrogels with SiO_2–Au nanoshells for controlled drug delivery

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Received 28 April 2007; accepted 9 August 2007
Available online 19 August 2007

Abstract

Silica–gold (SiO_2–Au) nanoshells are a new class of nanoparticles that consist of a silica dielectric core that is surrounded by a gold shell. These nanoshells are unique because their peak extinctions are very easily tunable over a wide range of wavelengths particularly in the near infrared (IR) region of the spectrum. Light in this region is transmitted through tissue with relatively little attenuation due to absorption. In addition, irradiation of SiO_2–Au nanoshells at their peak extinction coefficient results in the conversion of light to heat energy that produces a local rise in temperature. Thus, to develop a photothermal modulated drug delivery system, we have fabricated nanoshell-composite hydrogels in which SiO_2–Au nanoshells of varying concentrations have been embedded within temperature-sensitive hydrogels, for the purpose of initiating a temperature change with light. *N*-isopropylacrylamide-*co*-acrylamide (NIPAAm-*co*-AAm) hydrogels are temperature-sensitive hydrogels that were fabricated to exhibit a lower critical solution temperature (LCST) slightly above body temperature. The resulting composite hydrogels had the extinction spectrum of the SiO_2–Au nanoshells in which the hydrogels collapsed reversibly in response to temperature (50 °C) and laser irradiation. The degree of collapse of the hydrogels was controlled by the laser fluence as well as the concentration of SiO_2–Au nanoshells. Modulated drug delivery profiles for methylene blue, insulin, and lysozyme were achieved by irradiation of the drug-loaded nanoshell-composite hydrogels, which showed that drug release was dependent upon the molecular weight of the therapeutic molecule.

Keywords: Drug delivery; Nanoparticles; Protein release; Stimuli-sensitive; Controlled

1. Introduction

The lack of control of drug release from conventional drug formulations in response to physiological requirements have led to the development of controlled drug delivery systems [1,2]. In many diseases such as diabetes [3], heart disease [4], and thyroid diseases [5], the administration of a drug is only required at specific time intervals in which constant drug levels could lead to adverse effects. Hence, stimuli-sensitive drug delivery systems were developed to release a drug only in response to metabolic requirements or in the presence of specific stimuli. These environmentally-sensitive delivery systems have been developed to respond to a myriad of stimuli including the presence or absence of specific molecules [6–8], magnetic fields [9,10], ultrasound [11–13], electric fields [14,15], temperature [16–19], pH [20,21], and mechanical forces [22,23].

In addition to these stimuli, light has also been used as a stimulus for modulated drug delivery systems. Light-sensitive hydrogels have been categorized as either UV- or visible light-sensitive hydrogels. UV-sensitive hydrogels have been synthesized by the introduction of bis(4-dimethylamino)phenylmethyl leucocyanide into the polymeric matrix in which ionization of the leuco derivative with UV radiation resulted in discontinuous swelling at a constant temperature [24]. Visible light-sensitive hydrogels have been fabricated by the incorporation of light-sensitive chromophores such as the tri-sodium salt of copper chlorophyllin into poly(*N*-isopropylacrylamide) (NIPAAm) hydrogels in which the absorption of light by the chromophore resulted in the heating and subsequent collapse of the temperature-sensitive hydrogel [25].

Recently, a new class of light-sensitive hydrogels containing optically active metal nanoshells capable of absorbing near

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doi:10.1016/j.jconrel.2007.08.013

infrared (NIR) light was developed for controlled drug delivery. Sershen et al. incorporated gold–gold sulfide nanoshells into NIPAAm-*co*-acrylamide (AAm) hydrogels in order to initiate a temperature change with light [26]. These nanoshells were designed to absorb light at NIR wavelengths between 800–1200 nm, which can be transmitted through tissue with little attenuation due to the low absorption coefficients of water and hemoglobin on either side of this wavelength window [26]. Therefore, irradiation of the nanoshells within the hydrogel with a laser resulted in the conversion of light to heat energy that produced a reversible volume phase transition in the temperature-sensitive polymeric matrix.

Metal nanoshells are a relatively new class of nanoparticles consisting of a dielectric core nanoparticle surrounded by an ultrathin metal shell. These nanoshells have tunable plasmon resonances that are based on geometric construction [27]. The ratio of shell thickness to core diameter allows nanoshell peak resonance to be tuned while the overall dimensions of the particle allow the relative absorbing and scattering efficiencies to be manipulated [27–29]. Silica–gold (SiO_2–Au) nanoshells are a new class of nanoparticles that have a silica dielectric core, which is surrounded by a gold shell. In contrast to gold–gold sulfide nanoshells, the peak extinction of SiO_2–Au nanoshells are very easily tunable to absorb or scatter light strongly within the wavelengths of 650–900 nm that is commonly known as the NIR region [27]. This region is of significant biological importance and hence nanoshells are currently being investigated for use in the NIR region for a variety of biomedical applications including their use as diagnostic tools [30], contrast enhancements for imaging applications [31,32] and for laser tissue welding [33].

Hydrogels are three-dimensional matrices that have been used to develop many systems for the controlled release of therapeutic proteins [34,35]. Hydrogels based on the thermo-responsive polymer NIPAAm exhibit a lower critical solution temperature (LCST) above which the hydrogel undergoes a reversible volume phase transition at ~32 °C [36,37]. At temperatures below the LCST, the polymer exists in the soluble, expanded form but as the temperature is increased above the LCST, the polymer collapses and precipitates out of solution [38]. However, copolymers of NIPAAm have been prepared in order to alter the hydrophobicity and hence the LCST of NIPAAm. The fabrication of hydrogels consisting of NIPAAm and the hydrophilic monomer AAm results in the formation of hydrogels that have a thin surface layer that facilitates the release of soluble material as the hydrogel collapses above its LCST [36]. In addition, NIPAAm-*co*-AAm hydrogels consisting of 95% NIPAAm and 5% AAm monomers have an LCST of approximately 40 °C [26,39,40].

Therefore, to develop a photothermal modulated drug delivery system in which near IR light of a specific wavelength can be used to induce the collapse of a polymeric matrix loaded with model drug molecules and proteins, we have embedded SiO_2–Au nanoshells of varying concentrations within NIPAAm-*co*-AAm hydrogels. Moreover, these nanoparticles were designed to strongly absorb near IR light at ~808 nm, the emission wavelength of the laser used in these studies. The drug delivery profiles of methylene blue, insulin, and lysozyme were then obtained by photothermal irradiation of the resulting nanoshell-composite hydrogels.

2. Materials and methods

N-isopropylacrylamide (NIPAAm), acrylamide (AAm), *N*,*N*′-methylenebisacrylamide (MBAAm), and phosphorus pentoxide (P_2O_5) were purchased from Aldrich (Milwaukee, Wisconsin). Ammonium persulfate (APS), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED), tetrahydrofuran (THF), *n*-hexane was purchased from Sigma (St. Louis, Missouri). Insulin from bovine pancreas (MW 5800), lysozyme (MW 14, 700), β-casein (MW 25, 000), and bovine serum albumin (BSA) (MW 66, 000) were purchased from Sigma (St. Louis, Missouri). Bicinchoninic acid (BCA) protein assay was purchased from Pierce (Rockford, Illinois). Ready gel Tris–HCl gel, 4–15% linear gradient and Bio-rad silver stain plus kit were purchased from Bio-rad (Hercules, CA). EnzChek® lysozyme assay kit was purchased from Invitrogen Molecular Probes (Carlsbad, CA).

2.1. SiO_2–Au nanoshell fabrication

Nanoshells were made as previously described [28]. Briefly, silica cores were grown using the Stöber process, base catalyzed reduction of tetraethyl orthosilicate (Sigma-Aldrich, Milwaukee, WI) in ethanol [41]. The resultant silica nanoparticles were sized using scanning electron microscopy (SEM) (Philips FEI XL30). Particles with a polydispersity index (PDI) of less than 10% were used in subsequent steps. Reaction of the silica core nanoparticles with (3-aminopropyl) triethoxysilane (APTES, Sigma-Aldrich) provided amine groups on the surface of the core to allow for deposition of gold colloid. Gold colloid was prepared to a size of 2–4 nm in the method of Duff et al. and aged 2–3 weeks at 4 °C [42]. The colloid was then concentrated 20X through rotary evaporation and mixed with the aminated silica particles that facilitated the formation of gold nucleation sites in the subsequent reduction of gold from $HAuCl_4$ in the presence of formaldehyde. The reduction of gold around the initial colloid sites enabled the formation of gold islands that coalesced to form a contiguous gold shell. The extinction characteristics of the nanoshells were determined using a UV–Vis spectrophotometer (Carey 50 Varian, Walnut Creek, CA). MIE theory simulations based on previously published results and measured dimensions of the nanoshells were used to determine the extinction coefficients of the particles from which the concentration of the nanoshell suspension was calculated [27].

2.2. Hydrogel fabrication

Prior to use, NIPAAm was dissolved in THF and recrystallized in *n*-hexane so as to remove the *p*-methoxylphenol inhibitor. A molar ratio of 95:5 (NIPAAm:AAm), which has been previously shown to produce an LCST of ~40 °C was used to fabricate nanoshell-composite hydrogels by first adding 3.56 mL NIPAAm (1.75 M), 21.88 μL AAm (15 M), 51.78 μL