31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Novel Nano-Composite Biomaterials that Respond to Light

Kolin C. Hribar, Robert B. Metter, and Jason A. Burdick

Abstract— **Composites of nanoparticles and polymers are finding wide applications to alter material properties, conductivity, and utility. Here, we show that nano-composites can be designed to heat in the presence of near infrared light. This process is useful in transitioning materials through a transition temperature for a range of applications. For example, shape-memory materials (including polymers, metals, and ceramics) are those that are processed into a temporary shape and respond to some external stimuli (e.g., temperature) to undergo a transition back to a permanent shape and may be useful in a range of applications from aerospace to fabrics, to biomedical devices and microsystem components. In this work, we formulated composites of gold nanorods (<1% by volume) and biodegradable networks, where exposure to infrared light induced heating and consequently, shape transitions. The heating is repeatable and tunable based on nanorod concentration and light intensity.**

I. INTRODUCTION

THE temperature at which shape transitions occur in polymers can be controlled through properties that dictate either the glass transition temperature (T_g) or the melting temperature. This allows transition from a temporary shape to a permanent shape (typically controlled with covalent bonds) [1]. This heating is usually controlled by immersion in an environment that is at a different temperature, such as in a bath of water or when implanted. If the transition temperature is crossed during submersion/implantation, the shape change occurs. This may be useful in applications such as implantable stents, self-tying sutures, and for securing materials to tissues [2,3]. One drawback to the use of these materials is that the shape change is not completely controllable, in that the change happens nearly instantaneously when implanted. Thus, initiation of the transition externally could be useful for many biological applications, such as where light is exposed transdermally.

Light has been used in systems where photoactive moieties are incorporated; however, the molecular rearrangement that occurs is often permanent and the chemistry is not applicable to all polymer systems. Yet, there are advantages to using light in that there is spatial control to heating, heating can be defined to the implant/device and not the surroundings, and that the heating can be performed indirectly (e.g., transdermally). For transdermal light exposure, wavelengths are limited in that many do not penetrate tissues well. However, near-infrared wavelengths penetrate tissues and have been used extensively for the heating of nanoparticles *in vivo* [4], including for the thermal ablation of tumors. Thus, the combination of nanorods with polymers would provide a simple and versatile system for heating polymers.

II. MATERIALS AND METHODS

A. Polymer Synthesis

Poly(β-amino esters) (PBAEs) were synthesized by the conjugate addition of primary amines to diacrylates by mixing the liquid precursors and reacting overnight (90°C) with stirring. Macromer A6 was synthesized through the reaction of diethylene glycol diacrylate (A, Scientific Polymer Products, Inc.) and isobutylamine (6, Sigma) in a 1.2:1 molar ratio. The A6 molecular weight was confirmed to be ~1.3 kDa using ^{1}H-NMR (Bruker Advance 360 MHz, Bruker, Billerica, MA).

B. Nanorod Fabrication and Encapsulation

Nanorods were grown through a mixture of cetyltrimethylammonium bromide (CTAB), $HAuCl_4$•3H2O, silver nitrate, L-ascorbic acid, and a seed solution containing CTAB, sodium borohydride, and $HAuCl_4H_2O$ [5]. After mixing (2 hours), the nanorods were pegylated to alter their solubility using reaction with PEG-thiol (MW=5kDa). The nanorods were imaged on a transmission electron microscope (TEM, JEOL 2010F) at an accelerating voltage of 200 kV. Upon imaging (Figure 1), the nanorod dimensions were assessed using NIH Image Analysis. The absorption spectra of the nanorods were also collected (Beckman Coulter DU730 Life Science uv/vis spectrophotometer).

The photoinitiator 2,2-dimethoxy-2-phenyl acetophenone (DMPA, 0.5 wt%, Sigma) and nanorods were added to mixtures of the multi-functional macromer A6 and the mono-functional tBA. The polymerization behavior was monitored using attenuated total internal reflectance – Fourier transform infrared (ATR-FTIR, Nicolet 6700, Thermo Electron) spectroscopy with a zinc selenide crystal collecting a spectrum every 17 seconds with a resolution of 3.86 cm^{-1} for 10 minutes. A drop of the macromer/initiator solution (with or without nanorods) was placed directly on the horizontal crystal, covered with glass, and exposed from above to ultraviolet light (~1.5 mW cm^{-2}, 365 nm, Omnicure Series 1000, Exfo). The change in area of the double bond peak (~1630 cm^{-1}, normalized to the carbonyl peak at ~1730 cm^{-1}) was used to monitor double-bond conversion with light exposure.

Polymer films were made by injecting the monomer/initiator solution (without and with nanorods)

Manuscript received April 9, 2009. This work was supported by a Packard Fellowship in Science and Engineering. All authors are with the Department of Bioengineering, University of Pennsylvania, 19104 USA (JAB is the corresponding author, phone: 215-898-8537; fax: 215-573-2071; e-mail: burdick2@seas.upenn.edu).

978-1-4244-3296-7/09/$25.00

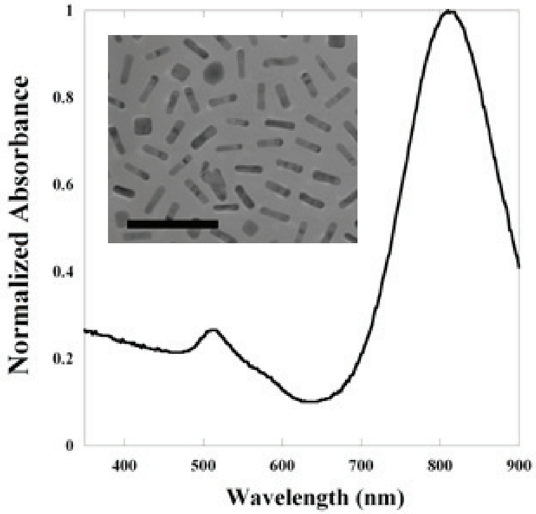

Fig. 1. Absorption spectra and TEM image (inset, bar = 100 nm) for PEG-modified gold nanorods.

between two glass slides and polymerizing with exposure to ultraviolet light (Blak Ray, ~10 mW cm^{-2}, 10 minutes). Cross-sections (~50 nm, Richtheart Jung Ultramicrotome) of polymer slabs embedded in an epoxy resin for TEM imaging (JEOL 2010, 80 kV). The viscoelastic behavior of the samples was determined using a Dynamic Mechanical Analyzer (Q800 TA Instruments) in a controlled strain mode at 1 Hz, an amplitude of 10 μm, and a heating rate of 3°C min^{-1} from -20°C to 55°C. The T_g is reported as the peak of the tan δ (the storage modulus over the loss modulus) curve.

C. Light Exposure

Composites were exposed to light with a Coherent Chameleon Ti:sapphire laser, mode-locked at 80 MHz, running at 770nm with up to 3.3W output power and 140fs pulse width. The beam was directed with gold-coated mirrors to the sample and expanded to about 7mm diameter at the sample position. Power levels used were 0.3 - 1.0W and selected by a combination of waveplate and polarizer. The sample temperature was measured at the back surface (1 mm depth) with a probe (Microtherma 2T thermometer and MT-D thermocouple probe, Thermoworks) immediately upon removal of the light.

III. RESULTS AND DISCUSSION

There are now many applicable biodegradable polymers for use in controlling network properties, including for use in shape memory applications [6]. PBAEs are one useful group of polymers and their properties are readily altered through parameters such as molecular weight and chemistry [7]. One macromer (termed A6) has previously been characterized extensively as a homopolymer and for cytotoxicity [8] and can be used to crosslink monofunctional molecules such as tBA. In this example, A6 acts as a crosslinker and degrades through hydrolysis of ester units.

Gold nanorods were synthesized using a previously reported seed-mediated growth process [5] and were further pegylated to alter their solubility. The nanorods (Figure 1) exhibit a characteristic morphology with an average length, width, and aspect ratio of 31.08 ± 4.52 nm, 9.24 ± 2.75 nm, and 3.64 ± 0.82, respectively, and typical absorbances for both the longitudinal and transverse plasmon peaks (Figure 1). The nanorods were added to a solution of A6, tBA, and photoinitiator at a range of concentrations (Table 1) and polymerized with ultraviolet light exposure. Importantly, there were no changes in the polymerization behavior in samples without and with nanorods (not shown); thus, there are no concerns with the particles interfering with the polymerization. The samples exhibited a purple color dependent on the concentration of nanorods incorporated and TEM images (Figure 2) indicate that the nanorods are dilute, that there are no visual changes in nanorod shape after encapsulation, and that there is no significant clustering of the nanorods in the networks.

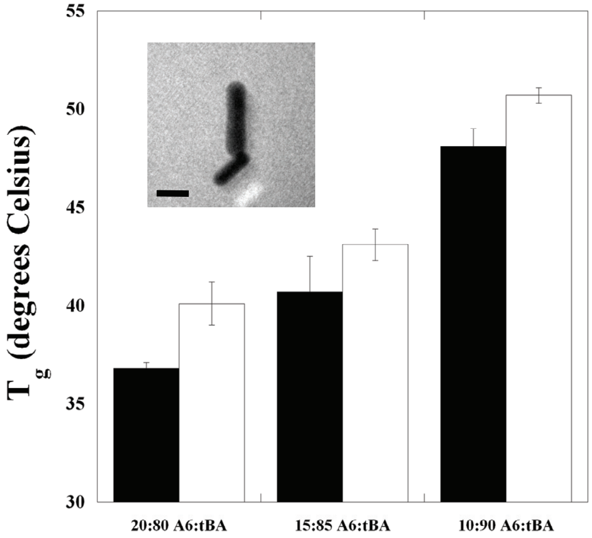

Fig. 2. Glass transition temperatures for various A6:tBA ratios without (black) and with (white) the mid concentration of nanorods incorporated and TEM image of gold nanorods embedded within a network (inset, bar = 30 nm).

Samples exhibited a typical profile for crosslinked networks with a decrease in the elastic modulus with increased temperature (transition from glassy to rubbery network), as well as a broad tan δ curve. An increase in the ratio of the crosslinker A6 to tBA in the networks increased the T_g of the polymers (Figure 2) by altering the crosslinking density, and the addition of the nanorods slightly increased the T_g for many networks. The influence of the addition of particles on the network properties is dependent on the interfacial interactions between the polymer and the particles. The samples lost very little mass with degradation (not shown), potentially due to the extreme hydrophobicity of tBA.

The polymers without and with nanorods were assessed for cytotoxicity using both indirect (non-contact) and direct (surface adhesion) methods, as well as with subcutaneous implantation (results not shown). There was no toxicity observed with the polymers in vitro, cells adhered to all of the samples, and there was only a mild inflammatory response observed. Importantly, none of these studies showed any differences between the samples with and without nanorods.

Significant and rapid heating was observed in samples that contained nanorods and was dependent upon both the concentration of nanorods and the light intensity. For example, 15:85 A6:tBA networks with the high concentration of nanorods heated ~50ºC when exposed to 0.3 W of infrared light. Essentially no change in temperature was observed for samples that did not contain nanorods. The heating was also reversible with intermittent light exposure, meaning the sample could be repeatedly heated and cooled with 5 minute intervals of light exposure and non-exposure.

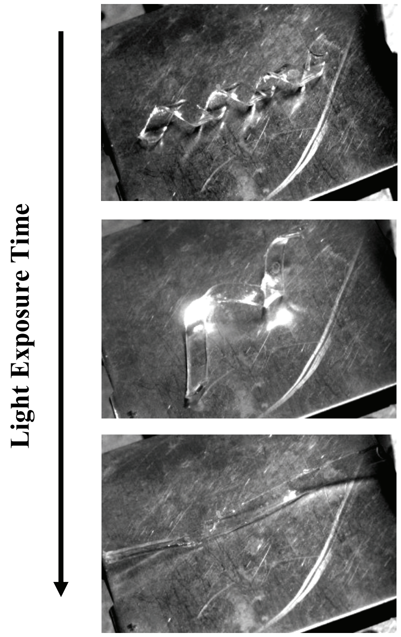

Fig. 3. Images of shape transitions of polymers fabricated from 15:85 A6:tBA networks with nanorods (mid concentration) after exposure to 0.3W infrared light. Complete transition took several minutes since the sample would change shape and move from the path of the light, yet shape changes were nearly instantaneous when the light was directed on the sample.

We aimed to illustrate the shape-memory effect with these light induced heating studies, where a network is held in a temporary and glassy shape and then changes to a permanent shape when heated past the T_g. Composites were crosslinked into rectangular strips, heated above their T_g, coiled around a small glass cylinder, and cooled to below their T_g. When the room temperature coiled samples were exposed to infrared light, they heated and changed back to their permanent rectangular shape (Figure 3). When the beam hit areas of the sample, the shape change was nearly instantaneous until the change moved the sample outside of the beam's path. This shape memory example illustrates the ability of embedded nanorods to heat a polymer sample through its T_g, as well as the spatial control that is possible.

In conclusion, we have developed a versatile method that utilizes infrared light to heat nano-composites of gold nanorods and biodegradable polymers. The heating can change the network from a glassy to rubbery system and alter the polymer from a temporary to permanent shape. The thermal transitions of the networks can be tuned through the crosslinker density and the introduction of nanorods. However, the nanorods do not influence the crosslinking reaction behavior, the cytotoxicity, or the tissue response of the networks. This technology is useful for a wide range of applications.

ACKNOWLEDGMENT

The authors acknowledge the assistance of Jamie Ifkovits and Dr. Thomas Troxler for assistance in mechanical characterization and laser exposure, respectively.

REFERENCES

[1] M. Behl, A. Lendlein, "Actively moving polymers," *Soft Matter*, vol. 3, pp. 58-67, 2007.

[2] M. Yoshida, R. Langer, A. Lendlein, J. Lahan, "From advanced biomedical coatings to multi-functionalized biomaterials," *Poly. Rev.*, vol. 46, pp. 347-375, 2006.

[3] A. Lendlein, R. Langer "Biodegradable, elastic shape-memory polymers for potential biomedical applications," *Science*, vol. 296, pp. 1673-1676, 2002.

[4] R. Weissleder, "A clearer vision for in vivo imaging," *Nature Biotech.*, vol. 19, pp. 316-317, 2001.

[5] T.K. Sau, C.J. Murphy, "Seeded high yield synthesis of short au nanorods in aqueous solution," *Langmuir*, vol. 20, pp. 6414-6420, 2004.

[6] K. Gall, P. Kreiner, D. Turner, M. Hulse, "Shape-memory polymers for microelectromechanical systems," *J. Micro. Sys.*, vol. 13, pp. 472-483, 2004.

[7] D.G. Anderson, C.A. Tweedie, N. Hossain, S.M. Navarro, D.M. Brey, K.J. Van Vliet, R. Langer, J.A. Burdick, A combinatorial library of photocrosslinkable and degradable materials," *Adv. Mater.*, vol. 18, pp. 2614-2618, 2006.

[8] A.R. Tan, J.L. Ifkovits, B.M. Baker, D.M. Brey, R.L. Mauck, J.A. Burdick, "Electrospinning of photocrosslinked and degradable fibrous scaffolds," *J. Biomed. Mater. Res. A*, vol 87A, pp. 1034-1043, 2008.