Triggered Molecule Release from Light-Responsive Polymer/Nanorod Composites

Kolin C. Hribar and Jason A. Burdick
Department of Bioengineering, University of Pennsylvania, Philadelphia, PA, USA

Statement of Purpose: Stimuli-responsive materials have become increasingly attractive in controlled drug release[1]. Near-infrared (NIR) light-activated materials have significant potential as implantable drug delivery systems because NIR light can penetrate deep into tissue and does not adversely damage the body's water and hemoglobin content[2]. We previously demonstrated that embedding gold nanorods (NRs) into a biodegradable polymer and exposing to NIR light produces a temperature change in the polymer[3] due to the nanorod's ability to absorb NIR light and convert to heat (i.e., photothermal effect)[4]. In this work, we apply this heating paradigm to trigger the release of small-molecule drugs from polymer networks.

Methods: The macromer A6 was synthesized through the reaction of diethylene glycol diacrylate (A) and isobutylamine (6) in a 1.2:1 molar ratio (MW≈1.3 kDa from ^{1}H-NMR). Gold NRs were synthesized using a seed-mediated growth method[5], modified with mPEG-SH and added to a pre-polymer solution of the macromer A6 (10wt%), tert-butyl acrylate (tBA) (70wt%) and 2-hydroxyethyl acrylate (HEA) (20wt%) with 0.5% (w/w) DMPA photoinitiator (Figure 1a). Polymer films were produced by injecting the pre-polymer solution between two glass slides with a 1-mm spacer and polymerizing with exposure to UV light (≈10 mWcm^{-2}, 10 min). Dynamic mechanical analysis (DMA) was used to assess the network mechanical properties (glass transition temperature was determined by taking the peak of tan δ, where tan δ is the ratio of loss modulus to storage modulus). Microspheres (≈40μm) were fabricated using a flow-focused microfluidics device[6] and polymerized in a 2% PVA solution under UV light for 10 minutes. Transmission electron microscopy (TEM) and backscatter micrographs were used to image NRs within the polymer. DSC was also used to determine the T_g of polymer films and microspheres. Doxorubicin (DOX, MW 523 Da) was loaded into the film (circular discs, ~28mg) and microspheres (40mg) via methanol swelling (MeOH was later evaporated out). Release studies were then performed, where samples were incubated for 24hrs at 37°C in solution (OFF), followed by exposure to 1.1W of NIR light (808nm) for thirty minutes (ON), for five OFF/ON cycles. DOX release was quantified using fluorescence (excitation: 480nm, emission: 590nm).

Results: We previously illustrated that this composite system heats with NIR exposure, dependent on NR concentration and light intensity, which can be used for shape-memory polymer applications[3]. Here, we utilized the same concept of triggered temperature increases to induce drug release. We aimed to control drug delivery kinetics by changes in molecule diffusion with temperature, as well as due to the polymer's glass transition temperature (T_g); when $T<T_g$, the polymer would conform to its glassy state, limiting drug diffusion, and when $T>T_g$, the polymer would be in its rubbery state and diffusion would be enhanced.

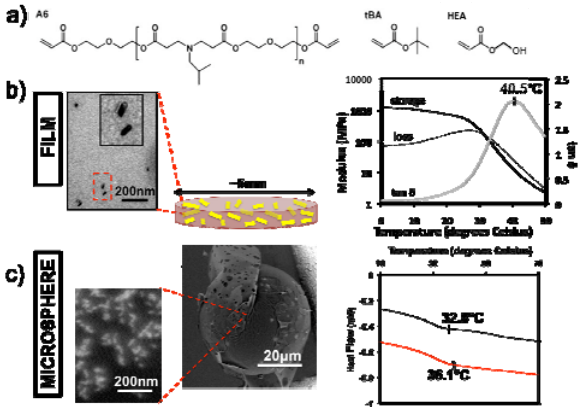

Figure 1. a) Chemical structures of macromer (A6) and monomers (tBA, HEA). b) Characterization of polymer-NR films: (left to right) visual representation as well as TEM image of polymer with NR and DMA results including storage modulus (black), loss modulus (dotted), and tan δ (grey). c) Characterization of microspheres: (left to right) backscatter micrograph of microsphere showing embedded NRs and DSC of microspheres with (red) and without (black) DOX.

We sought to obtain a T_g near or slightly higher than body temperature to limit passive diffusion of drug *in vivo*. Thus, we fabricated a polymer film composed of 10:20:70wt% A6, tBA, and HEA, respectively, with gold NRs, whose T_g was reported by DMA to be 40.5°C (Figure 1b). The T_g for microspheres with DOX was 36.1°C (Figure 1c). Next, we tested the triggered release from each system. Both the film and microspheres (Figures 2a and 2b, respectively) demonstrate a triggered release in response to NIR exposure and resulting heating, whereas only gradual DOX release is observed without light. A temperature increase of ~30ºC was observed with this heating regime. The film and microspheres reported a 4.8 or 2.7 fold increase in release, respectively, compared to samples without NIR exposure.

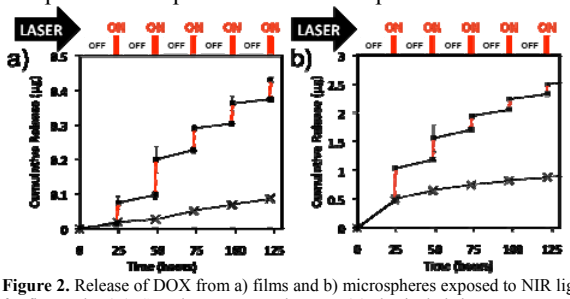

Figure 2. Release of DOX from a) films and b) microspheres exposed to NIR light for five cycles (■). Samples not exposed to NIR (×) also included.

Conclusion

This work demonstrates repeatable, triggered drug release behavior from a light-responsive polymer, in both film and microsphere forms, that is controlled by its glass transition temperature. This therapy has potential for multiple-cycle, non-invasive (e.g. injectable, biodegradable) drug delivery in localized areas (e.g. cancer therapy) and ongoing studies are investigating cellular responses to released molecules.

References: [1]Stuart, M. A. *Nat Mater* **2010,** *9* (2), 101-13. [2]Weissleder, R. *Nat Biotechnol* **2001,** *19* (4), 316-7. [3]Hribar, K. C. *Small* **2009,** *5* (16), 1830-4. [4]Huang, X. *J Am Chem Soc* **2006,** *128* (6), 2115-20. [5]Sau, T. K. *Langmuir* **2004,** *20* (15), 6414-20. [6]Shah, R. K. *Materials today* **2008,** *11* (4), 18-27.