Transdermal Gelation of Hyaluronic acid Hydrogels with Gold Nanorods and Near-Infrared Light

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Statement of Purpose: Hyaluronic acid (HA) materials are being investigated as injectable materials for widespread application (e.g., dermal fillers); yet, they are not without limitation (e.g., insufficient duration and limited mechanics[1,2]). Also, HA is often processed as particles that can be easily injected subdermally, since other means of gelation (e.g., radical polymerization with light) are difficult to implement. For example, ultraviolet light is commonly used to crosslink HA precursors, but has limited penetration through tissues. To address these issues, we developed a method to synthesize HA gels underneath skin using near-infrared (NIR) light, allowing for spatial and temporal control. In this system, gold nanorods (NRs) absorb NIR light and generate heat (tunable by NR concentration and light intensity), decomposing a radical initiator (VA-044) to crosslink methacrylated HA (MeHA). By varying the concentration of VA-044 and irradiation time, a wide range of gelation times and gel mechanical properties can be realized.

Methods: MeHA with 20% methacrylate modification was synthesized using a previously reported procedure.[3] Gold NRs were synthesized through a seed mediated process to give NRs with an aspect ratio of 4 (9 nm by 34 nm) and coated with thiol terminated polyethylene glycol.[4] The coated NRs were suspended in phosphate buffered saline (PBS) to give a mixture with a peak absorbance at 774 nm. Gel solutions were comprised of 4 wt% MeHA in PBS with varying concentrations of NRs and VA-044. The NIR source was an 808 nm diode laser at 1 W filtered to give either 0.3 or 0.6 W light to the sample. Bench top gels were synthesized by placing 50 µL of solution in an acrylic mold (4.8 mm diameter) and irradiating for various times with the NIR laser. The compressive moduli of these gels were calculated from the slope of the stress/strain curve generated by constant strain rate (10%/min) compression using dynamic mechanical analysis. *In vivo* transdermal gelation was investigated by subcutaneous injection of 50 µL of gel precursor solution with subsequent NIR irradiation for 10 min at 0.6 W using 6 week old wild type mice with hair removed prior to injection.

Results: MeHA solutions with only either NRs or initiator (VA-044) did not form gels when irradiated by NIR light (1 W). Both NRs and initiator were required to form gels. The modulus of the gels could be controlled by the concentrations of initiator as well as the irradiation time at a set laser intensity (0.3 W). By changing the irradiation time (Figure 1) a range of soft and stiff gels (0.9 – 10 kPa) were synthesized from the same solution (1.5 nM NR, 50 mM VA-044). With a set 10 min irradiation time (0.3 W laser power, 1.5 nM NR), varying the initiator concentration between 25 and 100 mM caused the modulus of the gel to vary between 2 and 11 kPa, further demonstrating the ability to control mechanical properties in this system.

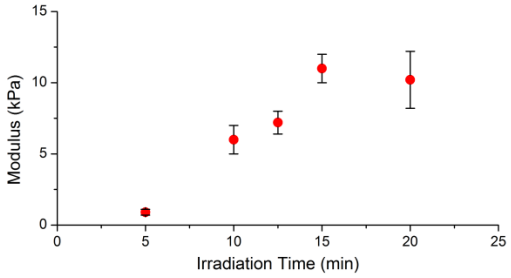

Figure 1. Compressive modulus of gels with 4 wt% MeHA, 1.5 nM NRs, and 50 mM VA-044 irradiated for various times with NIR at 0.3 W power.

In vivo, solutions that contained NRs and were not irradiated (+NR-NIR, Figure 2a), as well as solutions that did not contain NRs and were irradiated (-NR+NIR, Figure 2b) did not form gels, consistent with the bench top experiments. When both NRs and NIR light were used (+NR+NIR), gels formed under the skin (Figure 2c) that were free standing when excised from the skin (Figure 2d), demonstrating that gels could be formed transdermally.

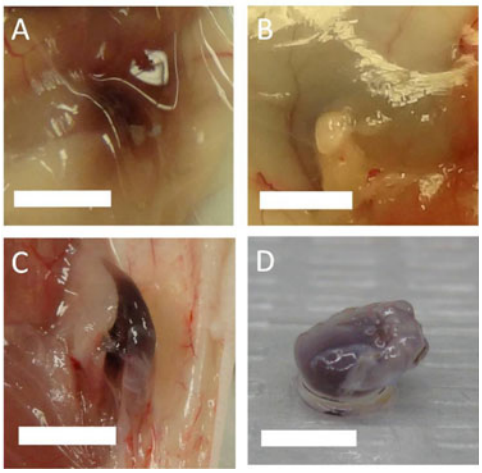

Figure 2. Photographs of subcutaneous injections in mice of HA gel precursor solution (a) +NR-NIR, (b) -NR+NIR, and (c) +NR+NIR with (d) excised gel from +NR+NIR swollen in formalin/PBS solution. Scale bar indicates 5 mm. NIR irradiation was for 10 min at 0.6 W power.

Conclusions: Using the heat generated by NRs interacting with NIR light, MeHA was gelled to create HA hydrogels. The modulus of the gels can be controlled by varying either the concentration of initiator or length of irradiation, allowing for the tuning of mechanical properties as desired. *In vivo* studies indicated that gels could be formed transdermally and that spatial control is possible since only regions irradiated resulted in gel formation. This spatial control is the subject of ongoing research.

References: [1]Bray D. Curr Opin Otolaryngol Head Neck Surg 2010;18:295–302. [2]Edsman K. Dermatol Surg 2012;38:1170–1179. [3]Burdick JA. Biomacromolecules 2004;6:386–391. [4]Hribar K. Small 2009;5:1830–1834.