Photoresponsive Hydrogels for Ophthalmic Drug Delivery

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Statement of Purpose: Photoresponsive hydrogels have the potential to act as a controllable drug delivery system and may be particularly suited for disease treatment in the posterior segment of the eye due to accessibility of the tissue to light. Intravitreal sustained-release delivery systems that respond to light stimuli are under development to control the rate of delivery in response to disease progression or regression resulting in a tunable treatment profile ideal for macular degeneration and diabetic retinopathy therapies.

The model reversible photodimerizing molecule anthracene can provide methods of controlling crosslinking of hydrogels when chemically grafted directly onto their backbone. Light irradiation above 365 nm causes anthracene dimerization while light under 300 nm causes its de-dimerization (Greene, 1955). Anthracene-based molecules used to facilitate the crosslinking of hydrogels have been synthesized and demonstrated to result in photosensitive crosslinking with potential for controlling drug delivery.

Methods: Anthracene-based, polyethylene glycol crosslinkers (PEG-anthracene) were chemically grafted via carbodiimide chemistry to alginate and hyaluronic acid (HA) polymer backbones. Light irradiation above and below 300 nm was used to effect hydrogel crosslinking and decrosslinking respectively. Grafting was verified via NMR and ninhydrin assays.

The effective crosslinking density of the photoresponsive hydrogels (photogels) was calculated from swelling data and the Flory-Rehner model. The loading and release of Coomassie Brilliant blue (CB) and proteins (myoglobin, lysozyme and albumin) from the photogels into PBS were used to assess the ability for the system to have altered release profiles in response to light and laser stimuli. Photogels were grown with ophthalmic cell lines to assess cytocompatibility.

Results: Spectrophotometry demonstrated the ability of the PEG-anthracene crosslinkers to dimerize and de-dimerize reversibly with light treatments. Grafting to alginate and HA above 70%, created photogels that demonstrated low cytotoxicity when grown with corneal epithelial cells and retinal pigment epithelial cells. In addition to UV induced crosslinking, light irradiation can further control the effective crosslinking density with 60 minute exposures of light at 365 nm (10mW/cm^2) effectively causing complete crosslinking in HA photogels when compared to control gels crosslinked with PEG (Figure 1). Photogel degradation rates were significantly increased after UV crosslinking treatments from 200 hours to over 3000 hours in PBS and from 48 hours to over 440 hours in 100 Units/mL of hyaluronidase.

Diffusion properties from the photogels were demonstrated through the decrease or increase in release rates of model compounds from the gels after specified UV treatments. Control gels crosslinked with PEG molecules were used as comparison to ensure any observations were artifacts of the grafted PEG-anthracene and were not due to UV changes to the bulk polymers. Release of model compounds was influence with UV. HA photogels with no UV treatment had complete delivery of CB and gel dissolution by 700 hours whereas irradiation with 365 nm light increased delivery times resulting in 32% of CB released at 2000 hours.

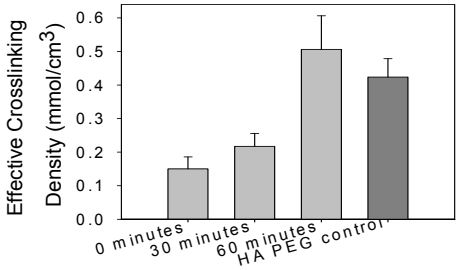

Figure 1. The effective crosslinking density of HA photogels increased with 365nm light treatments (n=4).

Furthermore, as illustrated in Figure 2, UV treatments of 365 nm could "turn off" protein release from the photogels which could subsequently be "turned back on" with laser treatments at 248 nm. The incorporation of photosensitive anthracene capped star-polyethylene glycol further increased the photoresponsiveness of the gels.

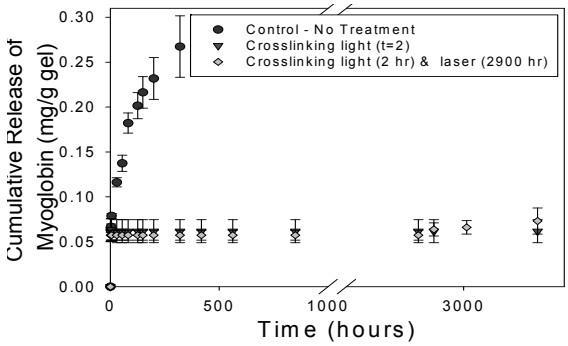

Figure 2. Release of myoglobin from HA photogels (n=3).

Conclusions: PEG-anthracene can act to control alginate and HA crosslinking and drug delivery in response to UV exposure. Its end group versatility opens possibilities to graft similar photosensitive crosslinkers to a variety of hydrogels. The system demonstrates the ability to delivery therapeutics in a controlled, light-responsive fashion. While drug delivery applications of these materials were investigated, other biomaterial and degradable material applications involving light induced changes in crosslinking may benefit from the technology.

References: Greene, F.D., *et al.* J Am Chem Soc. 1955:77,3852