Release Studies of Therapeutic Contact Lenses

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Introduction: This work highlights the extended release of ocular therapeutics via templated contact lenses, which have a strong potential to replace existing topical formulations. Topical formulations currently make up 90% of the ocular drug market, and a significant unmet need exists for non-invasive, ocular therapeutic devices that deliver drugs to the eye in a controlled and sustained manner. Treatments such as eye drops are inefficient because rapid fluid turnover on the eye surface washes away the drug before it has an efficacious effect. A biomimetic approach has been exercised to tackle the unmet need for the controlled loading and release of ocular drugs. Controlling and tailoring the release of ocular therapeutics via novel templated, recognitive contact lenses with significantly enhanced loading can solve these problems with increased bioavailability, less irritation to ocular tissue, and reduced ocular and systemic side effects. Enhanced drug loading and extended release in hydrogels can be achieved by configurational biomimetic imprinting (CBIP) techniques **[1, 2]** which involve the formation of a pre-polymerization complex between the template molecule and functional monomers by non-covalent chemistry. Inspired by Nature, we have successfully synthesized and characterized recognitive networks by choosing monomers on the basis of the non-covalent interactions found in biological systems or biological mechanisms of action. Characterization and optimization of these therapeutic lenses requires that their release characteristics be assessed under conditions present in the eye. We have performed in-vivo studies in a rabbit model to assess efficacy and have performed microfluidic in-vitro release studies to characterize and optimize therapeutic lenses. Whereas earlier methods relied on immersing the lens in a large volume of artificial lacrimal fluid, our model confines the lens in a chamber with the fluid capacity of the eye, and flows lacrimal fluid over its surface at the rate of tear flow in the eye.

Materials and Methods:

Synthesis of Hydrogel Lenses: Acrylic acid, acrylamide, 2-hydroxyethylmethacrylate, polyethylene glycol (200) dimethacrylate, azobisisobutyronitrile, ketotifen fumarate, and other drugs were purchased from Aldrich (Milwaukee, WI) and used as received. Hydrogels were synthesized in a temperature controlled, non-oxidative environment using free-radical UV photopolymerization. They were cut into disks of 14 mm diameter, and rinsed with DI water until drug and unreacted monomers could no longer be detected by spectroscopic monitoring. Control gels were prepared without the template molecule, following similar steps. Optical and mechanical studies agreed with results from conventional lenses. *Equilibrium Drug Binding/Loading:* Hydrogel disks were placed in concentrated solutions of drug and gently agitated on a Stovall Belly Button Orbital Shaker (Greensboro, NC). After 72 hours, the bound concentration in the gel was determined by mass balance. *In-vivo Drug Release Studies:* Male New Zealand White rabbits, approximately 4-months-old, were divided into two groups. One eye was treated in each rabbit and one eye remained untreated. Lenses of different curvatures were made and fit to each rabbit. The sample group received drug loaded contact lenses and tear fluid was collected by capillary action from the conjunctival sac using a micropipette with care to not touch the conjunctival or corneal surfaces. Levels of drug in tear fluid collected at multiple time points was measured by a Biotek Synergy Spectrophotometer or HPLC to determine in-vivo release profiles. The control rabbit group received drug via topical formulations at 1-2 drops every 8 hours. Tear collection and release profiles were collected in a similar manner to the sample group. *In-vitro Drug Release Studies:* Kinetic release studies were conducted in artificial lacrimal fluid (6.78 g/L NaCl, 2.18 g/L NaHCO3, 1.38 g/L KCl, 0.084 g/L CaCl2.2 H2O, pH 8). In the conventional model, the disks from the equilibrium binding step were placed in 30-300 mL of lacrimal fluid, continuously agitated with a Servodyne mixer from Cole Parmer Instruments at 120-300 rpm or placed in a Sotax dissolution apparatus. In the physiological flow model, the drug-loaded disk was placed within the chamber of a microfluidic device. The device was fabricated using poly-dimethylsiloxane and consisted of a 30 µl volume chamber, with an inlet and an outlet. A KDS101 Infusion Pump from KD Scientific (Holliston, MA) injected artificial lacrimal fluid into the chamber at 3 µl/min, while an outlet line removes fluid from the chamber at the same rate for collection at regular time intervals. Release of drug was monitored using a Biotek Synergy UV-Vis/ Fluorescence/ Luminescence Spectrophotometer (Goshen, NY).

Results/Discussion: We hypothesized that under physiological flow, therapeutic lenses would provide a sustained release profile.

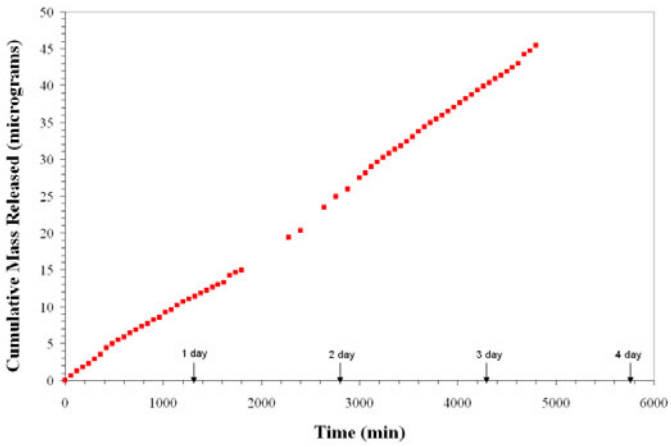

Figure 1: Release Profiles of Ketotifen Fumarate from Therapeutic Contact Lens in Physiological Flow.

In-vitro results show that under physiological flow conditions, drug is released in a linear manner and at therapeutic concentrations, indicating that such hydrogel lenses have the capacity to deliver sustained amounts of drug over an extended time period. Results demonstrate zero-order release (independent of concentration or time). *In-vivo* studies confirmed the potential of therapeutic lenses to provide a therapeutic concentration of drug for extended periods of time, highlighting the tremendous clinical potential of this technology as compared to topical drops with significantly lower bioavailability.

Conclusions: Templated contact lenses with tailorable loading and release were designed based on biological mechanisms. Within physiological flow, drug release approached zero-order kinetics and a therapeutic dosage can be delivered for an extended period of time.

References: **[1]** Venkatesh S, Sizemore SP, Byrne, ME. Biomaterials 2007, 28(4):717-724. **[2]** Venkatesh S, Saha, J, Pass S, Byrne ME. European Journal of Pharmaceutics and Biopharmaceutics 2008, *in press*.