Therapeutic Contact Lenses: *In-vitro* Release via Experimental Physiological Ocular Tear Flow Model

M. Ali[1], J. Zhang[1], J. Saha[1], S. Pass[1],S. Horikawa[2], J. W. Hong[2], M. E. Byrne[1]
1. Biomimetic & Biohybrid Materials, Biomedical Devices, and Drug Delivery Laboratories, Department of Chemical Engineering
2. Nanofluidics Laboratories, Materials Engineering
Auburn University, Auburn, AL, USA 36849.

Introduction: We have designed and fabricated a novel microfluidic platform for the characterization of therapeutic contact lenses under physiological conditions. A massive unmet need exists for 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 using novel biomaterials, to tackle the unmet need for the controlled loading and release of ocular drugs. Controlling and tailoring the release of ocular therapeutics via novel 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]** 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 human eye. Our microfluidic device is a major improvement over conventional techniques to characterize therapeutic lenses. Whereas earlier methods relied on immersing the lens in a large static volume of artificial lacrimal fluid, our model confines the lens in a chamber with the fluid capacity of the eye, and flows artificial lacrimal fluid over its surface at the rate of tear flow in the eye. By matching experimental conditions to actual conditions in the eye, we can optimize the release characteristics of therapeutic contact lenses prior to conducting *in-vivo* studies. This work will highlight the extended release of a number of ocular therapeutics via therapeutic contact lenses, which has a strong potential to replace existing topical formulations. Topical formulations currently make up 90% of the ocular drug market.

Materials and Methods:

Design and Synthesis of Microfluidic Device: A microfluidic device was fabricated using poly-dimethylsiloxane and consists of a 30 µl volume chamber, with an inlet and an outlet.

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.

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-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 mL of lacrimal fluid, continuously agitated with a Servodyne mixer from Cole Parmer Instruments (Vernon Hills, IL) at 120 rpm. In the physiological flow model, the drug-loaded disk is placed within the chamber of the microfluidic device. A KDS101 Infusion Pump from KD Scientific (Holliston, MA) injects 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 the physiological flow model of drug release would show that the therapeutic lens, under conditions similar to those in the human eye, would increase the release time and may provide a more linear and sustained release profile.

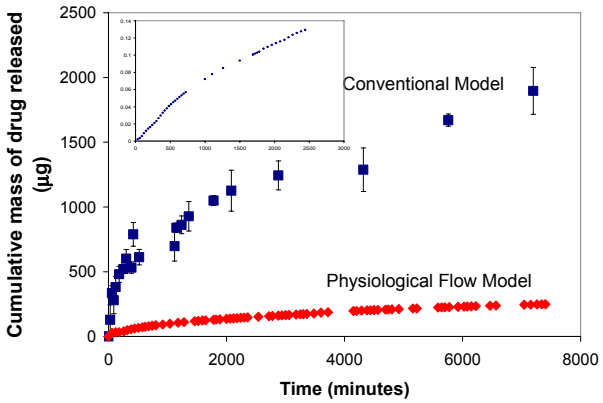

Figure 1: Release Profiles of Ketotifen Fumarate from Therapeutic Contact Lenses. Mass of drug released versus time under conventional release (■) and physiological flow (♦) conditions. (Inset is physiological flow release for 2 days to show linearity).

The results clearly show that under physiological conditions, drug is released in a linear manner and at much lower concentrations than conventional release studies suggested, indicating that such hydrogel lenses have the capacity to deliver sustained amounts of drug over an extended time period. Results demonstrate a slower release of drug approaching a constant rate of release and zero order release conditions (independent of concentration or time). Compared to the conventional model the release profile is drastically reduced (in 2 days 120 µg are released compared to approx. 1,200 µg in the conventional, perfect sink release study). Also, comparing to topical drops with 10% bioavailability, a therapeutic dosage is being delivered from the lenses. Also, the lenses have the potential to release for a significantly longer period of time (≈20x longer or 30 plus days).

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

References: **[1]** Venkatesh S, Sizemore SP, Byrne, ME. Biomaterials 2007, 28(4):717-724.