In-vitro Release of a Non-Steroidal Anti-Inflammatory from Daily Wear Therapeutic Contact Lenses

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Statement of Purpose: We have designed and synthesized novel therapeutic soft contact lenses (TSCLs) capable of tailorable loading and controlled release of the non-steroidal anti-inflammatory diclofenac sodium. A major obstacle facing traditional topical methods of ocular drug delivery is poor bioavailability; around 5-8 % of the applied drug is absorbed while the rest is removed by the natural turnover of tears or enters into systemic circulation before reaching the target tissue [1]. An immense need exists for ocular therapeutic devices that deliver drugs to the eye at a constant rate over an extended period of time to provide the necessary therapeutic dose, thereby eliminating the application of topical eye drop medication. Contact lenses are synthesized via biomimetic imprinting techniques to create macromolecular memory sites, which enhance the loading and control the release of diclofenac sodium, an anti-inflammatory therapeutic [2]. Our lab has developed a number of lenses for various therapeutics highlighting the platform combination device technology [3]. In addition, a microfluidic device was engineered and fabricated for a better characterization of therapeutic contact lenses under physiological conditions. Our microfluidic device is a significant improvement over conventional techniques of measuring release kinetics of therapeutic contact lenses. Whereas earlier methods relied on immersing the lens in a large fluid volume (i.e. infinite sink model), our model confines the lens in a chamber, and flows artificial lacrimal fluid over its surface at the volumetric tear flow rate of the eye.

Methods:

Design and Synthesis of Microfluidic Device

A microfluidic device was engineered and fabricated using poly-dimethylsiloxane. It possesses an inner chamber with an inlet and an outlet, and a radius of curvature of 9.00 mm ± 0.1. The device was then placed over a mount with radius of curvature of 8.75mm ± 0.1.

Synthesis of Daily Wear Contact Lenses

2-hydroxyethylmethacrylate and (diethylamino)ethyl methacrylate, azobisisobutyronitrile and diclofenac sodium were purchased from Sigma-Aldrich (Milwaukee, WI). Polyethylene glycol (200) dimethacrylate was purchased from Polysciences, Inc (Warrington, PA). All chemicals were used as received. Contact lenses with a base curve of 8.6 mm ± 0.2, a diameter of 15.3mm ± 0.2 and center thickness of 100 µm were synthesized varying the monomer to template ratio (M/T ratio) via free-radical UV photopolymerization.

In vitro drug release studies

Dynamic 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 infinite sink model, the drug-loaded lenses were placed in 450 mL of lacrimal fluid and continuously agitated at 45 rpm, in a Dissolution Apparatus from SOTAX Inc. (Hopkinton, MA). In the physiological flow model, the drug-loaded lens was placed within the chamber of the microfluidic device. A KDS101 Infusion Pump from KD Scientific (Holliston, MA) injected lacrimal fluid into the chamber at 3µL/min, while an outlet line removed fluid from the chamber at the same rate for collection at regular time intervals. Release of diclofenac sodium was monitored using a Synergy UV-Vis Spectrophotometer from BioTek Intruments (Winooski, VT).

Results/Discussion: The biomimetic contact lenses exhibited memory for diclofenac and demonstrated advantage over lenses created without memory by displaying a two-fold improvement in drug loading.

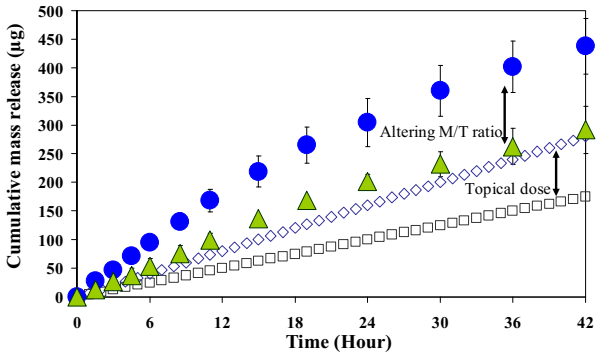

Figure 1: Release profiles of diclofenac from TSCLs at different M/T ratios and instilled topical eye drops. Release rates from poly[HEMA-co-DEAEM-co-PEG200DMA] lenses can be tailored by adjusting M/T ratios: M/T 67 (●) and M/T 200 (▲). The mass release rate delivered from eye drops for diclofenac is 0.02 µg/drop and is represented (at an hourly rate) assuming 8 drops (◊) and 5 drops (□).

In-vitro dynamic drug release was conducted under physiological flow conditions. A linear release profile was observed for up to 48 hrs, making these lenses ideal for daily disposable therapeutic lenses. Furthermore, the mass of diclofenac released by our lenses can be tailored to match the current recommended dosage from eye drops. By increasing the M/T, the release rate decreased from 11.2 µg/ hr to 7.35 µg/ hr. Increasing the M/T extended release time to 6 days. Furthermore, these lenses posses the same ocular clarity as commercial contact lenses.

Conclusions: Our ocular drug delivery system designed based on molecular homology to biological receptor binding sites offers a more effective method of ocular therapy by providing a constant and optimal dose of medication. The physiological flow model better mimics the finite tear turnover rates on the eye, which can help us, gain a deeper understanding of how therapeutic contact lenses would perform in *in-vivo* studies.

References:

[1] Mitra AK. 1993 Ophthalmic Drug Delivery Systems, New York, NY: Marcel Dekkar. pg. 37. **[2]** Vaughan AD, Zhang JB, and Byrne ME. AIChE Journal, 56(1), 268-279, 2010. **[3]** Venkatesh S, Sizemore SP, and Byrne ME. Biomaterials, 28, 717-724, 2007.

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