WHITE PAPER

OcuMedic,Inc. Technology

OcuMedic, Inc. creates new vision-corrective contact lenses or non-corrective **bandage** lenses to deliver medication continuously to the eye, replacing eye drops. ***The lead product in OcuMedic's pipeline for pre- and post-cataract surgery, LASIK, and corneal abrasion as a replacement for eye drops is the anti-inflammatory "first line" NSAID drug bromfenac sodium without preservatives to relieve pain and inflammation.*** All preservatives in testing and development have been eliminated removing issues of irritation, sensitivity, and toxicity as well open bottle contamination.

OcuMedic's patented technology creates a new architecture with memory for the drug within the polymeric network comprising the lens to enable continuous release of drugs to the eye while mimicking biological recognition in the design. As the drug moves from each memory site consisting of chemistry of multiple polymer chains that briefly non-covalently holds onto the drug within the lens structure, drug release from the lens is precisely controlled. ***OcuMedic's technology is a platform technology that works within existing lens manufacturing schemes and can be applied to various drugs or drug combinations leading to a number of products in OcuMedic's pipeline.*** Continuous drug release has been successfully verified *in vitro* and *in vivo* as well as other physiochemical properties of the lenses, which match those on the market today.

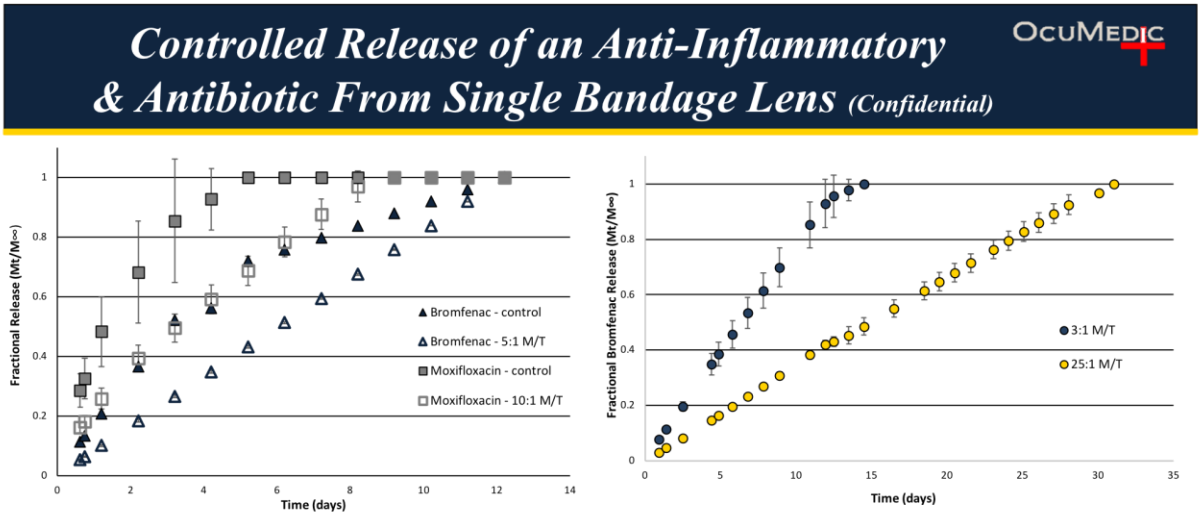

Figure 1. Release of an anti-inflammatory and an antibiotic from a single lens with macromolecular memory compared to control lenses. Release of a non-steroidal anti-inflammatory drug (bromfenac) and an antibiotic (moxifloxacin) from a single lens. Lenses with macromolecular memory demonstrated a lower release rate of both therapeutics than control lenses and were able to extend release up for over a week.

Figure 2. Release of bromfenac sodium from lenses with macromolecular memory at different M/T ratios. Lenses with a functional monomer to template ratio of 3:1 released their entire payload by 15 days while lenses with an M/T ratio of 25:1 were able to extend total payload release up to 30 days.

Figures 1 and 2 above highlight controlled release of the anti-inflammatory bromfenac and antibiotic moxifloxacin from a single lens. OcuMedic typically tests between three (3) to six (6) lenses per data point with the average value presented with standard deviation. In this data, the lenses were treated to a pre-wash then re-loaded with drug to test memory creation. Controls are tested for all OcuMedic systems, and Figure 3 shows that memory leads to a more controlled, extended, and linear drug release profile compared to control (a higher M/T ratio means more memory). Controls were run under the same conditions as the test lenses. The controls had the same chemistry and amount of chemistry intended to interact with the drug, thus exactly the same lens components, but the drug is not included in the lens production process so drug memory was not established and there is more deviation in the data as expected. Conventional lens on the market today loaded with these drugs would not be able to even achieve the release profile of the control data, uncontrollably releasing their contents in a few hours.

Figure 2 highlights OcuMedic's lead product for pre- and post-cataract surgery, LASIK and corneal abrasion with "first line"anti-inflammatory bromfenac release control with memory utilizing OcuMedic's novel microfluidic device, which closely simulates ocular in vivo conditions. The microfluidic instrument used in development matches the volumetric flow rate of tear fluid at ~3uL/minute and this more closely approximates and correlates to the release profile seen in vivo. With a range of memory or an M/T ratio spanning from three (3) to twenty-five (25), OcuMedic can program the release rate or time required to release the entire payload of drug leading to a predictable and stable in vivo drug concentration.

Questions sometimes arise on why do the 25:1 ratio lenses store more drug than a 3:1 ratio lens? The reason is a higher memory - a higher M/T ratio means that the lens loads more drug, and the creation of memory is established by drug loading increases, drug affinity increases, and drug controlled release. For drug-reloaded systems, more memory means higher loading at saturation. These concepts have been proven in a number of systems by OcuMedic and some systems are published. Details on the experimental procedure are available upon request and in some cases may require a NDA.

There is not a historical or an industry reason for studying the loading of drug in lenses, and it may seem that there is not much difference between memory lenses and control. The level of loading enhancement depends on the memory OcuMedic creates (e.g., some systems have 1.5 times and others can have 6 times or more compared to control – and even 1.5 times is a relatively big increase). This is performed to test memory and controls match in terms of chemistry, but they don't have memory for the drug. Conventional lenses on the market today would load substantially less than control. Lenses without OcuMedic technology (drug soaked conventional lenses) can load a little drug (and it depends on the lens chemistry and drug chemistry), but it is non-specific and has been *proven time and time again to be at low levels and to come out very quickly without delayed release in <1 hr. Drug soaked lenses have been tried for years and they do not work.*

Dr. Byrne and OcuMedic have published over thirty (30) articles on this topic. Company founder, Mark Byrne, Ph.D. is known internationally for his body of research work in high impact peer-reviewed journals with many highly cited papers. OcuMedic has proven the technique for both mono and combination drug lens. ***Published peer-reviewed papers are available upon request relating to a number of systems and in the papers one can view the materials and methods as well as lens/polymer characterization.*** *The lenses presented have mechanical, optical, and oxygen transport properties that match requirements of lenses on the market today. Additionally, papers are available that deal with the polymerization process and kinetics more than drug delivery.*

Competitively, OcuMedic is well positioned. Ocular drug delivery methodology exists with small deposited polymer reservoirs that have been developed and commercialized for placement under the sclera or as a punctal plug or in the cul-de-sac of the eye. These technologies require invasive procedures with complications and those that are less invasive such as Ocusert® by Alza and Lacrisert® by B&L suffered from the sensation of being a foreign body, premature expulsion, and they had drug burst issues with both that are currently off the market. Alcon/Oasis Medical has also developed the Proshield, Soft Shield collagen bandage that can be dipped/soaked in drug, placed on the eye, and dissolves, but there is *NO CONTROL OF DRUG RELEASE* with drug being released very quickly and foreign body sensation due to pieces/dissolution. Thus, it has limited utility. Contact lenses manufactured out of silicone hydrogels (SiHy) have proven biocompatible with high wear comfort, and are the ideal platform for drug delivery now with OcuMedic's optimized pharma kinetics with long duration of controllable release in the form of an **ocular bandage.**

Supporting Information

In vitro Dynamic Drug Release Studies **-** Dynamic release studies were conducted using two different *in vitro* methods, the conventional sink model and the physiological flow model using a novel microfluidic device developed by OcuMedic. In the infinite sink model, the drug-loaded lenses, loaded at a certain template concentration were placed in a large volume of artificial lacrimal fluid (6.78 g/L NaCl, 2.18 g/L $NaHCO_3$, 1.38 g/L KCl, 0.084 g/L $CaCl_2 \cdot 2\ H_2O$, pH 8), kept at a constant temperature of 34 ºC and continuously agitated at 45 rpm, in a dissolution apparatus from SOTAX Inc. (Hopkinton, MA). Preliminary studies were conducted to determine the amount of fluid, fluid turnover (if applicable) and mixing speed needed to approximate infinite sink analysis. In the physiological flow model, the drug-loaded lens was placed within the chamber of the microfluidic device. The lens was placed over a mount with radius of curvature matching the lens and the device was sealed against a glass plate using a flexible silicon mold. A KDS101 Infusion Pump from KD Scientific (Holliston, MA) injected lacrimal fluid into the chamber at 3 µL/min, while an outlet line removed fluid from the chamber at the same rate for collection at regular time intervals. Release of drug was monitored at specific time intervals using a Synergy UV-Vis Spectrophotometer at wavelength of maximum absorbance. The absorbance was recorded for three samples, averaged, and corrected by subtracting the relevant controls.

Optical Analysis Studies **-** Optical transmission studies were conducted by placing lenses or cutting small diameter films and placing in the bottom of a 96-well plate where absorbance values were measured via spectrophotometric monitoring (BioTek, Winooski, VT). All films were fully hydrated and tested at wavelengths of visible light (380 to 780 nm). The absorbance value of each well in water was calculated and subtracted from the data. Percent transmission values were calculated from the absorbance data.

Mechanical Analysis **-** Stress–strain data were obtained by performing tensile studies with a RSA III Dynamic Mechanical Analyzer (DMA), (TA Instruments, New Castle, DE). Storage and loss moduli were determined for swollen lenses. The rheological behavior of the hydrogel lenses when dry and fully swollen was measured in triplicate at 35˚C using DMA applying initial tension of 1 mN and angular frequencies of 0-100 Hz, with corrected offset load. DMA was also used to conduct tensile testing at a gauge length of 30 to 35 mm, and extended at a linear load stress and a constant rate of 4 mm/min.

Dk Measurements **-** The oxygen transmissibility of swollen contact lenses was measured on a Createch permeometer. The lens was placed between two cells, measuring oxygen transmissibility of the lens by detecting the small amount of electrical current produced between two dissimilar metals of the polarographic cell (gold and silver) via an electrolyte (saline). The amount of electrical current that was produced was proportional to the amount of oxygen available at the interface of the lens and cell.

Peer-reviewed publications and additional experimental details (which may require an NDA) available upon request.