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# Controlled Release of Multiple Therapeutics From Silicone Hydrogel Contact Lenses for Post-Cataract/Post-Refractive Surgery and Uveitis Treatment

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**Received:** July 13, 2021
**Accepted:** October 8, 2021
**Published:** December 6, 2021

**Keywords:** contact lens; molecular imprinting; ophthalmology; biomaterials; controlled drug delivery

**Citation:** DiPasquale SA, Uricoli B, DiCerbo MC, Brown TL, Byrne ME. Controlled release of multiple therapeutics from silicone hydrogel contact lenses for post-cataract/post-refractive surgery and uveitis treatment. Transl Vis Sci Technol. 2021;10(14):5, https://doi.org/10.1167/tvst.10.14.5

**Purpose:** This work demonstrates seven-day controlled and extended in vitro physiological flow dual release of multiple post-ocular surgery therapeutics from extended-wear contact lenses as a dropless alternative for treatment of uveitis and corneal inflammation, pain, and infection. Lens replacement each week optimizes treatment matching patient recall time with the ability to increase or decrease dosage.

**Methods:** Lenses were synthesized using molecular imprinting to create lenses with macromolecular memory for diclofenac sodium (DS) and dexamethasone sodium phosphate (DMSP), as well as bromfenac sodium (BS) and moxifloxacin (MOX). Drug uptake and release were analyzed, and physical properties were measured and compared to commercial standards.

**Results:** DS + DMSP–loaded lenses demonstrated seven-days-plus release of each, whereas controls released more than 85% of their payload within the first day. Lenses loaded with BS + MOX demonstrated release of BS and MOX for 11 and eight days, respectively. Structural analysis demonstrated statistically similar mesh size and average molecular weight between crosslinks between imprinted lenses and controls, suggesting that release extension was due to formation of macromolecular memory sites rather than a tighter polymer architecture.

**Conclusions:** Lenses demonstrated in this work have significant clinical applications as an eye drop alternative, possessing the ability to be worn continuously for one week while delivering a consistent amount of therapeutic for the duration of wear.

**Translational Relevance:** In vitro physiological flow release results demonstrate the clinical potential of therapeutic contact lenses as a dropless vehicle for ocular drug delivery.

## Introduction

Eye disease affects quality of life worldwide, with more than one billion individuals worldwide having preventable or treatable vision impairment.[1] According to the Lancet Global Health Commission, vision impairment results in an estimated $400 billion lost in economic productivity.[2] There is a pressing unmet need for better and more efficient methods of treatment for ocular diseases that result in better patient outcomes and an increased quality of care.[1,2]

The current state of the art for delivery of therapeutics to the eye is topical formulations in the form of solutions, suspensions, and ointments that currently account for more than 90% of the ophthalmic market.[3] Topical formulations are an inefficient and inefficacious method of ocular drug delivery with several major issues. Patient compliance is a major issue with regard to variability in dose sizes as patients have

been shown to miss doses and be unable to replicate the same drop angle, drop height, and squeeze force when administering a drop, resulting in variability in drop volume.[4] Even when ideally administered, topical formulations suffer from low bioavailability with only 1–8% of the applied therapeutic able to penetrate the eye, with the remaining 92% entering systemic circulation.[5,6] The natural barriers within the eye prevent applied therapeutics from quickly penetrating the eye, whereas tear turnover results in medication being quickly washed out, limiting the effectiveness of topical formulations.[7,8] These issues with topical formulations compound with one another resulting in a significantly inefficient and inconsistent method of treatment.

Since the inception of soft contact lenses, contact lenses that elute drugs have been studied as vehicles for a more effective method of treating ocular ailments because of their noninvasive nature and ability to partition molecules within the aqueous regions of the lens.[9] To date, numerous attempts have been made to deliver therapeutics via hydrogel contact lenses, starting with drug loading via equilibrium partitioning of drug into a commercial lens.[10–13] Although this method is the easiest to implement, requiring only a pre-existing contact lens and drug solution, this method offers no control over release rate with no additional mechanism slowing drug release, and early results demonstrated release profiles similar to topical formulations.[10–13] Several methods have been attempted to decrease and control drug release rate including carrier-mediated release,[14–20] release with diffusion barriers,[21,22] and molecular imprinting.[23,24] Unfortunately, after more than 50 years of development, there is currently no commercially available contact lens drug delivery system, with many methods of loading and release failing to produce lenses that control and extend therapeutic release duration, maintain necessary physical properties of a contact lens, and deliver a therapeutically relevant amount of drug.

In this article, we present novel extended-wear silicone hydrogel contact lenses that release multiple small molecule therapeutics from a single lens to be used to treat post-cataract, post-refractive surgery, uveitis, and corneal abrasion patients. The first lens system releases a nonsteroidal anti-inflammatory drug (NSAID) diclofenac sodium (DS) and a steroidal anti-inflammatory drug dexamethasone sodium phosphate (DMSP), and the second lens system releases an NSAID, bromfenac sodium (BS), and an antibiotic, moxifloxacin (MOX). These lens systems have significant applications as a dropless alternative for the treatment of ocular pain and inflammation and can be administered as a nonrefractive bandage or a refractive vision-corrective lens. Lenses possess the ability to be administered once a week and worn night and day continuously for seven days while releasing a consistent dose of therapeutic, offering better compliance than numerous topical drops and matching patient recall times. Replacing a lens each week also gives the clinician an opportunity to alter the dose. BS + MOX releasing lenses offer prophylaxis against infection. It also offers the potential benefits for effective treatment by controlling inflammation without compromising corneal endothelial regeneration/function or increasing intraocular pressure and pseudophakic cystoid macular edema by not using steroids.[25] NSAID alone has been demonstrated to be moderately more effective at controlling postoperative inflammation after cataract surgery and more effective at preventing pseudophakic cystoid macular edema without increasing intraoperative pressure.[26] Additionally, lenses that release only BS or NSAID/steroidal anti-inflammatory drug only offer the option for a single-dose antibiotic application via intracameral irrigation at the completion of surgery, which is becoming a more widely accepted standard of care and has been shown to reduce endophthalmitis risk by six to seven times.[26] A lens wear time of one week/seven days matches clinician standard of care recall or patient follow-up with treatment durations of two to six weeks post-cataract, six to 10 weeks for anterior uveitis, one week for refractive surgery, and one week for corneal abrasion. Typical treatment is one week with laser-assisted surgery and superficial abrasions, but complications and deeper abrasions may require an additional week after follow-up.

The controlled release rationale focuses on the use of a macromolecular memory strategy for drug loading and release. This method involves templating of the drug into the polymer network of the contact lens via addition of the drug to the prepolymer formulation with functional monomeric units that noncovalently bind the template drug. These monomer-drug complexes remain during the polymerization process, resulting in templating of the drug within the lens and formation of macromolecular memory sites. These sites offer strict control over loading, as well as release without negatively affecting physical properties of the lens such as oxygen transport, optical clarity, elastic modulus, and water content. Release control can be exhibited over a wide variety of template drugs via parameters such at the ratio of functional monomer to template (M/T ratio)[27] and a diversity of crosslinker or functional monomer.[28] This method of loading and release has been demonstrated by our laboratory to be effective for a wide range of molecules with a variety of different sizes and functionality.[27,29–33]

## Materials and Methods

### Synthesis of Silicone Hydrogel Contact Lenses

Methacryloxypropyl terminated polydimethylsiloxane (DMS-R11) and methacryloxypropyl-tris-(trimethylsiloxy) silane (TRIS) were purchased from Gelest, Inc. (Morrisville, PA, USA). N,N dimethyl acrylamide (DMA), ethylene glycol dimethacrylate, polyethylene glycol (200) dimethacrylate (PEG200DMA), diethyl aminoethyl methacrylate (DEAEM), diallyl dimethyl ammonium chloride (DADMAC), acrylic acid (AA), methacrylic acid (MAA), dexamethasone sodium phosphate (DMSP), diclofenac sodium (DS), bromfenac sodium (BS), and moxifloxacin (MOX), ethanol, and 2-hydroxy-2-methylpropiophenone were purchased from VWR (Radnor, PA, USA).

Silicone hydrogel contact lenses were synthesized using various mixtures of DMS-R11, TRIS, and DMA in addition to PEG200DMA, ethylene glycol dimethacrylate, DEAEM, AA, MAA, DADMAC, and ethanol with MOX, BS, DMSP, or DS added to the prepolymer formulation in various combinations. Photo-initiator 2-hydroxy-2-methylpropiophenone was added at a composition of <1% of total formulation.

Monomers were added at various monomer-to-template (M/T) ratios for each drug equating to up to 10 mol% of total formulation. M/T ratio refers to the molar ratio of the functional monomer to the template drug and dictates the amount of drug added to the prepolymer formulation such that no more than 10 mol% of the total formulation is functional monomer. Functional monomers were selected based on their ability to noncovalently complex with drug molecules. DEAEM and DADMAC were selected due to their positive charge and ability to form ionic bonds with negatively charged template molecules whereas MAA and AA were chosen to form hydrogen bonds with templates molecules that did not possess a charge. M/T ratios were normalized to the highest M/T ratio among all formulations. Control lenses were synthesized using the same macromers and monomers but without addition of template drug to the pre-polymer formulation. The pre-polymer formulation was vortexed for approximately one minute and then sonicated for 30 minutes at room temperature to remove dissolved gases and ensure full dissolution of the template drug.

A volume of 65 µL of the pre-polymer formulation was pipetted into polypropylene lens molds (dimensions swollen silicone lens 14.8 mm diameter, 8.4 base curve). Polymerization occurred via ultraviolet (UV) polymerization using an Omnicure S2000 (Excelitas Technologies Corp., Waltham, MA, USA), with an intensity of approximately 40 mW/cm$^2$ for a duration of two minutes. UV effects on the chemistry of loaded drugs was verified via $^1$H-NMR (400 MHz, Agilent Technologies, Santa Clara, CA, USA) to ensure that UV polymerization did not affect the chemical structure. Mass of drug within the lens was determined via drug uptake and release experiments via mass balance.

### Template Drug Binding Studies

All lenses were washed in 700 mL to 1 L of phosphate-buffered saline solution (PBS) in a Sotax AT Xtend Dissolution System (Sotax, Westborough, MA, USA) at 30 rpm. To verify washing, lenses were removed and placed in 2 mL of PBS and supernatant drug concentration was measured until no drug was observed releasing from the lens (lower limit of detection of ~0.5 µg/mL). Lenses that displayed additional drug elution were placed back in the dissolution apparatus. Effectiveness of the wash was determined via mass balance analysis during washing and release based on the mass of drug loaded within the lens, with more than 95% of the loaded drug released during the washing process. Template binding studies were performed by placing washed lenses of different M/T ratios in 3 mL of 150 µg/mL drug solution (BS, DS, or DMSP, in DI water) until equilibrium was reached, which was verified experimentally. Equilibrium concentration of the supernatant was measured via UV/Vis spectrophotometry (280 nM) and used to determine mass uptake via mass balance. For dry lens mass, lenses were dried in a vacuum oven (T = 30°C, 28 in. Hg vacuum) until weight change was less than 0.1% and dry masses were measured. Normalized drug mass uptake (µg drug/mg polymer) was determined for each M/T ratio. Control lenses were synthesized, washed, and loaded via the same method as templated lenses and analyzed for drug mass uptake. Imprinting factor for lenses at each M/T ratio was calculated by dividing normalized drug mass uptake by normalized drug uptake observed in controls.

### In Vitro Physiological Flow Release

Release studies were conducted via an in vitro physiological flow model using a microfluidic device (Fig. 1). The device was produced using polydimethylsiloxane. A mixture of 10:1 ratio of Sylgard 184 Silicone base and curing agents was prepared and stirred for four minutes, then poured onto a glass plate within a

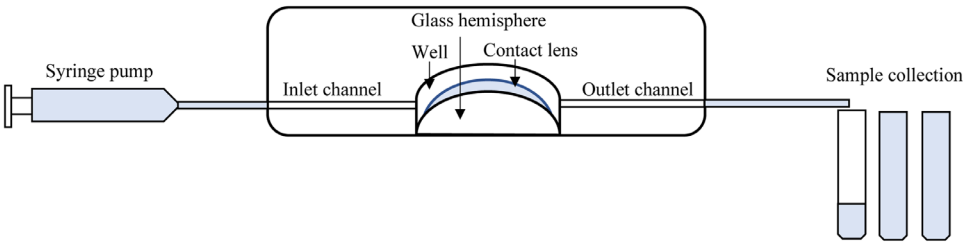


**Figure 1.** Depiction of physiological flow microfluidic device.

circular mold. Two needles (1.27 mm outer diameter) were placed into the mold to create an inlet and outlet for flow, and a hemisphere on the glass plate (9.00 ± 0.10 mm radius of curvature) created a well in which contact lenses were placed during release. The device was then cured at 60°C for six hours. Drug loaded lenses were placed in the well of the device and fixed into position with a glass hemisphere (8.75 ± 0.10 mm radius of curvature). The microfluidic device was then sealed onto a glass plate using metal clamps. A kd Scientific Model 220 syringe pump (kd Scientific Inc., Holliston, MA, USA) was used to inject solution (DI water or PBS) at ambient temperature (25°C) through the device at a rate of 3 µL/min, simulating physiological tear flow. Before release analysis, lenses were fully washed until no additional drug was observed eluting from the lens and then reloaded with the template drugs. Release samples were collected and analyzed at different time intervals via HPLC (Waters Corp, Milford, MA, USA) with tandem UV/Vis detector at a wavelength of 280. HPLC conditions consisted of a C18 column (3.8 µm diameter; Waters Corp, Milford, MA, USA) and mobile phase of 50% acetonitrile and 50% aqueous (1% formic acid, v/v).

## Physical Property and Structural Analysis

To determine optical transmittance, transmittance of visible light (450–700 nm) was measured through circular hydrogel lens segments, cut with a cork borer with a diameter of 1.5 mm. Each lens segment was placed in the bottom of a 96 well plate and hydrated in 200 µL of DI water along with a blank well containing only 200 µL of water, with care taken to ensure that there were no air bubbles present in any wells. Absorbance values of each well was measured in a Tecan Infinite M200 Pro spectrophotometer (Tecan, Männedorf, Switzerland), and absorbance values of blank wells were subtracted from wells containing lenses.

Contact angle with water was measured via sessile drop contract angle goniometry (Theta Flex Tensiometer, Nanoscience Instruments, Phoenix, AZ, USA). Contact lenses were plasma coated in a SPI Plasma Prep III Plasma Cleaner (SPI supplies, West Chester PA, USA), and 5 mm circular cutouts were cut from the lenses with a cork borer. Using a micropipette, a water droplet was placed on the surface of cutouts and contact angle was measured.

Elastic modulus was measured via synthesis of rectangular drug eluting silicone hydrogel sheets via UV photopolymerization using glass slides separated by 500 µm Teflon spacers. Dumbbell shaped tensile testing strips were cut from these sheets and analyzed for elastic modulus using a Shimadzu EZ-SX tensile tester (Shimadzu, Kyoto, Japan) at a gauge length of approximately 18 mm and stretched at a rate of 5 mm/min. Elastic modulus was determined by measuring the initial slope of the stress/strain curve. Hydrogels remained hydrated for the duration of the tests via aerosol diffusion of water.

Edge-corrected Dk was calculated according to ISO 18369.4 (Ophthalmic Optics – Contact Lenses – Part 4: Physiochemical Properties of Contact Lens Materials). Lenses swollen in PBS were stacked to create polymers of different center thicknesses, measured using an electronic micrometer. Each lens or lens stack was placed on a polarographic oxygen sensor (Createch/Rehder Dev Co., Greenville, SC, USA) with 8.7 mm base curve and analyzed using a 201T oxygen permeameter.

Equilibrium weight swelling ratio was determined by measuring the ratio of the swollen polymer weight to the dry weight. Synthesized lenses were dried until weight change was less than 0.1% in a vacuum oven and weight of the dried lenses was recorded. Lenses were swollen in DI water, and swollen mass was recorded. Equilibrium weight swelling ratio was calculated using the relationship:

$$q = \frac{W_S - W_d}{W_d}$$

where q is equilibrium weight swelling ratio, $W_s$ is weight of the swollen gel, and $W_d$ is weight of the dry gel.

Equilibrium volume swelling ratio was determined by measuring the ratio of the swollen volume to the dry volume. Volume of dried and swollen gels were determined using Archimedes principle. Equilibrium volume swelling ratio was determined using the relationship:

$$Q = \frac{1}{\upsilon_{2,s}} = \frac{V_S}{V_d}$$

where Q is equilibrium volume swelling ratio, $\upsilon_s$ is polymer volume fraction in the swollen state, $V_s$ is the volume of the swollen gel at equilibrium, and $V_d$ is the volume of the dry gel.

The average molecular weight between crosslinks was calculated by analyzing tensile properties of synthesized polymers as well as polymer volume fractions. The relationship to calculate molecular weight between crosslinks was as follows:

$$E = \left(\frac{RT\upsilon_{2,s}^{1/3}}{\bar{\upsilon}\bar{M}_c}\right) * \left(1 - \frac{2\bar{M}_c}{M_n}\right)$$

where E is the tensile modulus, R is the ideal gas constant, T is temperature, $M_n$ is the number average molecular weight of the polymer chains, $\upsilon_{2,s}$ is the polymer volume fraction in the swollen state, $\upsilon$ is the specific volume of the swollen polymer, and $\bar{M}_c$ is the average molecular weight between crosslinks.

Average molecular weight between crosslinks was used to calculate the average mesh size of synthesized polymers using the relationship:

$$\xi = \upsilon_{2,s}^{-1/3}\left(\frac{2C_n\bar{M}_c}{M_r}\right)^{1/2} l$$

where $\xi$ is mesh size, $\upsilon_{2,s}$ is the polymer volume fraction in the swollen state, $M_r$ is molecular weight of the repeat unit, $\bar{M}_c$ is the average molecular weight between crosslinks, $C_n$ is the Flory characteristic ratio, and $l$ is the length of the bond along the polymer backbone. Average molecular weight between crosslinks and mesh size were normalized to the highest values for each among all formulations.

## Results and Discussion

### Template Drug Binding Studies

Drug molecules added within the prepolymer formulation are hypothesized to complex with functional monomers, beginning the templating process. During polymerization, these complexes are hypothesized to create complexation points within multiple polymer chains which form macromolecular memory sites within the polymer structure. Drug reloading, dynamic release experiments, and network

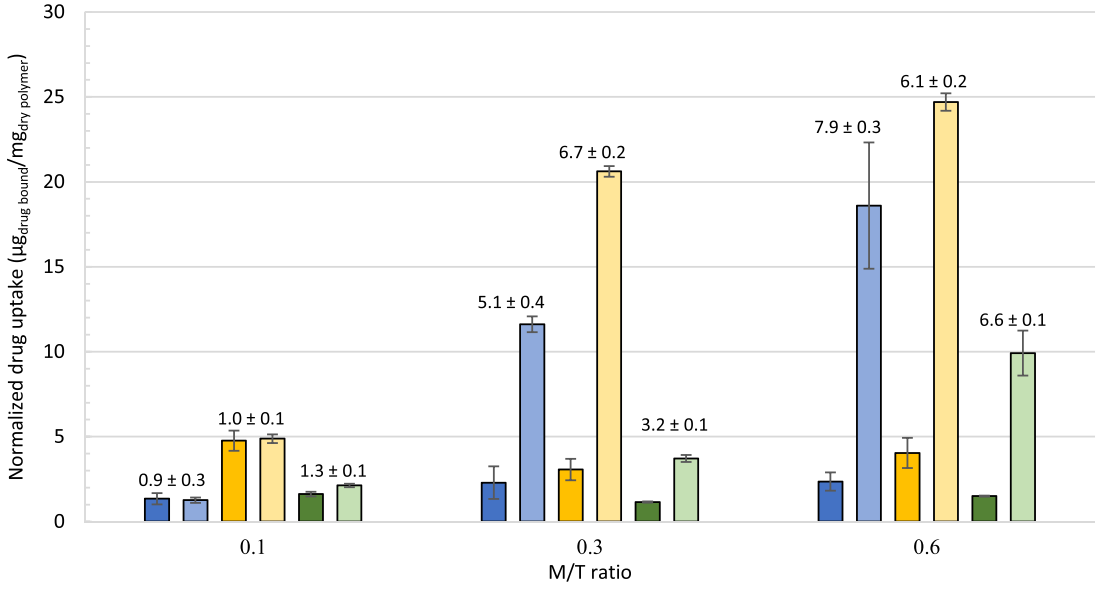


**Figure 2.** Equilibrium mass binding of DS, DMSP, and BS in lenses synthesized using the templating process and controls. Lenses were synthesized using the templating process at three different M/T ratios (0.1, 0.3, and 0.6) for each template molecule. Lenses were fully washed and loaded in concentrated template solutions (150 μg/mL) and remained until equilibrium was reached. ☐ indicate DS templated; ☐ indicate DS control; ☐ indicate BS templated; ☐ indicate BS control; ☐ indicate DMSP templated; and ☐ indicate DMSP control. All tests were performed with five replicates; *error bars*: ±SD.

structural analysis have been shown by our group to validate the hypothesis with various drugs.[27,29–32]

Equilibrium mass binding of DMSP, DS, and BS in templated silicone hydrogel contact lenses at different M/T ratios and controls are shown in Figure 2. DMSP templated lenses demonstrated equilibrium binding values of 2.1 ± 0.1 $\mu g_{drug}/mg_{polymer}$, 3.7 ± 0.2 $\mu g_{drug}/mg_{polymer}$, and 9.9 ± 1.3 $\mu g_{drug}/mg_{polymer}$ corresponding with normalized M/T ratios of 0.1, 0.3, and 0.6, respectively. Imprinting factor for DMSP templated lenses synthesized at M/T ratios of 0.1, 0.3, and 0.6 were 1.3 ± 0.1, 3.2 ± 0.1, and 6.6 ± 0.1 respectively, demonstrating an increase in drug binding compared to controls and supporting the hypothesis that macromolecular memory sites within the lens lead to an increase in drug uptake. DS templated lenses at different M/T ratios demonstrated equilibrium binding values of 4.9 ± 0.3 $\mu g_{drug}/mg_{polymer}$, 20.6 ± 0.3 $\mu g_{drug}/mg_{polymer}$, and 24.7 ± 0.5 $\mu g_{drug}/mg_{polymer}$ corresponding with normalized M/T ratios of 0.1, 0.3, and 0.6 respectively and imprinting factors of 1.0 ± 0.1, 6.7 ± 0.2, and 6.1 ± 0.2, respectively. Equilibrium mass binding of BS in BS templated lenses with M/T ratios of 0.1, 0.3, and 0.6 were 1.3 ± 0.2 $\mu g_{drug}/\mu g_{polymer}$, 11.6 ± 0.5 $\mu g_{drug}/\mu g_{polymer,}$ and 18.6 ± 3.7 $\mu g_{drug}/\mu g_{polymer}$, respectively, corresponding with imprinting factors of 0.9 ± 0.3, 5.1 ± 0.4, and 7.9 ± 0.3, respectively.

Equilibrium binding results for DS, DMSP, and BS demonstrated an increased drug uptake as M/T ratio increased. Controls demonstrated the lowest drug binding whereas the highest M/T ratios demonstrated the highest drug binding, with higher M/T ratios binding significantly more mass than controls synthesized with the same mol% of functional monomer. These results support the hypothesis that macromolecular memory sites lead to a higher drug uptake and increasing functionality within the lens leads to a higher degree of macromolecular memory site formation in lenses loaded via the templating process as the template drug. Controls in this study contained functionality that matched the template drug at the same concentration as templated lenses, with the only difference being the absence of template drug in the prepolymer formulation in controls. This suggests that the templating process leads to macromolecular memory site formation, which enhances drug uptake rather than only the presence of functional chemistry that interacts with the template drug.

## In Vitro Physiological Flow Release

Release via the microfluidic physiological flow device has been demonstrated by our lab to be a more effective method for correlation of in vitro results to in vivo.[27,33,34] Release via the microfluidic device more accurately replicates volume and flow dynamics within the tear film to more accurately predict in vivo drug release behavior of drug loaded lenses. Release results of BS loaded templated lenses synthesized at normalized M/T ratios of 1.0 and 0.12 are demonstrated in Figure 3A. Lenses synthesized at an M/T ratio of 0.12 released their drug payload in 14 days whereas lenses synthesized at an M/T ratio of 1.0 extended release up to 35 days, supporting the hypothesis that an increase in functionality within the lens led to an increase in memory site formation during synthesis, resulting in a decreased release rate. Average mass released from lenses synthesized with an M/T ratio of 0.12 was 4.6 ± 0.2 μg/d, whereas average mass release from 1.0 M/T lenses was 4.4 ± 0.1 μg/d.

Figure 3B shows in vitro microfluidic fractional dual release of DS and DMSP from DS + DMSP templated lenses and controls. Release of both DS and DMSP from control lenses occurred rapidly, with approximately 85% of the drug payload within the first day. By the second day, more than 95% of loaded DMSP was released, with the remaining small amount of drug (<5%) released by the following day. Approximately 90% of loaded DS had been released by day 2 with the remaining 10% released over the following two days. Drug release profiles from controls are expected to be slightly better than soaking commercial lenses, as controls contain functional monomers that noncovalently interact with the template drug but lack hypothesized polymer chain templating organization formed in presence of drug. Lenses synthesized with the templating process extended release of both DS and DMSP to over seven days and shifted the release curve downward toward a more constant release rate. Dual release of BS and MOX from lenses synthesized with the templating process and controls are shown in Figure 3C. Lenses synthesized using the templating process showed MOX release for eight days and BS release for 11 days. Controls demonstrated a faster release of MOX, with ~40% of the payload released within the first day and the majority released before day 4. Controls demonstrated 11 day release of BS, at a rate shifted to the left of templated lenses signifying a release profile that is less controlled and concentration dependent (further from zero order controlled release). Templated DMSP + DS loaded lenses released DMSP and DS at an average rate of 6.8 ± 1.9 μg/d and 11.4 ± 2.8 μg/d, respectively, whereas templated BS + MOX loaded lenses released BS at an average rate of 28.2 ± 8.6 μg/d and MOX at an average rate of 14.0 ± 5.0 μg/d. DMSP topical drops (0.1%, Maxidex) are administered four to six times daily, and DS topical

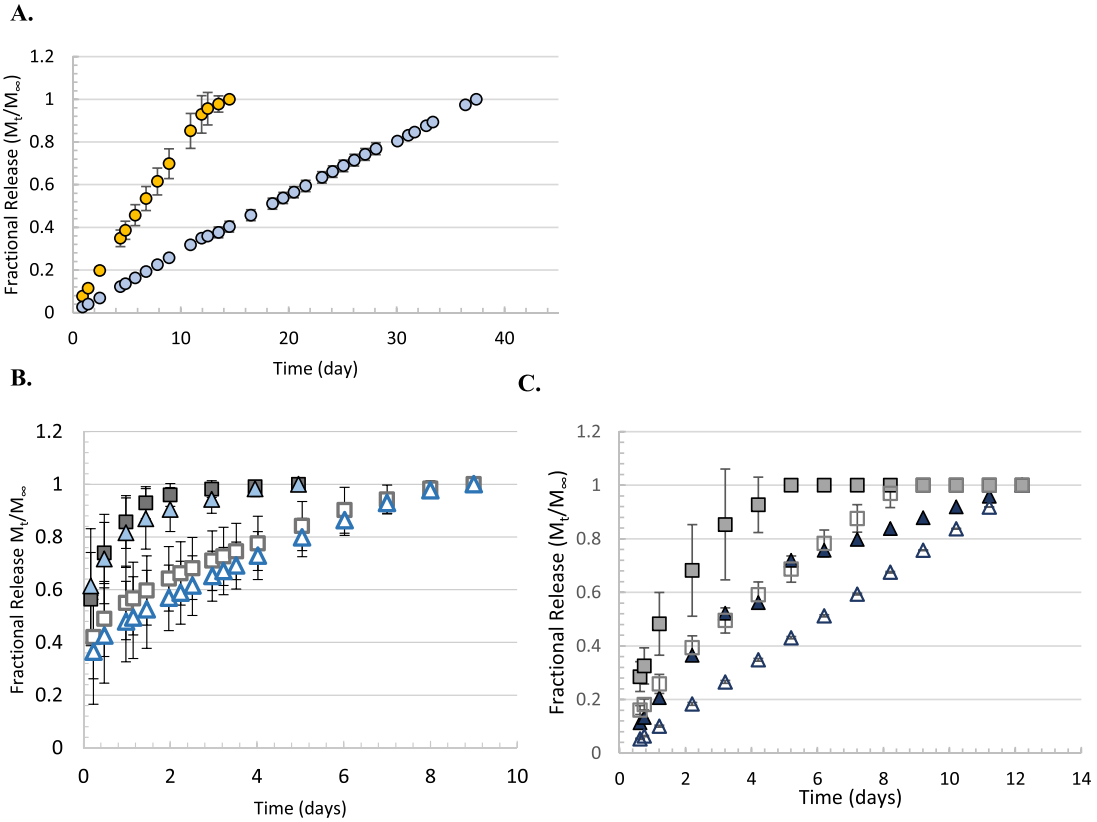


**Figure 3.** In vitro physiological flow release of various template molecules. (**A**) Release of bromfenac sodium from templated contact lenses synthesized at different M/T ratios. ● indicate 0.12 M/T ratio; ● indicate 1 M/T ratio. (**B**) Controlled dual release of DMSP and DS from templated lenses and controls. ■ indicate DMSP control, ▲ indicate DS control, △ indicate DS 0.2 M/T, and □ indicate DMSP 0.2 M/T. (**C**) Dual release of bromfenac sodium and moxifloxacin from templated lenses and control lenses. □ indicate MOX control, ▲ indicate BS control, △ indicate BS 0.2 M/T, and □ indicate MOX 0.4 M/T. All tests were performed with at least three replicates; *error bars*: ±SD.

drops (0.1%, Voltaren) are administered 4 times daily. Assuming a drop volume of 50 µL, each drop delivers approximately 50 µg of medication, resulting in 200 µg/d of applied DS and 200 µg/d of applied DMSP (4 drops/d). For topical drops, approximately 92% of the applied therapeutic is lost due to tear turnover,[5,35] resulting in an estimated therapeutic dosage of 16 µg/d of both DS and DMSP. Moxifloxacin topical drops (0.5%, Vigamox) are administered once daily, resulting in 500 µg/d of applied moxifloxacin and an estimated 40 µg/d dosage taking tear turnover into account. Bromfenac topical drops (0.09%, Xibrom) are administered twice daily, resulting in 90 µg/d of applied bromfenac and an estimated 7.2 µg/d dosage considering tear turnover. Release rates from therapeutic lenses approximates the expected therapeutic dosage of topical drops, however via alteration of the M/T ratio, the release rate can be tailored to achieve a different dosage.[27,33] Furthermore, it has been demonstrated that with a controlled release strategy, where lens release rate approaches absorption rate into tissue, losses of drug due to tear turnover are substantially reduced.[33]

Results from drug reloading and release analysis support the hypothesis that synthesizing lenses in presence of drug molecules and monomers with functional chemistry with affinity for the template drug resulted in an increase in drug binding and a slower, more controlled release. These results suggest that the templating process led to formation of macromolecular memory sites within synthesized lenses that delayed release and increased drug binding compared to controls. Results from BS release at different M/T ratios suggests that increasing functionality within the lens led to a greater degree of memory site formation which led to an increased release duration. $^{1}$H-NMR analysis demonstrated no difference in chemical structure between template drugs that had been subjected to UV polymerization and release from therapeutic lenses and drugs measured without any modification.

**Table.** Physical Properties of Templated Lenses

| | |
|---|---|
| DS + DMSP loaded lenses | |
| Elastic modulus (MPa) | 3.4 ± 0.6 |
| Contact angle | 16.4° ± 3.1° |
| Equilibrium weight swelling ratio | 0.30 ± 0.09 |
| Polymer volume fraction | 0.86 ± 0.01 |
| Dk (barrer) | 83 (95% CL: 70–101) |
| Dimension swollen lens BC (mm)/Dia (mm) (lens mold swelling/expansion ~5%) | 8.4/14.8 |
| Center thickness (mm) | ~0.085 |
| Duration of wear | 6 nights & 7 days/1 week |
| BS + MOX loaded lenses | |
| Elastic modulus (MPa) | 2.1 ± 0.5 |
| Contact angle | 22.6° ± 1.2° |
| Equilibrium weight swelling ratio | 0.20 ± 0.03 |
| Polymer volume fraction | 0.86 ± 0.02 |
| Dk (barrer) | 70 (95% CL: 53–103) |
| Dimension swollen lens BC (mm)/Dia (mm) (lens mold swelling/expansion ~5%) | 8.4/14.8 |
| Center thickness (mm) | ~0.085 |
| Duration of wear | 6 nights & 7 days/1 week |

All tests were performed with at least three replicates.

## Physical Property and Structural Analysis

Measured physical properties of DS + DMSP loaded lenses and BS + MOX loaded lenses are presented in the Table. Elastic modulus of DMSP + DS loaded lenses was 3.4 ± 0.6 MPa. Elastic modulus of BS + MOX loaded lenses was 2.1 ± 0.5 MPa. Elastic modulus of silicone hydrogel contact lenses generally ranges from 0.3 to 1.9 MPa[36] and is a tailorable property that can be adjusted by adjusting the amount of base monomeric units, using a longer chain silicone macromer unit, or using longer crosslinking units that allow for a more flexible polymer network. Contact angle of with water of DS + DMSO loaded lenses was determined to be 16.4° ± 3.1°, meeting the commercial standard for contact lenses of <100°.[37] BS + MOX loaded lenses also met this commercial standard, displaying a contact angle with water of be 22.6° ± 1.2°. Oxygen permeability (Dk) analysis resulted in a Dk of 83 barrer (95% Confidence Limit (CL): 70–101) or 83 × $10^{-11}$ ($cm^2$/sec)(ml $O_2$/ml × mm Hg) at 35°C (Dk intrinsic) in DS + DMSO loaded lenses and 70 barrer (95% CL: 53–103) at 35°C in BS + MOX loaded lenses. These values fall within the range of extended-wear silicone hydrogel lenses on the market today (60–175).[38] Light transmittance through DS + DMSP loaded lenses and BS + MOX loaded lenses was ≥ 96% @ 610 nm and greater than 90% across the visible spectrum, indicating that all lenses were optically clear (Fig. 4). Equilibrium weight swelling ratios of lenses

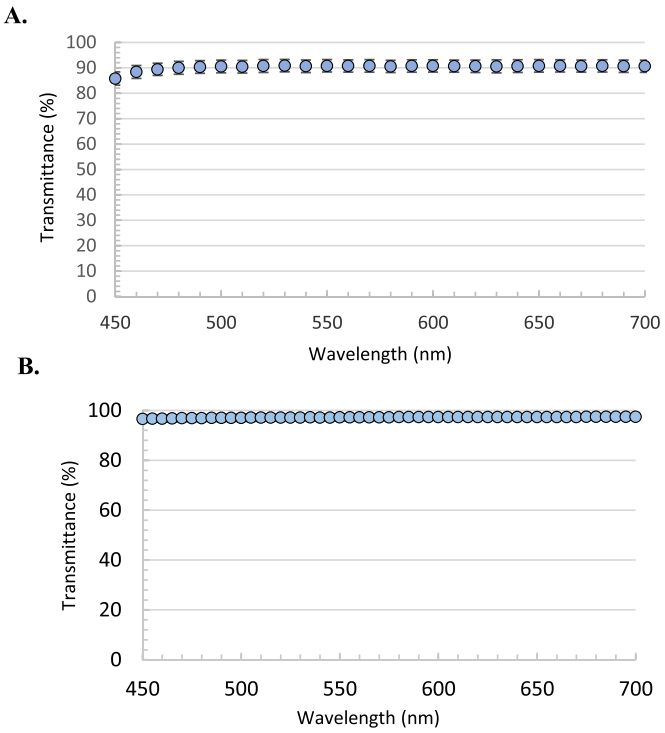


**Figure 4.** Optical transmittance of templated lenses loaded BS + MOX and DS + DMSP. (**A**) BS + MOX loaded lenses. (**B**) DS + DMSP loaded lenses. All tests were performed with at least three replicates; *error bars*: ±SD.

loaded with DS + DMSP was 0.29 ± 0.09 compared to 0.18 ± 0.03 in controls and 0.20 ± 0.03 in templated lenses loaded with BS + MOX compared to 0.23 ± 0.05

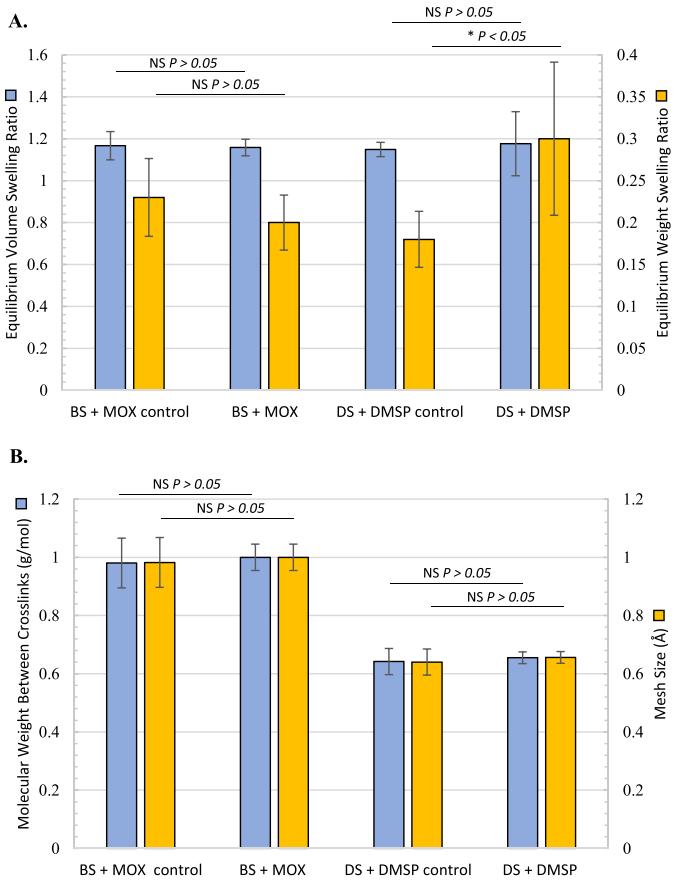


**Figure 5.** Structural analysis of lenses templated with BS + MOX and DS + DMSP. (**A**) Equilibrium weight swelling ratio and equilibrium volume swelling ratio. ▢ indicate equilibrium weight swelling ratio, and ▢ indicate equilibrium volume swelling ratio. (**B**) Molecular weight between crosslinks and mesh size. ▢ indicate mesh size, and ▢ indicate molecular weight between crosslinks. All tests were performed with three to six replicates (*t*-test, not significant [NS] $P > 0.05$, * $P < 0.05$; *errors bars*: mean ± SD).

in controls (Fig. 5), fitting within the acceptable range for silicone hydrogel contact lenses.[38]

Polymer volume fraction in the swollen state of DS + DMSP templated lenses was 0.86 ± 0.03 compared to 0.86 ± 0.05 in controls and 0.86 ± 0.02 in BS + MOX templated lenses compared to 0.87 ± 0.03 in controls. Normalized average molecular weight between crosslinks and mesh size of DS + DMSP templated lenses at an M/T ratio of 0.2 and corresponding controls, as well as BS + MOX templated lenses at an M/T ratio of 0.2 and corresponding controls are highlighted in Figure 5. Structural analysis indicated that for both BS + MOX templated lenses and DS + DMSP templated lenses, lenses synthesized with the templating process had a mesh size that was not statistically different than controls. These results suggest that formation of macromolecular memory sites lead to extended release and increased drug loading in templated lenses rather than a tighter polymer architecture or smaller mesh size.

## Conclusions

In this work, we have demonstrated dual release of diclofenac sodium + dexamethasone sodium phosphate and dual release of bromfenac sodium + moxifloxacin from silicone hydrogel contact lenses. DS + DMSP templated lenses were able to extend release of each therapeutic to over seven days at a consistent rate compared to controls that delivered over 85% of their loaded drug within the first day. Lenses delivered a therapeutically relevant amount of both DS and DMSP, equating to approximately two topical drops worth of DMSP and four drops of DS continuously each day for the duration of release. Lenses synthesized using the templating process displayed significantly increased drug uptake compared to controls, suggesting successful creation of macromolecular memory sites and increase in memory site formation as M/T ratio increased. The hypothesis that the templating process leads to formation of macromolecular memory sites was further supported by structural analysis of templated lenses and controls, which demonstrated statistically similar mesh size, average molecular weight between crosslinks, and polymer volume fraction.

BS + MOX templated lenses demonstrated an extension of MOX release from five to eight days and a decrease in release rate of BS compared to controls. Formation of macromolecular memory sites in BS loaded lenses was supported by several different studies. Drug uptake studies demonstrated a significant increase in BS uptake in templated lenses compared to controls and an increase in BS uptake as M/T ratio increased. Release studies from lenses templated in BS demonstrated an increase in release duration from 14 days to 35 days as M/T ratio increased from 0.12 to 1.0, suggesting that the increased amount of functional chemistry during the templating process led to an increase in memory site formation. Structural analysis indicated a statistically similar mesh size and polymer volume fraction to controls, suggesting that extended and controlled release was driven by macromolecular memory rather than a tighter polymer mesh.

The lenses demonstrated in this study have significant clinical interest as seven or more days' treatment of anterior uveitis and post-ocular surgery pain, inflammation and infection. The ability of lenses to control and extend the release of multiple molecules at the same time has significant potential for treatment of multiple symptoms using a single lens and

targeting multiple propagators of ocular inflammation with a single lens. This technology has the potential to replace topical formulations as a more consistent and more efficacious method of ocular drug delivery, taking dosing out of the patients' hands, as well as delivering a consistent amount of drug for the duration of treatment, leading to better patient outcomes.

## Acknowledgments

Supported by OcuMedic, Inc., Mullica Hill, NJ.

Disclosure: **S.A. DiPasquale,** None; **B. Uricoli,** None; **M.C. DiCerbo,** None; **T.L. Brown**, None; **M.E. Byrne,** OcuMedic Inc. (F, P, I, E, R, S)

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