1-4-2016

Controlled Release of Multiple Therapeutics from Silicone Hydrogel Contact Lenses.

Charles White
Auburn University

Stephen DiPasquale
Rowan University

Mark Byrne
Rowan University

Recommended Citation

White, C. J., DiPasquale, S. A., & Byrne, M. E. (2016). Controlled Release of Multiple Therapeutics from Silicone Hydrogel Contact Lenses. Optometry and Vision Science 93(4): 377–386.

HHS Public Access

Author manuscript

Optom Vis Sci. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:

Optom Vis Sci. 2016 April ; 93(4): 377–386. doi:10.1097/OPX.0000000000000849.

Controlled Release of Multiple Therapeutics from Silicone Hydrogel Contact Lenses

Charles J. White, PhD, **Stephen A. DiPasquale, PhD**, and **Mark E. Byrne, PhD**

Biomimetic & Biohybrid Materials, Biomedical Devices, & Drug Delivery Laboratories, Department of Biomedical Engineering, Rowan University, Glassboro New Jersey

Abstract

Purpose—The majority of contact lens wearers experience a significant level of ocular discomfort associated with lens wear, often within hours of wear, related to dry lenses, inflammation, protein adhesion to the lens surface, etc. Application of controlled drug release techniques has focused on the incorporation and/or release of a single comfort molecule from a lens including high molecular weight comfort agents or pharmaceutical agents. Previous studies have sought to mitigate the occurrence of only single propagators of discomfort. Clinical studies with eye drop solutions have shown that a mixture of diverse comfort agents selected to address multiple propagators of discomfort provide the greatest and longest lasting sensations of comfort for the patient. In this paper, multiple propagators of discomfort are addressed through the simultaneous release of four molecules from a novel contact lens to ensure high level of lens wear comfort.

Methods—Silicone hydrogel contact lenses were engineered via molecular imprinting strategies to simultaneously release up to four template molecules including hydropropyl methylcellulose (HPMC), trehalose, ibuprofen, and prednisolone.

Results—By adjusting the ratio of functional monomer to comfort molecule, a high level of control was demonstrated over the release rate. HPMC, trehalose, ibuprofen, and prednisolone were released at therapeutically relevant concentrations with varying rates from a single lens.

Conclusions—The results indicate use as daily disposable lenses for single day release or extended-wear lenses with multiple day release. Imprinted lenses are expected to lead to higher efficacy for patients compared to topical eye drops by improving compliance and mitigating concentration peaks and valleys associated with multiple drops.

Keywords

contact lens delivery; molecular imprinting; simultaneous molecule release; comfort

Of the nearly 35 million contact lens wearers in the United States, surveys indicate that up to 80% of wearers endure significant levels of discomfort over the course of wear, while at least 30% of these wearers suffer from severe discomfort.[1-4] This is a matter of high clinical

Corresponding author: Mark E. Byrne, Department of Biomedical Engineering, 201 Mullica Hill Rd, Rowan University, NJ 08028, byrnem@rowan.edu.

interest[4] and potential profit for contact lens manufacturers, and contact lens associated discomfort (CLAD)-related research and products have become a dominant market trend. The primary method of relief is by the application of macromolecular comfort agent eye drop solutions.[5] Contact lens associated discomfort is a complicated and multivariate process that incorporates numerous diverse propagators of discomfort. These propagators of discomfort result in significant levels of discomfort over the course of lens wear, beginning immediately upon inception of wear. Common propagators of lens wear discomfort include contact lens induced dry eye, fouling of the lens surface, disruption of the tear film, and corneal response to lens wear.

The potential clinical implications of the work are wide and far reaching. The ocular bioavailability of drugs topically applied to the eye is very poor. The majority of ocular agents/pharmaceutics are delivered via eye drops, which are grossly inefficient necessitating multiple drops various times a day leading to patient compliance issues and sub-optimal therapy. Also, delivering multiple agents typically requires many topical formulations with varied eye drop schedules. Thus, there is a substantial unmet need for more efficacious and non-invasive extended delivery of ocular agents, especially those that release multiple molecules in a controlled fashion. While this work focuses on lens comfort, controlling the release of multiple molecules has the potential to be applied to a number of treatment strategies.

To develop a true high comfort contact lens, the lens must be engineered to address multiple propagators of discomfort. To date, the most promising method of achieving this is through the release of macromolecular comfort agent from the lens surface and the application of molecular imprinting to lens formulations to control the rate of release of template molecules. The following reviews[6-9] and articles[10-22] are recommended as background to the method.

The principle of molecular imprinting exploits non-covalent associations between drug and monomers or macromers to create macromolecular memory sites during the polymerization reaction.[8-9] The drug is included in the pre-polymer formulation and influences the formation of the polymer network. Functional monomers are typically selected to have complementary functionality to the selected drug templates, thereby promoting intermolecular interactions, such as hydrogen bonding and ionic interactions, between the template molecule and functional monomer. When polymerization occurs, the resulting polymer network has memory segments where the drug molecules have been templated into the network structure with functional chemistry oriented to bind the template drug.[6-9] As the drug undergoes Brownian motion, the template temporarily resides in the affinity pocket formed by the memory site between multiple polymer chains, delaying the transport of the template. The template molecule will interact with numerous memory sites as it diffuses from the bulk of the lens to outside the lens surface.[22] However, just adding functional monomers to a pre-polymer and drug solution will not necessarily create an imprinted network. The functional monomers must be in sufficient concentration to create the interactions in sufficient quantity to retard diffusion through the network. If the functional monomer concentration is too low, effective imprinting will not occur. Also, the average molecular weight between crosslinks (*Mc*) or the molecular weight between junction points

within the network must be an optimal size as to allow drugs to pass through the network and small enough to allow effective interactions as the drug diffuses from the structure.[6-9] Experimentation is required to identify the effective monomer to template drug (M/T) ratio range for a particular system.

Molecular imprinting typically depends on drug molecules being dissolved in the monomer formulation or in a solvent instead of relying on other molecules to aid solubility.[8] Surfactants or emulsifiers can prevent the orientation of monomers with and around the drug molecule.[8] Also, the best results for macromolecule release and loading can be seen if the macromolecule conformation does not vary significantly from solution to the bulk polymer network.[8] In contact lenses where optical clarity is of paramount importance, the best results occur with miscible drugs and polymers, though use of immiscible drugs is not necessarily limited, especially when a biphasic silicone hydrogel lens is used. Once the drug is dispersed and the polymer network formed, release depends on the interactions between the drug and the functional chemistry polymerized into the network as well as diffusion among crosslink structure and steric influences.

Template molecules selected for this work include 120 kilodalton (kDa) hydroxylpropyl methylcellulose (HPMC), trehalose, ibuprofen, and prednisolone. The template molecules were selected for potential to alleviate propagators of ocular discomfort. Trehalose was selected for water retention properties [23] and has been investigated in ocular formulations.[24-27] HPMC (120 kDa) is commonly used in eye drop formulations to alleviate dry eye symptoms. Prednisolone and ibuprofen were selected for their anti-inflammatory properties to contribute to ocular comfort.

MATERIALS/METHODS

Contact lenses were prepared using a mixture of methacryloxypropyl-tris-(trimethylsiloxy) silane (TRIS), dimethyl acrylamide (DMA), and a silicone macromer material methacryloxypropyl terminated polydimethylsiloxane (DMS-R11). In addition, crosslinking monomers, ethylene glycol dimethacrylate and polyethylene glycol 200 dimethacrylate, and functional monomers, acrylic acid and vinyl phenol, were added to the lens formulation. Photo-initiator, Daracur 1173, was used to synthesize the pre-polymer into hydrogels. Denatured ethanol was also added to the lens mixture to ensure mixing and the formation of a homogenous lens solution. Four template molecules were selected for incorporation and release from the hydrogel lenses. The template molecules selected were 120 kilodalton (kDa) hydroxylpropyl methylcellulose (HPMC), trehalose, ibuprofen, and prednisolone.

DMA was purchased from Sigma Aldrich (Milwaukee, WI), and TRIS and DMS-R11 were purchased from Gelest, Inc (Morrisville, PA). All components were used as received. Darocur 1173, the photo-initiator, was purchased from Sigma Aldrich (Milwaukee, WI). Acrylic acid (AA), 4vinyl phenol (4VPh), (poly(ethylene glycol) (200) dimethacrylate (PEG200DMA), ethylene glycol dimethacrylate (EGDMA), and hydroxypropyl methylcellulose (HPMC) (MW = 120 kDa) were purchased from Sigma Aldrich (Milwaukee, WI) and were used as received. The four template molecules (HPMC, ibuprofen, prednisolone, and trehalose dihydrate) were all purchased from Sigma Aldrich.

All monomers were kept refrigerated at 4ºC. All template molecules were kept in a desiccator. Diphenyl amine, glacial acetic acid, and sulfuric acid (12 M) were purchased from VWR.

Synthesis of Silicone Hydrogel Contact Lenses

The lens material used is a silicone hydrogel contact lens material based on polydimethylsiloxane (PDMS). The lens formulation developed in this work is similar in composition to commercial contact lenses[20] but is not a commercially available material. Lenses were mixed from individual components. Equal mass (~1,000 μg) of DMS-R11, TRIS, and DMA were mixed and used to calculate the ratios of other components. Equal weights of EGDMA and PEG200DMA were added to a desired concentration between 0 and 10 wt% of the base formulation, and imprinting monomers (M) were then added between 0 and 10 wt% of the base formulation. Imprinting monomers were AA (HPMC, trehalose) and 4VPh (ibuprofen, prednisolone). Darocur 1173 was added to the solution to a concentration of 1% of the base formulation. The formulation was thoroughly mixed. The template molecules (T) were added to the desired concentration. Prior to mixing, trehalose dihydrate and HPMC were dried by placing the powdered sample in a drying dish and kept in a vacuum oven at 25ºC for 1 week or until the mass difference was less than 1%. After drying, the trehalose and HPMC was placed in sealed bottles and placed in a desiccator. The template(s) were then added to the predetermined concentration. The formulations were mixed at high shear mixing for up to 1 minute and then sonicated for 15 min to remove any dissolved gas or bubbles from the sample.

Trehalose dihydrate was dried in an oven for 24 hours at 34ºC to remove water from the powder. It was found that trehalose dihydrate was completely insoluble in the silicone hydrogel contact lens formulation. Trehalose displayed minimal solubility until glacial acetic acid was added as a co-solvent to 10 mass percent of the formulation. With the addition of the acetic acid, the dried trehalose was almost instantly dispersed into the lens pre-polymer formulation to high concentrations. Optically clear lenses (greater than 90% optical transmittance) containing 500 μg trehalose were then synthesized in the same matter as the HPMC lenses.

A fixed volume of the lens formulation was pipetted into lens molds (plano). Lenses were produced via UV polymerization using a UV light source (Novacure 2100, Exfo) with an intensity of approximately 25 mW/cm^2 for a duration of 1.5 minutes. The lenses were then removed from the mold and used immediately in dynamic release studies. Final thickness values for hydrated lenses were 100 μm. The initial mass of HPMC and trehalose in the lenses were 500 μg/lens. The initial mass of all other templates in the lenses were 150 μg/lens.

Physical Characterization of Contact Lenses

Optical transmission studies were conducted by cutting small diameter regions from the lens 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. All lenses had greater than 90% transmittance when hydrated and possessed physical properties acceptable to commercial lens values.

Mechanical property and stress-strain data was obtained by performing tensile studies on a dynamic mechanical analyzer (TA Instruments, Wilmington, DE). Hydrogels prepared in strips (in triplicate) were mounted on a dynamic mechanical analyzer (RSA III) at a gauge length of 30 to 35 mm, and extended at a constant rate of 4 mm/min. The gels were fully hydrated through the experiment, and hydration was maintained with an aerosol diffuser.

Dynamic Release Studies

Dynamic release studies were conducted using two different in vitro methods, the conventional sink model and the physiological flow model using a microfluidic device. All experiments were run in triplicate. The studies were conducted with the conventional sink model in order to sustain the greatest driving force, using a Sotax Dissolution Apparatus (Horsham, PA), in which loaded lenses were placed in 250 mL of DI water, artificial lacrimal solution (ALS - 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), 0.9% sterile saline solution (0.9% NaCl), 5% sterile saline solution (5% NaCl), or phosphate-buffered saline (PBS) solution. Various release studies were conducted to verify the adequate volume and stirring rate. In the Sotax apparatus, the release media was stirred at a constant rate of 30 rpm by paddles and kept at a constant temperature of 34 °C. For the physiological flow model, the drug-loaded lens was placed within the chamber of the microfluidic device, a technique that we have used previously[20]. A KDS101 Infusion Pump from KD Scientific (Holliston, MA) injected 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. The microfluidic device was engineered and fabricated using polydimethylsiloxane (PDMS). A mixture of 10:1 ratio of Sylgard 184 Silicone base and curing agent was prepared and stirred manually for 3-5 minutes. The mixture was placed under vacuum for an hour and was then poured into a mold constructed to create an inner chamber and two channels for flow. The inner chamber had a radius of curvature of 9.00±0.10 mm. The device was then cured at 60°C for 6 hours. A drug-loaded lens was placed over a mount with radius of curvature of 8.75±0.10 mm and the device was sealed against a glass plate. A syringe pump was used to pump solution through the device at the physiological flow rate of 3 μL/min, and the concentration was measured at different time intervals.

Assays and Template Molecule Detection

HPMC concentration in the release medium was determined via HPLC (Shimadzu, Japan) equipped with a refractive index detector. The mobile phase was deionized water, and a flow rate of 1 mL/min was maintained throughout. A standard curve of refractive index and known HPLC concentration was established, and percent mass release curves were plotted for each lens.

Trehalose detection was performed with a photocalorimetric diphenyl amine (DPA) assay as recommended by the United States Pharmacopeia. Care was taken with samples containing

both HPMC and trehalose as both templates reacted with the assay. The concentration of HPMC was determined according to HPLC refractive index as described above. The assay response from the concentration of HPMC was subtracted from the overall assay to determine the concentration of trehalose.

Ibuprofen and prednisolone were detected via UV-Vis spectroscopy at 264nm and 240nm, respectively. Known concentrations of either molecule were used to calibrate the spectrometer.

RESULTS AND DISCUSSION

Release of 120 kDa HPMC

Release of HPMC from silicone hydrogel lenses in DI Water can be seen in Figures 1 and 2, respectively. It is important to note that the lenses in Figures 1 and 2 are the same lenses, with Figure 1 showing the first 24 hours of release. As the M/T ratio was increased from 0 to 4, the rate of release decreased. At M/T of approximately 4, a linear release rate was observed over the first 24 hours. At the end of the 24 hour period, approximately 50% of the HPMC reservoir remained in the lens. Figure 1B highlights our tumbling hypothesis that demonstrates the tumbling of the drug through the polymer network from one memory site to the next resulting in slower diffusion and delayed kinetics of release. As shown in Figure 2, the lens continued to gradually release 120 kDa HPMC for 7 days releasing the entire payload of HPMC in this period at a consistent rate. The control lens without any functional monomer released approximately 60% of the payload in 2 hours, and the entire HPMC payload between 8-10 hours. Other lenses released at various rates demonstrating the advantage of incorporating molecularly imprinting strategies into contact lenses delivery – the rate of release and duration can be programmed by the monomer template ratio (M/T). Thus, it is possible to release at a faster or slower rate depending on the duration of wear and/or patient and environmental conditions.

The lenses with an M/T of approximately 4 were also tested in the microfluidic device and demonstrated release control for a much longer period of time (Figure 3). In 7 days, only 22% of the loaded HPMC was released, and the entire payload was released in over 35 days (data not shown). The same mass was released in a quarter of a day in the larger volume release study. Thus, with more physiological flowrates, lenses will release for longer durations. This provides evidence that the in vitro release conditions are very important in adequately describing and comparing release. HPMC loading was ~500μg with ~20% released in 7 days leading to a lens release rate of 14-18μg/day. A 20μl drop of a 0.5% HPMC solution (5μg/μl) is 100μg/drop. However, approximately 92% is washed away very quickly predominantly due to quick tear turnover[8,23] resulting in a steady state estimate of ~8 μg per drop. Thus, the lens slowly delivers ~2 drops/day considering quick tear turnover. It is important to note that multiple drops will have significant concentration peaks and valleys, and it is difficult to predict the steady state effective concentration.

Since DI water is a poor model for ocular tear fluid, it was highly desirable to determine the effect that different release media would have on the effectiveness of the molecularly imprinted release rates. To this end, the lens release experiments were repeated in artificial

lacrimal solution (ALS), 0.9% sterile saline solution (0.9% NaCl), 5% sterile saline solution (5% NaCl), and phosphate-buffered saline (PBS) solution. As can be seen Figure 3, the presence of the salt ions in the release media had no noticeable effect on the release rate of HPMC. Though this effect was not unexpected, it could be a special case arising from the high molecular weight of the template molecule allowing HPMC to interact with several macromolecular memory sites simultaneously and encountering a greater number of steric obstacles and interferences to the reptation and diffusion of the comfort agent from the lens material that are not experienced by smaller template molecules.

Controlled Release of Trehalose and HPMC

Hydroxypropyl methylcellulose is an effective ocular comfort agent where the primary mechanism of action for comfort contribution is the increase in tear solution viscosity due to the presence of the HPMC, as well as the relatively mild water retention properties of each chain. The HPMC comfort agent is particularly effective at combating propagators of lens discomfort when incorporated into the bulk of the lens by reducing the rate and mass of protein adhesion, the rate of lens dehydration, and increasing wetting of the lens surface. These are major propagators of discomfort and are the predominant causes of discomfort at the end of the day/wear. However, HPMC provides little additional comfort at the beginning of wear, making HPMC more effective at providing comfort as lens wear continues beyond the first 6 hours of wear. Moreover, other comfort agents are more effective in the retention of water than HPMC. This is important for initial wear period where the loss of tear fluid/water volume is the predominant propagator of discomfort at the initiation of lens wear.

For this reason, it was desirable to engineer the HPMC-eluting lens to include an additional comfort agent into the contact lens for release during the first 4-8 hours of lens wear to ensure high initial levels of comfort. The molecule selected for this purpose was the disaccharide trehalose. The water retention properties of trehalose were found to be extremely high for the small molecule, binding 28 water molecules per trehalose molecule. This value is similar to those found for low molecular weight hyaluronic acid. Comfort index values are a novel method proposed by our lab to correlate the benefit of different species of comfort agents. The index value was developed by correlating intrinsic viscosity, water retention, viscosity, zero-shear viscosity, etc. to comfort agent molecular weight and concentration.[23] The comfort index for trehalose was found to be 98, primarily due to the high water retention value. However, this is desirable as an initial wear comfort agent. Trehalose was also selected as a template molecule to demonstrate the effectiveness of molecular imprinting to control the release of a low molecular weight comfort agent.

Trehalose release from silicone hydrogel lenses is presented in Figures 4 to 6. Figure 4 highlights control over releases as M/T is increased. The duration of mass release was very short in the control lens, i.e. less than 20 minutes. However, by altering the ratio of acrylic acid to trehalose (M/T ratio) from 0 up to 6, the release duration was extended to 6-8 hours. Considering trehalose is a much smaller molecule than HPMC, the release times are significantly smaller in comparison. No statistical difference was observed between the release rate measured in various release media, DI water, or saline solution (Figure 5). These

results suggest that salt ions within the release media do not affect release, thus no further release studies were performed in saline solution.

Release of trehalose was also measured in the small volume, continuous flow microfluidic apparatus (Figure 6). For the M/T~4 lenses, the release was linear reaching 90% payload release in 24 hours. Other lenses with lower values of M/T released much more quickly, releasing the payload before end of wear for a daily disposable lens. Thus, an imprinting strategy leads to a viable solution in terms of release control and duration. For the M/T~4 lenses, trehalose was released at a steady rate of ~17μg/hr for 24hrs (or 408 μg /day) which is close to the hypothesized effective amount from commercial eye drops (Thealoz, 3% solution, 20μL drop). A 3% solution (30μg/μl) corresponds to ~600 μg trehalose/drop. However, approximately 92% is washed away very quickly predominantly due to quick tear turnover[8,23] resulting in a steady state estimate of ~48 μg per drop. Thus, the lens, which releases trehalose very slowly is hypothesized to be equivalent to delivering ~8.5 drops per day. The imprinted lenses will perform much better for patients, significantly decreasing the concentration peaks and valleys that occur with multiple drops as well as compliance issues involving the application of multiple drops.

Release of a Cocktail of Comfort Agents and Molecules

Optically clear lenses (greater than 90% optical transmittance) were synthesized containing both 500 μg 120 kDa HPMC and 500 μg trehalose. The primary propagator of discomfort with initial lens wear is the sensation of dryness and disturbance of the tear film and tear volume. We hypothesize that the short release rate of the trehalose would provide high initial comfort early in lens wear. After the release of trehalose is complete, a significant mass of HPMC would still be releasing. We hypothesize that release of multiple molecules simultaneously is the most promising method to ensure high comfort for the full duration of lens wear. It was found that the presence of the large volume of HPMC in the bulk of the lens helped reduce the rate of trehalose release slightly and extended the release duration by 2 hours (conventional sink model, Figure 7). This will extend the release by a factor of 3 or 6 hours in a physiological environment (considering the correlation between the conventional and microfluidic date for this data set). The size of the HPMC served as a diffusion barrier for the transport of the trehalose, but trehalose is of insufficient molecular weight to affect the release of HPMC.

Additional molecules were also incorporated into lenses. The cocktail of molecules for the combination release devices were 120 kDa HPMC, trehalose, prednisolone, and ibuprofen (Figure 8). Prednisolone and ibuprofen are close in physiochemical characteristics (high hydrophobicity) and have similar release profiles (Figure 8, conventional sink model). Due to their hydrophobic nature and interactions, they take more time than trehalose to transport from the lens (30% payload release in 1 day). Without imprinting mechanisms, the release of both of these molecules was complete in approximately half a day. Considering loading amounts of each drug at 150μg per lens, approximately 45 μg are released in one day. This generally correlates with complete payload being released in 3.3 days in this release environment (rate of 45 μg/day). A prednisolone topical eye drop (1% or 10μg/μl, 20μl/drop) will deliver 200 μg/drop. Losing ~92% quickly due to tear turnover decreases the effective,

steady state amount to ~16μg/drop. Thus, these lenses have the potential to deliver therapeutically relevant amounts. A typical lower dosage is 2 drops per day or 32 μg/day.

CONCLUSIONS

Macromolecular memory engineering via imprinting mechanisms is a valuable tool in the controlled release of multiple therapeutics from contact lenses. This technology offers the highest potential to release multiple molecules at various programmable rates for the duration of contact lens wear and has the potential to significantly enhance efficacy and convenience of ocular drug administration. The release of comfort molecules is also a promising method to ensure high comfort during contact lens wear. For this purpose, novel lens technologies were developed for the controlled delivery of various molecules for use in both extended and daily wear contact lenses. With the high level of control over the release rate demonstrated through the application of molecular imprinting, some molecules may be better suited to be released at various stages of wear and contribute to various elements of comfort. We highlighted the successful controlled release of up to four molecules per lens, to address multiple propagators of contact lens discomfort.

ACKNOWLEDGMENTS

We thank the various funding agencies (NIH Grant G00008141, U. S. Department of Education GAANN Award P200A120244). M.E. Byrne is founder of OcuMedic, Inc. a company commercializing technology in this space, and M. E. Byrne and C. J. W. are listed on patents relating to this technology.

REFERENCES

1. Chalmers RL, Begley CG. Dryness symptoms among an unselected clinical population with and without contact lens wear. Cont Lens Anterior Eye. 2006; 29:25–30. [PubMed: 16448840]
2. Pritchard N, Fonn D, Brazeau D. Discontinuation of contact lens wear: a survey. Int Contact Lens Clin. 1999; 26:157–62. [PubMed: 11384832]
3. Doughty MJ, Fonn D, Richter D, Simpson T, Caffery B, Gordon K. Patient questionnaire approach to estimating the prevalence of dry eye symptoms in patients presenting to optometric practices across Canada. Optom Vis Sci. 1997; 74:624–31. [PubMed: 9323733]
4. Jones L, Brennan NA, Gonzalez-Meijome J, Lally J, Maldonado-Codina C, Schmidt TA, Subbaraman L, Young G, Nichols JJ. The TFOS International Workshop on Contact Lens Discomfort: Report of the Contact Lens Materials, Design, and Care Subcommittee. Optom Vis Sci. 2013; 54:37–70.
5. Highsmith J. Ophthalmic therapeutic drugs - technologies and global markets. BCC Market Research Report. 2010
6. Byrne ME, Salian V. Molecular imprinting within hydrogels II - progress and analysis of the field. Int J Pharm. 2008; 364:188–212. [PubMed: 18824226]
7. Byrne M, Park K, Peppas N. Molecular imprinting within hydrogels. Adv Drug Deliv Rev. 2002; 54:149–61. [PubMed: 11755710]
8. White CJ, Byrne ME. Molecularly imprinted therapeutic contact lenses. Expert Opin Drug Deliv. 2010; 7:765–80. [PubMed: 20408742]
9. Alvarez-Lorenzo C, Concheiro A. Molecularly imprinted polymers for drug delivery. J Chromatogr B Analyt Technol Biomed Life Sci. 2004; 804:231–45.
10. Venkatesh S, Saha J, Pass S, Byrne ME. Transport and structural analysis of molecular imprinted hydrogels for controlled drug delivery. Eur J Pharm Biopharm. 2008; 69:852–60. [PubMed: 18502630]

11. Venkatesh S, Sizemore SP, Zhang JB, Byrne ME. Therapeutic contact lenses - a biomimetic approach towards tailored ophthalmic extended delivery. PMSE Preprint. 2006; 69:766–7.
12. Ali M, Horikawa S, Venkatesh S, Saha J, Hong JW, Byrne ME. Zero-order therapeutic release from imprinted hydrogel contact lenses within in vitro physiological ocular tear flow. J Control Release. 2007; 124:154–62. [PubMed: 17964678]
13. Venkatesh S, Sizemore SP, Byrne ME. Biomimetic hydrogels for enhanced loading and extended release of ocular therapeutics. Biomaterials. 2006; 28:717–24. [PubMed: 17007923]
14. Ali M, Byrne ME. Controlled release of high molecular weight hyaluronic acid from molecularly imprinted hydrogel contact lenses. Pharma Res. 2009; 26:714–26.
15. Ali, M. Masters thesis, Masters of Science. Auburn University; Auburn, AL: 2007. Therapeutic contact lenses for comfort molecules.
16. Alvarez-Lorenzo C, Hiratani H, Concheiro A. Contact lenses for drug delivery - achieving sustained release with novel systems. Amer J Drug Deliv. 2006; 4:131–51.
17. Hiratani H, Alvarez-Lorenzo C. Timolol uptake and release by imprinted soft contact lenses made of n,n-diethylacrylamide and methacrylic acid. J Control Release. 2002; 83:223–30. [PubMed: 12363448]
18. Hiratani H, Alvarez-Lorenzo C. Nature of backbone monomers determines the performance of imprinted soft contact lenses as timolol drug delivery systems. Biomaterials. 2004; 25:1105–13. [PubMed: 14615176]
19. Hiratani H, Mizutani Y, Alvarez-Lorenzo C. Controlling drug release from imprinted hydrogels by modifying the characteristics of the imprinted cavities. Macromolecular Bioscience. 2005; 5:728–33. [PubMed: 16082622]
20. White CJ, McBride MK, Pate KM, Tieppo A, Byrne ME. Extended release of high molecular weight hydroxypropyl methylcellulose from molecularly imprinted, extended wear silicone hydrogel contact lenses. Biomaterials. 2011; 32:5698–705. [PubMed: 21601274]
21. Hiratani H, Fujiwara A, Tamiya Y, Mizutani Y, Alvarez-Lorenzo C. Ocular release of timolol from molecularly imprinted soft contact lenses. Biomaterials. 2005; 26:1293–8. [PubMed: 15475059]
22. Vaughan AD, Zhang JB, Byrne ME. Enhancing therapeutic loading and delaying transport via molecular imprinting and living/controlled polymerization. AICHE J. 2010; 56:268–79.
23. White CJ, Thomas CR, Byrne ME. Bringing comfort to the masses: a novel evaluation of comfort agent solution properties. Cont Lens Anterior Eye. 2013; 37:81–91. [PubMed: 23999507]
24. Matsuo T. Trehalose versus hyaluronan or cellulose in eyedrops for the treatment of dry eye. Jpn J Ophthalmol. 2004; 48:321–7. [PubMed: 15295655]
25. Matsuo T, Tsuchida Y, Morimoto N. Trehalose eye drops in the treatment of dry eye syndrome. Ophthalmology. 2002; 109:2024–9. [PubMed: 12414409]
26. Matsuo T. Trehalose protects corneal epithelial cells from death by drying. Br J Ophthalmol. 2001; 85:610–2. [PubMed: 11316726]
27. Luyckx J, Baudouin C. Trehalose: an intriguing disaccharide with potential for medical application in ophthalmology. Clin Ophthalmol. 2011; 5:577–81. [PubMed: 21654884]

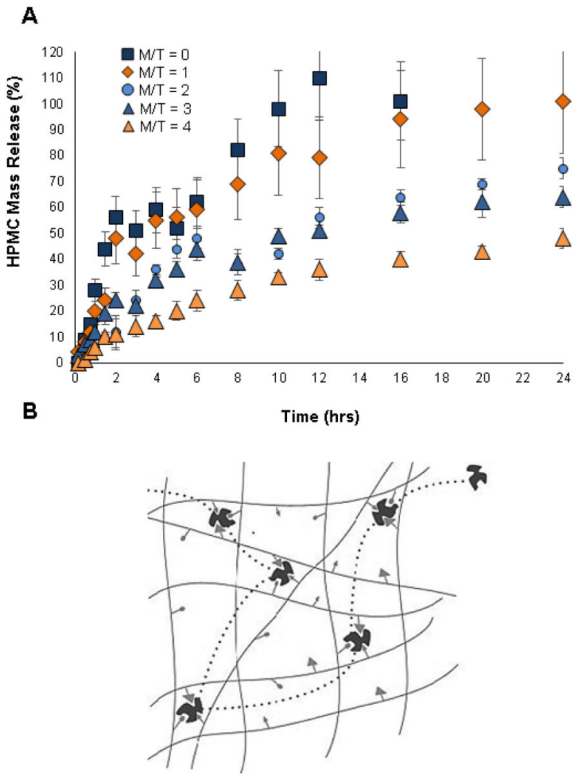

Figure 1.

(A) Release of HPMC from imprinted silicone hydrogel contact lenses at various M/T ratios – short times. HPMC (*120 kDa*) was incorporated and released from imprinted lenses at various M/T ratios. The ratios include 0, 1, 2, 3, 4. At M/T ~ 4, a linear steady release rate was observed. **(B)** The tumbling hypothesis. The drug is delayed through non-covalent interactions with memory sites within the polymer network resulting in slower diffusion and delayed kinetics of release.

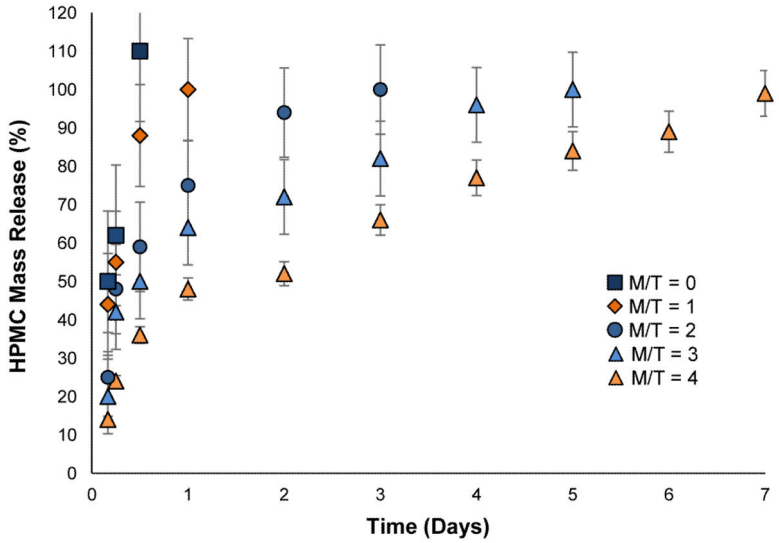

Figure 2.

Release of HPMC from imprinted silicone hydrogel contact lenses at various M/T ratios – long times. HPMC (*120 kDa*) was incorporated and released from imprinted lenses at various M/T ratios. The ratios include 0, 1, 2, 3, 4. At M/T ~ 4, a relatively linear and steady release rate was observed.

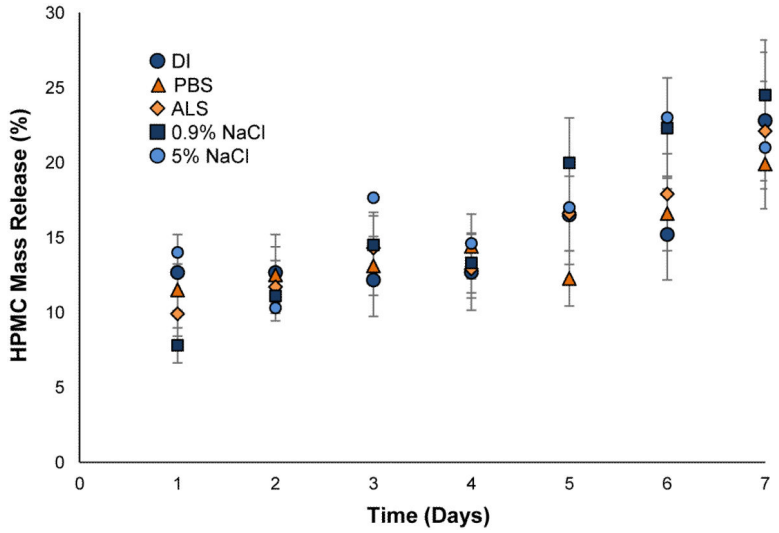

Figure 3.

Imprinted silicone hydrogel lens release of 120 kDa HPMC at physiological flowrates in different release media. Microfluidic Release was performed on M/T~4 lenses in different types of release media including DI water, artificial lacrimal solution (*ALS*), 0.9% sterile saline, 5% sterile saline, and phosphate buffered saline (*PBS*). No statistically significant difference was observed between the media. These lenses show strong potential for continuous extended-wear HPMC releasing lens for all currently approved FDA wear times with variation in the M/T ratio.

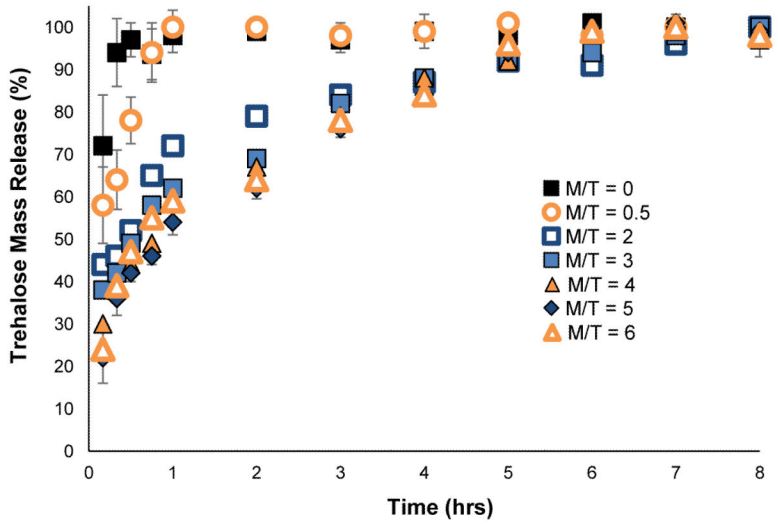

Figure 4.

Release of trehalose from imprinted silicone hydrogel contact lenses at various M/T ratios. Trehalose mass release profiles were observed from imprinted lenses formulated at various M/T ratios including 0, 0.5, 2, 3, 4, 5, 6. As the M/T ratio increased, the delay in release rate was less and less significant between samples. Beyond M/T ~ 3, there was very little statistical significance.

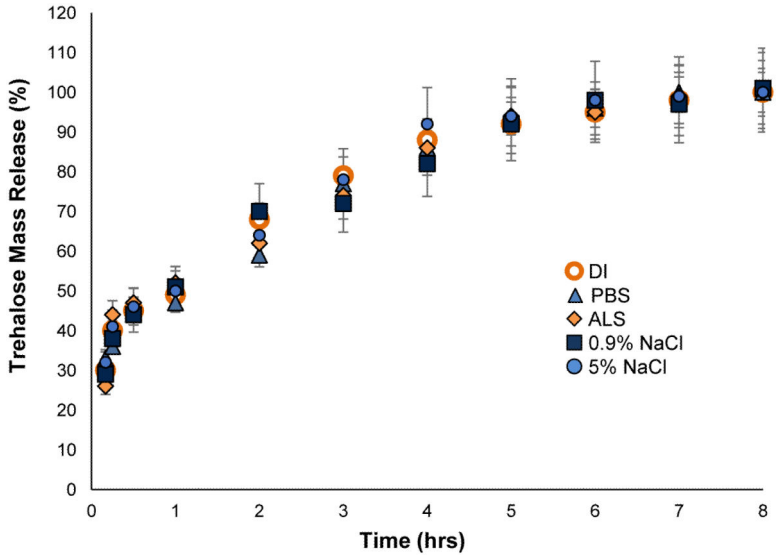

Figure 5.

Release of trehalose from imprinted silicone hydrogel lenses in different release media. Release of trehalose was performed on M/T~6 lenses in different types of release media including DI water, artificial lacrimal solution (*ALS*), 0.9% sterile saline, 5% sterile saline, and phosphate buffered saline (*PBS*). No statistically significant difference was observed between the media.

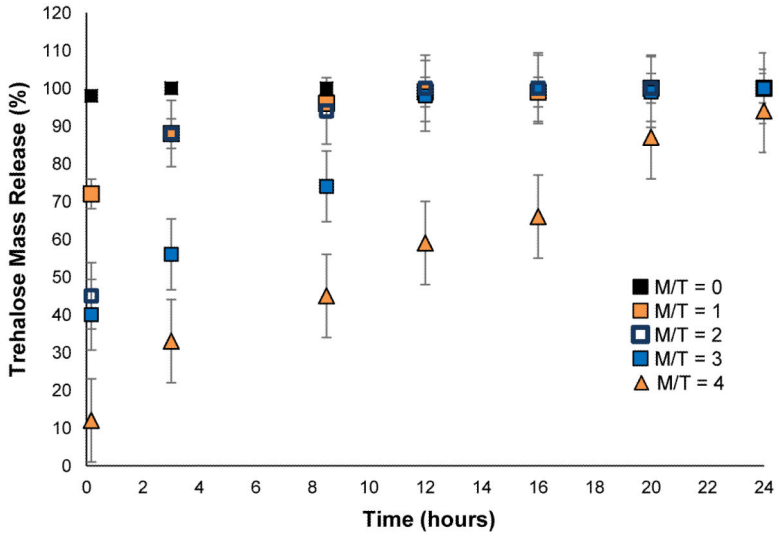

Figure 6.

Trehalose release from imprinted silicone hydrogel lenses at physiological flowrates. Trehalose was incorporated and released from imprinted lenses at various M/T ratios. The ratios include 0, 1, 2, 3, 4. At M/T ~ 4, a linear steady release rate was observed and these lenses have strong potential to be a daily wear silicone hydrogel lens with release for duration of wear.

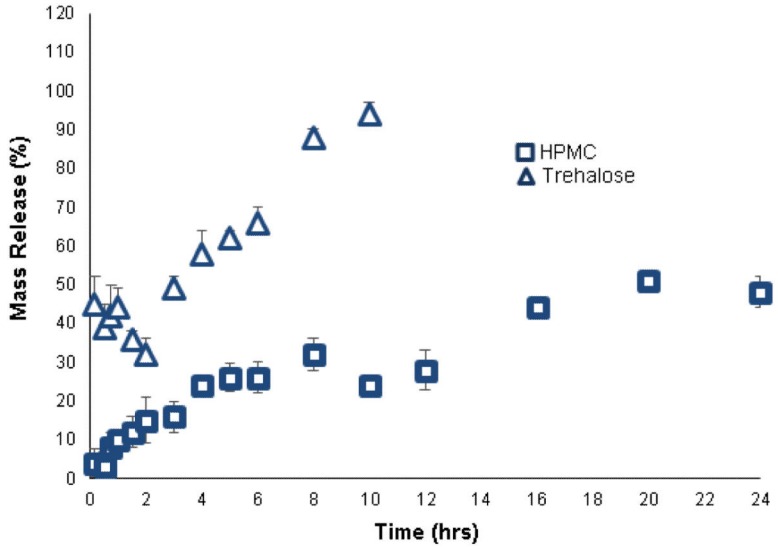

Figure 7.

Simultaneous release of 120 kDa HPMC and trehalose from imprinted silicone hydrogel lenses. Trehalose (M/T=6) and 120 kDa HPMC (M/T=4) were both incorporated into imprinted lenses (*500 μg of each/lens*) for simultaneous release from a single contact lens. Trehalose was incorporated for its high water retention properties and was intended to alleviate sensations of dryness, which is the primary propagator of discomfort during initial wear. The release duration of trehalose was desired to be completed within the first 12 hours. As lens wear continues, other propagators of discomfort become predominant.

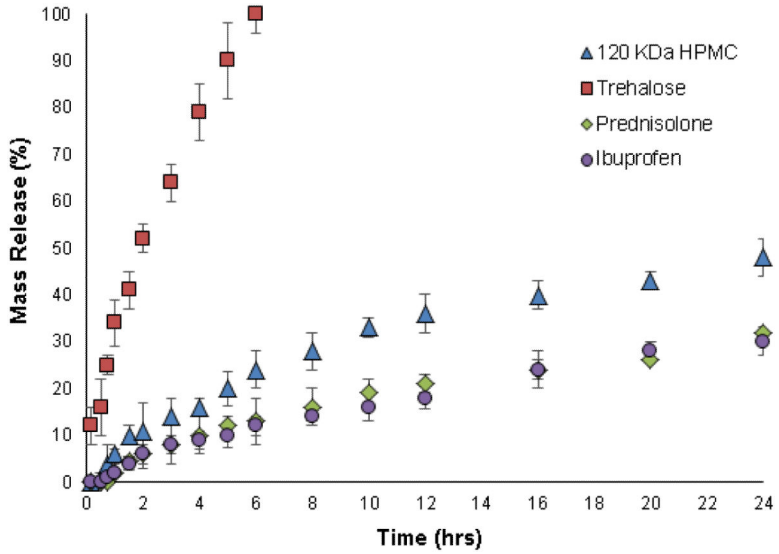

Figure 8.

Release of a diverse selection of molecules from imprinted silicone hydrogel lenses. A set of comfort molecules were selected to demonstrate the diversity of the engineered imprinted lenses to deliver a diverse cocktail of comfort molecules simultaneously. The group of molecules included 120 kDa HPMC, trehalose, prednisolone, and ibuprofen.