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Combining modeling of drug uptake and release of cyclosporine in contact lenses to determine partition coefficient and diffusivity

Olivia L. Lanier, Miranda Manfre, Sandesh Kulkarni, Claire Bailey, Anuj Chauhan *

Chemical and Biological Engineering Department, Colorado School of Mines, Golden, CO 80401, United States

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ABSTRACT

Ophthalmic drug delivery via eye drops is inefficient because only about 1-5% of the drug permeates the cornea during the short residence time of a few minutes. Contact lenses are receiving considerable attention for delivering ophthalmic drugs because of higher bioavailability and the possibility of sustained release from hour to days, and possibly longer. The drug release durations from contact lenses are typically measured *in vitro* and it is challenging to relate the *in vitro* release to *in vivo* release, particularly for hydrophobic drugs which may not exhibit sink release *in vitro* and *in vivo*. The *in vitro* release can be fitted to diffusion equation to determine the partition coefficient and diffusivity, which can then be utilized to model *in vivo* release. The Higuchi equation is frequently used to model the short time release from a contact lens to determine diffusivity with the implicit assumption that the release is under sink conditions and the starting concentration in the lens was uniform. Both conditions may be violated when measuring release of hydrophobic drugs from contact lenses because the diffusivity and partition coefficient, and also the time needed for equilibrium are not known a priori. Here we develop a method to use the data for both loading and release of cyclosporine, which is a common hydrophobic ophthalmic drug, to determine the partition coefficient and diffusivity. The proposed approach does not require sink conditions and also does not require the lens to be fully equilibrated during loading, which may take almost a month for lenses considered here. The model is based on solving the diffusion equation in the gel along with a mass balance in the fluid. The model equations are solved numerically by finite difference. When the value of partition coefficient is high, such as it is for cyclosporine, the dynamic data is only sensitive to a ratio of partition coefficient and diffusivity, and this ratio had to first be determined from the loading data. Then the two unknown parameters were obtained by minimizing the error between the model prediction and experimental data. The method was used to determine D and K for several silicone hydrogel formulations with varying ratio of hydrogel and silicone fractions.

1. Introduction

In lieu of the disadvantages associated with eyedrops for ocular drug delivery such as low bioavailability and patient compliance (Hsu et al., 2014; Schultz, 2014; Farkouh et al., 2016), the use of contact lenses to deliver drugs has been explored for treatment of ocular diseases. Contact lenses made from silicone or hydroxyethyl methacrylate (HEMA) hydrogels can be can be loaded with drugs either through dissolving the drug into the water phase of the lens (Peng et al., 2011; Karlgard et al., 2003) or through binding the therapeutic to the polymer matrix (Dutta et al., 2013; Willcox et al., 2008). Contact lenses do not require frequent application, and it is expected that they will improve patient compliance as it is estimated that 45 million people in the US wear contact lenses (Cope et al., 2016). The drug released from the contact lens has a longer residence time in the post lens tear film (POLTF) than eye drop residence time in the tear film, leading to higher flux into the cornea (Bourlais et al., 1998; McNamara et al., 1999). Plus, contact lenses will reduce the drug inflow into the nasolacrimal sac, which will reduce uptake into the bloodstream and potential side effects (Xinming et al., 2008).

A contact lens divides the tear film into the pre and the post tear films, which are the films in front and back of the contact lens, respectively (Glasson et al., 2006). After placement of a lens on an eye, the drug released into the post lens tear film disperses radially to get out from the post-lens tear film and diffuse across the cornea to reach aqueous humor (Xinming et al., 2008; Kakisu et al., 2013). The drug that diffuses into the pre-lens tear film will likely be absorbed by the

* Corresponding author.
E-mail address: chauhan@mines.edu (A. Chauhan).

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conjunctiva or drain out via the canalicular drainage into the nasal cavity. The release dynamics *in vitro* could be significantly different from *in vivo*, and thus the *in vitro* release duration may not accurately reflect the *in vivo* release duration. Since sustained release is a key advantage of using contact lenses, determining the expected *in vivo* release duration is critical to development of contact lenses for treating ophthalmic diseases. There are multiple approaches for measuring or estimating *in vivo* release including using animal models (Kakisu et al., 2013; Ciolino et al., 2014), developing *in vitro* models to simulate *in vivo* release (Tieppo et al., 2012), and modeling the *in vivo* release based on parameters determined by fitting the *in vitro* release (Hsu et al., 2013). For a contact lens with diffusion-controlled transport, the uptake and/or release of drugs can be modeled by diffusion equation with appropriate boundary conditions. The partition coefficient (K) and diffusivity (D) in the contact lens must be determined by fitting the *in vitro* release to the diffusion model. The measured parameters can then be utilized to predict the *in vivo* pharmacokinetics.

The diffusivity of drugs in contact lenses is typically determined by soaking the lenses in a drug solution and measuring the reduction in drug concentration in fluid over time. Alternatively, a lens loaded with drug could be soaked in release medium, and mass of drug released with time can be measured over time. The dynamic fluid concentration can then be fitted to the diffusion model. To simplify the approach, the short time data is frequently fitted to the Higuchi equation to determine the diffusivity and the total mass of drug loaded can be used to calculate the partition coefficient. However, Higuchi equation, which is the short time solution to the model is only valid if the sink conditions are maintained and the lens concentration was uniform at the start of the release. Both conditions may not be valid for hydrophobic drugs with high partition coefficients and long equilibration durations. A priori the time for equilibration is not known and so it is not possible to know how long the lens must be soaked to achieve equilibrium. For example, prior studies on transport of cyclosporine in commercial contact lenses-soaked lenses in drug solutions for a week, and then fitted the release data to the Higuchi equation to determine the diffusivity (Peng and Chauhan, 2011). The time for reaching equilibrium was however longer than 7 days and thus the diffusivity obtained from the fit was not accurate. In another recent study the release of cationic drugs from contact lenses loaded with fatty acids was measured, and the short time release was fitted to Higuchi equation (Torres-Luna et al., 2020). In this study the release duration was shown to be about a month even though the time for equilibration during loading was shown to be a day, and so the release was likely under non-sink conditions.

There are many publications in literature on using detailed mechanistic models to model drug release from hydrogels including many excellent reviews (Siepmann and Siepmann, 2008, 2012). Based on these publications, the lack of sink conditions can be factored into the model by solving the diffusion equation with mass balance in the fluid and equilibrium at the interface between the fluid and the lens. However, as shown later in this paper, attempts to model the uptake of cyclosporine into the lenses led to multiple solutions of D and K fitting the data, which led us to develop the method that is the focus of this paper to accurately determine the D and K. We used an analytical approach to show that the initial drug uptake of cyclosporine into the silicone hydrogel lenses is sensitive only to the product $K\sqrt{D}$ and thus infinite sets of D and K lead to the same fits. Thus, instead of fitting D and K separately, we obtain only the product $K\sqrt{D}$ by fitting the transient loading data. This product is then fixed for the release studies and the release data is fitted to the model to determine K and D. By following this approach, we convert both loading and release fits to single parameter fits, rather than two parameter fits. This approach is useful to model drug transport in contact lenses when the lenses are not fully equilibrated during loading, i.e., the duration of drug loading is shorter than the time for equilibration. In such cases the concentration of the drug in the gel is not uniform at the end of the loading or the begging of the release. To our knowledge, this approach is not reported previously in literature and considering the growing interest in developing contact lenses for drug delivery, the approach developed here could be useful to researchers.

To establish the validity of the approach for a range of parameters, we manufactured hydroxyethyl methacrylate and silicone hydrogel contact lenses of varying compositions. The silicone contact lenses varied in their ratios of key components including: the macromer, bis-alpha,omega-(methacryloxypropyl) polydimethylsiloxane, which ensures solubilization of the hydrophobic and hydrophilic components; the hydrophobic monomer, tris; and the hydrophilic monomer, N,N-dimethylacrylamide (DMA). This proposed approach for fitting loading and release data to obtain diffusivity and partition coefficient of drugs will be useful to researchers exploring delivery of hydrophobic drugs by contact lenses, and the approach can be utilized to other devices as well. The reported values of D and K for cyclosporine could be used to predict *in vivo* release of cyclosporine which is useful for a number of ophthalmic indications including chronic dry eye syndrome and corneal graft transplantation (Lallemand et al., 2017). Also, the data on dependency of D and K on the formulation can be useful for understanding the impact of composition in structure and transport in silicone-hydrogel contact lenses.

2. Materials and methods

2.1. Materials

Dimethylacrylamide (DMA), 3-methacryloxypropyltris(trimethylsiloxy)silane (TRIS), 1-vinyl-2 pyrrolidone (NVP), ethylene glycol dimethacrylate (EGDMA), alpha tocopherol (Vitamin E), hydroxyethyl methacrylate (HEMA), and cyclosporine were purchased from Sigma Aldrich (St. Louis, MO). bis-alpha,omega-(methacryloxypropyl) polydimethylsiloxane was purchased from Gelest Inc. (Morrisville, PA). 2,4,6-trimethylbenzoyl-diphenyl-phosphineoxide (TPO) was purchased from J&K Scientific Lt. (Beijing, China). Matlab (Mathworks, Natick, MA) and Excel (Microsoft, Redmond, WA) software were used for data analysis and fittings.

2.2. Lens synthesis

Molds for lenses were 3D printed using the Anycubic Resin Printer (Shenzhen, China) and reverse molds were then made using Sorta-Clear 39 from Smooth-On, Inc. (Macungie, PA). The 3D printed molds were used to make the Sorta-Clear rubber molds (Fig. 1*b*). Then, 80 μL of monomer formulation was placed into the rubber mold and the cap was placed onto it and crosslinked using UV-Vis. The silicone hydrogels were prepared by polymerizing a high ion permeability hydrophilic monomer along with a high oxygen permeability silicone monomer. Dimethylacrylamide (DMA) was used as the hydrophilic monomer, 3-

Fig. 1. Photograph of the lens manufactured by using the 3D printed molds.

methacryloxypropyltris(trimethylsiloxy)silane (TRIS) as the hydrophobic monomer and bis-alpha,omega-(methacryloxypropyl) polydimethylsiloxane as the macromer to ensure solubilization of these two components. Additionally, 1-vinyl-2 pyrrolidone (NVP) was added to increase water content and ethylene glycol dimethacrylate (EGDMA) was added for controlled crosslinking. Before adding EGDMA for crosslinking, the lens formulations were nitrogen purged for 15 minutes. The various silicone formulations measured are shown in Table 1, and a photo of an example of the synthesized lens is shown in Fig. 1. Hydroxyethyl methacrylate (HEMA) lenses were prepared by adding 2.7 ml HEMA, 2 ml DI water, and 10 µl EGDMA. Hydrogels were prepared by free radical bulk polymerization of the monomers using UV photoinitiation in the MaestroGen UV light system (Hsinchu City, Taiwan) with 2,4,6-trimethylbenzoyl-diphenyl-phosphineoxide (TPO).

2.3. Characterization of water content

The water content of the lenses was measured by weighing their dry weight and hydrated weights. First, empty glass vials were weighed. Then, lenses were rinsed with DI water and placed in the vial and air dried for two days. The weight with dry lens and glass vial was then used to get the dry lens weight. Lenses were then soaked in PBS for 2 days. The lenses were dabbed with Kimwipes to remove excess water and then their hydrated weights were recorded.

2.4. Lens transmittance

Lens transmittance was measured using UV-Vis spectroscopy in the range of 200-1000 nm. Lenses were placed over the light aperature.

2.5. Drug loading

Cyclosporine was loaded into the lenses by soaking the lenses in 5 ml of 17.5 µg/ml cyclosporine-PBS solution until equilibrium. At the end of the drug loading period, lenses were removed from solution and blotted with Kimwipes to remove excess drug solution. Drug concentrations over time during loading were measured using Genesys 150 UV-Visible spectrophotometer from Thermo Scientific (Waltham, MA) and quartz cuvettes. An absorbance range of 200-215 nm was measured and fit to a calibration curve of known concentration.

2.6. Drug release

After loading and blotting, the lenses were transported to 3 ml PBS and the release of cyclosporine was measured over time using the same methods as drug loading. The release supernatant was replaced with fresh 3 ml PBS after each measurement.

2.7. Calculation of diffusion and partition coefficients

Transport of drug in contact lenses can be described by the following one-dimensional diffusion equation,

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial y^2} \tag{1}$$

with the following boundary conditions

Table 1
Formulations of silicone lenses synthesized in this study. Units in mL.

Formulation	Macromer	Tris	DMA
1	0.8	0.8	0.8
2	0.8	0.4	1.2
3	1.2	0.6	0.6
4	1.2	0.4	0.8

$$C\ (t,\ y=H) = KC_f(t) \tag{2}$$

$$\frac{\partial C}{\partial y}(t,\ y=0) = 0 \tag{3}$$

where H is the half-thickness of the lens, equal to approximately 75 µm for the synthesized lenses, C_f is the concentration of the fluid, and D and K are diffusivity and partition coefficient of cyclosporine in contact lenses. The coordinate system for the lens is defined in Fig. 2.

The curvature of the lens was neglected for simplicity of the model. This did not have a significant effect on the results as the thickness of the lenses (approximately 150 microns) was less than the corneal radius of curvature (about 1.2 cm) (Li and Chauhan, 2006). Finally, the initial condition for the loading phase is,

$$C_f(\ t=0) = C_i \cdot \text{and} \cdot C(\ t=0, y) = 0 \tag{4}$$

where C_i is the initial concentration in fluid. For large fluid volumes or small partition coefficients, the mass of drug taken up by the lens is a small fraction of the initial mass of drug in the solution and thus the concentration in the loading solution remains relatively unchanged, i.e $C_f(\ t)\ = C_i$. In this condition, these equations can be solved to analytically obtain the following expression for the concentration in the lens,

$$C = KC_i\left(1 - \sum_{n=0}^{\infty}\frac{(-1)^n 4}{(2n+1)\pi}\cos\left(\frac{(2n+1)\pi}{2H}y\right)e^{\frac{-(2n+1)^2\pi^2}{4H^2}Dt}\right) \tag{5}$$

where n is an integer for the number of terms in the series summation. The concentration in the fluid can then be obtained by solving the following mass balance

$$\frac{V_f dC_f}{dt} = -2DA\left.\frac{\partial C}{\partial y}\right|_{y=H} \tag{6}$$

where A is the cross-sectional area of the lens and V_f is the volume of the fluid. The above equation can be integrated to yield the following expression for the fluid concentration,

$$C_f = C_i - KC_i\frac{(2AH)}{V_f}\left(1 - \sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2}e^{\frac{-(2n+1)^2\pi^2}{4H^2}Dt}\right) \tag{7}$$

As time approaches infinity, the fluid concentration approaches equilibrium given by the following expression,

$$C_f\big|_{t\to\infty} = C_i - KC_i\frac{(2AH)}{V_f} = C_i - KC_i\frac{V_{lens}}{V_f} \tag{8}$$

where $V_{lens} = 2AH$ is the volume of the lens.

As stated earlier, the above expression assumes that the concentration in the fluid does not decrease significantly which based on the

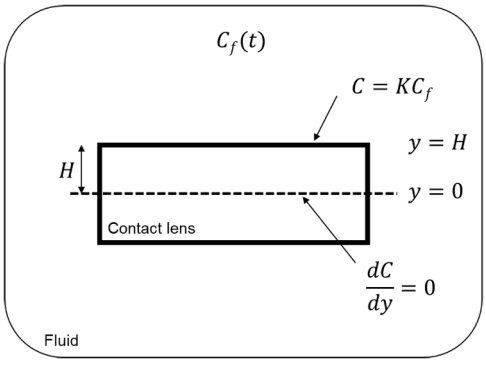

Fig. 2. Coordinate system used for the contact lens as a flat sheet in solution.

above expression implies, gives the following. The above expression is only valid if the decrease in concentration $K\frac{V_{lens}}{V_f} \ll 1$, which implies that $KV_{lens} \ll V_f$. This condition is not satisfied for cyclosporine, which is hydrophobic, so the analytical solution presented above is not valid, and the mass balance equations must be solved numerically to obtain the concentration in fluid as a function of time, which can be fitted to the experimental data to obtain the diffusivity and partition coefficient.

The finite difference approach was used to numerically solved Eqs. (1) and (6) subject to the boundary conditions (2) and (3) to obtain the time dependent concentration in fluid. The two unknown parameters D and K were then obtained by minimizing the error between the model prediction and the experimental data for each of the formulation. While fitting the fluid concentrations during the loading phase to the non-sink model, it was observed that when K is high, the dynamic data is sensitive only to $K\sqrt{D}$ except in the long-time limit as the system approaches equilibrium, and thus determining values of both K and D is not reliable.

To explain the reason for this behavior the transport problem was scaled by defining the following variables, $\frac{C}{K} = C^*$ and $\frac{y}{\sqrt{D}} = y^*$. It is noted that the scaled parameters were intentially kept dimensional because the goal here is to fit the data for concentration to time.

In terms of the scaled variables, the following governing equation and boundary conditions is obtained,

$$\frac{\partial C^*}{\partial t} = \frac{\partial^2 C^*}{\partial y^{*2}} \tag{9}$$

with boundary conditions:

$$\frac{dC^*}{dy^*}\left(t,\ y^* = \frac{H}{\sqrt{D}}\right) = 0 \tag{10}$$

$$C_f(t,\ y^* = 0) = C^* \tag{11}$$

Next, the accumulated drug release can be solved by:

$$V_f \frac{dC_f}{dt} = -2\sqrt{D}K\frac{\partial C^*}{\partial y^*} \tag{12}$$

In the above formulation, the diffusivity D appears in the boundary condition at y = H but that boundary condition only impacts the concentration profile in lens after the mass transfer boundary layer reaches the center of the lens. For large K, the concentration in the fluid may be very low by the time the mass transfer boundary layer reaches the center of the lens or in some cases the loading experiment may not be conducted till equilibrium is reached. In such cases, the governing equation D and K appears as $\sqrt{D}K$, which implies that the time dependent fluid concentration will be sensitive only to $\sqrt{D}K$. Samples were loaded for six days, which was not sufficiently long to achieve equilibrium and that explains why the model predictions were sensitive to $\sqrt{D}K$. In this case, several combinations of K and D can fit the loading data. To address this issue, only the product $\sqrt{D}K$ was obtained from fitting the loading data and then this product was used along with the data in the release phase to determine both D and K. The approach applied for fitting the release data is described below.

In the release phase of the study, the gels loaded with drug were placed in fresh buffer and dynamic concentrations were measured. For drugs with high K, the amount of drug that will be released at equilibrium is small, and thus the fluid was replaced periodically to allow for 100% of the drug to be released. The release phase is governed by the same set of equations Eqs. (1) and ((6)) and boundary conditions Eqs. (2) and ((3)) as the loading phase but with a different initial condition. The initial condition in the release phase must reflect the concentration in the gel at the start of the release experiment. For lenses fully equilibrated with the loading solution, the initial condition in the lens is a uniform concentration equal to $KC_{l,eq}$, where $C_{l,eq}$ is the equilibrium concentration in the loading phase. However, if the gels were not loaded until equilibrium was achieved, which can be the case for drugs with low diffusivity such as cyclosporine, then the initial condition is not a uniform concentration in the lens. To address this issue, a numerical solution for gel concentration obtained at the end of the loading phase using the best-fit value of $\sqrt{D}K$ was applied and it was used as the initial condition for the release phase. Subsequently, equations Eqs. (1) and (6)) and boundary conditions (Eq. (2) and ((3)) were solved numerically using finite difference to predict the concentration in fluid as a function of time. Since the product $\sqrt{D}K$ is already determined based on fitting the loading phase, there is only one independent fitting parameter for the release phase. K was used as the fitting parameter and its best fit value was obtained by minimizing the difference between the experimental and the model for the release phase.

An experimental data set for loading and release 3 concentrations for formulation 2 was used to illustrate this process. In Fig. 3a, the error in the fit is shown as a function of the best-fit parameter $K\sqrt{D}$. The error is defined as the sum of the square of the difference between the measured and calculated concentrations. Fig. 3b shows the comparison of the experimental data and the predicted concentration vs. time data using the value of $K\sqrt{D}$ at which the error in Fig 3a reaches the minimum. Multiple curves are shown in Fig 2b for the same value of $K\sqrt{D}$ but different values of K to illustrate the point that the predictions depend only on the combined parameter $K\sqrt{D}$. Fig. 3c shows the error in the fitting of the release data as a function of the best-fit parameter K. Finally, in Fig. 3d, the experimental release data for dynamic concentrations in fluid is compared with the predicted values using the optimized value of K at which the error in Fig 3c is minimum and value of $K\sqrt{D}$ fixed from the loading. This same approach is repeated with each of the three sets of gels using the loading and release data for each gel, and then the mean and standard deviations are calculated for D and K. The same approach is then used for each of the five formulations.

3. Results

3.1. Cyclosporine loading

Lenses were synthesized using the molds as described in the methods section, and a photo of an example of the synthesized lenses can be seen in Fig. 1.

The uptake data for each silicone lens type was fit for 2 days of drug loading and for 5 days loading for the HEMA lens. The fits of the loading can be seen in Fig. 4. Note that only one of the runs for each lens type are shown in Fig. 4, but at least three runs per type were plotted for analysis. The ratio of $K\sqrt{D}$ was found using these fits (n = 3). It shows that the HEMA lenses took up less drug than the silicone formulations tested.

3.2. Cyclosporine release

Cyclosporine was then released from all lens types in PBS, with the PBS replaced after each measurement. The replacement of PBS can be easily integrated into the finite difference solution by reducing the fluid concentration to zero. The ratio $K\sqrt{D}$ that was found from fitting the loading data was used for the release fitting, and the release data for the various lenses can be seen in Fig. 5. The experimental data is denoted by star symbol and the modeling predictions are plotted as the yellow dash lines. The solid orange lines are plots connecting the theoretical data at the time points of the experimental measurements. The model predictions (dashed yellow lines) are discontinuous at all time points when fluid was replaced. The discontinuity in slope implies that the rate at which drug was diffusing out from the lenses increased after the fluid replacement, which implies that the release was under non-sink conditions. It can also be seen that the slope of the yellow dashed lines approach zero in many cases prior to the fluid replacement which is a clear sign that the system approaches equilibrium prior to the fluid replacement, which again implies that the release was under non-sink

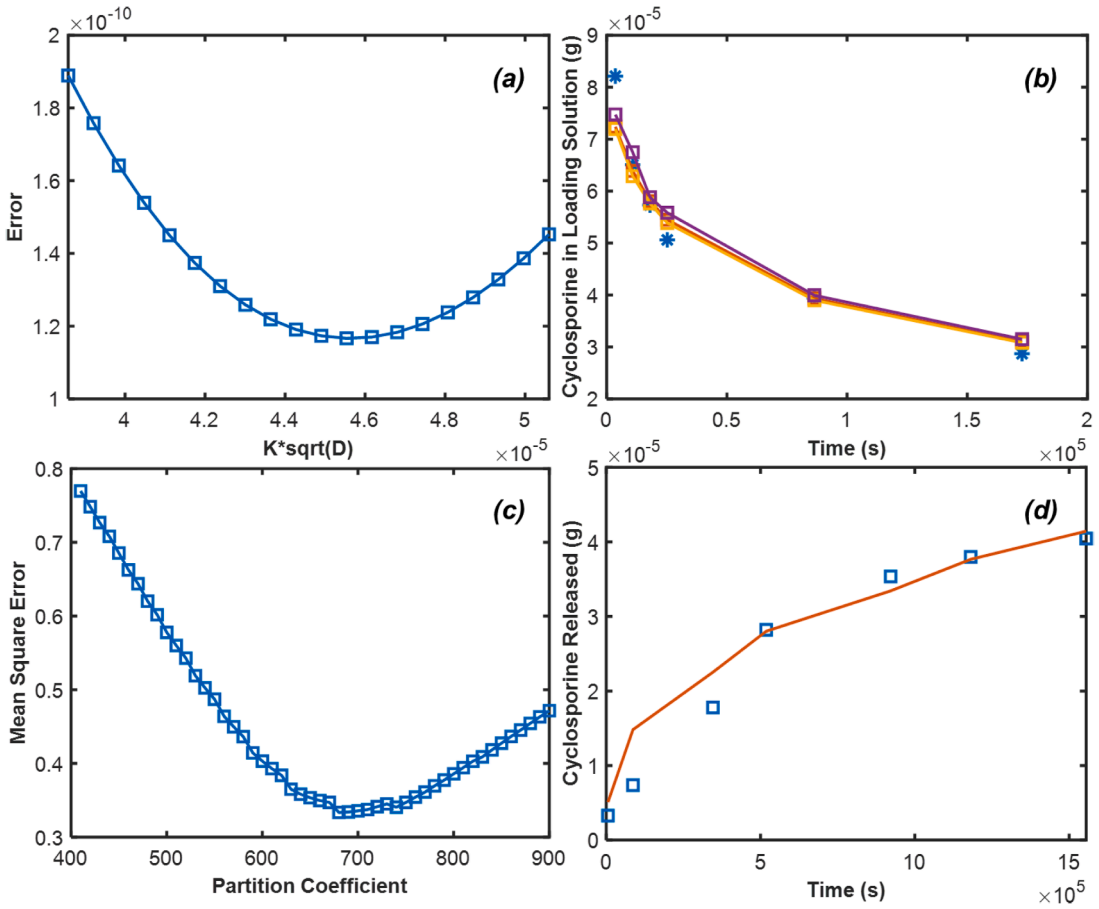

Fig. 3. Error in the loading fit as a function of the best-fit parameter $K\sqrt{D}$ (a); and multiple curves for the same value of $K\sqrt{D}$ but different values of D (including 1.0e-14* [0.1000 0.5000 0.0200]) to illustrate the point that the predictions depend only on the combined parameter $K\sqrt{D}$ (b); Error in release fit as a function of partition coefficient K after fixing the value of $K\sqrt{D}$ (c), and comparison of the experimental data points and model fit for release (d).

conditions.

The HEMA based lenses had the lowest partition coefficient, and the drug release duration from HEMA based lenses was much shorter than the release from silicone lens formulations due to the smaller partition coefficient. HEMA lenses finished releasing after approximately 10 days and release conditions were close to sink-conditions based on the overlap of the yellow and the orange curves. The silicone hydrogel lenses are still releasing after 30 days (not shown) but the release conditions were non-sink as evident from the significant differences between the yellow and the orange curves. Only the first 18 days of release was fit in Matlab because cyclosporine has been shown to degrade after prolonged controlled release (Goyal et al., 2015; Friis and Bundgaard, 1992).

Values for partition coefficient were varied and plotted as a function of mean square error. When the error was minimized (as shown in Fig. 3), the value of partition coefficient was found. Then, the value for diffusivity was calculated using the value of

$K\sqrt{D}$ and partition coefficient K. The partition coefficient and diffusivity for each formulation were determined and can be seen in Table 2. Based on the fitted values of diffusivity, we can calculate the expected release time from the lenses under sink conditions. Fir diffusion-controlled release, the time for equilibration which is also the time for release under sink condition can be estimated as H^2/D. Using a value of 100 μm for H and fitted values of diffusivity in Table 2, we get a equilibration time of 4.2, 21.5, 60.6, 88.5, and 22.6 days for formulations 1-4 and HEMA, respectively. This implies that using the Higuchi equation to calculate diffusivity will require loading the lenses for as long as 20-80 days for most formulations, followed by measuring release in a large fluid volume that should be much larger than the product of the partition coefficient and the lens volume. Alternatively, the fluid must be replaced frequently but it is not possible to know the required frequency without solving the mass transfer problem numerically as was done here.

For the silicone-based lenses, some trends could be seen from the data. Form 1 has the highest diffusivity value and the most tris of any of the formulations, which indicates that tris could play a role in increasing diffusivity. Form 1 and 2 had less macromer (0.8 ml vs. 1.2 ml for Form 3 and 4) and they had the lowest partition coefficient values, which indicates that increasing the amount of macromer could play a role in increasing the partition coefficient. The macromer ensures that the hydrophobic and hydrophilic components are solubilized. Since macromer is required to form an interface between the silicone regions and the hydrophilic DMA regions, a decrease in the macromer ratio beyond a critical value could lead to a transition from a bicontinuous structure to a dispersed structure, with either silicone or hydrophilic continuous phases depending on the ratio of DMA to tris.

Form 1 and 2 have the same macromer; Form 1 has more tris and less DMA compared to Form 2, and it has a lower K value, and higher diffusivity. Similarly, Form 3 and 4 have the same macromer, Form 3 has more tris and less DMA compared to Form 4, and it has a lower K value and higher diffusivity. These results again indicate that tris could play a role in increasing diffusivity and that having more tris and less DMA could lead to a lower partition coefficient.

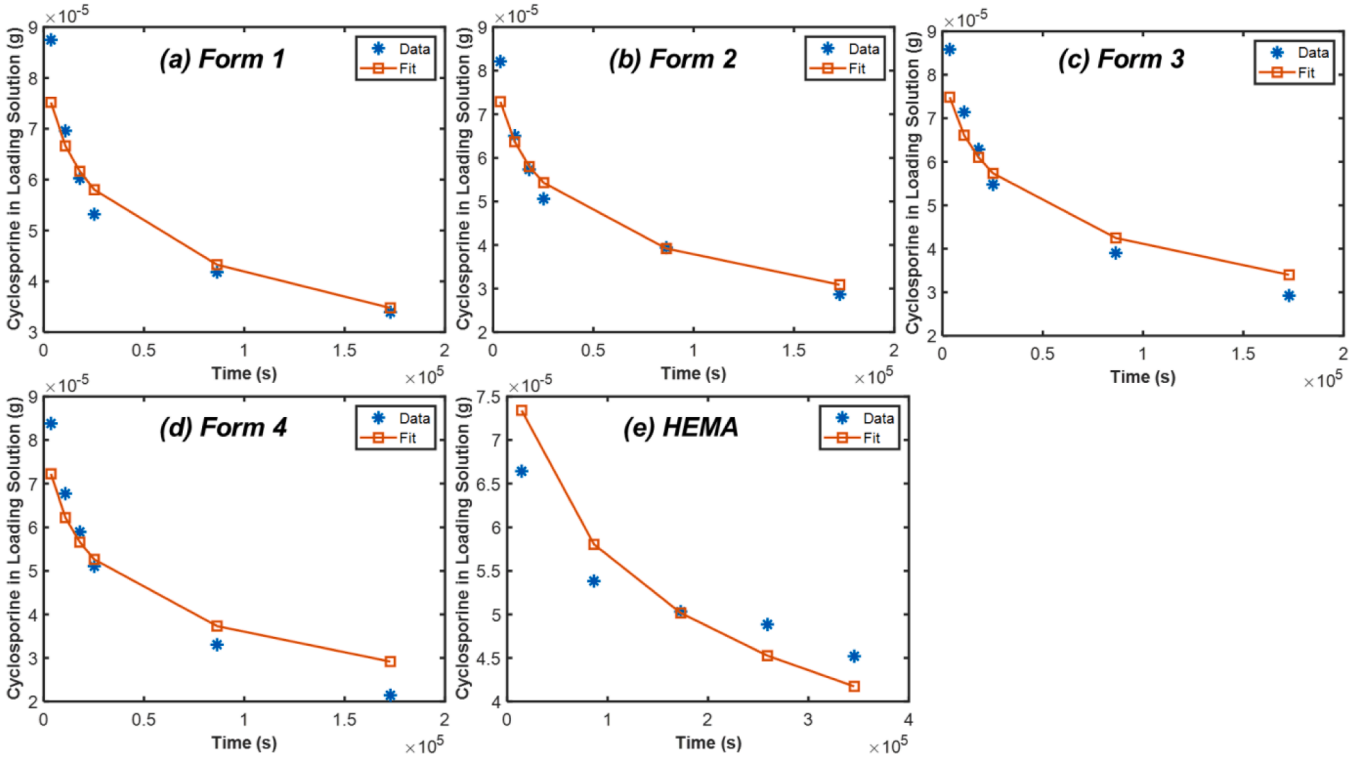

Fig. 4. Experimental loading data and fits to one-dimensional diffusion equation for different lens types: Form 1 (a); Form 2 (b); Form 3 (c); Form 4 (d); and HEMA (e).

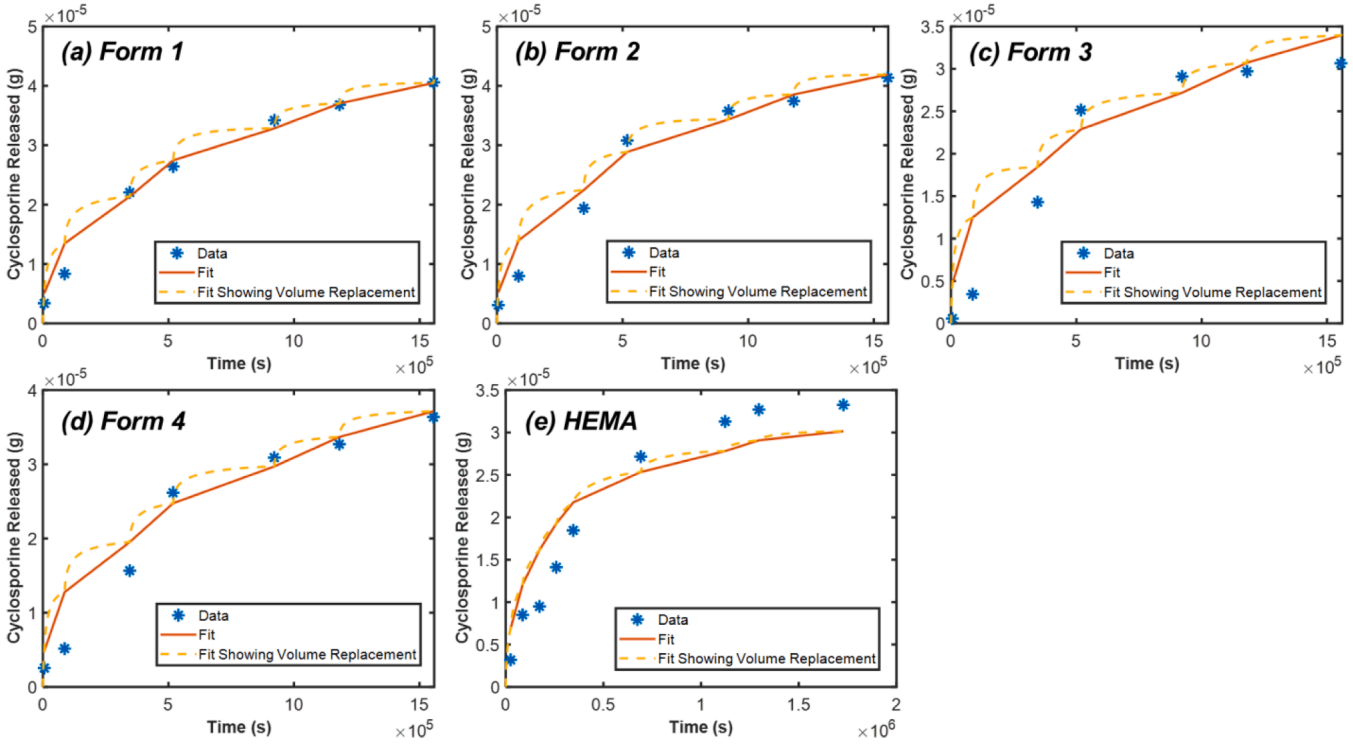

Fig. 5. Comparison of measured and fitted cumulative cyclosporine release. The yellow line from fitting shows the predicted concentration as a function of time and the solid orange line is a curve connecting predicted concentrations at the specific time points where release medium was replaced. An overlap of the yellow dashed and the orange solid lines will signify release was under sink conditions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Results for average partition coefficient and diffusivity values of the various formulations tested with standard deviation (n ≥ 3).

Formulation	$K\sqrt{D}$			Partition Coefficient, K			Diffusivity, D (m^2/s)		
1	8.18E-05	±	9.31E-06	530	±	198	2.38E-14	±	3.34E-15
2	4.77E-05	±	2.01E-06	700	±	10	4.65E-15	±	8.29E-18
3	3.86E-05	±	3.03E-06	950	±	85	1.65E-15	±	1.68E-17
4	3.82E-05	±	9.19E-06	960	±	255	1.13E-15	±	1.44E-16
HEMA	1.50E-05	±	5.38E-07	225	±	78	4.42E-15	±	5.28E-16

3.3. Water content and transmittance

The water uptake of the various silicone lens formulations can be seen in Fig. 6. The water content positively increases with amount of DMA added to the formulation. These results indicate that the hydrophilic monomer in the lens composition play a role in the water content of the lens, and can be adjusted depending on the appropriate water content needed for the desired application of the hydrogel. It should be noted that HEMA lenses had higher water uptake than the silicone lenses, at 46.8 ± 4.7%.

All of the lens formulations were visually transparent and the transmittance of all lens formulations were comparable around 80% to 90% as shown in Fig. 7.

4. Discussion

Lenses of various formulations were synthesized and used for loading and release of cyclosporine. The loading data was first fit in Matlab (see Fig. 4) to obtain values for the ratio of $K\sqrt{D}$. It was shown that HEMA lenses took up less drug than the cyclosporine lenses. The release data was then fit to the one-dimensional diffusion equations and the ratio of $K\sqrt{D}$ was set (see Fig. 4). The value for K was varied and plotted against mean square error to find the value that minimized error. It was necessary to fit the data in this manner since cyclosporine is a hydrophobic drug with high partition coefficient and so both uptake and release were conducted under non-sink conditions and the loading was conducted for times less than the time needed to achieve equilibrium. Values for K and D are shown in Table 2.

The sink conditions were not maintained despite the total PBS volume being replaced after each measurement. The dotted yellow line in Fig. 5 from fitting shows that equilibrium was still being reached between measurements, which did not allow for perfect sink conditions. In order to have sink conditions, the PBS volume would have needed to be increased above the 3 mL that was used or need to be replaced much more frequently. For a lens volume of about 50 μl and a partition coefficient of 600, a fluid volume of about 300 mL may be needed to ensure that the decrease in concentration during the loading phase is negligible.

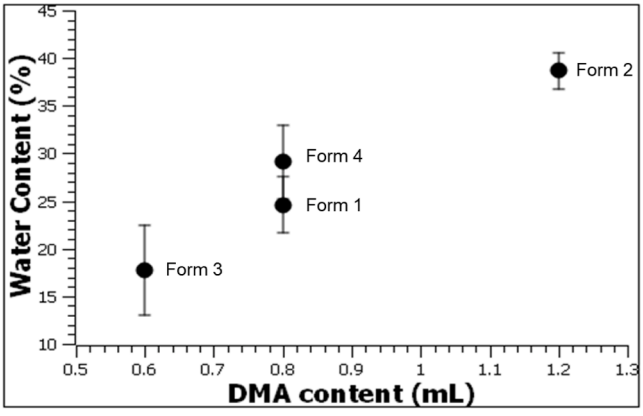

Fig. 6. Water content of the lenses as a function of hydrophilic monomer (DMA) in the silicone lens formulation.

In the literature, many studies assume to have perfect sink conditions for hydrophobic drugs like cyclosporine and fit the data to established models such as the Higuchi model which assumes sink conditions are maintained during the time in which the Higuchi model is fitted to the data (Torres-Luna et al., 2020; Liu et al., 2007; Ata et al., 2020,; Guidi et al., 2014,; Rezk et al., 2019,; Long et al., 2019). It is certainly feasible to design the uptake and release experiments to achieve sink conditions, but the validity of the sink assumption must be tested by either calculations or measuring release with different initial volumes and fluid replacement frequencies. If the release is under sink conditions, the cumulative release profiles will not be impacted by fluid volume or replacement frequencies. This issue has been noted previously by other researchers (Tieppo et al., 2014). Therefore, our fitting method will be useful for correctly fitting the data even if the loading and release occur under non-sink conditions. Additionally, using the Higuchi equation for release would require the lens to be loaded for about 20-80 days, which is difficult for a number of reasons including possible degradation of the drug.

After fitting, a few trends in the data for D and K were observed based on the formulation. HEMA lenses had the lowest K value and finished releasing the loaded cyclosporine after ~10 days. The silicone lenses all released cyclosporine for over 30 days, but the release was under non sink conditions which means that the release durations will be lower under sink conditions. The diffusivity of cyclosporine in HEMA and Form 2 are comparable which means that that the release duration under sink conditions will be comparable. However, the measured release durations were considerably longer for Form 2 because the conditions were non-sink. It is not clear whether the in vivo conditions will mimic a sink environment and so the in vivo release durations may be longer for Form 2 due to the higher partition coefficient. Nonetheless, if the purpose of the in vitro release is to characterize the transport, reporting release durations is not appropriate if the release conditions are non-sink.

It was shown that Form 1 which had the highest amount of tris in the formulation had the highest diffusivity. Plus, it was shown that lenses with more tris and less DMA had a lower K and higher D value. These results indicate the increase in tris could lead to higher diffusivity. Tris is the hydrophobic monomer and DMA is the hydrophilic monomer. Our previous results have shown that if tris is increased too much, the lens can create a dispersed structure, which led to a decrease in ion permeability due to the dispersed tris phases (Peng and Chauhan, 2012). Additionally, the formulations with lower macromer content had a lower partition coefficient. The macromer ensures solubilization of the hydrophilic and hydrophobic monomers, so a better solubilization could lead to better drug loading and a higher K value. Not having enough macromer could also cause the structure of the lens to change from bicontinuous to dispersed. These results indicate that the amounts of macromer, tris, and DMA must be carefully selected in order to maintain the dispersed lens structure and optimize the uptake and release of drug. Macromer and DMA should be increased, while tris should be decreased, although the ratios should all remain within a reasonable range to each other for the effects to balance out.

In the literature, diffusivity values to the power of 10^{-16} m^2/s were obtained for ACUVUE® OASYS™ commercial lenses and partition coefficient around ~678 (Peng and Chauhan, 2011). These results indicate a partition coefficient similar to formulations 1 and 2 in this study but

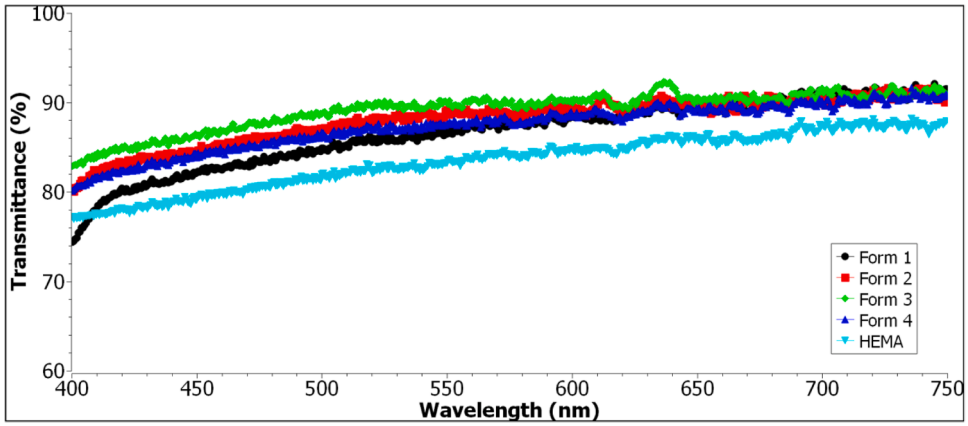

Fig. 7. Transmittance of lenses. The transmittance is about 90% in the visible spectrum.

the diffusivity for the commercial lenses is about an order of magnitude lower than the ones we found in our study. It was also shown that vitamin E barriers can be added to the lenses to reduce the diffusivity value (Peng and Chauhan, 2011). Another study found a diffusivity value of cyclosporine from synthesized HEMA lenses to be 1.44×10^{-14} m^2/s, which is an order of magnitude higher than the diffusivity of our synthesized HEMA lenses potentially due to differences in polymerization conditions (Kapoor et al., 2017). In a study by another group, loaded cyclosporine was released in 3 days (Başbağ et al., 2014); however, it is difficult to compare the release duration to the current study which was performed under different conditions.

Clinically, cyclosporine is delivered as an oil in water emulsion based eyedrop (28 μg) given twice per day (Allergan, 2017), with a determined bioavailability of 0.78 μg/day being delivered to the cornea (Gupta and Chauhan, 2011). Contact lenses are expected to have a much higher bioavailability, around 50% (Peng and Chauhan, 2011). Thus, the developed lenses should be capable of delivering a clinically relevant dose to the cornea for extended durations. Beyond use as contact lenses, hydrogels for the extended delivery of cyclosporine have several other potential applications. Cyclosporine is often used as an immunosuppressant to prevent rejection after organ transplants and to treat autoimmune diseases like rheumatoid arthritis. Topical application of cyclosporine for non-ophthalmic uses, such as through drug-eluting hydrogel bandages, seems most promising in treating dermatological ailments. Typically, in these types of cases, cyclosporine is delivered orally in conjunction with topical steroids. Treatment regimens involving both low doses (5 mg/kg/day) and high doses (6-14 mg/kg/day) of cyclosporine have been successful in causing acrodermatitis continua of Hallopeau (ACH), a condition that causes pustular eruptions on patients' fingers and toes, to go into remission (Ranugha et al., 2013). Pyoderma gangrenosum (PG), an ulcerative disease that primarily affects patients' legs, has also been successfully treated with oral cyclosporine and corticosteroids. In fact, researchers assert that combined corticosteroid and cyclosporine therapies should be considered the primary treatment for PG (Reichrath et al., 2005). However, similar to eye drops, there is concern about the current treatments due to side effects and drug interactions that arise from cyclosporine entering systemic circulation. Therefore, the application of a cyclosporine eluting hydrogel bandage could potentially reduce the toxicity while treating localized dermatological conditions (Sternberg et al., 2007)

5. Conclusions

A fitting approach to determine K and D is developed that is particularly useful for hydrophobic drugs with high values of K and low values of D. We calculate the ratio of $K\sqrt{D}$ using loading data and then fit the release data to fit values of K with the value of $K\sqrt{D}$ fixed from the uptake. This fitting approach can also be used when the system does not equilibrium during uptake and thus the initial condition for release is not a uniform concentration which is a requirement for the Higuchi equation. For hydrophobic drugs with high partition coefficients, sink release would require a very large fluid volume and/or high frequency of fluid replacement which may be difficult to achieve. The approach developed here could be useful for fitting uptake and release data for hydrophobic drugs in contact lenses as well as other types of devices.

This study also looked at various formulations of hydrogels for the effect on cyclosporine. By manipulating the formulations for the hydrogels, cyclosporine release can be changed. The effects of formulation showed differences in the values of diffusivity and partition coefficient. Notably, more tris led to increased diffusivity and more macromer led to lower partition coefficient. The macromer ensures solubilization of the hydrophilic and hydrophobic monomers, so it is reasonable that below a critical value of macromer, the lens structure could be altered to a dispersed form. Further, it was shown that increased DMA in the formulation increased the water content of the lens. Therefore, it was shown that it is critical to balance the amount of DMA, tris, and macromer added to the formulation in order to obtain the desired release kinetics and lens properties. In the future, more lens properties will be evaluated to synthesize lenses that are ideal for extended wear to deliver cyclosporine at clinically relevant values.

Author contributions

OLL: methodology, software, validation, data curation, formal analysis, supervision, writing – original draft preparation. SK: data curation. MM: data curation, writing. CB: data curation. AC: conceptualization, model writing, writing – review and editing, supervision, project administration, funding acquisition, formal analysis. All authors have read and agreed to the published version of the manuscript.

Declarations of Conflicts of Interest

The authors declare no conflict of interest.

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