Controlled release of ciprofloxacin from PLGA-coated contact lenses to treat eye infections

BEE 4530: Computer-Aided Engineering – Applications to Biomedical Processes

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1. Executive Summary

Topical ophthalmic solution, commonly known as eye drops, have long been the most widely-used method for ocular drug delivery. The drug delivery method, however, is characterized pulse delivery to the eye, which results in three consecutive stages: an initial period of overdose, a fairly short period of therapeutic concentration, and an extended period of sub-therapeutic concentration. This problem is further exacerbated by reflex tearing and blinking, which further dilutes and disperses the drop, causing merely 1%-7% of the drug delivered to be absorbed[1,2]. In recent years, researchers have proposed several designs of drug-eluting contact lenses to address this issue. However, failure to achieve sustained drug release through zero-order release kinetics remains a prevailing problem. An imperative design requirement in an effective drug-eluting contact lens is for the initial burst of release that is characteristic of all mass transfer be followed by a sustained period of nearly constant flux. This allows the drug to remain within a therapeutic concentration range in the eye for a prolonged period of time. Further, the lens must be biocompatible and safe for use. In this study, a contact lens was modeled based on the work of Ciolino et al. to release ciprofloxacin, a common antibiotic for treatment of infections caused by a variety of gram positive and gram negative bacterium, with zero-order release kinetics over many days. COMSOL Multiphysics software was employed to design and stimulate the model within the parameters of commercially available contact lenses. To control for zero-order release, a dual polymer system was used, with an inner polymer film containing ciprofloxacin coated by a transparent polymer commonly used in contact lenses. The former polymer modeled represents poly(lactic-*co*-glycolic)acid (PLGA), which is biocompatible and has demonstrated ability to control zero-order release kinetics[3]. This is possible since PLGA degrades with time, maintaining a relatively constant driving force of diffusion despite a finite source of drug. The latter polymer modeled represents pHEMA, which is not biodegradable. By assuming that the radius of the eye is much larger than the contact lens thickness, a two-dimensional, axisymmetric simulation of the system was created with the eye containing the following layers: tear film, epithelium, stroma, and aqueous humor (Figure 1). The model was run with a starting PLGA molecular mass of both 118 kDa and 18 kDa, with initial ciprofloxacin mass of 20mg (1:1 ratio with 118kDa PLGA). Thus, the effect of altering the ratio of drug to PLGA was monitored. The results determined that both 118kDa and 18kDa PLGA show sustained release of ciprofloxacin for one month after a quick initial burst, with the 18kDa PLGA system exhibiting a higher steady state flux. The geometry also proved to be superior, with the design showing a 100% increase in ciprofloxacin concentration in the eye after 50 days over a design with PLGA spanning the width of entire lens. This study thus exhibits prolonged zero-order release kinetics at a therapeutically relevant concentration can be achieved with a contact lens. This prototype can be extended to further applications of ocular drug delivery and have enormous implications in the treatment of eye infections.

2. Introduction

2.1. Background

Topical ophthalmic solutions (eye drops) currently account for nearly all cases of ocular drug delivery for treatment of eye infections and glaucoma.[1]The drops are administered by pulse delivery, resulting in a large burst of drug when the drops are administered. However, each drop is quickly diluted and washed away by reflex tearing. The small surface area of the cornea and the short contact time with the drops causes only 1% to 7% of the drug to be absorbed by the eye.[1] Consequently, large amounts of ocular drugs must be delivered to be effective. Since the drug is quickly washed away, the concentration of drug in the eye decreases significantly with time. Therefore, drops must be administered repeatedly, leading to widely oscillating drug concentrations in the eye. Ideal treatments require constant therapeutic drug levels. Elderly patients may also have difficulty using the drops properly and always remembering to administer them.

Designing a sustained release system for ophthalmic drugs can avert this problem. Drug delivery through a hydrogel was introduced as early as the 1960s, with most clinicians indicating that they would prefer to use contact lenses over eye drops. While researchers have successfully designed contact lenses for delivery that are both comfortable and biocompatible, it has been difficult to engineer a system that demonstrates constant drug release, zero-order kinetics. Since sustained release is driven by diffusion, which is dependent on the concentration gradient of the drug, most sustained release systems deliver drug in a large burst during the first few hours followed by low, subtherapeutic levels of drug elution.

2.2. Research Review

Ciolino et al. performed a study aimed at designing a contact lens that allows for steady and controlled release of drug into the eye. A dual-polymer contact lens was used to obtain the desired zero order release kinetics. The inner layer contained a biodegradable PLGA compound, of either 18 kDa or118 kDa, containing the molecule of interest, either fluorescein or the drug ciprofloxacin. This PLGA-ciprofloxacin layer was then coated with pHEMA, a clear, non-biodegradable compound that is used in contact lenses.

To test the contact lens' ciprofloxacin release kinetics, the contact lens was placed in a phosphate-buffered saline (PBS) solution. The PBS solution has the same pH, salinity, and temperature as the human tear film to mimic drug release into the eye. At predefined intervals, the PBS solution was removed, tested using high pressure liquid chromatography to determine the mass of ciprofloxacin present and returned. Tests were conducted for a total of 4 weeks, since this is the maximum amount of time for which contact lenses are approved.

It was found that without the aid of the contact lens, free fluorescein powder in PBS resulted in rapid dissolution of all of the fluorescein. When a simple PLGA layer containing fluorescein was used without a surrounding pHEMA layer, the fluorescein was released quickly and zero-order kinetics were not obtained. However, when a pHEMA layer coated the PLGA-fluorescein layer, the contact lens demonstrated sustained zero-order release kinetics for 4 weeks for both fluorescein and ciprofloxacin. And the release continued even at 100 days. Other parameters were found to influence the release kinetics, such as the ratio of PLGA to ciprofloxacin or fluorescein or the mass of PLGA used. The low molecular weight PLGA

(18kDa) yielded faster ciprofloxacin release than the high molecular weight PLGA (118kDa). It was found that the contact lens using 118 kDa PLGA released 134 µg of ciprofloxacin per day. If the eye produced 3 µL of tears per minute, which is greater than the average tearing rate, then the lens would produce a ciprofloxacin concentration of 31 µg/µL in the tears, which is significantly above the therapeutic level of 2 µg/µL.[1]

Therefore, Ciolino et al. effectively designed a contact lens that allowed for the zero-order release kinetics of ciprofloxacin over the course of 4 weeks. The amount released could be fine-tuned by changing the ratio of PLGA to ciprofloxacin or by changing the molecular weight of the PLGA used. This design, which is effective at drug delivery to the eye, could be used for a wide range of applications and drugs.

In order for the release of ciprofloxacin from the contact lens to follow zero order kinetics, degradation of the PLGA has to be considered. Since the drug is constantly diffusing out, the gradient is thus steadily being depleted. So for the driving force to remain the same and maintain constant release, the drug must be able to diffuse through the PLGA more easily as time progresses (i.e. the diffusivity must increase).

The study performed by Ciolino et al. was simply experimental and, in modeling the delivery of ciprofloxacin to the eye, degradation of the PLGA layer must be considered. Since PLGA is biodegradable, its molecular weight and diffusivity vary with time[2]. Faisant et al. modeled the molecular weight and diffusivity and derived Eqns. 1 and 2, as seen in Appendix A.

2.3. Goals and Design Objectives

We wish to employ COMSOL Multiphysics to determine and model the conditions at which this zero-order kinetics occurs. One of the lenses was designed with PLGA with molecular mass of 118 kDa and another with molecular mass of 18 kda.[1]Furthermore, we will determine the concentration profile of ciprofloxacin during the time of treatment. The minimum inhibitory concentration (MIC_{90}) of ciprofloxacin to kill 90% of the bacteria is 2 µg/mL.

We intend to use COMSOL to model ciprofloxacin release from a PLGA-coated contact lens, and to determine the effects of the initial ciprofloxacin concentration on the release kinetics. Additionally, our model eye includes the different layers (i.e. epithelium, stroma, and aqueous humor) which vary in diffusivity. We are taking into account that some of the drug is washed away due to tearing by including a degradation term in our governing equation. From the release profile of ciprofloxacin, we plan to model drug concentration at different points on the surface of the eye to determine if the drug concentration on the eye is at a therapeutic level (above MIC_{90}).

2.4. Problem Schematic:

A schematic of the proposed design is shown below.

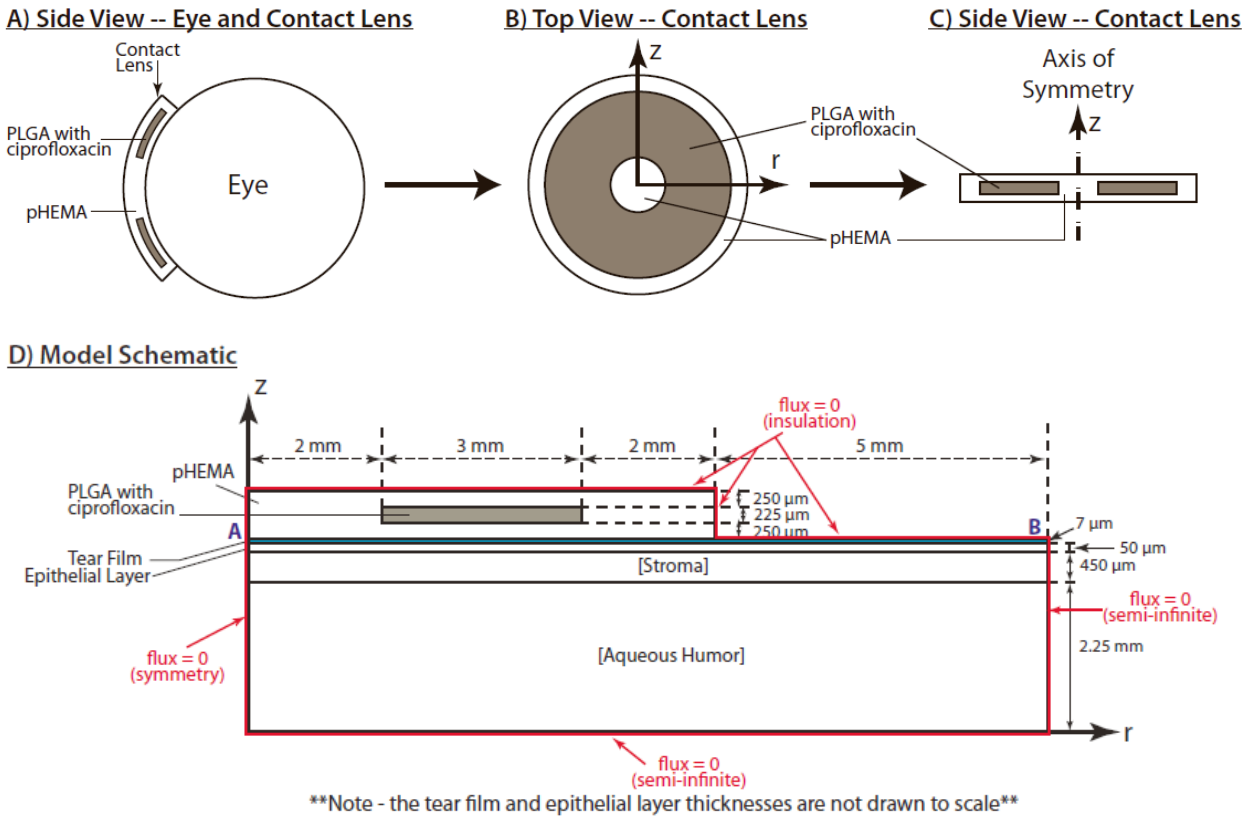


Figure 1: Problem schematic for contact lens made of PLGA with ciprofloxacin, coated with pHEMA. **A)** Side view of contact lens on eye. **B)** Top view of contact lens. **C)** Side view of contact lens. **D)** Schematic of contact lens with eye layers, including dimensions, as modeled in COMSOL. Boundary conditions are displayed in red. Points A and B are the boundary between the contact lens and the eye.

3. Results and Discussion

3.1. Qualitative Description of Process

Following the procedure in Ciolino et al., the initial mass of ciprofloxacin in the PLGA polymer layer was set as 20mg. Since the dimensions of the system were known (Figure 1), and the molecular mass of ciprofloxacin is 331.4 Da, the initial concentration of the ciprofloxacin in the PLGA was determined to be $4.066 * 10^3$ mol/m^3. The diffusion path of the drug was monitored in COMSOL over a 50-day period. This was done for cases where the PLGA had a molecular mass of either 18 kDa or 118 kDa and when the PLGA was assumed either to degrade, altering diffusivity as seen in Figure 10, or not degrade, retaining the initial diffusivity values calculated above (section 2.2). All input parameter values are listed in Table 1 in Appendix A, below. Three specific parameters of interest were calculated over time: average

concentration of ciprofloxacin in the contact lens, cumulative mass of ciprofloxacin released from the contact lens, and the mass flux of ciprofloxacin out of the lens and into the eye.

The average concentration of ciprofloxacin in the contact lens, that is, in both the PLGA and pHEMA layers, was calculated at each time point in two steps. The integral of ciprofloxacin concentration values over the entire volume was calculated for both PLGA and pHEMA and summed. This value was then divided by the sum of the volume integral in both lens layers, giving the average concentration in the entire lens (Figure 2). When degradation was considered, the results showed an initial burst of steep concentration change that leveled out to a linear decrease in concentration with time.

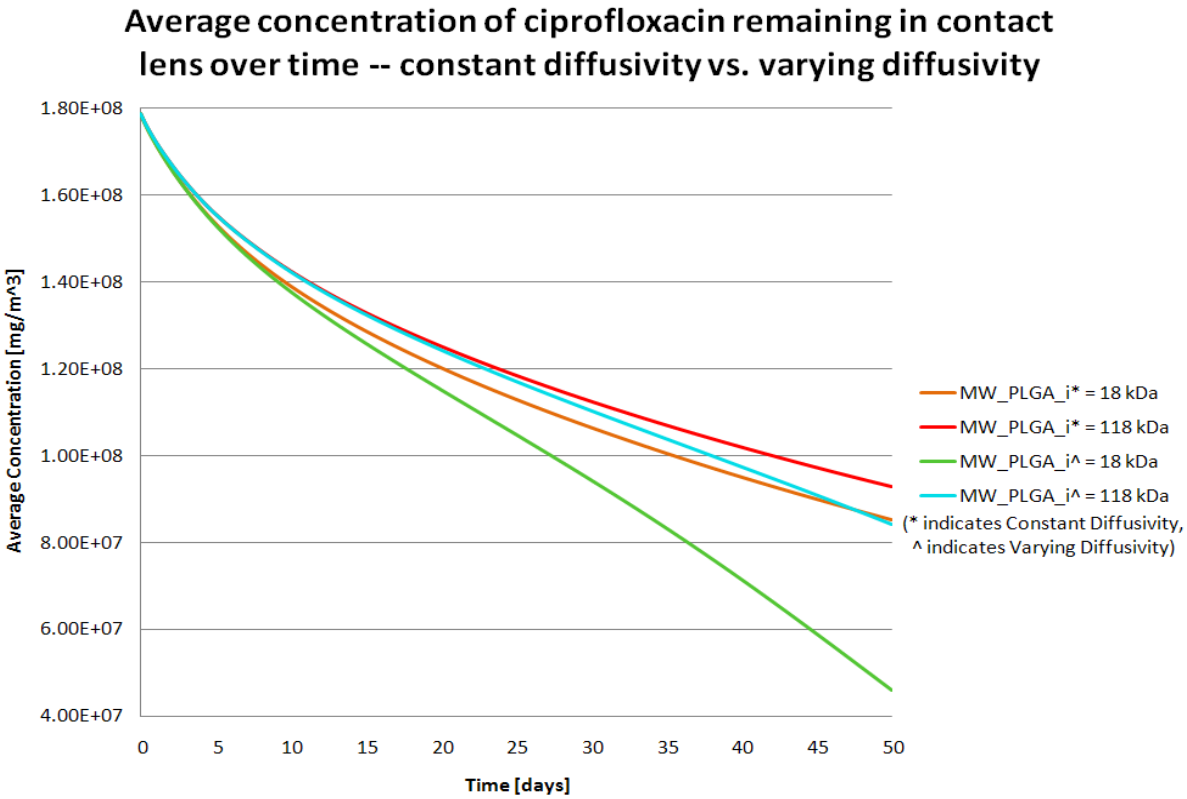


Figure 2: Average ciprofloxacin concentration in the contact lens (pHEMA and PLGA) over time. Orange represents a lens with an initial PLGA molecular weight of 18 kDa and constant diffusivity/no degradation, red represents a lens with an initial PLGA molecular weight of 118 kDa and a constant diffusivity/no degradation, green represents a lens with an initial PLGA molecular weight of 18 kDa and a diffusivity varying according to Figure 10, and blue represents a lens with an initial PLGA molecular weight and a diffusivity varying according to Figure 10.

Mass flux of ciprofloxacin out of the contact lens was also determined using boundary integration. A surface integral of ciprofloxacin flux was computed across the interface between the contact lens (pHEMA surface) and the eye (tear film). Since drug diffused into the eye, the flux was negative. The absolute value of the flux was multiplied by the molecular weight of ciprofloxacin to yield the mass flux of ciprofloxacin entering the eye (Figure 3). For PLGA with an initial molecular weight of 118 kDa, the flux has a quick initial bursts and then settled to a sustained, nearly constant value since the decreasing concentration gradient driving flux is counteracted by the increasing diffusivity shown in Figure 10. That is, mass flux it is roughly linear with a slope of approximately zero, indicating a constant release rate. However, the

diffusivity increases significantly more for the lens with an initial PLGA molecular weight of 18 kDa than for 118 kDa (Figure 10), which overcompensates for the decreasing concentration gradient. This leads to an increase in mass flux with time after approximately 25 days for the lens with an intial PLGA molecular weight of 18 kDa.

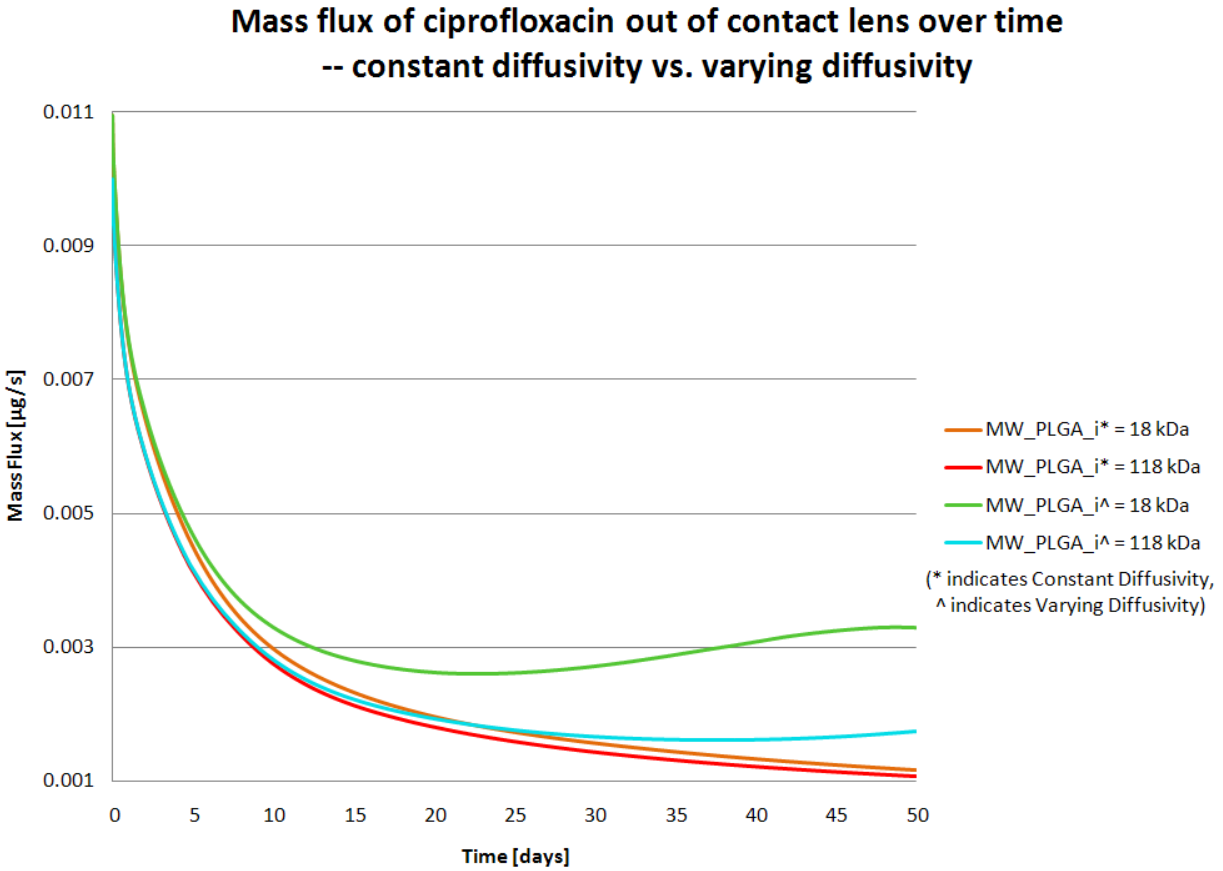


Figure 3: Flux of ciprofloxacin out of the contact lens and into the eye over time (across surface AB shown in Figure 1). Orange represents a lens with an initial PLGA molecular weight of 18 kDa and constant diffusivity/no degradation, red represents a lens with an initial PLGA molecular weight of 118 kDa and a constant diffusivity/no degradation, green represents a lens with an initial PLGA molecular weight of 18 kDa and a diffusivity varying according to Figure 10, and blue represents a lens with an initial PLGA molecular weight of 118 kDa and a diffusivity varying according to Figure 10.

Lastly, the average concentration shown in Figure 2 was multiplied by the volume of the lens to convert to mass remaining in the lens system. At each time step, this value was subtracted from the initial mass of ciprofloxacin in the PLGA (20mg) to give the cumulative mass released from the contact lens (Figure 4, below). As expected, the initial burst seen in early time steps leveled out to approximately a linear increase of mass release with time, which varied depending upon the initial diffusivity value of PLGA used.

3.2. Accuracy Check

To assess the accuracy of our model, we compared the cumulative mass of ciprofloxacin released over the first 28 days from the contact lens with 118kDa PLGA to results obtained by Ciolino et al. (Figure 4).[1]

We obtained the cumulative mass of drug released from the contact lens by first calculating the average concentration of drug remaining in the contact lens (Figure 2), then multiplying this value by the lens volume and subtracting it from the initial mass of ciprofloxacin in the contact lens, 20mg. Using the values mentioned above, specifically $D_0 = 4.9 * 10^{-16}$ m^2/s the mass released in the model was nearly two-fold higher than the experimental results (Figure 4). Therefore, one or more of the parameters must have contributed to the inaccuracy of the model.

The amount of ciprofloxacin released from the contact lens depends on the diffusivity within the lens, but this value was not given by Ciolino et al. Faisant et al. found that for non-sterilized PGLA particles, D_0 is approximately $2.1 * 10^{-16}$ m^2/s instead of $4.9 * 10^{-16}$ m^2/s for sterilized PLGA, so the cumulative amount of drug released was recalculated using this lower D_0 value. This yielded results significantly closer to those seen by Ciolino et al.

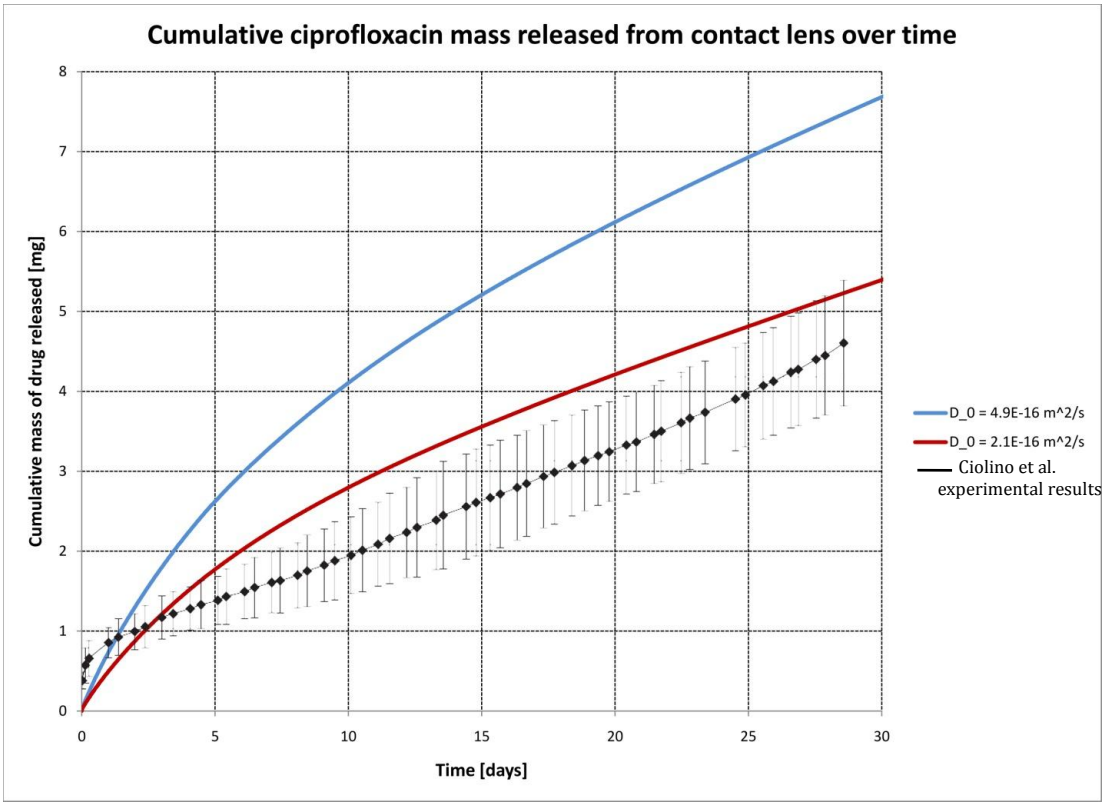


Figure 4: Cumulative ciprofloxacin release from pHEMA-coated PLGA contact lens over 30 days, with degrading PLGA with an initial molecular weight of 118 kDa, as calculated by our model and found experimentally by Ciolino et al. The contact lens initially contained a total mass of 20 mg of ciprofloxacin. Data from Ciolino et al. are mean ± standard deviation. (Adapted from Figure 6 of Ciolino et al.)

3.3. Sensitivity Analysis

To perform a sensitivity analysis, we varied our diffusivities, molecular mass, and degradation rates input variables by adding and subtracting 20% from each value (Table 3). By varying the values in COMSOL, we obtain the graph below, which shows the results from our sensitivity analysis on all 11 variables (Figure 5).

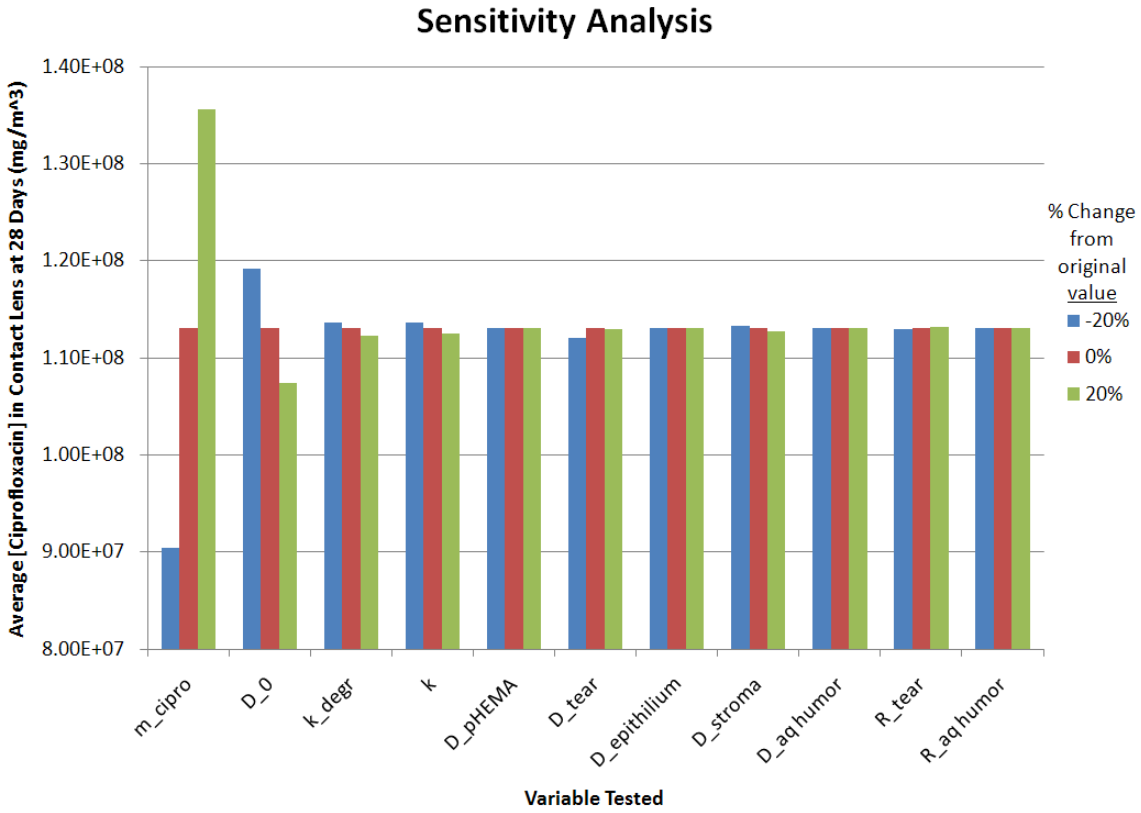


Figure 5: Sensitivity analysis was performed on the 11 variables in Table 3. Values +/- 20% from the original values were used in COMSOL and the resulting average ciprofloxacin in the contact lens after 28 days was measured.

The initial mass of ciprofloxacin had the greatest influence on the average concentration of ciprofloxacin in the contact lens at 28 days. Clearly, when the initial mass was increased, the average concentration of ciprofloxacin in the contact lens at 28 days was greater than the original value. In addition, increasing the diffusivity of ciprofloxacin resulted in a significant drop in ciprofloxacin concentration in the lens. Similarly, when the initial diffusivity was decreased, there was a significant increase in the amount of ciprofloxacin remaining in the contact lens after 28 days. The degradation constant of PLGA (k_{degr}), the constant k, and the diffusivity in the tear layer minimally influenced the concentration of ciprofloxacin in the contact lens. The diffusivities of the pHEMA layer, epithelium, stroma, and aqueous humor did not cause the concentration of ciprofloxacin in the contact lens to change significantly, nor did the degradation constant in the tear layer and aqueous humor change the ciprofloxacin concentration. Thus, it is more important to have extremely accurate data for the initial mass of ciprofloxacin and the initial diffusivity in PLGA than for the other variables.

4. Conclusion and Design Recommendations

4.1. Interpretation of Results

The underlying goal of this modeling process was to model a PLGA-coated contact lens and determine the conditions at which ciprofloxacin is delivered to the eye with zero order kinetics, allowing for sustained release. Another goal of our contact lens model was for it to allow for a concentration of ciprofloxacin in the eye layers to be above the therapeutic threshold.

When a constant diffusivity was used for the PLGA layer, zero-order drug release is not exhibited from either lens. The average concentration of ciprofloxacin in the lens did not decrease linearly with time (Figure 2) and the mass flux out of the lens decreased progressively as time increased (Figure 3), indicating non-constant release kinetics. As a result, it was reasoned that the diffusivity in the PLGA layer could not be modeled as a constant. In fact, PLGA degrades over time, resulting in a varying diffusivity as described by Faisant et al.[2]

Once PLGA degradationis considered, drug release from the lens follows zero order kinetics. Since the drug is constantly diffusing out, the gradient is thus steadily being depleted. For the driving force to remain the same and maintain constant release, the drug must be able to diffuse through the PLGA more easily as the gradient dissipates (i.e. the diffusivity must increase). In Figure 10, the diffusivity function implemented in COMSOL for the PLGA layer was plotted versus time for both the 18 kDa and 118 kDa molecular weight of PLGA, indicating that the diffusivity in the PLGA increases over time.

As seen in Figure 2, when PLGA degradation is included, the average concentration of ciprofloxacin in the contact lens (pHEMA and PLGA) decreases according to zero-order kinetics for both molecular weights of PLGA. There is an initial burst of drug released followed by steady release for prolonged periods of time, extending past 4 weeks. The initial burst is expected since initially there is a drastic concentration difference between the eye and the lens (i.e. the lens contains all of the drug while the eye has a concentration of zero). Following the initial burst, the average concentration decreases linearly since the decreasing concentration gradient is counteracted by the increasing diffusivity in the PLGA layer.

The mass flux of ciprofloxacin out of the contact lens and into the eye was also used to evaluate if our model obeys zero order release kinetics. As is seen in Figure 3, there is an initial burst with high flux followed by a fairly constant flux of ciprofloxacin between the contact lens and the eye.

Lastly, the cumulative ciprofloxacin release from pHEMA-coated PLGA contact lens over 30 days was plotted to check for zero order release kinetics. Figure 4 again demonstrates that there is an initial burst followed by a roughly linear increase.

After confirming that our model displays zero order release kinetics, the ciprofloxacin concentrations in the various regions of the eye were plotted to check whether concentrations would reach therapeutic levels. The therapeutic concentration of 2 μg/mL, which kills 90% of bacteria in the eye, was reached in the tear region and the superficial layers of the cornea, which is where most bacteria grow. Therefore, the contact lens would successfully treat eye infections according to our model. The ciprofloxacin concentration in the aqueous humor is over three orders of magnitude lower than on the surface of the eye. However, since ocular drug delivery does not intend to treat infections in the aqueous humor, the low levels are not problematic.

Implementing this 2D axisymmetric model of ciprofloxacin being released from a contact lens into the eye allowed for the determination of the necessary conditions needed to achieve zero order release kinetics and a therapeutic level of ciprofloxacin in the eye. It was shown that, under the given conditions, the contact lens exhibits sustained zero order release of ciprofloxacin for one month and achieves a concentration of ciprofloxacin in the eye that is above the 2 μg/mL therapeutic threshold. The model being used was shown to be accurate, since it agreed with the results obtained by Ciolino et al. Additionally, mesh convergence and sensitivity analysis were performed and have furthered our model's validity.

4.2. Design Recommendations

Although Ciolino et al. used the lens geometry shown in Figure 1, simpler contact lens geometries are possible for a sustained release system. Contact lenses with the geometry used by Ciolinoet al. (as shown in Figure 1 and Figure 7) and a similar but simpler geometry, where the PLGA layer was a complete disk extending the diameter of the lens (as shown in Figure 6 and Figure 8), were modeled to evaluate the importance of the donut-shaped PLGA layer geometry. In both lenses, the total mass of ciprofloxacin initially in the PLGA layer was held constant at 20 mg, the PLGA had an initial molecular mass of 118 kDa, and the PLGA degraded causing diffusivity to increase as shown in Figure 10. Surface plots of ciprofloxacin concentration in the eye after 28 days were generated for each geometry (Figure 11). After 28 days, the Ciolino lens demonstrated ciprofloxacin concentrations in the tear film and epithelial layer of approximately 2.0 μg/mL. However, the simplified geometry only generated ciprofloxacin concentrations of approximately 0.725 μg/mL in the same regions, which is below the therapeutic concentration. This is because much of the ciprofloxacin diffused into the upper pHEMA layer and became concentrated there in the simplified geometry lens (data not shown). The hole in the PLGA layer in the Ciolino et al. lens allows ciprofloxacin to always diffuse from any point in the lens downward into the eye through the pHEMA layer. Since the Ciolino et al. geometry allowed for over twice as much drug transfer into the eye, we recommend designing a lens with a similar geometry to that in Figure 1.

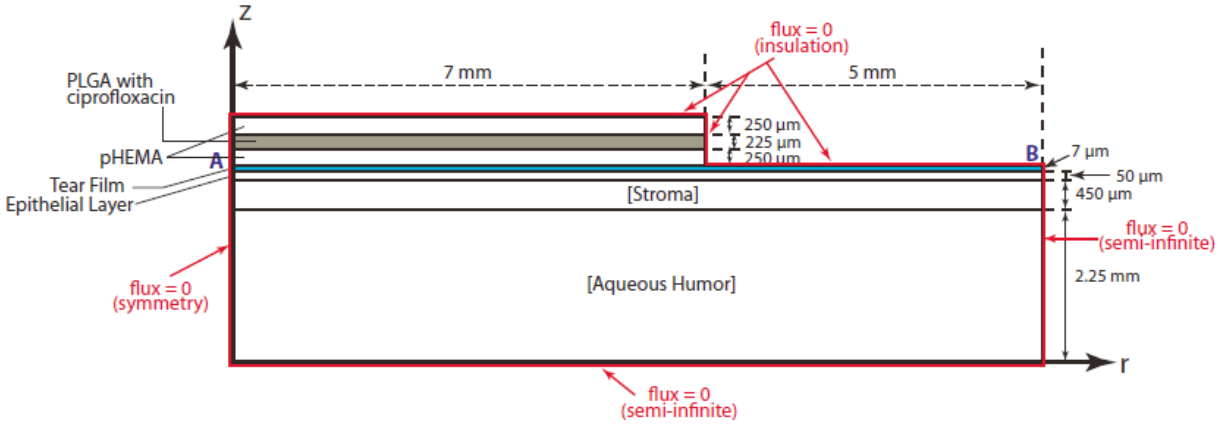
In addition to the geometry, we recommend using an initial PLGA molecular mass of 118 kDa. This molecular mass caused more constant ciprofloxacin flux than the 18 kDa PLGA, as seen in Figure 3. As described above, the 118 kDa case generated therapeutic concentrations of ciprofloxacin in the tear film and epithelial layer of the eye after times as great as 28 days, which is the longest approved usage time for a contact lens. The precise dosage can be easily tuned by varying the total mass of ciprofloxacin initially contained in the PGLA layer during lens production. In addition, a slightly lower initial PLGA molecular mass could potentially be used to increase the rate of drug delivery as desired.

4.3. Realistic Constraints

In order to realistically manufacture the contact lens, there are certain limiting constraints in the design process which can be recognized by considering the perspective of both the manufacturer and the consumer. The manufacturer is primarily concerned with economic and health safety constraints, as we all as with manufacturability of the product. Our design of a PLGA-coated contact lens that releases ciprofloxacin is both cost-efficient and manufacturable. The cost will not greatly exceed regular contact lenses, since PLGA and pHEMA are commonly

produced polymers. Furthermore, our model can be used to optimize the geometry and the molecular weights of all the components for a particular purpose, so the optimal characteristics can be determined and the contact lens can easily be produced. This will allow the manufacturer to sell this product at a competitive price to consumers. The efficacy of the drug delivery, as seen by the steady-state release, and the biocompatibility (and hence health safety) of the lens will encourage consumers to buy the lens. Clinical trials will have to be carried out to determine other safety limitations of the contact lens, such as the possible consequences if the patient forgets to remove the contact lens for an extended period of time. Furthermore, consumers will probably desire the lens to be disposable and obviously the lens should not be a hazardous waste material when discarded.

5. Appendix A: Mathematical statement of problem



Governing Equation:

Figure 6: Problem schematic for contact lens where PLGA is coated with pHEMA, except PLGA is a complete disk extending across the entire radius of the lens instead of just from 2 mm to 5 mm in the regular model shown in Figure 1. Points A and B are the boundary between the contact lens and the eye.

Mass Transfer: $\frac{\partial c}{\partial t} = \boldsymbol{D}\left(\frac{1}{r}\frac{\partial c}{\partial r}\left(r\frac{\partial c}{\partial r}\right) + \frac{\partial^2 c}{\partial z^2}\right) - \boldsymbol{r_A}$

Initial Conditions:

$c_{eye}(t=0) = 0\frac{\mu g}{ml} = 0\frac{mol}{m^3}$

$c_{pHEMA}(t=0) = 0\frac{\mu g}{ml} = 0\frac{mol}{m^3}$

$c_{PLGA}(t=0) = 4.066 * 10^3\frac{mol}{m^3}$

Boundary Conditions:

(Listed in schematic above in red) Flux across all external boundaries is zero due to symmetry, insulation, or semi-infinite conditions.

PLGA Degradation:

$MW(t) = MW_0 e^{-k_{degr}t}$ (Eqn. 1)

$D(t) = D_o + \frac{k}{MW(t)}$ (Eqn. 2)

Where k_{degr} is the first-order degradation constant of the polymer, MW_0 is the molecular weight of the non-degraded polymer, D_o is the diffusion coefficient for the drug in the non-degraded polymer, and k is a constant. Faisant et al. experimented with PLGA of MW_0, 78.4kDa. They found that k_{degr} is 0.46 weeks^{-1}, D_o is 4.9 * 10^{-12}cm^2/s, and k is $2.1 * 10^{-11} cm^2 * kDa/s$ for sterilized PLGA microparticles. These constants were used with the above equations to extrapolate appropriate values for 18 kDa and 118 kDa PLGA:

$D_{18kDa} = 6.1054 * 10^{-12}$ cm^2/s

$D_{118kDa} = 5.3151 * 10^{-12}$ cm^2/s

Table 1: Input Parameters.

Variable	Description	Value	Citation
m	Initial mass of ciprofloxacin	20 µg	1
D_o	Diffusion coefficient for the drug in the non-degraded polymer	4.9E-16 m^2/s	2
k_{degr}	First order degradation constant of the polymer	7.6058E-7 s^{-1} = 0.46 $week^{-1}$	2
k	A constant	2.1E-15 m^2/s	2
D_{pHEMA}	Diffusivity in pHEMA	9.9E-10 m^2/s	3
$D_{tear\ film}$	Diffusivity in the tear film	5E-9 m^2/s	3
$D_{epithelium}$	Diffusivity in the epithelium	6.022E-11 m^2/s	4
D_{stroma}	Diffusivity in the stroma	8.72E-13 m^2/s	4
$D_{aqueous\ humor}$	Diffusivity in the aqueous humor	5E-9 m^2/s	5
$R_{tear\ film}$	Degradation rate in the tear film	-1E-4*c	3
$R_{aqueous\ humor}$	Degradation rate in the aqueous humor	-3E-3*c	3

6. Appendix B: Solution strategy

Solver:

The direct (UMFPACK) solver was used to solve the algebraic equations.

Time Stepping:

Our model was run for a total of 30 days. The time step used was 30 minutes.

Tolerance:

The relative tolerance was 0.01 and the absolute tolerance was 0.0010.

Mesh:

We used a free mesh that placed the most elements in the PLGA, pHEMA, tear film, and epithelial subdomains, since those areas experience the most ciprofloxacin diffusion. The maximum element size and element type were tabulated for each subdomain (Table 2). This yielded a fine mesh that had fairly short computation times and ran reliably without causing the computer to run out of memory (Figure 7).

Table 2: Free mesh parameters.

Subdomain/Boundary	**Maximum Element Size (m)**	**Element type/method**
1. Aqueous humor	$2.5 * 10^{-3}$	Triangle (advancing front)
2. Stroma	$1.0 * 10^{-3}$	Triangle
3. Epithelial layer	$1.0 * 10^{-3}$	Triangle
4. Tear film	$1.0 * 10^{-3}$	Quad
5. pHEMA	$2.5 * 10^{-3}$	Triangle
6. PLGA	$1.0 * 10^{-3}$	Triangle
pHEMA/Tear film boundary	$2.5 * 10^{-4}$	---

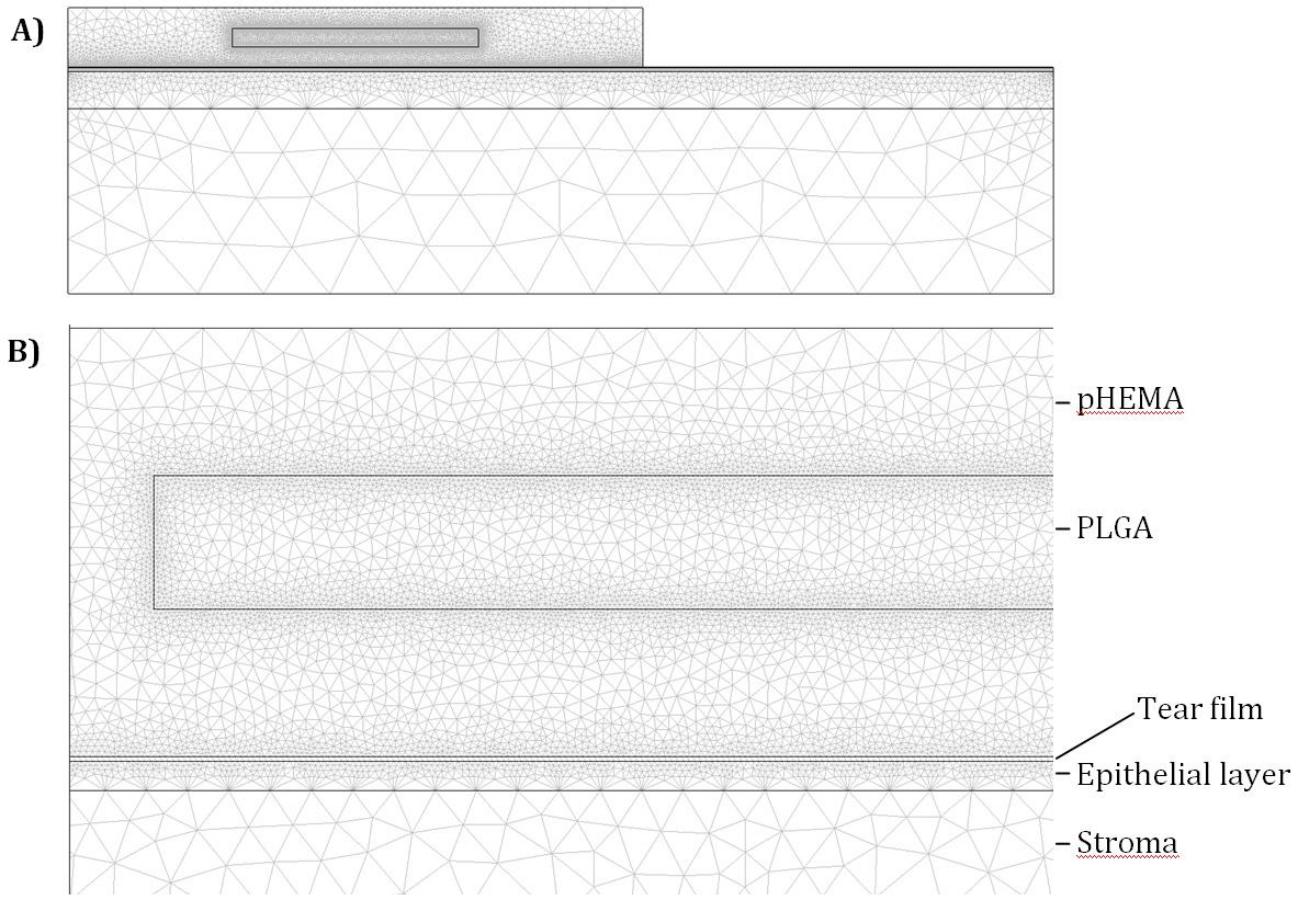


Figure 7: Mesh for contact lens and eye, with the dimensions shown in Figure 1. **A)** View of mesh for entire problem schematic. **B)** Close-up view of mesh for pHEMA, PLGA, tear film, epilthelial layer, and stroma subdomains.

The mesh for the wide PLGA layer, where the PLGA was a complete disk extending the diameter of the contact lens as diagrammed in Figure 6, is shown below (Figure 9). It used the free mesh parameters listed in Table 2.

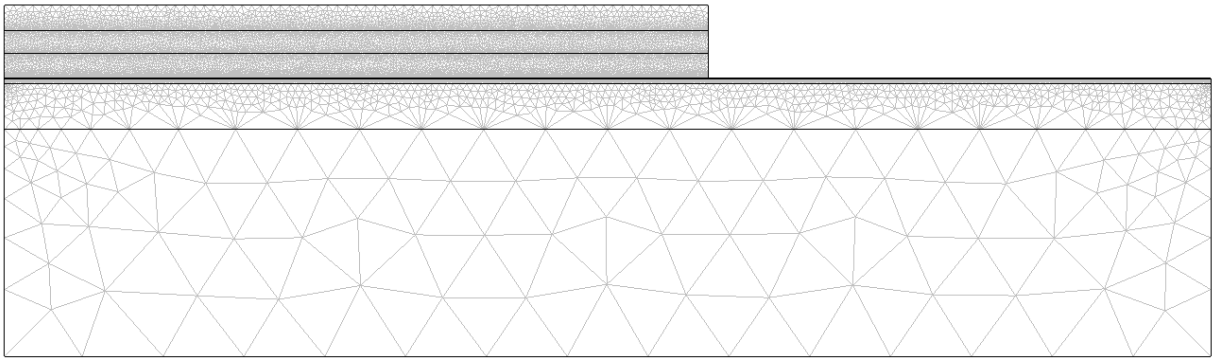


Figure 8: Mesh for contact lens and eye, with the dimensions shown in Figure 6.

Mesh Convergence:

For mesh convergence analysis, the element sizes listed in Table 2 were scaled proportionally. The concentration of ciprofloxacin remaining in the contact lens after 50 days and compared for different mesh sizes. As shown in Figure 9, the concentration does not vary with increasing mesh size after a mesh size of approximately 16000 elements. Thus, we minimized any discretization errors by using this mesh size.

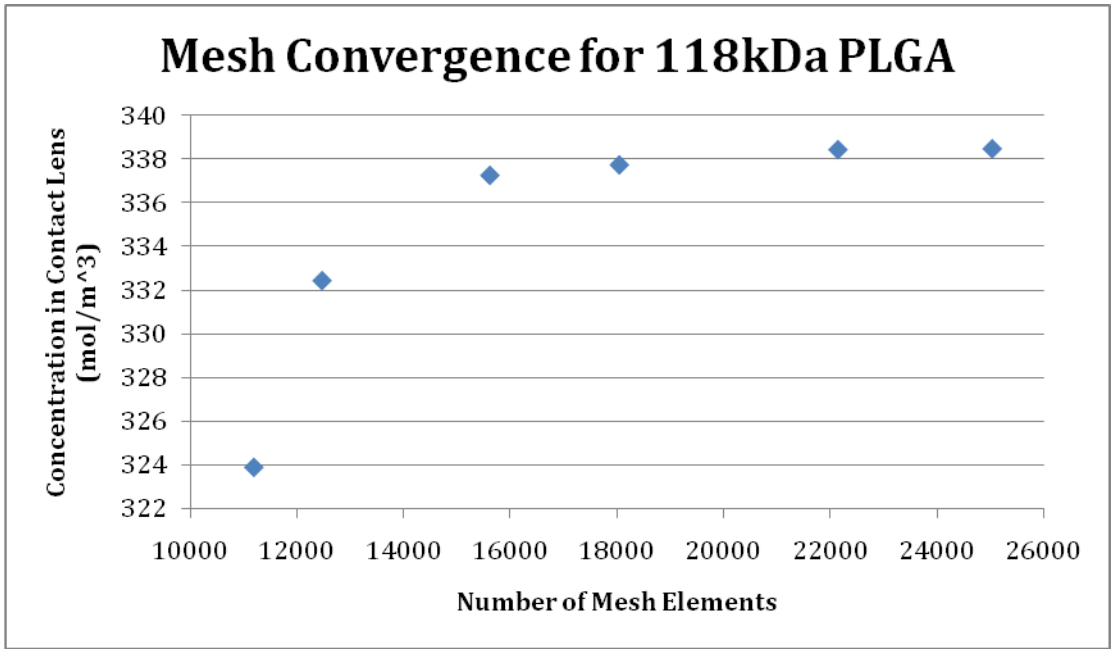


Figure 9: Mesh convergence analysis, showing the average concentration of ciprofloxacin remaining in the lens made of 118 kDa PLGA after 50 days vs. the number of mesh elements.

7. Appendix C: Additional visuals

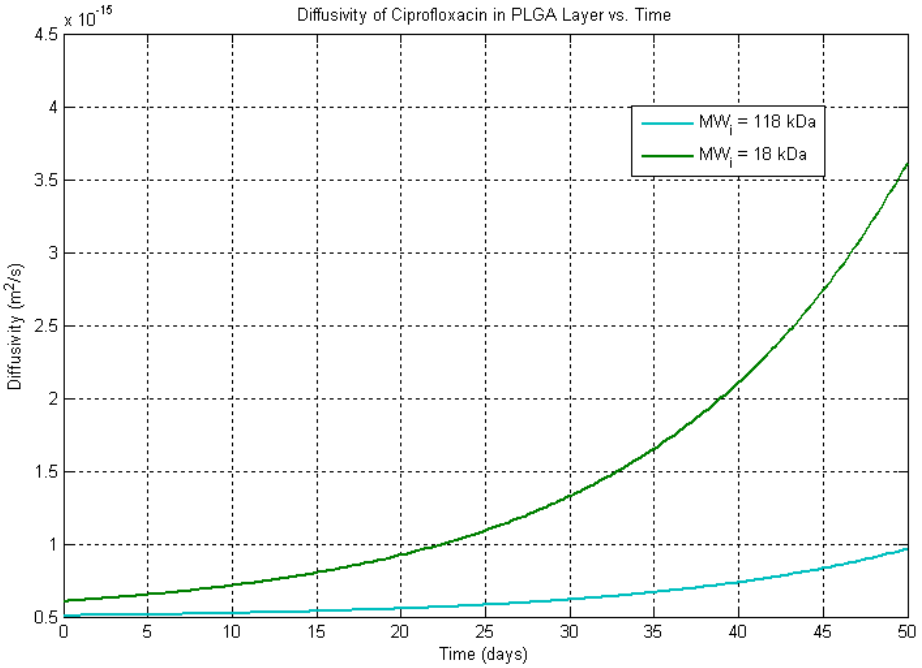
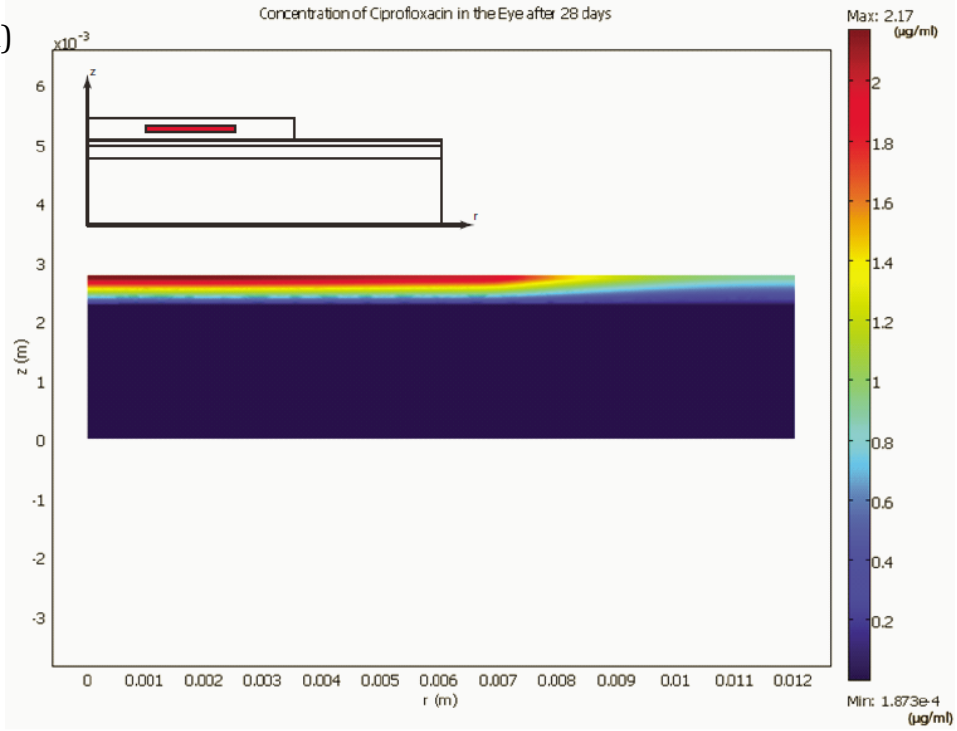


Figure 10: Varying diffusivity in the PLGA layer of the contact lens over time for an initial PLGA molecular weight of 18 kDa and 118 kDa.

(A)



(B)

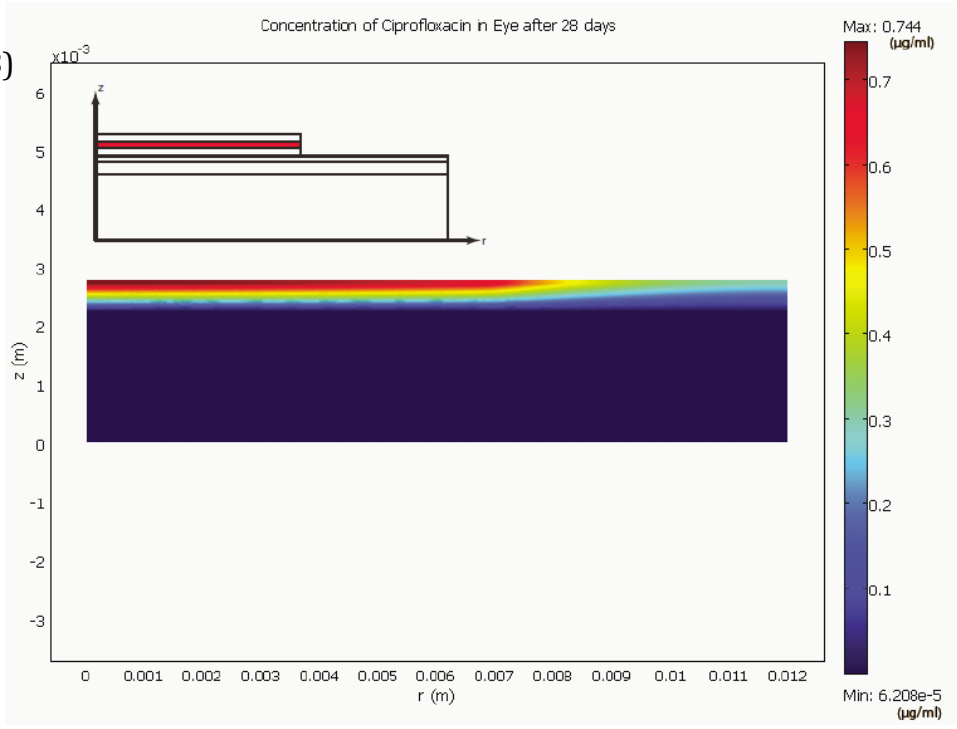


Figure 11: (A) Surface plot of ciprofloxacin concentration in the eye at $(t = 28days)$with the actual PLGA geometry in the contact lens, as shown in the schematic in Figure 1. The contact lens is not included in this plot. The initial molecular mass of PLGA modeled is 118 kDa. **(B)** Surface plot of ciprofloxacin concentration in the eye at $(t = 28days)$with the PLGA spanning the entire width of the contact lens, as shown in the schematic in Figure 7. The contact lens is not included in this plot. The initial molecular mass of PLGA modeled is 118 kDa.

Table 3: Variables to be tested for sensitivity analysis, as well as the current value used and the range of values that will be tested.

Variable	**Minus 20%**	**Current value**	**Plus 20%**
$m_{ciprofloxacin,PLGA}(t=0)$	16 µg	20 µg	24 µg
D_0	3.92E-16 m^2/s	4.9E-16 m^2/s	5.88E-16 m^2/s
k_{degr}	6.08464E-7 s^{-1}	7.6058E-7 s^{-1} = 0.46 $week^{-1}$	9.12656E-7 s^{-1}
k	1.68E-15 m^2kDa/s	2.1E-15 m^2kDa/s	2.52E-15 m^2kDa/s
D_{pHEMA}	7.92E-10 m^2/s	9.9E-10 m^2/s	11.88E-9 m^2/s
$D_{tear\ film}$	4E-9 m^2/s	5E-9 m^2/s	6E-9m^2/s
$D_{epithelium}$	4.8176E-11 m^2/s	6.022E-11 m^2/s	7.2264E-11 m^2/s
D_{stroma}	6.976E-13 m^2/s	8.72E-13 m^2/s	10.464E-12 m^2/s
$D_{aqueous\ humor}$	4E-9 m^2/s	5E-9 m^2/s	6E-9m^2/s
$R_{tear\ film}$	-1.2E-4*c	-1E-4*c	-.8E-4*c
$R_{aqueous\ humor}$	-3.6E-3*c	-3E-3*c	-2.88E-3*c

8. Appendix D: References

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