

Treating Glaucoma with Porous Contact Lens

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BY:

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Executive Summary

Glaucoma is a family of diseases that afflicts 65 million people worldwide. Primary open angle glaucoma is the most common type of glaucoma. This is characterized by increased intraocular pressure (IOP) within the eye that results in vision loss. Current therapeutic drugs include Timolol and Brimonidine which studies have shown to yield a greater decrease in IOP through combined drug therapy than monotherapy. In 2007 Combigan, an eye drop that combines the therapeutic effects of Timolol and Brimonidine, was approved for use by the FDA. This project proposes a method for treating glaucoma through delivery of Combigan via a contact lens through which the drugs will diffuse into the eye over a period of time.

We modeled the diffusion of two drugs, Timolol and Brimonidine, through four layers of the human eye. The drug was delivered via a contact lens, so that the concentration of drug in the aqueous humor would remain above the minimum effective dosage for longer than if it were delivered via eye drops. We calculated the concentration of each drug in all layers of the eye for 12 hours. Our model was verified by experimental data in the published literature. Our model failed to deliver solely Timolol or Brimonidine for 12 hours, which was our goal, but still was significantly more effective than eye drops. However, throughout the twelve hours there was at least one drug in the aqueous humor and since both drugs lower IOP through different mechanisms our model did deliver treat the glaucoma for the whole twelve hours. If it were possible to lower the diffusivity of Timolol through the stroma, this would allow for Timolol to remain longer in the aqueous humor thus making the contacts better at treating glaucoma.

A sensitivity analysis demonstrated that our model was robust in the tear film and relatively robust in the contact lens. However, the model was particularly sensitive to diffusivity in the stroma layer, as the stroma acts as the final barrier to aqueous humoral penetration and is quite thick. Brimonidine was delivered at a more constant rate, but at a lower concentration than Timolol. It also took six times longer than Timolol to reach its maximum concentration in the aqueous humor. Drug delivery via contact lenses is a feasible technology as more effective than eye drops, but can be improved by designing a time-release drug that diffuses more slowly. Further research needs to be conducted in order to investigate the practicality of this method.

Key words: Glaucoma, drug delivery, contact lens

Introduction

Glaucoma is a family of diseases that afflicts 65 million people worldwide (2). The most common type of glaucoma is primary open angle glaucoma (POAG), which affects 3 million Americans (1). This type of disease is characterized by increased intraocular pressure (IOP) within the eye that results in optic nerve damage and subsequent vision loss (1). The increased IOP (normal range 12-22mmHg) results from a malfunctioning drainage system in the form of canals around the iris (1). A healthy drainage system facilitates the uptake of aqueous humor into the bloodstream (1, Figure 1). However in the case of POAG, the inner drainage canals become clogged, which results in fluid and pressure build-up that further damage the sensitive meshwork over time (1, Figure). Since POAG progresses slowly over years, an early diagnosis and treatment helps impede vision loss. Available treatments include medicines, laser trabeculoplasty, conventional surgery or a combination of the three (3). However, current trends show that fewer people are opting for invasive surgery as improved early detection methods for glaucoma enable patients to control IOP through medications (4). Treating glaucoma through drugs poses advantages such as being non-invasive with limited side effects (3).

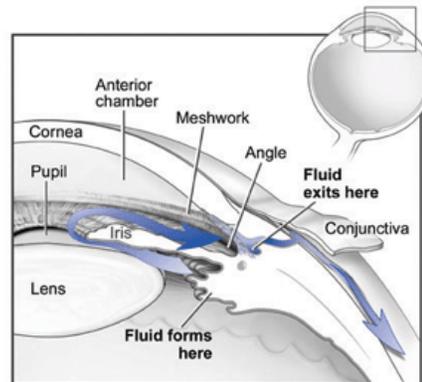


Figure 1. Normal fluid drainage in the human eye (3).

There are currently many drugs on the market for patients to choose from. Two of the most widespread and effective of these drugs are Timolol Maleate and Brimonidine Tartrate. Timolol is a non-selective beta-blocker that reduces the production of aqueous humor (8). Over time, it has been shown to reduce IOP by 26 to 38% (8). Meanwhile, Brimonidine is a selective alpha adrenergic receptor agonist that reduces IOP by reducing aqueous humor production and increasing uveoscleral outflow (9). Studies have shown exciting results that that a combined treatment of Timolol and Brimonidine yields a greater decrease in IOP than monotherapy (6, 7). In 2007 Combigan, an eye drop that combines the therapeutic effects of Timolol and

Brimonidine, was approved for use by the FDA (5). This project proposes to model the delivery of Combigan to the eye via an alternative method, a contact lens.

Schematic

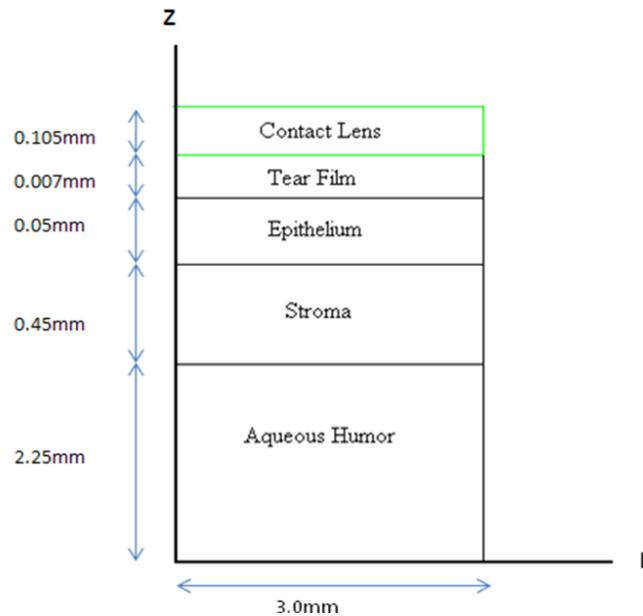


Figure 2. The contact lens and different layers of the human eye.

Design Objectives

- Create a model of the eye to simulate drug diffusion
- Compare our results to experimental data to verify model.
- Introduce realistic complications to the model to better simulate a human eye.

For this project, we plan to model the diffusion of two drugs, Timolol Maleate and Brimonidine Tartrate, through a contact lens and the top four layers of the human eye. The eye will be modeled as a rectangular 2-dimensional region comprised of the contact lens, the tear film, the epithelium, the stroma, and the aqueous humor. Diffusion is primarily, in the z direction. For boundary conditions, all boundaries will be insulating except for the bottom of the aqueous humor region, which will have zero drug concentration. Both drugs will have an initial concentration only in the contact lens region. The process of diffusion will be modeled over a time course of 12 hours.

Results and Discussion

We modeled the diffusion of two drugs, Timolol and Brimonidine, through a contact lens and four layers of the eye. In our model, both drugs are present in the contact lens at the same time; thus both drugs diffuse at the same time. We have not found any literature claiming that the drugs react with each other, so our model assumes that there is no cross-reactions. We used the parameters displayed in Appendix A for initial concentrations and diffusivities. The initial concentrations were based on the concentration of drug in Combigan brand eye drops. We ran the simulation for 12 hours (43200 seconds). See Appendices B for details on calculations and time-stepping. We also modeled a scenario where no contact lens was used, but drug was applied via an eye drop, so that the same total mass of drug is applied. In this model, all of the same parameters were used, except the boundary at the top of the top of the tear film was the initial concentration of the drug instead of insulated.

Figure 3, left graph shows a profile of the average concentration of each drug in the aqueous humor over 12 hours. Figure 3 right graph shows the concentrations of each drug at the boundary between the stroma and aqueous humor over time. The maximum concentration of Timolol was $5.66 \cdot 10^{-8}$ mol/cm³, and was reached at 28 minutes, 20 seconds. The concentration rose sharply over the first 30 minutes, and then decayed much more slowly, remaining above 10 µg/mL for 120 minutes. By 320 minutes, the concentration was less than 1 µg/mL. The maximum concentration of Brimonidine was $7.55 \cdot 10^{-9}$ mol/cm³, and was reached at 213.2 minutes. The concentration of Brimonidine increased and decayed at a much slower rate than Timolol. Both figures show that there is not any significant drug concentration in the aqueous humor at the end of 12 hours.

Figure 3 shows that our contact model cannot keep the concentration of either drug in the eye high enough for 12 hours. One way to improve this could be to modify the drug to diffuse slower. In fact, in an early simulation trial, a diffusivity value was entered erroneously as two orders of magnitude too small. In this trial, the concentration of the drugs in the aqueous humor never decayed. This prevented our results from being confirmed by experimental data, but is much better from a design perspective.

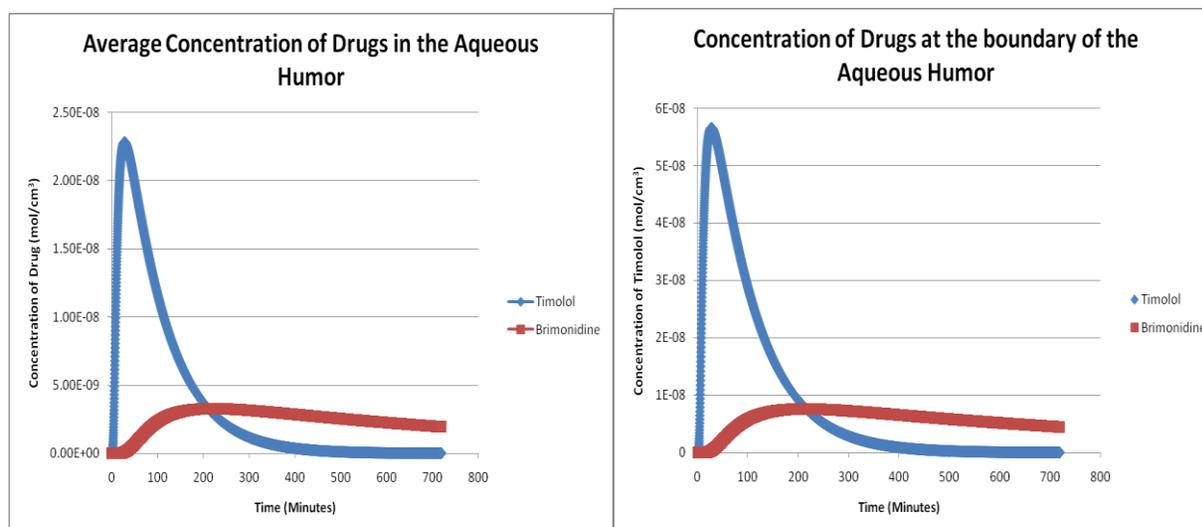


Figure 3: (Left) Average Concentration of each drug in the aqueous humor over time. (Right) Concentration of each drug at the boundary between the stroma and the aqueous humor over time.

In Figure 3, the average results confirm the single-point results. Timolol diffuses much more quickly than the Brimonidine. The Timolol reaches its maximum concentration at 27 minutes, 20 seconds. The Brimonidine reaches its maximum concentration at 3 hours, 35 minutes, 10 seconds.

To test the accuracy of these results, we did an accuracy check against published experimental data. We were unable to find literature exactly matching our model. However, in 2006, Wei et al experimentally measured Timolol concentration in the aqueous humor of rabbits after given eye drops. After adjusting the initial concentrations, we were able to compare our results to Wei's results. Figure 4 (left) shows Wei's results, the right graph shows our eye drop model's results for the concentration of the drugs at the same point in the aqueous humor.

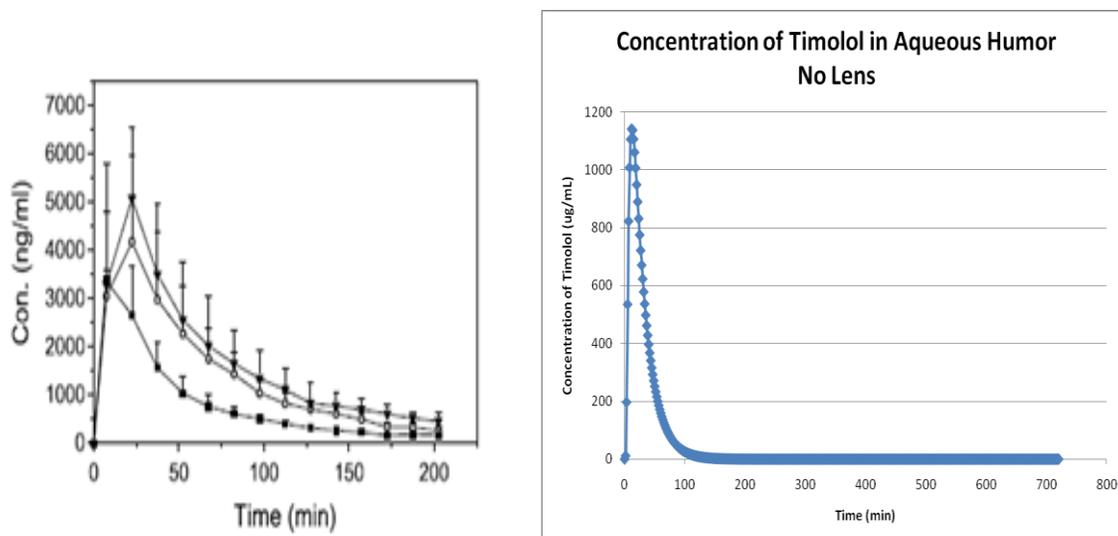


Figure 4: (Left) Results from Wei, *et al.* Pharmacokinetics of Timolol in aqueous humor sampled by microdialysis after topical administration of thermosetting gels. (Right) Concentration of Timolol in the aqueous humor when delivered via eye drops.

As shown in Figure 4 our results match the results of Wei. Our peak value is higher, but this could be due to the fact that our parameters were for the human eye, not the rabbit eye. Our graph shows the proper shape, with a rapid increase in concentration followed by a slower decline. In both models, concentration was negligible by 150 minutes.

The model in figure 6 can also be used to compare contact lenses and eye drops as delivery vectors for the drug. In the eye drop model, the concentration of Timolol reached 1141 $\mu\text{g/mL}$ in only 11 minutes, 40 seconds. However, it decayed rapidly. It also dropped below 10 $\mu\text{g/mL}$ at 120 minutes, and dropped below 1 $\mu\text{g/mL}$ after only 172 minutes. Thus, although our contact lens failed to maintain aqueous humor concentration for 12 hours, it still maintained aqueous humor concentration for significantly longer than an eye drop would.

To determine the extent of mesh error, we performed a mesh convergence analysis. We ran our simulation under circumstances of increasingly fine mesh. See Table 1 for the mesh dimensions used. Basically, the number of nodes remained constant in the r direction, and was consistently doubled in the z direction, and then the model was simulated for the full 12 hours. We then had COMSOL integrate to solve for the total amount of Timolol in the aqueous humor (in mol), as well as the total volume of the aqueous humor (in cm^3). These allowed us to calculate the average concentration of Timolol, and plot the change in average concentration as a function of the number of elements in the model.

Table 1: Mesh properties. All regions have 5 nodes in the r direction. Below are the number of nodes in the z direction for each region

region	6400 nodes total
Contact	160
Tear Film	80
Epithelium	160
Stroma	240
Aqueous Humor	640

Figure 5 displays the results of the convergence analysis for Timolol. As the number of elements increases, the concentration of Timolol in the aqueous humor appears to approach an asymptote. At 6400 elements, the concentration might still be increasing with increased mesh size; however the change between 3200 and 6400 is $5.5 * 10^{-16} \text{ mol/cm}^3$. We presumed the change in solution with additional computational elements would be increasingly negligible, and so for the sake of computing time, did not use more than 6400 elements for any solution.

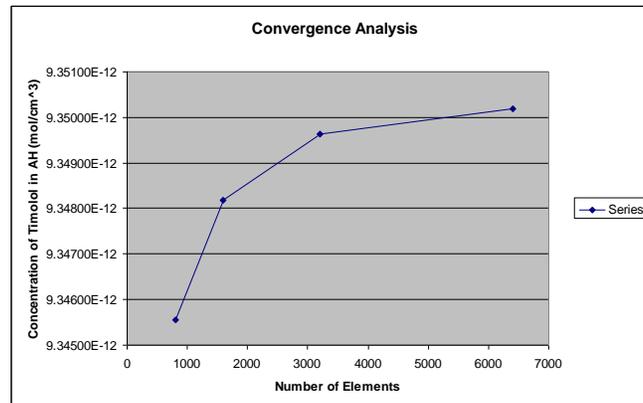


Figure 5: Mesh convergence analysis of Timolol in the aqueous humor.

Sensitivity Analysis

We performed a sensitivity analysis on the model by varying diffusivity of each drug component Timolol and Brimonidine in three regions (the contact lens, tear film, and stroma) using COMSOL, while keeping all other parameters constant. Increasing or decreasing the normal diffusivity parameter in each region by an order of a magnitude allowed us to determine the effect of changes in diffusivity in each region on the final drug concentration in the aqueous humor. This variation in diffusivity allowed us to gage the sensitivity of our model to such a range in diffusivity values. Figures 6 and 7 below are two summary plots for Timolol and Brimonidine that display the results of the sensitivity analysis. Figures 14-19, located in

Appendix C displays the results of diffusivity variation on drug concentration profile in the aqueous over a 12-hour period.

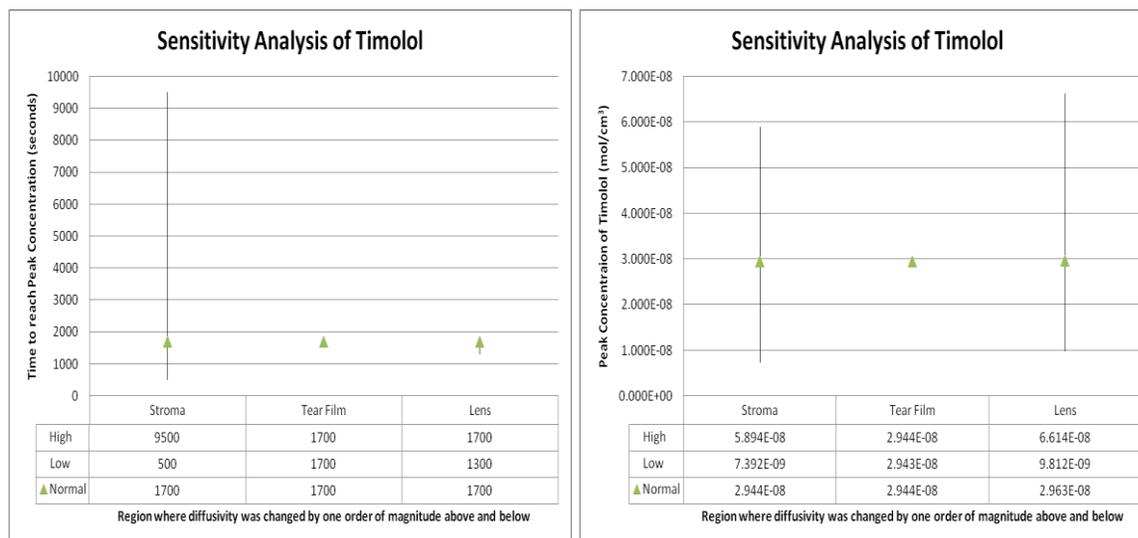


Figure 6: (Left) shows the sensitivity analysis of Timolol in regards to time to peak concentration. (Right) Shows the sensitivity analysis of Timolol in regards to peak concentration.

Notice in Figure 6 that changing the diffusivity values in the tear film by one order of magnitude in either direction barely changes the model. Although, changing the stroma diffusivity values drastically varied the results in regards to both time to peak concentration and peak concentration.

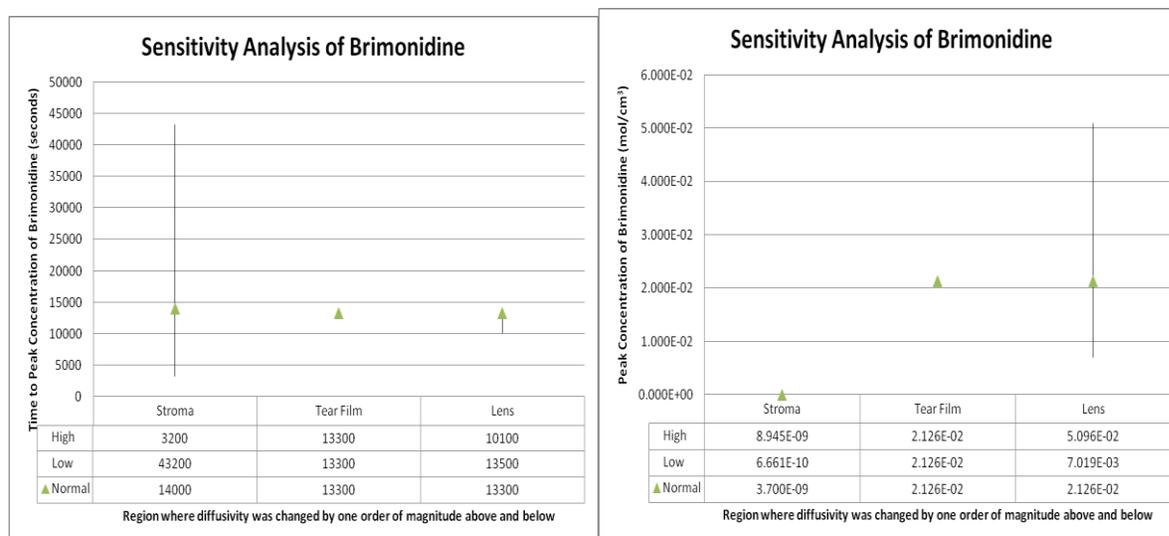


Figure 7: (Left) Shows the sensitivity analysis of Brimonidine in regards to time to peak concentration. (Right) Shows the sensitivity analysis of Brimonidine in regards to peak concentration.

Notice that in Figure 7 the same effects are shown as in Figure 6. The tear film is the least sensitive but the stroma is the most sensitive parameter.

The concentration profiles for Timolol at three different diffusivities in the contact lens, tear film, and stroma regions are displayed in Figures 14-16. Figures 14 and 16 clearly show a direct correlation between the magnitude of the diffusivity value and the peak concentration of Timolol during the 12-hour data collection period. For instance, the normal diffusivity value for Timolol diffusivity across the contact lens region is $9.9\text{E-}9 \text{ cm}^2/\text{s}$. As shown in Figure 14, the normal diffusivity resulted in a peak drug concentration of $2.96\text{E-}9 \text{ moles/cm}^3$, while increasing diffusivity to $9.9\text{E-}8 \text{ cm}^2/\text{s}$ resulted in a peak drug concentration of more than two times that value, $6.61\text{E-}8 \text{ cm}^2/\text{s}$ to be exact. Furthermore, decreasing the normal diffusivity in the contact lens resulted in a decrease in the peak drug concentration, which is $9.81\text{E-}9 \text{ moles/cm}^3$. This general trend of a direct correlation between diffusivity in the region and peak drug concentration is also observed in the stroma region (see Figure 16). In addition, this trend is also observed in the concentration profile for Brimonidine in Figure 17. Figures 15 and 18 show the concentration profile of Timolol and Brimonidine at various diffusivities across the tear film region. In each figure, the concentration curves overlap each other, implying that varying diffusivity across the tear film has very little effect on the concentration of each drug component in the aqueous humor. This result is logical since the tear film region is relatively thin (0.007mm) when compared with the contact lens (0.105mm) and the stroma (0.45mm), thus making any inhibitory or facilitating contributions to diffusivity minimal.

The results of our sensitivity analysis are summarized in Figures 20-25, also located in Appendix C. In these plots, we mapped out the relationship between the varied diffusivities versus the resulting peak drug concentration in the aqueous humor. After varying the diffusivities of Timolol and Brimonidine by plus or minus one order of magnitude, we observed where our model was most sensitive to the biological parameter of diffusivity.

In particular, the tear film exhibited behavior for both drug diffusivity changes that we did not expect to see, but can justify based upon physical principles. In both Figures 22 and 25, we saw a plateau develop in the curve, a region in which there is virtually no change in peak concentration in the aqueous humor with respect to changes in drug diffusivity in the tear film. This observation fits with the trends observed in Figures 15 and 18, in which the raw data plots showed little to no variation in drug concentration versus time. We concluded that because the

tear film is such a thin layer in the eye and consequently represents a small portion of the depth that the drug components must diffuse through in our model, even drastically increasing or decreasing the diffusivity of both drugs in that layer has almost no effect overall on the resulting drug concentrations in the aqueous humor. As the drug concentrations in the aqueous humor are the only area of interest to us in terms of the goal of our project, the treatment of glaucoma, we can say that drug diffusivity in the tear film is not as much of a limiting factor when compared to diffusivities elsewhere in the eye.

The “negligibility factor” that we observed through analysis of peak drug concentration versus diffusivity changes in the tear film did not occur, however, in our analyses of the stroma and the contact lens. We attribute this to the thickness of the two layers as well as the fact that, in particular, the stroma acts as a final barrier to drug access to the aqueous humor. In Figures 20 and 23, it is shown that the peak concentration of Timolol and Brimonidine in the aqueous humor is sensitive to the drug diffusivity in the lens and that these data are related linearly. However, the slopes of those lines versus the linear relationships displayed in Figures 21 and 24 (diffusivity changes made in the stroma layer) are significantly less in magnitude. This is indicative of the stroma acting as a barrier, because diffusivity changes in the final, thick layer before the aqueous humor inhibits drug transport, thus impacting the peak concentrations of drug achieved in the humor. In Figure 19, this concept is highlighted well by the raw data plot which shows that an increase in Brimonidine diffusivity in the stroma significantly increases the peak value for concentration in the aqueous humor, but decreasing it below the value used by the model decreases the peak concentration. In addition, we looked at the effects of changing the initial concentrations of each drug. We varied the initial concentration of each drug in the contact lens and observed the change in concentration at the boundary between stroma and aqueous humor. Below, Figures 8 and 9 show the effects of increasing and decreasing the initial concentration of each drug by 1 order of magnitude. Increasing the concentration of Timolol increases its residence time in the aqueous humor, but not to 12 hours. It is not reasonable to increase this concentration anymore; other means must be used if we are to reach 12 hours. Brimonidine seems to become a feasible option by simply changing the initial concentration.

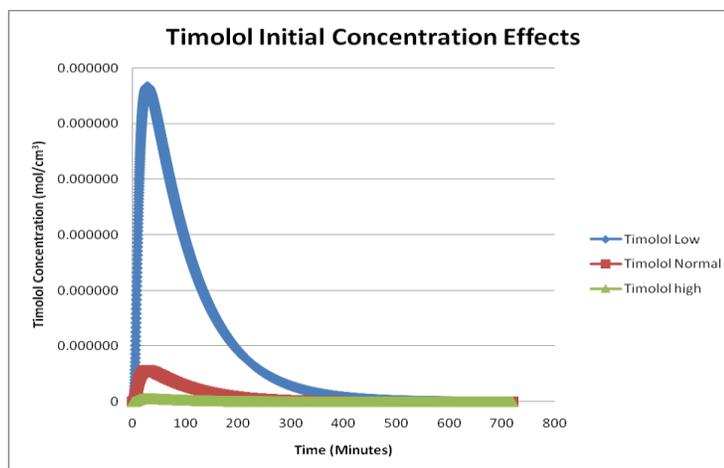


Figure 8: Change in concentration of Timolol at the aqueous humor boundary with variable initial concentration

Notice in Figure 8 that decreasing the amount of Timolol in the system shows the peak is reached at a higher value but at around the same time as the other two values of Timolol.

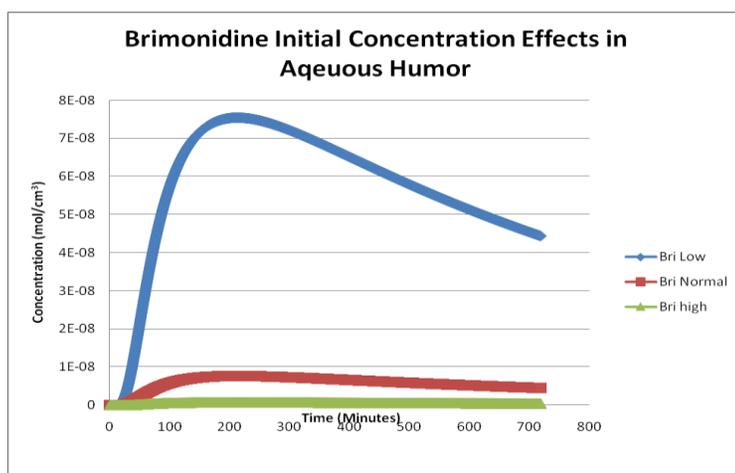


Figure 9: Change in concentration of Brimonidine at the aqueous humor boundary with variable initial concentration

Notice that in Figure 9, each graph has the same shape but the peak concentration varies when changing the initial concentration.

In a number of trials, the model returned unexpected results. All of these results were attributed to incorrect values for various parameters. Initially, the reaction rate of each drug was entered as a positive value. In other words, the drugs were being produced in the eye, rather than degraded. Later in our trials, we were still getting unexpected results. We discovered that the value for diffusivity in the stroma was reported in the literature as 10^{-7} cm^2/s , yet our results

would not match experimental data unless we used a significantly faster diffusion rate (10^{-5} cm^2/s). We presume that the reported value is incorrect.

One way to increase the amount of time that there is a non-zero concentration of Timolol in the aqueous humor is to delay the release of the drug from the eye drop. We wanted to model a delayed-release drug to observe the effect on aqueous humor concentration. First, we ran the simulation as it originally was, and recorded the concentration of Timolol at the bottom of the contact lens. We fit the concentration profile with a mathematical function. We made the assumption that, if the drug were delayed-release, it would be released at a lower, but constant concentration for some period of time before decaying, which would be described by the same function. We created a data file containing an artificial concentration profile that was constant at $\frac{1}{2}$ our initial concentration for 1 hour, and then decayed as expected, and imported this into COMSOL. Assuming that this took into account the action in the contact, we deleted the top sub-domain of our model, and set this concentration function as the boundary condition for the top of the tear film. Figure 10 shows the result. With this model, it takes a long time for the drug to build up in the aqueous humor. However, Timolol buildup is more gradual, and once it begins to buildup, it does not decay to zero during our time frame.

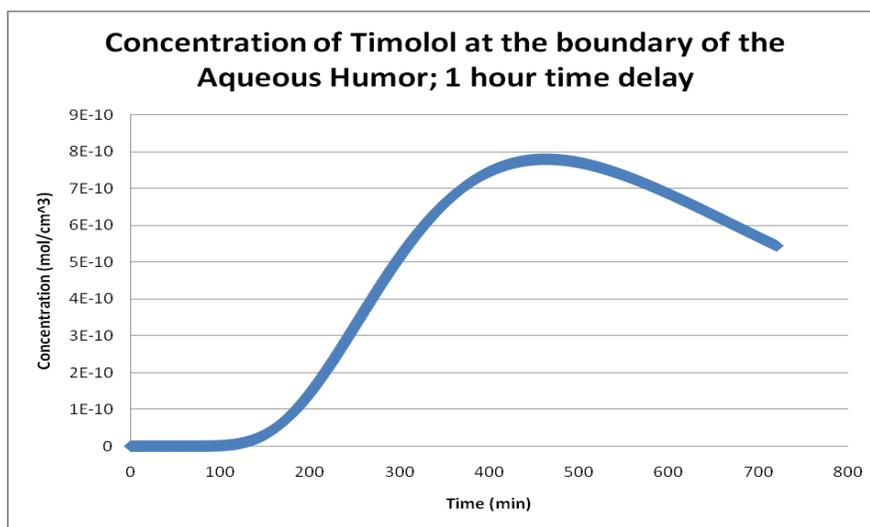


Figure 10: Concentration of timolol at the boundary of the aqueous humor when the drug is simulated to be time-released for one hour.

Notice that in Figure 10 that we have a delayed uptake in the drug. Although, with this delayed release the concentraion of the drug after reaching its peaks takes longer to decrease.

We considered simulating the effect of blinking on the concentration profile. However, Jonathan Cohan et al simulated blinking in a model of oxygen diffusion in the eye, and found that there was no effect on the results (28). With this in mind, we omitted this complication.

In an effort to make our model more realistic we modeled the same problem but with a curved geometry. We noticed that we get similar results. There graphs of concentration are similar but they do not exactly correspond because the area in the curved geometry is greater than that of the area in the rectangular geometry. The other factor is that when the simulation is run with the curved geometry there is a build-up of drug in the right corner because the drug in the lens has nowhere to go, since the bottom boundary is insulated. Thus, between the two geometries we have the same shape of a curve and this proves that our assumption to have the geometry rectangular is proved.

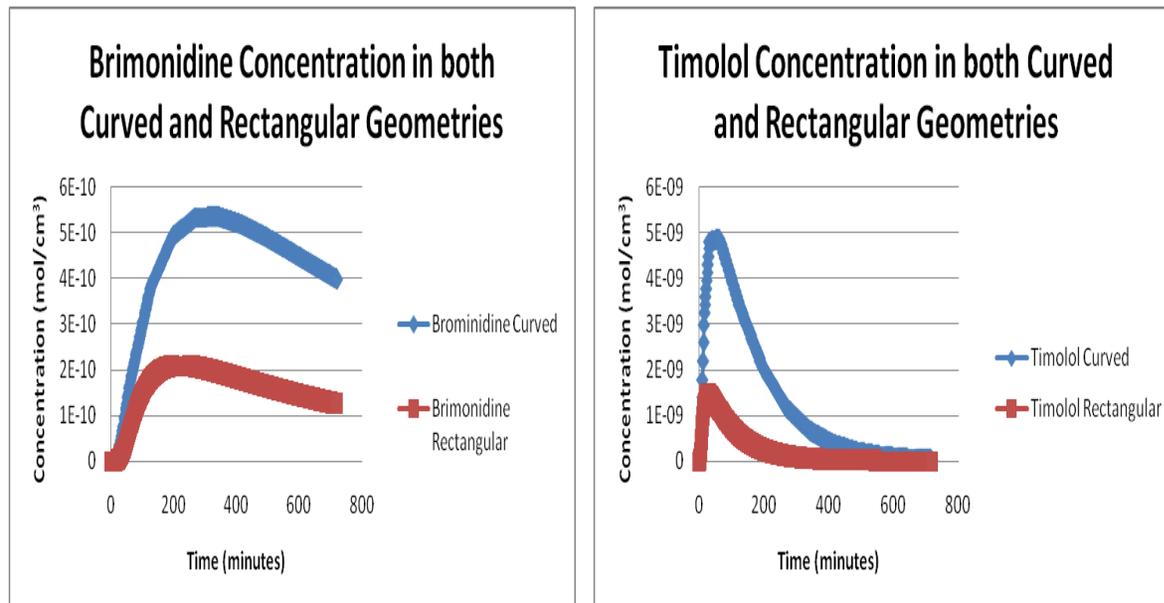


Figure 11. The graph to the left shows the Brimonidine Concentration at the Aqueous Humor and Stroma Interface over time. The graph to the right shows the same thing but for Timolol.

Notice in Figure 11 that both graphs at the same point in the geometry show similar shapes but different concentrations.

Conclusion and Design Recommendations

We developed a model that accurately models the diffusion of two drugs through the outer layers of the eye and into the aqueous humor, and used this to explore the feasibility of

using contact lenses for drug delivery. We discovered that, given the same initial concentration dosage of drug, a contact lens can maintain an acceptable concentration of drug in the aqueous humor for longer than an eye drop can. The length of time that the contact lens is effective can be further improved by delaying the release of the drugs. If it were possible to modify the Timolol to diffuse more slowly through the stroma, drug delivery would also be improved. Currently however, there always is at least one drug in the aqueous humor, so there is some lowering of IOP for the full 12 hours. It is possible that the contact lens needs to be made thicker to be able to hold enough drug. If the lens becomes too big to comfortably wear, then it is not useful for vision correction or glaucoma treatment. Thus, lens size is a limiting factor on feasibility. Another potential limitation is cost. Currently, the contact lenses are one-time use. Continued use of these contact lenses could become expensive, especially if the lenses are costly to manufacture. A solution to this would be to design the lenses to be “reloadable”. If the lenses could be soaked in solution to re-absorb drug, then the contact could be reusable.

There are both advantages and disadvantages to using our method. One obvious advantage is the ease of use. An eye drop user must remember to administer a dose at specific times during the day. Because of the rapid decay of drug concentration after a topical dose, eye drops must be applied many times a day. It is often difficult to self-administer eye drops, and the exact amount of drug administered is never known. A contact lens could be applied in the morning, and left all day. The dosage is more reliable, and need not be reapplied many times during the day. As we have shown, there will be a more gradual rise and fall of drug concentration, avoiding the sudden spike and decline in concentration caused by an eye drop.

Our method of treatment also has its disadvantages. There is potentially a danger of mistaking normal contact lenses with medicated ones, administering an unintentional dose. As previously mentioned, the cost of a contact lens treatment could be significantly higher than a

topical treatment. Furthermore, as mentioned, the thickness of these lenses could continue to be an issue. This brings up other issues, such as oxygen and moisture diffusion into the eye. Overall, we would recommend further study before considering this concept feasible for production and use.

Appendix A.

Governing Equation

$$\frac{\partial c_A}{\partial t} = D_{AB} \left(\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial c_A}{\partial r} \right) + \frac{\partial^2 c}{\partial z^2} \right) - R_A$$

Boundary conditions:

All boundaries are insulated, EXCEPT for the very bottom of the aqueous humor region, which is semi-infinite (concentration = 0).

Table 2. The values we used for each parameter (Datta). The initial concentration was converted from what is used in a typical eye drop of Combigan (13).

Parameter Name	Value for Timolol Diffusion	Value for Brimonidine Diffusion
Initial Concentration in contact lens (mol/cm ³)	1.57225 *10 ⁻⁵	4.52243*10 ⁻⁶
Diffusivity in eye drop	9.9 * 10 ⁻⁹	1 * 10 ⁻⁹
Diffusivity in tear film	5 * 10 ⁻⁵	1 * 10 ⁻⁵
Diffusivity in epithelium	6.022*10 ⁻⁷	1*10 ⁻⁷
Diffusivity in Stroma	8.72*10 ⁻⁷	1*10 ⁻⁷
Diffusivity in aqueous humor	5*10 ⁻⁵	1*10 ⁻⁵
Reaction rate in the Tear film	-1*10 ⁻⁴ * c	-1*10 ⁻⁴ * c
Reaction rate in the aqueous humor	-0.003*c	-0.001*c

Appendix B

To implement this problem into COMSOL 3.3 we set up the problem to solve for two diffusion problems at the same time. We used axis-symmetric for the geometry. We used a transient analysis. In solver parameters, the time we solved for is from 0 to 43200 seconds with a max 10 second time step and minimum of 0.0010 seconds. The relative tolerance is 0.001 and the absolute tolerance is 0.00010. These tolerances let COMSOL know how close convergence values to allow. We used the Direct (UMFPACK) linear system solver.

Mesh

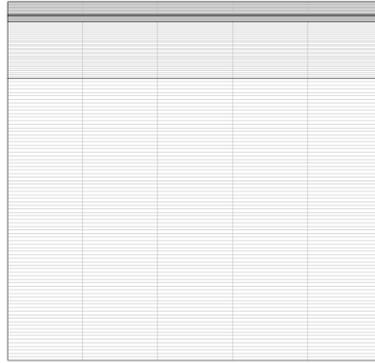


Figure 12. The mesh that we used for solving the problem.

We used a rectangular element for the mesh. Based upon our mesh convergence analysis we determined that we needed 6400 elements to maintain accuracy.

Table 3: Mesh properties. All regions have 5 nodes in the r direction. Below are the numbers of nodes in the z direction for each region

region	Normal (400 nodes)	Fine (800 nodes)	Finer (1600 nodes)	Finest (3200 nodes)	Finest (6400 nodes)	12800 Nodes
Contact	10	20	40	80	160	320
Tear Film	5	10	20	40	80	160
Epithelium	10	20	40	80	160	320
Stroma	15	30	60	120	240	480
Aqueous Humor	40	80	160	320	640	1280

Appendix C

COMSOL representation of drug concentration in the eye after a period of 12 hours.

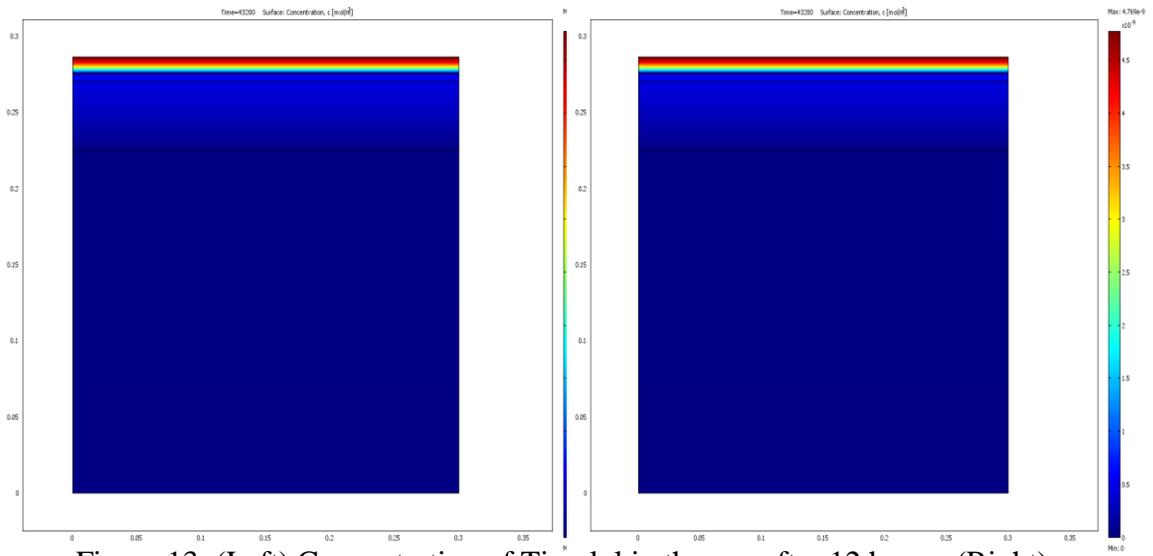


Figure 13: (Left) Concentration of Timolol in the eye after 12 hours. (Right) Concentration of Brimonidine in the eye after 12 hours

Sensitivity Analysis Results

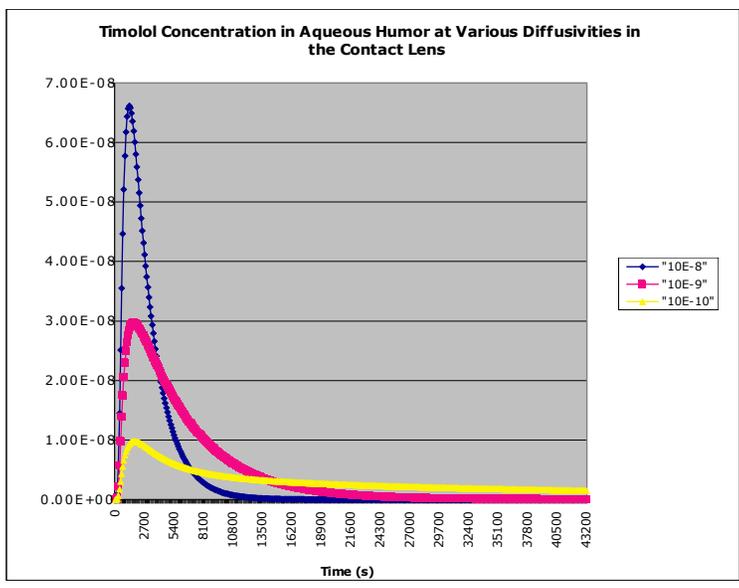


Figure 14. Timolol concentration in the aqueous humor region for diffusivities $9.9E-8$, $9.9E-9$, $9.9E-10$ cm^2/s of in the contact lens region.

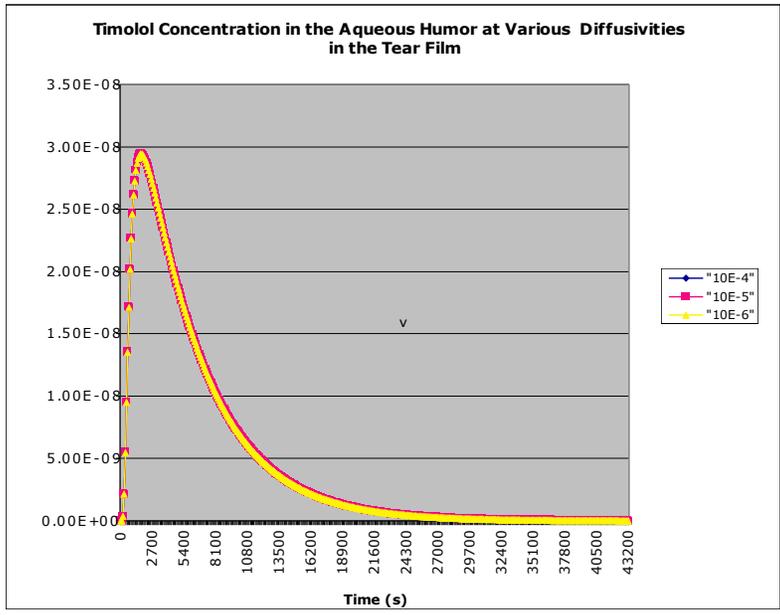


Figure 15. Timolol concentration in the aqueous humor region for diffusivities $5.0E-4$, $5.0E-5$, $5.5E-6$ cm^2/s of in the tear film region

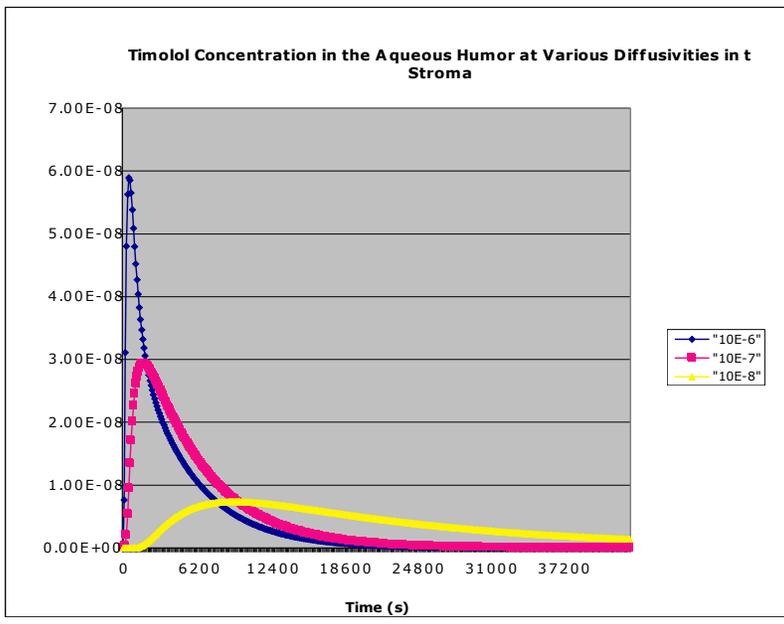


Figure 16. Timolol concentration in the aqueous humor region for diffusivities $8.72E-6$, $8.72E-7$, $8.72E-8$ cm^2/s of in the stroma region

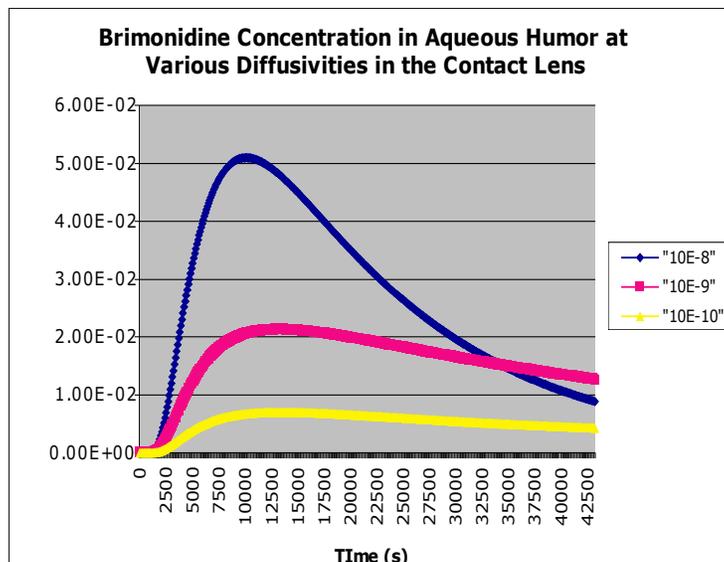


Figure 17. Brimonidine concentration in the aqueous humor region for diffusivities 1.0E-8, 1.0E-9, 1.0E-10 cm²/s of in the contact lens region.

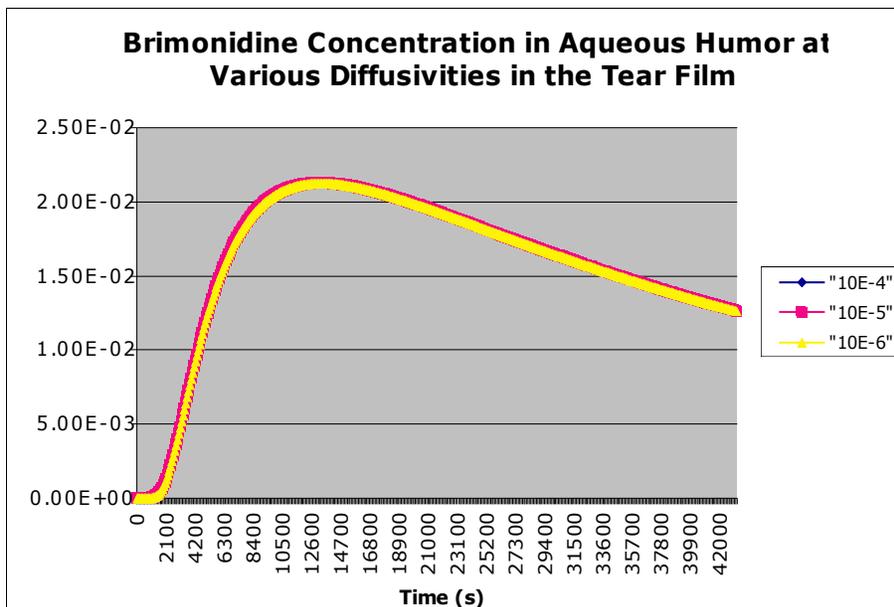


Figure 18. Brimonidine concentration in the aqueous humor region for diffusivities 1.0E-4, 1.0E-5, 1.0E-6 cm²/s of in the tear film region.

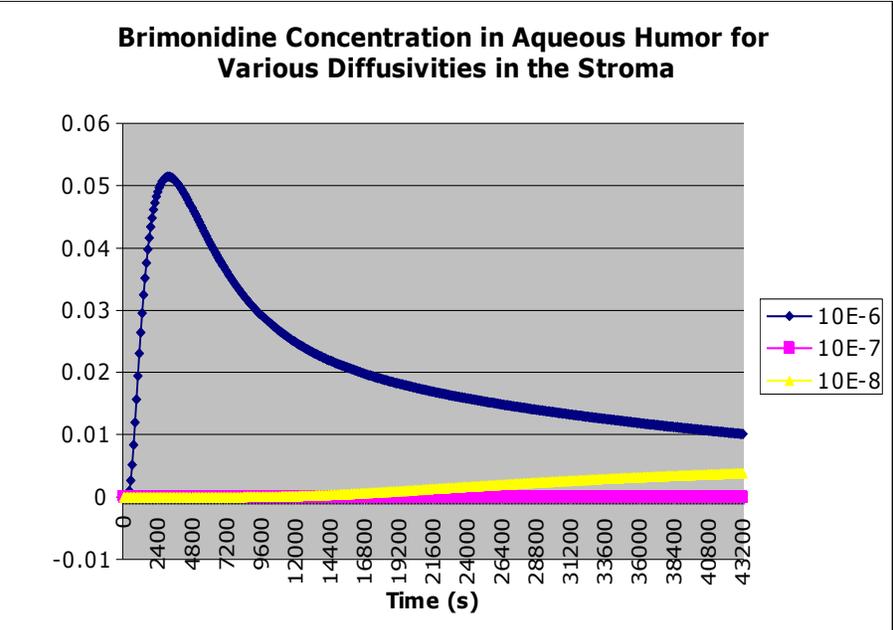


Figure 19. Brimonidine concentration in the aqueous humor region for diffusivities 1.0E-6, 1.0E-7, 1.0E-8 cm²/s of in the stroma region.

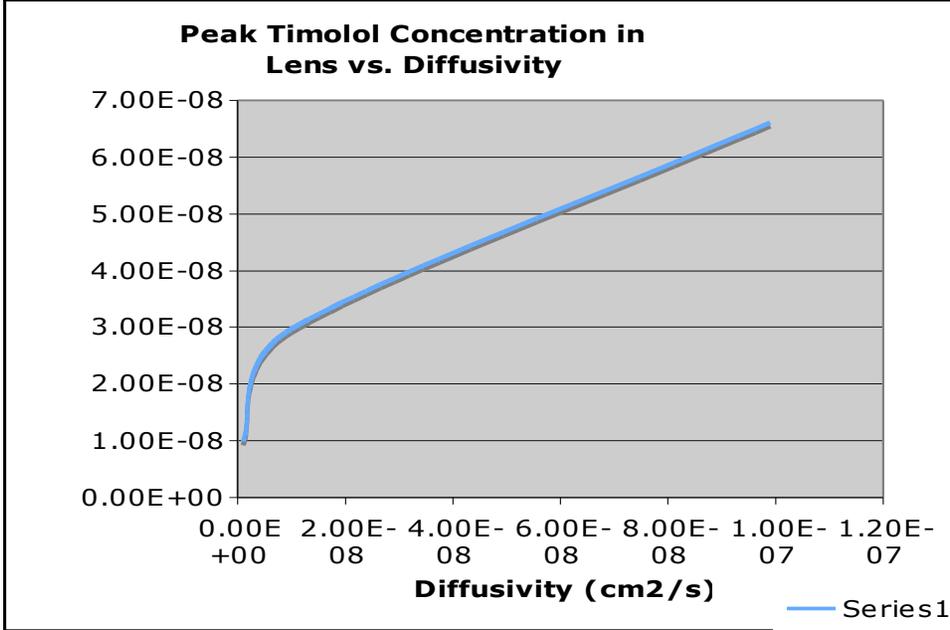


Figure 20: Plot of the peak Timolol concentration in the aqueous humor vs. varying drug diffusivity in the contact lens layer.

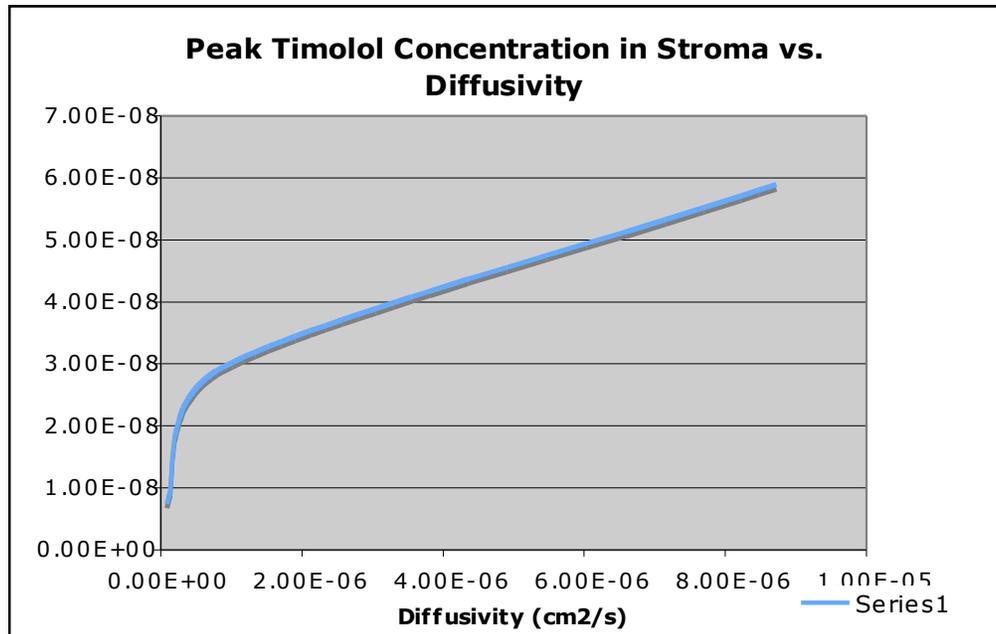


Figure 21: Plot of the peak Timolol concentration in the aqueous humor vs. varying drug diffusivity in the stroma layer.

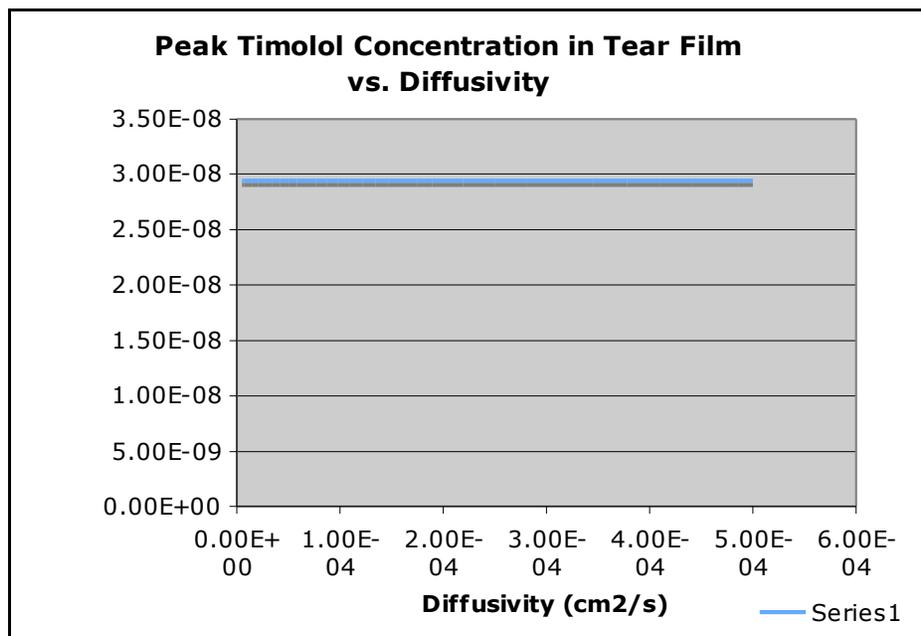


Figure 22: Plot of the peak Timolol concentration in the aqueous humor vs. varying drug diffusivity in the tear film layer.

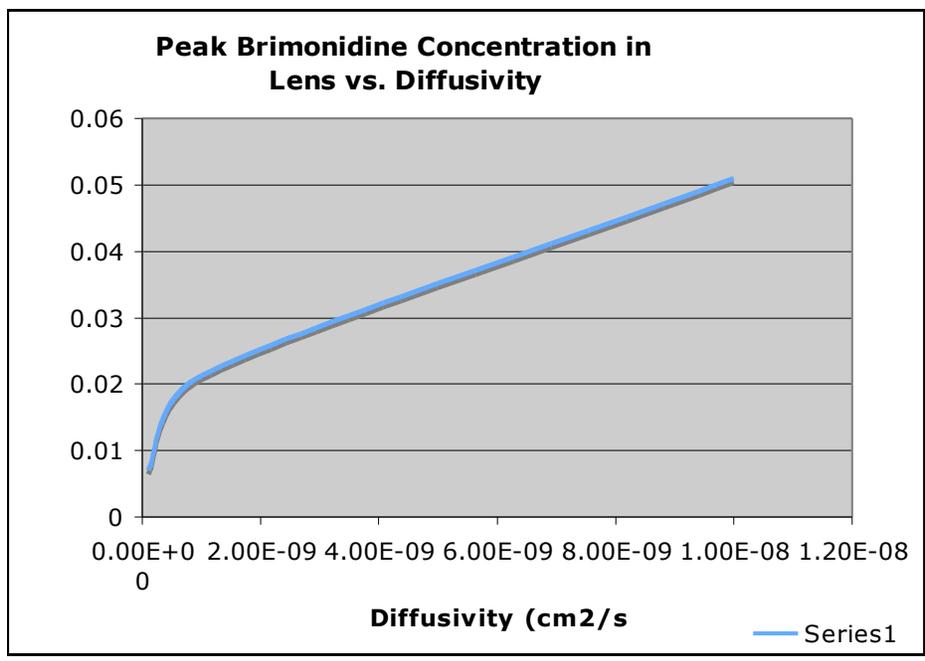


Figure 23: Plot of the peak Brimonidine concentration in the aqueous humor vs. varying drug diffusivity in the contact lens layer

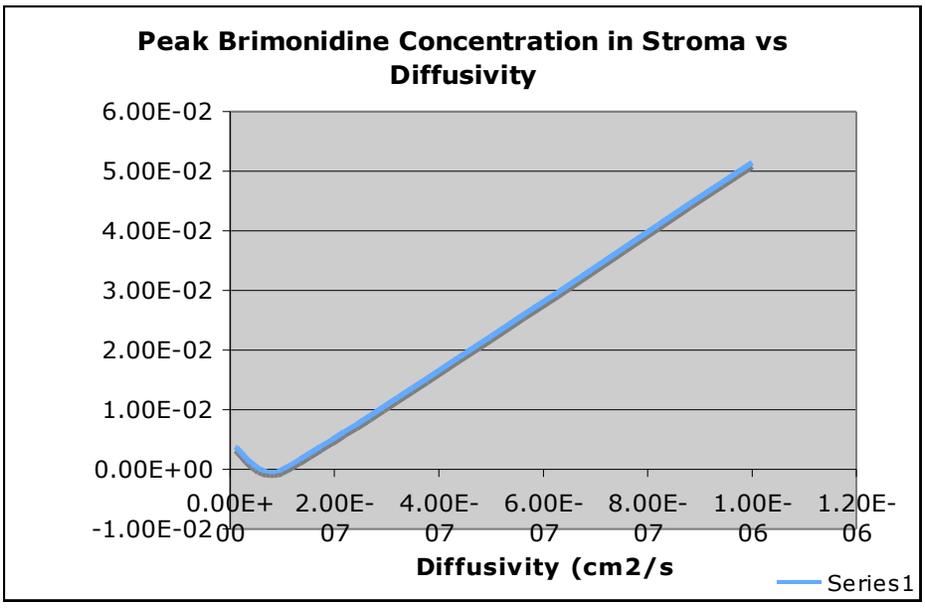


Figure 24: Plot of the peak Brimonidine concentration in the aqueous humor vs. varying drug diffusivity in the stroma layer.

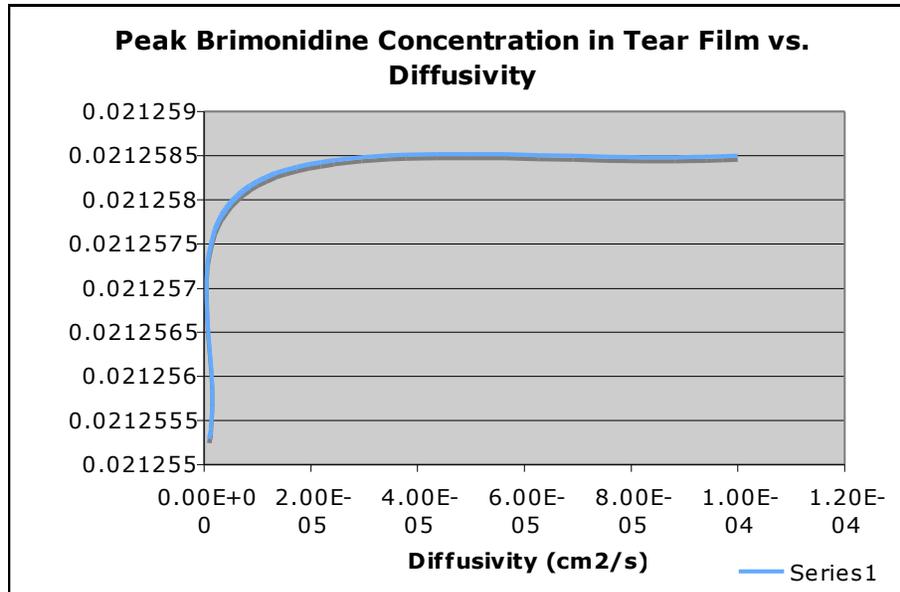


Figure 25: Plot of the peak Brimonidine concentration in the aqueous humor vs. varying drug diffusivity in the tear film layer.

Appendix D

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