

Final Project:

A Study of the Role of Therapeutic Contact Lenses in Drug Delivery

BEE 453:  
Computer-Aided Engineering:  
Applications to Biomedical Processes

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## A Study of the Role of Therapeutic Contact Lenses in Drug Delivery

### 1.0 Executive Summary

Glaucoma is an optical condition caused by pressure build up in the eye and is the leading cause of blindness. Current methods to treat glaucoma include medicated eye drops and oral medication, which are both inefficient methods of administration. Most of the medication in eye drops does not reach the target tissue. In addition, when taken orally, much of the drug circulates in the bloodstream instead of reaching the eye. This is a potential problem since drugs used to treat glaucoma, such as timolol maleate, are also prescribed to elevate hypertension. To avoid possible side effects, researchers have developed a novel method of drug delivery that involves enclosing the drug in the contact lens to be worn directly over the eye. The drug-encapsulated contact lens can deliver the drug to the target tissue more effectively.

This paper focuses on the drug delivery of the therapeutic contact lens in the treatment of glaucoma using a computer-simulated model created by FIDAP, a computational fluid dynamic software. The problem is modeled as mass transfer of timolol maleate over four layers (lens, tear, cornea, and aqueous humor) of an axis-symmetric cylindrical slab. Results show that with an initial concentration of 7 mg/g contact lens in the contact lens, the minimum effective concentration of 1.8  $\mu\text{g/mL}$  is achieved in the aqueous humor layer after 45 minutes. The contact lens continues to deliver the drug into the eye at above this concentration for another 75 minutes before dropping below the minimum effective concentration at 1.5 hours. Sensitivity analysis shows that cornea diffusivity is the most important parameter in the solution.

## 2.0 Introduction

Glaucoma is the leading cause of blindness in the United States (1). According to the Center for Disease Control and Prevention, over 8.7 million doctors' visits a year are glaucoma-related. Glaucoma refers to a group of diseases that gradually cause blindness. In the most common case of glaucoma, the trabecular network or the filtering drain in the eye is clogged. Normally, the aqueous humor, the fluid that nourishes the eye and keeps the cornea hydrated, drains out of the eye via this network. Due to the blockage, the aqueous humor cannot exit the eye as fast as the rate the ciliary body produces the fluid. This leads to fluid pressure build up and can damage the optic nerve in the eye, causing blindness (2).

Fortunately, with the proper treatment, blindness can be prevented in 90% of the cases (3). Conventional treatments included medicated eye drops, medication in pill form, laser and traditional surgery, or a combination of these methods. Recent studies show that therapeutic contact lens is another possible effective method of treating glaucoma (4). This study focuses on the use of hydrogel contact lens that contains encapsulated nanoparticles of a drug called timolol maleate as a treatment of glaucoma. Timolol maleate lowers the fluid pressure in the eye by reducing the production of the aqueous humor by the ciliary body (5). Thus, as long as the drug enters the aqueous humor, it will be able to act on the ciliary body. Drug delivery via therapeutic contact lens is more efficient and preferable than the eye drops because the drug is directed to the aqueous humors instead of being absorbed by other surrounding tissues of the eye (12).

## 3.0 Objectives

The objective of this paper is to model the drug delivery of timolol maleate from a hydrogel contact lens into the aqueous humor of the eye in the treatment of glaucoma. To simulate the mass transfer of the drug from the contact lens, through the tear layer, the cornea, into the aqueous humor, a computational fluid dynamics software, FIDAP, is utilized. The geometry is modeled and meshed using GAMBIT, a preprocessor for FIDAP. From this computational model, FIDAP is used to solve the mass transfer problem using a finite element method. The computational model is used to determine whether the contact lens method could deliver the minimum effective concentration needed in the aqueous humor. In addition, the effectiveness of this novel delivery method is compared with the traditional eye drop method of delivery.

## 4.0 Project Schematic:

The contact lens poly(HEMA/200MAA), is a cross-linked polymer capable of encapsulating drug molecules such as timolol maleate, within its porous matrix. Timolol maleate is released from the pores when the matrix swells as it is exposed to the eye. The drug is controlled-released and delivered to the affected site via diffusion through the different layers of the eye. From the cornea of the eye, timolol maleate reaches the aqueous humor to help reduce fluid produced by the eye and drain fluids already present in the eye. The overall effect is the ease of pressure build up in glaucoma patients.

### 4.1 Assumptions:

- There is homogenous distribution of nanoparticles (drug packets) in contact lens.
- There is axis-symmetric dimensional drug flow.

- There is no mass flow from the contact lens to the eyelid.
- There is negligible contact resistance between each interface; ie. disregard  $K^*$ , the partition coefficient.
- Constant properties in all layers.
- The diffusivity value for the cornea is the weighted average of the diffusivity values of the two layers composing the cornea: the epithelium and the stroma.
- The elimination of the drug in the tear and in the aqueous humor is close to the elimination (drug reaction) rate in water.
- Neglect evaporation of water from the eye and the effect of blinking.

## 4.2 Geometry

The model is developed by considering the mass diffusion of timolol maleate. A four-layered axis-symmetric slab is used to simplify the geometry of the problem. The slab consists of four layers: the contact lens (0.0105 cm) (6), the film of tear ( $7 \times 10^{-7}$  cm) (7), the cornea (0.05 cm) (8), and the aqueous humor (0.225 cm) (9). The aqueous humor layer is modeled as semi-infinite and thus the flux at the end of the aqueous humor layer. Figure 1 shows the model schematic with the labeled entity names used in FIDAP.

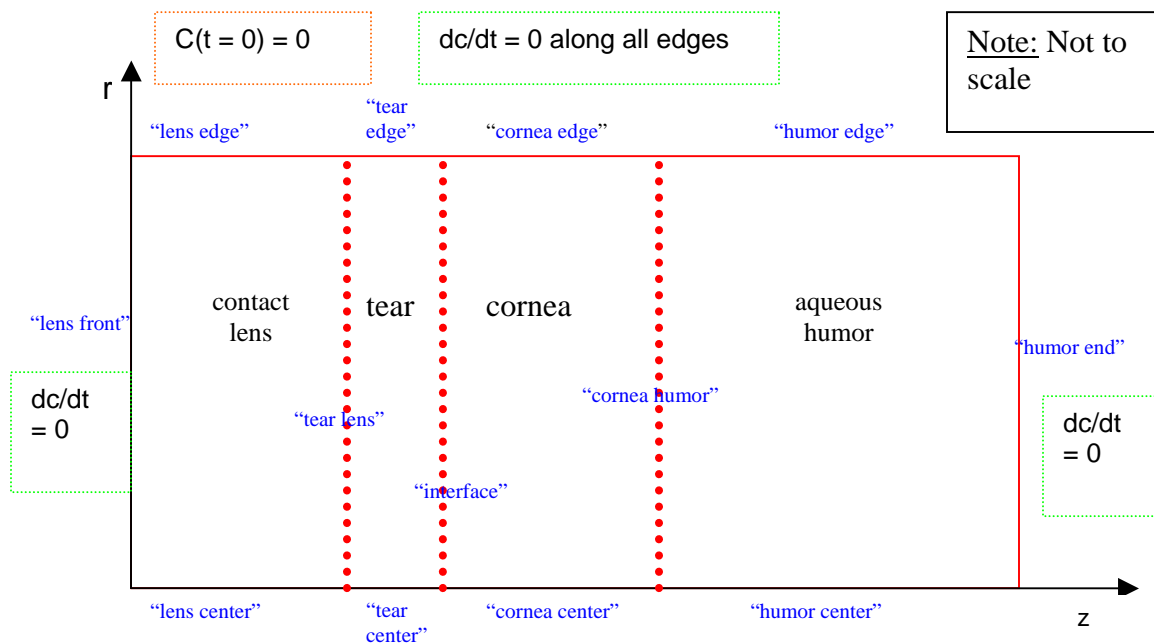


Figure 1: Model schematic with labeled layers, entity names, and boundary and initial conditions.

## 5.0 Solution Validation

Figures 2 and 3 show two solutions obtained from two different meshes for a node on the cornea-humor interface. Both graphs show a similar shape (initial step increase followed by a slightly slower decline to zero), and the highest concentrations of the graphs is within 10%

difference (6.01%<sup>1</sup>) of one another. This shows that our solution is not dependent on mesh size. The crude mesh is used in all subsequent analyses.

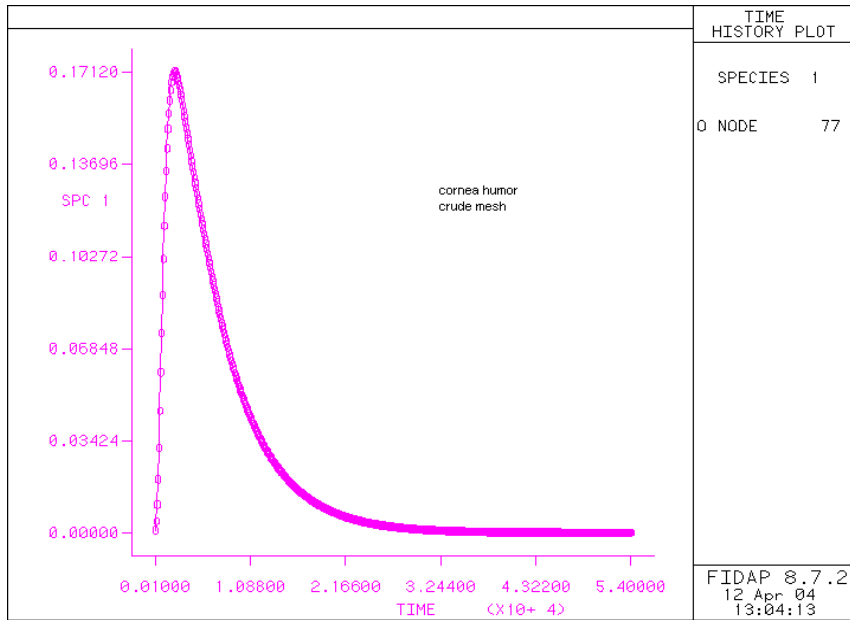


Figure 2: Graph for cornea-humor interface for a cruder mesh (total time = 15 hrs = 54000s).

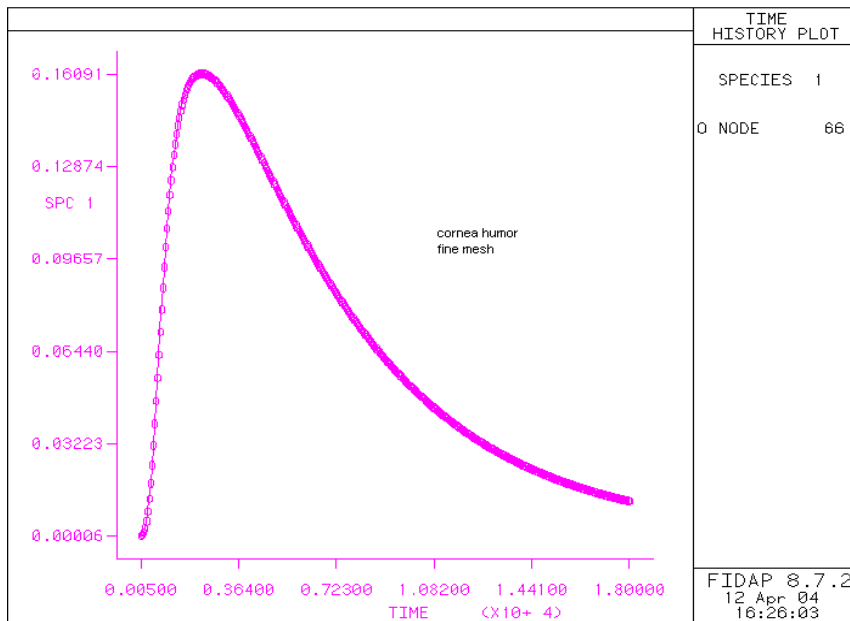
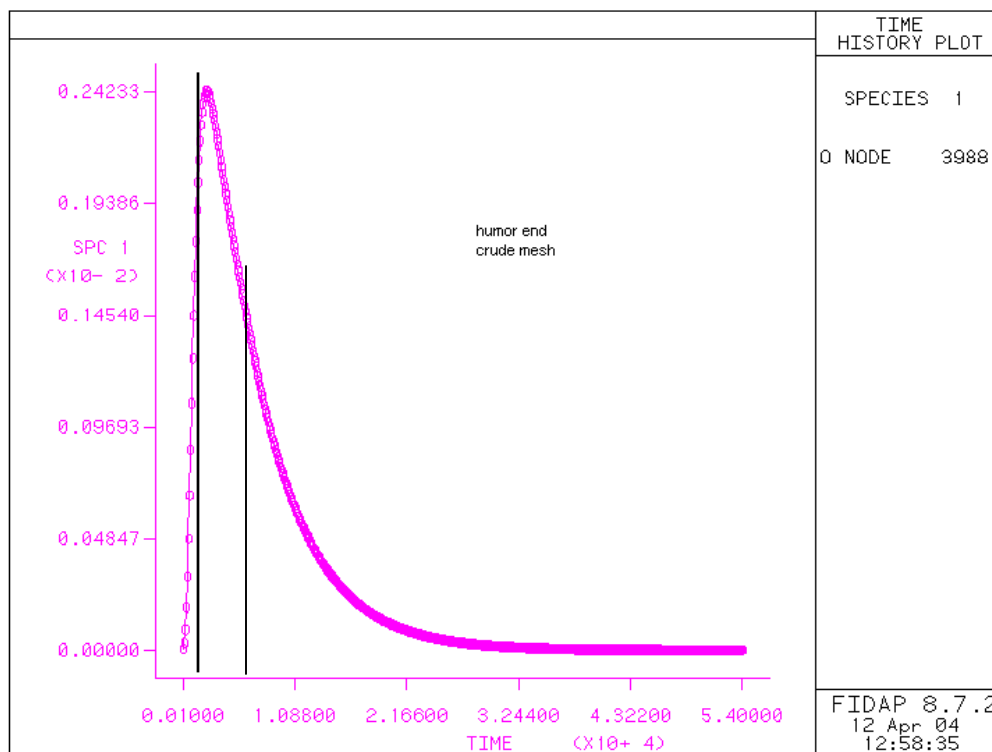


Figure 3: Graph at cornea-humor interface for a finer mesh (total time = 5 hrs = 18000s).

## 6.0 Results and Discussion

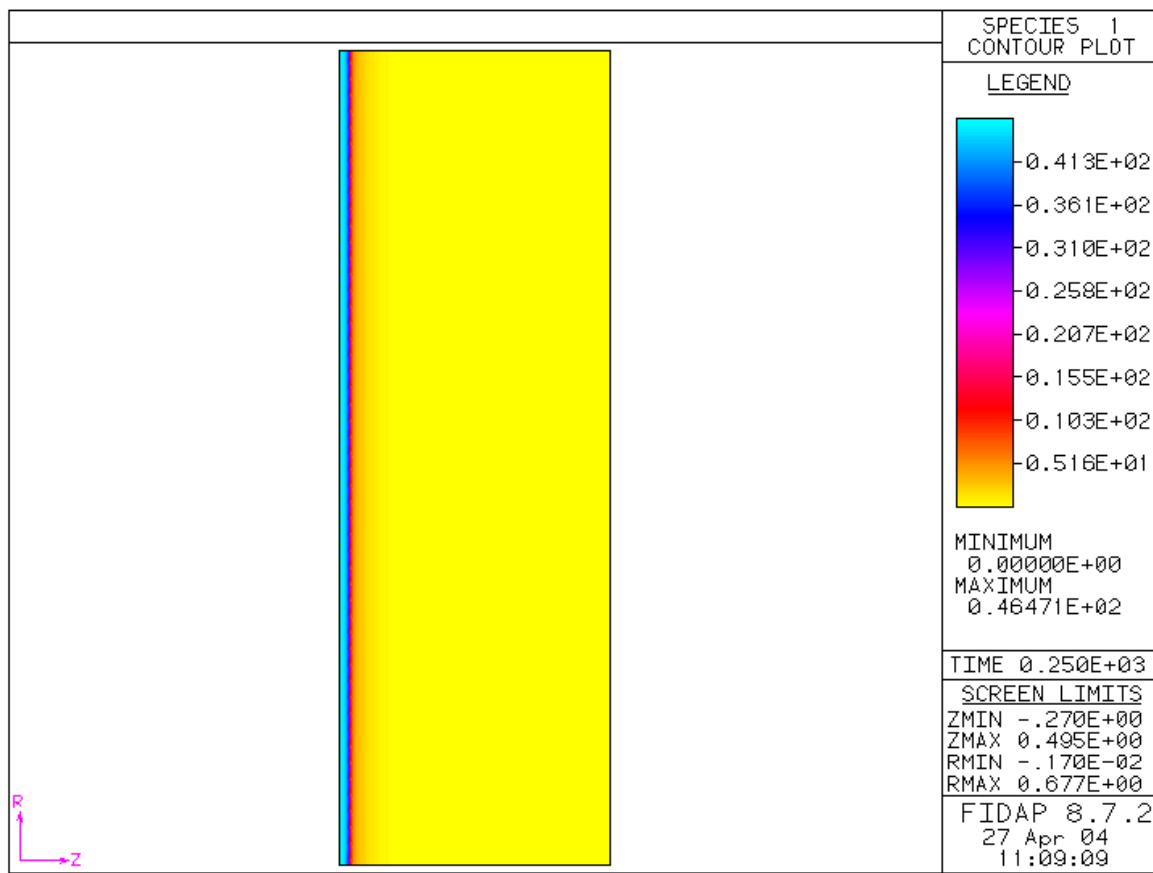
$$^1 \text{ calculation: \% difference} = \frac{|\text{crude} - \text{fine}|}{\text{crude}} = \frac{|0.17120 - 0.16091|}{0.17120} = 6.01\%$$

The objective of this project is to design a contact lens that can deliver a minimum of 1.8  $\mu\text{g}/\text{mL}$  of timolol maleate into the aqueous humor. This is the minimum effective concentration necessary before the interior fluid pressure starts to decrease. FIDAP calculations with the crude mesh (Figure 4) shows that the maximum diffused concentration is 2.4233  $\mu\text{g}/\text{mL}$  of timolol maleate in the aqueous humor. This concentration is attained after 45 minutes of continuous application. In addition, the contact lens can be removed after drug concentration has decreased below 1.8  $\mu\text{g}/\text{mL}$ , which occurs at 1.5 hours after application. Thus, the contact lens can deliver an effective amount of timolol maleate with greater efficiency than eye drops. Eye drops require several applications per day, with much of the drug lost through tear flow..



**Figure 4:** plot of the concentration at the end of aqueous humor layer by using the crude mesh.

Two contour graphs are produced at two different times within the 20-hour run-time period. The contour graph at 7 hours (Figure 5) shows that there is a high amount of drug concentrated at the outermost layers (left side of the graph) and a low amount in the aqueous humor layer. This dispersed concentration is due to the large difference between the diffusion rates in the lens and tear layers (3 orders of magnitude). Although it cannot be seen at this magnification, most of the drug has diffused out of the lens and concentrated at the cornea due to the low diffusivity constant of the cornea layer ( $5.429 \times 10^{-7} \text{ cm}^2/\text{s}$ ).



**Figure 5: A contour representation of the axis-symmetric model at 7hrs of total reaction time.**

However, at 15 hours (Figure 6), the contour graph showed that most of the drug has been eliminated and the concentration has dropped significantly. The concentration in Figure 6 is much lower than in Figure 5. However, timolol maleate concentration in the aqueous humor is more evenly distributed than Figure 5.. These two figures records the diffusion process of the drug from the contact lens into the aqueous humor.

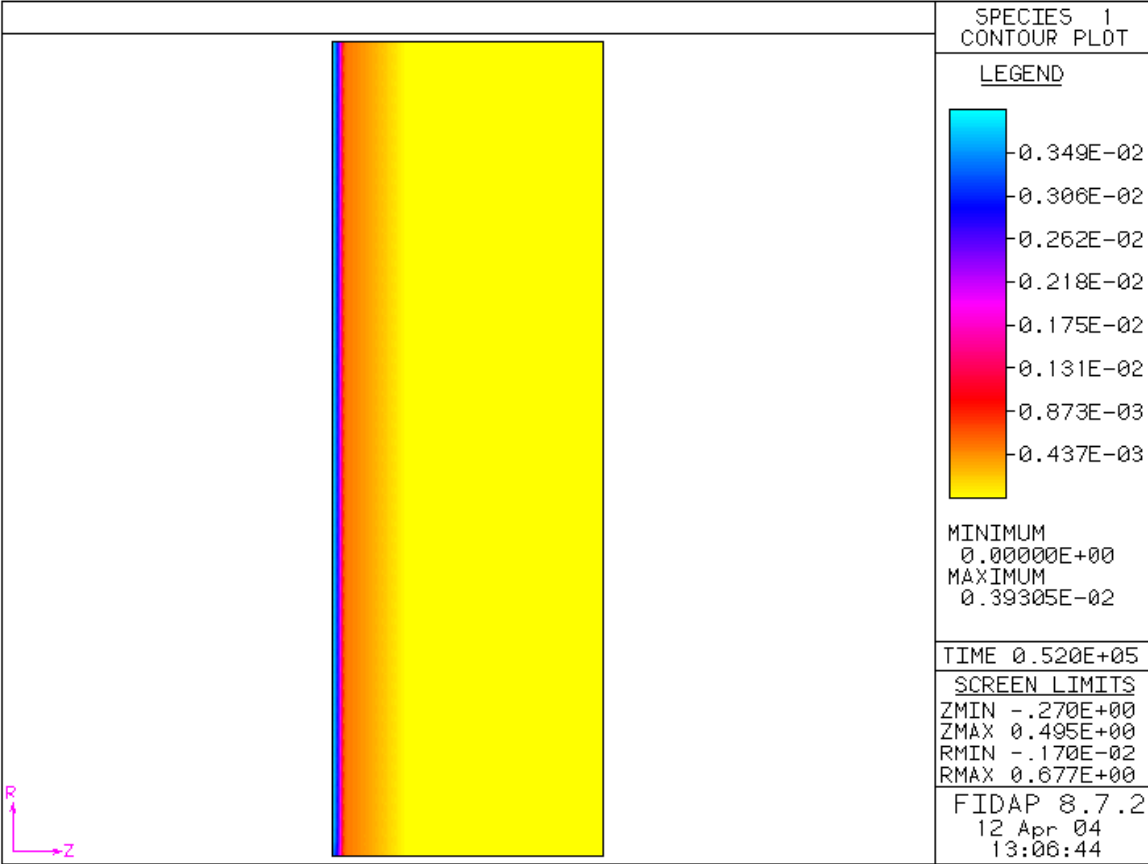
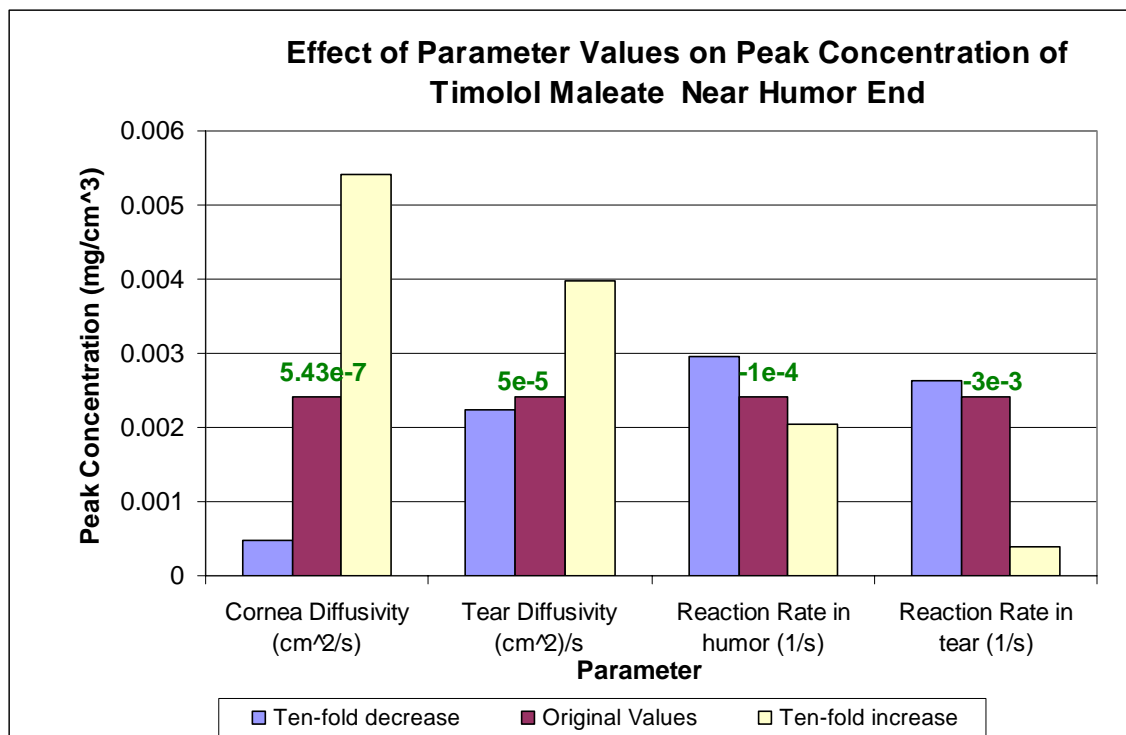


Figure 6: A contour representation of the axis-symmetric model at 15 hrs of total reaction time.

**7.0 Sensitivity Analysis**

In order to determine the effects of various properties on the solution, the values for the cornea diffusivity, tear diffusivity, elimination rate in humor, elimination rate in tear, and initial concentration of timolol maleate are varied. The original diffusivity and reaction rate constants are both decreased and increased by a magnitude of 10. The initial concentration of the drug is varied with a lower and higher value. The effect of this change in parameters on the peak concentration is observed for the cornea-humor interface and near the end of humor.





**Figure 7: Effect of ten-fold increase and decrease of parameter values on peak concentration of timolol maleate near end of the aqueous humor layer. The original values are shown in green.**

The varying of the parameters on the peak concentration show a similar trend in both the cornea-humor interface and near the end of the aqueous humor. Therefore, the analysis of the each of the parameters is only done on the concentration change in the cornea-humor interface (for the graph on the cornea-humor interface, refer to Figure C3 in the appendix). The general relationship is that an increase in diffusivity values increases the peak concentration, while an increase in elimination rates decreases the amount of drug that can reach the end of the aqueous humor.

### 7.1 Cornea diffusivity

The diffusivity coefficient in the cornea layer is chosen in our sensitivity analysis because of the difficulty in obtaining one consistent value for the cornea. The cornea layer is actually made up of several different layers, primarily with the stroma layer (diffusivity =  $6.022 \times 10^{-7}$  cm<sup>2</sup>/s) comprising 90% of total corneal thickness and the epithelial layer (diffusivity =  $8.72 \times 10^{-9}$  cm<sup>2</sup>/s) comprising 10%. The weighted average diffusivity value  $5.43 \times 10^{-7}$  cm<sup>2</sup>/s is used for our model.

From the figure, it can be seen that cornea diffusivity is an important factor in the solution. While all of the parameters are changed by the same order of magnitude, the change in cornea diffusivity has the greatest effect on the peak concentration. Specifically, when the cornea diffusivity values are plotted on a logarithmic scale, it shows a positive linear relationship with the concentration, as seen in figures C1 and C2.

The results from this sensitivity analysis suggest that in the GAMBIT model, the cornea layer should have been treated as two separate layers (an epithelial and a stoma layer) with their respective diffusivity values for more accurate results.

## 7.2 Tear diffusivity

The diffusivity of the drug in tear is assumed to be the same as the diffusivity of the drug in water (diffusivity =  $5 \times 10^{-5}$  cm<sup>2</sup>/s), so sensitivity analysis is done to see if this was a valid assumption. In the original solution, the graph peaked around 3300s at a concentration of 0.17120 mg/mL at the cornea-humor interface. When tear diffusivity is lowered, the graph reaches a maximum slightly faster, at 2900 s, with a concentration of 0.15783 mg/mL. There is a 7.81% difference in the maximum concentration achieved. Similarly, there is a 7.80% difference in the maximum concentration at the end of the humor layer when tear diffusivity is changed. This shows that the final solution is not very sensitive to changes in the value for tear diffusivity. However, when the tear diffusivity values is increased by a factor of ten, the peak concentration increased by 64%. The assumption that the drug diffusivity in the tear is the same as that in the water, is only useful if the actual diffusivity value in the tear is lower than the drug diffusivity in water.

## 7.3 Drug elimination rate in humor

The other reaction term in our drug concentration model is the rate of elimination of the drug in the aqueous humor layer. Figure 7 shows a reasonable decrease in peak concentration as elimination rate increases. Decreasing and increasing the elimination rate by ten-fold, resulted in a 21.4% and 18.5% difference in peak concentration respectively. This suggests that the solution is highly sensitive to the rate of drug elimination in the humor.

## 7.4 Drug elimination rate in tear

The original solution at the cornea-humor interface with  $K = -3 \times 10^{-3}$  s<sup>-1</sup>. It is evident from figure 7 that the ten-fold increase in the reaction rate result in a sharp decrease by 68.3% in peak concentration. Decreasing the rate ten-fold resulted in an 8.2% difference in peak concentration. It can be seen from the difference that the rate of drug elimination in tear is crucial to the final solution, especially when the rate is increased.

## 7.5 Initial concentration

Sensitivity analysis for initial concentration of the drug in the contact lens is done by changing the value from 46.5mg/mL (original) to 40mg/mL and 55mg/ml. The shape of the graphs remains relatively the same, with a 16.2% difference in the maximum concentration at the cornea-humor interface. An increase in initial concentration to 55 mg/mL changes the peak concentration by 10.6%. From Figure 8, it can be concluded that initial concentration has some effect on the final solution. Near the end of the humor, the highest concentration occurs at the original initial concentration value obtained from research papers, which indicates that the optimal initial concentration is used in our solution.

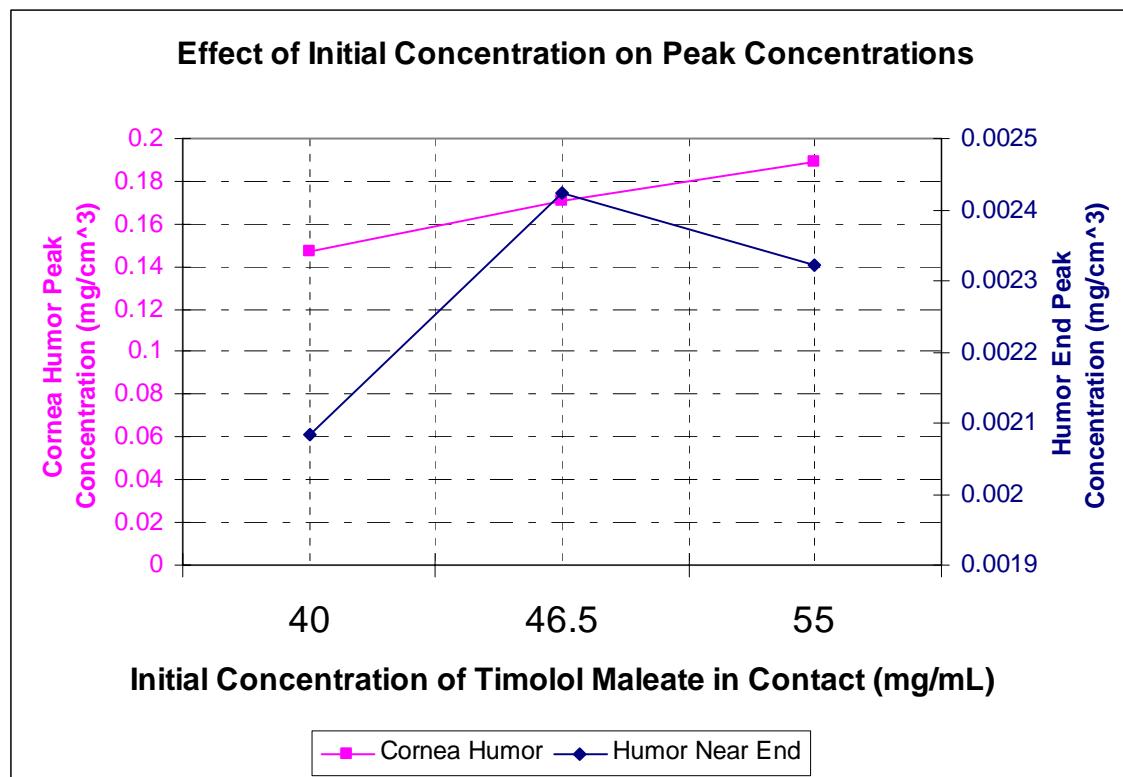


Figure 8: Effect of initial concentration on peak concentration in both the cornea humor interface and the end of humor.

## 8.0 Design Process

There are eight major criteria for design: economic, sustainability, ethnical, social, environmental, manufacturability, health and safety, and political. These criteria can be grouped into three point of views on the product: the manufacturer's perspective, the consumer's perspective, and the waste collector's (post-consumer) perspective. Because these three types of people have different priorities and needs, they place different requirements and limitations on the product. Thus, the ultimate design is a compromise that maximizes the criteria set by all three groups.

### *The Consumer*

Five out of eight design criteria concern the consumer: economic, health and safety, social, ethnical, and political. This is expected because the consumer is the principal consideration in a design – the product is made to solve their problem. In designing contact lenses for drug delivery, anyone can be the target patient. Economically, since there are people in the entire range of economic sectors, the goal is to design a product that is affordable by all. Currently regular disposable daily contact lenses are priced at approximately \$20 per box of 30 lenses and glaucoma eye-drops at approximately \$8-20 per 5 mL of 0.25% timolol maleate (10), (11). Our aim would be to design a product that can be sold at a comparable price. Economically in another sense, customers expect the product to be efficient. Users will expect drug-delivering contact lenses to be effective and easy to wear. It should also be disposable, since glaucoma does not occur so often that a person will need reusable lenses at hand.

Furthermore, single-use lenses will be more convenient for the user. Customers will be looking for something inexpensive that works.

This product does not have many social or ethical concerns, with the possible exception of animal/human testing. However, since it is a drug delivery system, there are several important health and safety considerations. The dosage that each contact lens should contain and how long it can be worn are two of the most crucial, because a concentration that is too high will cause a stinging sensation in the eye and a concentration that is too low will not alleviate the pressure buildup. Ultimately, clinical experiments will need to be carried out to determine these parameters. Whether the product can be used on patients with previous eye surgery or other eye conditions should also be investigated. Finally, children or the elderly might be recommended not to use this product.

### *The Manufacturer*

The manufacturer is mainly concerned with manufacturability, sustainability, economy, and safety. Manufacturability includes various concerns: availability of the necessary components, costs of production, shelf life of product, and required facilities or technologies. Ideally, the product should be made from readily available standardized parts, can be stored for a long time, can be manufactured with existing technologies at accessible facilities, and is inexpensive to produce. Contact lenses for drug delivery is not yet available in the market. However, they have been successfully manufactured at laboratories and experimented on with rabbits. It is very likely that this product will become commercially available in the next ten years.

Economy is a criteria valued by the manufacturer as well because no one would want to sell a product that cannot bring a profit. Related to this is the sustainability of the product: manufacturers want to be assured that the design is one that would not become obsolete for a long time and can adapt new technologies to make it last in the market. Finally, safety is also of importance to manufacturers. Automated plants would be optimal if possible, but if not, safety precautions should be outlined and safety facilities built (for example, fume hoods for volatile hazardous chemicals).

### *The Waste Collector*

After the device has served its purposes, the final recipient of the device will be the waste collector. Again, the product should be made safe for disposal. Since this product is intended to be used by everyday people, it should be made so that it can be treated like normal garbage. We expect that drug-delivering contact lenses will not be a problem in this aspect since normal contact lenses can be disposed of through conventional waste treatment methods. Finally, product biodegradability is also a concern. The materials used to produce the contact lenses should meet environmental standards. In essence, a good design would be one that solves problems without causing any in the process.

## 9.0 Appendix A

### 9.1 Governing Equations

The species equation in cylindrical coordinates is used. There is no convection and no variation in theta direction.

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

A governing equation is needed for each layer since the properties vary for each. In addition, there is an elimination term for the tear and the aqueous humor, which is treated as a zeroth order reaction term in the governing equation. There is no reaction in the lens and the cornea.

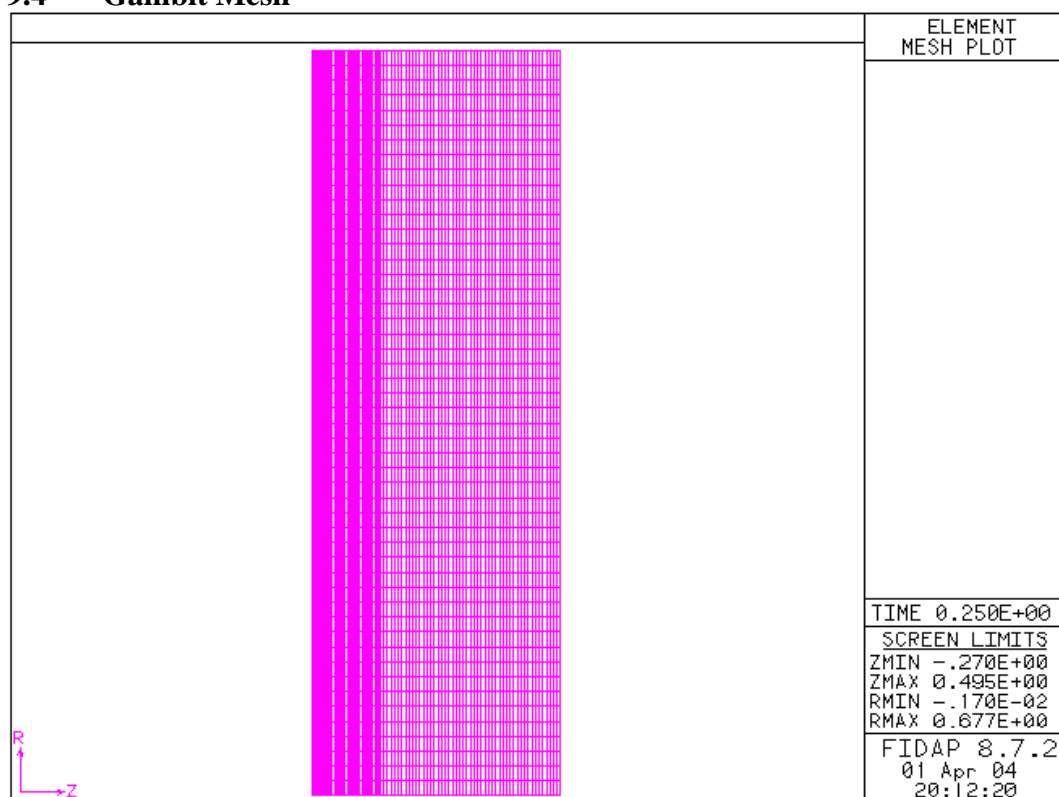
### 9.2 Boundary Conditions

The flux is zero for the following boundaries: “lens center,” “lens front,” “lens edge,” “humor center,” “humor end,” “humor edge,” “cornea edge,” and “cornea center.” These conditions are set because the geometry of the slab has an axis of symmetry along the center and there is no drug leaving the edges or evaporating from the contact lens. Additionally, since the aqueous humor is semi-infinite, the flux and concentration at the “humor end” is zero.

### 9.3 Initial conditions

The initial concentration of the drug in the contact lens is  $46.5 \text{ mg/cm}^3$  (4) and zero for the other three layers.

## 9.4 Gambit Mesh



## 9.5 Input parameters

### Constants Used

Table A1 shows the constants used and where they were obtained. These values were obtained from journal articles and the majority of them were obtained from experiments done on rabbit eyes. Often a range of values was found, usually within the same order of magnitude. In these cases, the average value was taken. In the sensitivity analysis, the effect of this assumption was tested.

**Table A1: A summary of the constants used.**

<u>Description</u>	<u>Location</u>	<u>Value</u>	<u>Units</u>	<u>Obtained from</u>
initial concentration	lens	7	mg/g dry hydrogel	(13)
diffusivity	tear	1.40E+09	cm <sup>2</sup> /s	(14)
diffusivity	cornea	7.35E-07	cm <sup>2</sup> /s	(15), (16)
diffusivity	humor	5E-5	cm <sup>2</sup> /s	(17)
diffusivity	lens	9.9 E -9	cm <sup>2</sup> /s	(18)
reaction rate (elim)	tear	0.18	min <sup>-1</sup>	(18)
reaction rate (absorp)	cornea	0		
reaction rate (elim)	humor	0.32	hr <sup>-1</sup>	(18)
thickness	lens	0.105	mm	(6)
thickness	tear	7	μm	(7)

thickness	cornea	0.5	mm	(8)
thickness	humor	2.25	mm	(9)
diameter	lens	0.675	cm	(6)

### Problem Menu

Axis-symmetric	- we are taking the center of the contact lens to be the axis of symmetry (see Geometry section)
Incompressible	- tears is assumed incompressible (constant density)
Transient	- we are interested in the transient state of the problem
Laminar	- tear flow is laminar (and not turbulent)
Linear	- eliminates second derivative (convective term) in GE
Newtonian	- the fluid is Newtonian (behaves like water).
NoMomentum	- momentum is not considered in the problem. eliminates velocity (and thus convective) terms.
Isothermal	- heat equation is not solved in the problem (assumes constant temperature).
Fixed	- surfaces in geometry are fixed (no free surface).
NoStructural	- includes any entity that is defined as subject to elastic deformation
NoRemeshing	- mesh cannot be changed.
SinglePhase	- flow has only one phase.

### Solutions Menu

SEGR. = 100	-
Relaxation Factor (HYBR)	-

### Time Integration Menu

Time Integration = backward	- uses implicit method ( $t + \Delta t$ ), which is more stable.
No. Time Steps = 400	- solution has fixed number of time steps
Starting Time = 0	- starting time is at 0s
Ending Time = 54000	- ending time is at 7200s (we are modeling the linear portion of drug release; 60% in 2 hours)
Time Increment = 250	- each time increment is 250s
Time Stepping Algorithm FIXED = 1	- variable step integration, DT is time increment for initial NOFIXED time steps only
Variable Window: WINDOW	- allows more flexibility in the error control for the VARIABLE time increment option.
No. fixed steps: NOFIXED	- number of fixed increment backward Euler steps, default= 3

### Defining Entity

name	type	[info] – description
lens	solid	[species = 1, MDiff = “drug in lens”] – contact lens

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tear	solid	[species = 1, MDiff = “drug in tear”] –tear film
cornea	solid	[species = 1, MDiff = “drug in cornea”] – cornea
humor	solid	[species = 1, MDiff = “drug in humor”] – aqueous humor
lens front	plot	- boundary between air and lens
lens center	plot	- axis in the lens layer
lens edge	plot	- lens layer at the circumference
tear center	plot	- axis in the tear layer
cornea center	plot	- axis in the corneal layer
tear edge	plot	- tear film at the circumference
tear lens	plot	- boundary between contact lens and tear film
interface	plot	- boundary between tear film and cornea
cornea end	plot	- boundary where cornea meets aqueous humor in eye
cornea edge	plot	- cornea at the circumference
cornea humor	plot	- boundary between cornea and humor
humor center	plot	- axis in the humor layer
humor end	plot	- humor at the circumference

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#### Defining Property – Diffusivity

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tear drug = $14 \times 10^8 \text{ cm}^2/\text{s}$	- diffusivity of the drug in tear film
tear cornea = $0.735 \times 10^{-6} \text{ cm}^2/\text{s}$	- diffusivity of the drug in cornea layer

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#### Initial Conditions

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Tear	- species, constant at 0
Cornea	- species, constant at 0
interface	- species, constant at 0

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#### Boundary Conditions - BCFLUX

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tear center	- species, constant at 0
cornea center	- species, constant at 0
cornea end	- species, constant at 0
cornea edge	- species, constant at 0
tear edge	- species, constant at 0
tear lens	- species, constant at $0.5589 \text{ mg}/\text{cm}^2$ (total concentration over surface area of contact lens – this needs to be adjusted to 60% of concentration over total surface area)
interface	- species, constant at 0

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## 10.0 Appendix B: Results- Additional Graphs

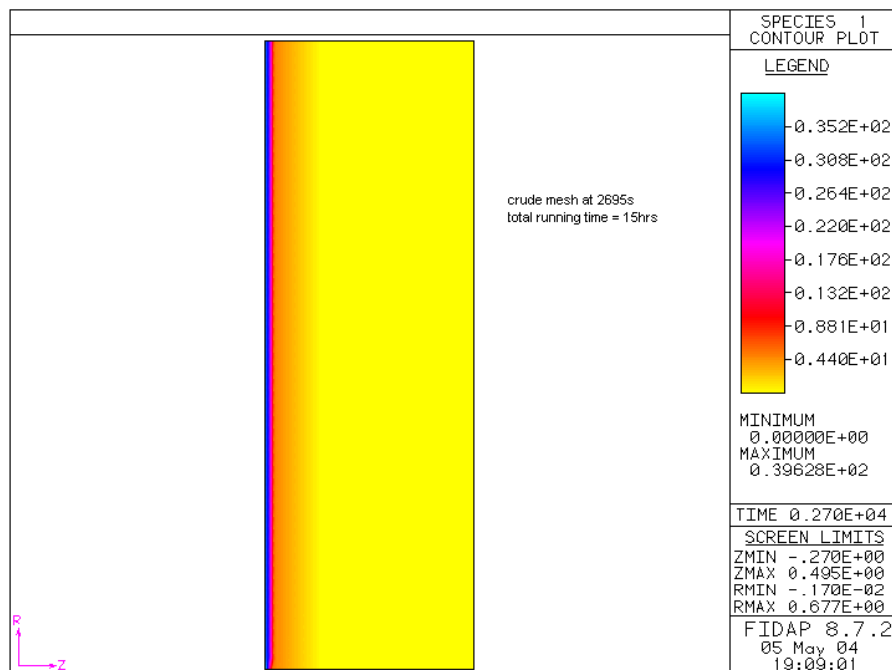


Figure B1. A contour representation of the axis-symmetric model at 45 minutes of total reaction time for the crude mesh when drug is at maximum concentration in humor layer.

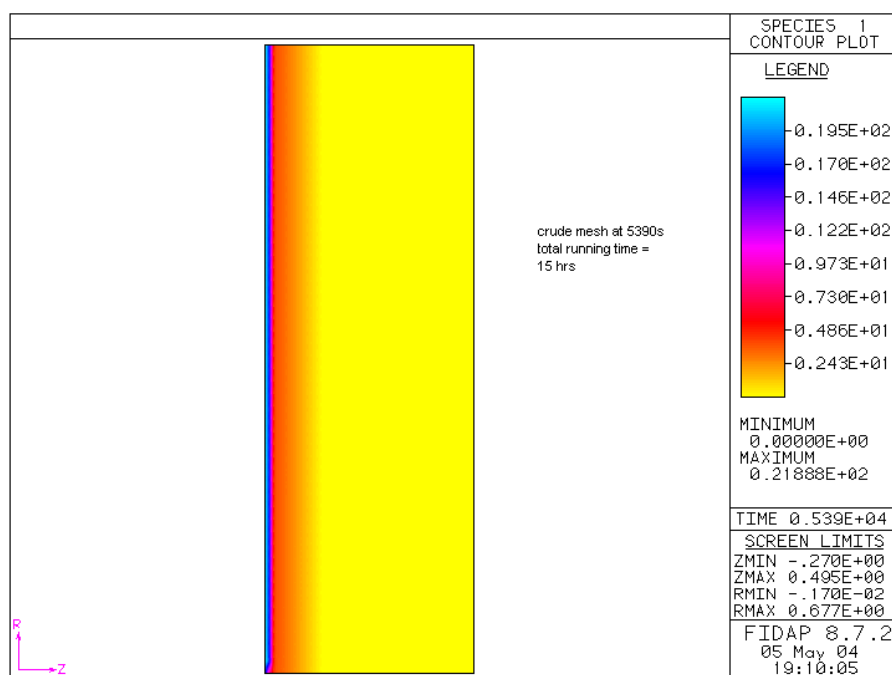


Figure B2. A contour representation of the axis-symmetric model at 1.5 hours of total reaction time for the crude mesh when drug concentration is less than the minimum effective concentration. Note that the color gradient between the two contours does not match up.

The initial concentration history plot for the lens layer (Figure B3) shows that concentration indeed starts at 46.5 mg/mL. It decreases sharply from 0 seconds to 3.1 hours,

then slowly converge to zero after 6 hours. Because of its linear portion at the initial 3 hours of application, our contact lens drug delivery system can possibly be modeled as steady state diffusion.

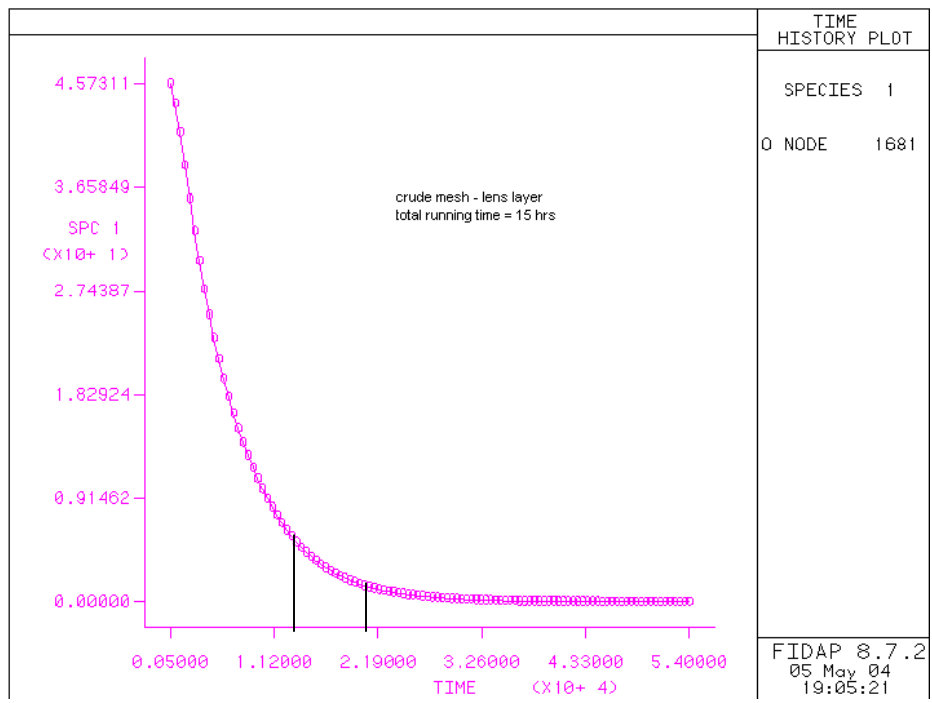


Figure B3. A history plot of concentration at the lens layer using the crude mesh. At about 11220 seconds or 3.1 hours, the diffusive rate starts to decrease dramatically and reach zero around 21900 seconds or 6.1 hrs.

11.0 Appendix C: Sensitivity Analysis- Additional Graphs

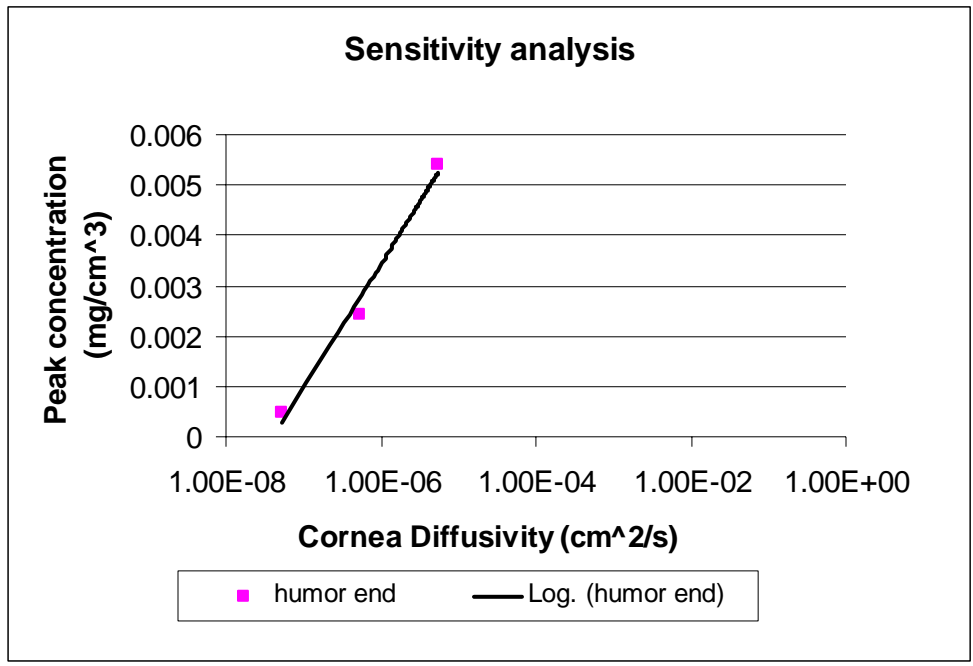


Figure C1: Logarithmic relationship between cornea diffusivity and peak concentration near the end of the humor.

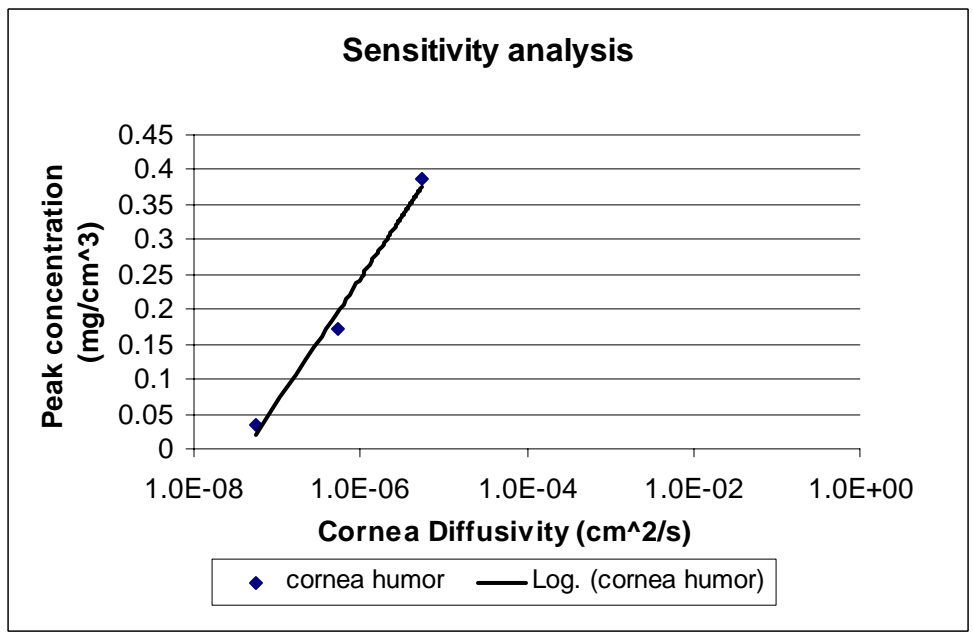


Figure C2: Logarithmic relationship between cornea diffusivity and peak concentration at the cornea-humor interface.

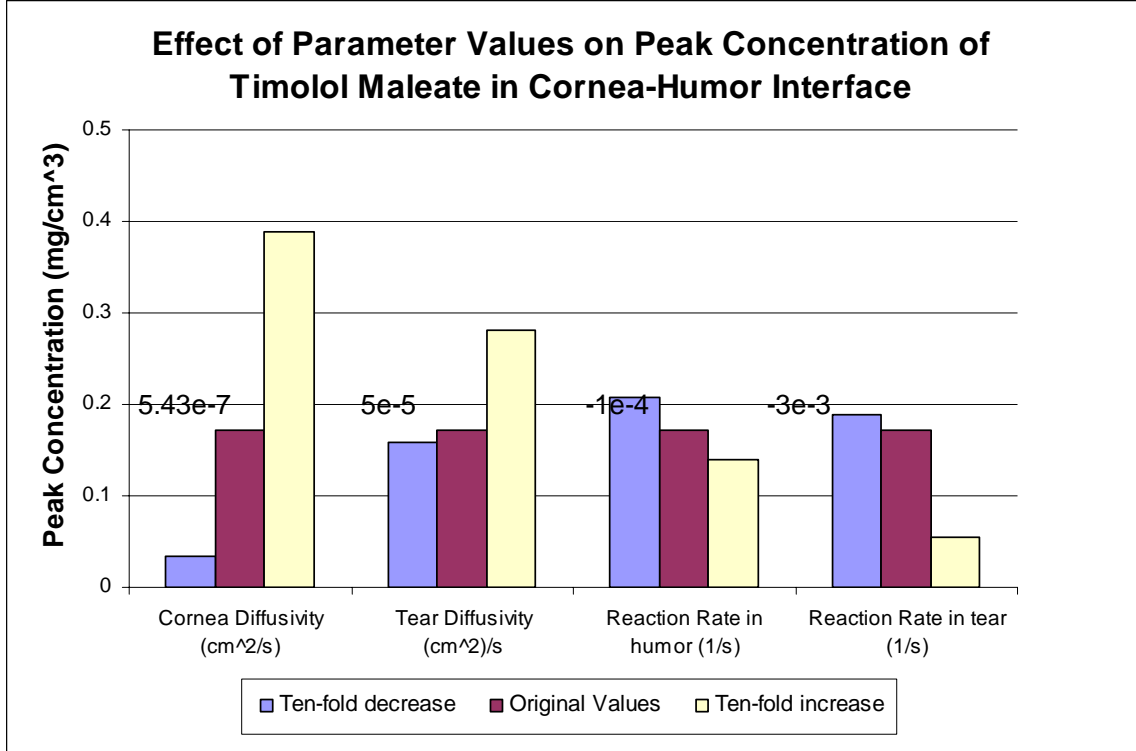


Figure C3: Effect of ten-fold increase and decrease of parameter values on peak concentration of timolol maleate at the cornea-humor interface. The original values are shown in above the bars.

## 12.0 Appendix D – Input File

```

/
/ INPUT FILE CREATED ON 10 Apr 04 AT 17:47:50
/
/
/ *** FICONV Conversion Commands ***
/ *** Remove / to uncomment as needed
/
/ FICONV(NEUTRAL,NORESULTS,INPUT)
/ INPUT(FILE= "april9.FDNEUT")
/ END
/ *** of FICONV Conversion Commands
/
TITLE

/
/ *** FIPREP Commands ***
/
FIPREP
PROB (AXI-, INCO, TRAN, LAMI, LINE, NEWT, NOMO, ISOT, FIXE, NOST, NORE,
SING,
    SPEC = 1.0)
EXEC (NEWJ)
SOLU (SEGR = 100, VOLC = 0.100000000000E-02, SCHA = 0.000000000000E+00)
TIME (BACK, NSTE = 360, TSTA = 0.000000000000E+00, TEND = 18000.0, DT =
50.0,
    FIXE)
RELA (HYBR)
    0.00000000000E+00, 0.00000000000E+00, 0.00000000000E+00, 0.00000000000E+00,
    0.00000000000E+00, 0.00000000000E+00, 0.00000000000E+00, 0.00000000000E+00,
    0.30000000000E+00, 0.00000000000E+00, 0.00000000000E+00, 0.00000000000E+00,
    0.00000000000E+00, 0.00000000000E+00, 0.00000000000E+00, 0.00000000000E+00,
    0.00000000000E+00, 0.00000000000E+00, 0.00000000000E+00, 0.00000000000E+00,
    0.00000000000E+00, 0.00000000000E+00, 0.00000000000E+00, 0.00000000000E+00,
    0.00000000000E+00, 0.00000000000E+00, 0.00000000000E+00, 0.00000000000E+00
ENTI (NAME = "cornea", SOLI, SPEC = 1.0, MDIF = "drug in cornea")
ENTI (NAME = "humor", SOLI, SPEC = 1.0, MDIF = "drug in humor", SPEC = 1.0,
    MREA = "humor")
ENTI (NAME = "lens", SOLI, SPEC = 1.0, MDIF = "drug in lens")
ENTI (NAME = "tear center", PLOT)
ENTI (NAME = "cornea center", PLOT)
ENTI (NAME = "cornea humor", PLOT)
ENTI (NAME = "cornea edge", PLOT)
ENTI (NAME = "tear edge", PLOT)
ENTI (NAME = "tear lens", PLOT)
ENTI (NAME = "interface", PLOT)
ENTI (NAME = "lens center", PLOT)
ENTI (NAME = "lens front", PLOT)
ENTI (NAME = "lens edge", PLOT)
ENTI (NAME = "humor center", PLOT)
ENTI (NAME = "humor end", PLOT)
ENTI (NAME = "humor edge", PLOT)
ENTI (NAME = "tear", SOLI, SPEC = 1.0, MDIF = "drug in tear", SPEC = 1.0,
    MREA = "tear")
DIFF (SET = "drug in tear", CONS = 0.500000000000E-04)

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DIFF (SET = "drug in cornea", CONS = 0.543000000000E-06)
DIFF (SET = "drug in humor", CONS = 0.500000000000E-04)
DIFF (SET = "drug in lens", CONS = 0.990000000000E-08)
REAC (SET = "tear", CONS, TERM = 1, KINE)
  -0.3000000000E-02, 0.0000000000E+00, 0.0000000000E+00, 0.1000000000E+01,
    0.0000000000E+00, 0.0000000000E+00, 0.0000000000E+00, 0.0000000000E+00,
    0.0000000000E+00, 0.0000000000E+00, 0.0000000000E+00, 0.0000000000E+00,
    0.0000000000E+00, 0.0000000000E+00, 0.0000000000E+00, 0.0000000000E+00,
    0.0000000000E+00, 0.0000000000E+00, 0.2730000000E+03
REAC (SET = "humor", CONS, TERM = 1, KINE)
  -0.1000000000E-03, 0.0000000000E+00, 0.0000000000E+00, 0.1000000000E+01,
    0.0000000000E+00, 0.0000000000E+00, 0.0000000000E+00, 0.0000000000E+00,
    0.0000000000E+00, 0.0000000000E+00, 0.0000000000E+00, 0.0000000000E+00,
    0.0000000000E+00, 0.0000000000E+00, 0.0000000000E+00, 0.0000000000E+00,
    0.0000000000E+00, 0.0000000000E+00, 0.2730000000E+03
BCNO (SPEC = 1.0, ENTI = "humor end", CONS = 0.000000000000E+00)
BCFL (SPEC = 1.0, ENTI = "cornea edge", CONS = 0.000000000000E+00)
BCFL (SPEC = 1.0, ENTI = "tear edge", CONS = 0.000000000000E+00)
BCFL (SPEC = 1.0, ENTI = "humor edge", CONS = 0.000000000000E+00)
BCFL (SPEC = 1.0, ENTI = "lens front", CONS = 0.000000000000E+00)
BCFL (SPEC = 1.0, ENTI = "lens edge", CONS = 0.000000000000E+00)
ICNO (SPEC = 1.0, CONS = 46.5, ENTI = "lens")
ICNO (SPEC = 1.0, ZERO, ENTI = "tear")
ICNO (SPEC = 1.0, ZERO, ENTI = "humor")
ICNO (SPEC = 1.0, ZERO, ENTI = "cornea")
END
/ *** of FIPREP Commands
CREATE(FIPREP,DELE)
CREATE(FISOLV)
PARAMETER(LIST)

```

### 13.0 Work Cited

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- (2)
- (3)
- (4)
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