Optimizing Release from Reservoir Microcapsules

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1.0 Executive Summary

Cytomegalovrius (CMV) retinitis is a common symptom of vision loss found in 20-30% of all acquired immunodeficiency syndrome (AIDS) sufferers. While there are no drugs that can cure permanent retinal damage by CMV, the drug ganciclovir has demonstrated efficacy against human cytomegalovirus infections and has been considered a first-line therapy in the treatment of sight-threatening cytomegalovirus infection in immune-compromised patients. The FDA-approved Vitrasert® implant, which is inserted at a localized region of the eye, is the current method of delivering ganciclovir intraocularly to patients with CMV. The Vitrasert® is a disc-like reservoir microcapsule that encapsulates ganciclovir in a polymer-based system. Maintaining a constant level of drug in the infected eye region is an important requirement in the design of this implant. The more constant the rate of drug release from the microcapsule, the more effective the drug will be. The objective of our model is to measure the diffusion of the ganciclovir release from the Vitrasert® into the surrounding tissue and to ensure toxic levels of the drug is not sustained. To accomplish this objective, the implant is simplified via axis-symmetry from a 3-D cylinder into a 2-D rectangle with homogeneous material properties, while the skin is reduced to a quarter-circle around our capsule. With our model, we are able to optimize the characteristics of the microcapsule to facilitate near constant drug release, which would be beneficial for many pharmaceuticals working with drug release from reservoir microcapsules.

Key Words: cytomegalovirus retinitis, ganciclovir, Vitrasert®, microcapsule, constant release rate

2.0 Introduction

2.1 Background and Importance

Modern Drug Delivery[1]

Cytomegalovirus (CMV) Retinitis, a member of the herpes virus family, is one of the most common causes of vision loss in patients with acquired immunodeficiency syndrome or otherwise known as AIDS.[2] Since AIDS is caused by the human immunodeficiency virus (HIV) which attacks the body's immune system, eye infections is a common symptom.

Cytomegalovirus is found in about 20-30% of AIDS sufferers and causes a serious impairment in sight.[2] CMV causes vision loss in one of the following manners: through the direct attack of the retinal tissue which destroys the cells needed for vision stimuli, or causing the patient to be more susceptible to retina detachments that are difficult to repair. Retina detachments can also cause cataracts to develop compounding the severity of vision loss in patients with CMV.

Currently, there exists no cure for the permanent vision damage caused by CMV. There exists, however, several effective medications to treat this disease. One common treatment is the incorporate of ganciclovir into a reservoir microcapsule, which is then implanted into a region of tissue close to the infection site. The drug will diffuse into the localized surrounding tissue from the implant allowing the drug to be administrated for a prolonged period of time.

Ganciclovir is a nucleoside analogue with antiviral activity against human cytomegalovirus and herpes simplex virus types 1 and 2. For patients without renal failure, ganciclovir should be administered as a 1-hour intravenous infusion at a dosage of 2.5 mg/kg every 8 hours or 5 mg/kg every 12 hours for a duration of 14 to 21 days. A maintenance regiment of 5 mg/kg/day is recommended to prevent recurrences of cytomegalovirus infections. Those suffering with impaired renal function should receive reduced ganciclovir dosage. Ganciclovir administered at concentrations greater than 40 mg/L (155 μmol/L) is associated with local degeneration of retinal cells and disorganization of retinal layers marking the minimum toxicity bounds.

The Vitrasert® is a FDA-approved reservoir microcapsule with encapsulated ganciclovir that has been prescribed to treat patients with CMV. The implant is inserted surgically in the posterior segment of the eye that is located in the proximity of the site of infection; releasing an

effective drug dosage for longer periods of time without damage to healthy tissues. The current Vitrasert® can continue to release ganciclovir between six to eight months. When the drug is depleted, the implant can be removed and a new Vitrasert® can be inserted. In a study done by Bausch & Lomb Surgical's Phase III trial of 188 AIDS patients with CMV Retinitis, the Vitrasert® implant has shown to delay the disease progression significantly.[3]

2.2 Microcapsules

Microcapsules are used in drug delivery because they allow controlled release rates due to slow diffusion. There are three main types of microcapsule release: reservoir diffusion, monolithic diffusion, and biodegradable microcapsule release. For our report we will focus on the first type: reservoir diffusion, which consists of a small reservoir of suspended drugs encapsulated by a spherical polymer matrix (See *Figure 1).*
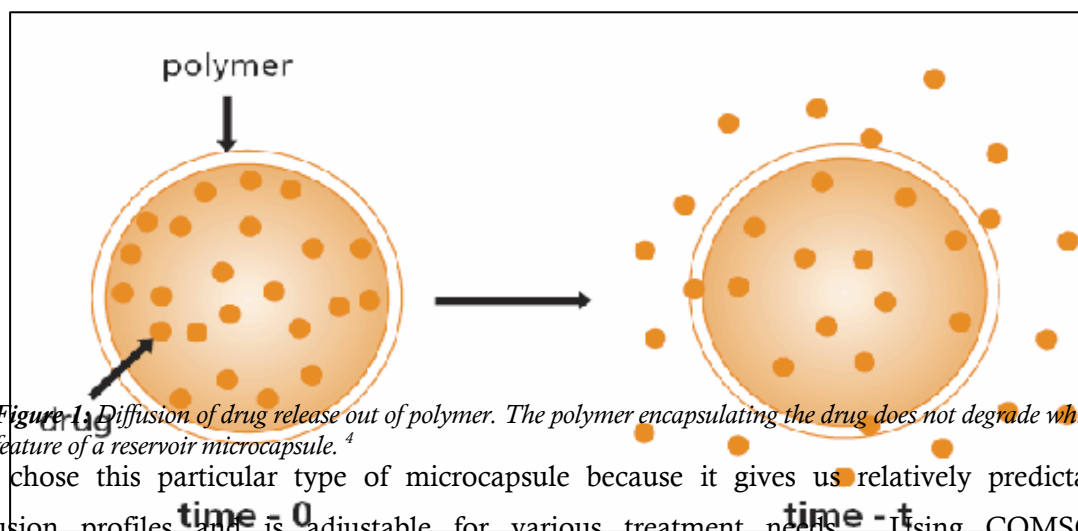
Figure 1: Diffusion of drug release out of polymer. The polymer encapsulating the drug does not degrade which is a feature of a reservoir microcapsule. [4]

We chose this particular type of microcapsule because it gives us relatively predictable diffusion profiles and is adjustable for various treatment needs. Using COMSOL, computational fluid dynamic software and inputting known properties for ganciclovir diffusion through the polymer layer, we can vary the capsule's geometry and concentration in the reservoir to obtain a release profile suitable for the patient.

In general, we want a release profile that is slow in order to sustain delivery of drug for at least several months while maintaining a drug concentration between the MEC (Minimum effective concentration) and MTC (Minimum toxic concentration); these values vary with different drugs.[5]

3.0 Design Objectives

In our model, we decided to study the rates of drug release from reservoir microcapsules and apply these findings to optimize the rate of ganciclovir released from the Vitrasert® into the site of infection. Our main design objectives are as follows:

1. Model the diffusion of ganciclovir release from the Vitrasert® microcapsule into surrounding tissue
2. Optimize the properties of the microcapsule that has a constant rate of drug release for a given amount of time
3. Determine whether toxic levels of the drug would be obtained during usage.

4.0 Project Schematics

4.1 Assumptions

To simplify our drug diffusion model in a reservoir microcapsule, we will be making the following the assumptions.

1. The microcapsule is cylindrically uniform and will be modeled as a cylinder shape.
2. Uniform properties throughout the tissue used in the model.
3. The drug will be released only from the top and bottom surfaces of the microcapsule.
4. There will be no angular variation in the drug diffusion, which results in a two-dimensional axi-symmetry problem.
5. All of the drug released from the microcapsule is diffused directly into the tissue.

4.2 Geometry

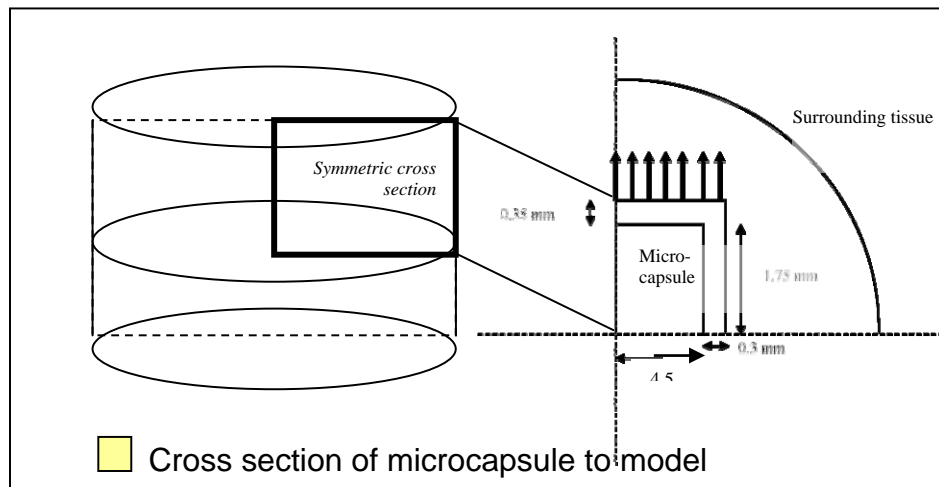The geometry of our microcapsule model created in COMSOL is replicated in *Figure 2*.

Figure 2. *Diagram of the microcapsule and modeling parameters.*

5.0 Results and Discussion

5.1 Defining the Mesh

In order to study the diffusive rate at which ganciclovir suspended in fluid is released from the Vitrasert®, a computational fluid dynamic (CFD) modeling program was used. The CFD software, called COMSOL Multiphysics 3.3, enabled the creation of unstructured computational mesh that is well suited for incompressible flow and transport problems. The mesh of the surrounding tissue and within the microcapsule was simulated in accordance with the mesh within the microcapsule wall. There is a greater mesh density within the walls because these regions experience a greater fluctuation in the flux of the drug (see *Figure 3*).
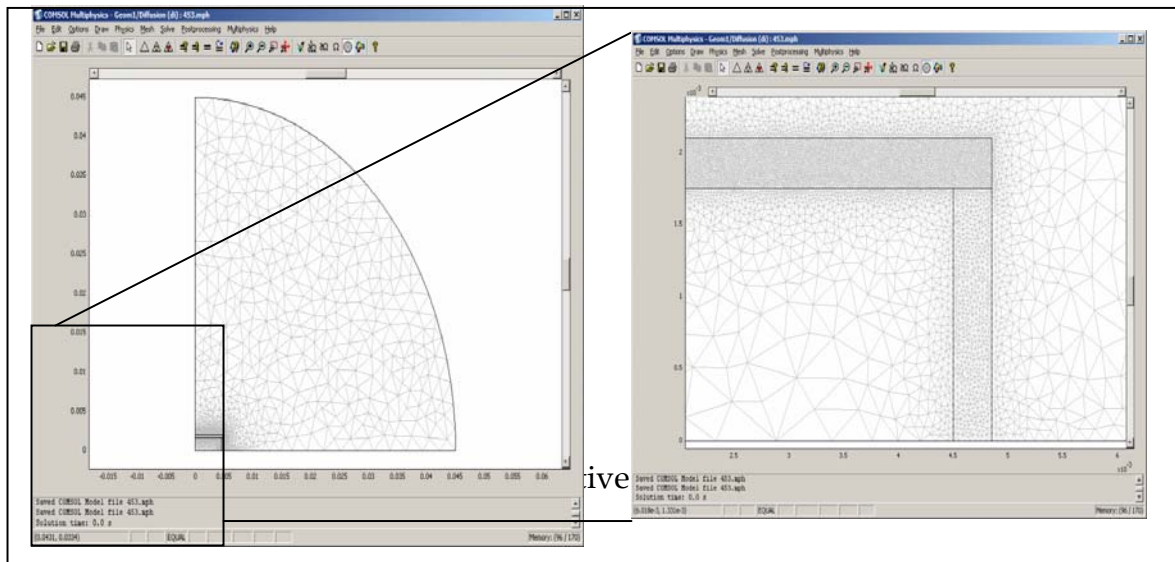

Figure 3. *Mesh diagram of microcapsule, microcapsule walls, and surrounding tissue. Number of elements in the microcapsule wall is 15,342.*

The Vitrasert® reservoir microcapsule implant is designed to release an effective drug dosage to the tissue for a period up to 6 months. To run our simulations, we obtained values from literature regarding the diffusivity of the retinal tissue, the microcapsule and its polymer wall in addition to the rate of elimination of ganciclovir in the tissue. To produce a reasonably accurate model which describes the drug release of the Vitrasert®, we obtained accurate values for the initial drug dosage found in the current Vitrasert®. These values are all detailed in Appendix C.

The initial value condition (t=0) was simulated via COMSOL (*see Figure 4*) where a red region indicates high drug concentration and blue regions have very little or zero drug present. Note that at time =0, no drug has diffused from inside the microcapsule into the wall.
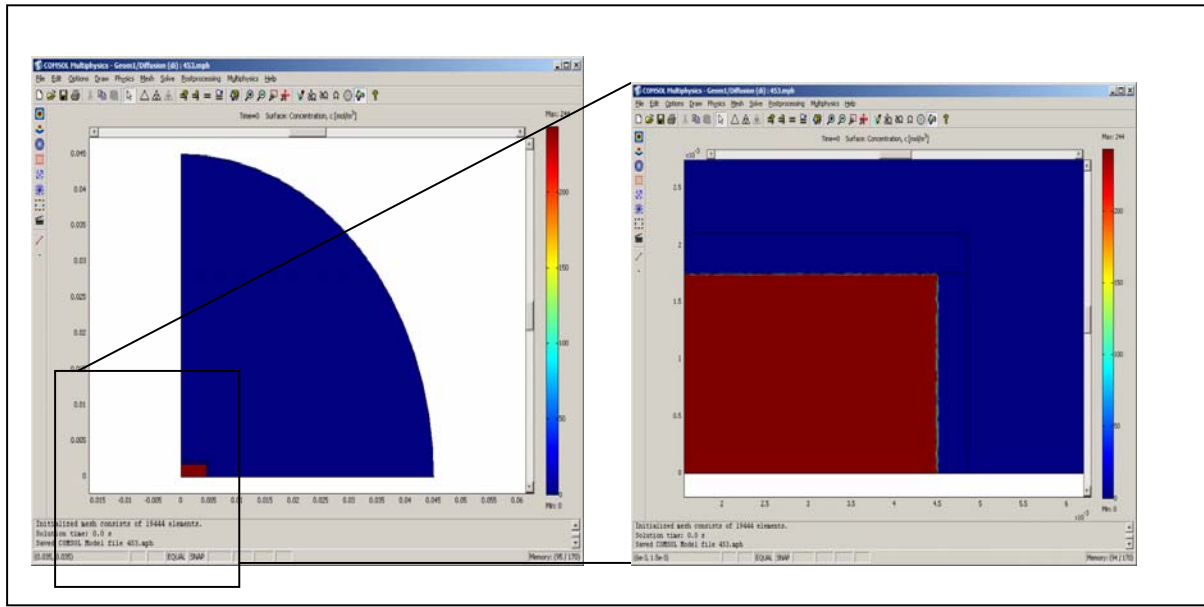

Figure 4. *Contour plot of microcapsule, microcapsule wall, and surrounding tissue at initial time*

Since it was difficult to find in literature the diffusivity value of the microcapsule wall, the simulation was run for approximately 270 days at a time step of 86400 and repeated with a one thousand-fold and ten thousand-fold decrease in the D_{wall} value. *Figure 5* shows the release profile of ganciclovir from the microcapsule into the tissue taking into account the diffusion and the elimination rates of the drug within the tissue. In these figures, regions that exceed limits of the contour scale bar appear as white. In *Figure 5(A) and 5(B),* the contour plots are shown for 2 and 30 days respectively, because after each of these days at its respective D_{wall} value, there was hardly any drug left in the tissue. Too large of a diffusivity value in the microcapsule wall may be the culprit for such an occurrence.
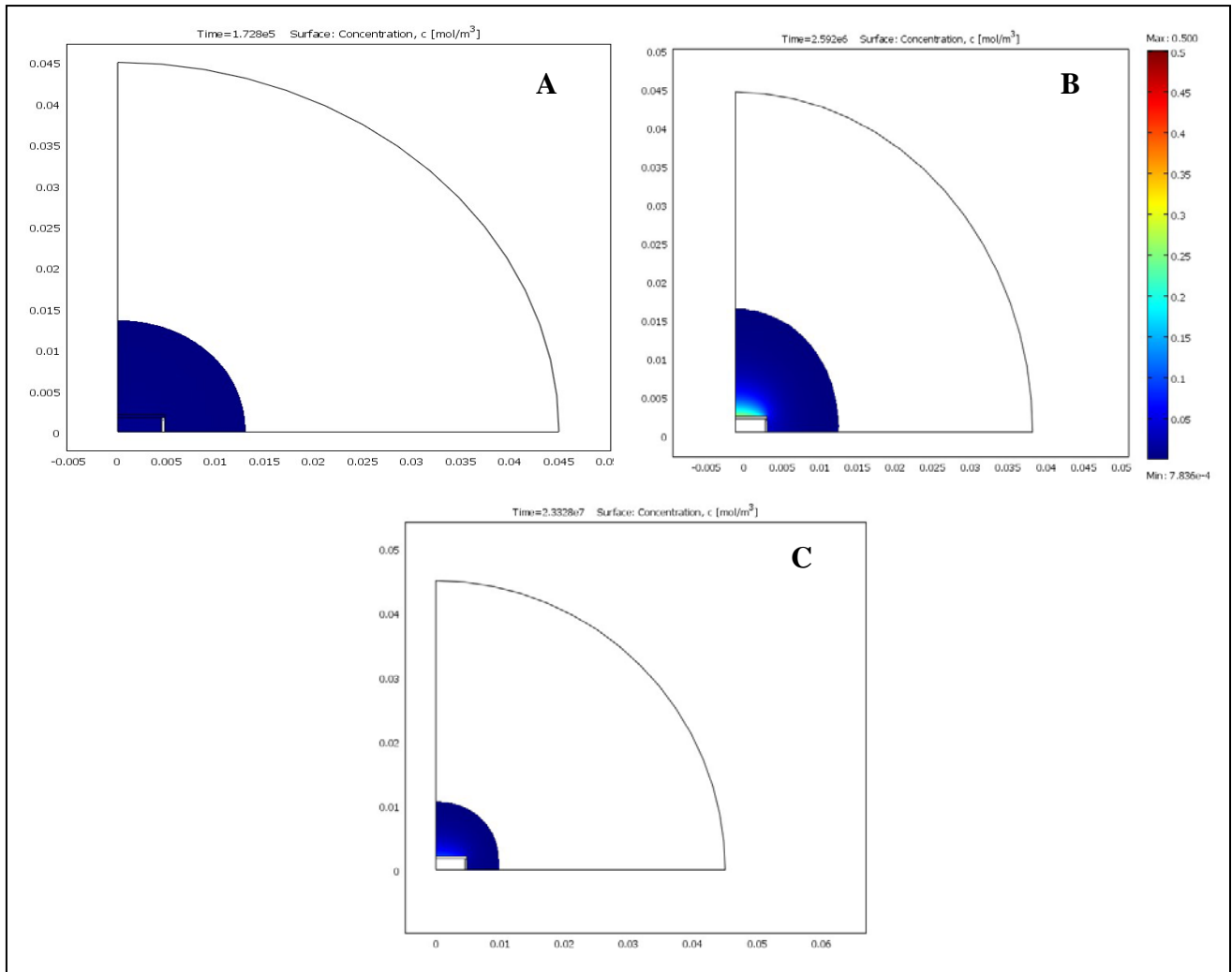

Figure 5. *Contour plot of microcapsule, microcapsule wall, and surrounding tissue after (A) 2 days (B) 30 days and (C) 270 days. The corresponding diffusivity values of the microcapsule wall are (A) 2.8 X 10^{-10} m^2/s, (B) 2.8 X 10^{-13} m^2/s and (C) 2.8 X 10^{-14} m^2/s. All concentrations not in the range of 0.00078 mol/m^3 and 0.1567 mol/m^3 were shaded white.*

Figures 6 and *7* show that with a decrease in the value the wall diffusivity, the life of the microcapsule can be extended. Comparison of the five diffusivity values ranging from 2.8 X10^{-10} m^2/s to 2.8X10^{-14} m^2/s, a diffusivity of 2.8 x 10^{-14} m^2/s was selected for our optimization model. This is because at this value, the peak concentration remains under any toxic concentration levels and show a sustained concentration over time.

Figure 6. *Graph of concentration (mol/m³) v. time (s) of ganciclovir in tissue for microcapsule wall diffusivity ranging from 2.8 x 10¹⁰ m²/s to 2.8 x 10¹² m²/s over the course of 270 days.*

6.0

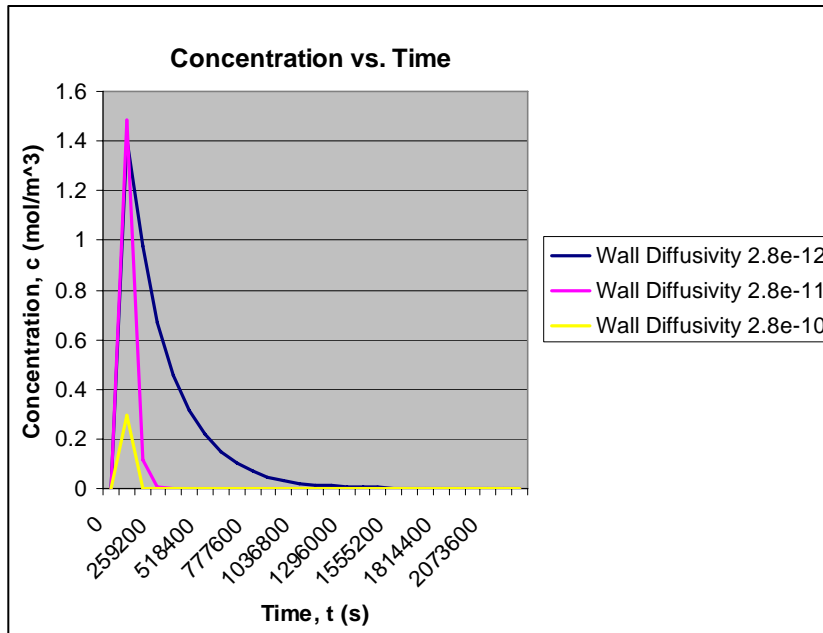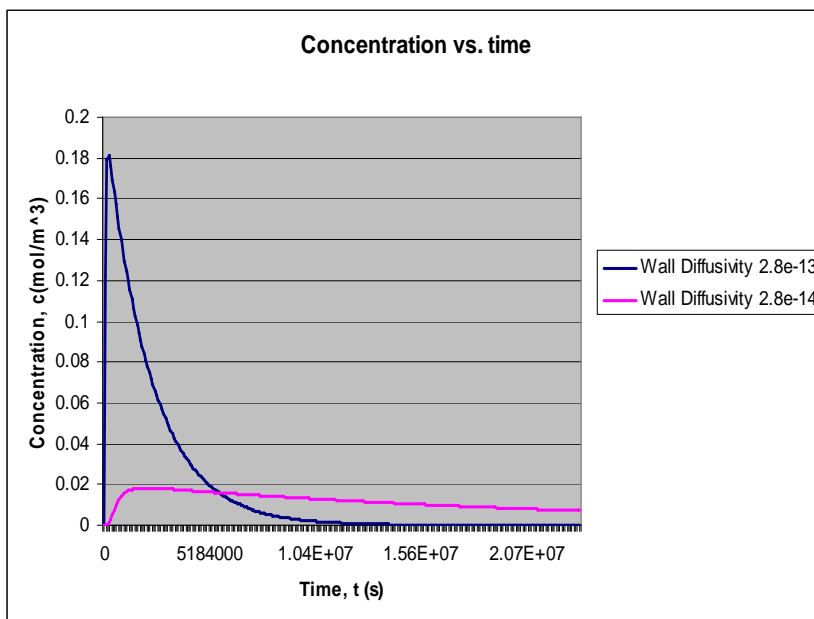**Figure 7.** *Graph of concentration (mol/m³) v. time (s) of ganciclovir in tissue for microcapsule wall diffusivity ranging from 2.8 x 10¹³ m²/s to 2.8 x 10¹⁴ m²/s over the course of 270 days.*

Sensitivity Analysis

6.1 Diffusivity of Microcapsule Wall - D_{wall}

Sensitivity analysis was performed to see how the diffusivity of the microcapsule wall, D_{wall}, affects the average concentration of drug in the tissue after 270 days. The sensitivity analysis was run using diffusivity values in addition to the five that were used to obtain the results. *Figure 8* below depicts what would be expected when varying D_{wall} by orders of ten.
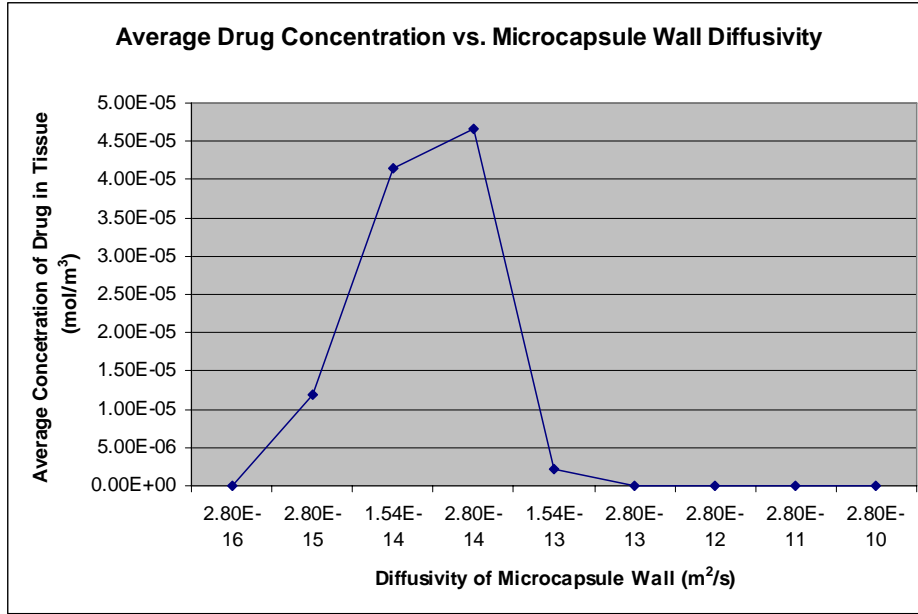

Figure 8. *Graph of average concentration of drug in the tissue (mol/m³) vs. diffusivity of microcapsule wall (m²/s) at 270 days.*

A D_{wall} value of 2.80 x 10⁻¹⁴ m²/s is the optimal value for the largest average concentration of the drug in the tissue after at 270 days. Values higher than this allow the drug to diffuse through the wall too quickly so concentration in the tissue is zero at this time. At higher diffusivities, the capsule would be empty at this time. Diffusivities lower than the optimal D_{wall} value show less significant changes when compared to values higher than the optimal D_{wall} value. This can be attributed to slower diffusion of the drug through the microcapsule wall. The slower diffusion allows the drug to not deplete after 270 days; however, the average concentration of the drug in the tissue will not be as high. If the diffusivity is too low, then diffusion of the drug through the microcapsule wall will be so slow that the concentration of the drug in the tissue will never reach any significant concentration to be effective. Figure 10 shows that drug diffusion through the microcapsule is very sensitive to D_{wall}. It would be important to validate the value of D_{wall} through experimentation as any changes in this parameter could change the lifespan of the microcapsule.

6.2 Initial Concentration within Microcapsule

A sensitivity analysis was performed on the initial concentration within the microcapsule for a D_{wall} value equal to 2.80 x 10^{-14} m^2/s. Because this D_{wall} value was determined to be the optimal value, it was not important to analyze the sensitivity of initial concentration with respect to the other D_{wall} values used. For this sensitivity analysis, the effect of initial concentrations 10% and 20% larger and smaller was compared with the original initial concentration used in the model. For each of these initial concentrations, the model was solved for a final time of 270 days and the average concentration of the drug in the tissue was determined. The results are tabulated in Table 2 and depicted in *Figure 9* below.

Initial concentration (mol/m^3)	Avg. concentration at 270 days (mol/m^3)	Percent change
195.2	3.75 x 10^{-5}	19.55
219.6	4.20 x 10^{-5}	9.78
244	4.66 x 10^{-5}	0
268.4	5.18 x 10^{-5}	11.23
292.8	5.60 x 10^{-5}	20.22

Table 1. *Average concentration of drug in the tissue at 270 days after varying initial drug concentration inside the microcapsule.*
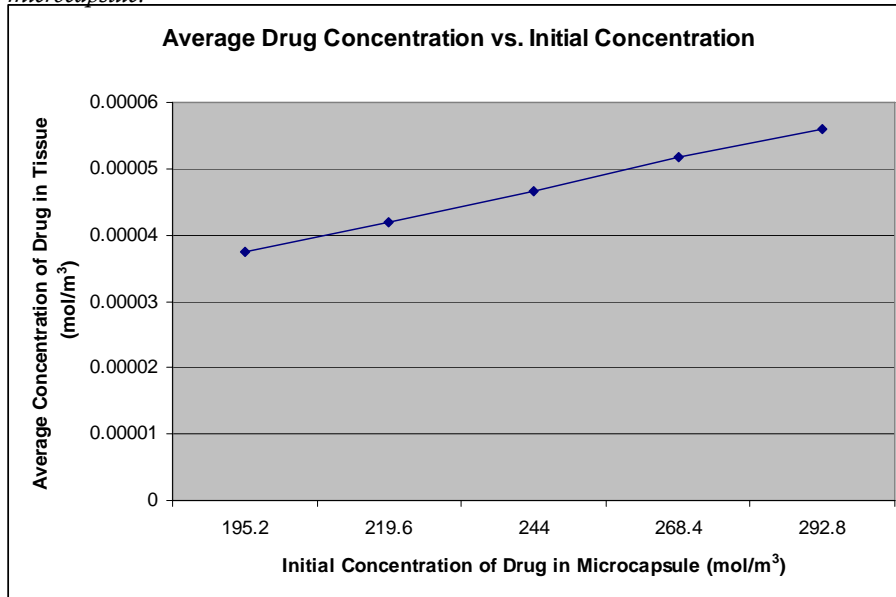

Figure 9. *Graph of average concentration of drug in tissue (mol/m^3) vs. initial concentration of drug in microcapsule (mol/m^3) after 270 days.*

From the results, we found that the initial concentration appears to affect average concentration in a linear manner. Therefore, 10-20% increase or decrease in initial concentration changes average concentration by approximately 10-20% as well. More exact values for percent change are tabulated in Table 2 above. These results show that while initial concentration does affect average concentration, it is not as sensitive of a parameter as D_{wall}. The initial concentration can be varied in experimentation if small changes in average concentration are desired.

6.3 Microcapsule Wall Thickness

A sensitivity analysis was performed on the microcapsule wall thickness for a D_{wall} value equal to 2.80 x 10^{-14} m^2/s. Because this D_{wall} value was determined to be the optimal value, it was not important to analyze the sensitivity of wall thickness with respect to the other D_{wall} values used. For this sensitivity analysis, the affect of wall thickness up to 30% larger and up to 20% smaller was compared with the initial wall thickness used in the model. For each wall thickness, the average concentration of the drug in the tissue was calculated at 270 days. Table 3 below tabulates the results of this analysis.

Wall Thickness (mm)	Avg. concentration at 270 days (mol/m^3)	Percent change
0. 28	4.47 x 10^{-5}	4.26
0. 315	4.61 x 10^{-5}	1.23
0.35	4.67 x 10^{-5}	0
0.385	4.72 x 10^{-5}	1.25
0.42	4.63 x 10^{-5}	0.78
0.455	4.65 x 10^{-5}	0.44

Table 2. *Average concentration of drug in the tissue at 270 days after varying the microcapsule wall thickness*

The above results show that the model is not sensitive to the thickness of the microcapsule wall at the optimal value for D_{wall}. Even for a change as large as a 20% decrease and 30% increase in wall thickness, the percent change in average concentration is only 4.26% and 0.44% respectively. This means that when creating the microcapsule, natural variations in wall thickness between microcapsules would not affect the overall ability of the microcapsule to deliver the drug to the tissue.

7.0 Conclusion and Optimization Recommendations

7.1 Optimization of Design

Further testing was performed using COMSOL's animation feature to depict which regions are between the MEC and MTC for our drug. This was accomplished by setting our contour graph's range between 0.00078361 mol/m^3 – 0.157 mol/m^3; this now shows our geometry in color in regions where the drug is effective, and in white when outside the range we want. Two preliminary videos were made for this test: one over 30 days (½ day time steps) with our specifications from last time. It was seen that by 20 days, the tissue region within our target concentrations had already diminished. A second video was created with a 10-fold reduction in diffusivity through the wall over 90 days (1 day time steps). This showed that with proper tweaking of the wall, our drug easily affected a tangible volume of tissue over 3 months. More importantly, it also confirms that our model is useful for design optimization. These videos (and others, in the future) are available on CD format and are also available online:

http://video.google.com/videoplay?docid=-5865080372626890235
http://video.google.com/videoplay?docid=-2173838320026871988

7.2 Problems Encountered

Initially, our group spent a significant amount of time familiarizing ourselves with using COMSOL. After working through several program tutorials in addition to the help of Vineet Rakesh, we were able to apply what we learnt in COMSOL to develop a working model for a first-order drug release from a microcapsule. Several attempts were made in perfecting our model's schematic drawing to produce quality results. For example, we discovered how to rescale the color legend containing the contour colors so that it starts at 0 instead of some arbitrary negative value. This allows us to obtain more realistic results of the drug diffusion process as well as to see ranges of effective drug concentration over a certain period of time. Moreover, we improved our model after learning how to set a flux = 0 at an interior boundary which is what we needed to represent the microcapsule wall that is impermeable to ganciclovir.

One major problem that stumped us for a while was the generation of a negative concentration value after running our simulation at a certain t > 0. We realize that this was only the case for

certain regions in the tissue. Thus, in order to overcome such an error, all our calculated results and sensitivity analysis is a comparison using the average concentration found in the tissue. This way, any negative values will be offset by more accurate drug concentration elsewhere in the tissue.

After spending an arduous amount of time looking through literature for diffusivity values of microcapsule wall and coming up empty-handed, we decided to determine the optimal value through our model instead. Using the knowledge that the Vitrasert® implant should last 6-8 months, we were able to back calculate the necessary value for the wall diffusivity. This value is particularly important because a change by a magnitude of 10 could result in shorter drug release duration causing patients suffering from CMV to receive more frequent implants.

Lastly, we often experienced "not enough memory" and "not enough space" errors when defining our mesh or calculating a solution at a large time value. This is particularly frustrating as oftentimes these errors would crash the program forcing us to restart without any of our data saved. To overcome the memory, we reduced the number of mesh elements within the microcapsule wall so that our model could still output a solution. To prevent exceeding the storage space, a greater time step value was implemented in order to obtain solutions at greater time values. However, by increasing the time step, many data points in between was left unrecorded. Thus, without using faster PCs, these errors will remain limitations to using the COMSOL software for our modeling needs.

7.3 Design Recommendations

We offer two recommendations for further improvements that can be considered while using COMSOL to model a first-order drug delivery from a microcapsule:

- **More computing power:** This would allow for smaller time steps to be used, more storage space for data, obtain results in less time and thereby increasing overall accuracy of simulation.
- **Model different geometries:** While we modeled our microcapsule similar to that of the Vitrasert® which simplified the problem to a 2-D cylinder, we did not examine whether or not other geometries will produce a better constant drug release profile. Examining various geometries can be useful in determining the best shape for a microcapsule implant.

7.4 Conclusion

With our simplified capsule geometry and basic diffusion with first order reaction model, we were able to optimize our capsule's release profile such that a significant volume of surrounding skin was in the desired concentration window between the MEC and MTC for a prolonged period of time. In fact, in our optimized case with diffusivity equal to 2.8×10^{-14} m^2/s, the drug was seen to persist for nearly 6 months, which matches literature values of 6 to 8 months. We conclude that our model is indeed sufficient for feasibility studies of microcapsules. Companies wishing to test out different capsule designs could use our model in COMSOL as an initial check on whether the design is possible. Building a more accurate model is possible but would require further experimentation and increased complexity.

8.0 Appendix A: Mathematical Statement of the Problem

8.1 Governing Equations

Diffusion Equation for 2-D Transient Drug Delivery from microcapsule into tissue

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2}$$

Diffusion Equation for 2-D Transient Drug Delivery within tissue

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} - r_A$$

8.2 Boundary Conditions

Microcapsule

Assume that drug is only released from the top and bottom surfaces.

- On the left boundary: species flux = 0
- On the right boundary: species flux = 0
- On the bottom boundary: species flux = 0

Surrounding Tissue

Assume drug concentration goes to 0 by the time it hits the edge of the tissue

8.3 Initial Conditions

- Initial drug (ganciclovir) concentration in tissue = 0 mg/ cm^3
- Initial drug (ganciclovir) concentration in Vitrasert® = 4.5 mg/ cm^3

9.0 Appendix B: Mesh Convergence Analysis

9.1 Mesh Convergence

In determining whether an appropriate mesh was selected for our model, we will show that by making a finer mesh, the average concentration of our drug delivered to the tissue will not significantly change. Currently, our model is created such that by altering the number of elements in the mesh of the wall in which drug diffuses; the mesh in the tissue region and within the microcapsule will also conform by the same factor. Hence, by illustrating the average drug concentration in the tissue at varying number of mesh elements within the capsule wall, we can determine an optimal and effective mesh necessary for obtaining a constant solution while using minimal computer memory. From our analysis in *Figure 12*, the number of elements chosen for our model is 15,342.
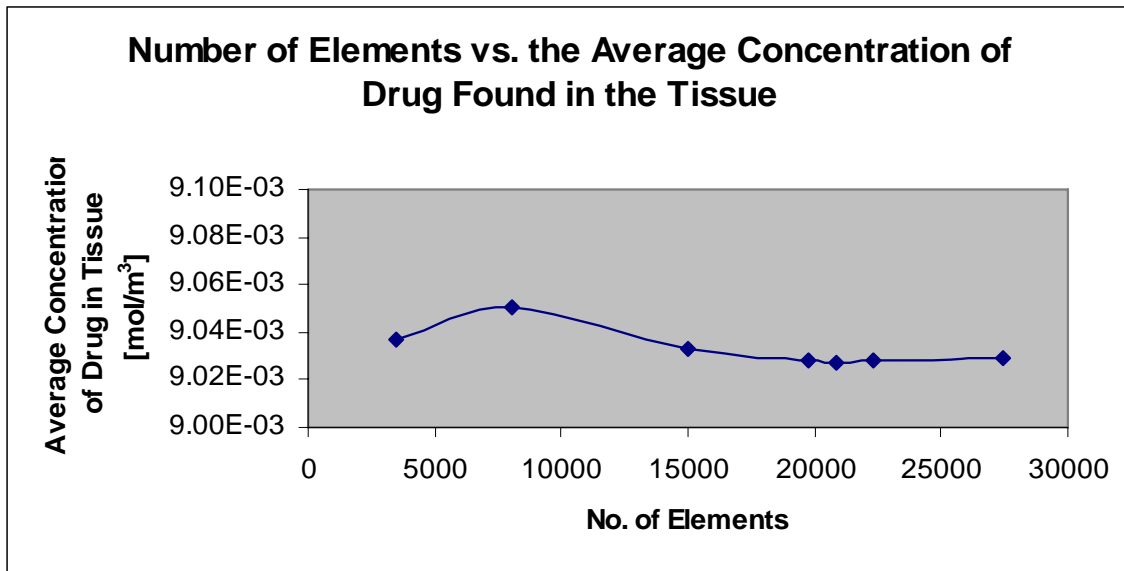

Figure 12. *Graph of the number of elements vs. the average concentration of drug in the tissue (mol/m³). After 15,000 elements, the mesh can be seen to begin to converge since the plots approaches steady state.*

10.0 Appendix C: Input Parameters

Parameter	Value
Diffusivity of Tissue[8], D_{tissue}	5.1×10^{-10} m²/s
Diffusivity of Microcapsule[8], $D_{microcapsule}$	2.8×10^{-10} m²/s
Diffusivity of Microcapsule Wall, D_{wall}	2.8×10^{-10} - 2.8×10^{-14} m²/s
Rate of Elimination of Drug in Tissue[9], R_A	0.00005 mol/m³s
Initial drug concentration in microcapsule[3], C_o	244 mol/m³

Table 3. *Summary of parameters and its associated values used by COMSOL in this simulation.*

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