pH-Dependent Drug Delivery Systems

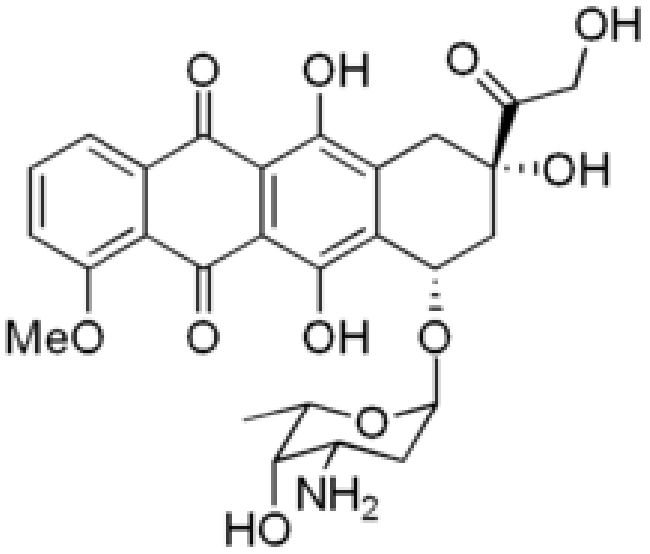

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Table of Contents

Executive Summary

Gastric carcinoma, or stomach cancer, is a major disease in the world today. Although it only accounts for about 2% of all cancer cases in the United States, it is much more prevalent in nations such as Korea, Japan, Great Britain, South America, and Iceland. While the most common treatment for gastric carcinoma is surgery, there are chemotherapeutic alternatives including the application of doxorubicin, also known as Adriamycin®.

However, as with nearly all chemotherapy drugs, doxorubicin causes dose-dependent toxicity that results in severe biological side effects and, potentially, death. Many of the adverse effects of doxorubicin may be attributed to the fact that it is normally administered intravenously; thus, although the drug's target is the stomach, the doxorubicin is systemically rampant. Hence, we have developed a delivery system for doxorubicin that we hope will limit the drug's action to the stomach alone.

We begin with a means for encasing the doxorubicin inside two types of hydrogels whose diffusive properties vary depending on temperature and pH levels, such that diffusion may be maximized in the stomach and minimized at all other locations inside the gastrointestinal tract. This original design was modeled as a 1-D radial line to represent the spherical shape of the pill. After investigation, another design involving a hollowed out hemisphere was modeled and tested. Results comparison shows that the second design scheme is superior to the first both in outward drug flux and in the amount of drug able to be delivered.

Ultimately, results of the study showed that pH-dependent drug release can be attained at a steady and reliable rate, with significantly greater rates of release inside the stomach. However, we were unable to attain a clinically adequate amount of total doxorubicin release with our model designs. Still, it may be possible to achieve medically useful results with pH-dependent drug delivery systems given certain technological improvements in the future.

Introduction

Drug specificity is a complicated problem in medicine today. Most drugs are ingested or intravenously released into the bloodstream, thus affecting the whole body. Site-specific drugs usually rely on antibody/antigen interactions, but current technology on these drugs is limited. We propose a drug encapsulation system that diffuses a specific drug based on pH and temperature changes in the body. Our model drug for this study will be doxorubicin, which may effectively combat gastric carcinoma but also has the threat of causing dose-dependent toxicity. The goal is to present a drug delivery system based on hydrogels whose diffusive properties vary depending on the pH and temperature of their surroundings such that their maximum diffusivity is attained inside the human stomach. Hence we hope to be able to reliably transport doxorubicin into the stomach while limiting drug release in other areas of the body.

The most widely used method of doxorubicin application today is injection, which systemically disperses the drug throughout the body and leads to undesirable side effects including nausea, neutropenia, heart arrhythmias, congestive heart failure, dilated cardiomyopathy, and death. Other attempts have been made at developing drug delivery systems to limit these ill effects, but all have their downsides. For example, various species' erythrocytes have been used as drug carriers, but doxorubicin tends to diffuse from these cells to plasma more quickly than desired, thereby defeating the purpose. As a countermeasure to this, experimenters treated the erythrocytes with glutaraldehyde to successfully slow the doxorubicin release, but neglected to address the toxicity of glutaraldehyde as well as the possible adverse effects on the doxorubicin drug as a result of glutaraldehyde treatment. These combined problems are inspiring pharmaceutical scientists to develop new synthetic forms of drug delivery that can help mitigate these undesirable effects while maximizing targeted drug delivery.

We believe that our delivery method will be different because our encapsulating materials are fully biocompatible, and should not produce any unforeseen effects on the doxorubicin itself. Furthermore, experimenters at Cornell University have already performed tests specifically with doxorubicin in order to determine the pH-dependency of its diffusion in dextran hydrogels, with positive results. Therefore we feel that our models and their comparison may shed light into the area of synthetic hydrogel drug delivery and its applications in future research.

Design Objectives

We will use Comsol Multiphysics to test our model designs of orally delivered hydrogel-mediated doxorubicin diffusion in physiological human body conditions. Our objectives are:

- To determine whether an appropriate dose of doxorubicin can be delivered. This will show whether our model system is viable for doxorubicin delivery. Rxlist gives the usual recommended dose for doxorubicin treatment as 60 to 75 mg/m^2, which translates to approximately 130 mg, or 2.39×10^{-4} mol of drug, for a normal adult male.

- To determine whether there is a significant difference between drug release inside the stomach versus the rest of the body, particularly the intestines. This will provide justification for our delivery system as opposed to the existing intravenous delivery system.

- Given the first two objectives, to achieve a steady and reliable release profile of doxorubicin inside the body. This will work toward making the final product medically viable.

Model Design I: Three-Layered Hydrogel Sphere

We will begin our approach to this problem by modeling the drug delivery vehicle as a sphere with three 1mm layers. The innermost layer will be made of dextran hydrogel crosslinked with methacrylic anhydride at a degree of substitution (DS) of 0.24. We chose DS = 0.24 because that value corresponded with the greatest difference in doxorubicin diffusivity in a study conducted by Kim and Chu (2000). The diffusivity difference with varying pH comes from the expansion or collapse of the hydrogel matrix due to molecular interactions in the crosslinked fibers of the hydrogel. Essentially, the pore size of the hydrogel increases with decreasing pH. The work by Kim and Chu also suggested an initial concentration of 1 mg/mL (or 0.6897 mol/m^3) of doxorubicin. The second layer will also be dextran-methacrylate hydrogel, but it would have no initial concentration of doxorubicin. This second layer is designed to act as a barrier so that the drug will not all diffuse out of the capsule at once; rather, we want drug release to occur over a period of six hours. This is approximately the amount of time that we estimate the spheres will remain inside the stomach. The final outer layer would be made of a temperature-sensitive biodegradable hydrogel composed of poly(ethylene oxide) and poly(L-lactic acid). A 2D representation of the spherical delivery system is presented in Figure 1 below:

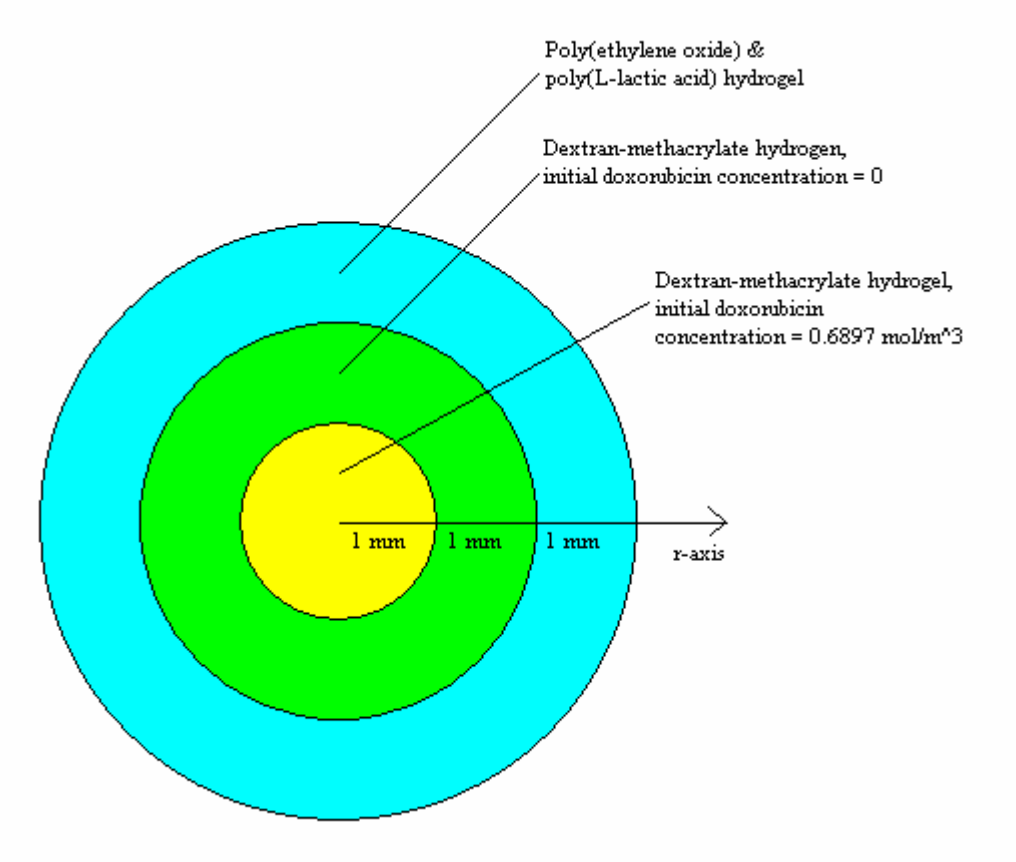


Figure 1 - 2D Representation of Spherical Drug Delivery Capsule

Our input model for Comsol is represented by the Figure 2 below:

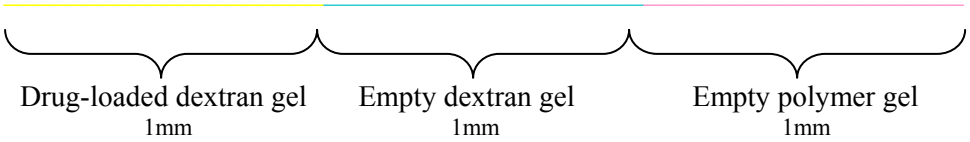


Figure 2 - 1D Model of Drug Delivery Capsule for Comsol

We were able to model our sphere in Comsol in 1D geometry by adjusting the standard governing equation and by using axisymetrical and insulating boundary conditions at the left and right ends, respectively. To see our governing equation and boundary and initial conditions in greater detail, please refer to Appendix A.

As previously mentioned, we attempted to simulate the physiological conditions of ingesting these spheres as closely as possible by assuming that the spheres would remain in the stomach for six hours before passing into the intestines. We also assumed that the pH of the stomach would remain relatively constant at pH = 3.0, as opposed to the more basic intestines at approximately pH = 7.4. This affected our choice of input parameters which are displayed in Table 1.

Table 1 – Model Design I Input Parameters

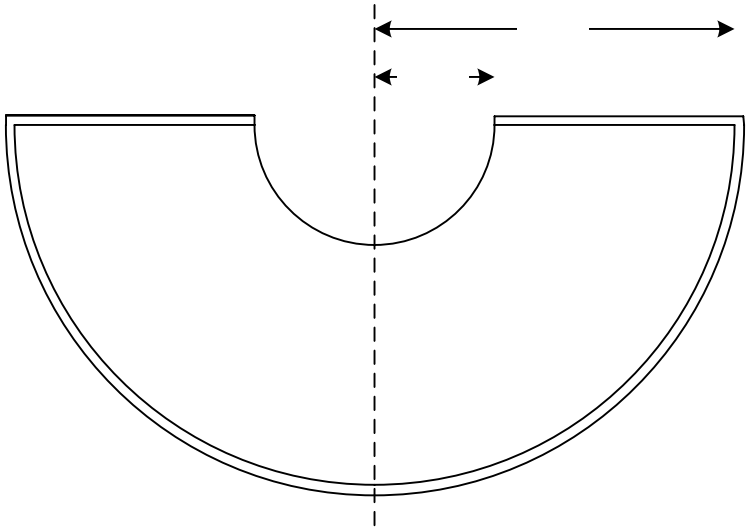
Spherical Design Input Parameters			
	pH = 3.0	pH = 7.4	
Initial Concentration[1]	0.6897	0.6897	mol/m^3
Dextran-Methacrylate Hydrogel Diffusivity[1]	1.972E-11	1.047E-11	m^2/s
Polyethylene oxide Hydrogel Diffusivity[2]	1.933E-11	1.933E-11	m^2/s

1: Kim and Chu 2000; 2: Jeong, et al 1997, Verma 2005

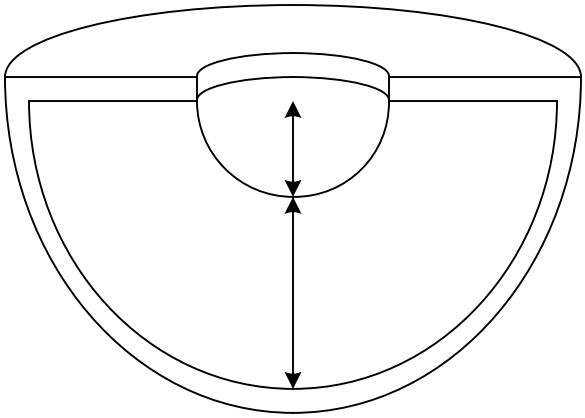
Our goal is to achieve reliable release of drug over the course of six hours at normal stomach conditions (temperature = 37°C, pH = 3.0) with a significantly lower rate of release at other values of temperature and pH.

Model Design II: Dextran-Methacrylate Hemisphere

Our second model is considerably different from the first. Instead of dealing with a spherical hydrogel with diffusion from the outer spherical surface, we are now looking at a hemisphere with a hollowed center. The center core is 1.0 mm in diameter with the outer hemisphere being 3.0 mm in diameter. Drug is released from the exposed surface of the hollow center while the other surfaces are covered with a biocompatible, completely impermeable polymer layer such as polyetheretherketone (PEEK). This can be more clearly seen in Figure 3, which maps out the geometry and dimensions of the second design.



(A)



(B)

Figure 3 – A) Cross-section cut from the side of the hemisphere drug delivery capsule. Note the impermeable outer layer and drug releasing divot. B) The hemispherical design again emphasizing three dimensional aspects of the pill.

The input parameters are modeled on the original design and literature by Kim and Chu, incorporating the initial value of 0.6897 mol/m^3 along with the same values for Dextran hydrogel diffusivity at pH = 3.0 and pH = 7.4 (Table 2).

Table 2 – Model Design II Input Parameters

Hemispherical Design Input Parameters			
	pH = 3.0	pH = 7.4	
Initial Concentration[1]	0.6897	0.6897	mol/m^3
Dextran-Methacrylate Hydrogel Diffusivity[1]	1.972E-11	1.047E-11	m^2/s

1: Kim and Chu 2000

We were able to model this geometry in Comsol as a 2-D quarter circle with symmetry around the axis penetrating the hollowed center. The boundary conditions used are as follows:

1) $\frac{\partial c_A}{\partial t} = 0$ at r = 1.5 mm and the top edge
2) $c_A = 0$ at r = 0.5 mm because we assume instant drug removal
3) Our model is axi-symmetric around the hollow center

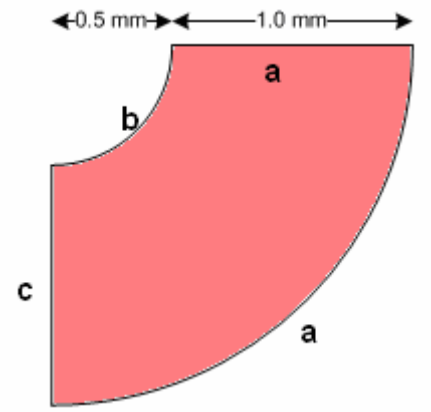


Figure 4 – 2D Axisymmetric Profile for Hemispherical Model in Comsol

As mentioned in our Design Objectives, our model design was intended to deliver an adequate amount of doxorubicin to the patient, as well as to deliver that drug in a relatively steady stream with respect to time. We suspected that the first objective would not be achieved, so we attempted to compensate by reaching for the greatest ratio of drug released per unit of drug delivery particle volume.

From our previous modeling with the multi-layered drug delivery sphere, we guessed at an initial radius of 1mm for the dextran-methacrylate hydrogel layer. This translates into a sphere of total radius 1.5mm, with a 0.5mm-radius dimple in the center. To verify these results we ran a mesh convergence that may be viewed in Appendix B.

Results and Discussion

Model Design I – Three-Layered Hydrogel Sphere

The objective of the modeling experiment was to show the behavior of a three-layered hydrogel sphere and its ability to deliver doxorubicin to the stomach in order to act as a safer and more selective form of chemotherapy. Figure 5 below shows the average concentration vs. radial distance from the center of the sphere.

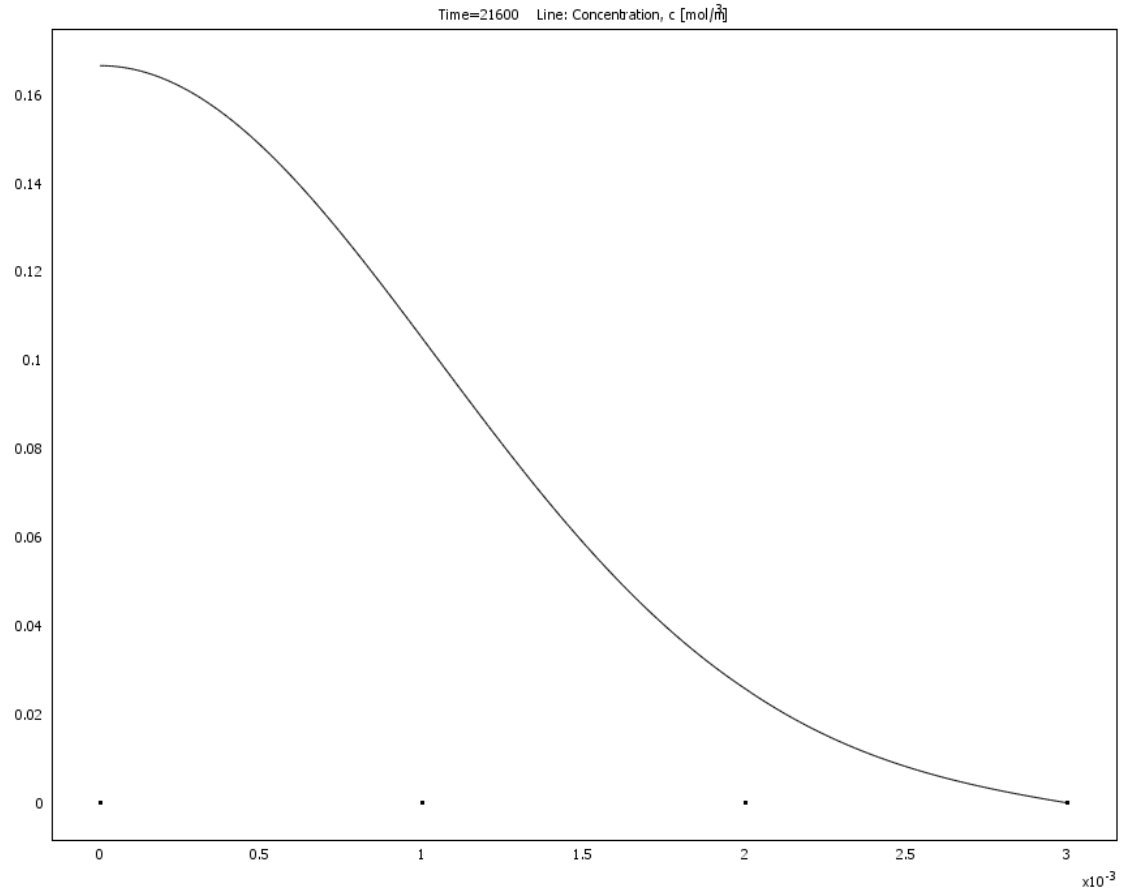


Figure 5 - Average Concentration vs. Radial Distance (Time = 6 hr)

This graph portrays how the average concentration decreases more sharply in the dextran-methacrylate layers ($0 < x < 2$mm) and levels off in the hydrogel polymer layer. This is expected because the protective hydrogel polymer layer has an 84% larger diffusivity constant than the dextran layer. This also portrays our boundary condition of zero concentration at the surface, assuming immediate removal of the drug once free of the gel sphere.

Another factor we modeled was the total amount of drug released from the modeled system plotted against a time variable. Figure 6 and Table 3 below shows the amount of doxorubicin released for the two different pH levels that we were considering. It is

apparent that at the lower pH of the stomach, more drug is released due to the chemical properties of the gel material. The higher pH of the small intestine shows a much lower amount of drug released. Over a period of 6 hours, the amount of drug released in the pH = 3.0 system is 3.57 times larger than that released in the pH = 7.4 system.

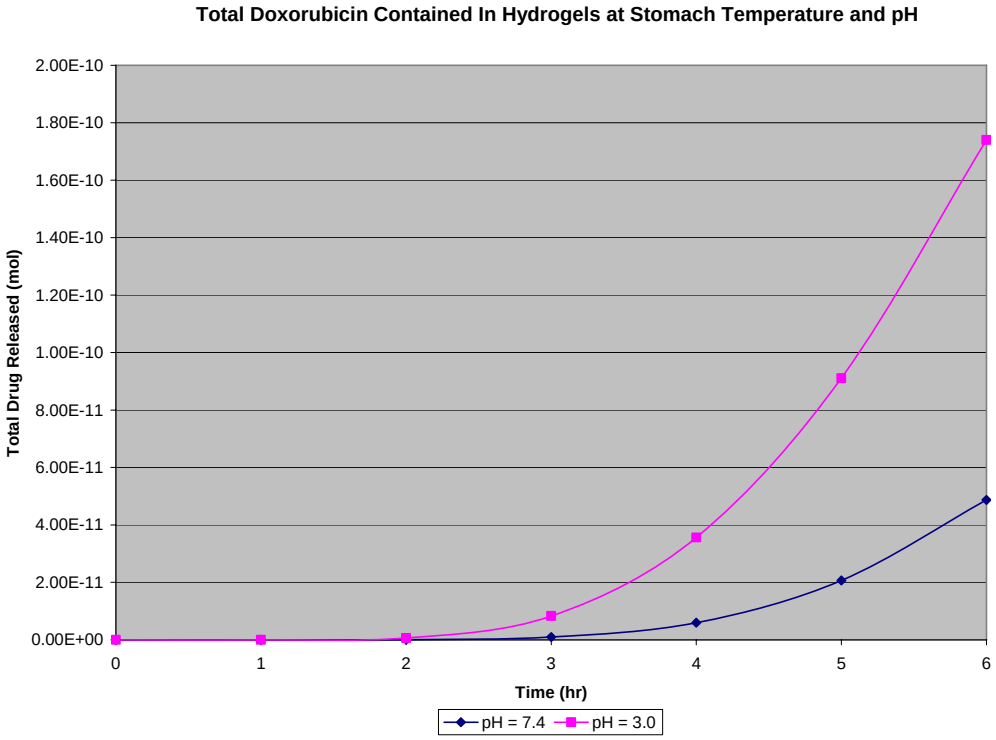


Figure 6 – Model Design I Total Doxorubicin Released vs. Time (pH = 3.0 & pH=7.4)

Table 3 – Doxorubicin Released Over Time From Model Design I

	Stomach pH		Intestinal (Systemic) pH	
Time (hrs)	Drug Remaining (mol)	Drug Released (mol)	Drug Remaining (mol)	Drug Released (mol)
0	2.89E-09	0.00E+00	2.89E-09	0.00E+00
1	2.89E-09	0.00E+00	2.89E-09	3.00E-15
2	2.89E-09	5.00E-14	2.89E-09	6.62E-13
3	2.89E-09	9.97E-13	2.88E-09	8.28E-12
4	2.88E-09	5.98E-12	2.85E-09	3.57E-11
5	2.87E-09	2.06E-11	2.80E-09	9.11E-11
6	2.84E-09	4.87E-11	2.71E-09	1.74E-10

Problems arise with this design including non-linear transient drug release along with a very small amount of total drug released. A linear rate for drug release is desirable because it allows the release mechanism to stay in check and be monitored more easily by physicians. As seen in Figure 6, the release rate increases exponentially and shows possible problems with sudden and delayed dosage. This can be dangerous due to the extreme bio-toxicity of doxorubicin. A sharp sudden dose could damage the stomach because of too high a concentration. It could also lead to problems with the duodenum

and small intestine because the release is delayed until the end of the six hour period. Furthermore, the overall amount of doxorubicin released stands at 1.74 x 10^{-10} moles after six hours in the stomach, which corresponds to only 9.46 x 10^{-5} mg, or 7.27 x 10^{-5} percent of an effective dose.

Model Design II – Dextran-Methacrylate Hemisphere

Our second design modeled the release of doxorubicin from a single dextran-methacrylate hydrogel layer within a 3 mm OD hemisphere with a 1 mm OD divot in the core. To do a true comparison between this and the original spherical model, we plotted the amount of drug released versus time, seen in Figure 7. This plot can be compared to the data in Figure 6 to see how our models differ.

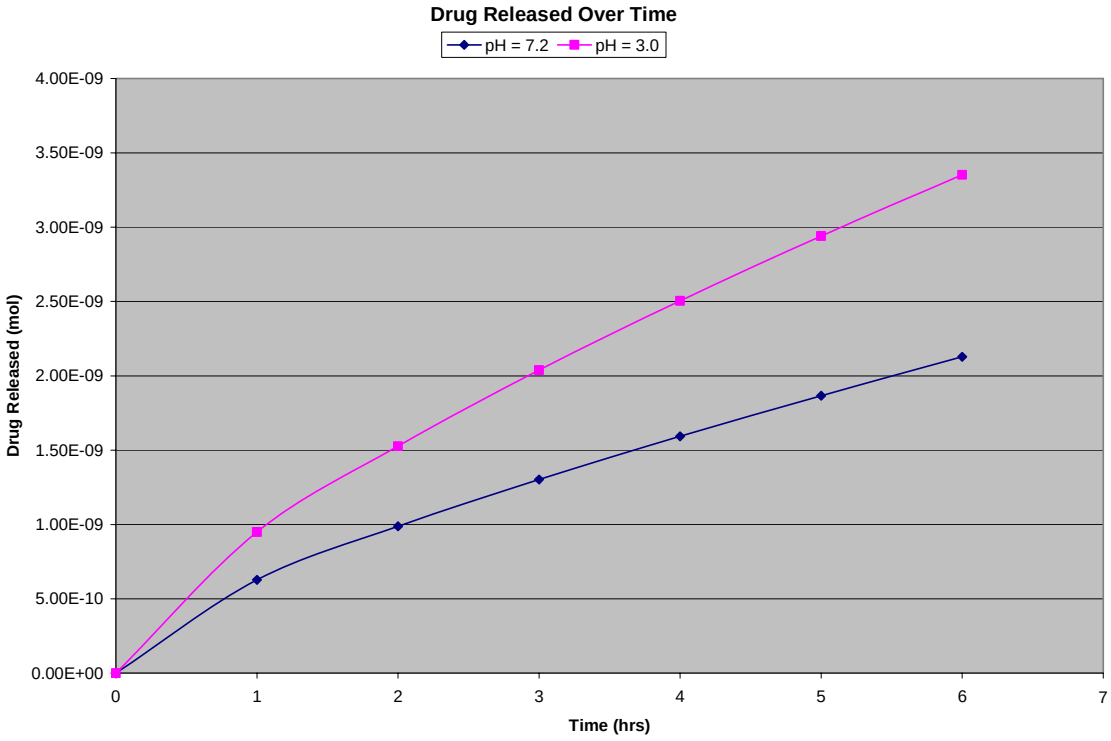


Figure 7 - Model Design II Total Doxorubicin Released vs. Time (pH = 3.0 & pH=7.4)

As shown in Figure 7, the total amount of drug released for the hemispherical model is twenty times larger than that of the spherical multilayer design (3.35 x 10^{-9} mol versus 1.74 x 10^{-10} mol). This is a vast improvement, though still only 0.0014% of an effective dose. The major quality of the second design is that the rate of drug release becomes linear after the first hour in the pH = 3.0 setting. This is optimal when compared to the exponential growth of the original design because it is easier to predict and control the drug release behavior within the body.

Table 4 – Doxorubicin Released Over Time From Model Design II

	Stomach pH			Intestinal (Systemic) pH		
Time (hrs)	Drug Remaining (mol)	Drug Released (mol)	Total Drug Released (mol)	Drug Remaining (mol)	Drug Released (mol)	Total Drug Released (mol)
0	4.69E-09	0.00E+00	0.00E+00	4.69E-09	0.00E+00	0.00E+00
1	4.21E-09	4.74E-10	9.49E-10	4.38E-09	3.14E-10	6.28E-10
2	3.93E-09	7.63E-10	1.53E-09	4.20E-09	4.94E-10	9.88E-10
3	3.67E-09	1.02E-09	2.04E-09	4.04E-09	6.51E-10	1.30E-09
4	3.44E-09	1.25E-09	2.50E-09	3.89E-09	7.96E-10	1.59E-09
5	3.22E-09	1.47E-09	2.94E-09	3.76E-09	9.33E-10	1.87E-09
6	3.01E-09	1.68E-09	3.35E-09	3.62E-09	1.06E-09	2.13E-09

In order to check how well-optimized the 1.5mm-radius size was for the hemispheric drug delivery system, we contrasted it with two other sizes: one larger (3mm-radius) and one smaller (0.6mm-radius). The larger hemisphere kept a linear drug release profile and delivered more doxorubicin overall, but had a lower drug release to volume ratio. The smaller hemisphere had a considerably larger drug release to volume ratio, but had a more curved drug release profile, thus defeating the purpose of the revised geometry. Hence, we concluded that the 1.5mm-radius hemisphere was adequately appropriate for the final model.

Table 5 – Size Optimization

Total Radius	Initial Drug (mol)	Final Drug (mol)	Drug Released (mol)	Total Drug Released (mol)	Drug Release per Volume Ratio
0.6 mm	3.00E-10	2.35E-11	4.67E-09	9.33E-09	1.03E-08
1.5 mm	4.69E-09	3.01E-09	1.68E-09	3.35E-09	2.37E-10
3 mm	3.75E-08	3.25E-08	4.99E-09	9.99E-09	8.83E-11

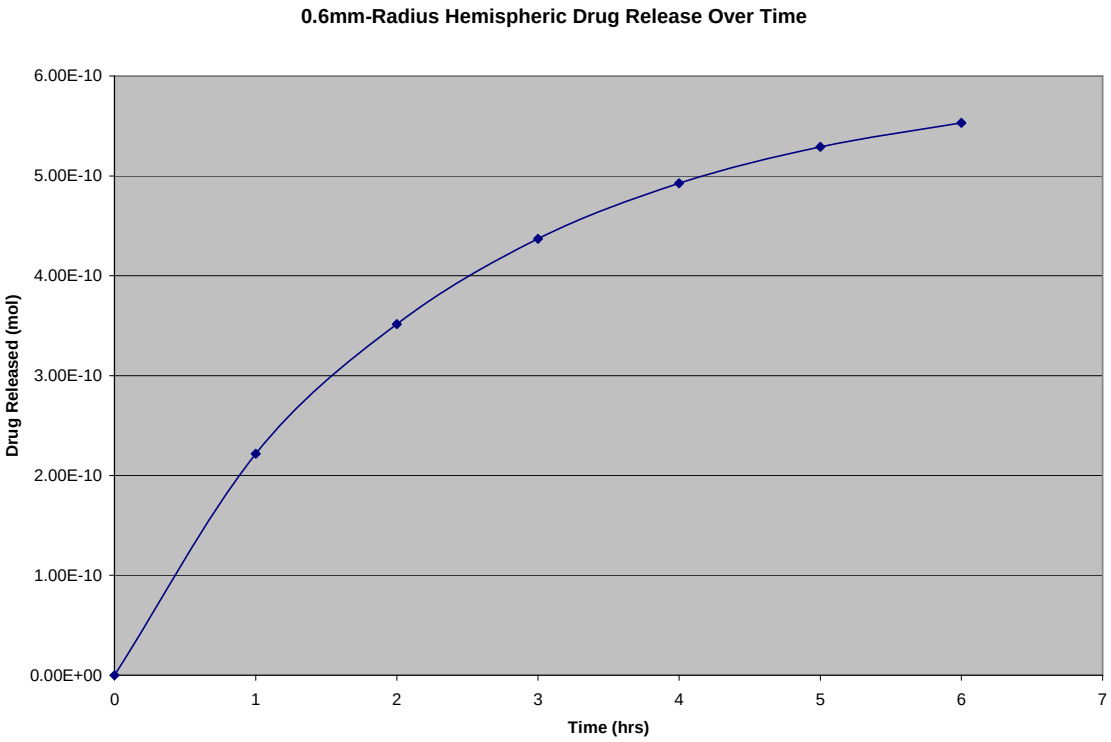


Figure 8 - 0.6mm-Radius Hemispheric Drug Release Over Time

Once we came to the point of deciding on a 1.5 mm radius hemisphere, we conducted the simulation and solved for the solution at t = 21600 seconds. We obtained a contour plot to show the amount of drug as one moves to the center of the sphere toward the release edge.

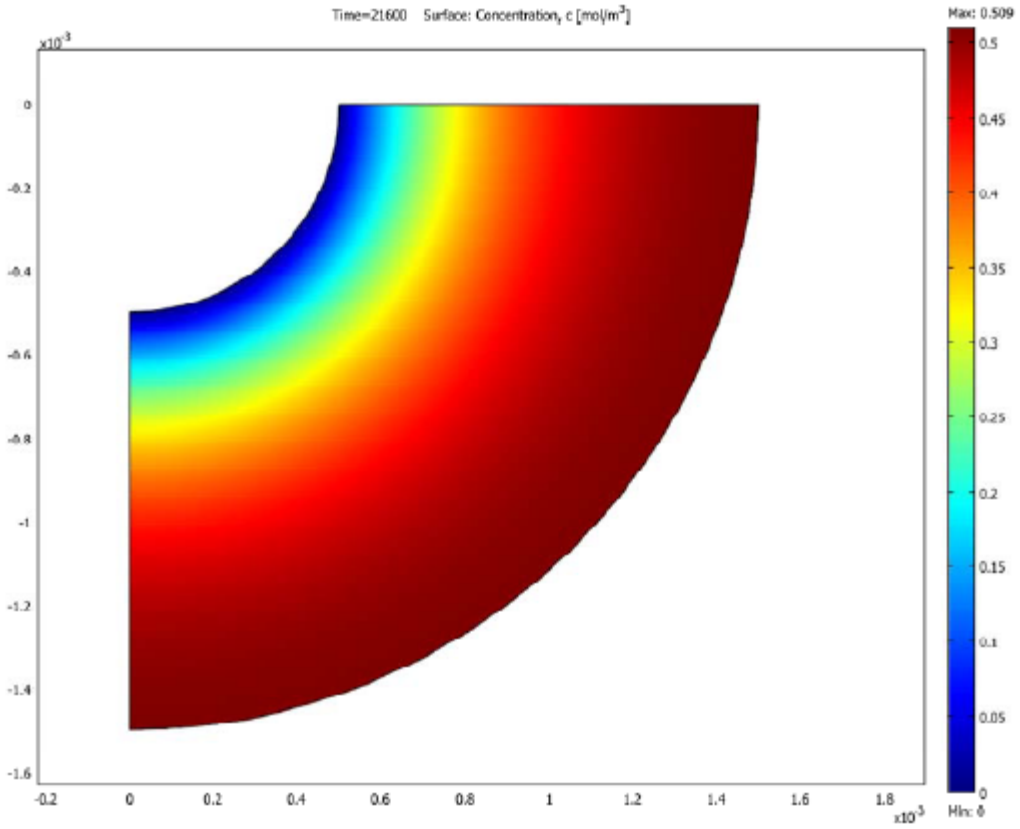


Figure 9 – Concentration Contour Plot of Model Design II

Sensitivity Analysis Work (Model Design II)

The following sensitivity analysis portrays how the amount of drug released varies at difference values of initial concentration, diffusivity, and maximum mesh size. The diffusivity and initial concentration values are set to be at 75%, 100%, and 125% of the design parameters. The values used are shown in the table after the graph.

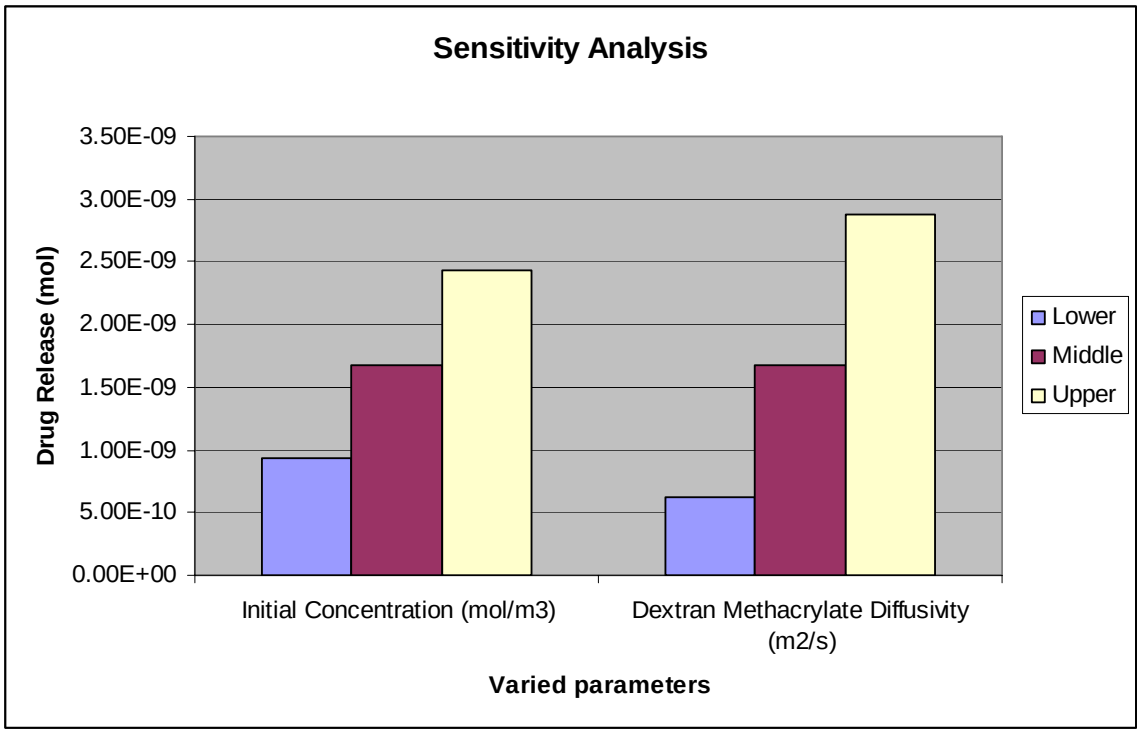


Figure 10 - Sensitivity Analysis plot

Table 6 – Sensitivity Analysis data

Initial Concentration (mol/m^3)	Drug Released (mol)	Percent Change
0.5173	2.26E-09	-20.0
0.6897	3.01E-09	0
0.8621	3.76E-09	24.7
Dextran Methacrylate Diffusivity (m^2/s)	Drug Released (mol)	Percent Change
4.93E-12	6.24E-10	-62.7
1.972E-11	1.67633E-09	0
4.437E-11	2.87E-09	71.2

It is apparent in Figure 10 that varying the initial concentration and the diffusivity values produce similar trends in the amount of drug that is released from the spherical gelatin capsule. Increasing the diffusivity allows more of the drug to be released. This can be

supported by a higher temperature or a lower pH than is defined in our original design parameters of 37ºC and 3.0 pH.

Initial Concentration

As shown in Figure 11, initial concentration has the weakest influence on the amount of drug which can be released from the hydrogel sphere. When we decrease the initial concentration to 75% of the original value (0.5173 mol/m^3), we see a 20% decrease in the amount of released drug. Similarly, we are presented with approximately a 24.7% increase in the drug released when we simulated the drug release at the higher initial concentration.

We can conclude that the initial concentration shows little room for improvement, because the same percentage change in drug concentration must be added to obtain the same percentage change in drug released. Therefore, if we double the initial concentration we shall subsequently double the drug released.

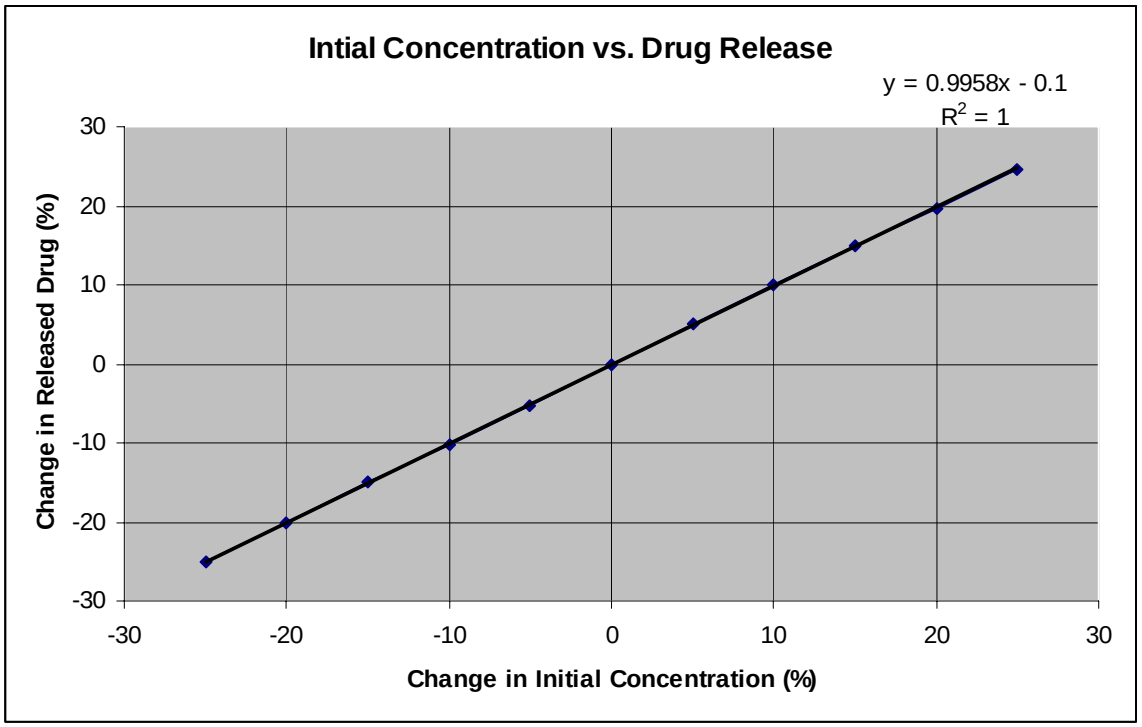


Figure 11 - Initial Concentration vs. Drug Release (Hemisphere)

Dextran-Methacrylate Diffusivity

The diffusivity change in our dextran methacrylate layer shows the biggest increases as presented thus far. When the diffusivity value is increased by 125% of the original (4.437×10^{-11} m^2/s) we see a 71% increase in the amount of drug released. Reducing the diffusivity to 4.93×10^{-12} m^2/s caused a 63% decrease in the amount of drug released. This is the layer containing the drug and therefore has the highest effect on the doxorubicin released due to the changes in diffusivity. The detailed correlation is shown in the following graph with a linear fit to detail the slope of the regression.

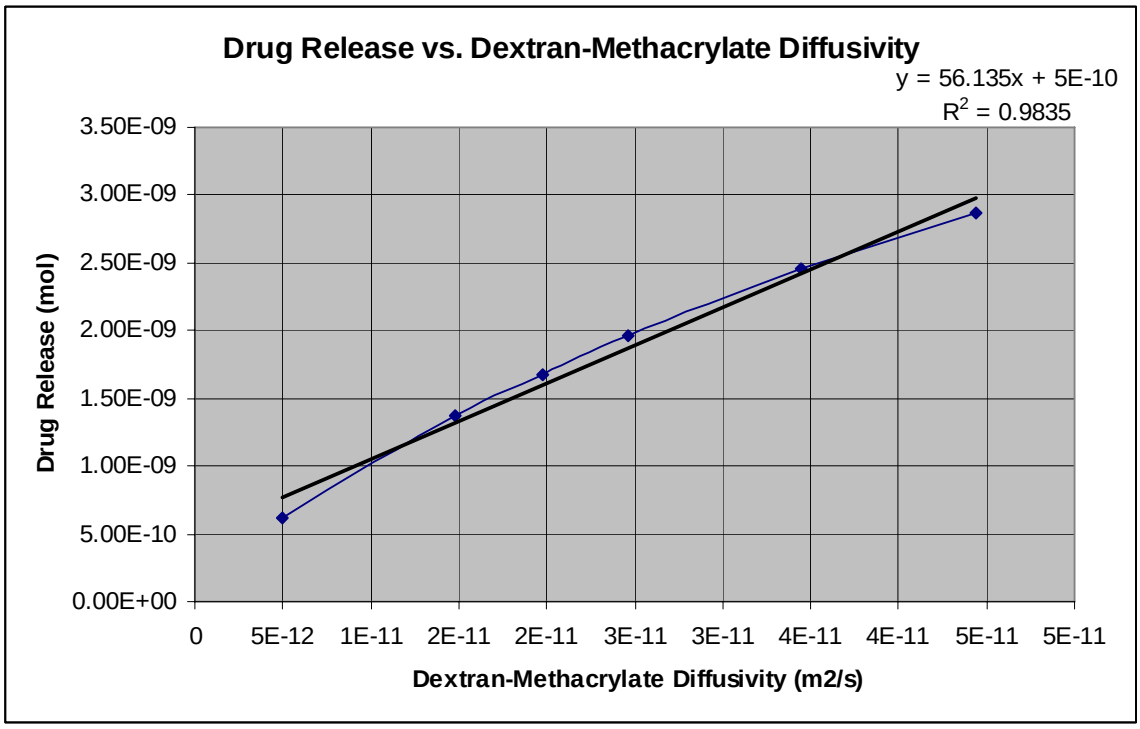


Figure 12 - Drug Release vs. Dextran-Methacrylate Diffusivity (Hemisphere)

Design Constraints

The first criteria we took into account for our design were health and safety. Currently, doxorubicin is widely used in chemotherapy, but doses above 550 mg/m^2 can be lethal. The drug is typically injected intravenously, so this has not yet been a problem in treatment. Our capsule is administered orally, though, so we needed to ensure that the drug had a constant flux that did not exceed the threshold dosage. We also designed our drug to only be active in the low pH of the stomach to reduce side effects that come with intravenous treatment, but further testing must be done with our encapsulated drug to determine new side effects.

Ethical considerations must also be taken into account when testing our product. Animal testing will be the first phase of testing, and although this brings many ethical debates on its own, human testing will take the most consideration. Because this is a drug that treats cancer, human lives are at stake. We must be able to prove that our capsule delivers the drug as effectively or better than the intravenous treatment for it to be tested at all. We expect our simulations and future animal testing will ensure that this is true.

Other design criteria which we took into account were economics, manufacturability, and sustainability. According to Biocompare.com, the price for doxorubicin is currently listed at $109 per 10 mg. We expect the price of our encapsulated drug to be comparable, and the overall treatment will be more economically favorable for the consumer because it does not involve any extra costs that come with intravenous treatments and hospital visits. The manufacturing will include technology similar to other pill producing processes, which mainly involves the photopolymerization reactions utilized when making our hydrogels. Our research has found minimal environmental impact from photopolymerization. Furthermore, the shelf life of our product will be long because the capsule is designed only to be active at body temperature. Finally, our product will be sustainable for very long because doxorubicin has been long-established and widely used as an effective drug in cancer treatment.

Conclusions and Design Recommendations

Our model designs saw both success and failure with respect to our original Design Objectives. Model Design I, the three-layered hydrogel spheres, was inadequate in that it failed to deliver an appropriate amount of doxorubicin in a single dose and yielded an inconsistent level of drug release over time. It did succeed in achieving a significantly higher doxorubicin release in the stomach than in the intestines and systemic circulation. Model Design II, the dextran-methacrylate hemispheres, provided a significantly greater amount of total drug released (though still not a complete dose) and also had a considerably greater amount of outward flux in the stomach pH conditions than in the systemic pH conditions. Furthermore, Model Design II improved on Model Design I by providing a nearly linear drug release profile over the six hours of simulation.

Through this study, we have obtained theoretical, though not yet experimental, evidence that it is indeed possible to have a drug delivery system that can specifically target the stomach while withholding drug from the rest of the body. We have shown that such drug release can occur at a controlled, steady rate given the correct choice of geometry. However, our study also suggests that our particular system of doxorubicin delivery via dextran-methacrylate hydrogel carriers is not adequate for the task. The amount of drug delivered in a realistic time frame is simply not enough to have any worthwhile effect on gastric carcinoma in a typical patient.

Thus, our design recommendations must focus on making improvements on the raw amount of drug that may be released from our delivery particles. One such improvement could be the development of a new type of hydrogel (or other substance) that could retain the pH sensitivity of dextran-methacrylate while also being able to hold a greater initial concentration of doxorubicin or analogous drug. Otherwise, new carrier substrates could be created to hold similar initial concentrations of drug, but with greater overall diffusivity values so that greater proportions of stored drug could be released in the given time period. One final improvement that could be made in this field would be an experimental analysis of how much doxorubicin would be necessary for gastric carcinoma treatment if administered inside the stomach. Since we only had data dealing with systemic intravenous application of the drug, we had to assume that the total amounts that we came up with were inadequate; yet, it is possible that the total amount needed could be significantly less given stomach lining absorption.

Appendix A

Model Design I – Three-Layered Hydrogel Sphere

The overall Governing Equation for mass transfer in a sphere is the following:

$$\frac{\partial c_A}{\partial t} + (v_r \frac{\partial c_A}{\partial r} + v_\theta \frac{1}{r}\frac{\partial c_A}{\partial \theta} + v_\phi \frac{1}{r\sin\theta}\frac{\partial c_A}{\partial \phi}) = \ldots$$

$$D_{AB}(\frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial c_A}{\partial r}) + \frac{1}{r^2\sin\theta}\frac{\partial}{\partial \theta}(\sin\theta\frac{\partial c_A}{\partial \theta}) + \frac{1}{r^2\sin^2\theta}\frac{\partial^2 c_A}{\partial \phi^2}) + R_A$$

We can eliminate the generation term because there is no drug generation within the nanoparticle. Furthermore, we can eliminate the convection term because none exists within the particle. Lastly, we can ignore diffusion elements in the θ and φ directions because our purpose is to model outward flow. Thus, the simplified Governing Equation is as follows:

$$\frac{\partial c_A}{\partial t} = D_{AB}\frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial c_A}{\partial r})$$

The Boundary Conditions that we will use are as follows:

1. Drug concentration everywhere outside of the particle is equal to zero.
   $c_A\big|_{r=200} = 0$
2. Drug flux is equal to zero at r = 0.
   $\frac{\partial c_A}{\partial r}\big|_{x=0} = 0,\ \frac{\partial c_A}{\partial r}\big|_{y=0} = 0$

The Initial Conditions are:

1. Drug concentration inside the core is equal to the initial concentration 0.6897 mol/m^3:
   $c_A\big|_{r\le 50} = 0.6897\ \text{mol/m}^3$
2. Drug concentration everywhere else is equal to zero:
   $c_A\big|_{r>50} = 0$

Appendix B

Model Design II – Dextran-Methacrylate Hemisphere

Direct (UMFPACK) a linear system solver, was used to solve the algebraic equations.

Problem Statement

	Description
Geometry Type	2-D
Temperature Dependence	Problem Dependent on Temperature
Simulation Type	Transient: Concern with Amount of Drug Delivered over a period of time
Time Dependent	Problem dependent on Time
Flow Type	No Fluid Flow, No Momentum
Convective Term	No Convection
Surface Type	Geometry is fixed
Flow Regime	Drug is Incompressible

Time Integration Statement

Time Integration	Description
Time Step Algorithm	Increments of time is unchanging
Start Time	0
End Time	21600
Time Step	60
Number of Time Steps	360

Parameters

Parameter	Value
Times	0:60:21600
Relative tolerance	0.01
Absolute tolerance	0.0010
Times to store in output	Specified Times
Time steps taken by solver	Free
Manual tuning of step size	N/A
Initial time step	N/A
Maximum time step	N/A
Maximum BDF order	5
Singular mass matrix	Maybe
Consistent initialization of DAE systems	Backward Euler
Error estimation strategy	Include Algebraic

Boundary Settings

Point		**1**
Style	mol/m3	**{0,{0,0,0}}**

Subdomain Settings

Subdomain		1
Diffusion coefficient (D)	m^2s	1.972e-11
Time-scaling coefficient (Dts)	1	1
Concentration	mol/m^3	0.6897

Element Mesh: Model Design II – Dextran-Methacrylate Hemisphere

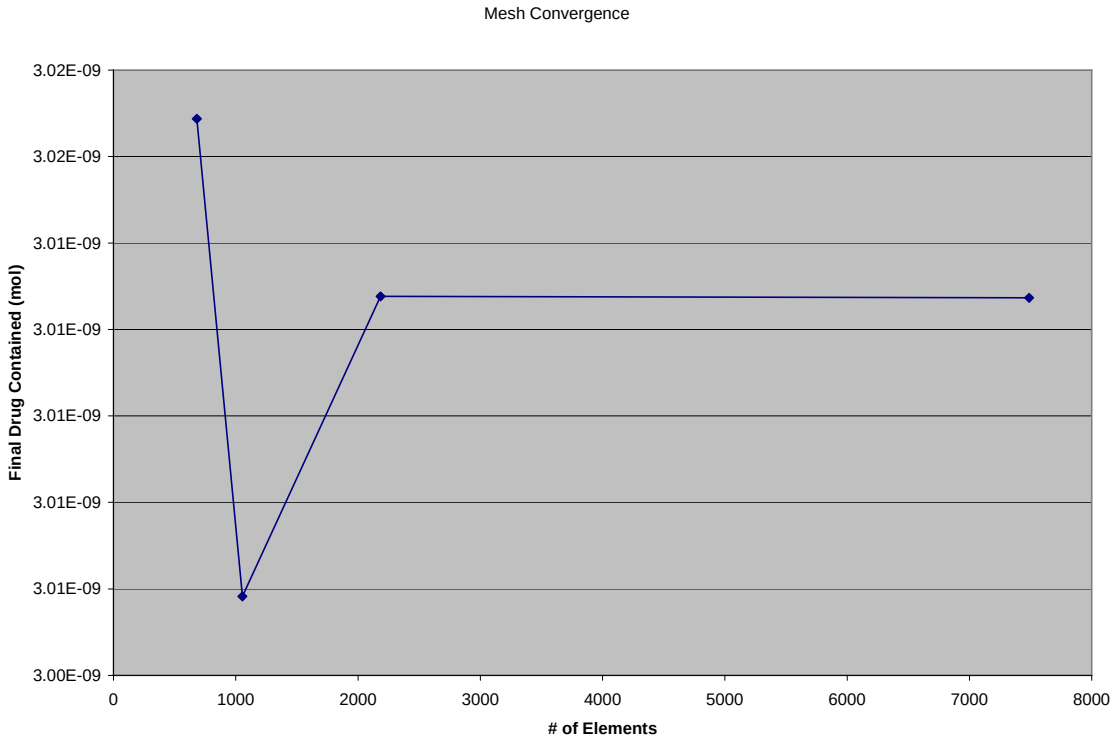


Figure 13 - 1.5mm-Radius Hemispheric Mesh

Since there is a negligible (<<0.01%) change between the last two points of the convergence, we decided to stay with the third value, which had 2184 elements. The actual structured mesh can be seen below and works well for the Comsol model.

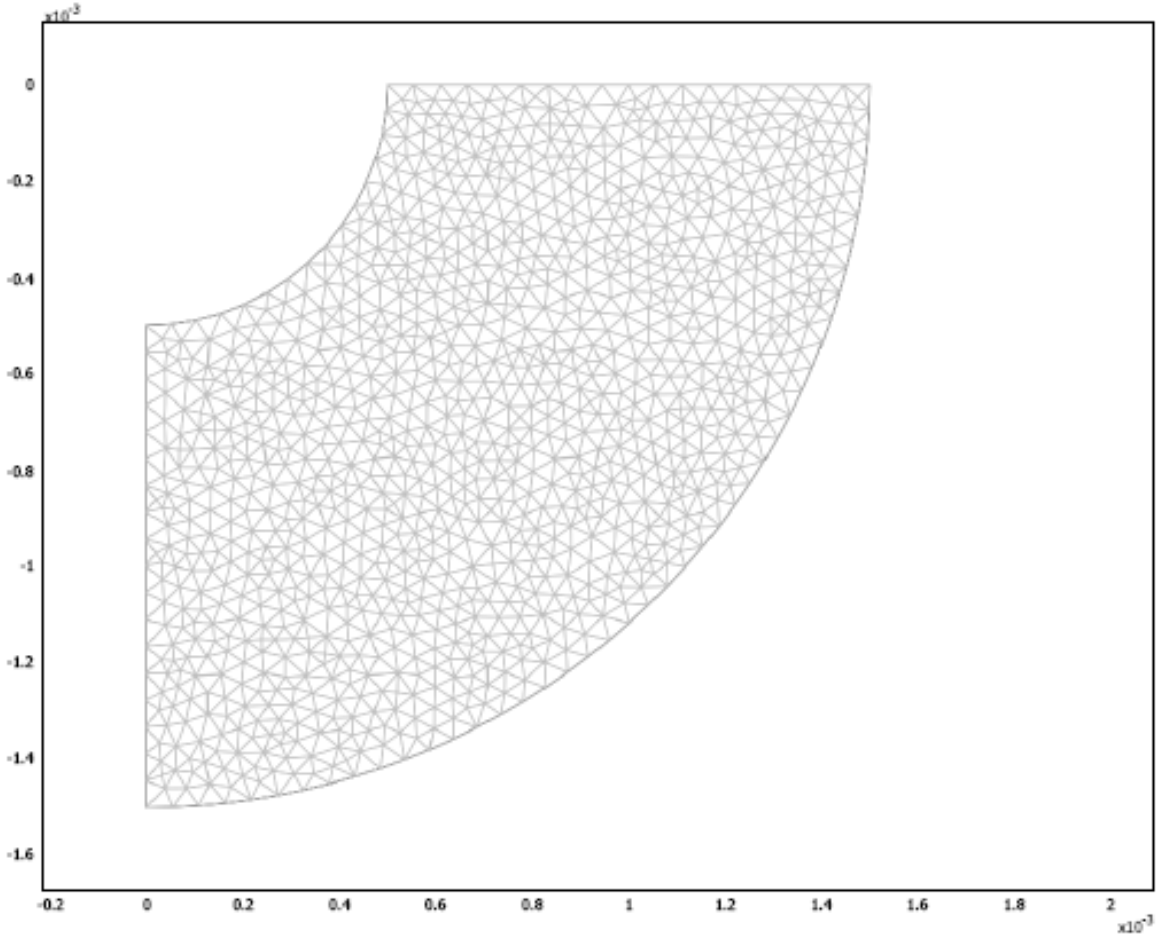


Figure 14 - Mesh for the Hemispheric Geometry

Note: Only Model Design II is featured here because it is our final design recommendation. The Comsol data and mesh information for Model Design I was discarded due to of its ultimate triviality.

Appendix C

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