Paclitaxel Drug Elution from a Biodegradable Stent

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Executive Summary

Recently, drug-eluting stents have become a common treatment for coronary heart disease. These stents are usually loaded with a drug that prevents restenosis. Unfortunately, there are risks associated with the placement of these metallic structures in the body. Stent thrombosis is one such problem, and can lead to restenosis despite the presence of drug. Advances in biomaterials have led to the development of biodegradable stents, which can reduce the risks associated with stents. However, since it is a relatively new technology, it is not known to what degree the biodegradability affects the drug releasing properties of the stent. We hope to characterize these effects and to determine if the biodegradability reduces the efficacy of the stent when compared to normal non-degradable stents. To accomplish this, we modeled a stent that diminished in size over time using COMSOL Multiphysics, and monitored the drug concentration in the nearby tissue. We established that our model was a viable predictor of actual stent behavior by comparing our simulated results with previous studies. We were then able to determine the optimal initial loading stent concentration of our modeled drug, paclitaxel, to ensure therapeutic levels in the tissue. Lastly, we found that drug concentrations in the tissue were not substantially different between the degradable and non-degradable models. This affirms the effectiveness of using biodegradable stents, showing them as a viable alternative to traditional metal stents.

Introduction

With the advent of the balloon angioplasty technique stents have become one of the major methods of treating obstructive coronary artery disease over the past decade. While this procedure is effective in alleviating symptoms of ischemic coronary artery disease, it can also hinder surgical revascularization; effectively blocks vessel side branches, prevents positive remodeling, requires long-term anti-platelet therapy, and predisposes the vessel to late stent thrombosis.

Advances in biomaterials have led to the development of biodegradable stents. Polymers such as poly(d,l-lactic acid) (P(DL)LA) and poly(d,l-lactic-co-glycolic acid) (P(DL)LGA) can be used to construct stents which can be broken down in the body over a relatively short period of time. This is particularly important in cardiology for several reasons. Considering the short-term need and the long-term complications with metallic stents, biodegradable drug-eluting stents may be a suitable alternative. These types of stents are completely broken down in the body, thereby eliminating the potential complications of arterial rupture, intimal hyperplasia, and thrombogenesis. More importantly, the risk of stent restenosis can be decreased by paclitaxel-eluting coronary stents, which significantly reduce neointimal hyperplasia after stent placement, resulting in increased vessel diameter, and reduced restenosis.

Paclitaxel is an antiproliferative compound that binds to tubulin and so inhibits the regular separation of chromosomes in dividing cells. Past research has shown that the use of paclitaxel-eluting stents has contributed to better healing and effective inhibition of restenosis. However, the stent must not degrade either too early or too late because a therapeutic concentration of the drug is desired in the tissue to inhibit restenosis. For this reason, the timing of the optimal degradation period must be taken into consideration. However, since drug-eluting stents are a relatively new technology, little research has been conducted characterizing these stents and their effects in the body.

Design Objectives

The goal of our project is to determine the drug release mechanism and the drug concentration profiles from P(DL)LA, P(DL)LGA stent-based delivery of paclitaxel in arterial tissue. Thus, we first needed to design a model which could accurately predict paclitaxel release behavior for both degradable and non-degradable stents. This would require obtaining information on the various geometries and physical parameters of the stent and drug.

We then hoped to determine the optimum initial loading of the stent, such that the concentration of paclitaxel in the tissue would remain within therapeutic bounds for the duration of the stent's presence in the body, a period of about thirty-two days. This is essential because paclitaxel at too high a concentration can cause cytotoxic effects in the tissue. However, it is also necessary for the drug to remain above a certain level in order to ensure proper prevention of restenosis.

Lastly, we wished to confirm the viability of biodegradable stents for treating coronary artery disease. Since this is a relatively new technology, it is necessary to ensure that they maintain the same level of efficacy as the more traditional metal stent treatment. The effects of the receding stent edges will alter the distribution of drug in the tissue. However, we hope to show that the concentration of paclitaxel in the arterial wall does not differ significantly from that of metal stents.

Schematic

The model assumes that the drug diffusion occurs at the following three regions, the PLA polymer, the drug-loaded PLGA polymer, and the arterial tissue. A 2D axis-symmetric model about the center of the lumen was used to represent the implanted stent. The stent was assumed to be non-slipping and directly in contact with the tissue. We modeled the stent as a thin slab in contact with a large segment of arterial tissue. The stent is composed of two layers: a thicker insulating containing no drug initially, and a thin layer in between the first layer and the tissue, which is loaded with drug. These two layers degrade from their thin ends at a fixed rate.

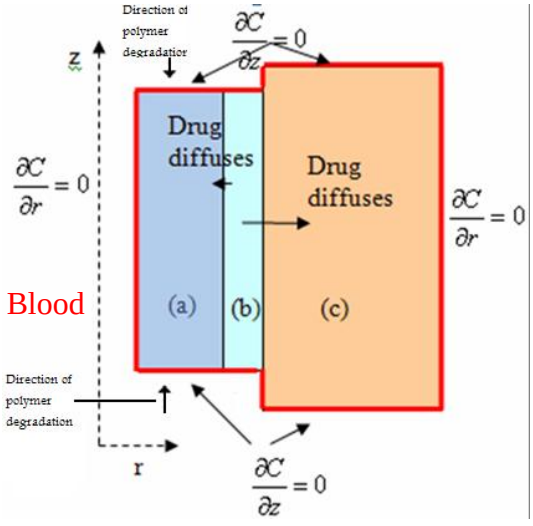

Figure 1: Schematic of COMSOL model. (a) Relatively low-diffusivity polymer P(DL)LA to minimize diffusion in the r direction. (b) Drug-loaded polymer, P(DL)LGA. (c) Arterial tissue. Governing equation Figure not drawn to scale.

Some simplifications to our model had to be incorporated so that it could be effectively implemented in COMSOL. We found literature values on the solubility of paclitaxel in water, which was found to be very small. We therefore assumed that the solubility in plasma was also negligible, which allowed us to disregard mass transfer into the blood. The degradation rate and manner we also simplified; real stents do not degrade in a linear fashion and usually develop pores rather than degrading along a single axis. Lastly, we assumed the pharmacokinetics of paclitaxel to be first-order kinetics. This is a reasonable approximation from data we found from previous studies.

Results and Discussion

Initial Load

We used the drug concentration from Venkatasubramanian (2008) as the paclitaxel drug concentration in the stent (69.30 µM). With our model, we noted a sharp rise in tissue concentration within the first 10 hours. At the initial load used by Venkatasubramanian, we found that the spike in drug concentration (see Figure 11) in the tissue would be above the therapeutic maximum of 10,000 nM. The concentration used in their research was to treat cancer tissue where toxicity was less of a concern; we on the other hand are attempting to determine a concentration suitable for healthy tissue. We then reduced the initial load in our stent to 60% of the value used by Venkatasubramanian in 10% increments.

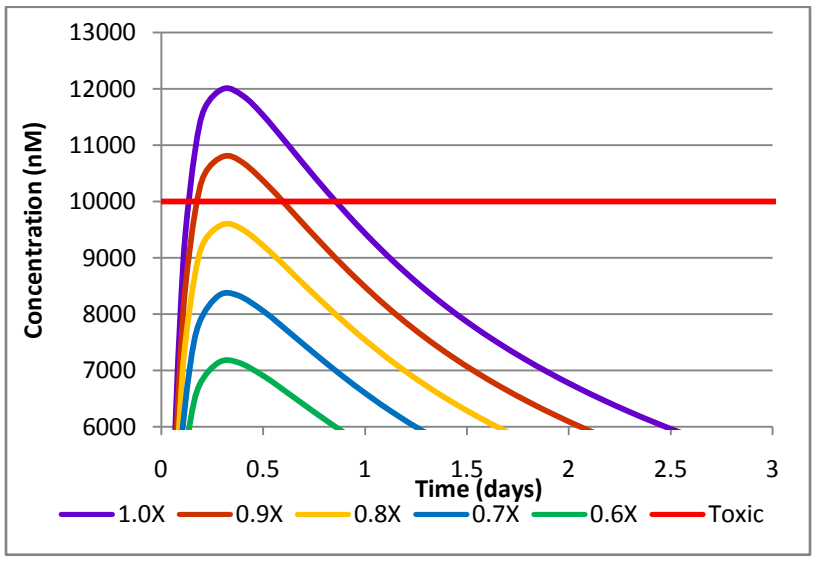

Figure 2: Concentration at center, 5 microns deep in the tissue at various initial loads.

It was determined that at 80% the peak concentration would be below toxic levels while maintaining the highest therapeutic concentration at day 32 (Figure 12). At this load, drug concentration in the tissue 5 µm from the stent would peak at 9,596 nM.

Tissue Concentration

As expected, there is a higher concentration of paclitaxel near where the stent was implanted. The region of the coronary artery that has a drug concentration higher than the minimum concentration (100 nM) is indicated by the red and green areas. The line shows where the concentration is 100 nM.

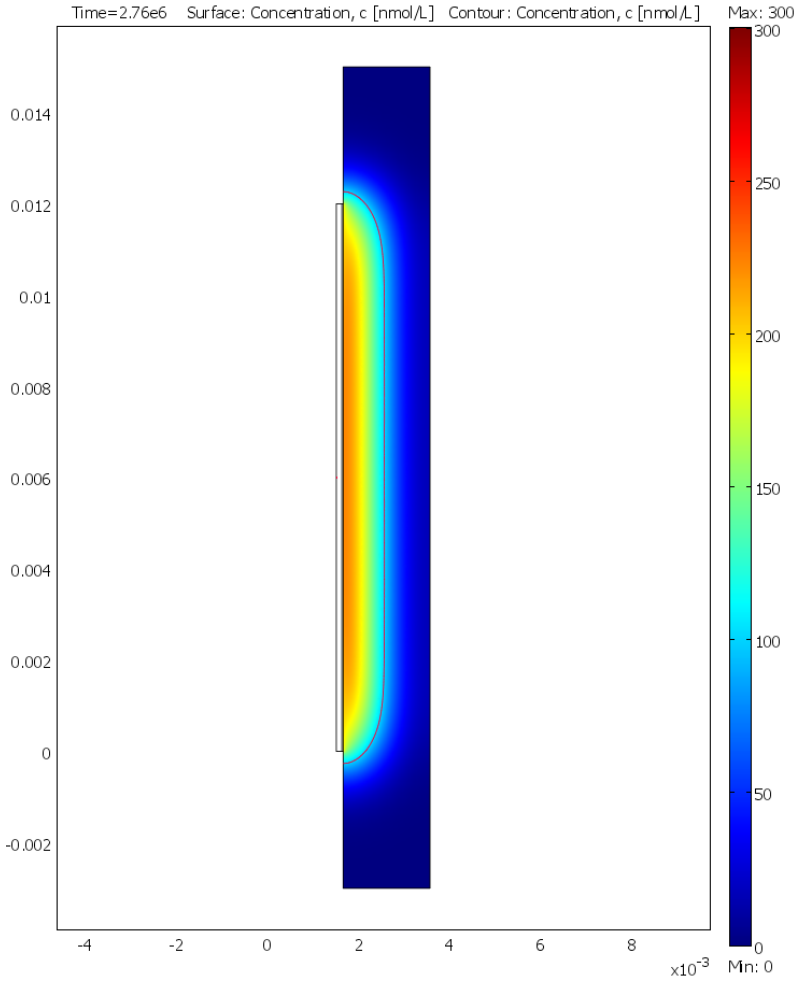

Figure 3: Surface plot of final paclitaxel concentration (after 32 days). Line indicates 100 nM.

It is clear that the region immediately surrounding the stent contains a therapeutic concentration of the drug, thus we can assume that there is a low likelihood of restenois, since the area with the highest probability of blockage (near the stent) is also the area with the highest concentration of the drug. Particularly the fact that the drug persists in the tissue after the stent has degraded is a marked improvement over drug coated metal stents.

Moving versus Nonmoving Models

After determining the optimum initial load of our stent, we compared our moving model of the biodegradable stent (degradation) with a modified nonmoving model (no degradation) to see if the degradation of the biodegradable stent causes any significant changes in drug concentration in tissue as compared to a traditional non-degrading stent. We chose a point at z=11mm, r=1.85mm (1 mm from the end of the original stent length, and 0.2mm depth into the tissue) because we reasoned that differences in drug concentration would be most visible in tissue nearer the edge of the stent. In this area, the shortening of the stent may result in lowered drug concentration.

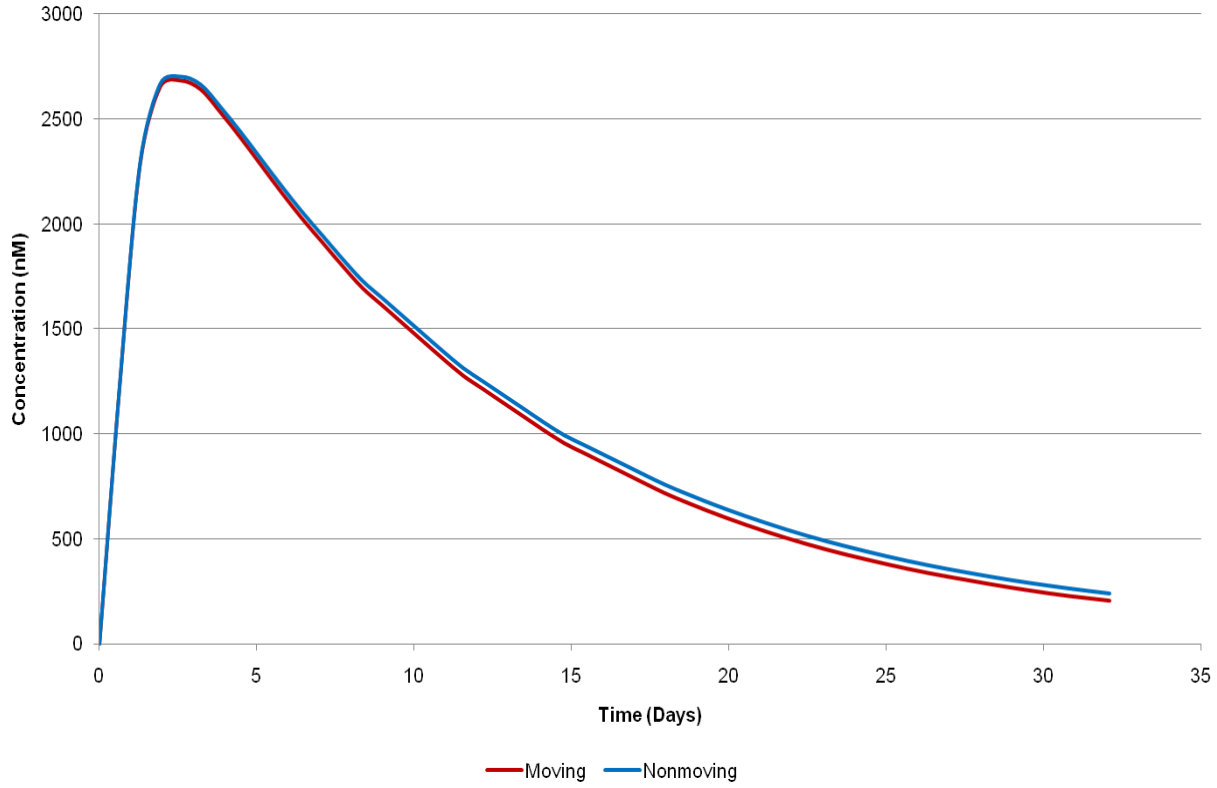

Figure 4: Comparison of concentration at a single point between non-moving and moving model.

After running both models and comparing the drug concentration over time at our chosen point, we see that the moving model has a very similar concentration profile as the non-moving model (Fig. 5). We recognize that the drug concentration is slightly lower in the moving model than in the nonmoving model, but the difference is not apparent until about 5 days after initial time. The concentration from the moving model remains similar to that of the nonmoving model, and both models stay well above the minimum therapeutic concentration of 100nM and under the toxicity limit of 10,000 nM throughout the duration of the simulation. Thus, we conclude that our moving model, representing a biodegradable stent, is as effective as the nonmoving model, representing a non-degrading stent, in delivering appropriate concentrations of paclitaxel into the tissue.

Validation

To validate the release profile of our model over time, we examined the experiment reported by Levin et al. in 2004 in which the authors investigated the release profile of paclitaxel into calf internal carotid arteries over a period of 72 hours by measuring the total concentration present in the tissue at different times. The authors presented the release profile as a normalized drug concentration, a fraction of the final drug concentration. We used our model and modified the tissue diffusivity and initial load to those reported in the study to simulate their experiment conditions and compared the results.

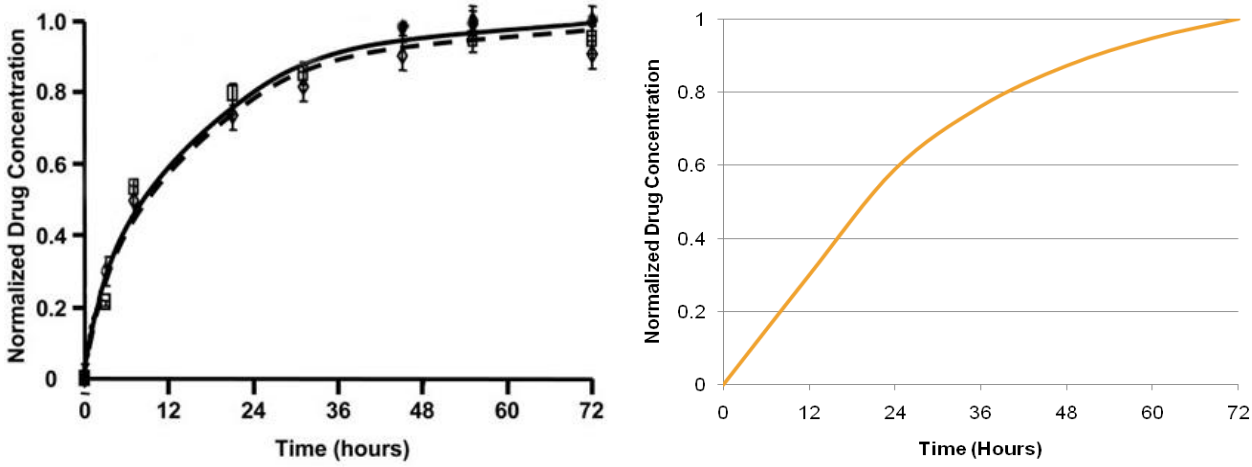

Figure 5: Comparison of Paclitaxel release from previous experimental data (left, Levin et al. 2004) and our simulation (right)

We observed that the release curve we obtained is very similar to that from the study. Our simulation underestimates the amount of drug released in the first day, but closely corresponds to the release profile in the second and third days of the experiment. We feel that this comparison validates the release profile of paclitaxel over time as simulated in our model.

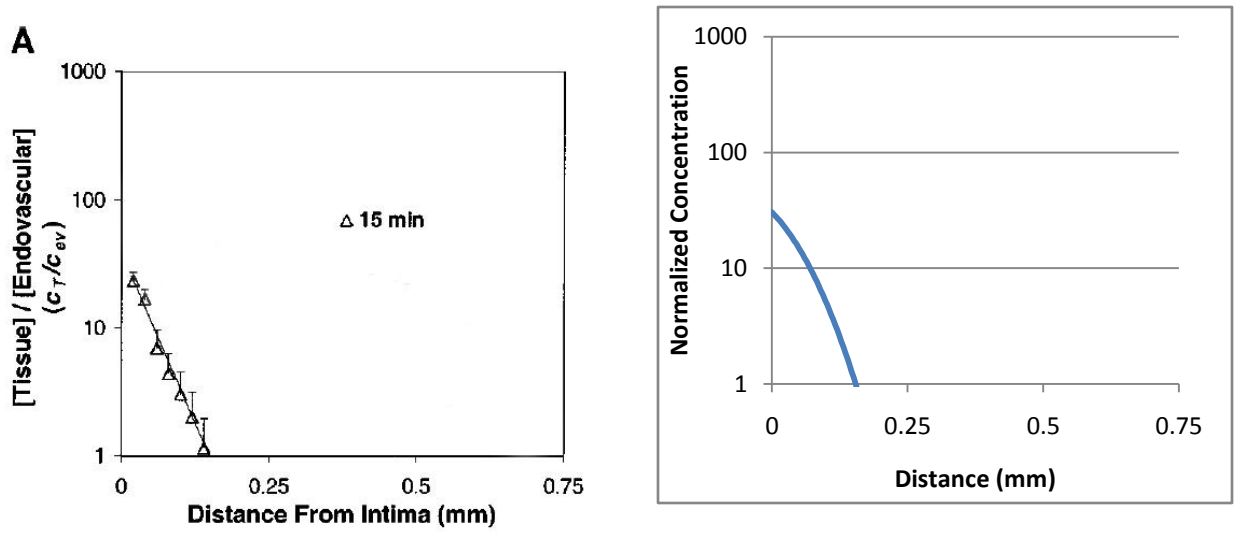

Figure 6: paclitaxel drug concentration in tissue normalized to initial stent concentration from our model (right) and previous experimental data (left, Creel 2000).

We adjusted our model to the geometry used in a previous experiment which used calf carotid arteries (Creel et al., 2000), and found that our model closely mimics their measured experimental values (Fig. 8). We used a drug diffusivity of $2.91 \cdot 10^{-13}$ m^2/s with an initial stent load of 0.017 mg/L and observed our results after 15 minutes. Looking at the concentration gradient, we see the same results as the authors in their endovascular drug delivery experiment. The profile at later times were not evaluated since the experiment done by Creel was such that the tissue diffusivity varied as the experiment changed over time due to steric hindrance, nonspecific binding, and an experimentally imposed pressure gradient.

Sensitivity Analysis

We evaluated the concentration in the tissue at the center of the stent, at a point 0.2 mm within the arterial tissue (r=.00185, z=.006 for the field values in COMSOL). We analyzed three parameters of our model; drug diffusivity in the tissue and stent, and drug degradation in the tissue. Since our model changed over time, we wanted to assess both the short and long-term effects of varying these parameters on our results (Figure 9).

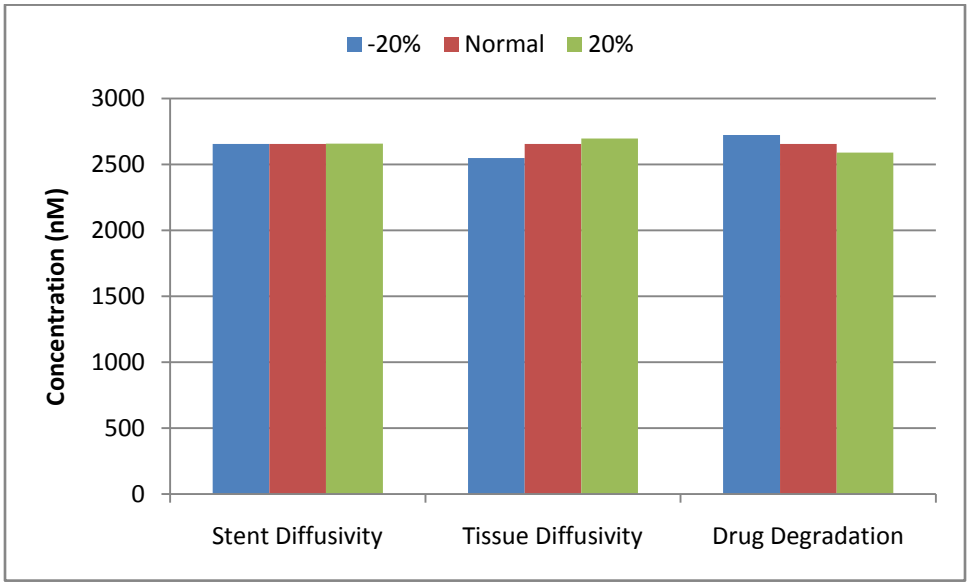

Figure 7: Sensitivity analysis at day 2.5.

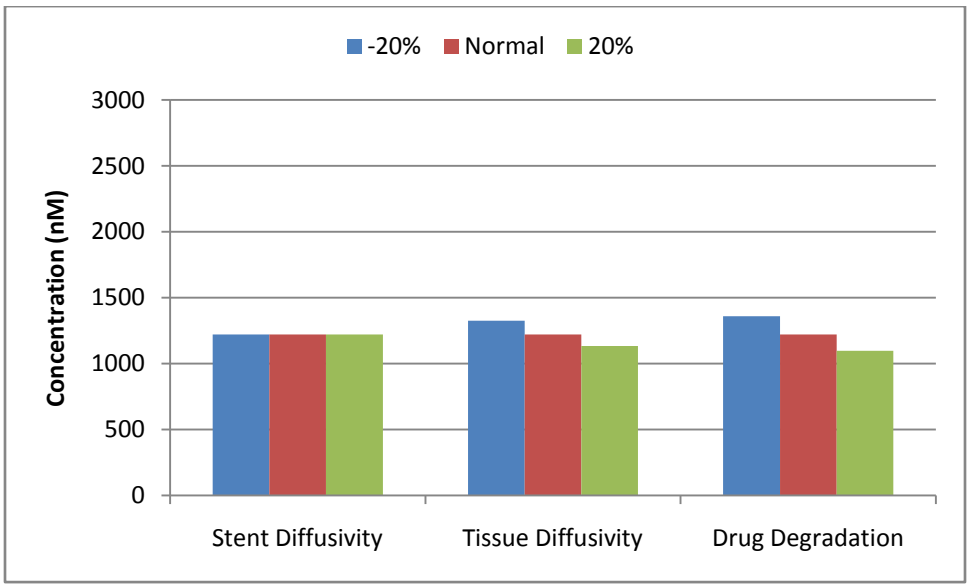

Figure 8: Sensitivity analysis at day 12.

We found that stent diffusivity had little effect on the resulting concentration at both days 2.5 and 12. However, both tissue diffusivity and degradation rate exhibited a similar magnitude of sensitivity. This sensitivity for both parameters was also slightly greater at twelve days as opposed to the 2.5-day condition. It is interesting to note that increasing tissue diffusivity produced a higher concentration on day 2.5, while lowering concentration on day 12, and vice versa. Altering tissue degradation produced the same trend for both time points. As drug is initially entering the tissue, a higher diffusivity facilitates movement from stent into the arterial wall. However, at the later time point, most of the drug has already been transferred out of the stent. Thus, the higher diffusivity makes it easier for drug to leave the region near the stent/tissue interface (the location of the test point) and move deeper into the tissue.

Conclusion

Results indicate that the proposed biodegradable stent model is effective in delivering a therapeutic level of Paclitaxel to tissue surrounding the coronary artery. By implementing our parameters, boundary conditions, and initial conditions, the model displays stent degradation at the ends in the z-direction (up and down) and successful transport of the drug into tissue. Concentration of Paclitaxel in this region next to the stent is greater than the minimum therapeutic value. In order to validate our model two past experiments that focused on Paclitaxel drug elution from a stent was looked at. First, a calf coronary artery was compared to our model. Implementing Creel's experimental parameters, our model was able to show a Paclitaxel release profile from the stent and tissue interface to .14mm in the tissue layer after 15 minutes. Our release profile closely resembles Creel's. Hence, our model is supported by this literature as it delivers a realistic drug concentration within tissue. Second, a calf carotid artery was compared to our model. Utilizing Levin's experimental parameters, our model was able to show a Paclitaxel 72 hour release profile. Besides the initial underestimation of the drug concentration for first 24 hours, our model closely mimics Levin's experimental results. This supports the usefulness of our time-release profile and our model.

Our model showed that the literature initial tissue Paclitaxel concentration beyond the therapeutic concentration range as it was over 10,000 nM. After using different fractions of this initial concentration, the most effective therapeutic concentration was found to be 80% of literature value. Results indicate that this initial concentration produces a release profile with concentrations that stay in therapeutic range through at least 32 days. This initial concentration of Paclitaxel ensures therapeutic delivery of the drug.

Simulation with both of our stent models biodegradable and non-biodegradable showed similar Paclitaxel concentration profiles. Besides the slightly lower concentrations from day 5 to day 32, the biodegradable model, which moves or degrades at the ends, is nearly identical to the non-biodegradable model.

By comparing our model with past experiments and showing that our model degrades and delivers drug at an appropriate level, a simple biodegradable stent model has been developed. However, more research that supports our assumptions or takes into account more specific details of a biodegradable stent must be conducted in order to further validate our model. Assumptions including low drug solubility in blood plasma, linear stent degradation, and first order drug kinetics can be addressed in future models. By including solubility of drug in blood plasma a convective term in the mass transfer can be added to represent blood flow that removes the drug from the stent polymer layers. Stent degradation occurs through pores within the stent and is at an exponential rate. Complex drug kinetics is generally higher than first order. Accounting for these realistic scenarios and parameters that are more accurate, a more effective biodegradable stent model can be developed.

This loss in concentration due to rapid early stent biodegradation may be taken into account in the future stent design. Overcoming these losses may allow for a lower initial concentration and a more therapeutically effective drug release into the tissue. The obtained drug release profile seemed to simulate real-life Paclitaxel release in tissue when compared with established release profiles. However, due differences in models of release (in vivo or in vitro), species' tissue type, and parameters such as diffusivities more research accounting these variations must be conducted to confirm our results. The sensitivity analysis showed that variation in tissue diffusivity can change concentration levels, and should be a main concern for stent design. A

higher or lower initial drug concentration in the stent may be needed depending on the diffusivity of the tissue. Research taking into account these types of variations may prove helpful in future biodegradative drug releasing stent models.

Design Recommendations

Regarding the health safety hazards of the biodegradable stent, there are areas of concern including Paclitaxel toxic concentration and side effects. Research has shown that adverse events have occurred with Paclitaxel stents including subacute and late thrombosis, aneurysm formation and hypersensitivity reactions in humans. Paclitaxel may cause hypersensitivity reactions due to the interaction between these elements in the body through natural metabolic reactions such as hydrolysis. These problems should be our main areas of concern, therefore, our contribution to ongoing research and development for an improved model is greatly needed.

Due to the complexity of the human body the manufacturability of PLA, PLGA polymer stents seems to be challenging. There are existing synthesized PLA, PLGA drug loaded stents, however their specifications and requirements have not been thoroughly evaluated. Problems including incompatibility due to poor polymer quality or processing (residual solvents, catalysts, and monomers), inflammatory degradation residues, inefficient viscoelastic and mechanical properties, and inadequate drug release profile are all barriers to stent manufacturing. These biodegradable stents do not have metal stent struts. Therefore, the mechanical support structure of stent has to be designed accordingly to compensate, and the more delicate polymers require tighter manufacturing control to ensure proper fabrication with sound structural composition. Our model has shown the potential efficacy of the stent, however these other specifications must be met before any fabrication can take place.

Appendix A

Governing Equation

Mass transfer equation with transient, diffusion and generation terms.

$$\frac{\partial c}{\partial t} = D\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c}{\partial r}\right) + \frac{\partial^2 c}{\partial z^2}\right] + r$$

Boundary Conditions

All boundary conditions are set to have zero flux.

$$\frac{\partial c}{\partial r} = \frac{\partial c}{\partial z} = 0$$

We justify the zero flux boundary conditions for the tissue by modeling the tissue as significantly larger in size than the stent. Effects at these far off boundaries are thus deemed negligible. The zero flux condition of the P(DL)LA layer is justified because it has been established that paclitaxel solubility in water is very low, about 0.3513 uM. Since blood plasma is largely water, these effects negligible and the zero flux condition is established for this polymer layer.

Initial Conditions

$c_{P(DL)LA} = c_{tissue} = 0$

$c_{P(DL)LGA} = 69.30\ \mu M$ (Venkatasubramanian 2008)

Physical Parameters

Table 1: Physical parameters used.

Parameter	Value	Source
P(DL)LA thickness	120 µm	Lao, 2007
P(DL)LGA thickness	30 µm	Lao, 2007
Stent Length	12 mm	Tamai, 2000
Coronary artery (inner) radius	1.5 mm	Kaimkhani, 2004
Coronary artery thickness	1.9 mm	Gradus-Pizlo, 2003
Tissue diffusivity	1.1×10^{-13} m^2/s	Venkatasubramanian, 2008
P(DL)LGA diffusivity	5.7×10^{-13} m^2/s	Alexis, 2004
P(DL)LA diffusivity	4.9×10^{-16} m^2/s	Alexis, 2004
Stent Degradation Velocity	2.1724537×10^{-9} m/s	Lao, 2008
Length of time of interest	32 days	Lao, 2008; Alexis, 2004
Paclitaxel half life in tissue	17000 minutes	Fung, 1998
Paclitaxel degradation coefficient	$-6.79556059 \times 10^{-7}$ $mol/(m^3 s)$	Calculated from Fung, 1998
Paclitaxel cytotoxic threshold	10,000 nM	Bennett, 2003
Paclitaxel Therapeutic Range	100 nM – 10,000 nM	Sheikh, 2000

The degradation coefficient was calculated assuming a degradation model of the form $c = c_0 e^{-\alpha t}$ with the differential form $\frac{\partial c}{\partial t} = -\alpha c$ and solving for the coefficient of t using the half life from literature.

Appendix B

Implementation

We implemented the stent degradation by approximating the degradation rate as linear. By using degradation rates determined by Fung (1998), we calculated the time it would take for the stent to be reduced to 4% of its initial mass. We linearized this rate and modeled the sent as a moving mesh within COMSOL with mass loss occurring at the both ends of the stent (in the z-axis), with the presence of the P(DL)LA layer to act as a barrier to degradation in the r direction. We determined the velocity of the mesh at either end to be $2.172 \cdot 10^{-9}$ m/s. At this velocity, the stent persisted 31.9 days.

Solver Parameters

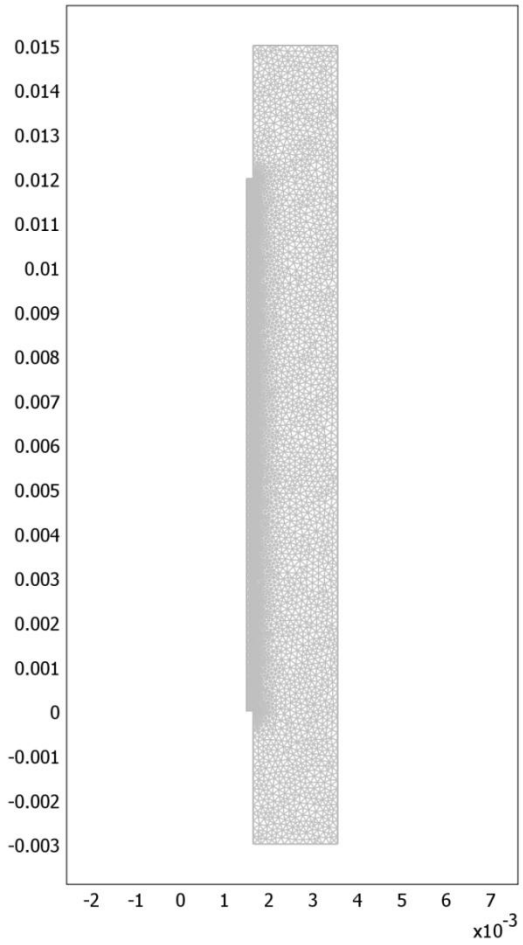

Figure 9: Model mesh.

The algebraic equations were solved using the direct method, not the iterative. The simulation lasted 2592000 seconds (30 days) with time steps at every 86400 seconds (one day), allowing the solver to take free time steps since our output time steps are relatively large. The relative tolerance of the solver was set to 0.01 and absolute tolerance of the solver was set to 0.0010. This limits the size of the local error in each element in the Finite Element Method that the solver utilizes. The variable in question is the concentration of drug in each element, making sure that the maximum error in any element does not exceed 0.0010.

Three noded elements (2D triangles) were used in an unstructured mesh. To improve accuracy of the model, the mesh was unevenly distributed such that more elements were present at the tissue – stent interface (Fig. 2). Since this is the area where the greatest amount of change is likely to be occurring, more elements at this location would improve the simulation.

Mesh Convergence

We performed mesh convergence by calculating the average concentration of drug in the tissue subdomain at the end of 32 days by subdomain integration of the concentration divided by integrated volume using several meshes of varying number of elements, then plotting the average concentration in the tissue versus number of elements.

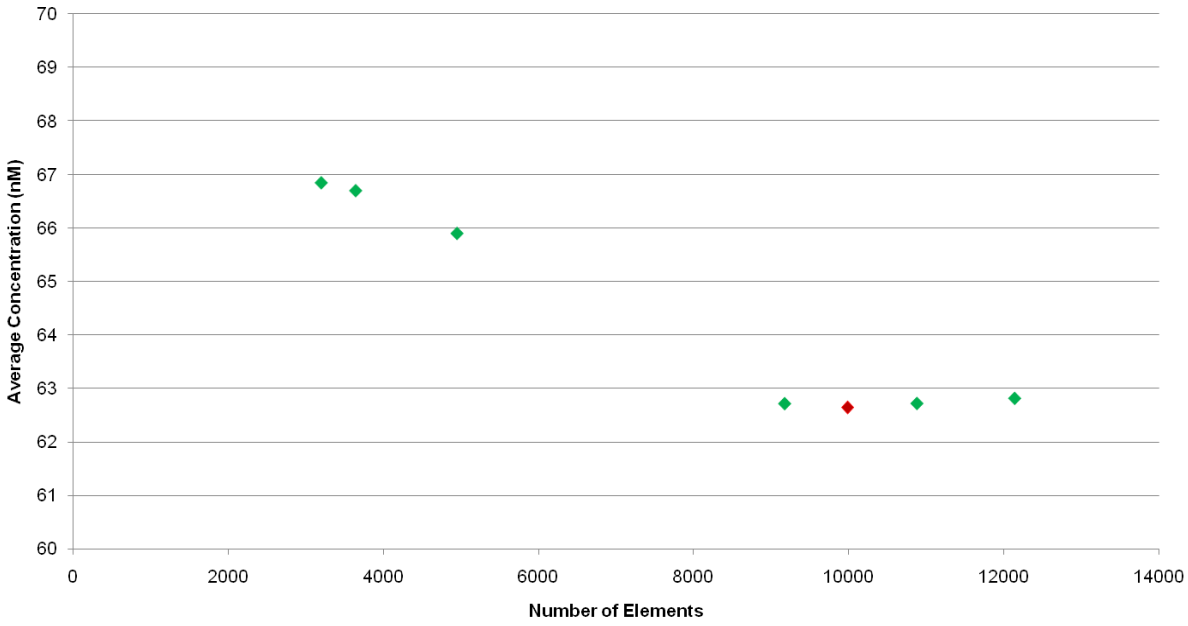

Figure 10: Average concentration of paclitaxel in tissue versus number of elements

We noticed that the values continue to oscillate a little around an average of about 62.7nM, but the difference is very small. Thus we concluded that the mesh converges around 10880 elements.

Appendix C

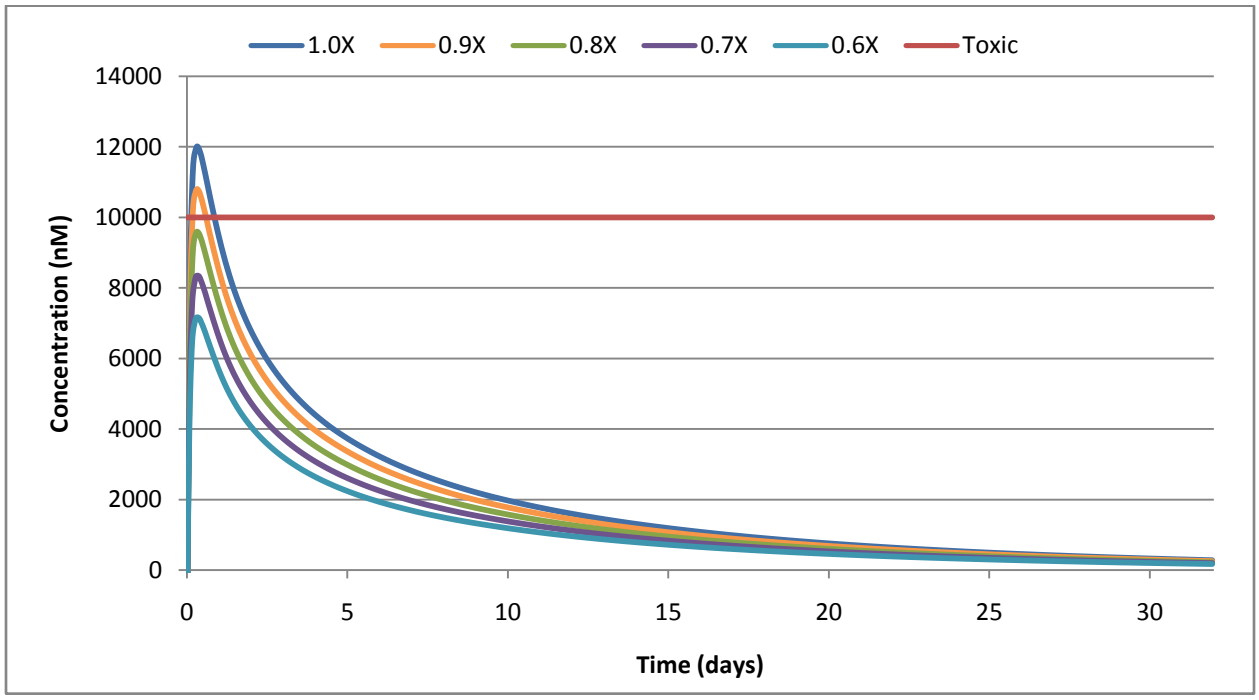

Figure 11: Concentration at center, 5 microns deep in the tissue at various initial loads.

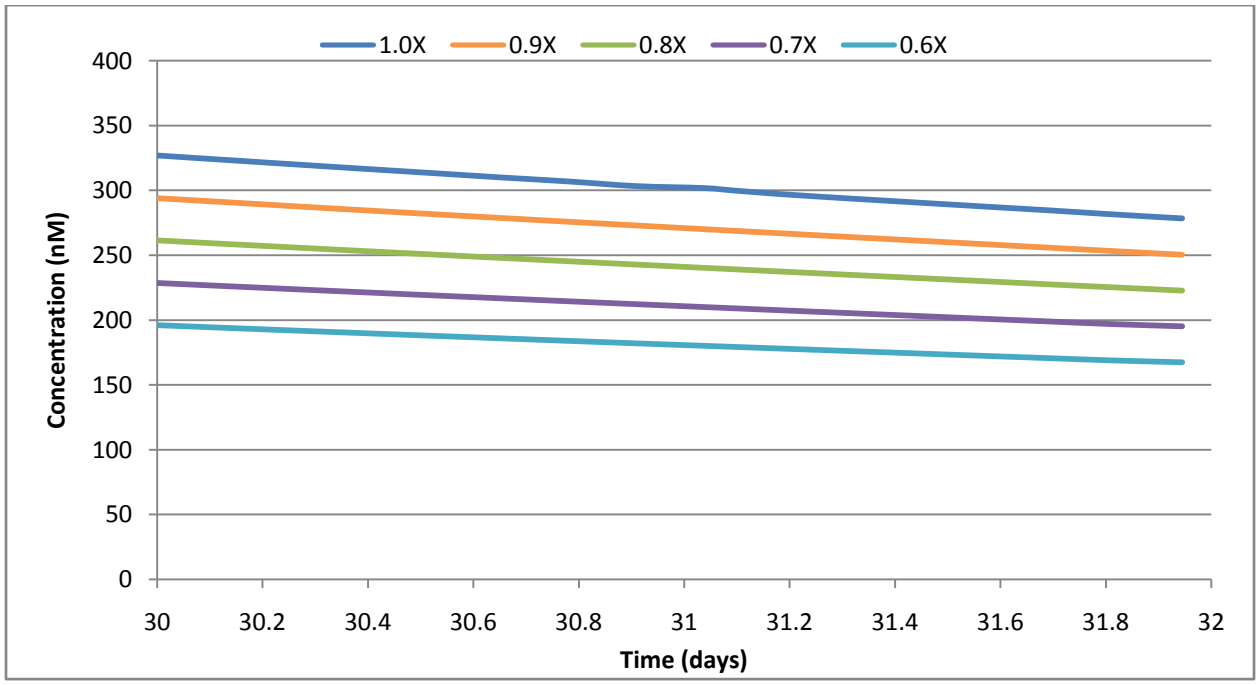

Figure 12: Concentration at center, 5 microns deep in the tissue at various initial loads. Zoomed into last 2 days.

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