Sublingual Nitroglycerin Delivery for Treatment and Prevention of Angina Pectoris

BEE 4530: Computer-Aided Engineering: Applications to Biomedical Processes

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Table of Contents

1. Executive Summary 3
2. Introduction 4
2.1 Background 4
2.2 Research Review 4
3. Design Objectives 6
4. Schematic 6
4.1 Original Schematic 6
4.2 Simplified Schematic 7
5. Methods 8
6. Mesh convergence and final mesh 11
7. Results 13
8. Validation/Accuracy Check 16
9. Sensitivity Analysis 17
9.1 Diffusivity of Nitroglycerin into the Sublingual Mucosa 18
9.2 Diffusivity of Nitroglycerin into the Saliva 18
9.3 Magnitude of salivary flow velocity 19
9.4 Frequency of salivary flow directional change 19
9.5 Summary 20
10. Design Modification – Nitroglycerin Strip Model 21
10.1 Model Schematic 21
10.2 Methods 21
10.3 Boundary Conditions and Numerical Inputs 21
10.4 Results 22
11. Conclusions 26
11.1 Manufacturability and Economic Constraint 27
11.2 Health Safety Constraint 27
Appendix A: Mathematical statement of the problem 28
Governing Equations 28

Boundary Conditions and Initial Values 28
Input Parameters 29
Appendix B: Solution strategy 29
Mesh 29
Appendix C: Additional visuals 31
Average Flux into Bloodstream vs. Time Graphs – Sensitivity Analysis 31
References 35

1. Executive Summary

This project is the first-ever attempt at modeling sublingual drug absorption. COMSOL Multiphysics was used as a software platform for creating a computer model of a nitroglycerin tablet placed beneath the tongue. The goal was to realistically simulate the transfer of nitroglycerin from a sublingual tablet to the bloodstream over time. Data reported in scientific literature was used as the quantitative basis for modeling nitroglycerin diffusion into the saliva and sublingual mucosa. The model includes passive diffusion into the tongue and bottom of the mouth, salivary flow created by sublingual salivary glands, and gradual shrinking of the tablet due to breakdown in saliva. This model was used to evaluate whether or not a sublingual nitroglycerin strip would be a more efficient vehicle of drug delivery.

COMSOL was used to create a model of nitroglycerin drug delivery via a sublingual tablet. Concentration profiles were then produced for various time points and the flux of drug entering the bloodstream over time was determined. These profiles were used to calculate the concentration of nitroglycerin in the blood at any given time. In the literature, the values of nitroglycerin diffusivity in the saliva and oral tissues were given as ranges of values. To ensure that the model was representative of the entire range of diffusivity values, a sensitivity analysis was performed. Flow rates for saliva were also altered using sensitivity analysis to account for variation between individuals. Upon completion of the nitroglycerin tablet model, COMSOL was used to alter the tablet's geometry into that of a sublingual strip, thereby creating a different nitroglycerin delivery model. The concentration profiles and quantitative values generated using each model were compared to evaluate the theoretical relative efficacy of each vehicle of nitroglycerin delivery.

A calculated blood concentration of 79.94 pg/mL at two minutes helped validate the accuracy of the tablet model by proving the computed concentration falls within a range of literature values at that given time. The tablet is shown to dissolve completely in 28.5 seconds which also corresponds with the literature value. As part of a sensitivity analysis, the diffusivity of nitroglycerin into the sublingual mucosa was altered by an order of magnitude. The results showed that plasma concentration was greater for a higher diffusivity when compared to a lower one. Changing the diffusivity of saliva as well as varying the saliva flow all increased the overall blood concentration after one minute of administering the tablet. The end results were significantly influenced by parameter fluctuation suggesting the importance of using accurate values. The strip model gave a plasma concentration five orders of magnitude greater than the tablet after two minutes. A significant improvement in efficiency is seen the strip model.

These COMSOL models serve as a proof-of-concept design study demonstrating that nitroglycerin delivery via a thin sublingual strip with the same amount of nitroglycerin as the tablet is more efficient than the tablet. A higher concentration of nitroglycerin diffused into the blood plasma in one minute with the strip model compared to the tablet model. These findings are a valuable first step in discovering a new method of sublingual nitroglycerin delivery to treat and prevent angina pectoris.

2. Introduction

2.1 Background

Over seven million people in the United States suffer from a condition known as angina pectoris (Lab Test Online 2012). Angina is chest pain or discomfort that is caused by temporary insufficient blood flow to the heart (Graboys and Lown 2003). It is often described as a "constricting" or "suffocating" feeling that lasts anywhere between one and fifteen minutes (What is Angina? 2011). Pain can also be felt in the left shoulder, arm, neck, jaw, or back (Graboys and Lown 2003). Although angina does not indicate a heart attack, it is generally a symptom of coronary heart disease (CAD), the most common heart disease in American adults (What is Angina? 2011). A patient with CAD suffers from atherosclerosis, a narrowing of blood vessels, which prevents sufficient oxygen rich blood from reaching the heart (Lab Test Online 2012). Angina pectoris is triggered by varying stimuli from person to person and can change over time as the condition worsens. Some examples include, but are not limited to, physical or emotional stress, extreme temperatures, or exercise (Lab Test Online 2012). Treatments for angina vary, but commonly involve the use of nitroglycerin (What is Angina? 2011). Nitroglycerin is a vasodialator that causes blood vessels to widen thereby allowing adequate amounts of oxygen to reach the heart (Graboys and Lown 2003). Commonly, nitroglycerin is administered in the form of a tablet to be taken orally. This allows the drug to take affect quicker than it would if in the form of a patch, cream, or even an injection.

2.2 Research Review

Nitroglycerin has been used to treat angina pectoris since 1879. It was approved by the FDA in 1938. However, it was not until recently that its mechanism as a vasodialator was understood (Ogbru 2009). Nitroglycerin, a member of the group of drugs called nitrates, is known to widen arteries and veins thereby decreasing the preload on the heart muscle. When nitroglycerin is used the heart is required to do less work by since oxygenated blood can reach the heart more easily, and thus angina chest pain is lessened (Ogbru 2009). Nitroglycerin's vasodialative properties were demonstrated in a study by Brown et. al who showed that the cross sectional area of various sized vessels increased an average of 18% when patients were treated with sublingual nitroglycerin (Brown, et al. 1981). It was thought in the late 1970s that this was due to the generation of nitric oxide in smooth muscle (Ignarro 2002). Later studies further revealed that nitroglycerin causes a chemical reaction to occur between the nitro compound and a thiol, a sulfhydryl containing compound, to generate an intermediate known as S-nitrosothiol (Ignarro 2002). This intermediate decomposes and releases nitric oxide (NO), a free radical that acts as a signaling molecule and a powerful vasodilator. (Ignarro 2002)

Currently, the oral route is the favored method for drug delivery, as it is inexpensive, convenient, and adaptable. In addition, it possesses some significant advantages over other methods of drug delivery such as transdermal drug diffusion or injection. In oral drug delivery, transport of drug begins with diffusion of drug through the oral mucosa. Drugs are rapidly absorbed into the reticulated vein and are transported through the facial veins, the internal jugular vein, and then the brachiocephalic vein, and are finally drained into the general circulation. (Li and Robinson 2005) Drugs entering the vascular system through the jugular vein bypass hepatic first-pass metabolism (enzyme-mediated degradation) allowing less of the drug to

be administered. This rapid systemic delivery improves bioavailability of the drug, and decreases immunogenic responses. (Li et al) The noninvasive nature of oral administration is preferred by patients. Higher permeability of the buccal mucosa compared to other transepithelial routes makes this a quicker route of delivery. (Jasti, Venugopal and Xiaoling 2005) Onset of action of sublingual tablets occurs within 1-3 minutes; while ingestible gel filled tablets require over 10 minutes to take effect. (Bauer and Seifert 2005)

More specifically, sublingual drug delivery is the preferred route of oral delivery for drugs that benefit from a quick onset of pharmacological relief. Narang et al. 2010 reported that sublingual drug absorption is three to ten times greater than oral drug absorption. The superior absorption capabilities of the sublingual route can be attributed to a number of specific qualities of the sublingual epithelium. The sublingual mucosa is considerably more permeable than any of the other three oral mucosas (buccal, gingival, and palatal) (Goswami, Jasti and Li 2008) since it is stratified non-keratinized squamous epithelium. While much of this greater permeability can be explained by the non-keratinization of the sublingual epithelium, another main feature which contributes to rapid sublingual absorption is the thickness of the sublingual mucosa.

While the buccal, gingival, and palatal mucosas have thicknesses of 200, 250, and 500-600 μm, respectively, the sublingual mucosa is only about 100-200 μm thick (Narang and Jyoti 2011). The sublingual epithelium is reported to be 8-12 cell layers thick (Goswami, Jasti and Li 2008) whereas the epithelium of the buccal mucosa allegedly consists of 40-50 cell layers (Shojaei 1998). The relative thinness of the sublingual mucosa and epithelium further justifies the higher rate of drug absorption via the sublingual route.

In addition to higher permeability and smaller dimensions, the sublingual method of drug delivery is favorable because of the high vascularization of this area (Narang and Jyoti 2011). De Boer et al. 1984 maintains that the rich blood and lymphatic vessels are very important to the drug absorption propensity of the sublingual region. Sublingually, the drug is able to pass directly into the systemic circulation. Furthermore, no additional water or chewing is necessary to dissolve or process drugs administered sublingually. Salivary glands are located underneath the tongue which produce mucin and help promote the production of saliva according to Narang et al. 2010. The sublingual area is constantly washed by significant amounts of saliva which quickly dissolves drug tablets that are placed underneath the tongue.

Sublingual drug absorption can be affected by three different factors according to Narang et al. First, since drug absorption through the sublingual mucosa is primarily through passive permeation, the drug must be slightly more lipophilic than would be required by gastrointestinal absorption. Second, the drug must be soluble in saliva and at the pH of saliva. Third, the drug must not exhibit a tendency to bind to oral mucosa and must have an oil-water partition coefficient in the range of 40-2000. Finally, as long as the drug is created with optimization of these parameters in mind, the sublingual delivery route can be extremely convenient, accessible and effective.

Since sublingual drug delivery seems to be a commonly preferred method of delivery, the question of using the sublingual route of administration to deliver nitroglycerin is certainly merited. In fact, Riseman et al. (Riseman, Altman and Koretsky 1958) published a study, which

specifically compared the efficacy of nitroglycerin administered sublingually, subcutaneously, and orally. The frequency of response, as defined by the number of patients whose exercise tolerance was increased before angina was induced, was one hundred percent. The superiority of sublingual delivery of nitroglycerin is unmistakable.

While sublingual nitroglycerin tablets are used by numerous angina victims worldwide, the convection and diffusion of the tablet underneath the tongue is poorly understood. COMSOL is therefore useful in modeling this drug transfer process in order to better comprehend nitroglycerin sublingual delivery and how it varies from person to person in accordance with individual salivary flow rates and oral diffusivities. COMSOL was also used to model nitroglycerin delivery via a sublingual strip and to conclude that this method of delivery might prove superior to tablet delivery in the future.

3. Design Objectives

The five main objectives of this modeling project are as follows:

1. Create realistic and accurate models of sublingual nitroglycerin delivery via tablet and strip
2. Determine the flux of nitroglycerin into the bloodstream over time
3. Determine the nitroglycerin plasma concentration over time
4. Perform sensitivity analysis to evaluate how saliva and mucosa diffusivities and saliva flow affect sublingual nitroglycerin delivery
5. Compare drug absorption via sublingual tablet and strip and assess relative efficiency of each vehicle

4. Schematic

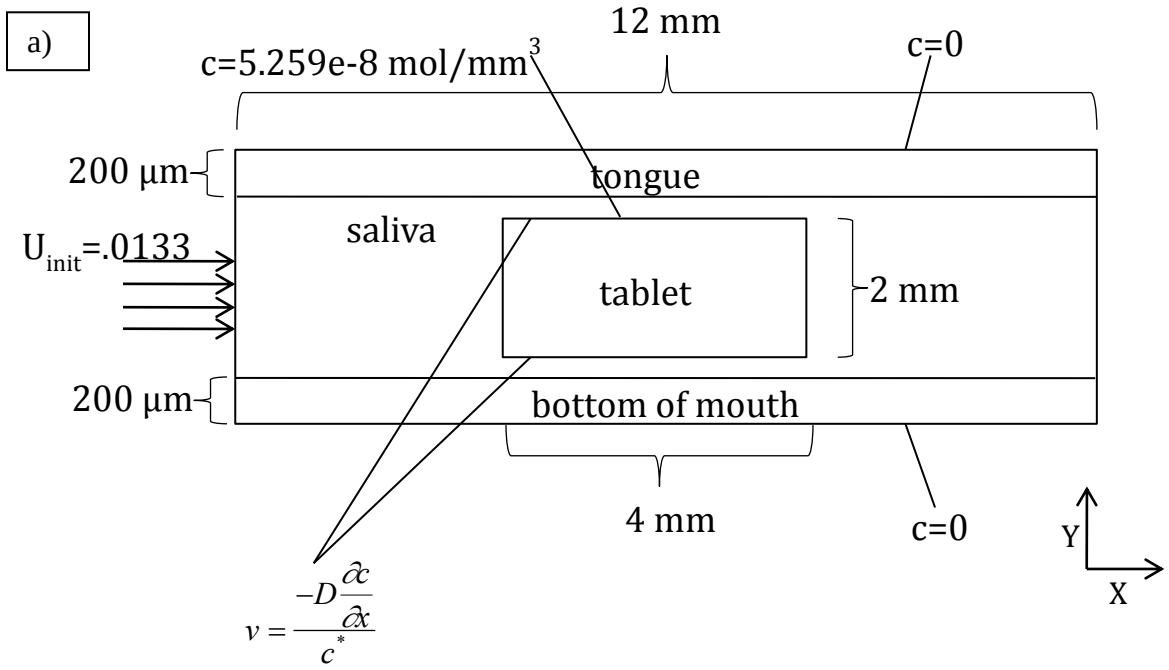
4.1 Original Schematic

Figure 1 below is an image that conveys what is actually happening during sublingual nitroglycerin delivery via a tablet. The patient places the nitroglycerin tablet underneath the tongue and then gently lowers their tongue and keeps it in place allowing saliva to cover and flow over the tablet. The tablet then breaks down in the saliva releasing the drug which eventually makes its way into the sublingual mucosa on the bottom of the tongue and the bottom of the mouth and into the bloodstream.

Figure 1: Sublingual Nitroglycerin Tablets. Image of drug tablet being placed underneath the tongue to enable sublingual nitroglycerin delivery. (Nandini 2011)

4.2 Simplified Schematic

For the purpose of computer modeling, the system depicted in Figure 1 above needed to be simplified before constructing the model in COMSOL. The tablet was modeled as a very thin cylindrical pill with a diameter of 4 mm and a height of 2 mm. The tablet is surrounded by saliva. At the top is the bottom of the tongue and at the bottom is the bottom of the mouth; both contain blood vessels located at a depth of 200µm. Since the boundary conditions change after the tablet has dissolved, there are two schematics provided in the Figure 2 below.



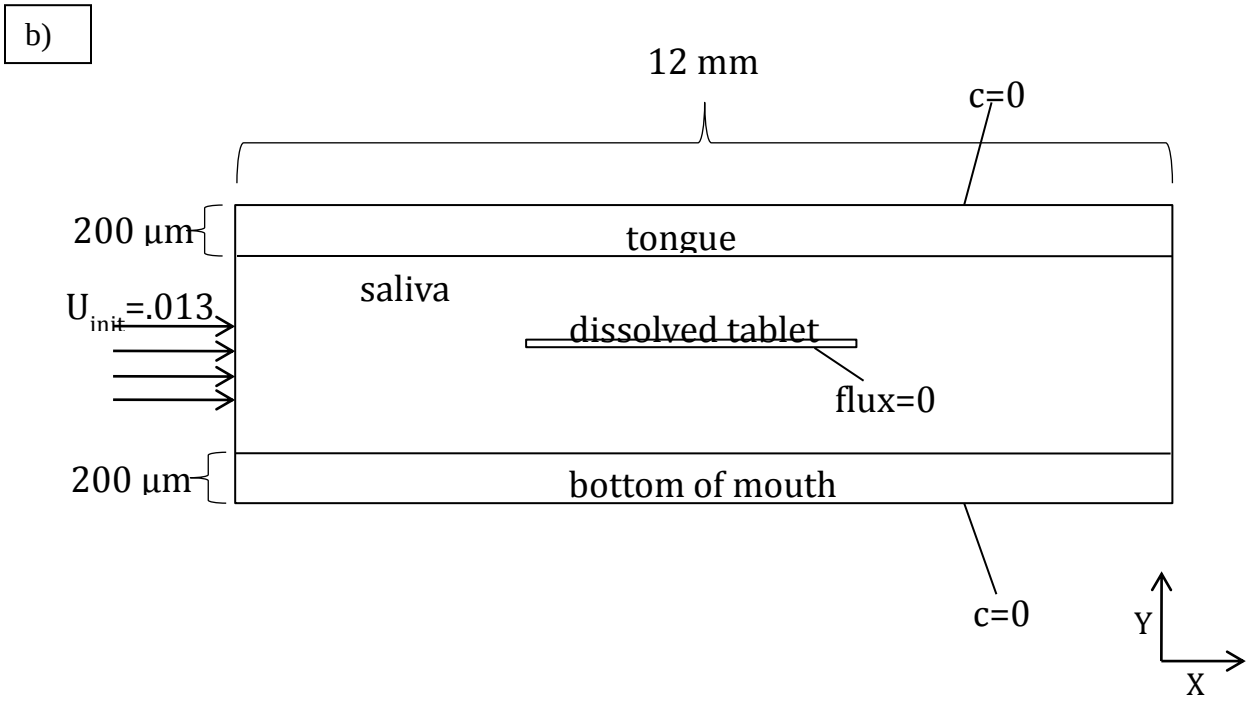


Figure 2: Simplified sublingual tablet schematic. Schematic with dimensions that were input into COMSOL in order to model sublingual nitroglycerin delivery via tablet. a) Schematic with boundary conditions for t=0 to t=28.6 seconds (dissolve time). b) Schematic with boundary conditions for t=28.6 to t=500 seconds.

The two schematics, Figure 2a and 2b, must be run as separate models in COMSOL. The schematic in Figure 2a is run until the tablet is dissolved, then the boundary conditions are altered and the model corresponding to Figure 2b is run until completion. The initial conditions for part b of the model are inputted as the end results from part a.

5. Methods

Sublingual nitroglycerin delivery in COMSOL was modeled as a two dimensional mass transfer process. Although the drug is realistically transferred out of the tablet in all three dimensions, the model is simplified as two dimensions since the drug concentration gradient in the 'z' direction is constant and thus does not need to be considered with regard to this model.

Below is the governing equation for 2D transient mass transfer with drug diffusion in both the x and y dimension and convection due to saliva flow in the x direction. The equation is:

$$\frac{\partial c_a}{\partial t} + u_x \frac{\partial c_a}{\partial x} = D_a \left(\frac{\partial^2 c_a}{\partial x^2} + \frac{\partial^2 c_a}{\partial y^2} \right) \qquad (1)$$

where c_a is the concentration of the drug, u_x is the convective velocity in the x direction, and D_a is the diffusivity of nitroglycerin through saliva or the sublingual mucosa.

In order to determine the exact velocity of the saliva flow at each point along the x dimension, the Navier-Stokes equation for fluid flow was implemented. It is necessary to use the Navier Stokes equation to ensure that the velocity of the saliva is calculated at each individual position in the sublingual cavity and that the velocity is not assumed to be constant. This governing equation for fluid flow is shown below:

$$\rho\left(\frac{\partial u}{\partial t} + u_x \frac{\partial u}{\partial x}\right) = \rho g + \mu\left(\frac{\partial^2 u}{\partial x^2}\right) - \frac{\partial P}{\partial x} \qquad (2)$$

where ρ is the density of saliva, u_x is the velocity of the saliva, g is the force of gravity, μ is the viscosity of saliva, and $\frac{\partial P}{\partial x}$ is the change in pressure in the x direction.

This equation is only applicable to the middle region which contains saliva. This is specified in COMSOL by setting the initial and inlet velocity in both the tongue and the bottom of the mouth as equal to zero. In the saliva region, however, while the initial velocity is set to zero, the inlet velocity was set to 0.0133 mm/sec, which is the flow rate of saliva underneath the tongue due to the sublingual salivary glands as reported in the literature (Dawes 1993). At the saliva/bottom of the tongue boundary, saliva/tablet boundary and saliva/bottom of the mouth boundary, a "no slip" condition was specified so that the velocity of saliva flow at each of these interfaces is set to zero.

Next, in order to account for the fact that the tablet gradually dissolves with time when placed beneath the tongue, a "moving mesh (ALE)" was added to the model. It was assumed that the tablet only shrinks in the y direction and that it shrinks by dissolving from the surface inward while the concentration at the outermost surface of the tablet remains constant. The velocity with which the top and bottom boundaries of the tablet are moving/shrinking is defined as follows:

$$v = \frac{\Delta x}{\Delta t} = \frac{-D\frac{\partial c}{\partial x}}{c^*} \qquad (3)$$

where v is the shrinking velocity,where $-D\frac{\partial c}{\partial x}$ is the flux of the drug at the tablet/saliva interface, and c* is the concentration of nitroglycerin at the tablet surface.

Thus, the velocity at which the tablet shrinks is proportional to the surface flux of mass lost from the tablet. The top and bottom of the tablet move with a velocity of equal magnitude but opposite sign so that the boundaries eventually meet. To determine the average surface flux, the model was solved and a plot of total flux at the top boundary of the tablet (coordinates: (4-8, 2.45) was generated. This plot is shown in Figure 3.

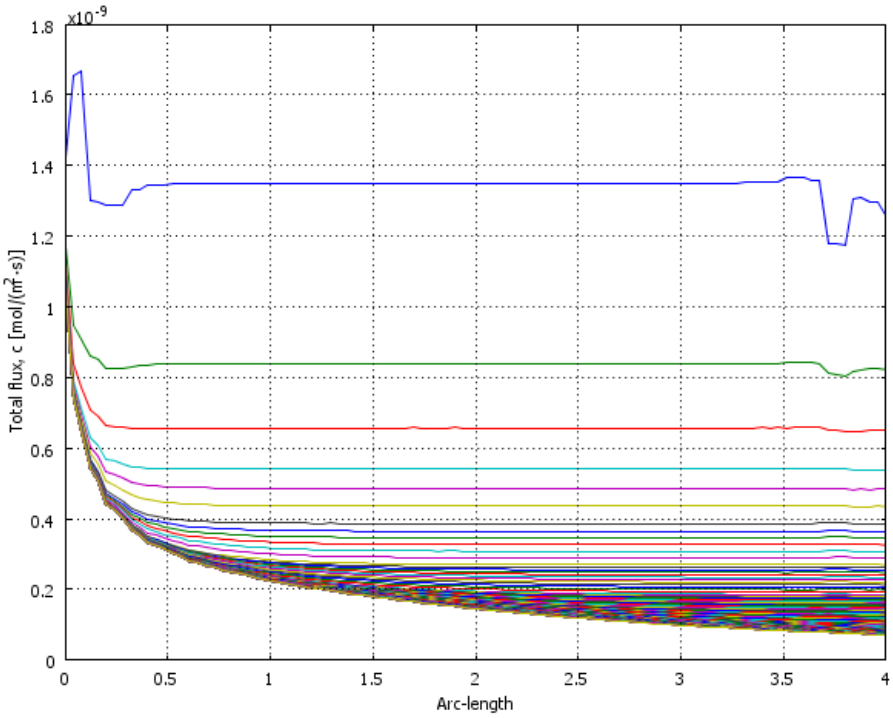


Figure 3: Total mass flux from top boundary of tablet over time. Graph of total flux (mol/m2/s) out of the top boundary of the tablet; each curve represents a different time point. The top most blue line represents t=0 seconds.

This plot shows that the total flux out of the top boundary of the tablet varied from about 0.1 x 10^{-9} to 0.83 x 10^{-9} mol/mm^{2}sec over the time that the model ran. Therefore, the value 0.5 x 10^{-9} mol/mm^{2}sec was selected as the approximate flux out of tablet to be used to determine shrinking velocity. The velocity of the top and bottom surfaces of the tablet were thus defined as follows:

$$v_{top} = -\frac{0.5 \text{ x } 10^{-9}}{5.259 \text{ x } 10^{-8}}\left[\frac{mm}{s}\right] \qquad (4)$$

$$v_{bottom} = +\frac{0.5 \text{ x } 10^{-9}}{5.259 \text{ x } 10^{-8}}\left[\frac{mm}{s}\right] \qquad (5)$$

The top boundary moves in the –y direction and is therefore defined as negative while the bottom boundary moves in the +y direction and so it defined as positive.

This provided a starting point for determining the shrinking velocity. However, to make the model more accurate, the flux over the top tablet boundary as a function of time needed to be determined. To do this, the previously described model was solved. Then, the average total flux over the top tablet boundary was calculated every thirty seconds. These values were entered as a function of time called "tabflux" and the intermediate times were interpolated. As a result, the velocities of the top and bottom surfaces were defined as the following equations.

$$v_{top} = -\frac{\text{tabflux(t)}}{5.259 \text{ x } 10^{-8}}\left[\frac{mm}{s}\right] \qquad (6)$$

$$v_{bottom} = +\frac{\text{tabflux(t)}}{5.259 \text{ x } 10^{-8}}\left[\frac{mm}{s}\right] \qquad (7)$$

When the boundaries meet, the tablet is considered to be entirely dissolved and so the tablet boundaries stop moving and the flux along the boundaries is set to zero. These new boundary settings are implemented into a second COMSOL model and the final conditions of the previous model are set as the new initial conditions.

A final addition to the model was the concept of "saliva sloshing." In reality, saliva does not flow in one direction in the sublingual cavity. In order to simulate the more random flow of saliva underneath the tongue, the velocity was modeled as a time-dependent oscillating function. At the first time point saliva is set to flow from left to right with an inlet velocity equal 0.0133 mm/sec as stated above. At the next time point, the velocity switches directions and flows from right to left and follows this cyclical pattern for the entirety of the model. The leftmost saliva boundary was set as an inlet with a velocity pattern that followed the cyclic pattern described above. This was implemented in COMSOL by referencing a .txt file with the inlet velocity values at each time point. Each alternating second inversed the velocity magnitude to model the sloshing motion and times in between were interpolated.

6. Mesh convergence and final mesh

A mesh convergence analysis was performed to determine what size mesh was necessary. The parameter tracked was the total concentration of drug in the tongue at 105 seconds (the approximate time that the tablet has completely dissolved). This was calculated for each different mesh by integrating the concentration gradient in subdomain 3 (the tongue). Once a certain number of mesh elements is reached, this value should no longer change, regardless of the number of additional mesh elements. The solution should not be dependent on the mesh chosen. The plot in Figure 4 was used to identify a sufficient mesh.

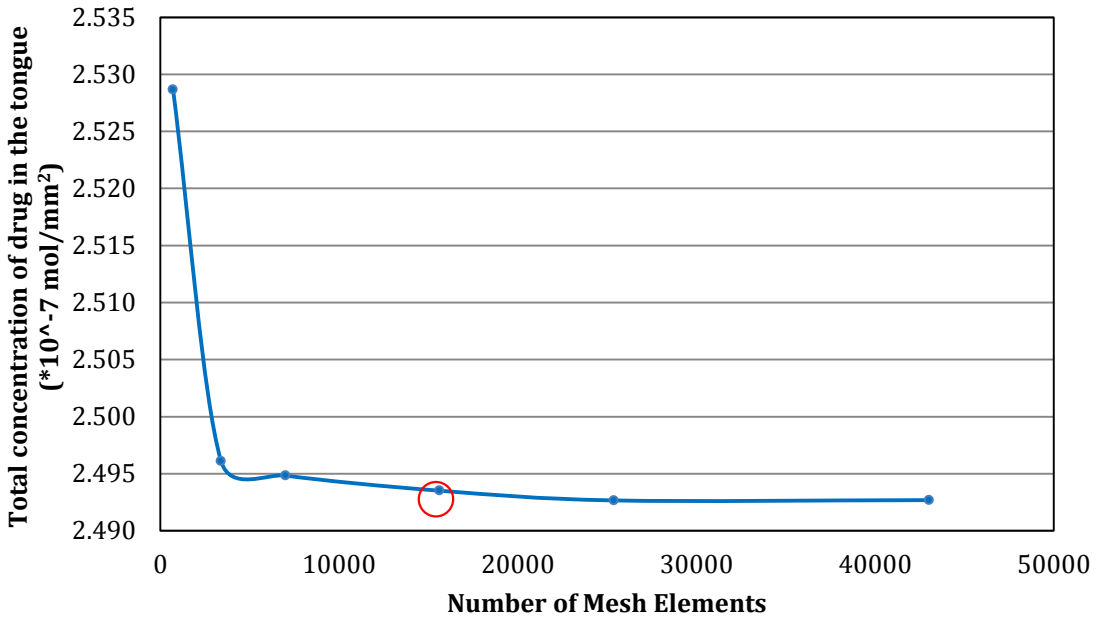


Figure 4: Mesh Convergence Analysis (at 105 seconds). The total concentration of nitroglycerin in the tongue at a given time plotted versus various numbers of mesh elements. The value converges at about 15,000 elements as marked by the red circle. After that point, the solution is no longer dependent on the mesh size used**.**

The plot begins to stabilize once the mesh reached about 10,000 mesh elements. It seems that at all meshes finer than this value the total concentration of drug in the tongue is about 2.493e-07 mol/mm^2 at 105 seconds. Since the mesh does not affect the solution above 15,000 mesh elements, it was decided that the mesh circled in red with 15,624 mesh elements (that is, a mesh with 0.1 as the maximum element size in the domains and 0.04 as the maximum element size in at the boundaries) would be used for all future calculations, to save computing time.

The final mesh chosen is a free parameter mesh with the maximum element size equal to 0.1 and a maximum element size at the boundaries of 0.04. The boundaries that have a finer mesh are the boundary from saliva to tongue, the boundary from saliva to the bottom of the mouth, and all four tablet boundaries. Since there is a higher drug concentration gradient at the tablet boundaries, these regions should have a finer mesh to reduce the error. Similarly, the boundaries between saliva and sublingual mucosa (the tongue and bottom of the mouth) were meshed to have a smaller element size. This was done because the profile changes as the drug diffuses from the saliva into tissue with a different diffusivity value and a more detailed profile could be beneficial in those regions. For these reasons, the six boundaries listed above have a maximum element size of .04. The final mesh is shown below in Figure 5.

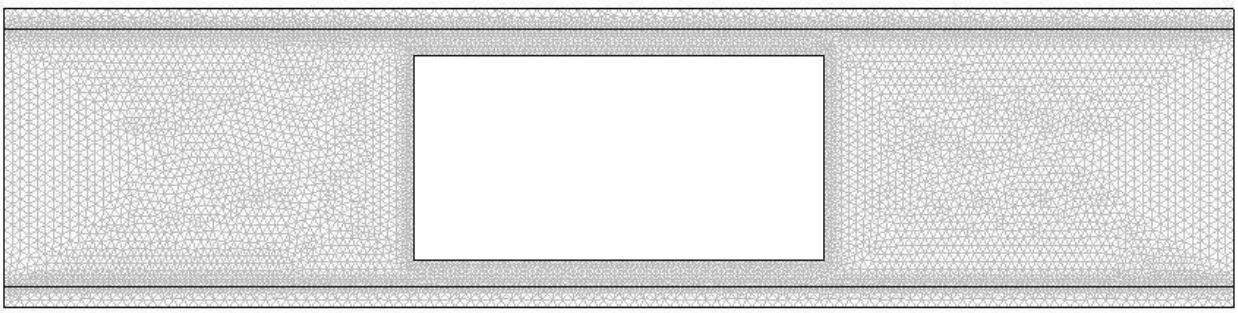


Figure 5: Final Mesh. Max element size in all three subregions is equal to 0.1. Max element size on boundaries is equal to 0.04.

It should be noted in Figure 5 that elements around the boundaries with the greatest concentration gradient are much smaller than the elements far from these boundaries in order to reduce error.

7. Results

After running the model, an animation was generated to give a visual display of the drug delivery process over a five minute time period. The surface plots in Figure 6 below show snapshots at different time points throughout the process of drug delivery from the tablet. Drug is shown diffusing from the tablet into the saliva and subsequently into the tongue and the bottom of the mouth, and then into the bloodstream.

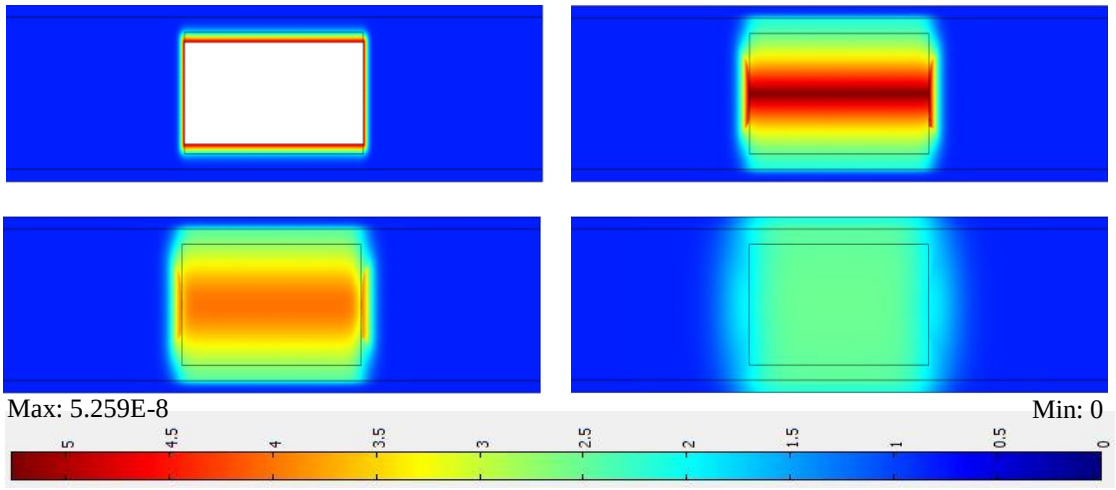


Figure 6: Surface plots of sublingual nitroglycerin tablet. The nitroglycerin concentration gradients at various time points are displayed in units of mol/mm^2. Clockwise from the top left: Times displayed are at 5 seconds, 28 seconds, 35 seconds, and 180 seconds.

The tablet dissolves for the first 28.5 seconds. The time point just before the tablet is completely dissolved can be seen in the top right image in Figure 6 above. In this image the highest concentration of nitroglycerin is at the very center where the last sliver of the tablet remains and the concentration of drug gradually decreases further away from the center. After

the tablet is completely dissolved, at 28.5 seconds, the flux of drug at the tablet boundaries is set to zero so no additional drug is released into the saliva. Once the tablet has disappeared, nitroglycerin in the saliva continues to diffuse towards the tongue and bottom of the mouth through the sublingual mucosa and into the blood stream, as shown in the bottom left image in Figure 6. At 180 seconds, the concentration of nitroglycerin in the entire visible system is significantly lower since most of the drug has entered into the bloodstream.

Next, a graph of the average flux of nitroglycerin entering into the bloodstream as a function of time was created. COMSOL was used to generate total flux values at 1000 different location points on the tongue/bloodstream boundary and the bottom of the mouth/bloodstream boundary at various time points. At each time point the total flux values were averaged to determine the average flux into the bloodstream at that time point. A graph of average flux of nitroglycerin into the bloodstream versus time is show in Figure 7 below.

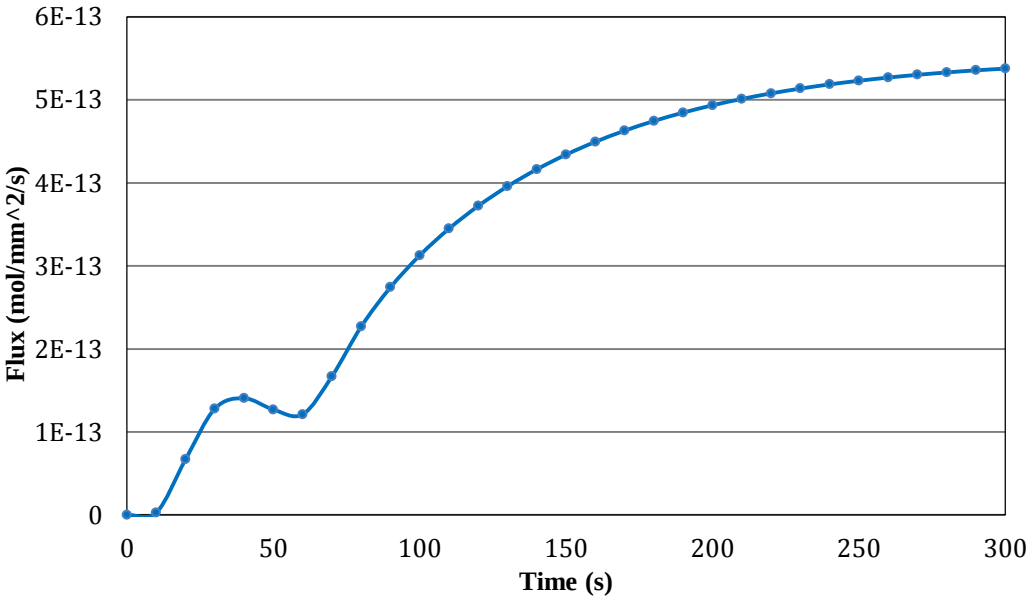


Figure 7: Average flux of nitroglycerin into the bloodstream over time.

Figure 7 above can be used to visualize the trend of nitroglycerin flux into the bloodstream during the total duration that the model was run (300 seconds). The flux increases as the drug diffuses through the saliva, mucosal membrane, and into the blood. A dip in the graph can be seen between about 45 and 65 seconds, which is most likely due to the increased distance the drug must diffuse as the tablet shrinks. Since the tablet is shrinking faster than the drug is diffusing, the boundaries that the drug must cross to enter into the sublingual mucosa and finally reach the blood stream are becoming increasingly far away. Once the tablet is completely dissolved, the flux again increases. Figure 7 shows that at five minutes, the flux has begun to level out, and will presumably decrease to zero as all the nitroglycerin has diffused into the blood or out of the saliva.

In order to determine the nitroglycerin blood plasma concentration (BPC) at any given time point, the graph of average flux into the bloodstream as a function of time (Figure 7 above) was integrated using the Reimann sums estimation technique. At each ten second interval the

average flux over the very top boundary (into the bloodstream) was used to determine the total amount of drug that had entered into the bloodstream by that time point in the following way:

$$BPC = \frac{\left(\begin{matrix}Flux\ integrated \\ for\ 10\ second\ interval\end{matrix}\right)\times\left(\begin{matrix}Total\ area\ through \\ which\ drug\ is\ entering \\ the\ bloodstream\end{matrix}\right)\times\left(\begin{matrix}Molar\ mass \\ of\ nitroglycerin\end{matrix}\right)\times\left(\frac{10^{12}\ pg}{1\ g}\right)}{(Blood\ plasma\ volume)} \qquad (8)$$

The total area through which the drug is entering the bloodstream has been estimated as two surfaces, the bottom of the tongue and the bottom of the mouth, each which has dimensions of 12 x 4 mm (total area = 48 mm^2). The values necessary to implement the above equation can be found in Table 1 below.

Table 1: Values used to calculate total blood plasma concentration

Property	**Value**
Total area through which drug is entering the bloodstream	96 mm^2
Molar mass of nitroglycerin	227 g/mol (Wikipedia 2012)
Blood plasma volume	5000 mL (Taggart, Starr and Starr 1989)

Like any drug, nitroglycerin is gradually degraded in the bloodstream. The half-life of nitroglycerin in the bloodstream is reported in the literature to be about 3 minutes (180 seconds) (RxMed n.d.).The decaying rate constant of nitroglycerin in the bloodstream was found as follows:

$$\lambda = \frac{-\ln\left(\frac{1}{2}\right)}{t_{1/2}} \qquad (9)$$

$$\lambda = 0.00385\ sec^{-1}$$

The following equations were then used to determine how much of the drug was lost due to degradation in the bloodstream, at each ten second time point.

$$\frac{d(Vc)}{dt} = -D\frac{dc^*}{dx}A - \lambda cV \qquad (10)$$

$$\frac{dc}{dt} = -D\frac{dc^*}{dx}\frac{A}{V} - \lambda c \qquad (11)$$

where $-D\frac{dc^*}{dx}$ is equal to the flux of drug into the bloodstream, A is the area over which the drug diffuses, V is the volume of the blood plasma, λ is the decaying rate constant and c is the concentration of drug the bloodstream.

The calculated value of $\frac{dc}{dt}$ was subtracted from the blood plasma concentration at each time point to calculate the blood plasma nitroglycerin concentration which incorporates degradation of the drug in the bloodstream. Figure 8 shows the blood plasma concentration as a function of time with and without degradation of nitroglycerin according to the nitroglycerin tablet model generated in COMSOL.

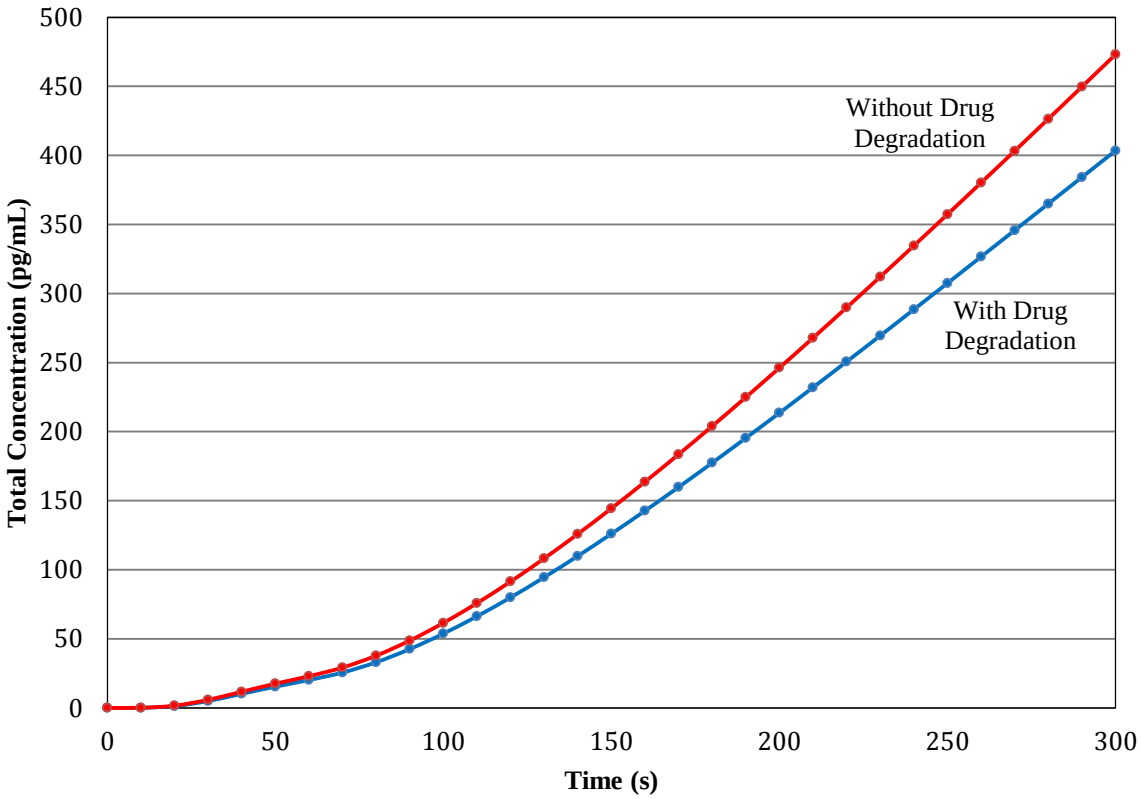


Figure 8: Concentration of Nitroglycerin in blood plasma as a function of time. Graph shows blood plasma concentration both with and without drug degradation in the bloodstream.

Figure 8 shows that the blood plasma nitroglycerin concentration increases steadily over time from 0 to 300 seconds. The blood plasma concentration is in the effective range of 20-400 pg/mL (Bauer and Seifert 2005) for angina treatment between about 70 and 300 seconds, which is consistent with what has been reported in the literature (Bauer and Seifert 2005).

8. Validation/Accuracy Check

In order to validate the model, the total concentration in the blood stream at a given time was compared to values found in the literature. The required blood plasma concentration for nitroglycerin to take effect, as a treatment for angina, is between 20 pg/ml and 400 pg/ml. The literature review revealed that this would occur on average between two and three minutes, although this time varies from patient to patient. The total blood plasma concentration at the two minute time point was therefore analyzed. To do this, the total flux over the very top boundary of the model was computed, which represents the total flux into the bloodstream. Since COMSOL only gives the total flux at each position at a certain time point, the flux over the entire boundary was determined as the sum of the total flux at each location on the boundary at a certain time point. A graph of total flux into the bloodstream was plotted as a function of time. This graph was then integrated using the Riemann sums technique to calculate the total flux of nitroglycerin into the bloodstream at 120 seconds (2 minutes). The area under the flux curve was calculated to

be 2.0984E-11 $\frac{mol}{mm^2}$. This value was then multiplied by the area by which the drug is passing over. The area is 12 mm long by 4 mm in the z direction. (Note that here it was assumed that there is no change in flux in the z direction.) This number was multiplied by two because equal amounts of drug are assumed to enter into the bloodstream via the bottom of the tongue and the bottom of the mouth. The total amount of drug then needs to be converted into grams by multiplying by the molar mass. Assuming an average of 5L of blood in every patient, the concentration in grams per mL can be computed. Finally, the degradation of the nitroglycerin in the blood was taken into account by using the method described in the Results section above. A decay constant of 0.0385 sec^{-1} was used to calculate the actual effective concentration at each time point. The validation calculation is seen explicitly below.

$$BPC\ of\ nitroglycerin\ at\ 120\ seconds\ (no\ degradation) = \frac{\left(2.0984 * 10^{-11}\ \frac{mol}{mm^2} \cdot (12mm \cdot 4mm \cdot 2) \cdot 227\ \frac{g}{mol} \cdot \frac{10^{12}\ pg}{1\ g}\right)}{5000ml} = 91.46\ \frac{pg}{ml} \qquad (12)$$

$$BPC\ of\ nitroglycerin\ at\ 120\ seconds\ (with\ degradation) = 79.94\ \frac{pg}{ml}$$

According to the nitroglycerin sublingual tablet model, the blood plasma concentration does reach an effective concentration within the value reported in the literature, 1-3 minutes (Bauer et al). The minimum effective concentration of nitroglycerin, 20 pg/mL, is reached in less than forty seconds.

Literature values for *in vitro* oral tablet dissolving time are cited to be between 5 and 30 seconds (Klancke 2003). The dissolving time for the tablet in the model above is 28.5 seconds, which is in agreement with the literature values. Based on these two points of validation, it can be concluded that nitroglycerin drug delivery via a sublingual tablet has been accurately modeled.

9. Sensitivity Analysis

There are four main parameters that were altered for sensitivity analysis:

1. Diffusivity of nitroglycerin in saliva: Since currently this value is approximated as the diffusivity of nitroglycerin in water, the value was altered by 10% to account for the minimal difference in the properties of water and saliva are as reported in literature.
2. Diffusivity of nitroglycerin in sublingual mucosa: This value has been approximated as the diffusivity of the drug in buccal (cheek) mucosa which was estimated from literature values of nitroglycerin in the skin. It is documented in the literature how much more diffusive the buccal mucosa is as compared to the skin. This parameter was varied by an order of magnitude since a great deal of approximation was used.
3. Magnitude of salivary flow: Since salivary flow rates vary from person to person, a range of magnitudes were used to ensure that the model is applicable to the majority of individuals.

4. Frequency of salivary flow directional change: A range of salivary flow frequencies was tested to account for difference between salivary flow in individuals.

The concentration in the bloodstream at 60 seconds, taking into account drug degradation in the blood, was compared for the sensitivity analysis. One minute was chosen as the time to compare the concentration values since it is longer than the maximum dissolving time, and allows some time for additional diffusion. For each case of the sensitivity analysis, the concentration was computed as described in the validation section.

9.1 Diffusivity of Nitroglycerin into the Sublingual Mucosa

In the nitroglycerin tablet model, 1.76E-04 mm^2/sec was used as the value of nitroglycerin diffusivity both in the bottom side of the tongue and on the very bottom of the mouth. This sublingual mucosa diffusivity value was approximated as the diffusivity of the buccal mucosa. Since the buccal mucosa is reportedly 4 to 4000 times more diffusive than the skin (Shojaei 1998), the diffusivity of nitroglycerin in the buccal mucosa was approximated by increasing the diffusivity of nitroglycerin in the skin by a factor of 400. In order to analyze how this estimation may have affected the results of the model, a sensitivity analysis was performed on this parameter. The sublingual mucosa diffusivity value was both decreased and increased by an order of magnitude resulting in a low diffusivity value of 1.76E-05 mm^2/sec and a high diffusivity value of 1.76E-03 mm^2/sec. The corresponding flux vs. time graphs can be seen in Appendix C, Figures C1 and C2. It makes sense that the flux of nitroglycerin into the blood is much greater for the high diffusivity of the mucosal region. The low diffusivity graph shows flux values that are an order of magnitude less than the values corresponding to high diffusivity.

Figure 9 shows that changes in the sublingual mucosa diffusivity value are proportional to changes in the nitroglycerin plasma concentration at one minute. Decreasing the sublingual mucosa diffusivity by an order of magnitude decreases the concentration reached after one minute. With a lower sublingual mucosa diffusivity value, it takes much longer for the drug to move through the bottom of the tongue and the bottom of the mouth to reach the blood vessels. The opposite is true for increasing the sublingual mucosa diffusivity value. Since changing the diffusivity value of the sublingual mucosa affects the concentration in the bloodstream drastically, the plasma concentration is quite dependent on sublingual mucosa diffusivity.

9.2 Diffusivity of Nitroglycerin into the Saliva

Since the diffusivity of nitroglycerin into saliva is not well reported in the literature, the diffusivity of nitroglycerin in saliva was approximated as the diffusivity of nitroglycerin in water. Saliva is composed of 98% water, and thus this is a reasonable assumption to make. Therefore, this diffusivity value is only varied by +/- 10% instead of an order of magnitude. The flux vs. time graphs for both cases can be seen in Appendix C, Figures C3 and C4. The flux into the bloodstream for both cases are on the same order of magnitude, however the flux reaches a greater value in the high saliva diffusivity. This corresponds to what was predicted; since the nitroglycerin can diffuse into the surrounding fluid more easily, there will ultimately be a greater flux into the bloodstream.

Altering the diffusivity of the saliva had interesting effects. Both decreasing and increasing it by 10% caused a significant increase in concentration at one minute. Lower saliva

diffusivity means that nitroglycerin enters the saliva at a lower rate and diffuses through the saliva more slowly. Since the drug cannot diffuse in the x direction, through the saliva, as easily, the time that it requires for the drug to reach the sublingual mucosa is less than the time required for the drug to reach the far left and far right boundaries. Accordingly, less drug is lost out the sides of the model and more drug reaches the bloodstream. This results in a higher plasma concentration at one minute. When the diffusivity is increased by 10%, the drug can diffuse through the saliva more quickly. Thus, more drug reaches the sublingual mucosa and the bloodstream and so a higher plasma concentration at one minute is attained.

9.3 Magnitude of salivary flow velocity

To analyze the effect of salivary flow on the nitroglycerin tablet model, the model was run with flow values 50% greater and less than the utilized value. The normal model used a salivary flow rate of 0.01333 mm/sec while the 50% greater and less model used flow rates of 0.006667 mm/sec and 0.01999 mm/sec, respectively. The resulting total flux graphs are shown in Figures C5 and C6 in Appendix C. When comparing the two flux graphs, it is clear that the flux into the blood stream is much greater for the high magnitude case by about two orders of magnitude. This makes sense because the faster the saliva is moving, the faster the drug can dissolve and diffuse away into the blood.

The results from the sensitivity analysis were interesting since deviations from the original value resulted in an increased plasma concentration after one minute. For higher saliva flow rates, the flux of the drug across the surface of the tablet is greater, resulting in more surface convection and thus, a higher plasma concentration after one minute. For lower salivary flow magnitudes, less drug is being convectively forced far away from the center and lost into the peripheral saliva. Thus, more drug is able to diffuse directly into the sublingual mucosa and the plasma concentration at one minute is greater.

9.4 Frequency of salivary flow directional change

In an attempt to include the effects of convection due to salivary flow beneath the tongue, a piecewise function was created to specify the magnitude and direction of salivary flow velocity at each time point. Since salivary flow beneath the tongue is not uni-directional, the model instead models salivary flow as alternating between directions in the x dimension more akin to a "sloshing" motion. In the original model, the salivary flow switches directions every second. Since this is not documented in the literature, a sensitivity analysis was performed to see how switching the salivary flow direction every 0.5 seconds and every 2 seconds, affects the blood concentration at one minute. The flux vs. time results for each case may be seen in Figures C7 and C8 in Appendix C**.** The flux into the bloodstream for both sloshing cases is similar. Both are on the same order of magnitude, however, the faster sloshing results in a slightly greater flux.

The purpose of performing a sensitivity analysis on this parameter was to address both the estimations that were made to simulate saliva "sloshing" and the presumable variation between individuals. It is interesting to note that when the time between salivary flow directional changes was both decreased and increased, the plasma concentration at one minute was increased from the original value.

When the direction of fluid flow changes every 0.5 seconds, there is more surface convection over the tablet and so the flux of drug out of the tablet is greater. Subsequently, more drug will enter the tongue and bloodstream resulting in a higher plasma concentration after 60 seconds. Interestingly, when fluid flow changes direction every 2 seconds, the concentration of nitroglycerin after 60 seconds is greater than when fluid changes direction after 1 second. This defied the expectation that the concentration would be lower since there would be less total flux across the surface of the tablets. The expected decrease in flux may be counteracted by a larger distribution of drug in the mouth due to the increased fluid flow time. Given that saliva flows over the tablet for twice as long, the drug is being distributed over a wider area underneath the tongue. This would increase the area over which drug diffuses into the tongue thus increasing the total flux into the tongue and into the bloodstream and increasing the plasma concentration at one minute.. This effect may be enough to balance the decrease in convective flux for a 2 second fluid change but not for a 1 second fluid change.

9.5 Summary

A graphical summary of the sensitivity analysis results can be found in Figure 9 below. This graph shows how altering each of the four parameters (diffusivity in saliva, diffusivity in the sublingual mucosa, magnitude of salivary flow velocity and frequency of salivary flow directional change) changes the concentration of nitroglycerin in the blood plasma after one minute. Using the normal model parameters, at one minute the plasma has reached a nitroglycerin concentration of 20.13 pg/mL.

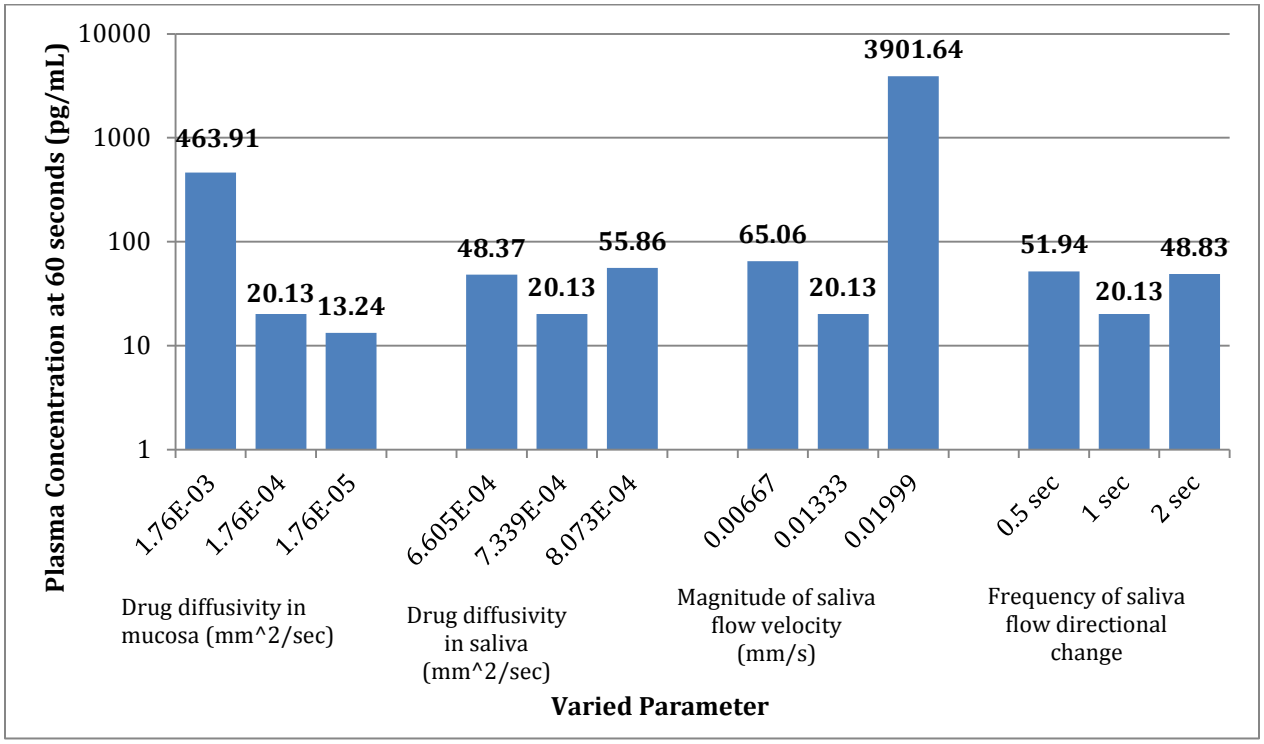


Figure 9: Sensitivity Analysis of Sublingual Nitroglycerin Tablet Model. Graphical display of how variation in four different parameters affects the blood concentration at one minute

Figure 9 shows that when the diffusivity in sublingual mucosa is varied in both directions, the concentration of drug in the blood at one minute changes respectively. Therefore a more exact value for nitroglycerin into the sublingual mucosa would be beneficial in producing the most physiologically accurate results in this model. Altering all of the other factors described results in an increase in blood plasma concentration. It became evident in this model that there will be large variation between individuals since each person will have various saliva properties. In all cases except for the low mucosa diffusivity case, the minimum effective concentration is reached in one minute.

10.Design Modification – Nitroglycerin Strip Model

10.1 Model Schematic

After analyzing the model for nitroglycerin delivery in tablet form, a thin strip was analyzed for comparative efficacy. Since strips require very little moisture to dissolve, drug is able to diffuse directly into the tongue. Thus in this model, the saliva layer with salivary flow was excluded and the strip was modeled as a thin layer between the bottom of the tongue and floor of the mouth. The strip schematic is presented in Figure 10 below.

Figure 10: Schematic of the nitroglycerin thin strip model. The strip is modeled with a thickness of 12 µm, a width of 20mm, and a length of 20mm. Since saliva is not necessary for strip dissolution, the salivary layer is excluded and the strip is modeled as being between the tongue and bottom of the mouth which can be modeled as one region due to physical similarity**.**

Since the strip was 20mm wide while the tablet was only 4mm, the cross section of the tongue modeled must also be expanded. Therefore, in the case of the strip, 40mm of the tongue must be modeled as seen in Figure 10 above.

10.2 Methods

Similar to the previous model, this process was modeled in COMSOL as 2D diffusion governed by the 2D transient mass transfer equation:

$$\frac{\partial c_a}{\partial t} = D_a\left(\frac{\partial^2 c_a}{\partial x^2} + \frac{\partial^2 c_a}{\partial y^2}\right) \qquad (13)$$

where c_a is the concentration of the drug and D_a is the diffusivity of nitroglycerin through the sublingual mucosa. Note that in this equation, unlike the equation for the tablet, the convective term is excluded since salivary flow is not present in this model.

10.3 Boundary Conditions and Numerical Inputs

A. The concentration in the strip is constant throughout the strip and throughout the duration of drug delivery:

$$c = \frac{0.3mg}{(0.012mm \cdot 20mm \cdot 20mm)} = 0.0625 \frac{mg}{mm^3}$$

A mass of 0.3mg of nitroglycerin is used to remain consistent with the amount in the tablet. Since the molar mass of nitroglycerin is 227 x 10^3 mg/mol the surface drug concentration can also be written as,

$$c = 2.753 \times 10^{-7} \frac{mol}{mm^3}$$

However, after a period of 10 seconds, which is within the range of thin strip dissolution time, the strip takes on a zero flux/insulation boundary condition since it has dissolved.

B. At the top boundary of the model and at the bottom of the model, the top of tongue and bottom of the mouth respectively, are the locations of blood vessels. At these locations, the drug enters the bloodstream so quickly that the drug concentration is essentially always equal to zero:

$$c = 0 \frac{mg}{mm^3}$$

C. The material properties that must be input into COMSOL before solving the model are the same as those shown in Appendix A, Table A1 except that this model was only run until a final time of 180 seconds.

10.4 Results

The results of the dissolution of the strip were generated in a manner identical to that of the tablet. One exception is that the area over which the nitroglycerin passes is 40mm wide by 20mm deep in the strip model, compared to the 12mm by 4mm in the tablet. The efficacy of the strip was assessed through comparison of the total flux into tongue over time and the plasma concentration of the drug over time as determined by both the strip model and the tablet model. The total flux of the drug into the tongue demonstrates behavior similar to what was seen with the tablet model. There is an increase in flux followed by a slight drop in the flux at the time the drug has been depleted. This decrease is then followed by an increase in flux as the remaining drug begins to diffuse into the bloodstream. Drug flux then slowly decreases since the drug has been totally removed from the oral cavity as seen in Figure 11 below.

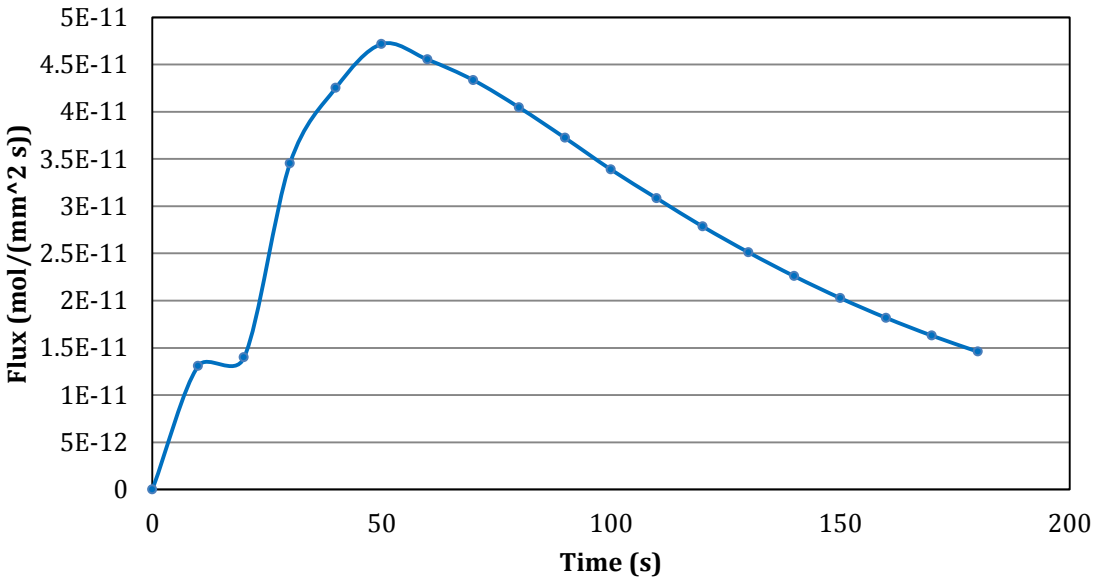


Figure 11: Total flux of nitroglycerin into the tongue for the thin strip model

When comparing Figure 11 to Figure 7 for the strip and tablet flux respectively, it is clear that the flux into the bloodstream for the strip is much greater. The maximum flux reached is more than two orders of magnitude greater than that for the strip. It is obvious from this that the strip is much more efficient.

The concentration of drug in the plasma versus time when the strip model is used also demonstrates the same behavior as the tablet model. Plasma concentration for the strip steadily increases throughout the three minute span as shown in Figure 12.

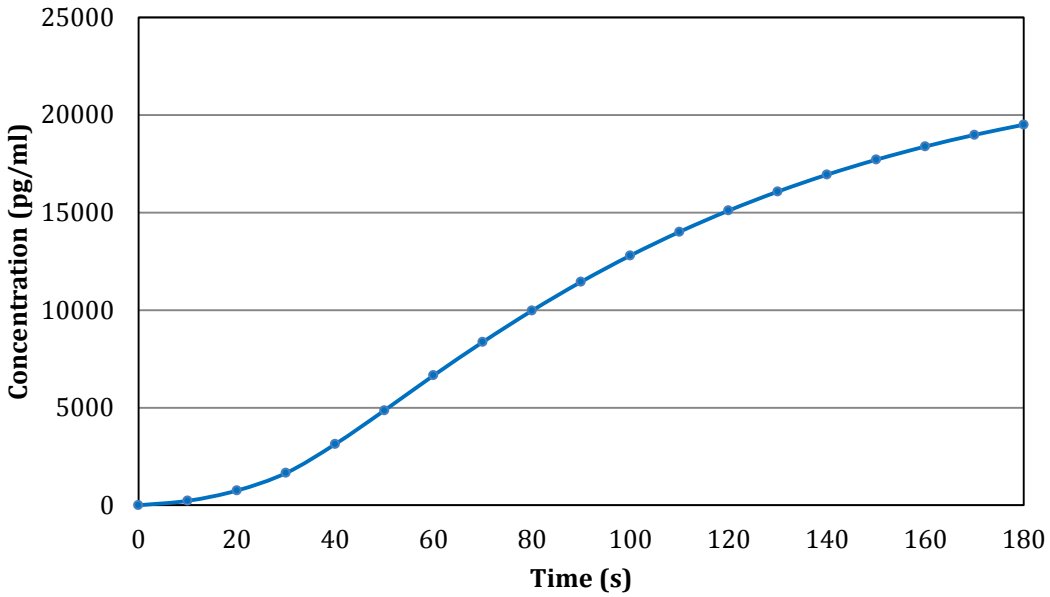


Figure 12: Concentration of nitroglycerin in the blood plasma versus time when using the strip model.

Figure 12 shows that a concentration of just under 20000 pg/mL is reached after three minutes of administering the strip, a concentration much greater than achieved by the tablet.

A comparison of the two models based on flux as well as plasma concentration clearly shows that the strip is a significantly more effective vehicle of drug delivery. Both the total flux and plasma concentration are two orders of magnitude greater with the strip. Thus, a greater quantity of drug enters the bloodstream when the strip is used. Below in Figures 13 and 14, the total flux vs. time and plasma nitroglycerin concentration vs. time are plotted for both models on a logarithmic scale.

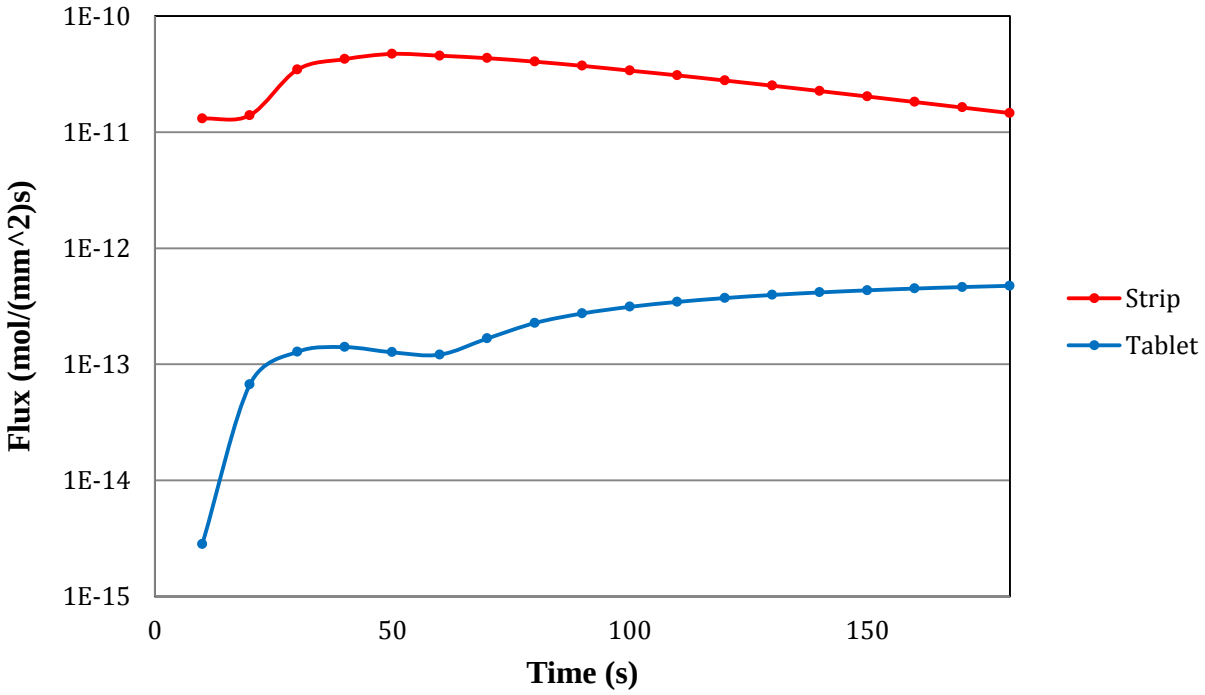


Figure 13: Total flux of drug into the bloodstream for both models on a logarithmic scale

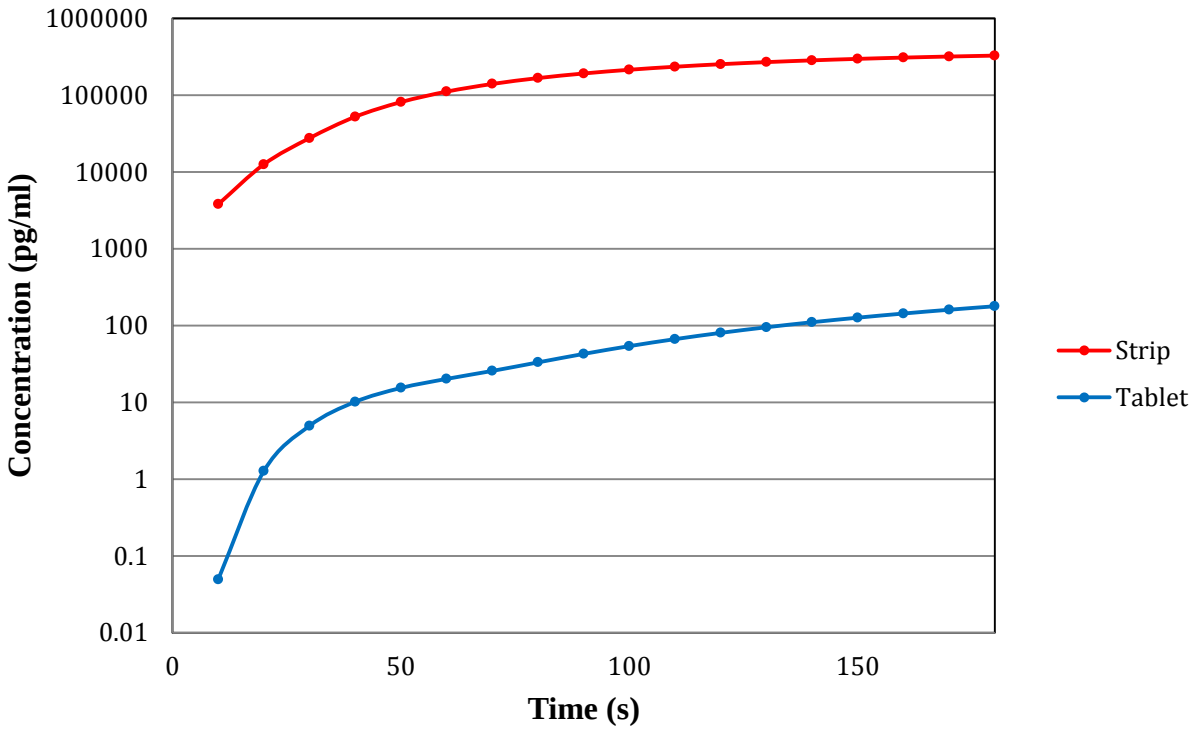


Figure 14: Concentration of nitroglycerin in the blood plasma for both models plotted on a logarithmic scale

Figure 13 shows that the flux of nitroglycerin into the bloodstream is, on average, two orders of magnitude greater for the strip in comparison to the tablet. As a result of this, the plasma concentration is greater at all times for the strip model, as shown in Figure 14. Given a total of 0.3mg of nitroglycerin in both the tablet and the strip, the maximum blood plasma concentration that could be achieved is 600,000 pg/mL (0.3mg/5000mL). This is assuming that all of the nitroglycerin enters the bloodstream and no degradation occurs, which is not physically possible. In the case of the strip, the plasma concentration at three minutes is approximately 326,600 pg/mL. The efficiency improvement achieved by the strip model is obvious.

11.Conclusions

Before this study, the exact method of sublingual nitroglycerin delivery had never been fully modeled nor understood. The COMSOL model created in this study accurately simulates the path of nitroglycerin from the tablet into the bloodstream taking into account saliva flow and a flux dependent drug dissolution rate. In this way, the first design objective was accomplished. The model enabled a better understanding of the sublingual drug delivery process for both tablet and strip nitroglycerin delivery vehicles.

The flux of nitroglycerin into the bloodstream as well as the plasma concentration were also calculated and plotted as a function of time; two variables that were not well understood previously, according to the literature. The time until full dissolution and time until the nitroglycerin takes effect were compared to literature values to validate the model. Sensitivity analysis showed that diffusivity of the tongue has a large effect on drug plasma concentration at a given time, as expected. In other cases, such as more frequent sloshing or faster saliva velocity, more nitroglycerin reached the blood within one minute of administering the tablet.

When comparing the sublingual tablet to the strip model, it was clear that a strip with the same initial amount of nitroglycerin as the tablet was much more effective. The greater surface area and faster dissolution time allows a much higher concentration of drug to reach the blood after one minute. Angina patients often take nitroglycerin medication prior to the onset of a heart attack when time is vital. Therefore a fast-acting and effective drug delivery vehicle is a top priority. For this reason, a nitroglycerin strip for angina treatment could be an important discovery from the perspective of pharmaceutical companies.

This concentration of nitroglycerin is attainable in a strip, with regards to manufacturing, according to Dixit et al., and so the potential of a nitroglycerin strip as an alternative angina treatment is undeniable. The research and development of a nitroglycerin strip for the treatment of angina pectoris could perform well in the current tablet-dominated market. The computer model designed in this study was beneficial because it served as a proof-of-concept study of the

nitroglycerin strip design. Computer modeling, in this instance, was able to replace costly preliminary experimentation and support the value of future research.

11.1 Manufacturability and Economic Constraint

While there are several theoretical benefits of the sublingual strip method, adopting this design does not come without economic and manufacturing constraints. While the design is supported by COMSOL modeling as demonstrated above, plenty of time is still needed for product development, preclinical and clinical trials, and FDA approval (Malke, et al. 2010). This entire process could take upwards of seven years. These stages of development require a great deal of time and money, while virtually no income being generated (Malke, et al. 2010). This, therefore, presents a time and financial constraint on the company. It is clear that not all pharmaceutical companies have the financial backing and time to convert to oral strip nitroglycerin delivery. Additionally, switching all the manufacturing devices would require significant effort, time, and money on the company's behalf. Luckily, similar devices have been previously invented so minimal engineering would be needed (Malke, et al. 2010). Regardless, a company may not have the available facilities or financial capability to undertake such a large endeavor. In these ways, replacing nitroglycerin tablets with nitroglycerin strips is severely restricted by manufacturability and economic constraints.

11.2 Health Safety Constraint

While it may seem clear that effectiveness of angina treatment can be increased by increasing the amount of nitroglycerin delivered to a patient, there are some health and safety limitations to this proposition. Too high a dose of nitroglycerin can cause shortness of breath, blurred or double vision, heart palpitations and rapid heartbeat, convulsions, fainting, and even comas (National Institute of Health 2011). This safety concern therefore places a constraint on the maximum drug concentration that can be included in the strip or tablet model. This restricts the design somewhat since there is a certain limit on the maximum drug allowed. However, the model shows such high plasma concentrations with the strip that it even seems viable to decrease the overall nitroglycerin concentration in the stip. This would help reduce expenses as well as side effects. Further testing would need to be conducted to determine the optimal amount of nitroglycerin.

Appendix A: Mathematical statement of the problem

Governing Equations

In the mucosal regions

Diffusion modeled by: $\frac{\partial c_a}{\partial t} = D_a(\frac{\partial^2 c_a}{\partial x^2} + \frac{\partial^2 c_a}{\partial y^2})$

In the saliva region (for tablet model only)

Convection and diffusion modeled by: $\frac{\partial c_a}{\partial t} + u_x \frac{\partial c_a}{\partial x} = D_a(\frac{\partial^2 c_a}{\partial x^2} + \frac{\partial^2 c_a}{\partial y^2})$

Navier Stokes modeled by: $\rho(\frac{\partial u}{\partial t} + u_x \frac{\partial u}{\partial x}) = \rho g + \mu(\frac{\partial^2 u}{\partial x^2}) - \frac{\partial P}{\partial x}$

Boundary Conditions and Initial Values

A. From the initial time until the time at which the tablet completely dissolves, the surface of the tablet, that is all four boundaries, is assumed to always be at a constant concentration:

$$c = \frac{0.3}{8\pi}\frac{mg}{mm^3} = 0.011937\frac{mg}{mm^3}$$

Since the molar mass of nitroglycerin is 227 x 10^3 mg/mol the surface drug concentration can also be written as,

$$c = 5.259\times 10^{-8}\frac{mol}{mm^3}$$

Once the tablet is completely dissolved this boundary condition changes and all four boundaries that once represented the tablet are set to be insulation boundary conditions so that the flux of drug at these boundaries is equal to zero.

B. At the very top boundary of the tablet model, 200µm into the tongue from the saliva, and at the very bottom of the model, 200µm deep into the bottom of the mouth, are the locations of the blood vessels. At this location, the drug enters the bloodstream so quickly that the drug concentration is essentially always equal to zero:

$$c = 0\frac{mg}{mm^3}$$

Input Parameters

The material properties that must be input into COMSOL before solving the model are shown in Table A1 below.

Table A1. Material properties for nitroglycerin sublingual tablet model. Table of values necessary to use COMSOL model of nitroglycerin sublingual tablet delivery.

Property	**Value**	**Unit**	**Reference**
Diffusivity of nitroglycerin in saliva	7.339e-4	mm^2/sec	(GSI Enviornmental 2010)
Diffusivity of nitroglycerin in tongue/bottom of the mouth	1.76e-4	mm^2/sec	(Shojaei 1998) (Nakamura, et al. 2001)
Flow rate of saliva at left most inlet boundary	0.0133	mm/sec	(Dawes 1993)
Concentration of drug at tablet surface	5.259e-8	mol/mm^3	(Bauer and Seifert 2005)
Initial drug concentrations in saliva/tongue/bottom of mouth	0	mol/mm^3	
Dynamic viscosity of saliva (in subdomain 2)	0.0016e-3	kg/mm^2sec	(Kusy and Schafer 1995)
Density of saliva	1e-6	kg/ mm^3	(Bijella, et al. 2005)
Results saved every	0.1	sec	
Final time	300	sec	

Appendix B: Solution strategy

The COMSOL linear systems solver direct (UMFPACK) was used to find the complete solution of this model. The problem was a transient model solved from 0 to 300 seconds with an initial time step of 0.005 and maximum time step of 0.1 manually entered in COMSOL. For the calculations, the default values for relative and absolute tolerance, 0.01 and 0.001 respectively, were used.

Mesh

The model was implemented into COMSOL as a 2-D rectangular model with several different layers. In the complete solution, a maximum element size of 0.1 was used throughout the subdomains with a maximum size of 0.04 along the boundaries of the tablet and saliva/mucosa interface where a greater gradient was expected. The mesh consists of triangular elements, each with three nodes.

A mesh convergence analysis was performed to assure the resulting drug concentration was not dependent on the mesh size used. The data from this analysis is presented below in Table B1.

Table B1. Mesh convergence analysis data. Data for mesh convergence analysis. Evaluated at 105 sec using the Reference frame. Subdomain 3 is the region of the bottom of the tongue from the saliva to the blood stream with a total area of 2.4 mm^2.

Max element size in subdomains	Max element size at boundaries (tongue, bottom of mouth, all 4 tablet boundaries)	**Number of Mesh Elements**	Integration of concentration gradient in subdomain 3 (mol/mm2)	**Total drug concentration in subdomain 3 (mol)**
0.5	No max	710	1.053605E-07	2.5287E-07
0.5	0.1	3394	1.040043E-07	2.4961E-07
0.1	No max	7008	1.039515E-07	2.4948E-07
0.1	0.04	15624	1.038962E-07	2.4935E-07
0.1	0.025	25376	1.038607E-07	2.4927E-07
0.05	0.025	43026	1.038618E-07	2.4929E-07

Appendix C: Additional visuals

Average Flux into Bloodstream vs. Time Graphs – Sensitivity Analysis

Below are graphs of the average flux into the blood stream versus time for each sensitivity analysis case.

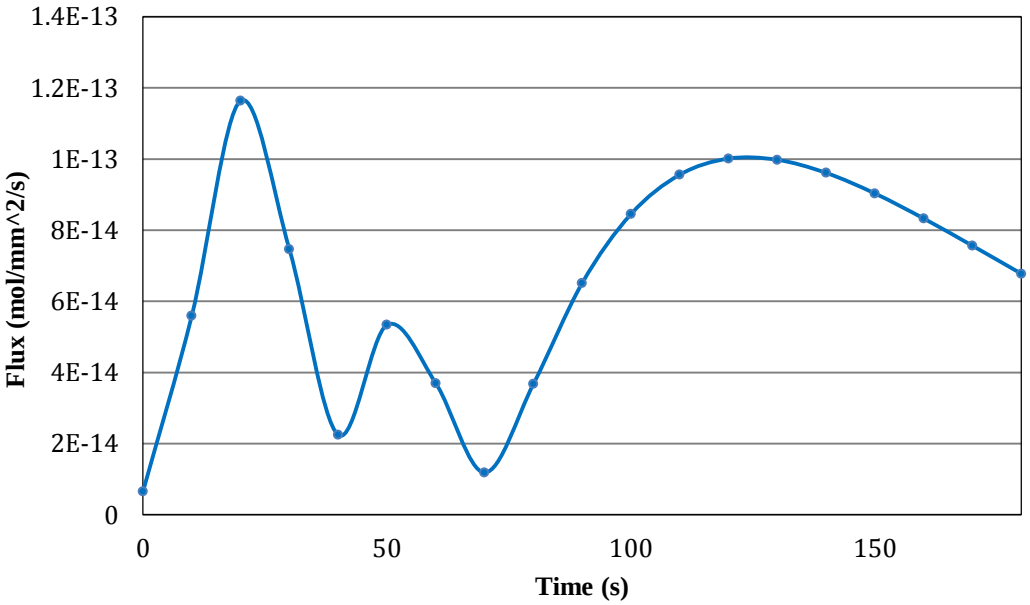


Figure C1. Flux vs. time graph for low sublingual mucosa diffusivity case (D=1.76e-5 mm^2/s)

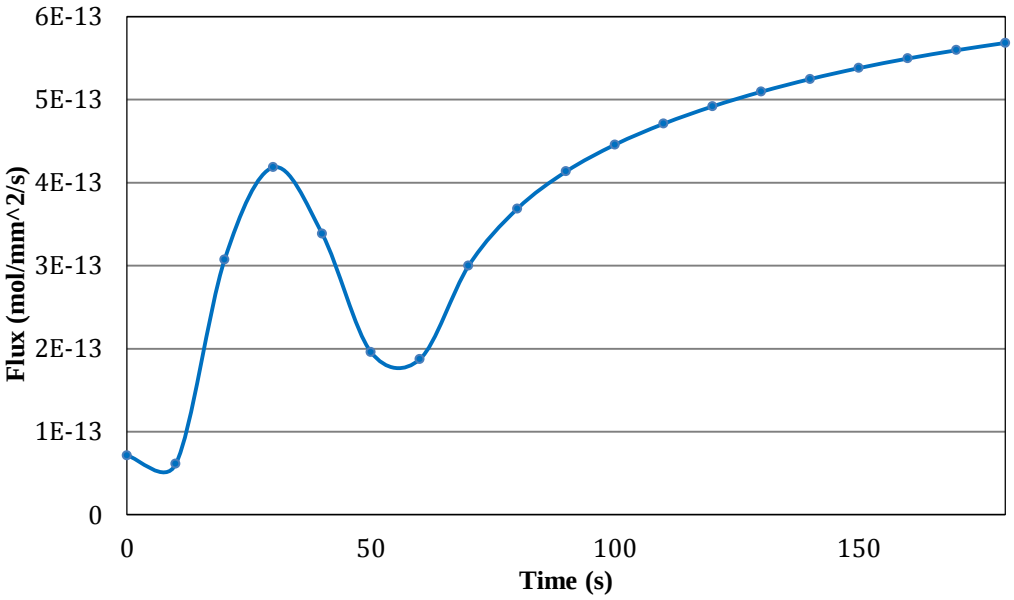


Figure C2. Flux vs. time graph for high sublingual mucosa diffusivity case (D=1.76e-3 mm^2/s)

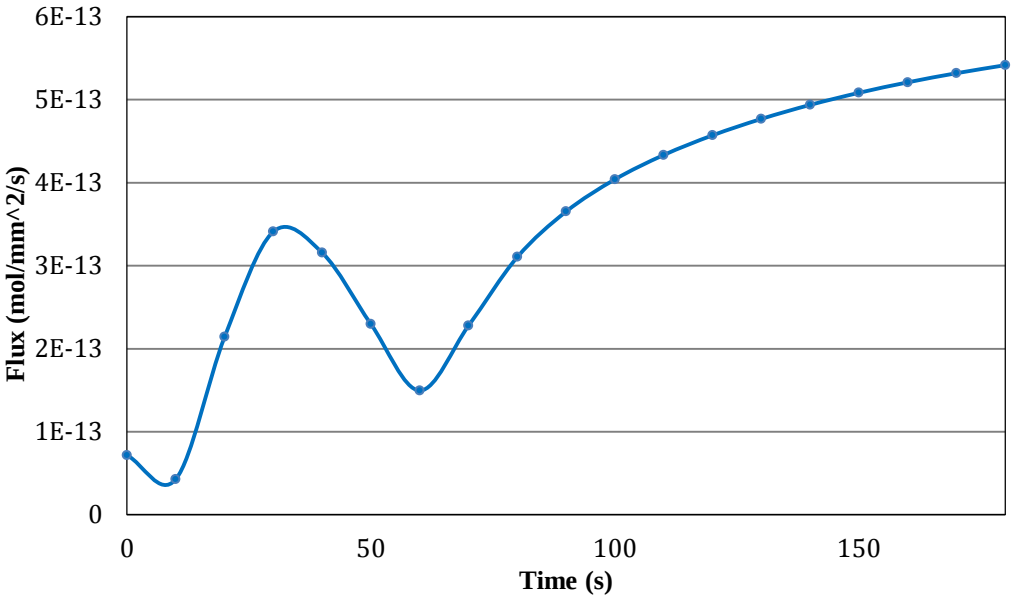


Figure C3. Flux vs. time graph for low saliva diffusivity case (D=6.605e-4mm^2/s)

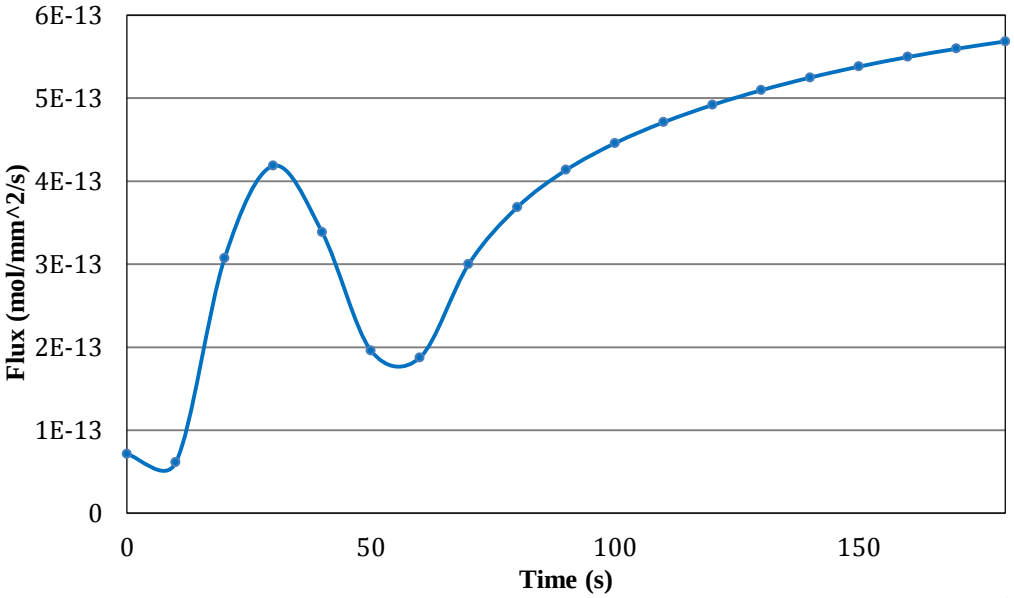


Figure C4. Flux vs. time graph for high saliva diffusivity case (D=8.073e-4 mm^2/s)

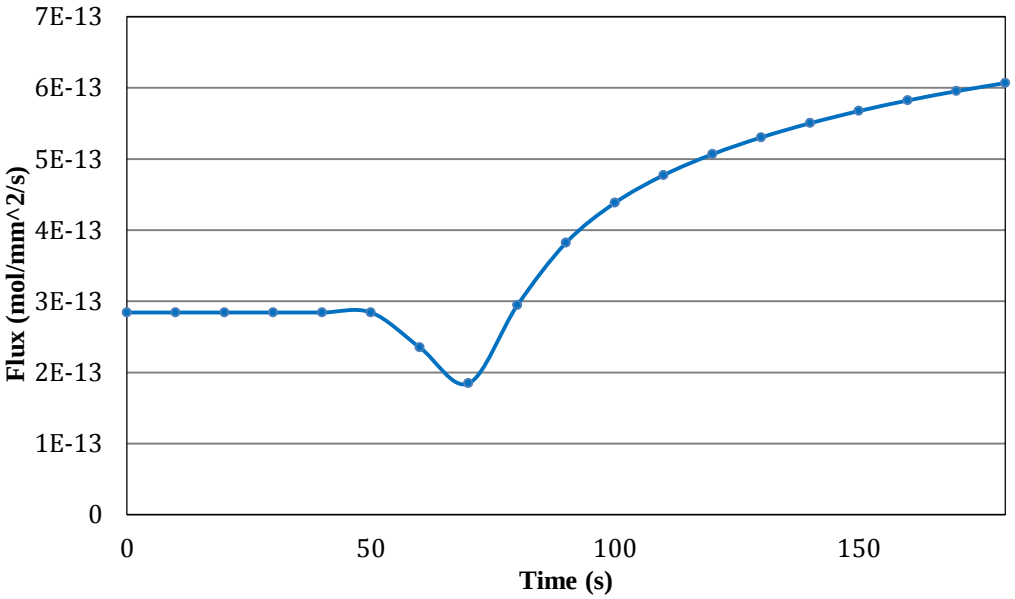


Figure C5. Flux vs. time graph for low saliva velocity magnitude (u=0.00667 mm/s)

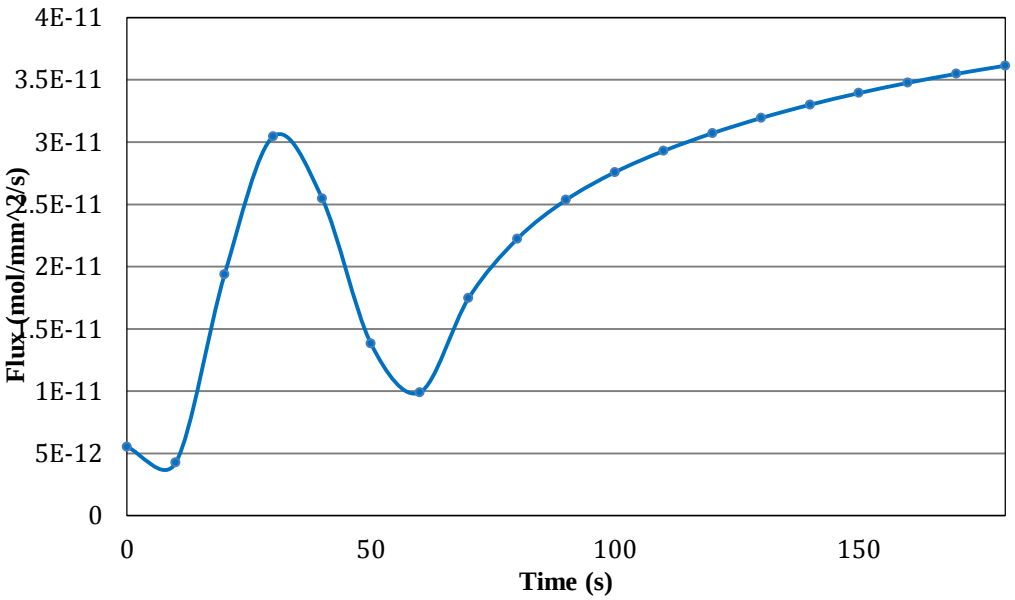


Figure C6. Flux vs. time graph for high saliva velocity magnitude (u=0.1999 mm/s)

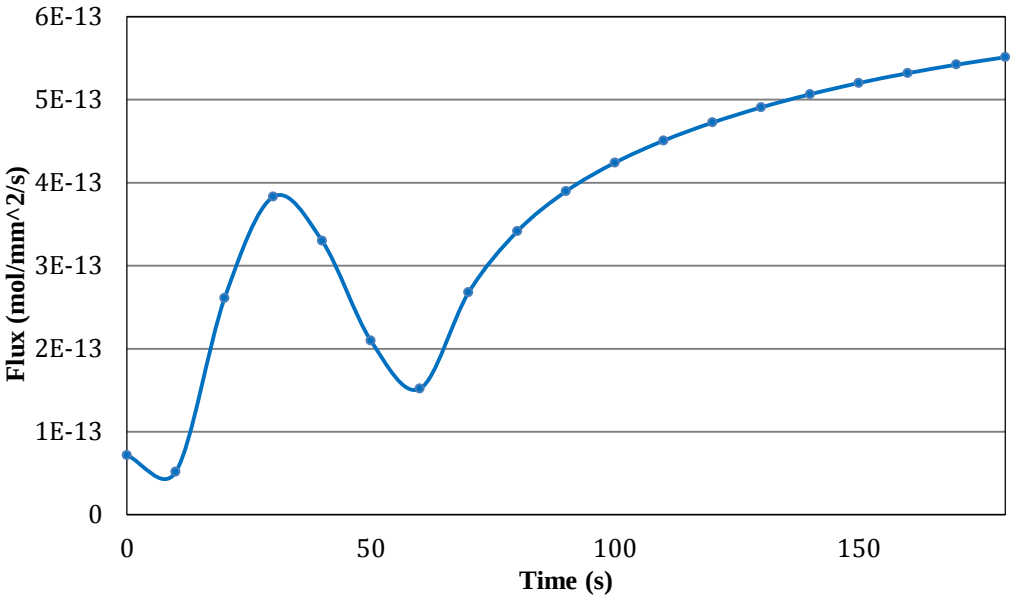


Figure C7. Flux vs. time graph saliva sloshing frequency every 0.5 seconds

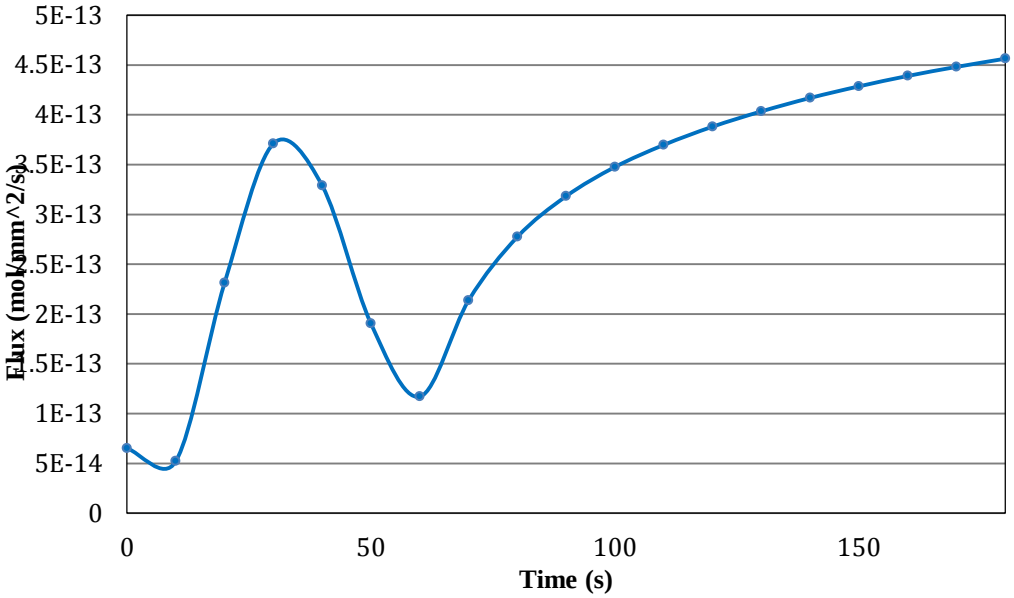


Figure C8. Flux vs. time graph saliva sloshing frequency every 2 seconds

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