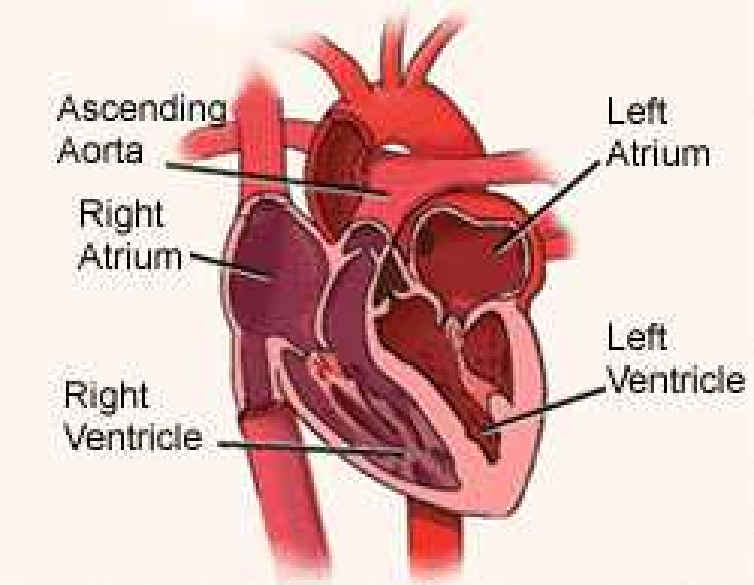
ANGINA PATCH: DRUG DELIVERY FOR CHEST PAIN



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May 5, 2006

Table of Contents

Final Design Project Report

Executive Summary 1

Introduction 2

Schematic 3

Design Objectives 3

Results 4

New Schematic with No Fat 5

Patch with Larger Drug Reservoir 7

36 Hour Patch Cycle 8

Sensitivity Analysis 9

Conclusions and Design Recommendations 11

Appendices

Appendix A:

- Original Schematic with Patch, Skin, and Fat: 13
- Modified Schematic without the Fat Layer: 14
- Governing Equation: 15
- Non-Dimensionalization: 16
- Input Parameters: 17
- Computing Drug Diffusion Into Skin: 18
- 36 Hour Cycle of Wearing the Patch on and Off: 19

Appendix B:

- Problem and Solution Statement: 20
- Time Integration Statement: 21
- Plot of Element Mesh: 22
- Convergence of Mesh and Time Step: 23
- FDREAD File: 24

Appendix C: Resources 25

Executive Summary

Angina pectoris is defined as chest pain due to lack of blood and oxygen to the heart. Nitroglycerin is an organic nitrate which treats angina by vasodilating both arteries and veins to increase blood flow to the heart. It is easy to develop nitroglycerin drug tolerance, and therefore drug application must occur at intervals of about 12 hours.
While commercial products such as Deponit are suitable for treating mild cases of angina, a larger, daily dose of 40 mg of nitroglycerin is needed to treat the most acute cases. The purpose of this study is to model the diffusion of nitroglycerin from a transdermal patch into the blood stream using the Deponit drug delivery system. We determined that Deponit was indeed unable to deliver the necessary 40 mg of drug. We therefore suggested a new patch which could treat acute angina, by modifying both patch geometry and the initial amount of drug in the reservoir. We also simulated drug delivery for a 36 hour period of wearing the patch for 12 hours, not wearing the patch for 12 hours, and then reapplying a new patch for another 12 hours. We found that drug continued to be delivered even in absence of patch and after 36 hours, only ~125 mg of drug was delivered. The modified *Thicker Patch* with a 10x thicker drug reservoir than Deponit can physically hold 142 mg of drug and deliver 40 mg within 12 hours. The modified patch is safe, non-toxic, cost effective, and capable of treating recalcitrant angina. To determine whether our assumptions were appropriate for our parameters, we performed two specific sensitivity analyses: varying the diffusivity of the skin and varying the diffusivity of the patch and the skin. From the sensitivity analysis we found that the amount of drug delivered to body is very sensitive to the diffusivity of the skin but insensitive to the diffusivity of the patch

Introduction

Coronary heart disease is the number one cause of death in America and is most commonly caused by heart attacks and angina. Angina pectoris is defined as chest pain due to lack of blood and oxygen to the heart muscle, which is generally caused by obstructions or spasms of the coronary arteries.

The drug most commonly used to treat angina is nitroglycerin, also known as glycerol tri-nitrate**.** Nitroglycerin is for emergency, hospital usage and is usually only prescribed for a few days. Nitrates dilate arteries by releasing nitric oxides which open up the smooth muscles in blood vessels. This vasodilation allows increased amounts of oxygen to flow to the heart to relieve chest pain. A convenient method of administering nitroglycerin is via transdermal patches.

"nitroglycerin is a dense, oily liquid that detonates if heated to 218°C" (Introduction to Mine Engineering) with a density of 1.6 g/cm^3 at 25°C. When prescribed as heart medication, tiny amounts of nitroglycerin are diluted by inert matter, making it completely non-explosive. A lethal dose of nitroglycerin ranges from 200-1000 mg. Side effects of nitrates include flushing, headaches, and low blood pressure.

Continuously worn patches have been shown to lead to drug tolerance within the first 24 hours of therapy. To prevent the development of drug tolerance, therapy incorporates nitrate-free periods. Although a minimum nitrate-free interval has not been defined, data shows that 10-12 hours of being nitrate free is sufficient. A typical treatment schedule includes a patch-on period of 12 -14 hours and a daily patch off period of 10 -12 hours.

Deponit is a popular, commercial angina patch manufactured by the German company Schwarz Pharma. Deponit is an acrylic, translucent, square patch with an area of 18 cm^2 and a total thickness of 0.1 mm. The patch can be applied to any part of the body free of hair and skin irregularities. The patch consists of three layers (Figure 1). The release liner protects the active surface of the drug containing matrix. The backing film adjusts to different skin conditions including sweat. The drug reservoir matrix holds nitroglycerin which is suspended in an acrylic co-polymer, such as polyethylene.

Figure 1: Deponit patch schematic

Deponit delivers nitroglycerin at 15 $\mu g/cm^2$ per hour. "Yet while products such as Deponit have received wide patient acceptance, the total daily nitroglycerin dose is not adequate to provide the substantial nitroglycerin doses required in the treatment of congestive heart failure or recalcitrant cases of angina pectoris" (US Patent Office). To treat these conditions a patient needs to obtain daily doses of at least 40 mg.

Schematic

The diagram below (Figure 2) indicates the thicknesses of each layer of patch, skin, and fat. Here we assume that the properties are uniform throughout the skin and that the drug must diffuse through a layer of fat before being absorbed by the blood vessels. The prior assumption was made due to the fact that diffusivity properties found in literature were uniform throughout the layers of skin. The latter assumption was made based on information provided by Professor Gorewit at Cornell University. Gorewit also provided the information that the diffusivity of nitroglycerin in fat is lower than that in skin, so it was therefore assumed to be ten times smaller.

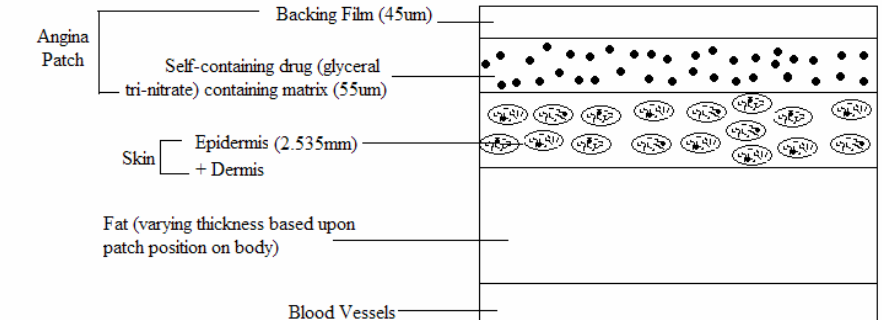


Figure 2: Diagram showing the dimensions of the three layers of the patch and skin

Refer to Appendix A for a thorough explanation of the various schematics used, the boundary conditions, initial conditions, simulation properties, and governing equation.

Design Objectives

The objective of this study is to analyze the diffusion of nitroglycerin from a transdermal patch into the blood using the Deponit drug delivery system. Assuming an initial drug concentration in the drug reservoir, the amount of nitroglycerin delivered to the body will be measured after 12 hours using FIDAP. The following are the main design objectives:

1. Confirm whether or not an effective amount of drug to treat congestive heart failure (40 mg cumulative) can be delivered to the body within 12 hours using the Deponit system.
2. Suggest a new patch, including a modified geometry and initial amount of drug in the reservoir, which can deliver 40 mg within this 12 hour window.
3. Model the diffusion of nitroglycerin over a 36 hour period, where the patch is applied for 12 hours, removed for the next 12 hours, and a new patch is applied again for 12 hours.
4. Determine whether toxic levels of nitroglycerin could be obtained during usage of the patch.
5. Evaluate the affect of patch position on the body to the amount of drug that can be delivered to the body will be studied. Different areas on the body have varying thicknesses of fat, which may influence the diffusion of drugs to the body.

Results

Preliminary Results for Original Schematic:

The schematic described above with the patch, skin, and fat was modeled on Gambit and analyzed using FIDAP. A 12 hours simulation was run, and the amount of drug that diffused from the patch and into the skin was calculated using the method in Appendix A.

Some difficulty was encountered when attempting to find the drug delivery to the body using this model. Initial results showed that no drug was able to completely diffuse to the blood vessels to be delivered to the body, as shown in the contour plot below:

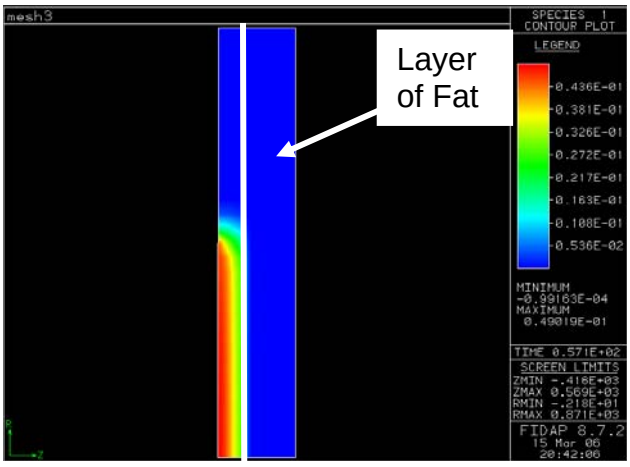


Figure 3: Contour of drug nitroglycerin Concentration after 12hr

In this figure, the fat layer is entirely blue, while the skin layer has variations in color, showing that nitroglycerin traveled through the epidermis & dermis, but not the fat. This was confirmed by the mean drug computation because at initial and final times the mean concentration of species was the same, indicating no diffusion of the drug into blood. As seen below, a clear drop in the concentration of the nitroglycerin exists where fat begins.

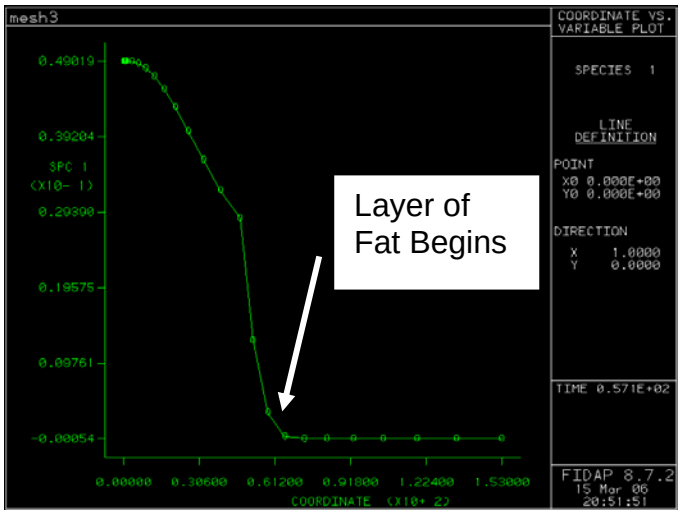


Figure 4: Plot of nitroglycerin species along the axis at end time of 12 hours

Therefore, no drug got into the blood stream since the drug was never able to diffuse all the way through the fat. These results were not anticipated because it was assumed that the drug would diffuse through the entire fat layer before reaching the blood.

These results led us to re-evaluate our model. There are two logical reasons for the lack of diffusion of drug through the layer of fat: the fat layer adds an extra 5.8mm for the drug to diffuse through, and the fact that the fat was assumed to have a lower diffusivity than that of skin. Since nitroglycerin patches exist and are known to work, such as Deponit, the error in these preliminary results was determined to be due to incorrect assumptions in the model. Upon further research of the physiology of skin, it was determined that there are many blood vessels prevalent in the dermis layer (which is above the fat layer) where the nitroglycerin can diffuse directly into the blood stream.

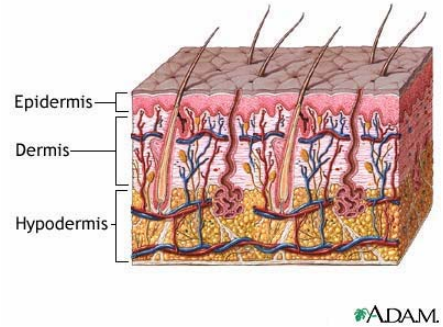


Figure 5: Cross section of skin showing location of blood vessels for drug diffusion

Therefore, the new model assumed that nitroglycerin diffuses through the skin and directly into the blood without having to pass through the subcutaneous fat. The new schematic for this model is similar to the previous one except that the fat layer has been removed, as seen above. (Please refer to Appendix A for the modified mesh schematic)

New Schematic With No Fat

With the newly formulated model, the first objective was met by setting the dimensions and properties of the patch to that of the Deponit patch. According to the information given by Schwartz Pharma, the patch delivers a flux of nitroglycerin of 15μg of drug per square centimeter of the patch. Even if it was assumed that this flux remains constant, only 3.24mg of drug would be delivered to the body after a 12hr period. Therefore, the only method to improve the performance of the Deponit patch system, without changing its geometry, would be to increase the initial concentration of nitroglycerin in the patch.

Therefore, the initial amount of drug needed in the patch to deliver 40mg of nitroglycerin in a 12hr period must be determined. However, FIDAP only allows us to simulate the forward solution: to find the drug delivery based on an initial concentration in the patch. Therefore, this is an inverse problem that can be solved by performing several iterations of the FIDAP simulation. The drug delivered to the body could be simulated for various

values of drug concentration in the patch until the concentration that delivers 40mg was determined.

The above procedure was used to determine the amount of drug needed in the Deponit patch for it to deliver 40mg of nitroglycerin to the body. As seen below, it was found that the relationship between the amounts of drug delivered to the body was proportional to the amount of drug initially in the patch indicated by the linear graph (Figure 6).

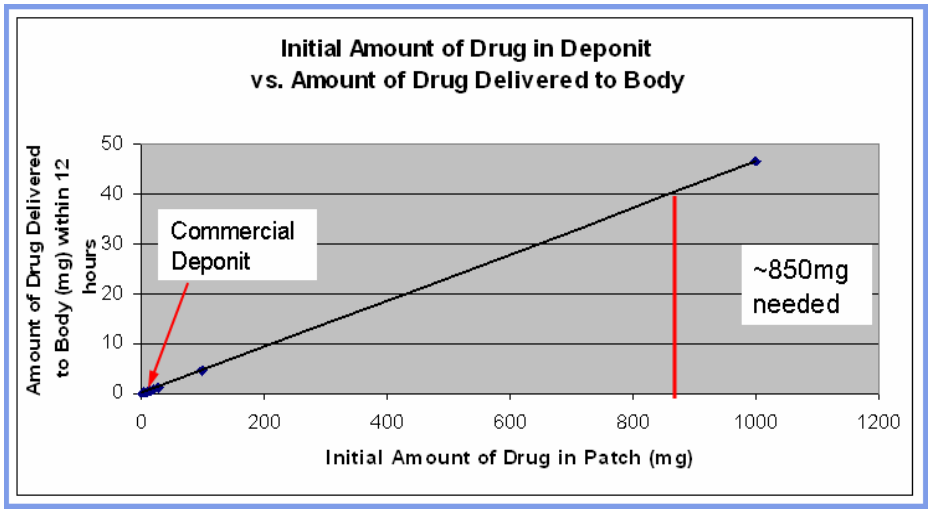


Figure 6: Amount of drug in Deponit vs. Amount of drug delivered to body

Intuitively, as the initial amount of drug in the patch increases, the amount of drug delivery in a 12 hour period increases. As shown in the graph above, the original Deponit design falls short of the required drug delivery. The amount of drug required in the Deponit patch system would need to be as high as 850mg of nitroglycerin.

There were two main problems associated with the above findings. The first problem was an issue of economics and efficiency: 850mg of drug is needed to only deliver 40mg to the body. This would cause the patch to become more expensive due to the unused nitroglycerin. The second problem dealt with the physical properties of nitroglycerin. As mentioned earlier, nitroglycerin is very explosive and remains stable in medical applications by diluting it in inert matter. The current patch would have 850mg of nitroglycerin in a volume of $0.099cm^3$. This means the patch would have a concentration of nitroglycerin of $8.59g/cm^3$. Not only would this be dangerous, but this would also be physically impossible to have this much nitroglycerin in such a small volume of a patch since the density of pure nitroglycerin at 25^oC is only $1.6g/cm^3$.

Therefore, the Deponit drug delivery system remains inadequate for delivering enough nitroglycerin to the body to treat recalcitrant cases of angina. The next step would be to redesign the geometry of the patch and perform the same analysis as above.

Patch with Larger Drug Reservoir

In the Deponit simulation, the drug reservoir was very thin (only 0.055 mm thick) and there was very little drug getting to the bloodstream. To allow a greater amount of drug to be placed into the drug reservoir, it was decided to increase the size of the patch's drug matrix and see how that affected the diffusion. The surface area of the patch was kept the same because it was believed that the limiting factor for this problem was the small thickness of the patch. A new schematic was developed where the drug matrix was increased from 0.055 mm to 0.55 mm with all other values remaining constant.

As before, the inverse problem was solved to find the initial amount of drug needed in the patch to deliver 40mg of drug in the body was determined. As the following graph indicates, only 142mg of drug was needed in the patch:

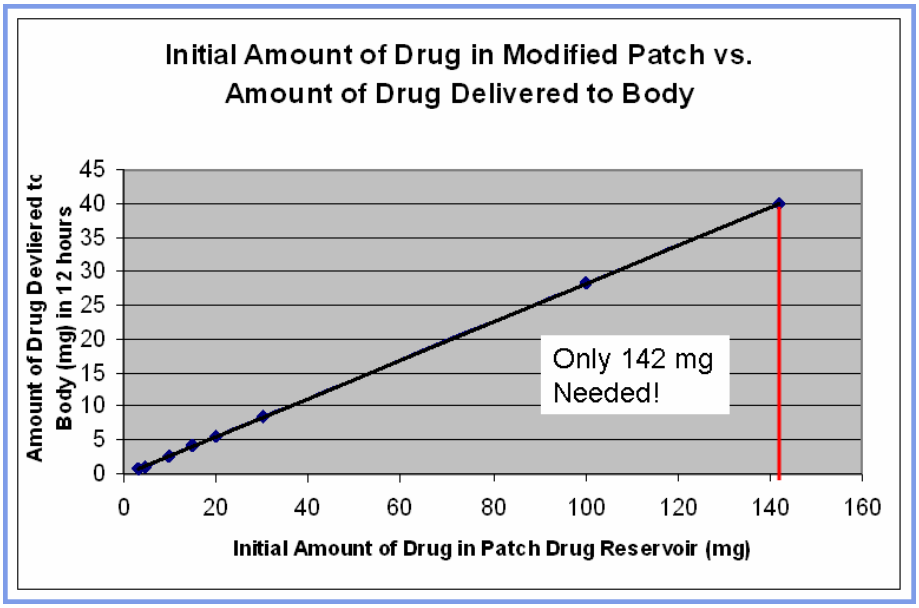


Figure 7: Initial amount of drug in the matrix vs. how much is actually delivered to the body

This result is better than that of the Deponit for two reasons: less nitroglycerin was needed overall, and the concentration of the nitroglycerin in the patch would be much lower because less drug was required in a larger patch. Due to the fact that less nitroglycerin was needed to deliver 40mg means there would be less wasted drug in the patch. Furthermore, this amount of drug in the patch was low enough to both physically fit in the patch and also remain dilute enough to be inert. This patch would have 142mg of nitroglycerin in a volume of $0.99cm^3$. This means the patch would have a concentration of nitroglycerin of $0.143g/cm^3$, compared to $1.6g/cm^3$ for pure nitroglycerin.

36 Hour Patch Cycle

Under normal conditions, the patch is applied for 12 hours, removed for 12 hours, and then a new patch is applied for another 12 hours. However, in the time that the patch is removed, drug still remains in the skin and can continue to diffuse into the blood. Even when the new patch is applied after 24 hours, there is still residual drug left in the skin from the first patch which can increase the dosage. We would like to see how the amount of drug delivered to the blood changes in this 36 hours cycle.

To model the 36 hour cycle, we used three separate, linked simulations. The first simulation was run for 12 hours with 142 mg in the drug reservoir and used the normal initial conditions, boundary conditions, and properties. The second simulation read the final amounts of drug in the skin from the first simulation. To mimic the removal of the patch, the patch initially had 0 mg of drug and the diffusivity of the patch was reduced to virtually zero. The third simulation read the amount of drug in the skin from the second simulation and was run for another 12 hours, but again the diffusivity of the patch was returned to its normal value and the patch had an initial drug amount of 142 mg to simulate the application of a new patch. The following graph and table describe the results:

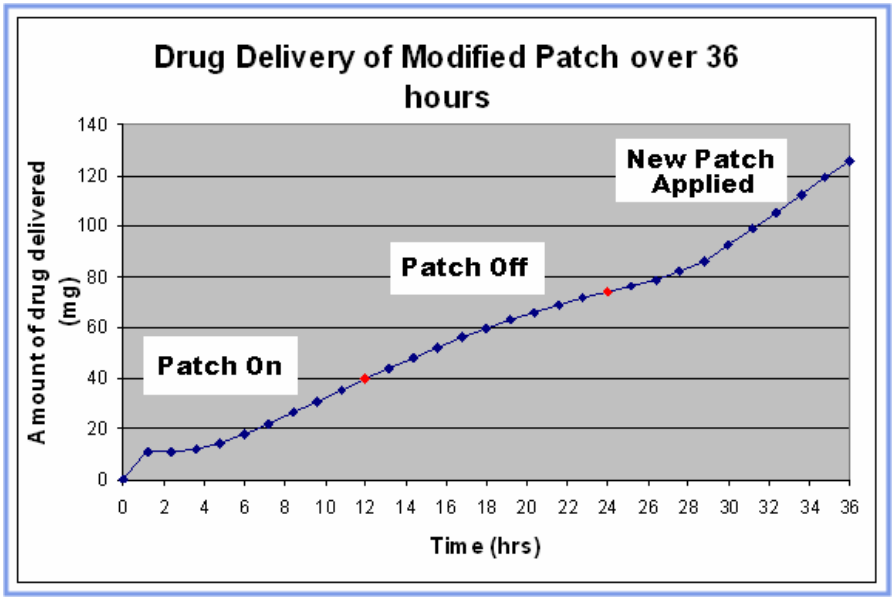


Figure 8: Drug delivery vs. time for a patch initially with 142 mg of drug

Drug Delivery After each 12hr Segment	Drug Delivery in 12hr Period (mg)	Total Drug Delivered (mg)
12 hours with Patch	40.025	40.025
12 hours without Patch	33.960	73.984
12 hours with Patch Again	51.803	125.788

Table 1: Drug Delivery after each 12hr period

As shown in Table 1, within the first 12 hour period, 40.025 mg of drug was delivered, which is sufficient to treat severe angina. But in the next 12 hours, even after the patch was removed, an additional 33.960 mg of residual drug in the skin from the first patch was delivered. Then when the new patch was applied for another 12 hours, 51.803 mg of drug was delivered for the same reason.

The information from the 36 hour patch application serves to help understand the delivery of the drug over several cycles of patch application. As shown in Figure 8, drug was still delivered during the 12 hour our period without the patch. Hence, the rate of drug delivery remains relatively constant over 36 hours as in the graph. Furthermore, the total amount of drug delivered over 36 hours was approximately 125mg of nitroglycerin. With a toxic dose of 200mg, it seems that the application of the patch for periods longer than 36 hours may become dangerous. However, the lethal dosage is stated for an immediate dosage of 200mg, rather than a dosage over 36 hours. Therefore, this level of drug delivery remains safe.

Sensitivity Analysis

Sensitivity analysis was performed to examine how changes in the skin diffusivity and patch diffusivity affected the amount of drug delivered to the body. The following graph (Figure 9) shows the dependency of drug delivered on the value of the diffusivity of the skin.

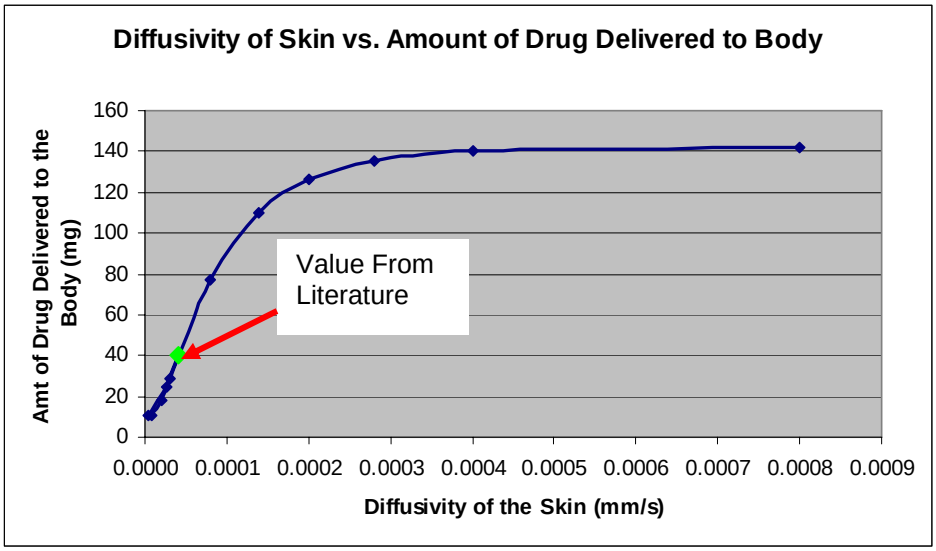


Figure 9: Sensitivity of D_{skin} using a constant D_{patch} = 0.05 mg/mm^3

The green dot represents the skin diffusivity value that we found in literature ($4x10^{-5}$ mm^2/s) used in our previous simulations. The amount of drug delivered to the body increased as the diffusivity of the skin increased until the diffusivity was about 0.0004 mm^2/s, which is where the graph leveled off with 99.99% drug going into the body. Initially there was a linear slope (amount of drug delivered to skin was proportional to the

diffusivity) before it leveled off. This occurred because the diffusivity of the skin got large enough to allow most of the drug to diffuse into the skin in a 12hr period.

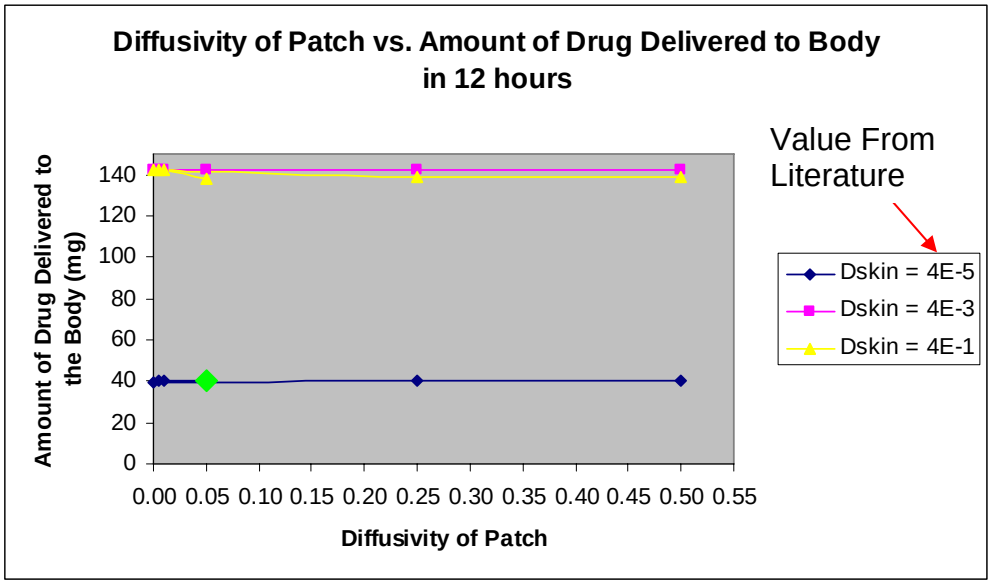


Figure 10: Sensitivity Analysis of varying D_{patch} and D_{skin}

The graph above (Figure 10) depicts the sensitivity analysis of the diffusivity of the patch at various values for the diffusivity of the skin. The green dot in the figure also represents the skin diffusivity and patch diffusivity values that we found in literature that we used in our main simulations. The figure above shows that even large differences in the magnitude of the diffusivity of the patch did not change the amount of drug delivered into the body despite various diffusivities of the skin. There was practically no variation in the amount of drug delivered despite increasing and decreasing patch diffusivities. Clearly, as the diffusivity of the skin increased, the amount of drug delivered to the body increased, with 100% drug delivery for $D_{skin} = 4x10^{-3}$ and $4x10^{-1}$ within 12 hours.

Thus, the amount of drug delivered to body is very sensitive to D_{skin}, but insensitive to D_{patch}. Since drug delivery is very sensitive to the diffusivity of the skin, it is important to validate the value of this parameter from experimentation and literature. Because drug delivery is relatively insensitive to diffusivity of the patch, any uncertainty error in this parameter does not greatly affect simulation results.

Conclusions and Design Recommendations

The objectives of this study were to analyze the diffusion of nitroglycerin from a transdermal patch into the blood stream using the Deponit drug delivery system. We wanted to specifically confirm whether or not Deponit could deliver an effective amount of drug to treat acute angina, suggest a new patch if Deponit was inefficient including a modified geometry and initial amount of drug in the reservoir, and model the diffusion of nitroglycerin over a 36 hour period.

It was determined that nitroglycerin is absorbed into the body without having to diffuse through the subcutaneous fat layer since there are already blood vessels in the dermis layer of the skin meaning that the drug would be delivered throughout the body without having to first diffuse all the way through the fat layer. Our first model with the fat layer did not work as no drug was delivered through the fat. For our second model, we removed the fat layer and therefore, could not study the affect of patch position on the body with variations in fat thickness to the amount of drug delivery.

We found that Deponit is ineffective at delivering the 40 mg of nitroglycerin within 12 hours needed to treat recalcitrant angina, even with an increased initial amount of drug. The commercial Deponit patch contains 3.24 mg of drug and delivers less than 1 mg in 12 hours. We found that the Deponit patch would need to contain 850 mg to deliver 40 mg of drug. Economically this means that more money would be wasted by the company to put a large amount of drug into the patch that only delivers approximately 5% of drug in reservoir to the body. Also in terms of manufacturability, it is not possible to fit 850mg of nitroglycerin in such a small patch reservoir.

Since Deponit was found to be ineffective at treating acute angina we needed to modify the patch. We found that the modified patch with a thicker drug reservoir only needs 142 mg of drug to deliver 40 mg to the body in 12 hours. By our calculations, this larger drug reservoir can physically hold 142 mg. The 142 mg of drug is safe, non-toxic (non-explosive amount), and more cost effective since less drug is wasted and needed in patch. Since there is less drug in the reservoir, it is less expensive to manufacture and therefore more economical.

Over a 36 hour period of wearing, removing, and applying a new patch it was found that the nitroglycerin continued to be delivered even in absence of the patch due to residual drug diffusing through the skin. Even after 36 hours, only ~125 mg of drug is delivered which is much less than the lethal dose of 200mg or more.

From our sensitivity analysis, we found that amount of drug delivered to body is very sensitive to the diffusivity of the skin but insensitive to the diffusivity of the patch. Thus when modeling it is important to obtain the correct diffusivity of the skin to ensure accuracy in the simulation and any uncertainty in the diffusivity of patch has little effect.

Design Recommendations

Based on the results from this study, possible improvements to the nitroglycerin transdermal drug delivery system include increasing the thickness of the drug reservoir and increasing the initial amount of drug in the patch. As previously shown, a larger initial amount of drug in the patch increases the total drug delivery in 12 hours. A thicker patch allowed for less drug needed in the reservoir and lead to a lower concentration of drug in the patch.

In spite of these findings, future work should study the dependence of drug delivery on the thickness on the patch. This study would require several meshes of the patch, which could be done in this study due to time constraints. Furthermore, in consideration of the patient, the comfort and convenience of the patch must also be considered when increasing its thickness.

As seen in the sensitivity analysis, the drug delivery of nitroglycerin is highly dependent on the diffusivity of the skin. We therefore strongly suggest validating the value of this parameter experimentally in future research.

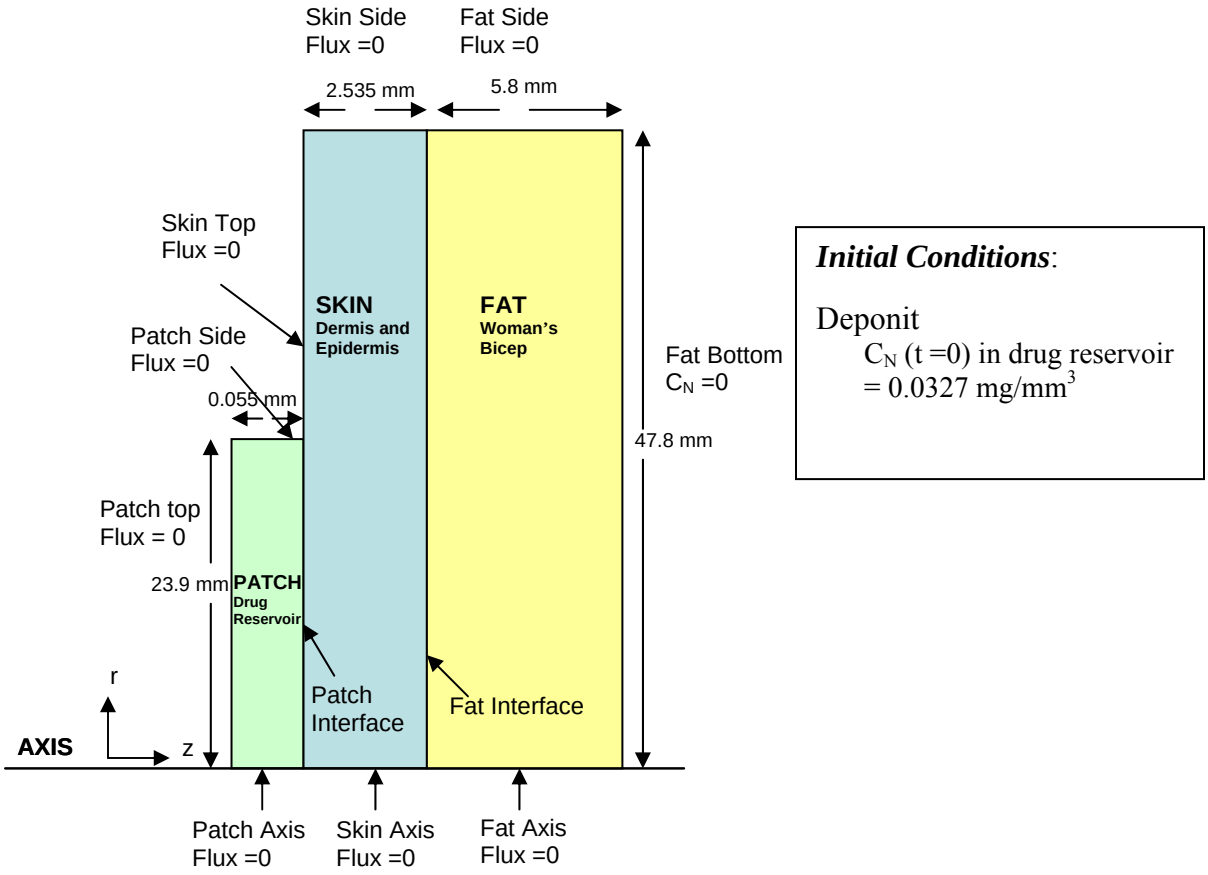
Although much research is yet to be done to improve treatment for recalcitrant cases of angina, we believe this study provides promising results for the modification of currently available transdermal patches.

Appendix A: Mathematical Statement of the Problem

Geometry: 2-D axi-symmetric problem

This geometry was chosen because the square shape of a transdermal patch could be approximated as a circular disc over a larger disc of skin and fat.

Original Schematic with Patch, Skin, and Fat



For Deponit, the actual concentration of drug within the patch was not given, so an estimation was made based upon the average flux that the patch is reported to provide:

Concentration of nitroglycerin in Deponit drug reservoir:

= [(Ave Flux) * (Surface Area of patch) * (Time)] / Volume of Patch

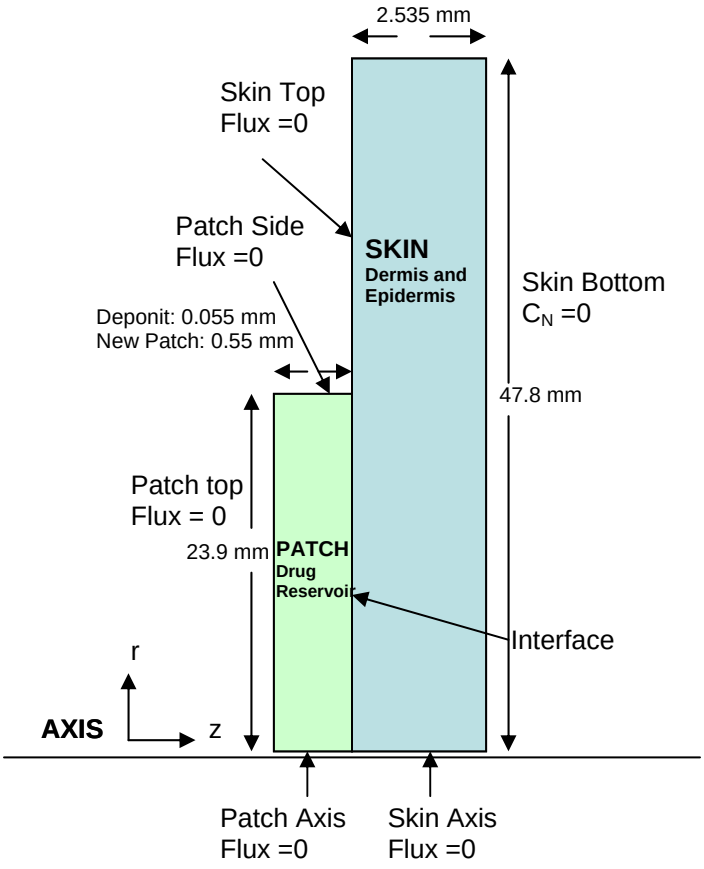
= [(15 µg/cm^2 per hour) * (18 cm^2) * (12 hour)] / 99 mm^3

= 0.0327 mg/mm^3

Modified Schematic without the fat layer:

Two different meshes were created for:

1. The original transdermal patch, Deponit
2. Our modified patch which can deliver 40 mg of drug within 12 hours



Initial Conditions:

Deponit

C_N (t =0) in drug reservoir = 0.0327 mg/mm^3

Modified Patch

C_N (t =0) in drug reservoir = 0.1434 mg/mm^3

Figure 1: Schematic of Deponit patch and our modified patch

The following assumptions were made:

- No nitroglycerin is consumed in the drug reservoir or skin
- Skin = epidermis + dermis
- Thickness of skin is characteristic of a women's bicep
- All drug that passes through the skin is absorbed directly by the blood

Governing Equation:

$$\frac{\partial c}{\partial t} + u_x \frac{\delta c}{\delta x} = D\frac{\partial^2 c}{\partial x^2} + R_A$$

Since we are modeling the diffusion of nitroglycerin as an axi-symmetric problem and there is no convection or species generation occurring, the diffusion equation in radial coordinates reduces to

$$\frac{\partial c_N}{\partial t} = D_N\left(\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c_N}{\partial r}\right) + \frac{\partial^2 c_N}{\partial z^2}\right)$$

r = radial distance
z = distance in the z direction
t = time
D_N = diffusivity of nitroglycerin in various mediums (skin, patch)
C_N = concentration of nitroglycerin

To increase the accuracy of our results, the physical properties and dimensions of our model will be non-dimensionalized to compensate for the small diffusivity values.

$$\frac{R^2}{D_N}\frac{\partial c_N}{\partial t} = \frac{1}{\left(\frac{r}{R}\right)}\left(\frac{r}{R}\frac{\partial}{\partial\left(\frac{r}{R}\right)}\right) + \frac{\partial^2 c_N}{\partial\left(\frac{z}{R}\right)^2}$$

Non-Dimensionalization:

Parameter	Non-Dimensionalized	Values for Deponit	Values for Modified Patch
r	$\frac{r}{R}$	R = 0.055	R = 0.55
z	$\frac{z}{R}$	R = 0.055	R = 0.55
t	$\frac{Dt}{R^2}$	R = 0.055 D = 4 x 10^{-5}	R = 0.55 D = 4 x 10^{-5}
d	$\frac{d}{D}$	D = 4 x 10^{-5}	D = 4 x 10^{-5}

We chose to not non-dimensionalize the concentration values as they do not affect the other non-dimensionazlied variables in the equation.

Non-Dimensionalized Mesh (using the Modified Patch):

Original Coordinates (z,r)	Non-Dimensionalized Coordinates (z,r)
(0,0)	(0,0)
(0,23.9)	(0, 43.45)
(0.55,0)	(1,0)
(0.55, 23.9)	(1,43.45)
(0.55, 47.8)	(1, 86.91)
(3.085, 0)	(5.609, 0)
(3.085, 47.8)	(5.609, 86.91)

Non-dimensionalized coordinates were determined by dividing all the original coordinates by R= 0.055 for the Deponit patch and R= 0.55 for the Modified Patch as shown in the example above.

Input Parameters:

For Diffusion

Parameter	Dimensionalized Value (mm^2/sec)	Non-Dimensionalized Value	Source
D_{patch}	0.05	1250	Hung, et al.
D_{skin}	4.00×10^{-5}	1	Mitchem, L
D_{fat}	4.00×10^{-6}	n/a	Estimation

D_{skin} is the diffusivity of nitroglycerin in the skin (includes dermis and epidermis) because only a single diffusivity value of nitroglycerin in skin could be found.

D_{patch} is the diffusivity of nitroglycerin in the drug matrix which is composed of 30% vinyl acetate.

D_{fat} was only used with the original schematic which was later modified.

For Time

Parameter	Dimensionalized Value	Non-Dimensionalized Value	Source
T_{intial}	0	0	N/A
T_{final}	12 hours = 43200 s	5.71	N/A
T_{step}	432 s	0.0571	N/A

Max number of time steps = 100 or 1000

For Concentration

Concentration was not non-dimensionalized. Concentration of drug was only found within the drug reservoir of the patch.

Parameter	Dimensionalized Value (mg/mm^3)	Source
Deponit : C_N	0.0327	Online Deponit website
New Patch : C_N	0.1414	FIDAP simulations

Computing Drug Diffusion into the Skin:

The mean computation on FIDAP was used to calculate the mean concentration of drug left in the volume of the patch, skin (and fat depending on the mesh being used). This concentration could then be used to find the total amount of drug left in the system by multiplying by the volume. Since the initial amount of drug in the patch is known from the initial condition in the patch, the drug delivered to the body could be found by the difference between the initial amount of drug and the drug remaining in the system after 12 hours.

For Deponit:

Volume of patch $= 18cm^2 * \left(\frac{100mm^2}{1cm^2}\right) * 0.055mm$

$= 99\ mm^3$

Volume of skin $= 2.535\ mm * \Pi * (47.8\ mm)^2$

$= 18196.32\ mm^3$

Total Volume $= 990\ mm^3 + 181196.32\ mm^3$

$= 18295.32\ mm^3$

For Modified patch:

Volume of patch $= 18cm^2 * \left(\frac{100mm^2}{1cm^2}\right) * 0.55mm$

$= 990\ mm^3$

Volume of skin $= 2.535\ mm * \Pi * (47.8\ mm)^2$

$= 18196.32\ mm^3$

Total Volume $= 990\ mm^3 + 181196.32\ mm^3$

$= 19186.322\ mm^3$

Amount of Drug Diffused into Skin:

= (Initial concentration in patch * Volume of patch) - (Mean concentration of drug calculated from FIDAP * Total Volume)

36 hour cycle of wearing the patch on and off (for Modified Patch):

To simulate wearing the patch for 12 hours, removing the patch for 12 hours, and adding a new patch for 12 hours we:

- Ran three separate simulations for each of the three periods
- Varied the initial conditions and patch diffusivity properties for each simulation
- Read the results from the previous simulation for the next simulation

Simulation	**Real Time (hr)**	**Entity**	**Initial Condition (mg/mm^3)**	**Dimensionalized Properties (mm^2/s)**
Patch on	0-12	Patch Skin	$C_N = 0.1434$ $C_N = 0$	$D_{patch} = 0.05$ $D_{skin} = 4 \times 10^{-5}$
Patch off	12-24	Patch Skin	$C_N = 0$ $C_N = 0$	$D_{patch} \sim 1 \times 10^{-11}$ $D_{skin} = 4 \times 10^{-5}$
Patch on	24-36	Patch Skin	$C_N = 0.1434$ $C_N = 0$	$D_{patch} = 0.05$ $D_{skin} = 4 \times 10^{-5}$

To simulate the removal of the patch, the C_N in the patch was set to 0 and the D_{patch} was set to 0. However within FIDAP, D_{patch} cannot be defined as 0, so for the patch off period, 0 was approximated as 1×10^{-11}.

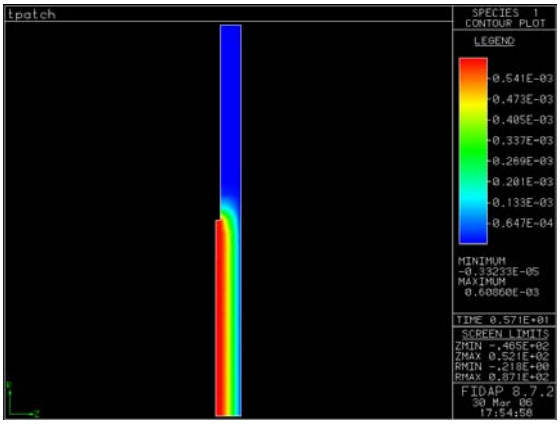


Figure 11: Patch on for 12 hours (file: tps1)

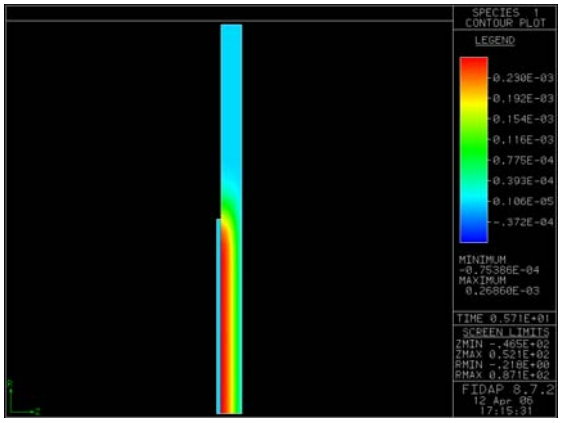


Figure 12: Patch off for 12 hours (file: tps2)

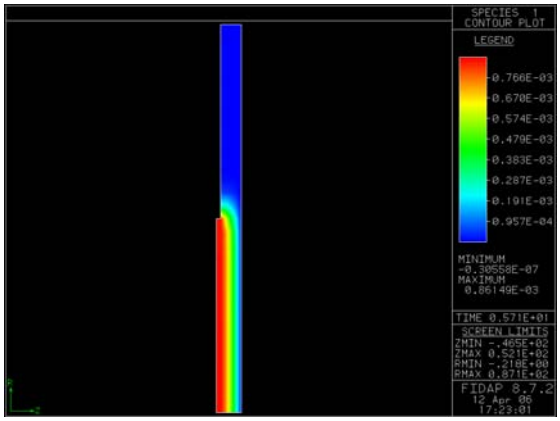


Figure 13: New patch on for next 12 hours (file: tps3)

Appendix B:

Problem Statement:

PROB (AXI-, ISOT, NOMO, TRAN, LINE, FIXE, NEWT, INCO, SPEC = 1.0)

Descriptor	Symbol	Explanation
Geometry Type	AXI	Axi-symmetric: Patch is assumed to be circular and the axis runs through the center of the patch
Temperature Dependence	ISOT	Isothermal: No heat equation used
Flow Type	NOMO	No momentum: There is no fluid flow
Simulation Type	TRAN	Transient: Interested in amount of drug delivered versus time
Convective Term	LINE	No convection occurring
Surface Type	FIXE	Geometry is fixed
Fluid Type	NEWT	If fluid was present, it would be Newtonian
Flow Regime	INCO	Drug is incompressible
Species Dependence	SPEC = 1.0	nitroglycerin is the only species being analyzed

Solution Statement:

SOLU (S.S. = 50, VELC = 0.100000000000E-02, RESC = 0.100000000000E-01, SCHA = 0.000000000000E+00, ACCF = 0.000000000000E+00)

Descriptor	Symbol	Value	Explanation
Solution Method	SS	50	Successive Substitution = 50 iterations per time step
Velocity Convergence	VELC	1×10^{-3}	Velocity convergence tolerance
Residual Convergence	RESC	1×10^{-2}	Residual vector convergence tolerance
Solution Change	SCHA	0	Default percentage change in solution magnitude
Relaxation Factor	ACCF	0	Acceleration of solver set to zero

Time Integration Statement:

TIME (BACK, FIXE, TSTA = 0.000000000000E+00, TEND = 5.71,
DT = 0.571000000000E-01, NSTE = 100)

Descriptor	Symbol	Value	Explanation
Time Integration	BACK	n/a	Backward integration using $(t + \Delta t)$
Time Step Algorithm	FIXE	n/a	Fixed time step
Start Time	TSTA	0	Beginning time is 0 sec
End Time	TEND	5.71	Ending time is 12 hours
Time Step	DT	0.0571	Time increment is 432 s
Number of Time Steps	NSTE	100	There are 100 fixed time steps

Note: Values of the start and end time are non-dimensionalized.

Plot of the element mesh

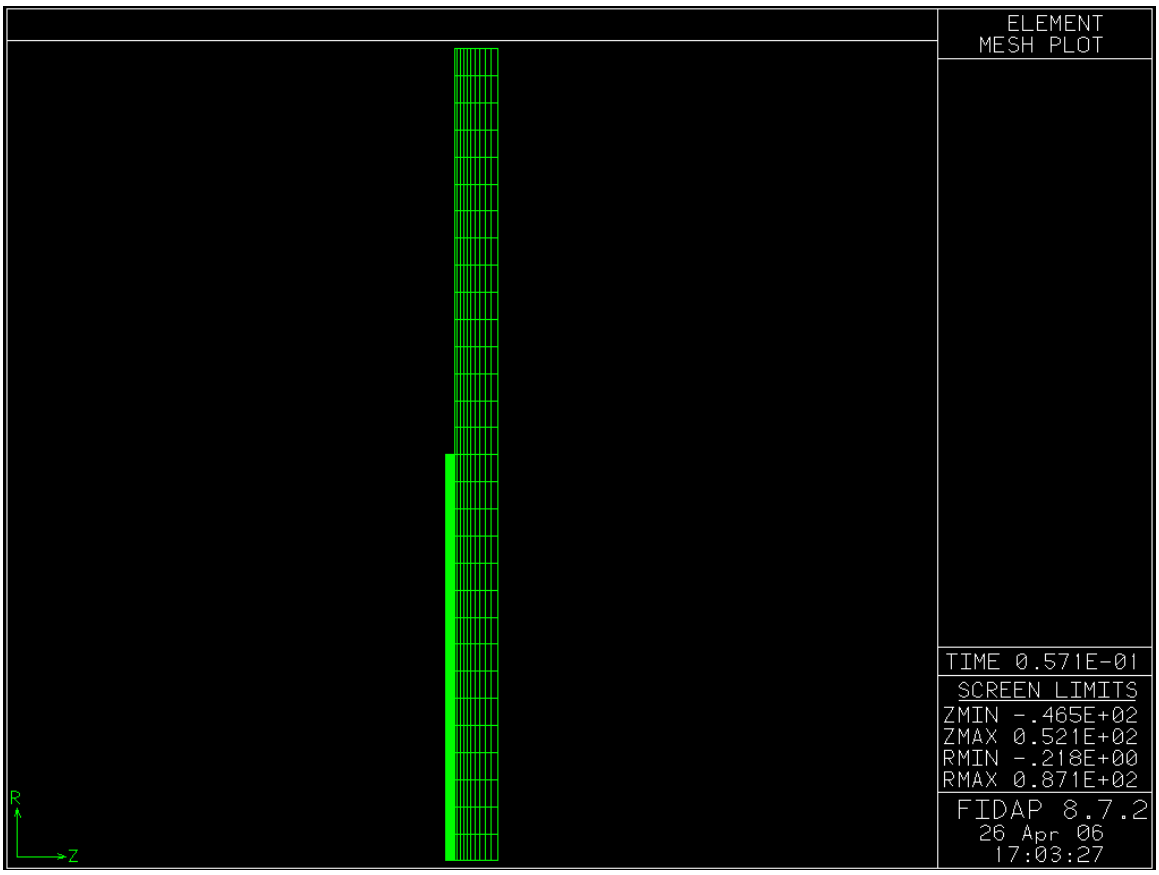


Figure 14: Plot of the elemental, non-uniform mesh

This mesh consists of two different layers: nitroglycerin drug matrix and the skin. The top layer is the very thin nitroglycerin reservoir. The skin layer consists of both the dermis and epidermis. The mesh is composed of structured quad elements. The mesh is non-uniform with more elements in the patch and at the patch/skin interface to account for the larger initial changes in drug concentration, while the mesh in the remainder of the skin is comprised solely of identically sized elements.

Convergence of Mesh

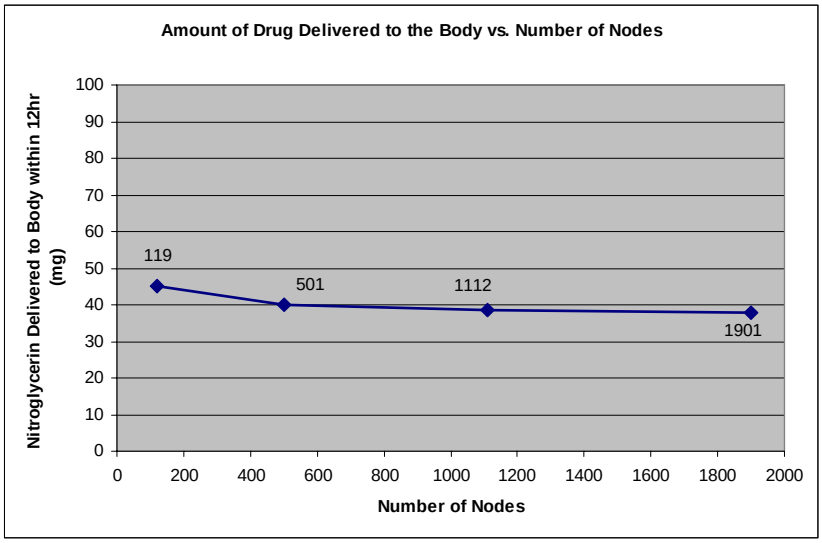


Figure 15: Mesh convergence

A mesh convergence test was performed to see the affect of changing the number of nodes on the amount of drug delivered to the body. As shown above, after about 500 nodes, the amount of drug delivered to the body did not change significantly with the number of mesh nodes. We chose to use 501 nodes to decrease the computation time while still maintaining a high level of accuracy.

Convergence of Time Step

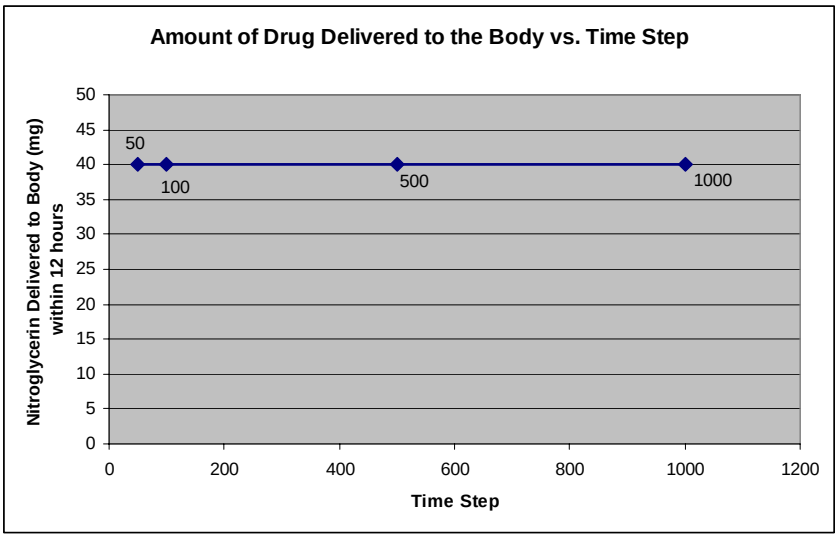


Figure 16: Amt of Drug Delivered to the Body vs. Time Step within 12 hrs using modified patch

As shown above, increasing the time step does create affect the final solution at all. Therefore, the time step of 100 was chosen to minimize the computation time, but still maintain a high level of accuracy.

FDREAD files

For patch on 12 hours

Files: tsp1

```
/  INPUT FILE CREATED ON 12 Apr 06 AT  17:12:35
/
/
/ ***  FICONV Conversion Commands ***
/ ***  Remove / to uncomment as needed
/
/  FICONV(NEUTRAL,NORESULTS,INPUT)
/  INPUT(FILE= "tps1.FDNEUT")
/  END
/  *** of FICONV Conversion Commands
/
TITLE

/
/ ***  FIPREP  Commands ***
/
FIPREP
 PROB (AXI-, ISOT, NOMO, TRAN, LINE, FIXE, NEWT, INCO, SPEC = 1.0)
 PRES (MIXE = 0.100000000000E-08, DISC)
 EXEC (NEWJ)
 SOLU (S.S. = 50, VELC = 0.100000000000E-02, RESC = 0.100000000000E-01,
       SCHA = 0.000000000000E+00, ACCF = 0.000000000000E+00)
 TIME (BACK, FIXE, TSTA = 0.000000000000E+00, TEND = 5.71,
       DT = 0.571000000000E-01, NSTE = 100)
 OPTI (SIDE)
 DATA (CONT)
 PRIN (NONE)
 POST (RESU)
 SCAL (VALU = 1.0)
 ENTI (NAME = "patch", SOLI, PROP = "mat1", SPEC = 1.0, MDIF = "C1_patch")
 ENTI (NAME = "skin", SOLI, PROP = "mat2", SPEC = 1.0, MDIF = "C1_skin")
 ENTI (NAME = "patchtop", PLOT)
 ENTI (NAME = "patchside", PLOT)
 ENTI (NAME = "patchaxis", PLOT)
 ENTI (NAME = "interface", PLOT)
 ENTI (NAME = "skintop", PLOT)
 ENTI (NAME = "skinside", PLOT)
 ENTI (NAME = "skinbottom", PLOT)
 ENTI (NAME = "skinaxis", PLOT)
 DIFF (SET = "C1_patch", CONS = 1250.0)
 DIFF (SET = "C1_skin", CONS = 1.0)
 BCNO (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "skinbottom")
 BCFL (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "patchtop")
 BCFL (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "patchside")
 BCFL (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "patchaxis")
 BCFL (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "skinside")
 BCFL (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "skinaxis")
 ICNO (SPEC = 1.0, CONS = 0.327000000000E-02, ENTI = "patch")
 ICNO (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "skin")
 EXTR (ON, AFTE = 5, EVER = 5, ORDE = 3, NOKE, NOFR)
END
/  *** of FIPREP Commands
CREATE(FIPREP,DELE)
CREATE(FISOLV)
PARAMETER(LIST)
```

Appendix C: Resources

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Internet Drug Index. *Transderm Nitro.* February 21, 2006. http://www.rxlist.com/cgi/generic/ntgtd_ids.htm

Introduction to Mine Engineering. *Nitroglycerin*. April 28, 2006. http://www.digistar.mb.ca/minsci/unit17/meu17-18.htm

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Mitchem, L and Mio, C and Snook, R.D. October 24, 2003. *Diffusion of transdermally delivered nitroglycerin through skin mimetics using photoacoustic and attenuated total reflectance spectrometry.* Department of Instrumentation and Analytical Science, UMIST, Macnchester, UK.

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Schwarz Pharma. *What is Deponit?* February 11, 2006. www.deponit.com

US Patent Office. *Patent # 4,681, 584 Transdermal delivery system for delivering nitroglycerin at high transdermal fluxes.* http://www.uspto.gov