An Analysis of the Ortho Evra Birth Control Patch

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Executive Summary:

The Ortho Evra Birth Control Patch is an effective alternative method of birth control. It releases two drugs, norelgestromin and ethinyl estradiol, and these two drugs diffuse through a person's skin and into their bloodstream. In order to analyze this process, we developed a 2-D, axisymmetric model of the diffusion of norelgestromin from the patch and through the skin. Through the use of a sensitivity analysis to determine the correct patch diffusivity, we were able to get an accurate representation of the physical process. We then modeled what would happen if the patch were removed for various periods of time, and we were able to determine that if the patch were removed for 24 hours or less, no significant disruption to the delivery of the drugs would occur. Finally, we also ran a simulation of wearing two different patches over the course of two weeks, and we determined that the concentration would normally encounter periodic rises and falls over the two-week period.

Introduction and Design Objectives:

Overview

There are many different forms of contraceptive devices that are available to women today. One such form of birth control is the Ortho Evra patch. What makes this method so unique is the ability to leave the patch on for seven days at a time instead of remembering to take a pill everyday. This diminishes the problem of forgetting to take the pill, which can cause many complications for women using that method. The makers of the Ortho Evra patch believe that the patch is just as effective as the pill and that it adheres well to the skin even during strenuous activities such as exercise, showering, and swimming. These aspects of the patch appeal to many consumers.

The Ortho Evra patch works the same way as many other patch medications work, such as pain management or smoking cessation patches. The medication lies in the patch and over time it diffuses into the skin and then into the bloodstream. Norelgestromin and ethinyl estradiol are the two drugs that are released by the Ortho Evra patch, however in this report we will only analyze the release of norelgestromin. These substances prevent pregnancy by preventing ovulation, thickening the cervical mucus so that sperm is less likely to enter uterus, and changing the endometrium to reduce the likelihood of implementation.[1]

Design Objectives

Our first objective in this project was to make an accurate model of the diffusion of norelgestromin through the skin. We used information given by the company as well as outside research to simulate the application of the patch to a sample of skin. Once the model was established, we analyzed what happened if the patch was removed from the skin for varying

[1] http://www.orthoevra.com/

amounts of time. We wanted to see how long the patch could be removed for without having a significant disruption in the delivery of the drugs. Finally, we also wanted to see how the concentration of norelgestromin in the body varies over a regular application period of two weeks.

In this report, we will first describe the initial stages of setting up the model, including drawing a schematic and developing boundary and initial conditions. Then, we will analyze the basic model and discuss how various parameters were decided upon. The next section will describe how removal of the patch for various amounts of time affects drug delivery, and finally we will show how the concentration of norelgestromin in the skin varies over a two-week period.

Schematic

We decided to treat the skin as a cylinder so that we could use an axisymmetric geometry to model the diffusion. The top two layers of the skin, the epidermis and the dermis, were modeled using the same diffusion coefficient. Based on a previous Gambit Tutorial, we decided to use $D = 1.11 \times 10^{-11}$ m^2/sec for the diffusivity of norelgestromin through both layers. The layer below the dermis is the subcutaneous layer, and we assumed that once the drug reaches this layer, it is instantaneously taken up by the blood stream and disappears. We approximated that the epidermis and the dermis together are 2 mm thick.[2]

The Ortho Evra patch was modeled as a circle. However, the real patch is a square with an area of 20 cm^2, so we assumed that the patch has a radius of 2.52 cm.[3] The thickness of the patch was approximated as 0.3 mm.[4] The diffusivity value used for the flow of norelgestromin

[2] http://www.pride.hofstra.edu/~BCIAVA1/BURNS.HTM
[3] http://www.orthoevra.com/active/janus/en_US/assets/common/company/pi/orthoevra.pdf#zoom=100
[4] Hadgraft, Jonathan. "Transdermal Delivery, Present and Future Perspectives." *The Drug Delivery Companies Report* Spring/Summer 2003.

through the patch was approximated as 1.11 x 10^{-14} m^2/sec. This value was decided as a result of a sensitivity analysis, which will be described later in this report.

Due to our axisymmetric geometry, we only needed to model half of the patch, as seen in the diagram below:

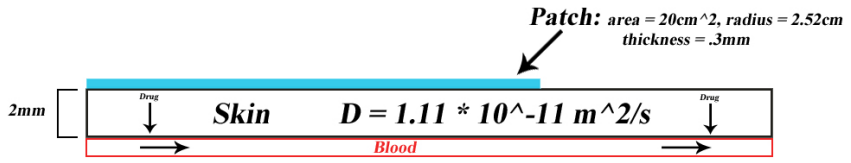


Diagram above represents a schematic of skin with the patch that has been cut in half.

Diagram to the right represents a schematic of the skin with the patch the way it was modeled with Gambit. The axis of symmetry is on the bottom.

We decided to include an additional 0.5 cm of skin to the side of the patch to see how the drug diffuses away from the center of the patch.

Governing Equations & Boundary Conditions

There is no heat transfer in this project, so we were only concerned with species transport. We also ignored the mass generation and convection terms because these processes did not take place in our model. The governing equation in 2-D therefore simplified to:

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

The boundary condition at the right of the diagram (where the drug enters the blood stream) was that the drug concentration equaled zero, due to the previous assumption that the drug disappears here. All other exterior boundaries were defined as the flux equaling zero, due either to symmetry or insulated boundaries.

Initially, we said that the patch has a starting concentration of 0.01 g/cm^3 for norelgestromin.[5] The skin had an initial concentration of zero for this drug.

Results:

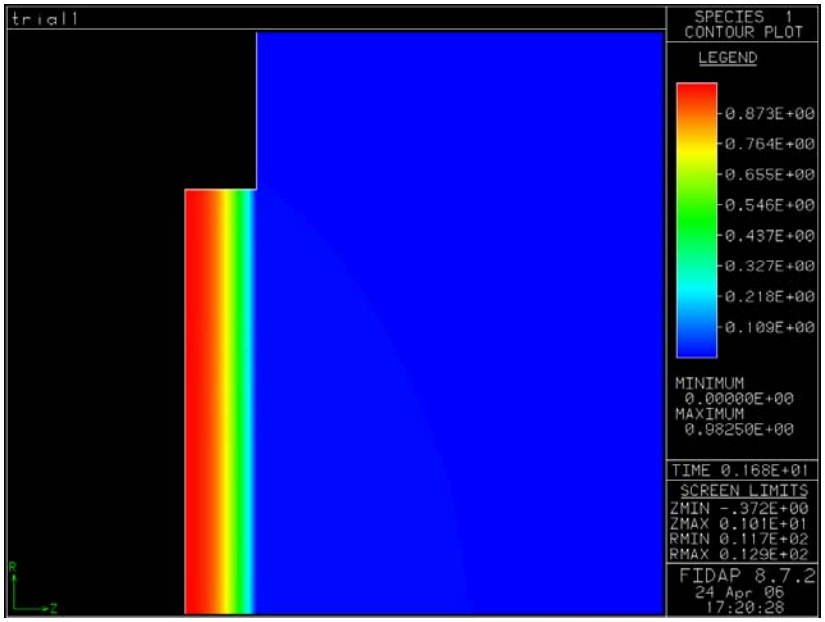
Idealized Model

Due to low diffusivity values, we had to non-dimensionalize our inputs. This process and the resulting non-dimensionalized values can be seen in Appendix A.

We did a transient model for 1 week (604,800 seconds), and we used a time step of 0.001 for accuracy. The mesh that we used can be seen in Appendix A.

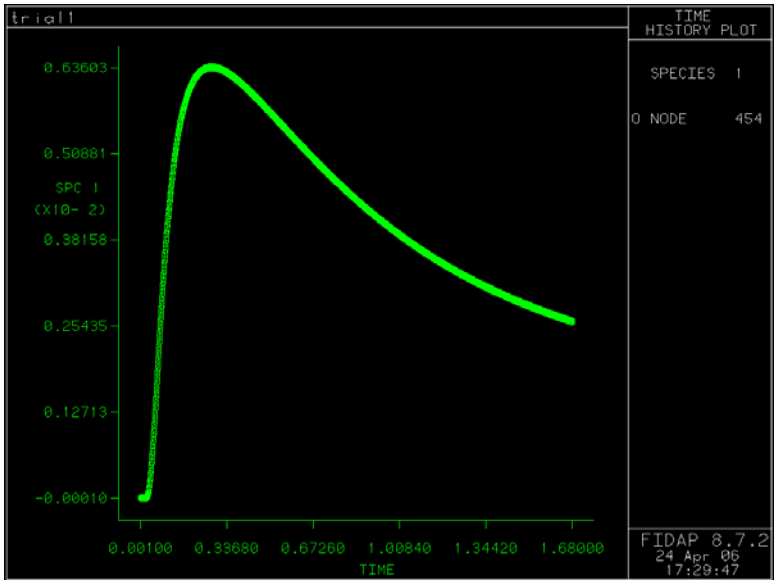
The following figure is a contour plot of the distribution of norelgestromin throughout the patch and the skin after one week. The picture is zoomed in to the upper left area of our diagram:

[5] http://www.orthoevra.com/active/janus/en_US/assets/common/company/pi/orthoevra.pdf#zoom=100



As can be seen in this figure, there is a large change in concentration throughout the patch, however the concentration of the drug in the skin is fairly constant throughout. This occurs due to the relatively low diffusivity value in the patch. Such a low value keeps the drug in the patch and prevents it from entering the skin, and once the drug enters the skin, it moves fairly freely towards the blood stream.

The following figure is a graph of concentration of drug versus time at Node 454, which is a node that is near the right boundary of the skin and very close to the blood stream. We decided to use this node to be representative of the concentration of norelgestromin that enters the blood stream at any given time. The graph covers the entire week of application:



This figure shows how the concentration of norelgestromin is initially at zero in the skin, yet it quickly increases to its maximum concentration around t = 0.3 (which is approximately 30 hours). The concentration then decreases, first fairly quickly and then less quickly.

These results confirm what we believed would occur before we ran the simulation. Additional diagrams for this trial can be seen in Appendix C.

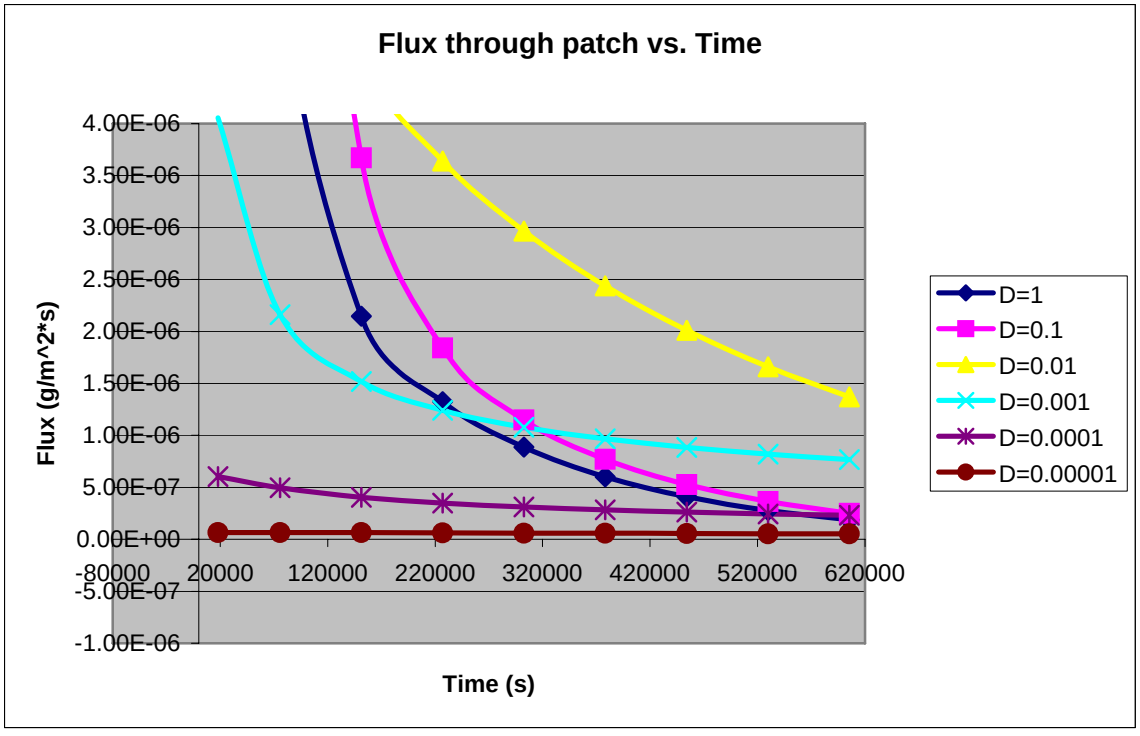
Sensitivity Analysis for Diffusivity Through the Patch

In order to determine the diffusivity value for the patch, we conducted a sensitivity analysis on this value. Based on an article, we found that the diffusivity through the patch would be less than through the skin, and it would be about 3 orders of magnitude smaller.[6] Since in our non-dimensional model the diffusivity of norelgestromin through the skin is 1, we approximated that the diffusivity value through the patch should be about 0.001. Additionally, based on the manufacturer's specifications, we knew that the flux of norelgestromin into the skin should be,

[6] Rohr, Uwe D., and Katrin Saeger-Lorenz. "17B-Estradiol Matrixpatch…" *Journal of Pharmaceutical Sciences* Vol. 91, No. 3, March 2002.

on average, 8.68 x 10^{-7} g/m^2s.[7] Therefore, we decided to run the simulation at varying patch diffusivity values. This enabled us to observe the effect of changing the diffusivity value on the model. To confirm that our assumed value is correct, we calculated the flux through the drug-skin interface and compared it to the expected average value.

We calculated the flux of norelgestromin at non-dimensional diffusivity values through the patch of 1, 0.1, 0.01, 0.001, 0.0001, and 0.00001 at nine different times throughout the week that the patch is on the skin. These values can be seen in the tables in Appendix C. We used this data to graph the flux of norelgestromin through the interface versus time, which produced the following graph:



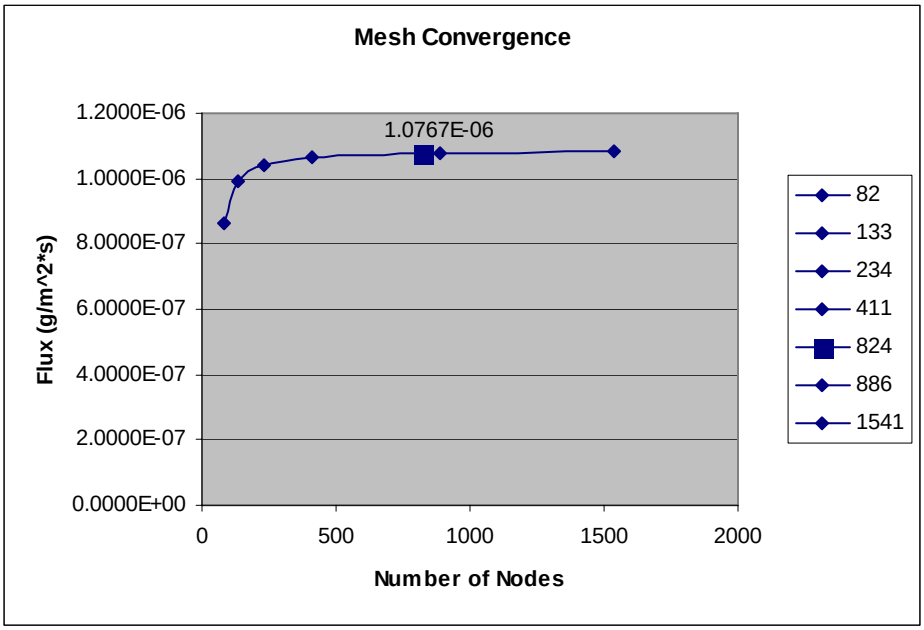
[7] http://www.healthcentral.com/druglibrary/408/ortho_evra.html

The graph shows that as time increases, the flux approaches a constant value. We see that as the diffusivity values become smaller, the variation in flux, as well as the value of the flux, approaches zero, due to the lack of mobility of the drug through the patch.

Our original goal was to find the value of diffusivity that allows us to obtain a flux value of 8.68×10^{-7} g/m^{2}s, and from the graph it can be seen that at a diffusivity of 0.001, the curve becomes constant at a flux that is closest to that value. Therefore we felt that 0.001 was the best choice of diffusivity for the final result.

Mesh Convergence

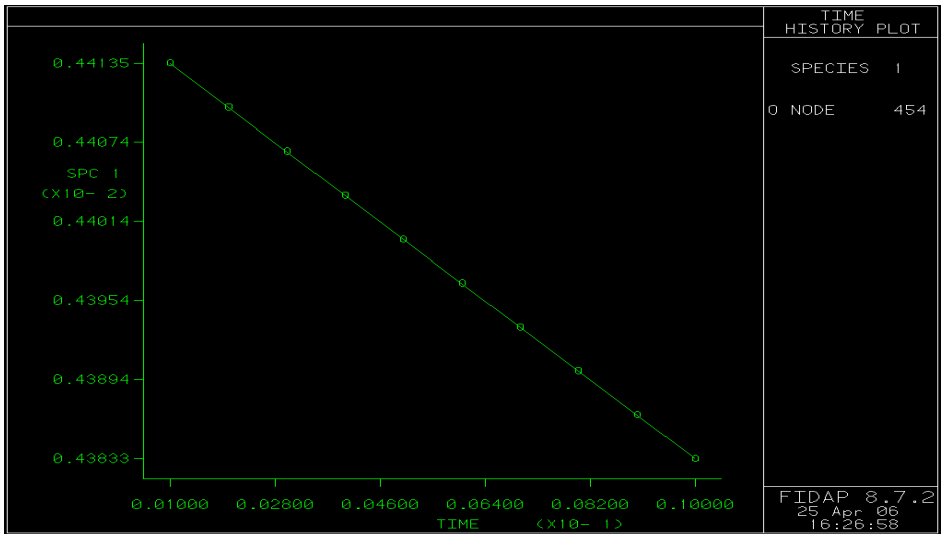
We conducted a mesh convergence analysis to make sure that the mesh we had used was accurate enough. In order to test this, we calculated the flux value at the patch-skin interface at t = 0.84 (3.5 days). Our original mesh had 824 nodes and a flux value of 1.077×10^{-6} g/m^{2}s. We then increased and decreased the number of nodes in the mesh and found the flux value at the same time in each case. Our results can be seen in the following graph:



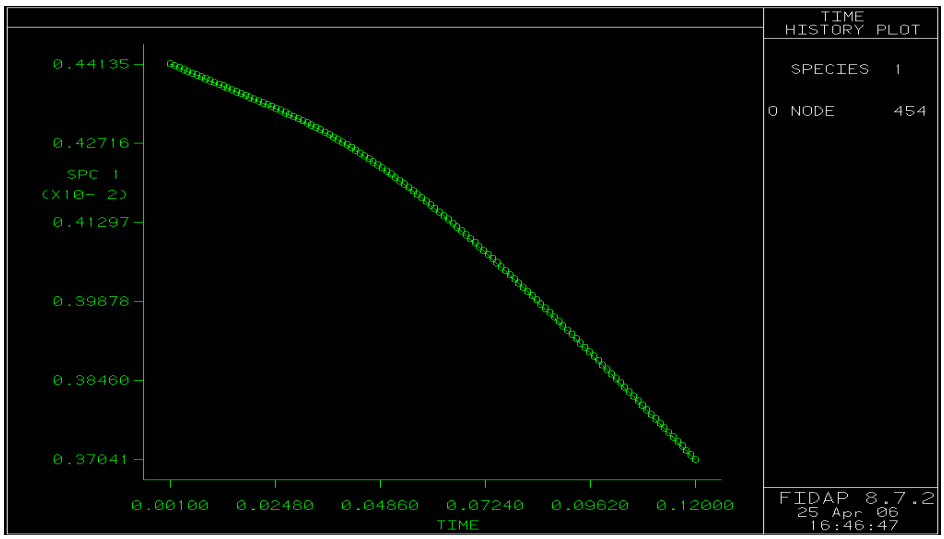
From the graph, we can see that at the highlighted point of 824 nodes, the flux value had already approached a constant value. Therefore we concluded that the original mesh used is accurate enough for the analysis of the diffusion through the Ortho Evra patch.

Patch Removal Analysis

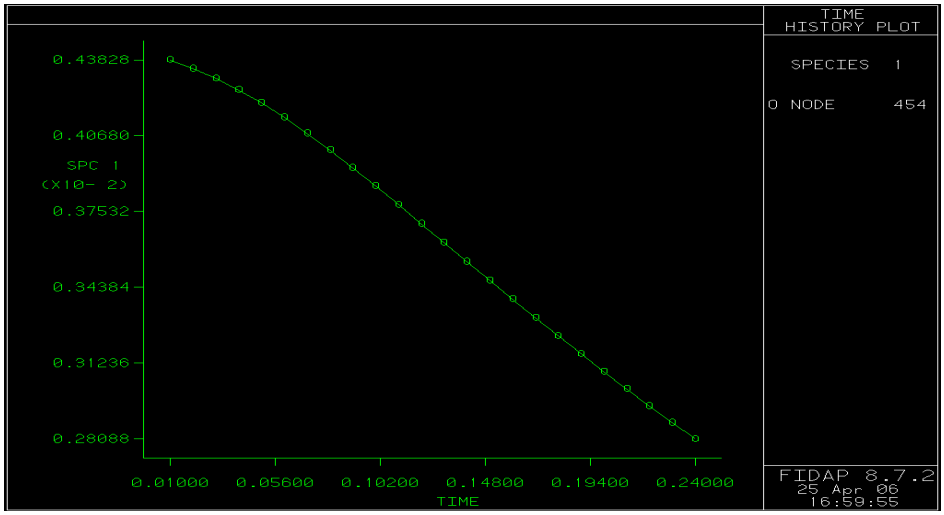
To examine the effects of norelgestromin diffusion, we decided to simulate what would happen if the patch were to fall off after half a week (3.5 days) and left off for a certain amount of time. In order to do so, we chose to look at how the skin's drug concentration decreased after the patch had been off for 1, 12, 24, and 48 hours. Just like our original trial, measurements were taken from Node 454 in order to represent the amount of drug entering the bloodstream since it is very close to the right boundary of the skin. The following graphs show the decreasing drug concentration when the patch is off for 1, 12, 24, and 48 hours respectively from left to right in each row. The concentration measurements in the first two time trials were taken every 6 minutes (t=0.001) whereas the data in the 24 and 48-hour simulations was evaluated at every hour (t=0.01).



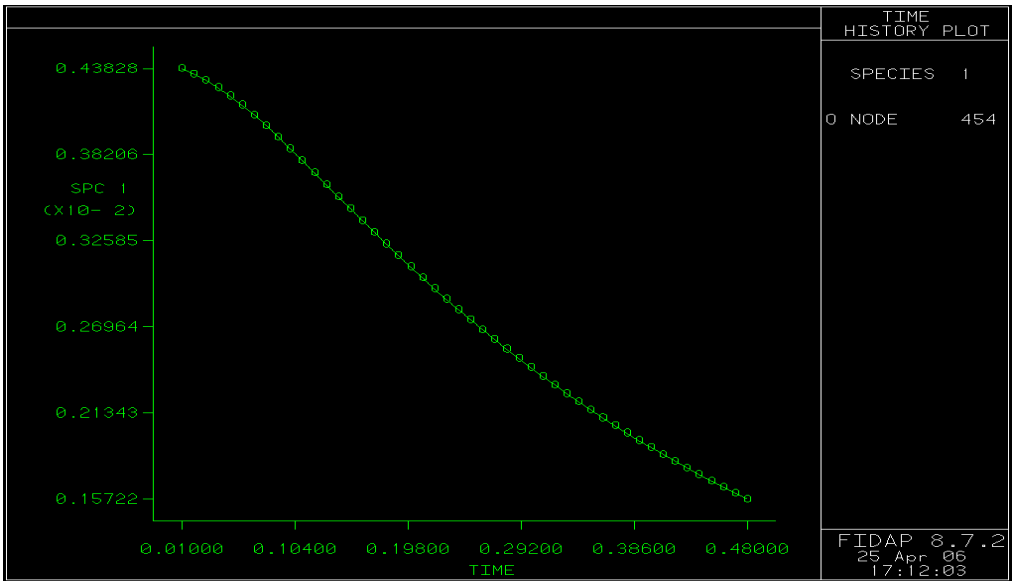
1 hour off



12 hours off



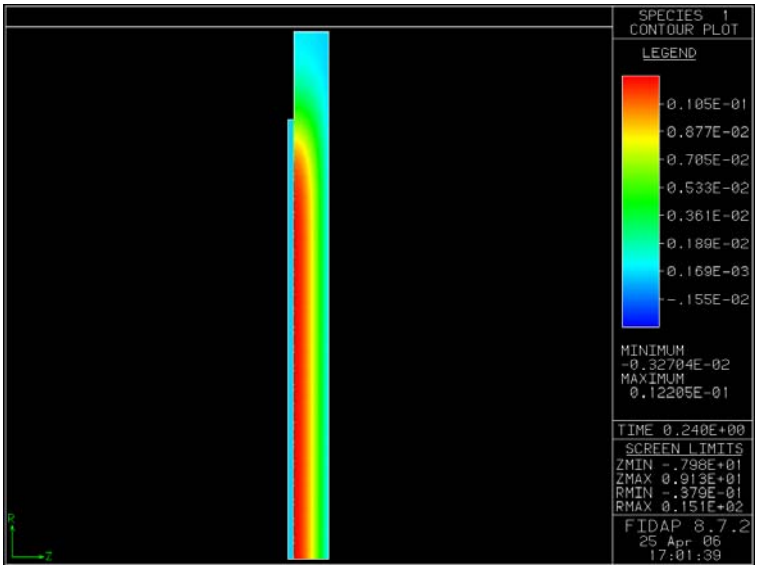
24 hours off



48 hours off

The drug seems to diffuse through the skin at a fairly constant rate, as seen by the similar sloping decrease. Thus, the minimum concentration reached at Node 454 at the end of each time trial decreased the longer the patch was off: 0.438×10^{-2}, 0.370×10^{-2}, 0.281×10^{-2}, and 0.157×10^{-2} in non-dimensionalized terms for 1, 12, 24, and 48 hours respectively. These graphs also show that the drug keeps diffusing into the skin for a short time, followed by a sharper decrease in concentration when there is no more drug delivery.

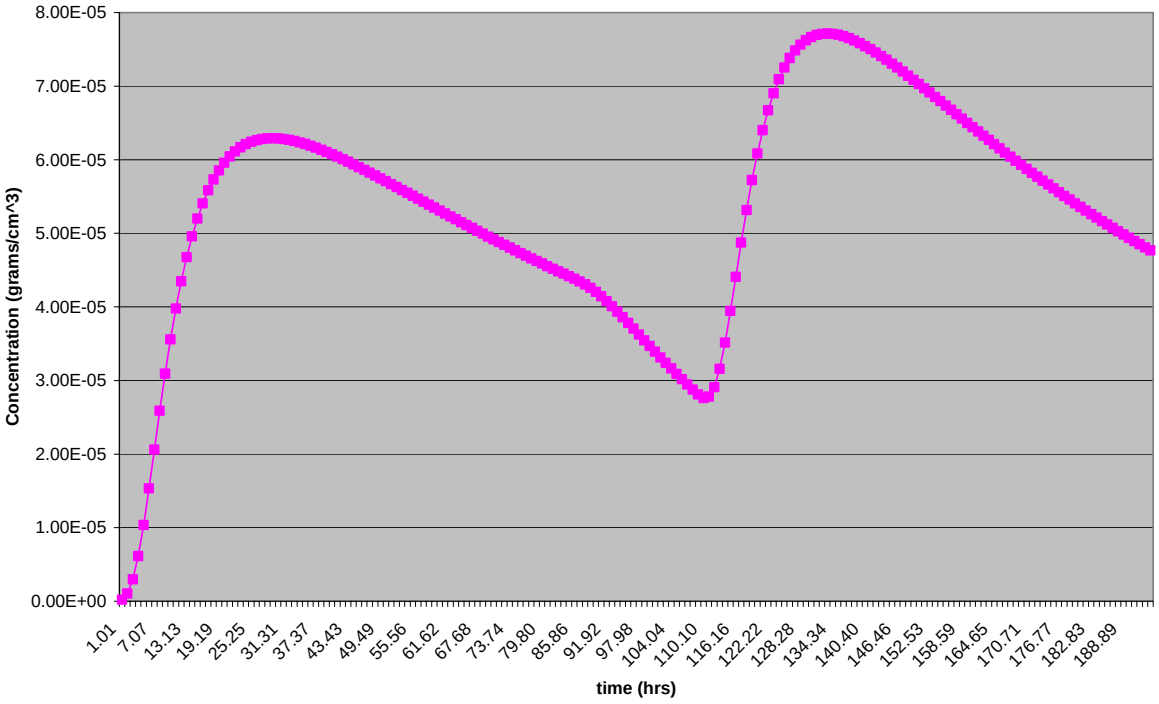
In order to see how the drug diffused through the skin, a contour map was taken at the end of each patch removal trial, as seen below. This figure shows drug concentration in the skin and non-existent patch (since it is removed at this point) after the patch was off for 24 hours.



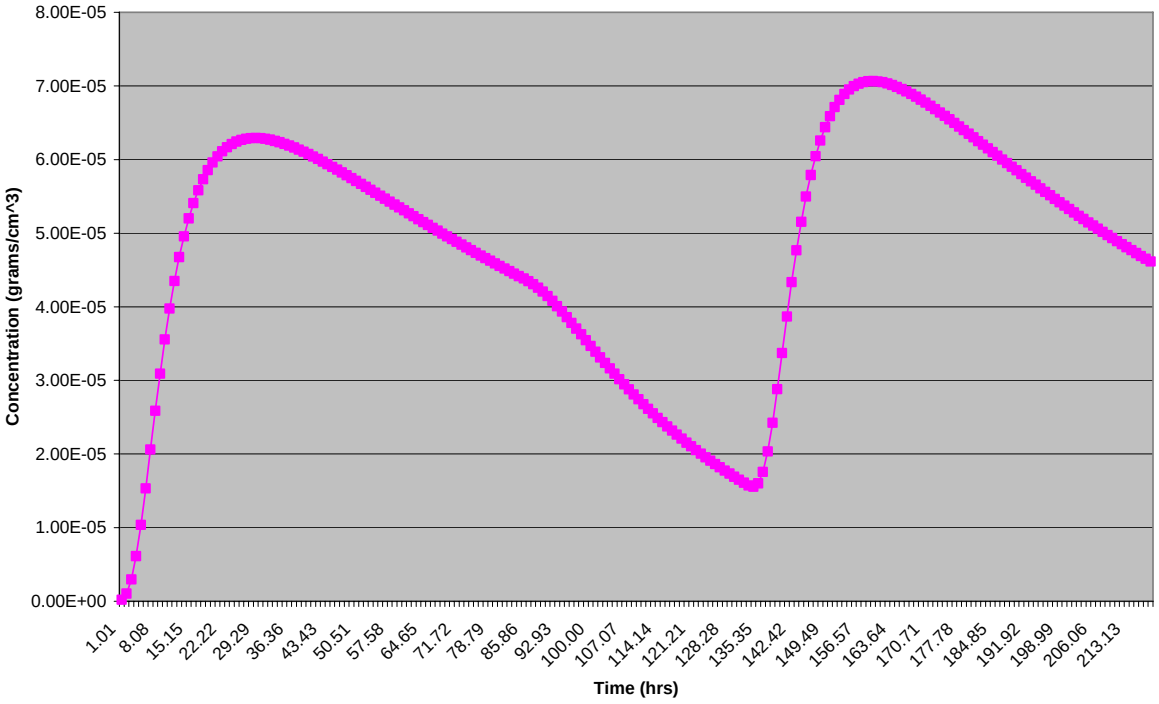
Other contour maps for the 1, 12, and 48 hour periods looked very similar since the drug diffused through the skin at a fairly steady rate. But, each figure has a different concentration gradient since the overall amount of norelgestromin in the skin is smaller when the patch is off longer.

To continue our analysis of patch removal, we looked at the change in drug concentration if a new patch was placed onto the same region after having the patch off for 24 or 48 hours. As seen in the following two figures, drug concentration takes a sharper decrease when the patch is taken off – followed by a sharp increase as a new patch is put on. The additional norelgestromin is added to the body before the effects of the original patch disappear, and the process builds up to achieve a higher maximum concentration than if it had been just the original patch. It can be seen in these figures that after the 24 hour removal and replacement, the maximum drug concentration is higher (approximately 7.7×10^{-5} g/cm^3) than that of the 48 hour removal (where max. = approx. 7.1×10^{-5} g/cm^3).

24 hour Patch Removal Followed by a New Patch

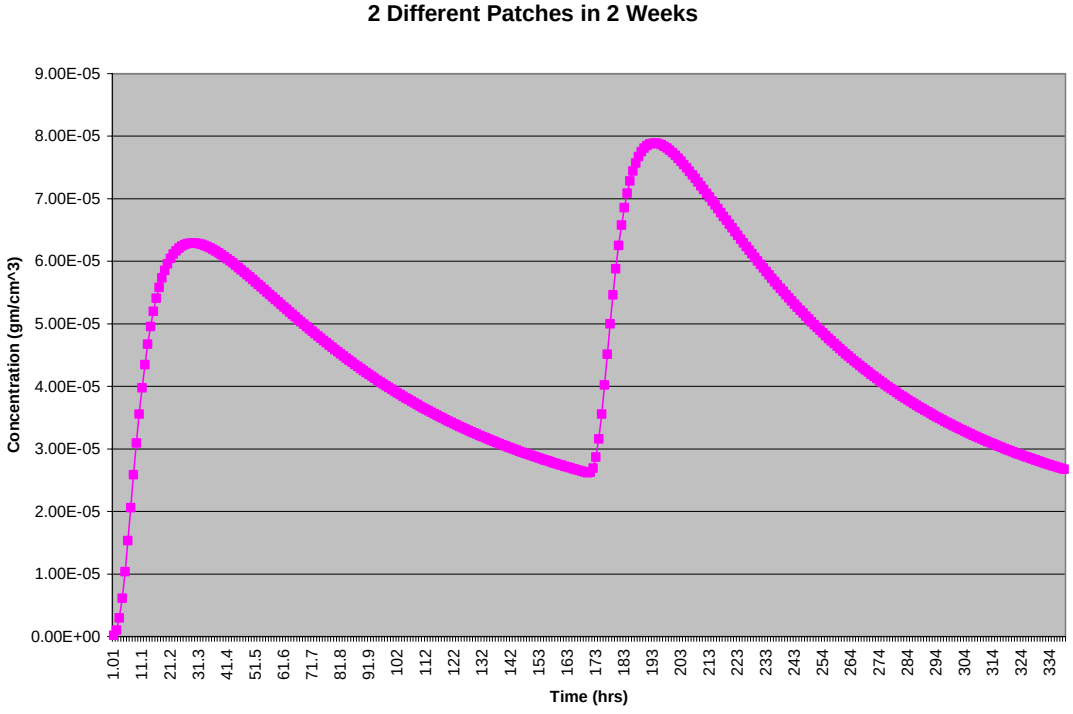


48 hour Patch Removal Followed by a New Patch



Changes in Concentration Over Two Weeks

To complete our study of the Ortho Evra drug diffusion we decided to take a look at what two consecutive weeks of patch-wearing (with replacement after one week) would do to the concentration of norelgestromin in the skin. The results were similar to when the patch was removed, but without such a sharp decrease in concentration between patches. As seen in the figure below, the shape of the concentration curve is basically the same as the normal trial, but when the patch is replaced the same increase occurs in addition to the original drug. Unlike the previous patch removal, where there was a time when no patch was on the skin, this trial kept the drug concentration higher – the range of concentration values varied only from a minimum of 2.7 x 10^{-5} g/cm^3 to a maximum of 7.9 x 10^{-5} g/cm^3 – whereas when the patch was missing for a certain amount of time, the range was lower.



Conclusions and Design Recommendations:

Design Recommendations

We were able to accomplish our original design objective of making an accurate model of the diffusion of norelgestromin through the skin. Based on our sensitivity analysis, the flux values that we were getting corresponded to those that the company said occurred.

In order to analyze how long the patch can be removed for without any negative consequences, we looked at the lowest concentration of norelgestromin in the skin after one week. By looking at the graph of concentration versus time for Node 454, this value corresponds to about 0.25×10^{-2} in non-dimensional concentration. We then looked at the graphs of Node 454 when the patch was removed for various amounts of time, and we saw if the concentration dipped below this value. For removing the patch for 1 or 12 hours, the concentration level did not drop to be near this value. For a 48-hour absence, the concentration fell well below that value to about 0.16×10^{-2}. However, when the patch was removed for 24 hours, the concentration level fell to be slightly above the threshold. We therefore determined that 24 hours is the maximum amount of time that the patch can be removed for without significant drops in norelgestromin levels in the skin. Any times longer than this will cause a significant disruption in drug delivery.

Finally, our 2-week analysis in which two patches are applied in series showed us that the concentration of norelgestromin in the skin rises with each additional patch that is applied. When a new patch is added, the drug that diffuses into the skin is in addition to the drug that is already there. This causes overall concentration levels to increase.

Discussion on Realistic Constraints

In terms of economics, the Ortho Evra patch is relatively inexpensive. The patch usually costs around $30 to $35 per month compared to the birth control pill, which costs over a range of $20 to $35 per month.[8] In addition, many of these costs and doctor visits are covered by health insurance. Also, many health and family clinics also offer birth control at a lower price. Therefore, money is not an issue with regard to production or sale of the Ortho Evra birth control patch.

The health and safety of the patients is always one of the biggest concerns of physicians. Like all other drugs, there are some side effects that may occur when taking the Ortho Evra patch which are the same when taking the pill. Such risks include blood clots, strokes, and heart attacks. Smoking cigarettes also increases these risks. However, most women do not experience any side effects. There are also some health benefits for women on the Ortho Evra patch. Such benefits include having more regular and lighter periods, fewer menstrual cramps, and a lower risk for ovarian and endometrial cancer.[9]

The ethical and social implications of the birth control patch are the same as those for any other contraceptive method. Religious views may conflict with using birth control, however most Americans agree that the use of birth control is an important option to have available. We believe that since the birth control pill is widely available, the Ortho Evra patch is merely an additional option that has the same effects as the pill.

Overall, when looking at these constraints, we believe that the Ortho Evra birth control patch is an effective, safe, and easy method of birth control.

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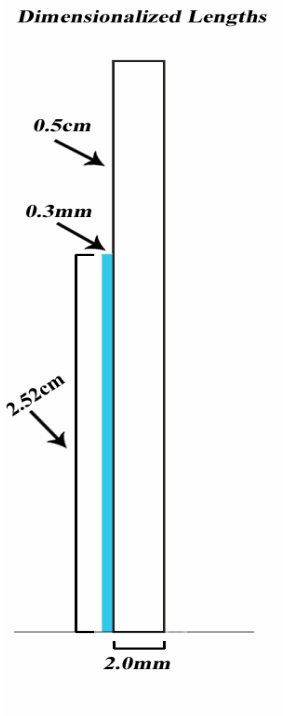
[8] http://kidshealth.org/teen/sexual_health/contraception/contraception_patch.html
[9] http://www.4woman.gov/faq/birthcont.htm

Appendix A: Mathematical Statement of the Problem

The figure below is a simplified version of our schematic:



We used 2-D, axisymmetric geometry with the axis of symmetry at the bottom of the figure. There is no heat transfer or fluid flow, so the only governing equation we need is for mass transfer. We ignore the mass generation and convection terms since these processes did not take place in our model. The governing equation simplifies to:

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

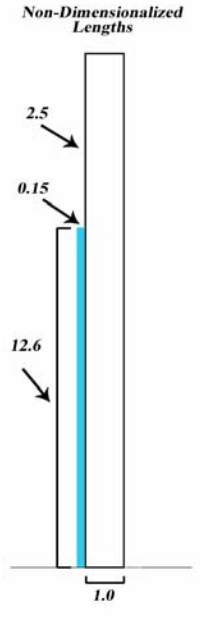
Aside from the boundary where the drug enters the bloodstream (right side of skin), all other boundaries are zero flux:

$$-D\frac{\partial c}{\partial r} = 0$$

For the right side of the skin, the boundary condition is that concentration equals zero, since we assume that the drug is swept away by the blood stream when it reaches this point.

There is initially no drug in the skin, so the initial condition there is that c=0. The starting norelgestromin concentration in the patch is 0.01 g/cm^3, as given in the prescribing information.[10]

Due to low diffusivity values, we had to non-dimensionalize our simulation. For lengths, we divided by L where L = 2 x 10^{-3} meters. The figure below is a schematic that includes the non-dimensional lengths used for the model:



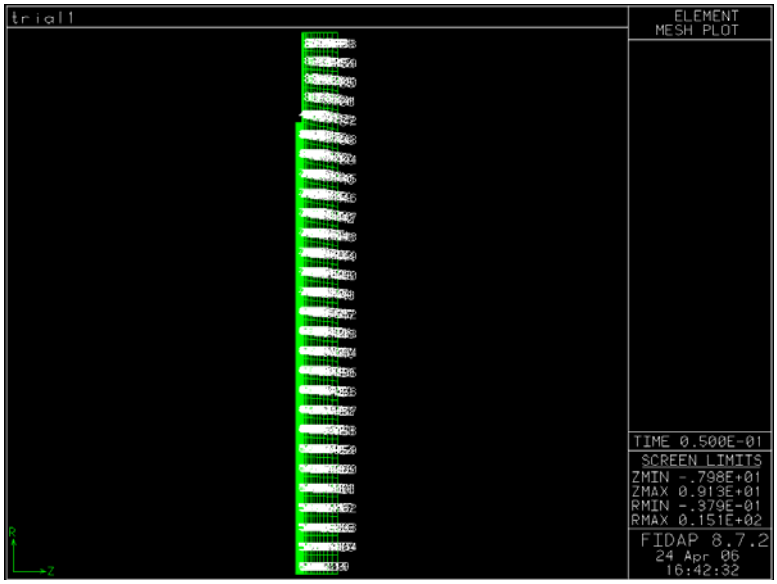
Concentrations were non-dimensionalized by dividing by c_∞ where c_∞ = 0.01 g/cm^3. The diffusivity of norelgestromin through the skin is 1.11 x 10^{-11} m^2/sec, and we used 1.11 x 10^{-14} m^2/sec as the diffusivity through the patch.[11] To non-dimensionalize the diffusivities, we divided each value by D_0, where D_0 = 1.11 x 10^{-11} m^2/sec. Finally, time was non-dimensionalized by multiplying by D_0 and diving by L^2. The following table summarizes our non-dimensionalized parameters:

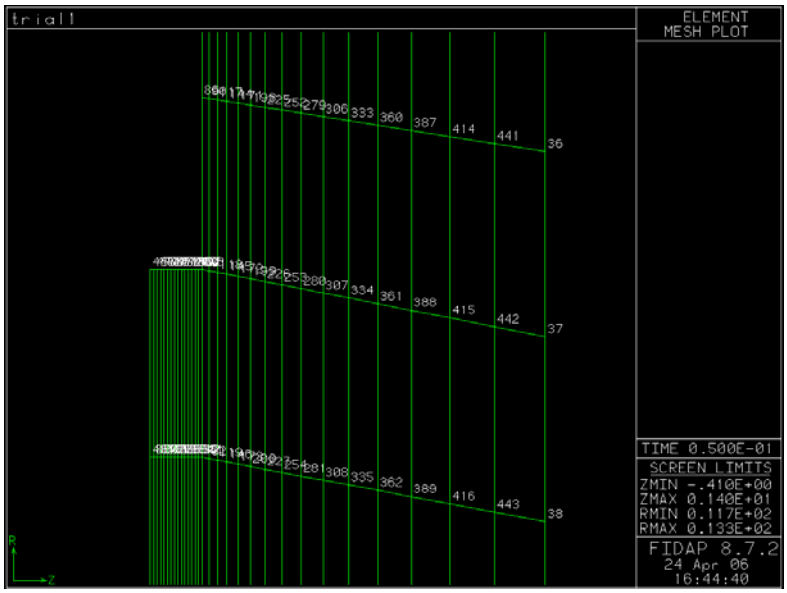
[10] http://www.orthoevra.com/active/janus/en_US/assets/common/company/pi/orthoevra.pdf#zoom=100

[11] Rohr, Uwe D., and Katrin Saeger-Lorenz. "17B-Estradiol Matrixpatch…" *Journal of Pharmaceutical Sciences* Vol. 91, No. 3, March 2002.

	Dimensions	Non-Dimensionalized
Initial Concentration in Skin	0	0
Initial Concentration in Patch	0.01 g/cm^3	1
Diffusivity of Norelgestromin in Skin	1.11 x 10^-11 m^2/sec	1
Diffusivity of Norelgestromin in Patch	1.11 x 10^-14 m^2/sec	0.001
Starting Time	0	0
Ending Time	604,800 seconds	1.68

The following two figures show a full and a zoomed in view of the mesh that was used in the simulation:





Appendix B: FIDAP Commands

Trial1.FDREAD file:

PROBLEM(axi-s, Isothermal, NoMomentum, Transient, LINEAR, FIXED, NEWTONIAN, INCOMPRESSIBLE, SPEC=1)
/ This is our problem statement: our model has an axi-symmetrical geometry, is isothermal & transient, does not have fluid velocity [no momentum equation], and has no convection (so it is linear).
SCALE (VALUE = 1)
SOLUTION (S.S.=50, VELCONV =0.001, RESCONV =0.01, SCHANGE =0, ACCF =0)
/ This is our solution statement: the method of Successive Substitution is used where 50 is the max. number of iterations per time step. The Solution Tolerance (VELCONV), Residual Tolerance (RESCONV), and Solution Change (SCHANGE) are as listed.
OPTION (SIDES)
EXTRAPOLATE(ON,AFTER= 5,EVERY= 5,ORDER = 3,NOKE,NOFREE)
PRESSURE (MIXED = 1e-009, DISCONTINUOUS)
TIMEINTEGRATION (BACKWARD, Fixed, TSTART = 0, TEND = 1.68, DT = 0.001, NSTEPS = 2000)
/ This is our Time Integration Statement: using the method “Unsteady Solver” the Start Time, End Time, Time Step, and Max. Number of Steps is defined. The solver used a backward Time Integration Algorithm where the Time Stepping Model is fixed.
POSTPROCESS (RESULTSONLY)
ENTITY(NAME = "SKIN", SOLID, PROPERTY = "mat1" , SPEC=1, MDIFF="C1_SKIN")
ENTITY(NAME = "PATCH", SOLID, PROPERTY = "mat2" , SPEC=1, MDIFF="C1_PATCH")
/ We set different material properties to the two zones: the skin & the patch.
DIFFUSIVITY (SET = "C1_SKIN", CONSTANT = 1)

DIFFUSIVITY (SET = "C1_PATCH", CONSTANT = 0.001)
/ The diffusivity constants were non-dimensionalized using the skin's diffusivity as $D_0 = 1.11 \times 10^{-11}$ m^2/sec and the diffusivity of the patch was 0.001 times that.
ENTITY (NAME = "L_SKIN", PLOT)
BCFLUX (SPEC=1, CONSTANT = 0, ENTITY = "L_SKIN")
ENTITY (NAME = "T_SKIN", PLOT)
BCFLUX (SPEC=1, CONSTANT = 0, ENTITY = "T_SKIN")
ENTITY (NAME = "R_SKIN", PLOT)
BCNODE (SPEC=1, CONSTANT = 0, ENTITY = "R_SKIN")
/ The boundary condition here at "R_SKIN" is set so that the drug concentration equals zero since the norelgestromin is taken up by the bloodstream there.
ENTITY (NAME = "SKINAXIS", PLOT)
ENTITY (NAME = "PATCHAXIS", PLOT)
/ The boundaries at these two edges are not set to specific conditions due to the axisymmetric geometry.
ENTITY (NAME = "L_PATCH", PLOT)
BCFLUX (SPEC=1, CONSTANT = 0, ENTITY = "L_PATCH")
ENTITY (NAME = "T_PATCH", PLOT)
BCFLUX (SPEC=1, CONSTANT = 0, ENTITY = "T_PATCH")
ENTITY (NAME = "INTERFACE", PLOT)
/ All exterior boundary conditions were set so that species flux equals 0, except for "R_SKIN" as explained above as well as internal boundaries such as "INTERFACE" and the boundaries at the axes.
ICNODE (SPEC=1, CONSTANT = 0, ENTITY = "SKIN")
/ The initial condition of the skin is 0 since there is originally no drug there.
ICNODE (SPEC=1, CONSTANT = 1, ENTITY = "PATCH")
/ The initial condition of the patch, where the starting concentration of norelgestromin is 0.01 g/cm^3, was non-dimensionalized to equal 1.

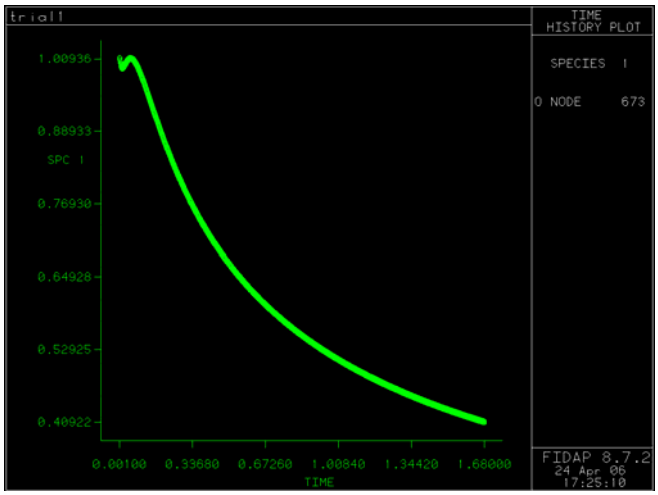
Trial1.FIINP file:

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 = 1.68,
DT = 0.100000000000E-02, NSTE = 2000)
/ TEND and NSTE varied depending on which of the patch removal trials was being modeled at the time. For 1, 12, 24, and 48 hour trials TEND was changed from 0.01, 0.12, 0.24, and 0.48 respectively. NSTE was decreased for the smaller trials in order to decrease simulation time.
ENTI (NAME = "SKIN", SOLI, PROP = "mat1", SPEC = 1.0, MDIF = "C1_SKIN")
ENTI (NAME = "PATCH", SOLI, PROP = "mat2", SPEC = 1.0, MDIF = "C1_PATCH")
ENTI (NAME = "L_SKIN", PLOT)
ENTI (NAME = "T_SKIN", PLOT)

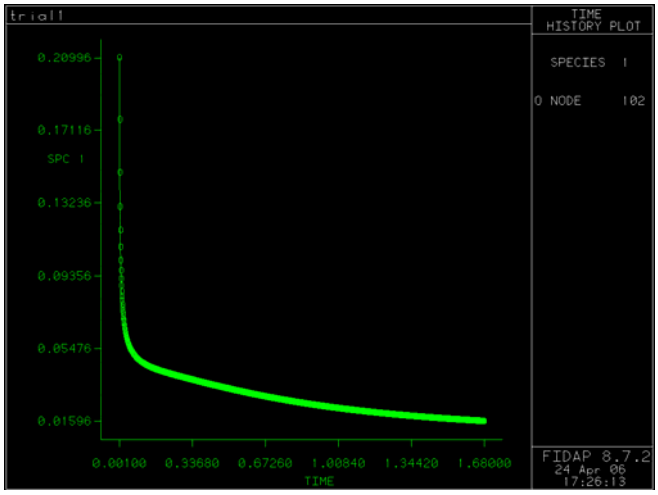
```
 ENTI (NAME = "R_SKIN", PLOT)
 ENTI (NAME = "SKINAXIS", PLOT)
 ENTI (NAME = "PATCHAXIS", PLOT)
 ENTI (NAME = "L_PATCH", PLOT)
 ENTI (NAME = "T_PATCH", PLOT)
 ENTI (NAME = "INTERFACE", PLOT)
 DIFF (SET = "C1_SKIN", CONS = 1.0)
 DIFF (SET = "C1_PATCH", CONS = 0.100000000000E-02)
/ This diffusivity constant for the patch was changed to 0.1E-14 when the patch was removed in
order to model the lack of drug diffusion.
 BCNO (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "R_SKIN")
 BCFL (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "L_SKIN")
 BCFL (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "T_SKIN")
 BCFL (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "L_PATCH")
 BCFL (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "T_PATCH")
/ An additional Boundary Condition was added here during the time that the patch was off: the
flux at INTERFACE for SPEC = 1.0 was constant at 0.
 ICNO (SPEC = 1.0, CONS = 0.000000000000E+00, ENTI = "SKIN")
 ICNO (SPEC = 1.0, CONS = 1.0, ENTI = "PATCH")
/ The initial condition in the patch was changed to 0 when the patch was taken off.
```

Appendix C: Additional Figures

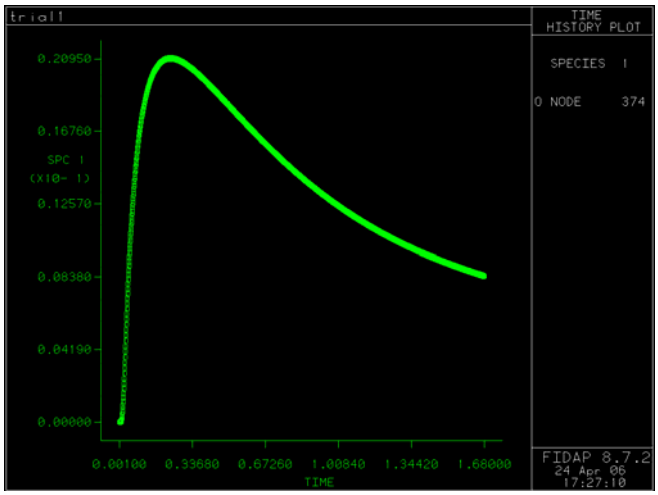
Concentration vs. Time Plot for Idealized Conditions, Node in Patch Near Interface:



Concentration vs. Time Plot for Idealized Conditions, Node in Skin Near Interface:



Concentration vs. Time Plot for Idealized Conditions, Node in Center of Skin:



Data Tables for Sensitivity Analysis:

Diffusivity = 1			**Diffusivity = 0.1**			**Diffusivity = 0.01**		
Time(nonD)	***flux (g/m^2*s)***	***flux(nonD)***	***time(nonD)***	***flux (g/m^2*s)***	***flux(nonD)***	***time(nonD)***	***flux (g/m^2*s)***	***flux(nonD)***
0.05	8.4915E-05	1.53E+00	0.05	5.2103E-05	0.9388	0.05	1.7505E-05	0.3154
0.21	6.0828E-06	0.1096	0.21	1.1322E-05	0.204	0.21	6.8487E-06	0.1234
0.42	2.14563E-06	3.87E-02	0.42	3.6697E-06	6.61E-02	0.42	4.6276E-06	8.34E-02
0.63	1.3259E-06	2.39E-02	0.63	1.8415E-06	3.32E-02	0.63	3.6402E-06	6.56E-02
0.84	8.88555E-07	1.60E-02	0.84	1.1500E-06	2.07E-02	0.84	2.9654E-06	5.34E-02
1.05	6.0162E-07	1.08E-02	1.05	7.7090E-07	1.39E-02	1.05	2.4376E-06	4.39E-02
1.26	4.0898E-07	7.37E-03	1.26	5.2764E-07	9.51E-03	1.26	2.0102E-06	3.62E-02
1.47	2.78222E-07	5.01E-03	1.47	3.6314E-07	6.54E-03	1.47	1.6606E-06	2.99E-02
1.68	1.88589E-07	3.40E-03	1.68	2.4942E-07	4.49E-03	1.68	1.3697E-06	2.47E-02

Diffusivity = 0.001			**Diffusivity = 0.0001**			**Diffusivity = 0.00001**		
Time(nonD)	***flux (g/m^2*s)***	***flux(nonD)***	***time(nonD)***	***flux (g/m^2*s)***	***flux(nonD)***	***time(nonD)***	***flux (g/m^2*s)***	***flux(nonD)***
0.05	4.0565E-06	7.31E-02	0.05	6.0273E-07	1.09E-02	0.05	6.5601E-08	1.18E-03
0.21	2.1623E-06	3.90E-02	0.21	4.9778E-07	8.97E-03	0.21	6.6156E-08	1.19E-03
0.42	1.5196E-06	2.74E-02	0.42	4.0504E-07	7.30E-03	0.42	6.3936E-08	1.15E-03
0.63	1.2426E-06	2.24E-02	0.63	3.4921E-07	6.29E-03	0.63	6.3437E-08	1.14E-03
0.84	1.0789E-06	1.94E-02	0.84	3.1141E-07	5.61E-03	0.84	5.9663E-08	1.08E-03
1.05	9.6737E-07	1.74E-02	1.05	2.8366E-07	5.11E-03	1.05	5.7665E-08	1.04E-03
1.26	8.8467E-07	1.59E-02	1.26	2.6218E-07	4.72E-03	1.26	5.5889E-08	1.01E-03
1.47	8.1974E-07	1.48E-02	1.47	2.4492E-07	4.41E-03	1.47	5.4174E-08	9.76E-04
1.68	7.6646E-07	1.38E-02	1.68	2.3055E-07	4.15E-03	1.68	5.2592E-08	9.48E-04

Appendix D: References

"Birth Control: Birth Control Patch."
http://kidshealth.org/teen/sexual_health/contraception/contraception_patch.html

"Birth Control Methods." http://www.4woman.gov/faq/birthcont.htm

Hadgraft, Jonathan. "Transdermal Delivery, Present and Future Perspectives." *The Drug Delivery Companies Report.* Spring/Summer 2003.

"Ortho Evra Drug Description." http://www.healthcentral.com/druglibrary/408/ortho_evra.html

"Ortho Evra Prescribing Information."
http://www.orthoevra.com/active/janus/en_US/assets/common/company/pi/orthoevra.pdf#zoom=100

"Ortho Evra: The Only Once-A-Week Birth Control Patch." http://www.orthoevra.com/

Rohr, Uwe D., and Katrin Saeger-Lorenz. "17B-Estradiol Matrixpatch…" *Journal of Pharmaceutical Sciences* Vol. 91, No. 3, March 2002.

"The Use of Non-Contact Ultrasound and Polarized Light in Burn Victim."
http://www.pride.hofstra.edu/~BCIAVA1/BURNS.HTM