

Ortho Evra:

How Effective is the Patch in

Women of Varying Weight

Ortho Evra: The Birth Control Patch: Drug Delivery Analysis

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Executive Summary:

This study researched the birth control patch, Ortho Evra and the diffusivity of the hormones, ethinyl estradiol and norelgestromin, into the body through the epidermis. We modeled that all of the species that diffused through the epidermis was completely absorbed into the body. We found that our model validated the amounts given by Ortho Evra for drug release. However, many of the constraints and boundary conditions were taken from the Ortho Evra research information. Our study also analyzed the effectiveness of the hormone in women of varying weight, from 120 pounds to 198 pounds. Results indicated that the patch becomes less and less effective with increasing adipose tissue. This increase in adipose tissue results in a decreasing diffusivity value for the epidermis. Our study also researched the effects of incorrect usage of the Ortho Evra patch. We modeled the scenario of the patch falling off after a given time and the continued effectiveness of the drug. Our values imply that if the patch falls off the woman is not protected. The woman must restart the cycle in-order to reach steady state, which provides the needed amount of drug to be effective.

Introduction:

Our study will explore the mass transfer effects of a birth control patch. The patch is very helpful and has become popular in the world of birth control because it allows the user to have constant protection without a daily pill. This helps prevent one of the major disadvantages of the pill – forgetting to take it. The patch can be placed on multiple parts of the skin and the drugs are then transferred to the blood stream from which they flow throughout the body. The manufacturing company has listed four specific spots to put the patch because of effective drug diffusivity values for those areas: the buttocks, the abdomen, the upper arm, and the upper torso. This study focuses on the only current company that produces a birth control patch, Ortho Evra. The dimensions of the area studied will be approximately the area of the patch, with a small area of skin surrounding it. We will have to construct a tissue layer for the body parts we use and find properties for skin, the drug, and patch

In tests it has been found that Ortho Evra is effective in 99 out of 100 women who use the product for the entire year, similar to that of the pill. In the 15 pregnancies found in the study of 3330 women, 5 of the women had a weight greater than 198 pounds. This was found to be statistically significant by the studies. We will model the difference in a woman of 125 pounds against that of a 200-pound individual. The difference will be monitored by adjusting adipose tissue levels in the skin, thus altering diffusivity values.

Design Objectives:

The goal of our project is to study the drug delivery form Ortho Evra into the bloodstream. We would like to look at what happens in women of varying weight as described in our Introduction.

We also wanted to test other problems with incorrect use. Since the patch is placed in four different areas of the body that can be high friction, we wanted to simulate what would happen if the patch fell off after a certain amount of time and whether a woman would still be protected.

Geometry, Boundary Conditions

We are modeling the diffusion of norelgestromin and ethinyl estradiol from the patch, through the skin and into the blood. We are modeling the square patch as a circle so that we may use axi-symmetric properties to simplify the problem in FIDAP. To get the same area, we approximate the radius of the circular patch to be 2.53 cm. We are also modeling the patch with .5 cm of skin around it to include diffusive spreading out from the edge of the patch. We used .5 cm instead of 1 cm because the skin is so thin that the drugs can't diffuse out very far before they have diffused into the blood.

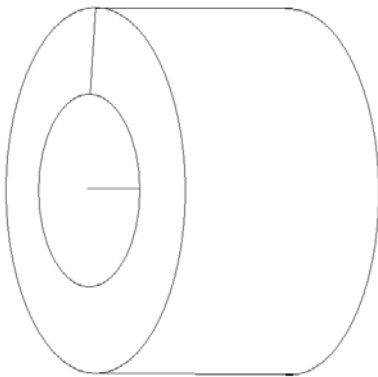


Figure 1. Schematic of our Patch and Skin Area.

As a result, our mesh is almost the same as during preliminary testing. We have reduced the size of the radius from 3.5 cm to 3 cm. Also, we have changed the interval sizes. There are now many more nodes closer to the patch than the blood in order to better capture the diffusion of the drug into the skin. See Fig 2. (attached) for a picture of the mesh.

For the solution, we are using the initial blood concentration of norelgestromin as $7 \times 10^{-4} \text{ g/m}^3$ and the initial flux at the patch – skin boundary as $8.849 \times 10^{-7} \text{ g/m}^2\text{s}$. The diffusivity of the skin layer is $5.55 \times 10^{-12} \text{ m}^2/\text{s}$. The diffusivity of skin has been obtained from speaking with two dermatologists: Michael Saltzman, and Dr. Richard Guy. The initial flux from the patch for ethinyl estradiol is $1.1789 \times 10^{-7} \text{ g/m}^2\text{s}$. These figures were used in FIDAP to obtain the following information displayed in Figures 3 and 4. The main problem we had in obtaining these solutions was with our dimensions. After changing our problem to non-dimensionalized terms we were able to obtain a proper solution. Our next section will explain how we non-dimensionalized the terms.

Non-Dimensionalizing our Problem:

Because FIDAP had trouble calculating a solution with such a small diffusivity, we decided to non-dimensionalize our mesh and governing equation. We divided the dimensions of the mesh by $1.2\text{e-}3$ meters, which is the actual length of the axis. This set the axis to a unit length of 1, but we also had to alter our equations for the time step and flux. Diffusivity is then set to 1 in FIDAP.

Original dimensions for mesh

Axis: $1.2 \text{ e-}3$ meters

Skin (including patch length): $3 \text{ e-}2$ meters

Patch length only: $2.5 \text{ e-}2$ meters

Non-dimensional mesh dimensions:

Axis: 1

Skin: 25

Patch: 20.8333

Time

Time = $D \cdot \text{Normal Time} / L^2$

Where normal time for an hour would be 3600 seconds, $L = 1.2 \text{ e-}3 \text{ m}$, $D = \text{diffusivity}$, $1.11 \times 10^{-12} \text{ m}^2/\text{s}$

Flux

Flux = Normal flux * L / D

Where normal flux = 8.849×10^{-7} g/m²s (norelgestromin value), L = 1.2 e-3 m, D = diffusivity, 1.11×10^{-12} m²/s

Results and Discussion**Qualitative Description of What is Happening:**

When looking at Figure 2 the drug is being delivered from the bottom 4/5 of the mesh from left to right. Some of the drug also diffuses upwards because of diffusion in all directions. In a three-dimensional sense our mesh is rotated along the bottom to create the schematic shown in Figure 1.

Since the dermis layer contains the dermal papillae we decided that would be the easiest place to model the drug delivery. This is why we have made the assumption of no dermal layer, only an epidermal layer. Once the drug reaches the blood it is completely washed away. Therefore we have no reaction term, and no half-life term.

Computational Results:

We ran the solution in FIDAP and obtained the contours for norelgestromin and ethinyl estradiol shown in Figures 3 and 4. We then obtained the plot shown in Figure 9 of the norelgestromin concentration at node 273, which shows that the system reaches steady state after two days. However, we need to determine if enough of the species was reaching the bloodstream over the course of a day after the system had reached steady state. To do this, we determined the flux over the capillary-epidermis boundary using FIDAP for several time intervals over the course of one day. We then utilized the trapezoid rule to calculate how much of the drug had reached the bloodstream. Our calculations showed that 149.722 micrograms of norelgestromin diffused into the blood

while 2.004 micrograms of ethinyl estradiol diffused into the blood. While the concentration for norelgestromin was incredibly accurate when compared to the Ortho Evra literature, the concentration for ethinyl estradiol was off by a factor of 10. The reason for this error is because we optimized the diffusivity value only for norelgestromin and not for ethinyl estradiol.

Mesh Convergence:

In order to show that our solution was independent of the mesh we created a refined mesh (Figure 5). Our original mesh had 400 nodes and was graded near the patch/skin boundary. In our new mesh we used 10,000 nodes. As shown by comparing the contour plots in Figures 3 and 6 we have similar values, proving that our solution was independent of the mesh created.

Sensitivity Analysis:

As stated in our introduction we wanted to look at a couple different scenarios when working with the birth control patch.

Women of Varying Weight:

For our sensitivity analysis we tried using different diffusivity values to test how our results changed. After speaking with our dermatologists, Dr. Guy explained that in women with increased weight there is an increase in the amount of adipose tissue. This causes the diffusivity value to decrease and it can do so up to 100-fold. For our study we modeled diffusivity values decreased by 10-fold and 100-fold. From the chart below one can see how the value changed the amount of the drug being delivered to the drug stream.

Diffusivity Constant (in)	Amount of Drug Reaching the Bloodstream over 24 hours at Steady State
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Original Value	149.7 micrograms
10 times smaller	45 micrograms
100 times smaller	.04 micrograms

The differences in values above can be explained by Figure 7. As seen in the figure the drug builds up near the surface and does not diffuse across the skin fast enough.

Therefore the effective amount of the drug is not being delivered to the body. (Note: These Values are For Norelogestromin Only)

Patch Falling Off

For our second sensitivity analysis we wanted to model what would happen if the patch fell off and whether the woman would still be protected . In order to do this we used the Time Function command in FIDAP. After a specified amount of time (as shown in the table below) we set our flux condition to 0 at the patch/skin interface. Figure 8 shows how the amount of drug being delivered changed at a specific node over time.

Time when Patch Falls Off (in days)	Amount of Drug Delivered in the Following 24 hours
3 Days	86 micrograms
2 Days	18 micrograms
1 Day	4 micrograms

As shown during the study with women of varying weight again the effective drug levels needed to keep the women protected will not be maintained if the patch falls off. (Note: These values are for Norelgestromin Only)

Conclusion and Design Recommendations:

In looking at the realistic constraints for our project we thought that four of them were important to discuss to the consumer: Economic, Sustainability, Health and Safety, and Social.

Economic – The patch is relatively inexpensive, about \$15/patch. In order to make a more effective patch for larger women we would need to somehow change the diffusivity of the skin, which seemed to be the problem. Perhaps finding a smaller drug that could penetrate easier.

Sustainability – the patch is obviously a one time use, and it is not suggested to be used if it falls off. The adhesion between the patch and skin is obviously very important for proper drug delivery.

Health and Safety – there are very few health risks associated with the patch. Most are the same from the pill. Girls will still have their menstrual cycles, etc. Some women experienced breast symptoms, headache, application site reaction, nausea, upper respiratory infection, menstrual cramps and abdominal pain. People who smoke also are prone to have additional cardiovascular side effects. The patch has been found ineffective in women of larger weight (over 198 pounds).

Social – the patch provides some social benefits such that the woman does not have to worry about taking the pill on a certain time regime, she is able to put aside her worries since the patch is working. On the other hand, the woman has a patch on her skin in some pretty visible areas at times. For the woman who has trouble remembering, or finds it inconvenient to take the pill out of her purse or pocket the patch is beneficial.

In order to create an effective birth control patch for women with increased adipose tissue, it might be necessary to design a larger patch. Our sensitivity analysis did not

include varying the size of the patch, but this could easily be incorporated into a future study. Also, the increased adipose tissue would result in a thicker mesh. This analysis is a cost-effective way in determining whether the Ortho Evra patch is an effective means of birth control for overweight women. It remains to be seen how much the cost will go up if the patch size is increased or a different drug is used in the patch. Using FIDAP to estimate whether these modifications are effective is a cost-saving measure, as it will decrease the costs for experimental testing of said modifications.

APPENDIX A: Mathematical Statement of the Problem

Governing Equation:

$$\frac{\partial c_D}{\partial t} + u \frac{\partial c_D}{\partial x} = D_D \frac{\partial^2 c_D}{\partial x^2} + r_D$$

Species equation

- C_D = concentration of drug
- t = time
- x = distance
- D_D = diffusivity constant

Mesh Schematic

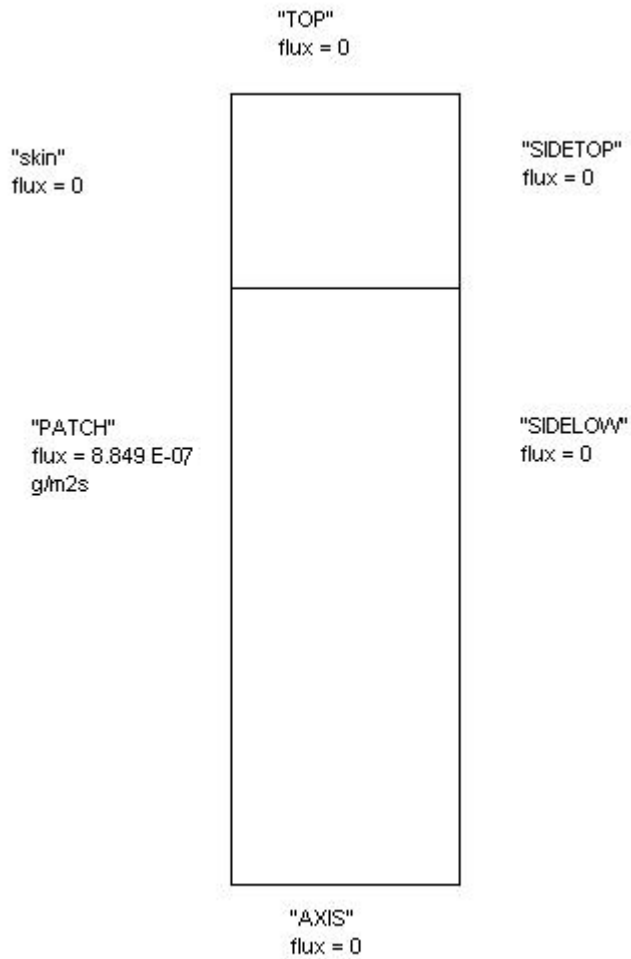


Figure 1A.

Boundary Conditions

For norelgestromin, we calculated the flux at the patch-skin boundary to be $8.849 \times 10^{-7} \text{ g/m}^2$. For ethinyl estradiol, the initial flux is $1.1789 \times 10^{-7} \text{ g/m}^2\text{s}$.

Initial Condition

$C = 0$ at $t = 0$ for all x

Diffusivity

Using information from several scientific journal articles, we decided on a diffusion coefficient of $5.55 \times 10^{-11} \text{ m}^2/\text{s}$, but that is for water. Our material is much larger of a molecule than water so it would diffuse slower. After speaking with Dr. Guy we have decided that our material would diffuse about 10 times as slowly. So we will use a coefficient of $5.55 \times 10^{-12} \text{ m}^2/\text{s}$.

From a similar study it was found that in skin tissue filled with lipids, the value would be much smaller. Therefore for a lipid-filled tissue, the diffusion would be $5.55 \times 10^{-14} \text{ m}^2/\text{s}$.

After using these values in FIDAP, the solution did not reach steady state in two days.

Therefore, we used a trial-and-error strategy to determine the diffusivity so that the system would reach steady state in two days. Our final value for the diffusivity was set at $1.11 \times 10^{-11} \text{ m}^2/\text{s}$.

Input Parameters

<u>Parameter</u>	<u>Value</u>
Diffusivity	$1.11 \times 10^{-11} \text{ m}^2/\text{s}$
Norelgestromin flux	$8.849 \times 10^{-7} \text{ g}/\text{m}^2$
Ethinyl Estradiol flux	$1.1789 \times 10^{-7} \text{ g}/\text{m}^2\text{s}$
Epidermis Thickness	$1.2 \times 10^{-3} \text{ m}$
Patch radius	0.25 m

APPENDIX B

Problem Command:

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

Our problem approximated a square patch as a circular patch with the same area so we could use an axisymmetric geometry. Everything used in the model incompressible and Newtonian. The problem is transient, but we are attempting to find when it reaches steady state. Though there are no fluid flows, if there were, they would be laminar. This means that there is no momentum as well. The problem did not consider any sort of heat transfer so it was isothermal without any convection. The project was also designed so that the structural solver and remeshing would be unnecessary. Also, there was no phase change. We only modeled one species at a time.

Execution Command:

EXEC (NEWJ)

This command tells FIDAP that it is working on a new problem so that it will not inherit anything from other problems that could be ongoing.

Solution Command:

SOLU (S.S. = 10, ACCF = 0.000000000000E+00)

This command tells FIDAP to use successive substitutions for each time step. It can use a maximum of 10 iterations for each solution.

Time Integration Command:

TIME (BACK, NSTE = 10000, TSTA = 0.000000000000E+00, TEND = 4.662,
DT = 0.100000000000E-01, VARI = 0.1, WIND, NOFI, INCM = 10.0)

This command shows FIDAP that there will be 10000 time steps with the following start and end times. The times are unusual numbers because they have been non-dimensionalized.

Entity Commands:

ENTI (NAME = "TISSUE", SOLI)
ENTI (NAME = "AXIS", PLOT)
ENTI (NAME = "SIDELOW", PLOT)
ENTI (NAME = "SIDETOP", PLOT)
ENTI (NAME = "TOP", PLOT)
ENTI (NAME = "skin", PLOT)
ENTI (NAME = "PATCH", PLOT)

This tells FIDAP each of the separate entities that are being used for this problem. Only the "TISSUE" entity is specified as a solid material because the other entities are boundaries. The "TISSUE" is the material in which the species will diffuse through.

Diffusivity:

DIFF (SET = 1, CONS = 1.0)

The diffusivity property has been non-dimensionalized to get over FIDAP's problem with very small diffusivity constants. The other constants are changed around the diffusivity in order to keep it at 1.

Boundary Nodes:

BCNO (SPEC = 1.0, ENTI = "SIDELOW", CONS = 0.000000000000E+00)

BCNO (SPEC = 1.0, ENTI = "SIDETOP", CONS = 0.000000000000E+00)

This was to ensure that the concentration at the initial time step for the side of the mesh without the patch was fixed at a constant concentration of zero.

Boundary Flux:

BCFL (SPEC = 1.0, ENTI = "PATCH", CONS = 95.665)

This sets the flux to come from the patch with a concentration that has been non-dimensionalized.

Initial Condition:

ICNO (SPEC = 1.0, ZERO, ENTI = "TISSUE")

Our initial condition assumed that the skin layer had none of the species in it before the patch was placed on the skin. Any species in the skin later would have to be the result of diffusion from the patch.

ATTACHMENTS

Figure 2. Unrefined Mesh

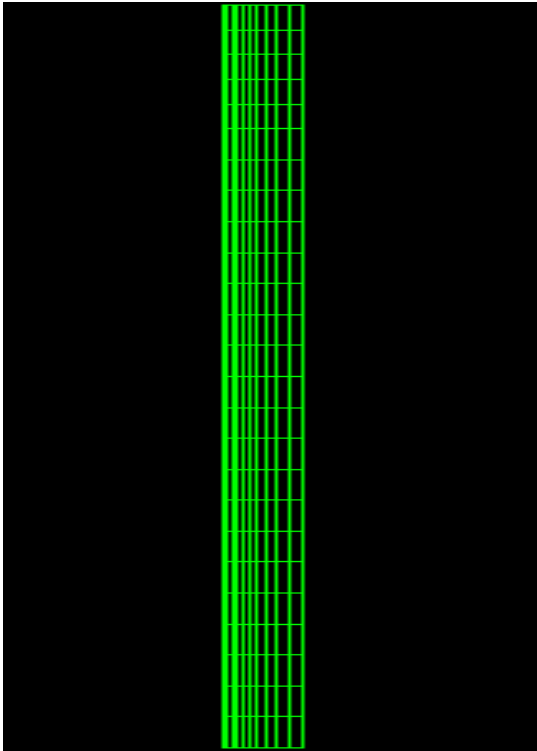


Figure 3. Norelgestromin Plot

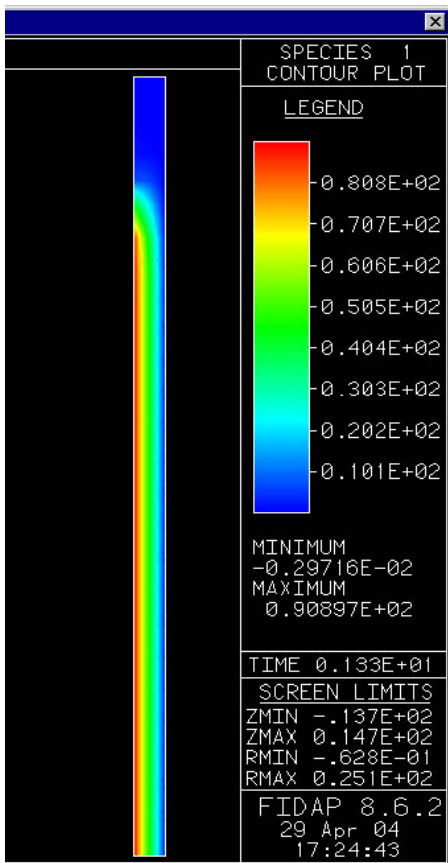


Figure 4. Ethinyl Estradiol Plot

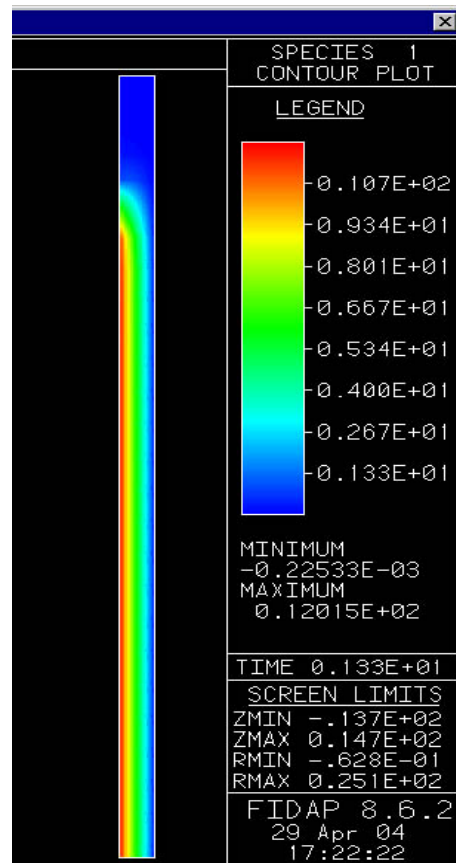


Figure 5. Refined Mesh with 10000 nodes

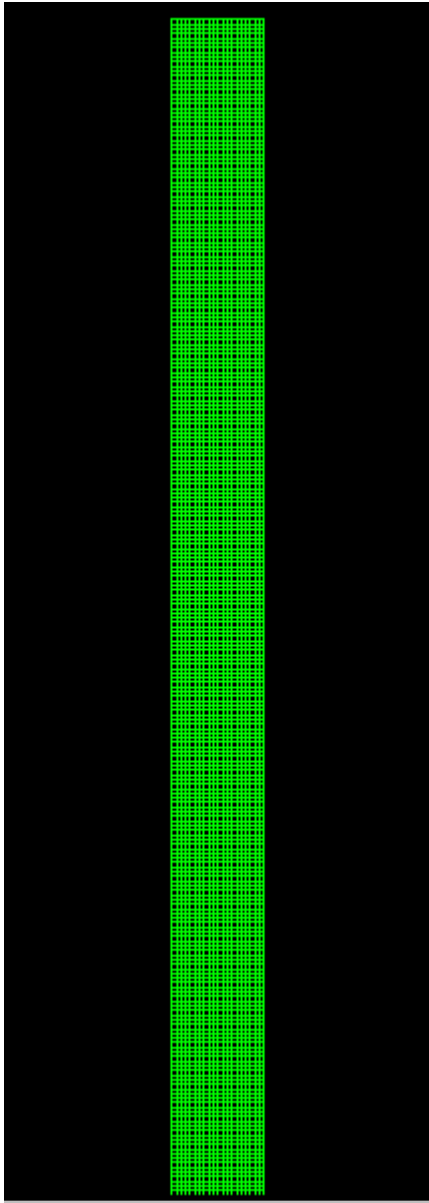


Figure 6. Refined Mesh Plot for Norelgestromin

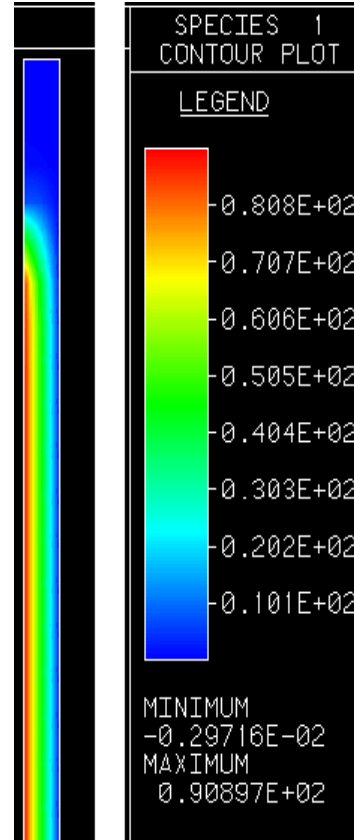


Figure 7. Diffusivity Constant for women of 198 lbs

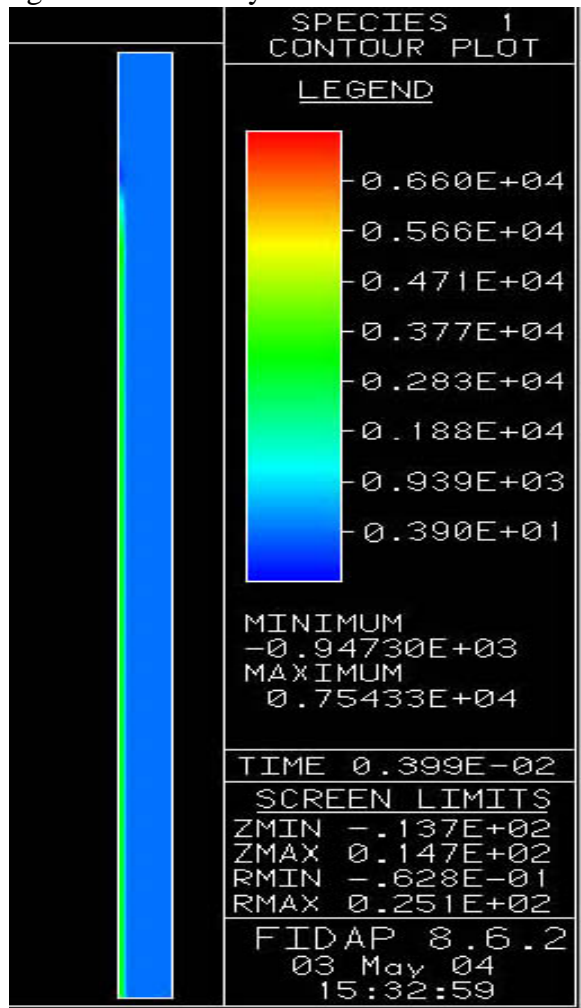


Figure 8. Concentration vs. Time

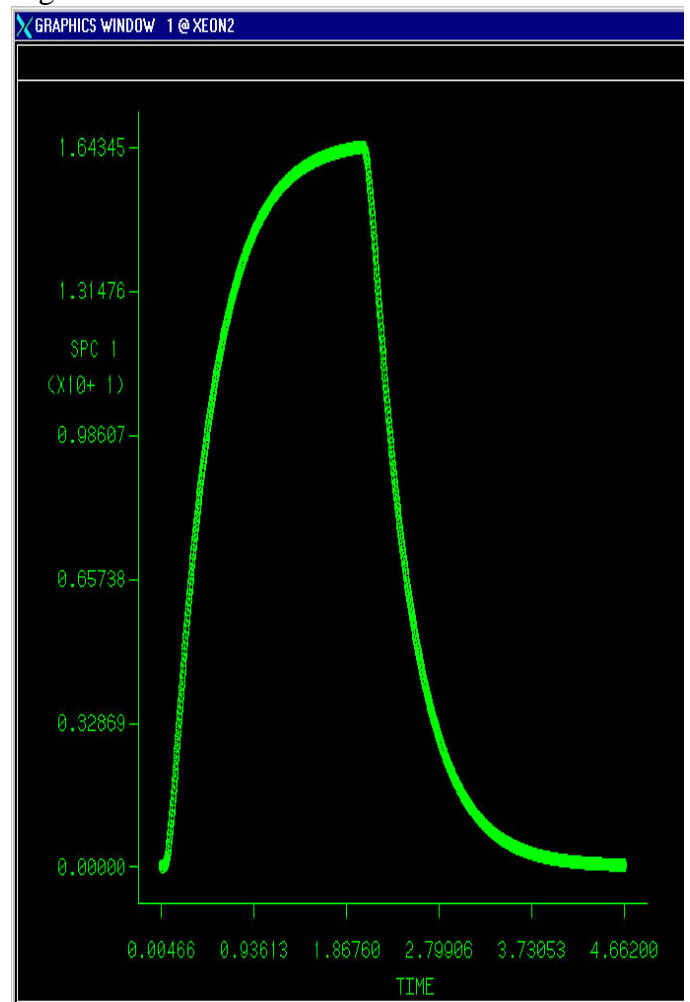


Figure 9: Plot of Norelgestromin Concentration at Node 273 over one week

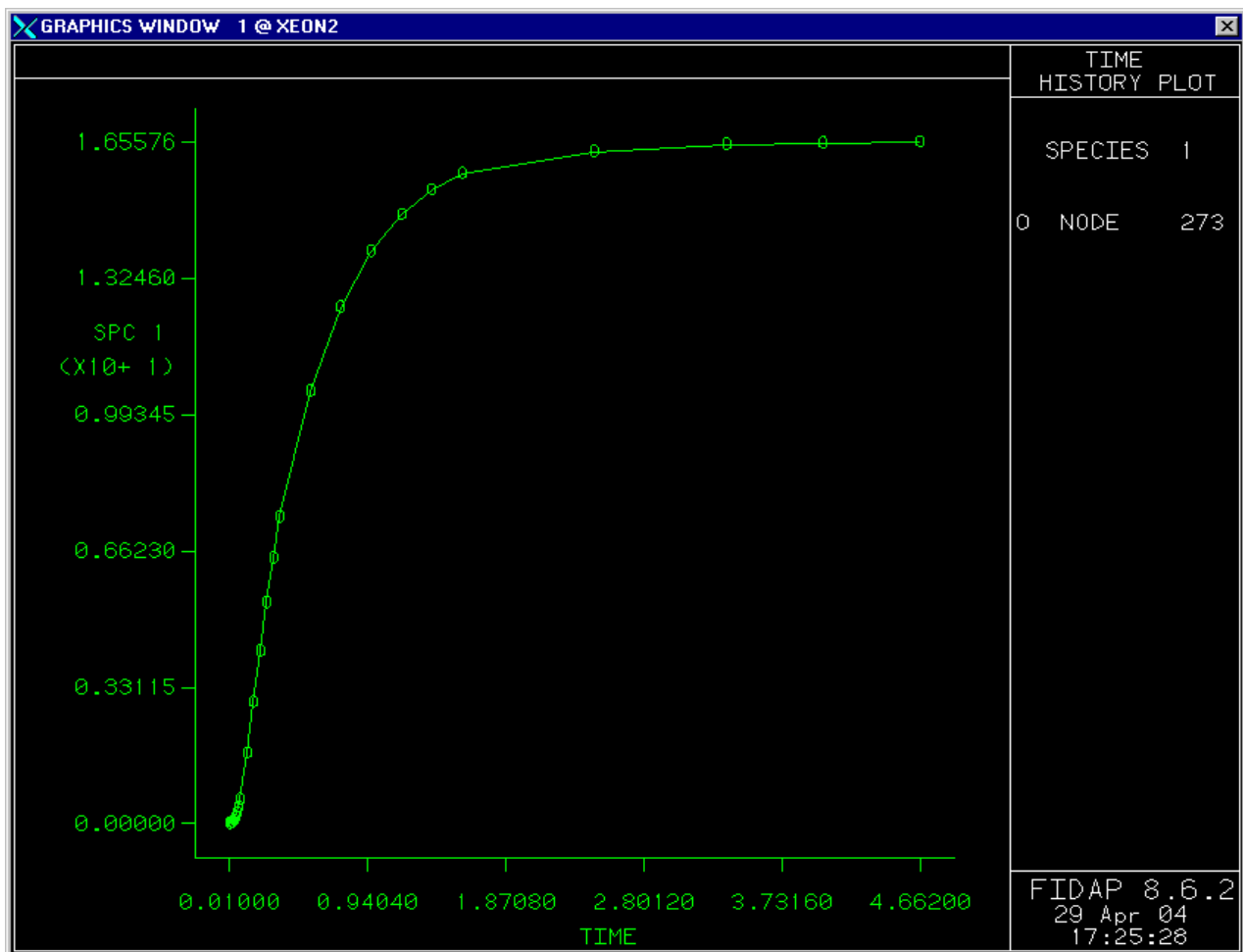


Figure 10: Original Mesh with Node Numbers

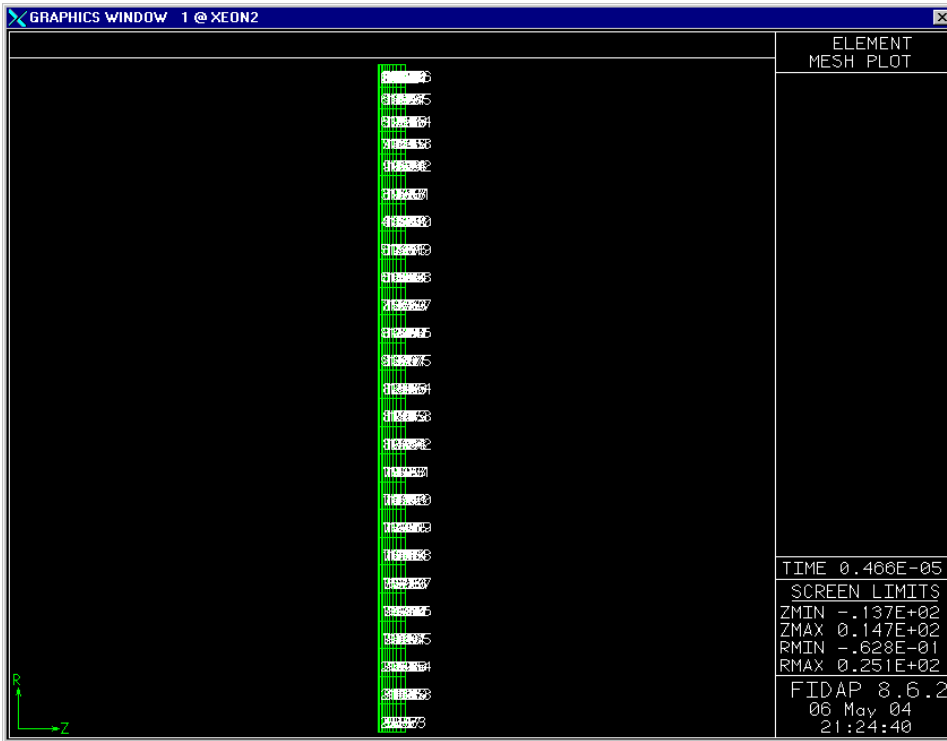


Figure 11: Location of Node 273 in Mesh

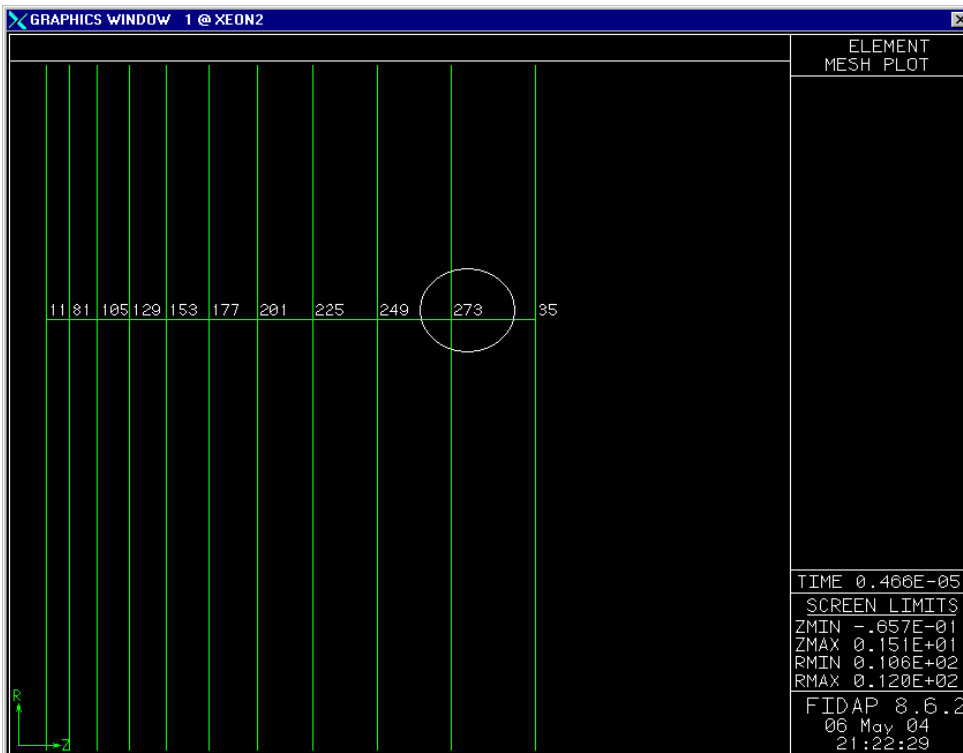
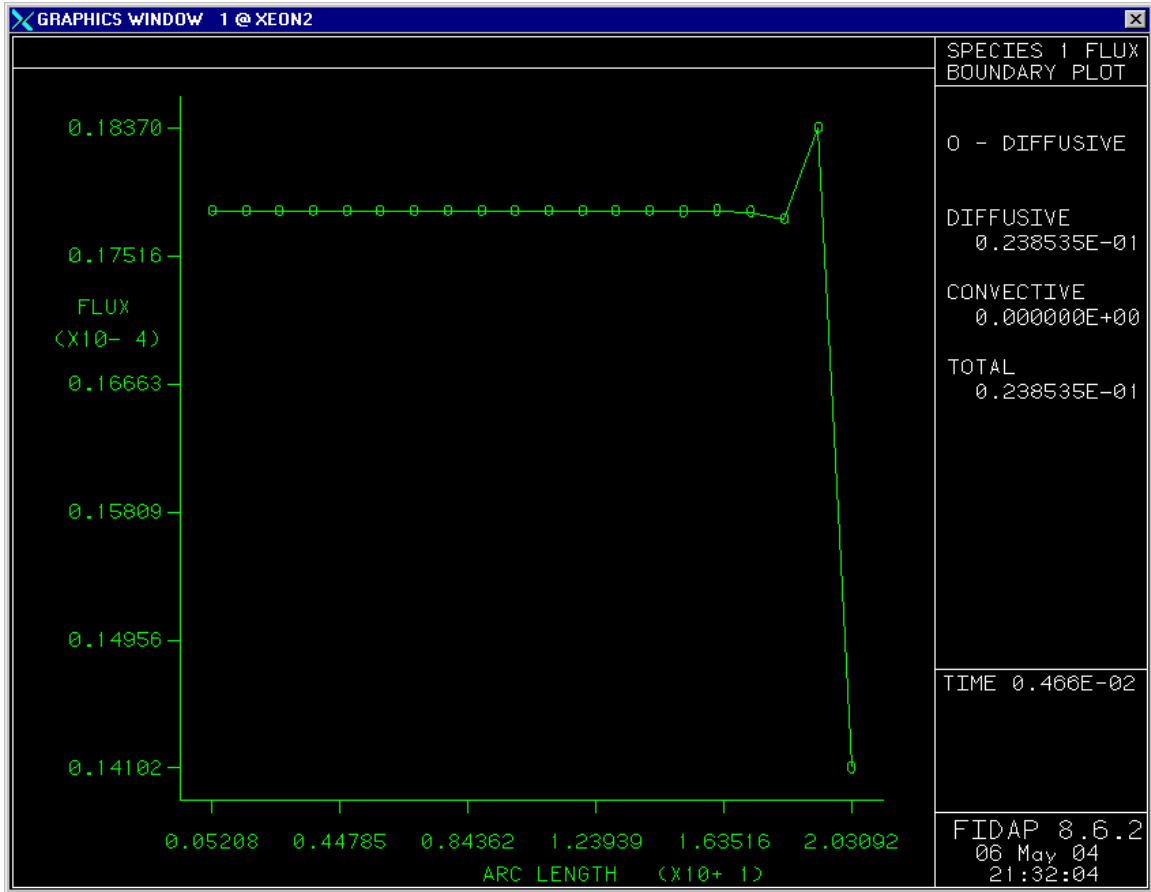


Figure 13: Sample Flux Plot Over Sidelow



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Ortho Evra Full US Prescribing Information.

<http://www.orthomcneil.com/products/pi/pdfs/orthoevra.pdf>

Rosado, Catarina and Rodrigues, Luis. 2003. *Solvent effects in permeation assessed in vivo by skin surface biopsy.* BMC Dermatology.

Schwindt, Doris A, Wilhelm, Klaus P., and Maibach, Howard I. September 1998. *Water Diffusion Characteristics of Human Stratum Corneum at Different Anatomical Sites In Vivo.* Journal of Investigative Dermatology.