

Hormone Delivery System: The Contraceptive Ring



Joanna Antisell
Tiffany Poon
Adam Borey
Jenna Briddell
Seth Palesch

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Professor Ashim Datta
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EXECUTIVE SUMMARY

The diffusion of estrogen from a contraceptive ring into the body was modeled to check company claims that the ring provides a low-dose flow of drug at constant levels for 21 days after a short initial period. An axi-symmetric geometry was used, illustrating the diffusion of estrogen out of the cross-section of the ring and through a mucosal layer, as well as the diffusion and absorption of the drug in the tissue region, which is the case for $\frac{3}{4}$ of the ring's surface area. A non-dimensionalized governing equation, with a transient, diffusion, and negative source term, was used to model the system. The source term was chosen by iterating, while the other terms were found or interpolated from scientific papers. After sensitivity analysis, the concentration of the drug in the tissue was found to remain constant after 4 days. In fact, it remained constant for 28 days, another claim of the company. The concentration of estrogen, a known carcinogen that can cause mood swings, nausea, and headaches at elevated or fluctuating levels, is at a lower level than other available hormonal contraceptives, supporting that it is a safer method.

INTRODUCTION

Many women use contraceptive methods that involve the hormones estrogen and progestin, which prevent the ovaries from developing and releasing mature eggs. This, therefore, prevents conception. Currently there are two well established types of birth control on the market. These possibilities are the pill form where the user ingests a large dose once a day for 21 days or the birth control patch is placed on the skin every week for three weeks out of the month. Women can also receive hormone shots or implants that last for four months. However, these methods only allow a menstrual cycle every four months, so they are difficult to compare to the other methods. All of these other methods can cause side effects such as headaches, blood clots, nausea, and breakthrough bleeding. However, there is a new form of birth control that comes in a flexible thin ring that is inserted into the vagina below the cervix. This ring is designed to release a continuous low dose of hormone that is absorbed by the vagina and distributed into the blood stream. The ring actually releases two derivatives of estrogen and progestin known as etonogestrel and ethinyl estradiol (Organon USA Inc. 2005). See Figure 1 for the chemical structures of both of these compounds. Because the ring is only changed once a month, it ceases the fluctuation of hormone levels that is normal in the other birth control methods.

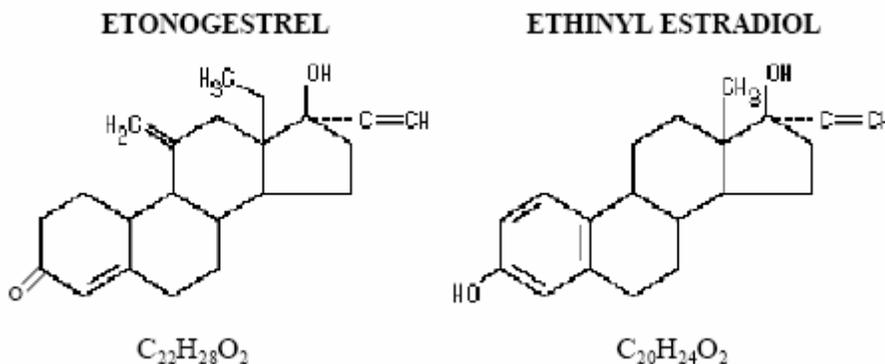


Figure 1: Chemical structures of Etonogestrel and Ethinyl Estradiol.

OBJECTIVES

- To compare the NuvaRing to other forms of contraception like the daily pill and the weekly patch.
- To model the release of the hormones, estrogen and progestin, showing that there is a constant rate of release.
- To determine whether or not the NuvaRing, as it is claimed to, can still release high enough hormone levels to still act as a contraceptive during the last 7 days of the 28-day menstrual cycle.

PROBLEM DEFINITION / SCHEMATIC

When this contraceptive device is placed inside the body, the two different hormones diffuse out of the circular ring. The physical dimensions of the flexible ring are an outer diameter of two inches and a cross-sectional diameter of 1/8 inch (Organon USA Inc. 2005, See). A more precise geometric schematic can be seen in Figure 2 (Organon USA Inc. 2005). The ring is designed to set the diffusion rate at a constant average of 0.120 mg of Etonogestrel and 0.015 mg of Ethinyl Estradiol per day over the 21-day period (Organon USA Inc. 2005). These two drugs are embedded in a polymeric matrix of Ethylene Vinyl Acetate (EVA) copolymers and magnesium stearate (Organon USA Inc. 2005). Etonogestrel has a diffusion constant of $1.54 \times 10^{-9} \text{ cm}^2/\text{s}$ in EVA (van Laarhoven 2002). The diffusion constant of Ethinyl Estradiol in EVA is not specifically stated in the literature. However, through some simple calculations and comparison to similar types of drugs in comparable tissues, it was found that Ethinyl Estradiol's diffusion constant in the EVA is about the same as Etonogestrel. In the vaginal tissue the two drugs have an estimated diffusion coefficient of $1.5 \times 10^{-7} \text{ cm}^2/\text{s}$. Again, this value was interpolated from the diffusion constants of the same drugs in similar tissues. Since both drugs have the same diffusion coefficients and they only differ in their initial concentrations in the ring, the simulation model only monitored the Etonogestrel concentrations.

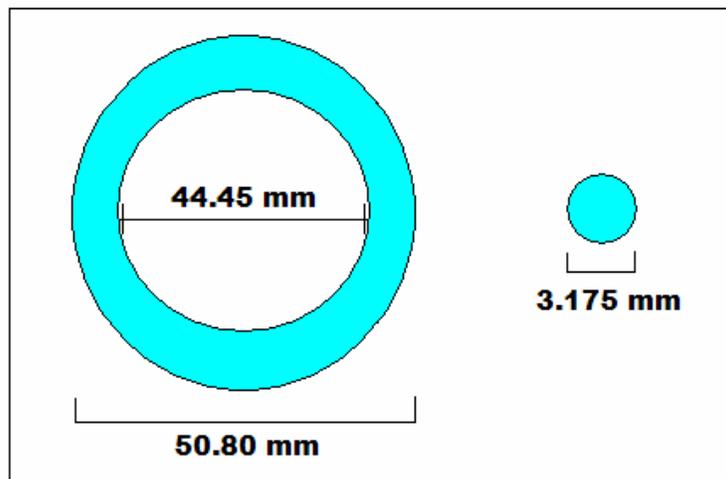


Figure 2: Dimensions of the birth control ring.

The drug diffusion out of the polymer ring and into the surrounding tissues occurs so that after 2-3 days the concentration of the drug reaches a maximum level. The concentration then levels off to a fairly constant blood concentration for the remainder of the 21 day time period (Organon USA Inc. 2005). Therefore, a transient time concentration model was used for this problem. However, the NuvaRing Company claims that the ring will safely function up to 7 days past the prescribed 21 day period. In

order to check the validity of this claim, the model was monitored to the 28 day mark. A distribution of blood concentration levels can be seen in figure 3, borrowed from the physician's prescription manual for the NuvaRing (Organon USA Inc. 2005).

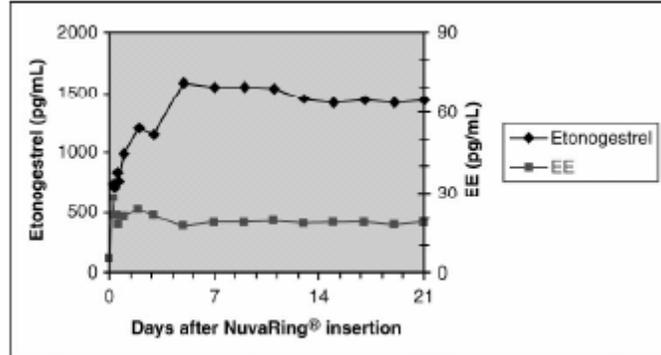


Figure 3: Concentration levels of Etonogestrel and Ethinyl Estradiol throughout the 21-day cycle.

Metabolic information is available for the drugs in the blood, but there is nothing to suggest that the hormones are degraded before reaching the bloodstream. Therefore, it can be assumed that there is no generation or degradation reaction in the polymer or tissue. However, the drugs are absorbed by the capillaries in the tissue. To account for this in the design, a negative source term was used in the tissue region. This source term will represent the capillaries that run throughout the tissue which are removing the drug continuously over time. Another assumption is that there is no convection due to the protected environment of the ring. Furthermore, diffusion values and length scales are very small for this problem, so a non-dimensionalized form of the governing equation was used. The final governing equation is:

Equation 1:

$$\frac{\partial c}{\partial \left(\frac{tD}{L^2}\right)} = \frac{\partial^2 c}{\partial \left(\frac{x}{L}\right)^2} - \frac{KL^2}{D}$$

Using FIDAP, this hormone delivery system was modeled to determine whether or not a constant rate of hormone release is achievable. It was assumed that hormone delivery is carried out entirely by diffusion, which was examined through differences in concentrations between the ring and the surrounding environment. Looking at figures 4 and 5, it is seen that approximately $\frac{3}{4}$ of the ring's surface is in contact with the mucosal fluid region (0.5mm thick) and then the muscular vaginal tissue (3.2 mm thick) (Tulikangas 2001). The remaining $\frac{1}{4}$ of the surface is exposed solely to vaginal fluid, which is assumed to be the same mucosal fluid. Therefore, diffusion will occur through these mediums accordingly. The initial concentration of the drugs were assumed to be zero in the tissues and at a universally distributed constant in the ring polymers. It has been found that the initial amounts of Etonogestrel and Ethinyl Estradiol is 11.7 mg and 2.7 mg respectively (Bellamy 2006). Using these values with the size of the ring, it was

determined that the initial concentrations in the ring were 9256.329 g/m^3 for Etonogestrel and 2136.076 g/m^3 for Ethinyl Estradiol. Published literature suggests that this is a safe assumption.

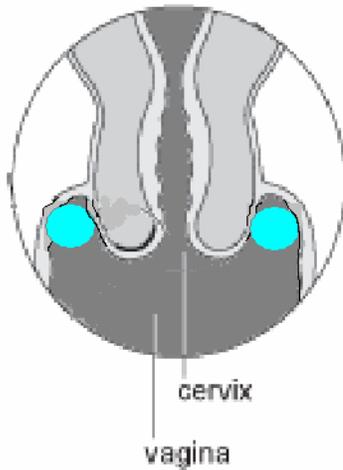


Figure 4: Diagram of the vaginal cavity.

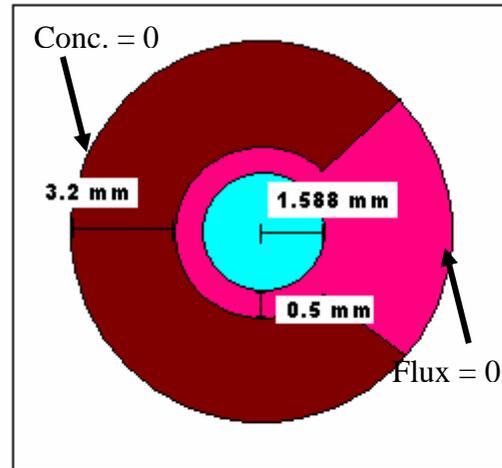


Figure 5: 2-D cross section of the 3-D ring showing the Tissue thicknesses and dimensions and boundary conditions.

To model this geometry, an axi-symmetric view of the problem was used. Figure 6 represents the 3D geometry of the ring and the surrounding tissue. A cross section of this was used to create the 2-D axi-symmetric geometry which is found in Figure 5. The geometry is divided into 3 separate regions: ring, mucus, and tissue.

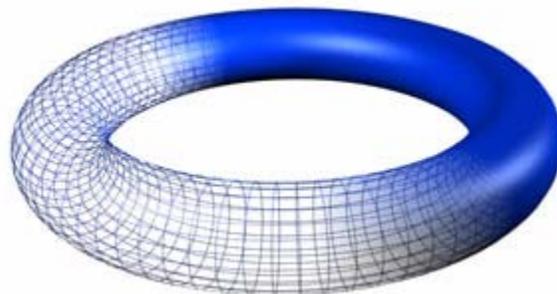


Figure 6: 3-D shape of ring frame.

MESH

Figure 7 represents the geometry and mesh created in GAMBIT using the 2D-axisymmetric geometry assumed. The computational region is set above the axis of rotation to create the torus shape. The three regions of the geometry are labeled in Figure 7 to demonstrate the 2-D geometry relationships present.

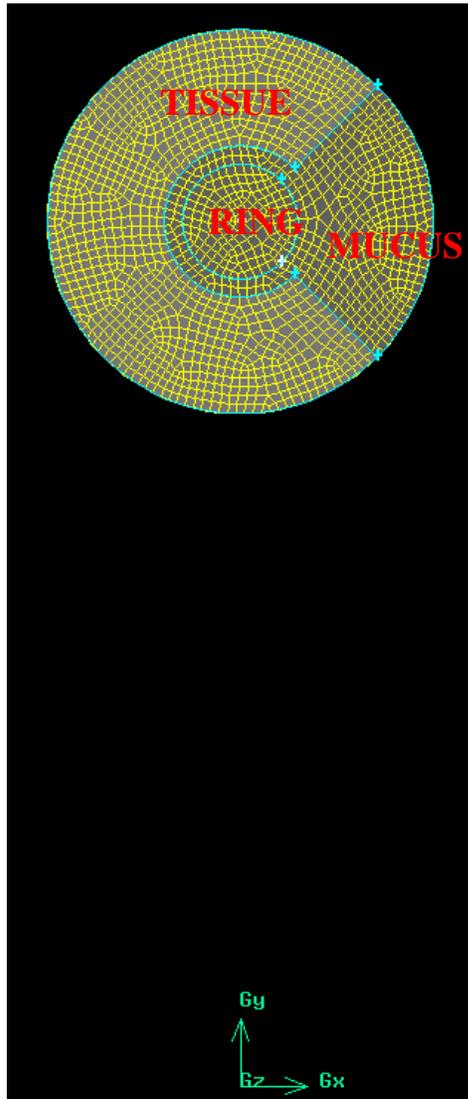


Figure 7: Mesh of ring and surrounding tissue in GAMBIT.

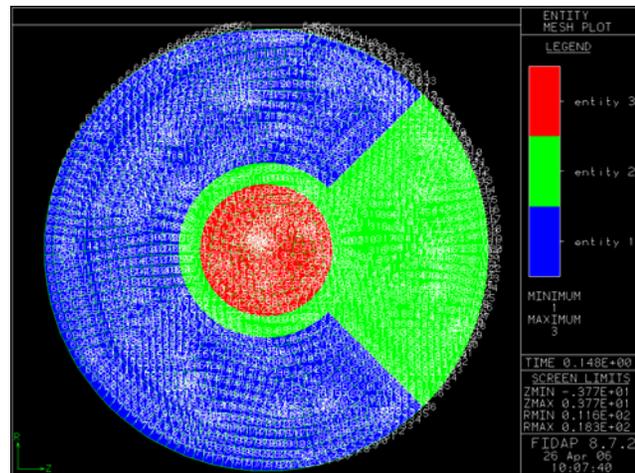


Figure 8: Mesh of ring and surrounding tissue in FIDAP.

Figure 8 is the meshed geometry created in FIDAP. The three regions of the geometry are accented in different colors. The blue region is the tissue, the green the mucosal region, and the red is the ring.

RESULTS AND DISCUSSION

The main purpose of this study is to demonstrate the constant hormone level that the birth control ring releases. All properties, boundary conditions, initial conditions, and governing equations used to simulate the problem are stated in Appendix A. Since it was found that both Etonogestrel and Ethinyl Estradiol have the same diffusivity in the system, only the diffusion of Etonogestrel was analyzed because Ethinyl Estradiol would be exactly the same.

The first step in the analysis of the model was to determine the magnitude of the source term that would be necessary to accurately model the physical process of continuous drug removal from the tissue region. To correctly identify this, a known value was necessary for comparison. Using the published data on the release rate of Etonogestrel from the ring and a simple calculation of the surface area of a toroid with the dimensions of the ring, the average flux over time out of the ring was calculated to be about 9596.48 (Non-dimensional). To do this comparison, the simulation was run over the 21-day period for different values of the source term and the flux was calculated after each simulation. Through iterations of this process, it was determined that a non-dimensional source term of about -300 would give an average flux out of the ring within an order of magnitude of the published value.

The current simulation was run for a 21-day period. Readings were taken at Day 1, 3, 4, 10, and 21 for Etonogestrel. The concentration through the tissue follows a sigmoidal curve that plateaus off after approximately 4 days, which follows information from published literature. The concentration level in the ring remains high and the diffusion is very small out of the ring so that it lasts for the entire 21 days.

The graphs below represent the diffusion of the drug out of the ring through the tissues. By the time Etonogestrel reaches the outer edge of the tissue it has been removed from the system and is assumed to have entered the bloodstream by absorption. Figure 9 below shows the change in concentration of Etonogestrel at the 5 different time measurements. Note that throughout the simulation, the right side of the ring region has a slightly lower concentration of the drug (can be seen by the faintly non-circular shape of the ring region) because the mucus has a high diffusion constant in the mucus region, therefore more of the drug has diffused out.

The measurement taken at Day 1, shows that the ring still contains most of the drug and that only a slight amount has diffused out of the polymer matrix. Most of the diffusion that has occurred has only entered the thin mucosal region surrounding the ring itself at this point in time. Readings taken at Day 3 and 4 are very similar to Day 1 except more of the drug has left the ring's matrix and has diffused through the tissue. This can be seen by the slightly decreased size of the ring's region and if you examine the graphs closely, you can tell that the mucus region on the right side of the graphs does have a slightly higher concentration. To fully see how the mucus region does actually contain a higher concentration please reference Appendix C. Day 10 displays a much more dramatic change in concentration than has been seen so far. A lot of the drug has

now left the ring and has been removed from the system. Finally by Day 21, it can be seen that the concentration in the ring polymer matrix has been significantly reduced in comparison to the concentration in the surrounding tissue. Additionally, note that in all of these plots, the concentration in the tissue region is almost uniform, which is what was expected and desired for this drug release system.

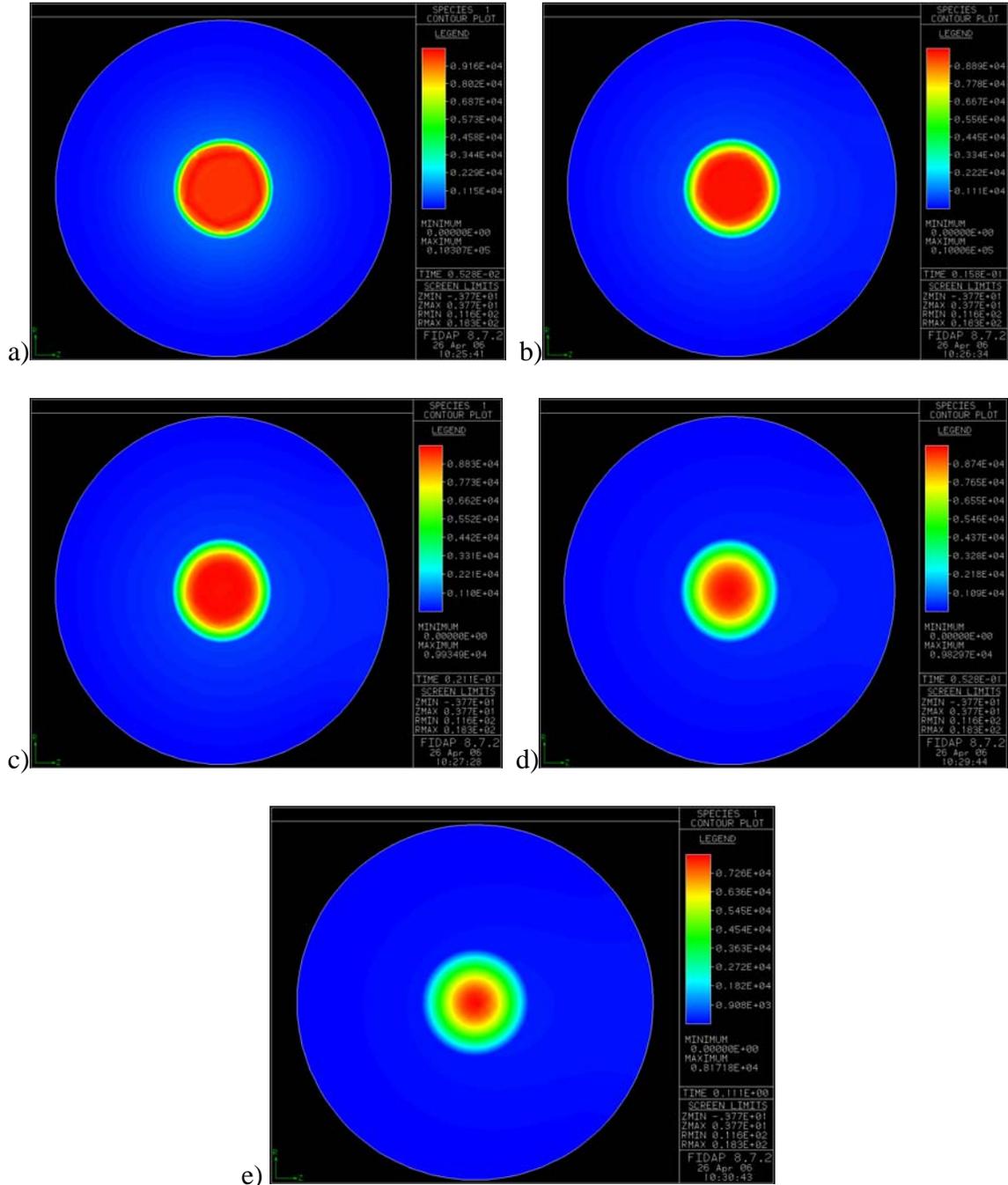


Figure 9: Concentration differences for species 1, Etonogestrel, at times:
a) $t = 86400\text{s}$ (1 day) = 0.005276, b) $t = 259200\text{s}$ (3 days) = 0.15829,
c) $t = 345600\text{s}$ (4 days) = 0.02111, d) $t = 864000\text{s}$ (10 days) = 0.05276,
e) $t = 8640000\text{s}$ (21 days) = 0.11087

To examine the differences in concentration of the two drugs over the 21 day period, a history plot was analyzed. See Figure 10 below for details. The readings were taken at the middle of the tissue region and at the center of the ring. The middle of the tissue can be assumed to be a fair estimate of the concentration in blood stream over time. Even if the concentration in the blood does not match with this value, the change over time in concentration in the tissue will give an estimate of how constant the level of hormone is in the blood stream. It was found that after about 4 days the concentration at the outer edge of the tissue levels off and slowly approaches a constant value. This agrees with data found in the literature that states that the level of hormone found in the blood stream reaches a constant level about 4 days after ring use is initiated.

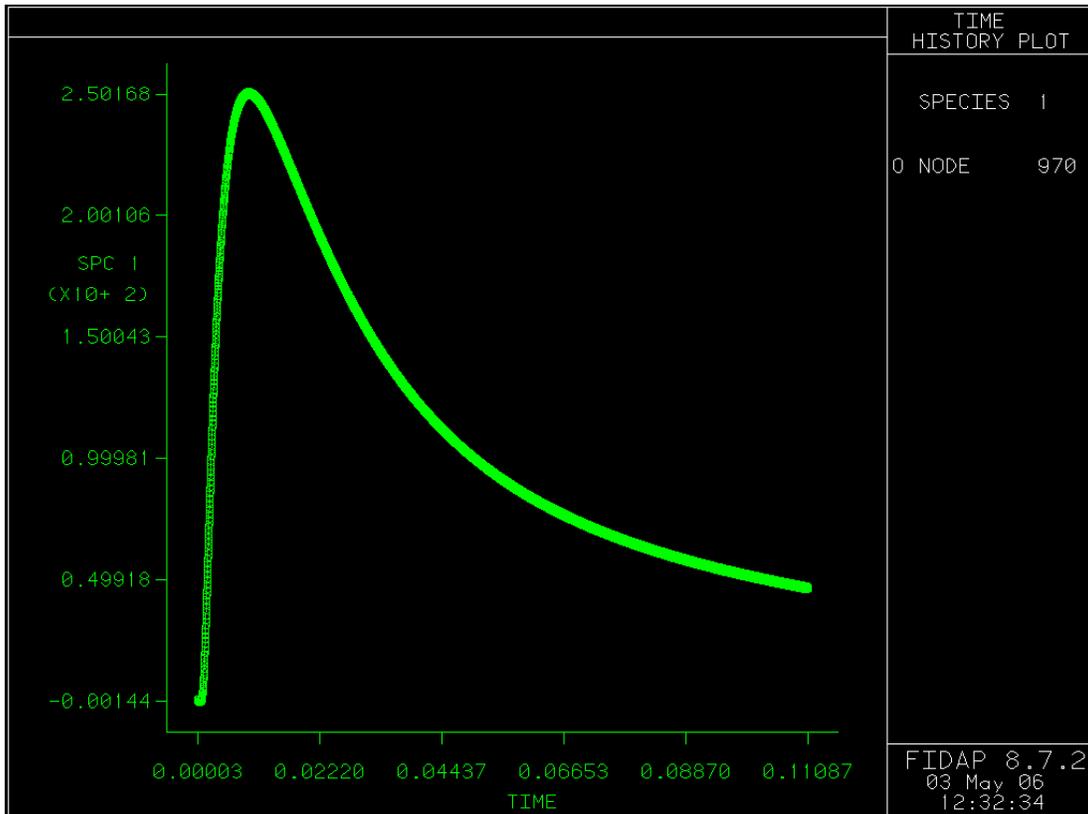


Figure 10: Change in Etonogestrel at middle of tissue layer over the 21 day period.

Additionally, a history plot was created that simultaneously graphed the concentration of Etonogestrel in several different places throughout the model to compare the overall levels of the drug. This can be seen below in Figure 11. From this analysis it can easily be seen that the overall concentration in the tissue and mucus stay fairly constant over the 21 day period. However the ring's concentration of Etonogestrel drops off after several days of use as would be expected. Finally, note that the concentration at the outer edge of the tissue region stays at zero for the entire 21 day period. This displays that the previously stated boundary condition has been successfully fulfilled in the model.

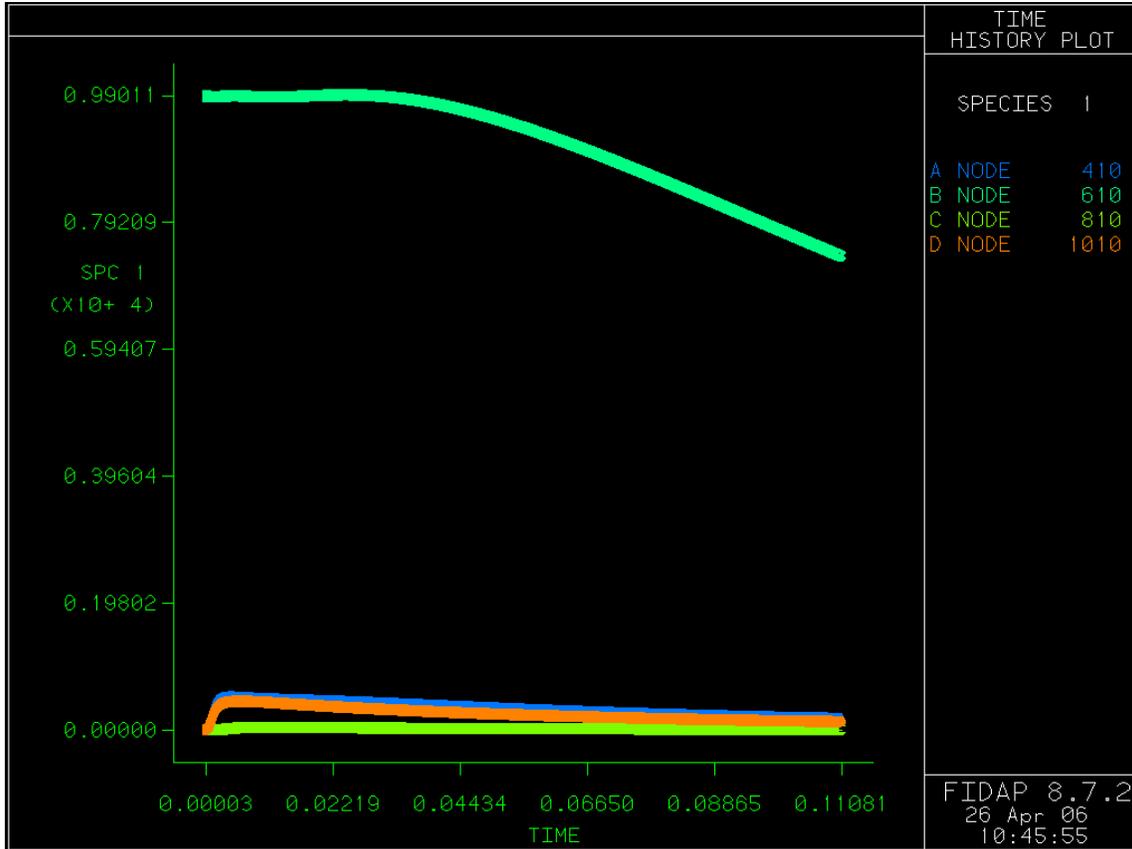


Figure 11: Change in Etonogestrel at outer edge of tissue layer (Light Green), inner edge of tissue (Blue), center of the ring (Green), and in the mucosal region (Orange) over the 21 day period.

Literature suggests that the ring will also last for an additional 7 days after the 21 day suggest use period, in case the ring is misused or somehow forgotten. This claim was also examined by allowing the simulation to run to 28 days. The results of this can be seen below in Figure 12 and Figure 13.

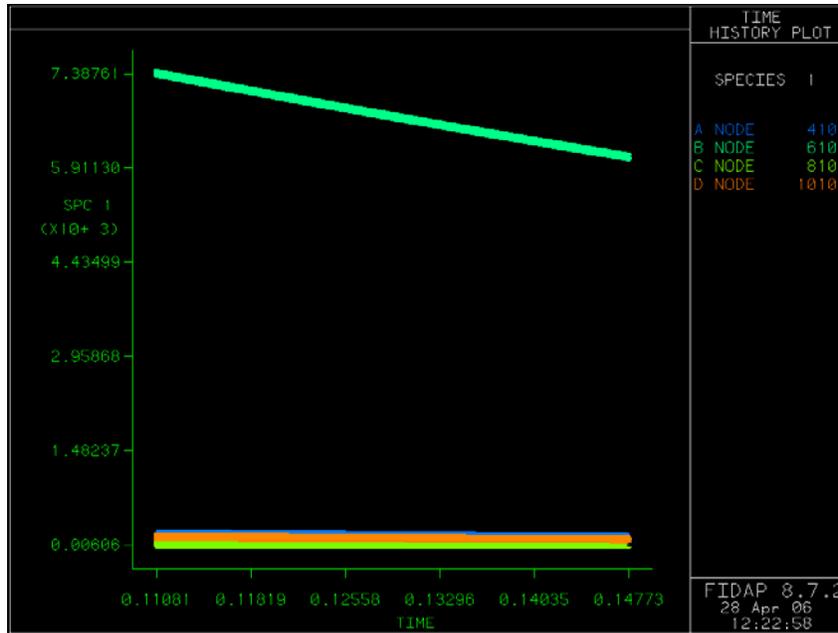


Figure 12: Change in Etonogestrel at outer edge of tissue layer (Light Green), inner edge of tissue (Blue), center of the ring (Green), and in the mucosal region (Orange) between day 21 and day 28 of the simulation period.

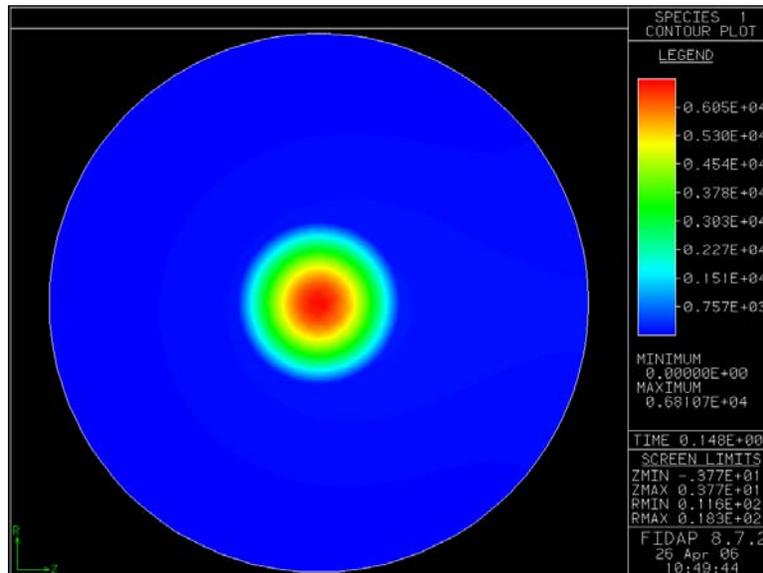


Figure 13: Etonogestrel concentration variation at Day 28.

From this analysis it was determined that the ring does in fact continue to work for the additional 7 days. From the figures above it can easily be seen that the concentration in the tissue region maintains the constant level of hormone for the additional 7 days. The concentration in the ring does continue to drop off linearly during the period. Further time analysis was not completed because there is no claim or proof that the ring will work correctly for any longer than the max of 28 days.

SENSITIVITY ANALYSIS

The first step in the sensitivity analysis for this study was to determine the number of elements needed for the mesh to converge. Six different meshes were created to analyze this sensitivity. The number of elements in each mesh was counted and graphed against the concentration at the center of the tissue, which was the region chosen because the drug uptake is fairly constant at this time, as well as the average concentration in all of the tissue. Measurements were taken after 10 days because it is at this point that the drug concentration is well into steady state and should be fairly constant. Figure 14 below shows the results of this analysis.

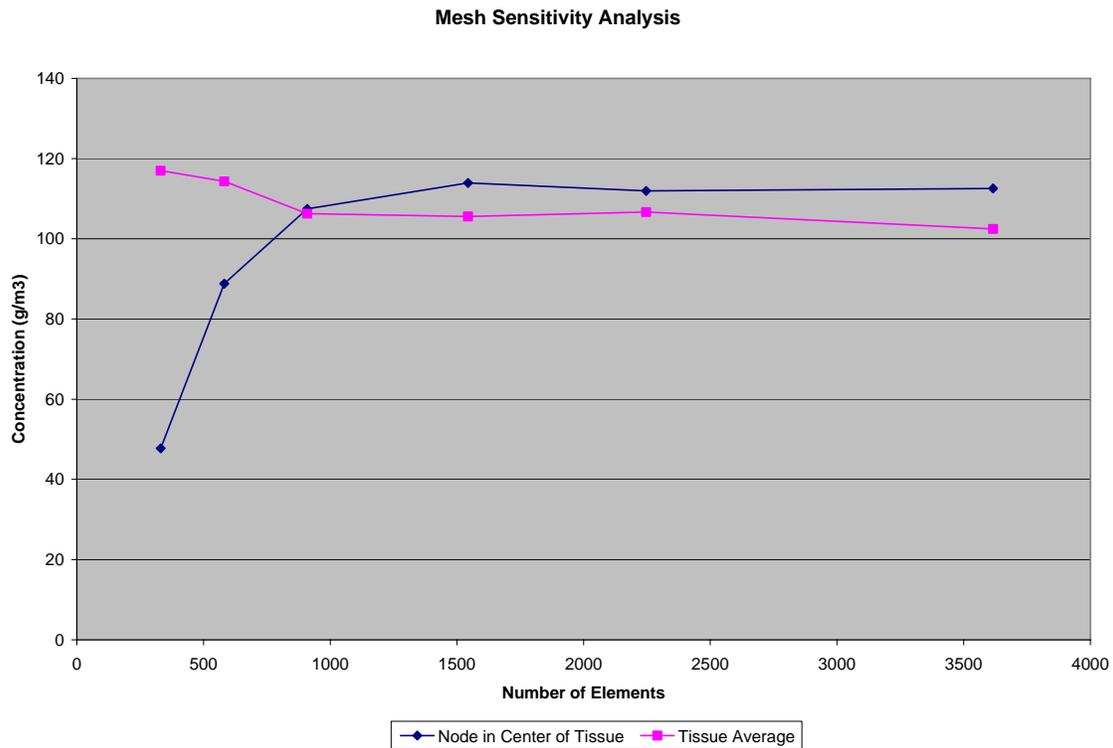


Figure 14: Mesh sensitivity analysis, number of elements versus concentration inside the tissue region.

Figure 14 shows that the mesh converges around the original number of 1544 elements. The change in computation time between 1544 elements and 2247 elements was negligible, so the original mesh with 1544 elements was used for the bulk of the analysis in this study.

Next the variables used in our model were tested using the optimized mesh. The variable that was the most difficult to find were the values for the diffusivity of the drug in the tissue region. It was decided to use a diffusion constant of $1.5 \times 10^{-7} \text{ cm}^2/\text{s}$ for Etonogestrel in the vaginal tissue and the mucus region. This decision was based on the comparison of other studies where the same drug diffused in similar tissues. To analyze the sensitivity of this constant on the model, different values for the diffusivity were used

in the simulation. Again tests were run over the 10 day period because it is safe to assume at the end of this time period that the drug concentration will be fairly constant. The diffusivity of Etonogestrel was varied greatly because it is important to see how it will affect the results of the model. To compare how the diffusivity will affect the solution, the concentration of Etonogestrel was measured at Day 10, both at a single node in the center of the tissue region, and by computing the average concentration in the tissue. The results of this are seen below in Figure 15.

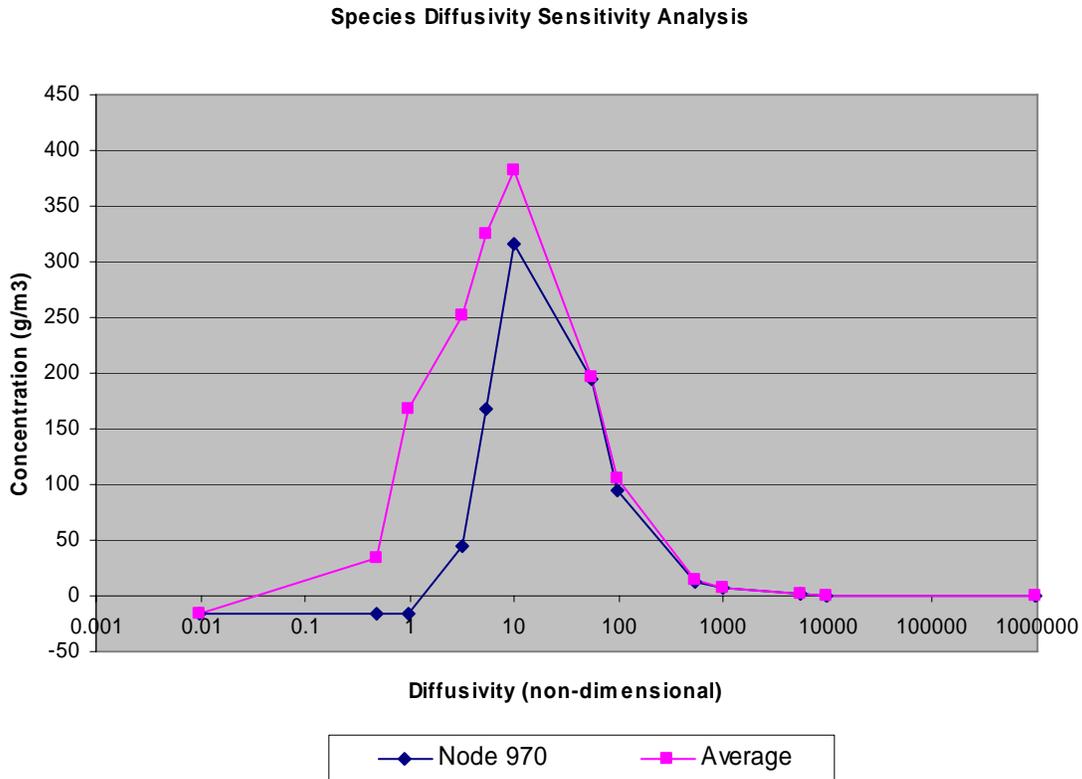


Figure 15: Diffusivity constant sensitivity analysis, diffusivity constant versus concentration in the tissue region.

From this analysis, it is very evident that the diffusivity greatly affects the output of this model. A log scale was used for the x-axis because the values varied over a very large region with most of the change only occurring in a very small section of the graph. The greatest region of change in the results is when the tissue and mucosal diffusivity is between around 1 and 1000. When the value for the diffusivity is below 1, Etonogestrel does not diffuse quickly enough in the tissue causing there to not be a high enough concentration in the tissue for the source removal term. This causes FIDAP to output negative values for the concentration in the tissue, which is physically impossible. For this reason, this region of the graph is inapplicable to the model.

Similarly, when the value for the diffusivity is above 1000, Etonogestrel diffuses far too quickly in the tissue and mucus regions and stops affecting the solution to the model. This is because at these high diffusivity values, Etonogestrel simply diffuses out

of the system through the outer tissue boundary. In the region between diffusivities of 1 and 1000, the diffusivity value does not need to change much to drastically affect the solution. The value found in the literature (97.403, non-dimensionalized) is within this region.

The source term used in the model is an approximation. No published literature could be found on this because in reality, Etonogestrel is being carried away through the many capillaries present in the tissue. For this reason the effect of the negative source term on the concentration in the tissue when the drug levels out to a solid rate was examined. This can be seen below in Figure 16.

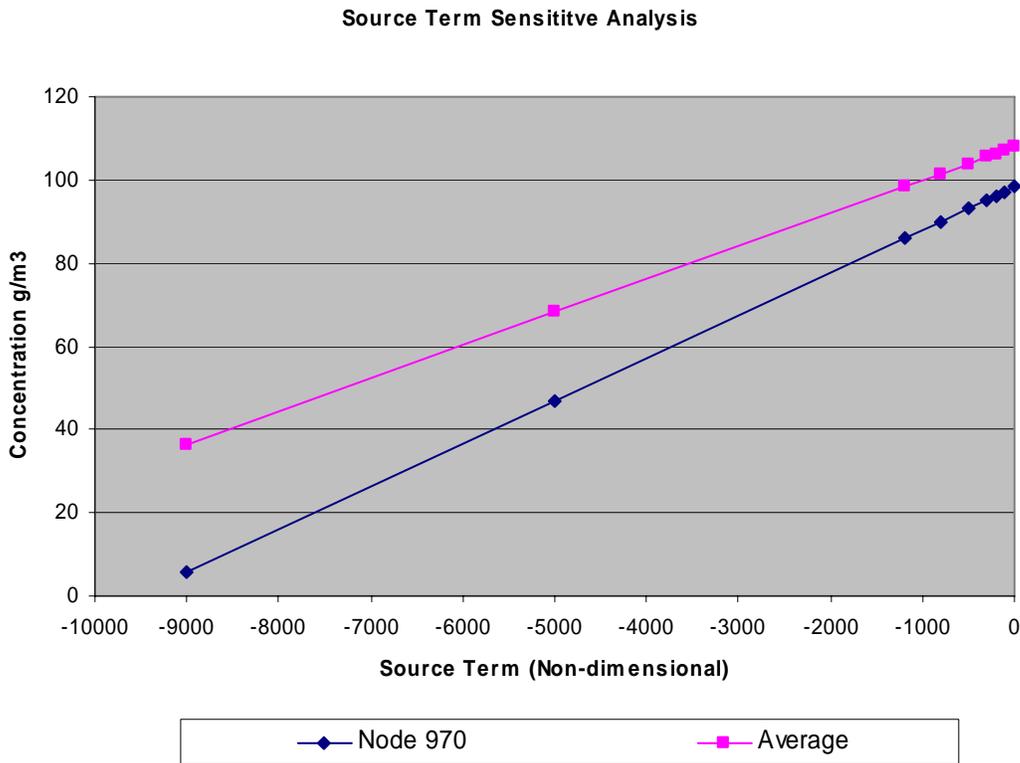


Figure 16: Source term sensitivity analysis, source term versus concentration in the tissue region.

From this analysis it is clearly evident that the source term will directly influence the effective concentration that is found in the tissue throughout the simulation. The connection between these two variables exhibits a positive relationship, in that when the source term is decreased the corresponding concentration in the vaginal tissue also decreases proportionally. Therefore, depending on the size of the source term implemented in the problem definition, the concentration found in the tissue should respond accordingly. This makes logical sense because the higher the rate that you are removing Etonogestrel from the tissue the region, then the lower the average concentration should be in the tissue itself.

CONCLUSION

In modeling the contraceptive ring, the main objective was to test the claim that the ring releases a constant level of hormone to the blood. This was demonstrated through simulations of the 21-day period for which the ring is worn. Results showed that although the concentrations of the hormones Etonogestrel and Ethinyl Estradiol do decrease in the ring, the concentration in the tissue region around it stay constant. Investigations were also made as to whether the ring could be worn for an extra week, as the company claims it can. The NuvaRing was modeled for that extra 7-day period and it was shown that the drug release remains constant and that the ring is still effective.

Economically speaking, the NuvaRing goes for about \$75.00 for each ring. Other forms of birth control, such as the pill, all cost around the same. For example, a brand name birth control such as Ortho Tri-Cyclen can cost up to \$85.00 for a month worth of pills (note – these values are not indicative of prices with insurance). The patch goes for about the same price as the pill, the Ortho Evra patch costing about \$85.00 for three patches (a month's worth). Although these prices vary with different distributors and insurance plans, they are not very different from each other.

The contraceptive ring is considered to be much safer than other forms of birth control. It emphasizes its low dose of hormone, releasing only 11.1 mg/h/ml of estrogen into the body throughout a 21-day period compared to oral contraceptives which releases about 22.5 mg/h/ml and the patch, which releases 37.5 mg/h/ml. Because the ring only has to be inserted once, its release of hormones stays constant. It can be concluded that the NuvaRing is a safer and more effective form of birth control because of the overall lower dose of hormone that is constantly released, minimizing side effects such as nausea, mood swings, and possible blood clots

APPENDIX A

GOVERNING EQUATIONS:

1) General species equation for the diffusion of Etonogestrel in the vaginal tissue

$$\frac{\partial c_a}{\partial t} + u \frac{\partial c_a}{\partial x} = D_a \frac{\partial^2 c_a}{\partial x^2} + r_a$$

2) Simplified species equation after the elimination of the convective terms

$$\frac{\partial c_a}{\partial t} = D_a \frac{\partial^2 c_a}{\partial x^2} - K$$

3) Non-dimensionalized species equation used for all simulations

$$\frac{\partial(c)}{\partial\left(\frac{Dt}{L^2}\right)} = \frac{\partial^2(c)}{\partial\left(\frac{x}{L}\right)^2} - \frac{KL^2}{D}$$

note: concentration does not have to be non-dimensionalized

BOUNDARY CONDITIONS & INITIAL CONDITIONS:

Table A1: Summary of Boundary Conditions for Modeled System

Boundary Region	Flux g/m ³ s	Conc. g/m ³
Outside Edge of Tissue	N/A	0
Outside Edge of Mucus	0	N/A

Table A2: Summary of Initial Conditions for Modeled System

Region	Conc. g/m ³
Tissue	0
Mucus	0
Ring	9876.97

INPUT PARAMETERS:

Parameters (dimensional):

Inner Radius of Ring	0.022225 m
Cross Section Radius of Ring	0.0015875 m
Thickness of Tissue	0.0032 m
Thickness of Mucus	0.0005 m
Time Step:	500 sec
Ending Time	21 days = 1,814,400 sec

Diffusivity:

-Ring	$1.54 \times 10^{-13} \text{ m}^2/\text{s}$
-Tissue	$1.50 \times 10^{-11} \text{ m}^2/\text{s}$
-Mucus	$1.50 \times 10^{-11} \text{ m}^2/\text{s}$

Etonogestrel concentration

-Ring	0 g/m^3
-Tissue	0 g/m^3
-Mucus	9876.97 g/m^3

Source Term

$$-1.8332 \times 10^{-5} \text{ g/m}^3\text{s}$$

Parameters (non-dimensional):

Note: used scaling factors of: $L = 0.0015875 \text{ mm}$ and $D = 1.54 \times 10^{-13} \text{ m}^2/\text{s}$

Inner Radius of Ring	14
Cross Section Radius of Ring	1
Thickness of Tissue	2.0157
Thickness of Mucus	0.3149

Time Step:	3.05344×10^{-5}
Ending Time	0.11087

Diffusivity:

-Ring	1
-Tissue	97.403
-Mucus	97.403

Etonogestrel concentration

-Ring	0 g/m^3
-Tissue	0 g/m^3
-Mucus	9876.97 g/m^3

Source Term

$$-300 \text{ g/m}^3$$

APPENDIX B

PROBLEM STATEMENT:

PROBLEM(axi-s, Isothermal, NoMomentum, Transient, LINEAR, FIXED, NEWTONIAN, INCOMPRESSIBLE, SPEC=1)

Axi-Symmetric	The geometry is modeled as the cross section of the ring. By rotating the circular geometry around the x-axis the ring is created. This creates a 2-D diffusion problem.
Isothermal	The model is assumed to have a uniform temperature equal to 37 degrees Celsius.
No Momentum	There is no fluid flow or momentum in the vaginal cavity and therefore the Momentum Equation is not solved during simulation.
Transient	The concentration throughout the tissue and ring changes over time.
Linear	There is no convection or fluid flow present in the system and the convective term is eliminated in the governing equations.
Fixed	The geometry does not deform.
Newtonian	All materials are assumed to be incompressible.
Incompressible	Newtonian
Species 1	Etonogestrel is present in the system.

SOLUTION STATEMENT

SOLUTION (S.S.=50, VELCONV =0.001, RESCONV =0.01, SCHANGE =0, ACCF =0)

TIME INTEGRATION STATEMENT

TIMEINTEGRATION (BACKWARD, Fixed, TSTART = 0, TEND = 0.11087, DT = 3.05344e-005, NSTEPS = 3640)

Backward	Using the implicit method
Fixed	The time increment was constant for all steps <i>note: there are no dimensions on the time</i>
Starting time	the starting time is at 0 <i>note: there are no dimensions on the time</i>
Ending time	The ending time is set to 0.11087 <i>note: there are no dimensions on the time</i>
Time increment	The time step is set to 3.05344 e -005 <i>note: there are no dimensions on the time</i>
Number of fixed steps	There are a maximum of 3640 time steps allowed

ENTITY STATEMENT

ENTITY(NAME = "TISSUE", SOLID, PROPERTY = "mat2" , SPEC=1,
MDIFF="C1_TISSUE")

ENTITY(NAME = "MUCUS", SOLID, PROPERTY = "mat2" , SPEC=1,
MDIFF="C1_MUCUS")

ENTITY(NAME = "RING", SOLID, PROPERTY = "mat1" , SPEC=1,
MDIFF="C1_RING")

ENTITY (NAME = "TISSUE INTERFACE", PLOT)

ENTITY (NAME = "TISSUE CAV TOP", PLOT)

ENTITY (NAME = "TISSUE CAV BOT", PLOT)

DIFFUSIVITY STATEMENT

DIFFUSIVITY (SET = "C1_TISSUE", CONSTANT = 97.403)

DIFFUSIVITY (SET = "C1_MUCUS", CONSTANT = 97.403)

DIFFUSIVITY (SET = "C1_RING", CONSTANT = 1)

BOUNDARY CONDITIONS STATEMENT

ENTITY (NAME = "TISSUE OUT", PLOT)
BCNODE (SPEC=1, CONSTANT = 0, ENTITY = "TISSUE OUT")

ENTITY (NAME = "RING INTERFACE", PLOT)

ENTITY (NAME = "MUCUS OUT", PLOT)
BCFLUX (SPEC=1, CONSTANT = 0, ENTITY = "MUCUS OUT")

INITIAL CONDITIONS STATEMENT

ICNODE (SPEC=1, CONSTANT = 0, ENTITY = "TISSUE")

ICNODE (SPEC=1, CONSTANT = 0, ENTITY = "MUCUS")

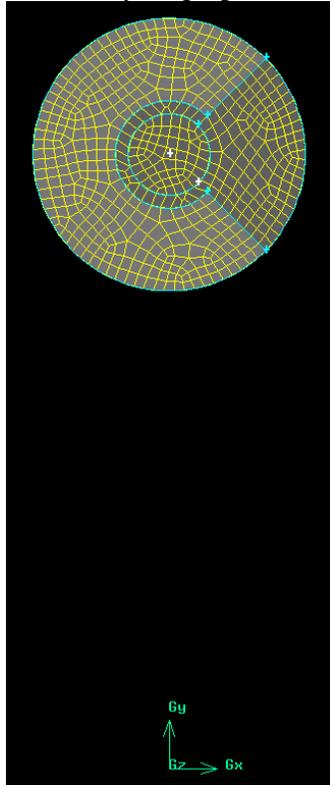
ICNODE (SPEC=1, CONSTANT = 9876.97, ENTITY = "RING")

SOURCE TERM STATEMENT

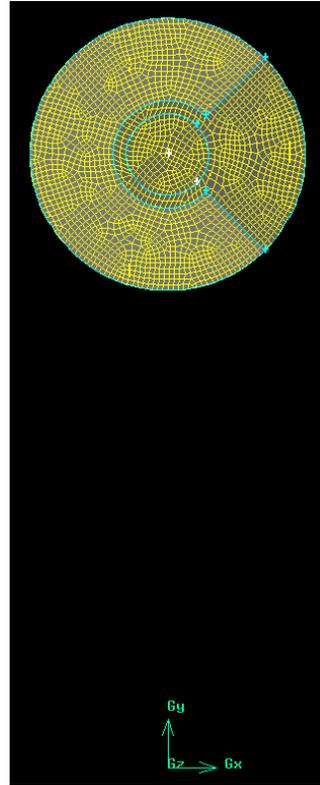
SOUR (SPEC = 1.0, CONS = -300.0, ENTI = "TISSUE")

ELEMENT MESH

Figure B1. Sample meshes used to determine mesh convergence. Please refer to Figure 9 for convergence analysis graph.



(a) 582 Elements



(b) 1544 Elements

Convergence Analysis:

Table B1. The number of nodes for each mesh that was produced.

Mesh	Number of Elements
1	331
2	582
3	909
4	1544
5	2247
6	3616

Note: Mesh #4 was used for all calculation steps and analysis.

APPENDIX C

Below are the 5 contour graphs seen in the results section with the colors inverted so that the concentration changes can be easily and thoroughly examined.

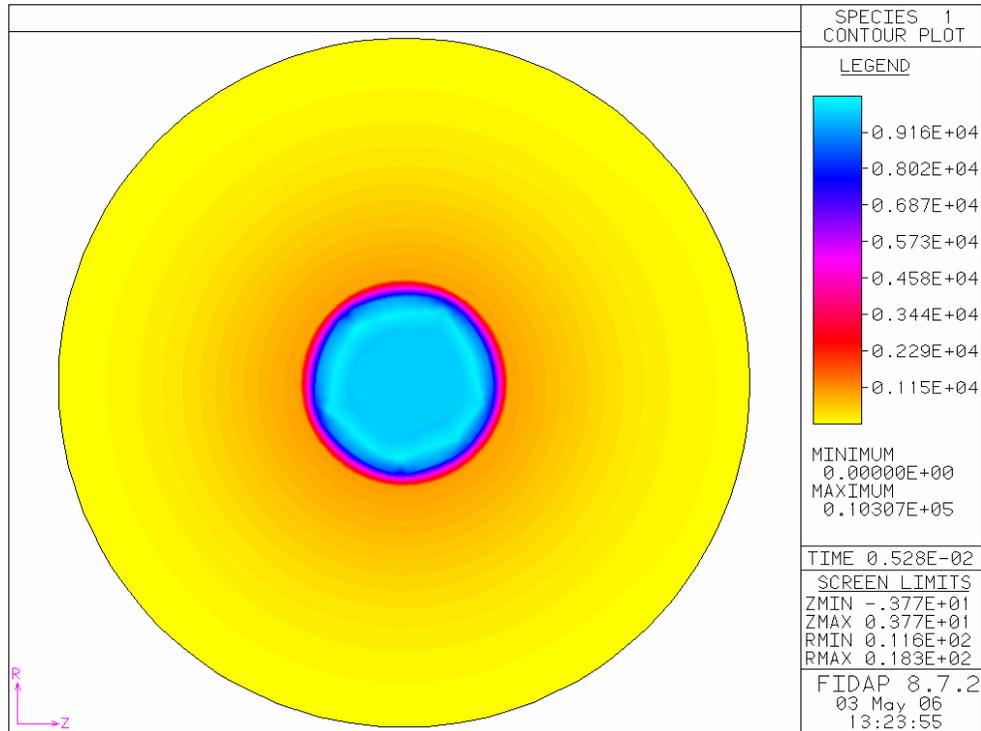


Figure C1: Etonogestrel concentration variation at Day 1.

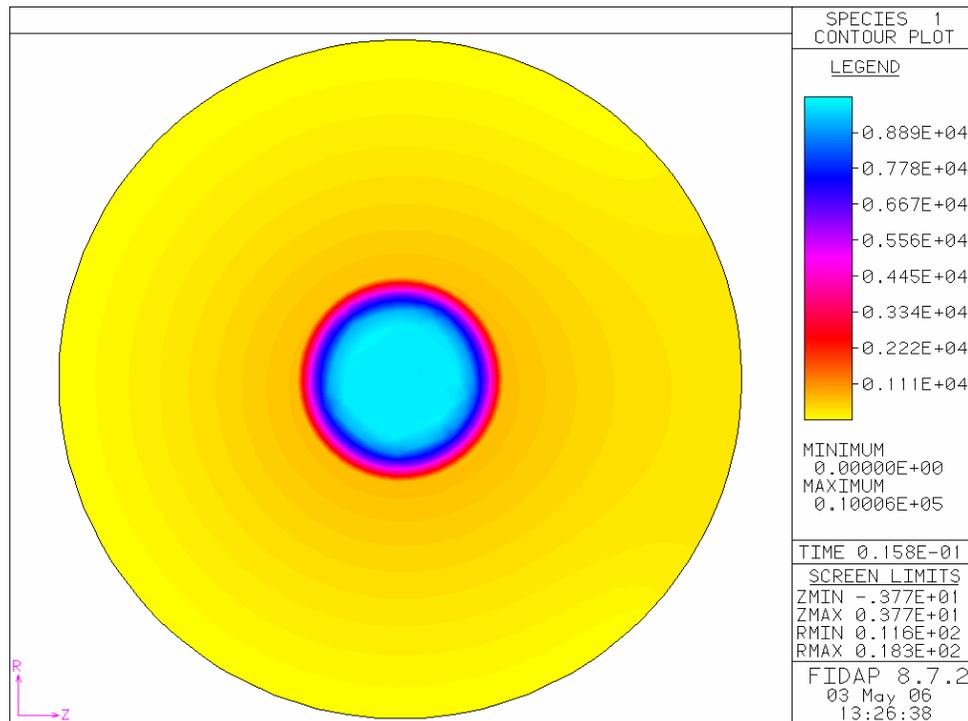


Figure C2: Etonogestrel concentration variation at Day 3.

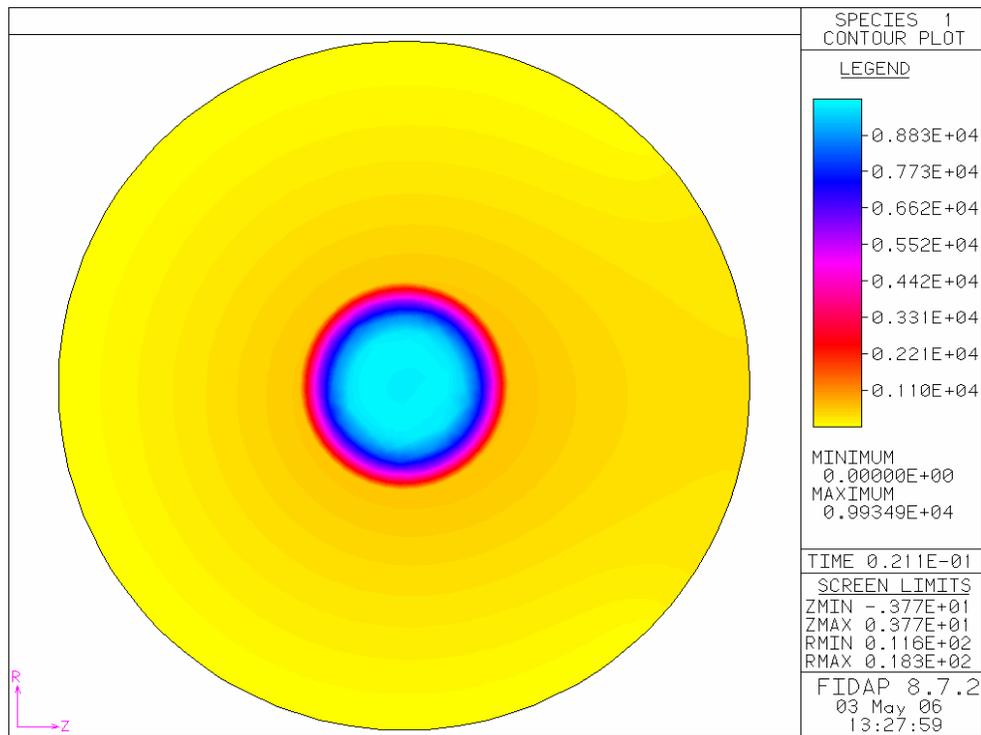


Figure C3: Etonogestrel concentration variation at Day 4.

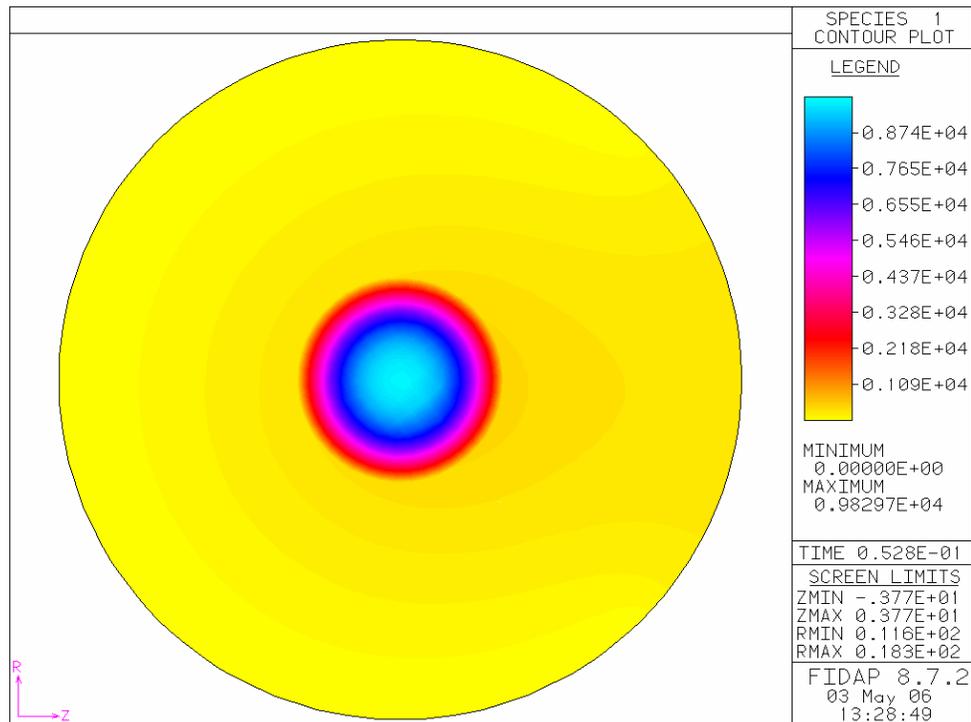


Figure C4: Etonogestrel concentration variation at Day 10.

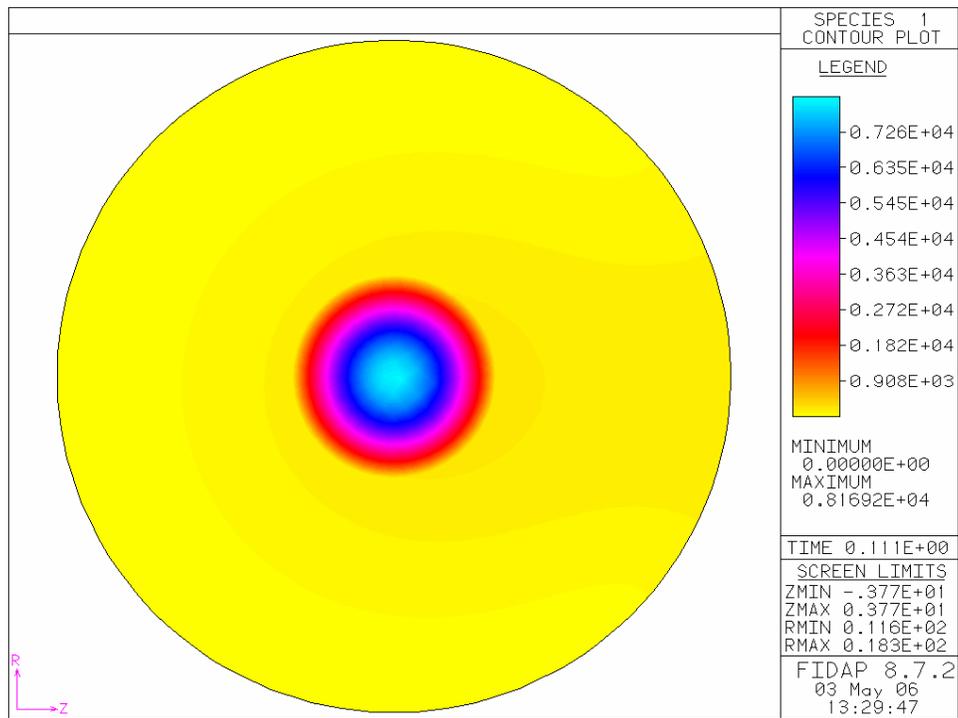


Figure C5: Etonogestrel concentration variation at Day 21.

APPENDIX D

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<http://web-meds.com/orthoevra.asp?banner=GBC&keywords=birth+control+patch>