# Modeling Transdermal Delivery of Contraceptive Hormones

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## Background and Introduction:

Wearable devices and other therapeutics are increasing in popularity for a number of reasons. They allow for more continuous monitoring and are less invasive and prone to human error than traditional methods. For example, insulin pumps continuously monitor the glucose levels in a person's bloodstream and release small amounts of insulin as needed. This is in contrast to the traditional method requiring a needle stick, manual testing of the glucose level in the blood, manual measuring of insulin to inject, etc. [1].

Contraception is another field in medicine that is undergoing this same trend toward less invasive methods. Contraception (also known as birth control) spread throughout the 20th century due to great progress in its efficacy, now providing an average of 90% success in pregnancy prevention [2]. 62% of women between age 15 and 44 actively use contraception [3]. The mechanism of action of birth control can be barrier-related, hormonal, chemical (e.g., copper IUD), and more permanent such as sterilization [4,5].

Our bioengineering problem focused on the contraceptive patch (specifically the Ortho-Evra brand) to better understand the mass transfer properties of transdermal diffusion of a drug through skin and develop a mathematical model to determine conditions for which this contraception method is efficient and reliable.

The skin is a complicated organ that protects from foreign contaminants, maintains a specific structure, and provides important elastic properties. The superficial skin layer, known as the epidermis, is 10-20 microns thick and is composed mainly of fully differentiated keratinocytes held together in a sheet that is shed and turns over at a relatively fast rate. The dermis contains hair follicles, sweat glands, multiple types of collagen fibers, a fat layer, and many small capillaries/microvessels that act to absorb what passes through the epidermis and dermis [6].

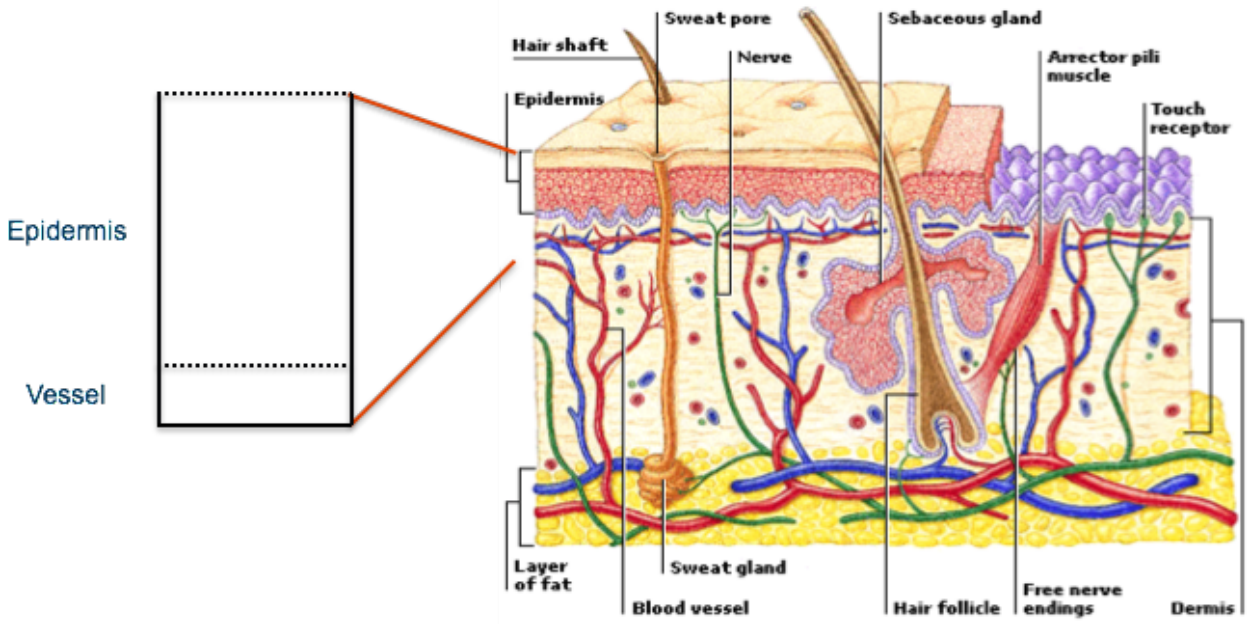


Figure 1: Skin Diagram and Model

Transdermal hormonal patches have several advantages over classic contraception methods. They provide constant and prolonged release of the drug and avoid gastric degradation of the active substance. They are non-invasive, easy to apply, and painless. The patch need only be replaced weekly and delivers a continuous dose of the drug, in contrast to the traditional method requiring the user to ingest a pill at the same time every day. Finally, studies have shown that patients show better compliance to this treatment than other methods [7].

The following figure is a list of previously FDA approved transdermal hormonal patches:

Table 1 | **Characteristics of transdermal patches***

| Active ingredient | Product name | Dose and size of patch | Dose delivered | Clinical indication |
|---|---|---|---|---|
| Clonidine | Catapres-TTS | 2.5–7.5 mg in 3.5–10.5 $cm^2$ | 0.7–2.1 mg in 7 d | Hypertension |
| Ethinyl oestradiol (EO), norelgestromin (N) | Ortho-Evra | 0.75 mg EO and 6 mg N in 20 $cm^2$ | 0.14 mg EO and 1.05 mg N in 7 d | Birth control |
| Fentanyl | Duragesic | 2.5–10 mg in $cm^2$ | 1.8–7.2 mg in 3 d | Analgesia |
| Lidocaine | Lidoderm | 700 mg in 140 $cm^2$ | 10–32 mg in 12 h | Post-herpatic neuralgia |
| Lidocaine (L), epinephrine (E) | Iontocaine | 20–50 mg L and 10–25 μg E in 5.7–11.1 $cm^2$ | 40 mAmin iontophoresis | Dermal anaesthesia |
| Nicotine | Habitrol Nicoderm-CQ Nicotrol Prostep | 8.3–114 mg in 3.5–30 $cm^2$ | 5–22 mg in 16–24 h | Smoking cessation |
| Nitroglycerin | Nitro-Dur Transderm-Nitro | 12.5–160 mg in 5–40 $cm^2$ | 1.2–11.2 mg in 12–14 h | Angina |
| 17β-oestradiol | Alora, Climara Esclim, Estraderm FemPatch, Vivelle, Vivelle-DOT | 0.39–20 mg in 2.5–44 $cm^2$ | 0.075–0.7 mg in 3–7 d | Hormone replacement |
| Oestradiol (O), norethindrone (N) | CombiPatch | 0.51–0.62 mg O and 2.7–4.8 mg N in 9–16 $cm^2$ | 0.15–0.20 mg O and 0.42–1.0 mg N in 3–4 d | Hormone replacement |
| Oxybutynin | Oxytrol | 36 mg in 39$cm^2$ | 11.7–15.6 mg in 3–4 d | Overactive bladder |
| Scopolamine | Transderm Scop | 1.5 mg in 2.5 $cm^2$ | 1.0 mg in 3 d | Motion sickness |
| Testosterone | Androderm Testoderm TTS Testoderm | 10–328 mg in 37–60 $cm^2$ | 2.5–6 mg in 1 d | Hypogonadism |

*This list contains FDA-approved transdermal patches (not including generics) listed on the FDA website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/).

**Figure 2: FDA Approved Transdermal Patches**

## Problem Statement:

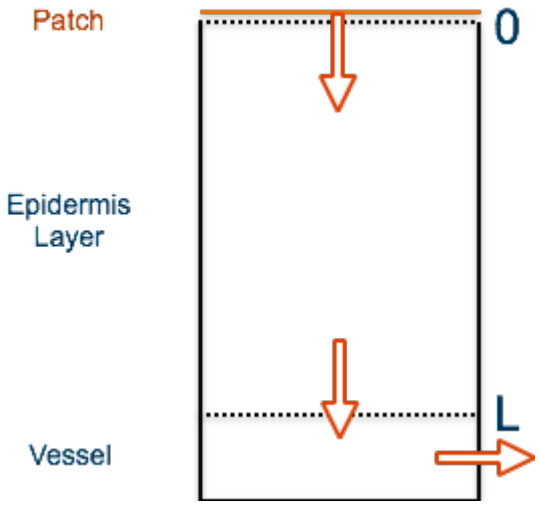


Figure 3: Chosen Problem Model

Our model of a transdermal hormonal contraceptive patch models the diffusion of chemicals through the skin layer. This problem was simplified as described below and solved both numerically and analytically.

Our problem was transformed into a partial differential equation which we solved analytically using the separation of variables method. Our simplifying assumptions are described below:

1. The skin was modeled as a homogeneous layer without variations due to hair follicles, sweat glands, and area-specific thickness affecting diffusivity. Variations due to changing pH and water content were also not considered.
2. The Ortho-evra patch is infinitely thin, allowing us to only consider the surface area of the patch.
3. We assumed that the patch was in perfect contact with the skin allowing for maximum diffusion of drug into the skin.
4. Blood flow in the capillaries was assumed to be very fast, allowing us to assume that drug concentration in the blood (at the maximum skin thickness point) was 0 at all time.
5. Patch concentration of the drug did not change over time and essentially constituted an infinite sink, allowing us to assume that there was zero flux at the patch-skin interface.

## Analytical solution using separation of variables:

Our system is modelled by the following general partial differential equation:

$$\frac{\partial C}{\partial t} = D\,\frac{\partial^2 C}{\partial x^2}$$

Where C(x,t) is the concentration of the drug throughout the skin layer, and is dependent on time t and displacement x. L is the distance from the surface of the skin where the patch is applied to the blood vessel underneath the skin layer. D is the constant of diffusivity.

Boundary conditions/initial conditions:

$$\frac{\partial C}{\partial x}|_{(x=0,t)} = 0; \quad C(x=L,t) = 0; \quad C(x,t=0) = C_0\delta(x)$$

Here we modelled a zero-flux boundary condition at the surface of the skin, meaning that the drug can only diffuse downward through the skin layer. We also assume that the concentration of the drug just below the skin layer is zero (the drug is fully absorbed into the bloodstream). Finally we modelled the initial application of the patch and subsequent release of the drug as an impulse at time t=0 multiplied by the initial drug concentration in the patch. As we have modelled the system using homogenous boundary conditions, we are now able to find an analytical solution using the method of Separation of Variables.

General equation for separation of variables:

$$C(x,t) = \varphi(x) * G(t)$$

Differentiating C(x,t) as required by PDE:

$$\varphi(x)\frac{\partial G(t)}{\partial t} = DG(t)\frac{\partial^2\varphi(x)}{\partial x^2}$$

Rearrange equations. Set equal to arbitrary constant, $\lambda$:

$$\frac{1}{DG}\frac{\partial G}{\partial t} = \frac{1}{\varphi}\frac{\partial^2\varphi}{\partial x^2} = -\lambda$$

Solve for G(t) and $\varphi$(x).

$$\frac{1}{DG}dG = -\lambda dt \qquad G(t) = G_0 e^{-D\lambda t}$$

$$\frac{\partial^2\varphi}{\partial x^2} + \lambda\varphi = 0 \qquad (y^2+\lambda) = \left(y + i\sqrt{\lambda}\right)\left(y - i\sqrt{\lambda}\right) = 0$$

$$\varphi(x) = c_1\cos\left(x\sqrt{\lambda}\right) + c_2\sin\left(x\sqrt{\lambda}\right)$$

Applying boundary conditions to general solution:

$$\left[c_1\cos\left(x\sqrt{\lambda}\right) + c_2\sin\left(x\sqrt{\lambda}\right)\right]G_0 e^{-D\lambda t} = C(x,t)$$

$$\frac{\partial C}{\partial x}|_{(x=0,t)} = 0 \qquad \left[-c_1\sqrt{\lambda}\sin\left(0*\sqrt{\lambda}\right) + c_2\sqrt{\lambda}\cos\left(0*\sqrt{\lambda}\right)\right]G_0 e^{-D\lambda t}$$

$$c_2 = 0$$

$$C(x=L,t) = 0 = c_1\cos\left(L\sqrt{\lambda}\right)G_0 e^{-D\lambda t}$$

$$c_1\cos\left(L\sqrt{\lambda}\right) = 0 \quad \lambda = \left(\frac{(2n+1)\pi}{2L}\right)^2, n = 0,1,2,3\ldots$$

Near-final solution:

$$C(x,t) = \sum_{n=0}^{\infty} C_n\cos\left(\frac{(2n+1)\pi x}{2L}\right)G_0 e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 t}$$

Representing solution using Fourier Series:

$$C_n = \frac{2}{L}\int_0^L C_0\delta(x)\cos\left(\frac{(2n+1)\pi x}{2L}\right)dx$$

Sampling around x=0 eliminates the cosine function:

$$C_n = 2 * C_0$$

Final Solution:

$$C(x,t) = \sum_{n=0}^{\infty} C_n \cos\left(\frac{(2n+1)\pi x}{2L}\right) G_0 e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 t}$$

### *Matlab Analytical solution*

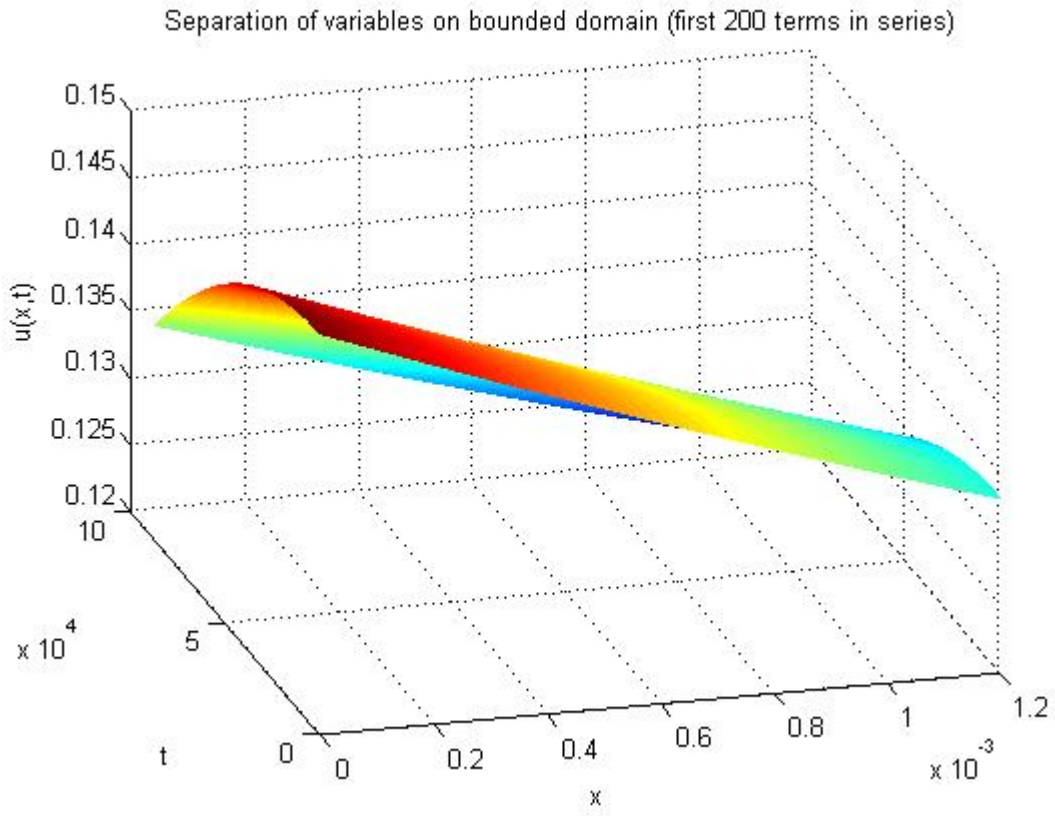


**Figure 4: Solution obtained through numerical solving of analytical solution**

## Numerical solution:

***Built-in Matlab pdepe solver***

In our model, the skin was modeled as a single layer with thickness x=L=1.2 mm. Diffusivity was constant throughout the skin and the microvessels absorbed 100% of the drug that diffused to them. The no-flux boundary condition at the surface, negligible concentration at the full skin thickness, and concentration impulse conditions are found above when solving the analytical solution. As expected, at the skin surface and all time, the concentration is constant at C0. Moving through the skin layer leads to a decrease in drug concentration through the skin.

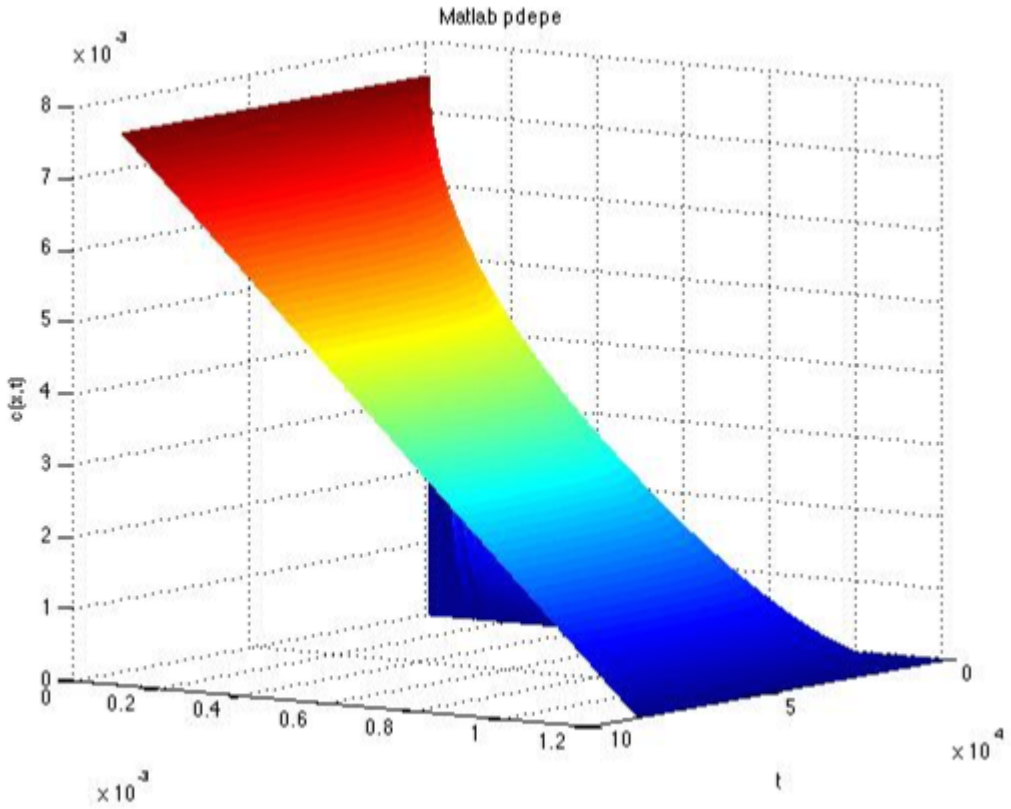


**Figure 5: MATLAB Built In Numerical Solver**

This numerical solution correlates fairly well with the generated analytical solution. The numerical solution is less linear in nature and seems to more accurately represent the diffusion activity through the skin.

Next we wanted to know how quickly the drug diffused into the skin, when a steady state appeared to be reached with our parameters, and what shape the graph was at various times. We analyzed these parameters at t=30 minutes, 4 hours, and 24 hours.

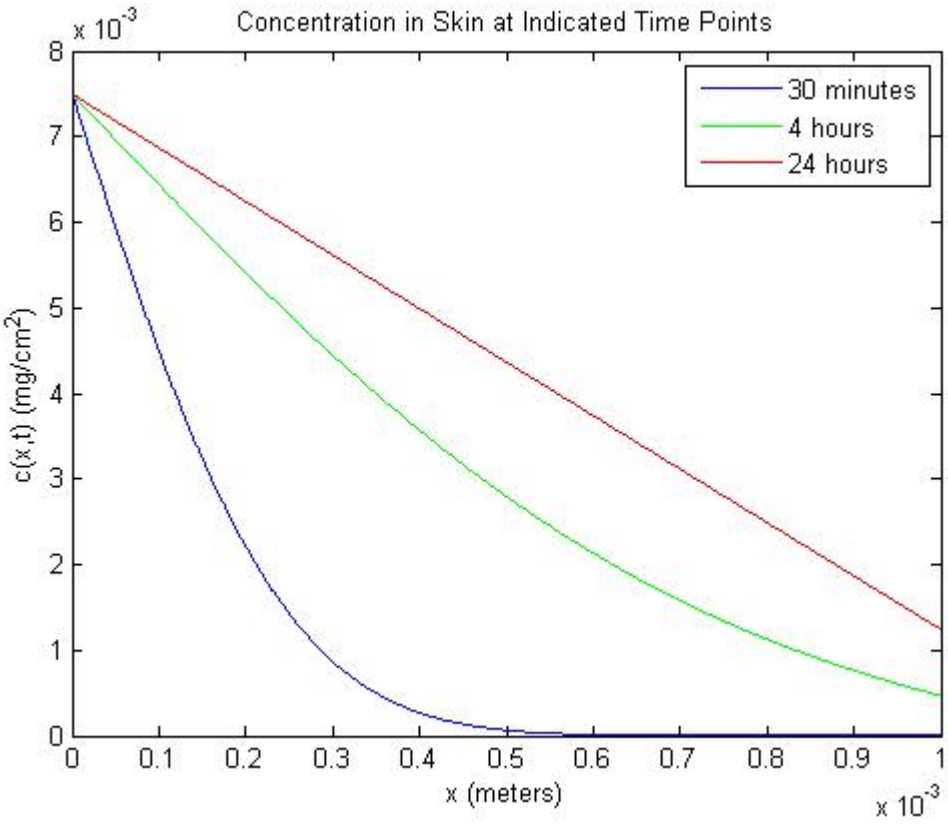


**Figure 6: Concentration Time Slices**

## Obesity Study [8]:

To test the overall effectiveness of the Ortho-Evra patch as an appropriate method of contraception, an initial trial study was done with approximately 3300 women. Of this total amount, the contraceptive was found to be ineffective in 15 cases, resulting in unwanted pregnancy. Within these 15 cases, 5 of the women were observed to weigh greater than 198 lbs. Due to the statistical significance of this observation, it was decided to further study the effectiveness of patch drug delivery as a function of varying subject weight.

Through this study it was determined that an increase of adipose (body fat) tissue let to a significant decrease in the diffusivity for the drug. This impedance to drug delivery was quite dramatic as the amount of body fat increased, and led to up to an 100 fold decrease in diffusivity at the most extreme. This significant drop in drug absorption made the Ortho-Evra patch a non-viable method of contraception for those women weighing in the obesity range.

The following plot is the result of our simplified emulation of the obesity study. From this plot it is easy to observe the drastic difference in drug concentration throughout the skin layer as a function of varying weight. Three diffusivity constants were taken from the obesity study in order to simulate varying levels of adipose tissue interference.

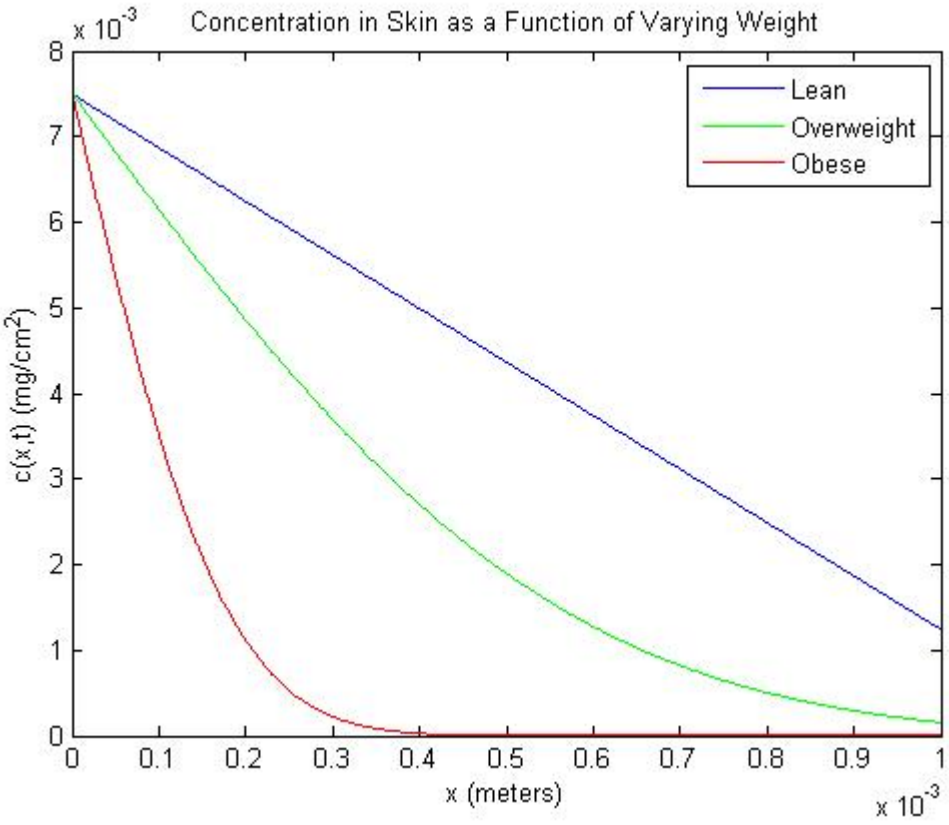


**Figure 7: Concentration Vs. Weight Study**

## Conclusions and Potential Improvements:

We were able to successfully model the 1-D diffusion of hormonal drug delivery through the skin layer. While this gave us a good indication of the general behavior of drug delivery, there are many improvements that could be made to our model. First, our model consisted of a simplified single slab skin model. It would be more accurate to measure the various layers of the skin and their respective impedances. We also modelled complete, instantaneous absorption of the drug into the blood stream once it reached the end of the skin layer. This could be made more accurate by taking into consideration the fact that the drug takes time to absorb, and may or may not be absorbed completely or uniformly over time. Finally, we chose to only model one of the drugs contained in the Ortho-Evra patch, as opposed to the simultaneous release of both drugs.

## Appendix :

### *Matlab code (Numerical Solution)*

```
function diffusion_pdeCG

close all
clear all
clc

%diffusion coefficient
global k1 k2 k3
k1 = 1.11*10^(-11); %estimated diffusion coefficient of lean epidermis
(cm^2/s)
k2 = 1.11*10^(-12); %estimated diffusion coefficient of overweight
epidermis (cm^2/s)
k3 = 1.11*10^(-13); %estimated diffusion coefficient of obese epidermis
(cm^2/s)

global L
L = .0012; %estimating thickness of skin to be 1.2mm

global Cd %initial concentration of drug in patch
Cd = .0075; %mg/cm^(2)

x = 0:.0000012:L; %x domain
t = 0:86.4:86400; %time domain
length(t);
length(x);

%Solution using MATLAB PDE Solver
sol_pdepe1 = pdepe(0,@pdefun1,@ic,@bc,x,t);
sol_pdepe2 = pdepe(0,@pdefun2,@ic,@bc,x,t);
sol_pdepe3 = pdepe(0,@pdefun3,@ic,@bc,x,t);

%3D solution mesh
figure(2)
mesh(x,t,sol_pdepe1')
title('Matlab pdepe')
xlabel('t')
ylabel('x')
zlabel('c(x,t)')

%Individual time slice for lean condition
figure(3)
snap1 = sol_pdepe1(20,:);
snap2 = sol_pdepe1(166,:);
snap3 = sol_pdepe1(1000,:);
plot(x,snap1,'b',x,snap2,'g',x,snap3,'r');
xlabel('x (meters)');
ylabel('c(x,t) (mg/cm^2)');
legend('30 minutes', '4 hours', '24 hours');
title('Concentration in Skin at Indicated Time Points')
xlim([ 0 0.001]);
```

```
%Same time for lean, overweight, and obese conditions
figure(4)
snap1 = sol_pdepe1(1000,:);
snap2 = sol_pdepe2(1000,:);
snap3 = sol_pdepe3(1000,:);
plot(x,snap1,'b',x,snap2,'g',x,snap3,'r');
xlabel('x (meters)');
ylabel('c(x,t) (mg/cm^2)');
legend('Lean', 'Overweight', 'Obese');
title('Concentration in Skin as a Function of Varying Weight')
xlim([ 0 0.001]);

% function definitions for pdepe:
% --------------------------------------------------------------
% Lean Condition
function [c, f, s] = pdefun1(x, t, u, DuDx)
% PDE coefficients functions

global k1
c = 1;
f = k1 * DuDx; % diffusion
s = 0; % homogeneous, no driving term

% --------------------------------------------------------------

% Overweight condition
function [c, f, s] = pdefun2(x, t, u, DuDx)
% PDE coefficients functions

global k2
c = 1;
f = k2 * DuDx; % diffusion
s = 0; % homogeneous, no driving term

% --------------------------------------------------------------

% Obese condition
function [c, f, s] = pdefun3(x, t, u, DuDx)
% PDE coefficients functions

global k3
c = 1;
f = k3 * DuDx; % diffusion
s = 0; % homogeneous, no driving term

% --------------------------------------------------------------

function u0 = ic(x)
% Initial conditions function
global Cd

u0 = Cd * (x==0); % delta impulse at center
```

```
% ---------------------------------------------------------------

function [pl, ql, pr, qr] = bc(xl, ul, xr, ur, t)
% Boundary conditions function
global Cd
pl = ul-Cd; % left boundary condition
ql = 0;  % no flux left boundary condition
pr = ur; % zero value right boundary condition
qr = 0;  % no flux right boundary condition
```

***Matlab code (Analytical Solution)***

```
function linanal(ns)
% Homogeneous PDE: Linear (1-D) Diffusion
% Analytical solutions on bounded and infinite domain
% BENG 221 example, 10/8/2013
%
% ns: number of terms in the infinite series
%
% e.g.:
% >> linanal(30);
%

% diffusion constant
global D
D = 1.11*10^(-11);

global L
L = .0012; %estimating thickness of skin to be 1.2mm

% domain
dx = 0.0000012; % step size in x dimension
dt = 86.4;  % step size in t dimension
xmesh = 0:dx:L; % domain in x; L/2 = 1
tmesh = 0:dt:86400;  % domain in t
nx = length(xmesh); % number of points in x dimension
nt = length(tmesh); % number of points in t dimension


% solution on bounded domain using separation of variables
sol_sep = zeros(nt, nx);
for n = 0:ns-1
    k = (2*n+1)*pi/2; % L = 2
    sol_sep = sol_sep + exp(-D*(k^2)*tmesh)' * cos(k*xmesh);
end

sol_sep = sol_sep.*.00075;

figure(1)
mesh(xmesh,tmesh,sol_sep')
title(['Separation of variables on bounded domain (first ',
num2str(ns), ' terms in series)'])
xlabel('x')
ylabel('t')
```

```
zlabel('u(x,t)')



% solution on infinite domain using Fourier
sol_inf = (4*pi*D*tmesh' * ones(1,nx)).^(-.5) .* exp(-(4*D*tmesh).^(-
1)' * xmesh.^2);

figure(2)
surf(xmesh,tmesh,sol_inf')
title('Gaussian solution on infinite domain')
xlabel('t')
ylabel('x')
zlabel('u(x,t)')
```

## References:


[1] Bergenstal, R. *et al.* Effectiveness of Sensor-Augmented Insulin-Pump Therapy in Type 1 Diabetes. *The New England Journal of Medicine*(2010). doi:10.1056/NEJMoa1002853

[2] Curtis, K., Tepper, N., Jamieson, D. & Marchbanks, P. Adaptation of the World Health Organization's Selected Practice Recommendations for Contraceptive Use for the United States. *Contraception* **87,** 513516 (2013).

[3] Current Contraceptive Use in the United States (2006-2010) and Changes in Patterns of Use since 1995, Jo Jones, William Mosher, Kimberly Daniels, Division of vital Statistics, Number 60 n October 18, 2012 (cdc.gov)

[4] Cea-Soriano, L., Rodríguez, L., Machlitt, A. & Wallander, M. Use of prescription contraceptive methods in the UK general population: a primary care study. *BJOG: An International Journal of Obstetrics & Gynaecology* **121,** 53–61 (2014).

[5] Department of Health and Human Services, Office on Women's Health. (2011). *Birth control methods fact sheet.* Retrieved June 4, 2012.

[6] MacNeil, S. Progress and opportunities for tissue-engineered skin. *Nature* **445,** 874–880 (2007).

[7] Current status and future potential of transdermal drug delivery. Prausnitz MR, Mitragori S, Langer R. Nat Rev Drug Discov. 2004 Feb;3(2):115-24.

[8] Kwiatkowski P., et al. Ortho Evra: How Effective is the Patch in Women of Varying Weight.