Scopolamine Delivery to the Skin Using a Transdermal Patch

BENG 221

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BACKGROUND

Scopolamine is drug used primarily for treating motion sickness and nausea through various administration methods including topical, oral, subcutaneous, ophthalmic and intravenous routes (1). However, one of the main issues with the drug is that it has a relatively short half-life and can have adverse effects on the body. When the transdermal route is used to deliver the drug, the adverse effects are minimized but the drug's effect is still maintained (2).

In this report, we will mainly focus on enhancing the transdermal delivery of the drug to the systemic blood flow through the use of permeation enhancers (3). To investigate the spread of the drug from the patch into the skin and surrounding tissue, the first part of our report uses a simple model that incorporates the diffusion and permeation coefficients of the skin and drug in order to mimic the delivery pathway of the drug. The model depicts the system as a two-compartment model taking into account the skin and patch as separate compartments linked by a common interface flux. In the second part of the report, we will investigate the delivery of the drug using a more complex three-compartment model where the skin is divided into the epidermis and dermis.

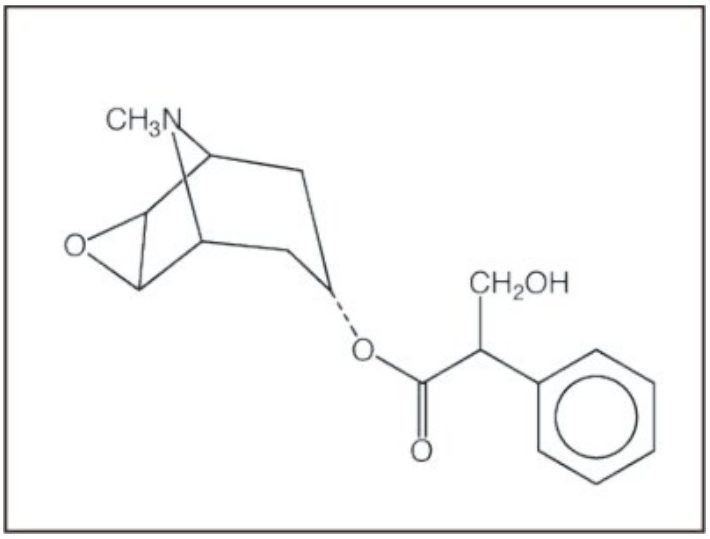


Figure 1. Structure of Scopolamine.

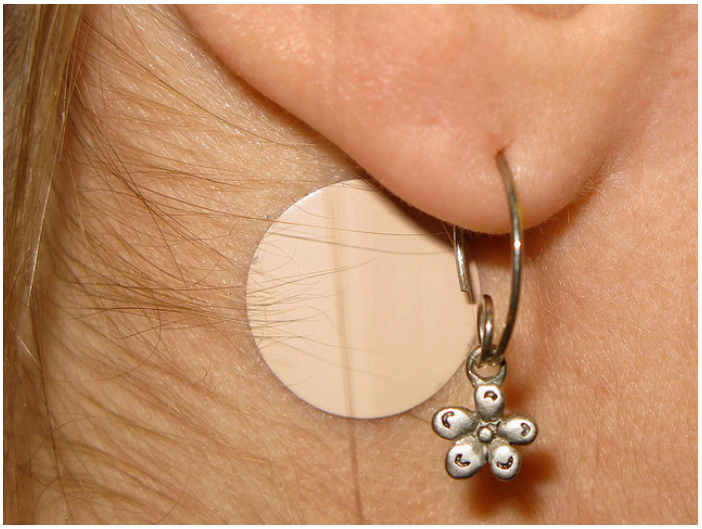


Figure 2. Scopolamine patch.

SIGNIFICANCE

The model of transdermal delivery of a drug through a multilayer skin model dependent on time and position of drug will allow us to find a delivery profile for a specific drug and fine tune the amount of drug delivered to the target site. Transdermal drug delivery is preferred over other delivery methods due to the fact that it is non-invasive and has relatively high patient compliance. It does not involve procedures that cause the patient pain, nor does it require frequent dosages that are frequently skipped by patients, thus negatively affecting the therapeutic effects of the drug. Knowing the concentration profile of the drug with respect to time will provide the information necessary to maintain therapeutic levels of drug in a patient.

PROBLEM STATEMENT

Scopolamine is a type of drug used to treat motion sickness and nausea. Recent studies have shown that permeation enhancers may improve overall drug delivery into the skin and surround tissues. To further investigate the effect of transdermal drug delivery method, clinicians and researchers decide to use transdermal patch to deliver scopolamine through the skin to the systemic blood flow. Model and determine the concentration profile of drug in the skin over time. Assume the patch has a uniform distribution of the drug over time.

PROBLEM SET-UP

Scopolamine delivery from the transdermal patch through the intervening skin layers and into the microvasculature underneath can be simplest modeled by Fick's 2nd Law of diffusion in one-dimensional Cartesian coordinates (Equation 1) (4). C is concentration of drug in the skin, t is time, x is position, and D is diffusivity.

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{1}$$

A simple schematic describing the system is shown in Figure 3. We consider the skin as one compartment. The drug diffuses freely from the patch to the skin in x-direction only over time. For simplicity, we will be only considering diffusion of drug through the skin ($0 \leq x \leq L$). The diffusivity of the skin is constant.

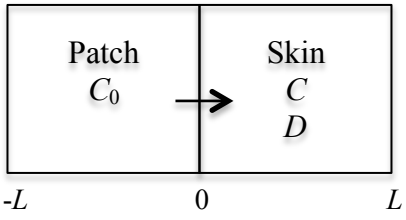


Figure 3. Simple schematic of the system in which the drug is diffusing from the patch to the skin.

Initially, the skin is free of drug, and the drug is uniformly distributed within the patch. A perfect sink condition is assumed because the drug diffusing through the skin is constantly carried away by blood circulation at $x = L$ (5). The initial condition here is $C(x, 0) = 0$, indicating that the drug concentration is zero in the skin at $t = 0$. Two boundary conditions are $C(0, t) = C_0$, assuming that the patch is a constant source of the drug over time, and $C(\mathrm{L}, t) = 0$, referring to the perfect sink condition.

ANALYTICAL SOLUTION

Differential Equation:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \quad (1)$$

Initial Condition:

$$C(x,0) = 0 \quad (2)$$

Boundary Conditions:

$$C(0,t) = C_0 \quad (3)$$

$$C(\mathrm{L},t) = 0 \quad (4)$$

The one-dimensional partial differential equation can be solved by separating into homogeneous and particular solutions.

$$C(x,t) = C_p(x,t) + C_h(x,t) \quad (5)$$

In this case, particular solution is the steady-state solution.

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} = 0 \quad (6)$$

$$\frac{\partial^2 C}{\partial x^2} = 0 \quad (7)$$

Integrate twice:

$$C_p(x,t) = A_p x + B_p \quad (8)$$

Apply boundary condition: $C(0, t) = C_0$*:*

$$C_p(0,t) = A_p(0) + B_p = C_0 \quad \rightarrow \quad B_p = C_0 \quad (9)$$

Apply boundary condition: $C(\mathrm{L}, t) = 0$*:*

$$C_p(L,t) = A_p(L) + C_0 = 0 \quad \rightarrow \quad A_p = -\frac{C_0}{L} \quad (10)$$

Substitute (9) & (10) into (8) to obtain particular solution:

$$C_p(x,t) = C_0 - \frac{C_0}{L}x \quad (11)$$

Homogeneous solution can be found by using separation of variables.

Let $C_h = \phi_h(x)G_h(t)$ (12)

Take derivative of C_h *with respect to t:*

$$\frac{\partial C_h}{\partial t} = \phi_h(x)\frac{dG_h}{dt} \tag{13}$$

Take second derivative of C_h with respect to x:

$$\frac{\partial^2 C_h}{\partial x^2} = G_h(t)\frac{d^2\phi_h}{dx^2} \tag{14}$$

Substitute (13) & (14) into (1):

$$\emptyset_h \frac{dG_h}{dt} = D\frac{d^2\phi_h}{dx^2}G_h \tag{15}$$

Equation (15) can be rearranged as:

$$\frac{1}{DG_h}\frac{dG_h}{dt} = \frac{1}{\emptyset_h}\frac{d^2\phi_h}{dx^2} \tag{16}$$

For two differential equations to be equal, both sides should be equal to the same constant:

$$\frac{1}{DG_h}\frac{dG_h}{dt} = \frac{1}{\emptyset_h}\frac{d^2\phi_h}{dx^2} = -\lambda \tag{17}$$

Equation (17) can be rewritten as a system of two ODEs:

$$\frac{1}{DG_h}\frac{dG_h}{dt} = -\lambda \tag{18}$$

$$\frac{1}{\emptyset_h}\frac{d^2\phi_h}{dx^2} = -\lambda \tag{19}$$

Solve for equation (18):

$$\frac{dG_h}{G_h} = -\lambda D dt \tag{20}$$

$$G_h(t) = G_0 e^{-\lambda D t} \tag{21}$$

Solving equation (19):

$$\frac{d^2\phi_h}{dx^2} + \lambda\phi_h = 0 \tag{22}$$

Characteristic equation of ODE is:

$$m^2 + \lambda = 0 \tag{23}$$

Solution to equation (23) where $\lambda>0$ is given as:

$$r = \pm i\sqrt{\lambda} \tag{24}$$

Thus, the form of the general solution to equation (22) is given as:

$$\phi_h(x) = b_1 \cos(\sqrt{\lambda}x) + b_2 \sin(\sqrt{\lambda}x) \tag{25}$$

General homogeneous solution of C(x, t) is given as:

$$\begin{aligned} C_h(x,t) &= \phi_h(x) G_h(t) \\ &= G_0 e^{-\lambda D t}\left[b_1 \cos(\sqrt{\lambda}x) + b_2 \sin(\sqrt{\lambda}x)\right] \\ &= e^{-\lambda D t}\left[A_n \cos(\sqrt{\lambda}x) + B_n \sin(\sqrt{\lambda}x)\right] \end{aligned} \tag{26}$$

To find the values of A_n and B_n, boundary conditions given will be applied. As stated before, the overall initial and boundary conditions for the system are the sum of the initial and boundary conditions for both homogeneous and particular solutions. Therefore, homogeneous boundary conditions will be found as below.

$$C(0,t) = C_h(0,t) + C_p(0,t) \tag{27}$$

$$C_h(0,t) = C(0,t) - C_p(0,t) = C_0 - C_0 = 0 \tag{28}$$

$$C(L,t) = C_h(L,t) + C_p(L,t) \tag{29}$$

$$C_h(L,t) = C(L,t) - C_p(L,t) = 0 - 0 = 0 \tag{30}$$

Apply boundary condition (28):

$$C_h(0,t) = e^{-\lambda D t}\left[A_n \cos(\sqrt{\lambda} \cdot 0) + B_n \sin(\sqrt{\lambda} \cdot 0)\right] = 0 \quad \rightarrow \quad A_n = 0 \tag{31}$$

Substitute equation (31) into (26):

$$C_h(x,t) = e^{-\lambda D t}\left[B_n \sin(\sqrt{\lambda}x)\right] \tag{32}$$

Apply boundary condition (30):

$$C_h(L,t) = e^{-\lambda D t}\left[B_n \sin(\sqrt{\lambda} \cdot L)\right] = 0$$

$$B_n \sin(\sqrt{\lambda} \cdot L) = 0 \tag{33}$$

For non-trivial solution, $B_n \neq 0$, so:

$$\sin(\sqrt{\lambda} \cdot L) = 0$$

$$\sqrt{\lambda} \cdot L = n\pi$$

$$\sqrt{\lambda} = \frac{n\pi}{L} \tag{34}$$

Substitute equation (34) into (32) to solve for homogeneous solution, $C_h(x,t)$:

$$C_h(x,t) = \sum_{n=0}^{\infty} B_n \sin\left(\frac{n\pi x}{L}\right) e^{-\left(\frac{n\pi}{L}\right)^2 D t} \tag{35}$$

Find homogeneous initial condition, $C_h(x,0)$:

$$C(x,0) = C_h(x,0) + C_p(x,0) \tag{36}$$

$$\begin{aligned} C_h(x,0) &= C(x,0) - C_p(x,0) \\ &= 0 - \left(C_0 - \frac{C_0}{L}x\right) \\ &= \frac{C_0}{L}x - C_0 \end{aligned} \tag{37}$$

Substitute initial condition (37) into equation (35):

$$C_h(x,0) = \sum_{n=0}^{\infty} B_n \sin\left(\frac{n\pi x}{L}\right) e^{-\left(\frac{n\pi}{L}\right)^2 D(0)} = \frac{C_0}{L}x - C_0$$

$$\sum_{n=0}^{\infty} B_n \sin\left(\frac{n\pi x}{L}\right) = \frac{C_0}{L}x - C_0 \tag{38}$$

Based on orthogonality of sines, $\int_0^L \sin\left(\frac{n\pi x}{L}\right)\sin\left(\frac{m\pi x}{L}\right)dx = \begin{cases} 0 \; when \; m \neq n \\ \frac{L}{2} \; when \; m = n \end{cases}$

So, when m = n, $B_m = \frac{2}{L}\int_0^L f(x)\sin\left(\frac{m\pi x}{L}\right)dx$*, where* $f(x) = \frac{C_0}{L}x - C_0$*:*

$$B_n = \frac{2}{L}\int_0^L C_0\left(\frac{x}{L} - 1\right)\sin\left(\frac{n\pi x}{L}\right)dx$$

$$B_n = \frac{2C_0}{L}\int_0^L \left[\frac{x}{L}\sin\left(\frac{n\pi x}{L}\right) - \sin\left(\frac{n\pi x}{L}\right)\right]dx$$

$$B_n = \frac{2C_0}{L}\left[-\frac{x}{n\pi}\cos\left(\frac{n\pi x}{L}\right) + \frac{L}{n^2\pi^2}\sin\left(\frac{n\pi x}{L}\right) + \frac{L}{n\pi}\cos\left(\frac{n\pi x}{L}\right)\right]_0^L$$

$$B_n = \frac{2C_0}{L}\left[-\frac{L}{n\pi}(-1)^n + \frac{L}{n\pi}(-1)^n - \frac{L}{n\pi}\right]$$

$$B_n = -\frac{2C_0}{n\pi} \tag{39}$$

Substitute equation (39) into (35) to get homogeneous solution:

$$C_h(x,t) = -\sum_{n=0}^{\infty} \frac{2C_0}{n\pi}\sin\left(\frac{n\pi x}{L}\right)e^{-\left(\frac{n\pi}{L}\right)^2 Dt} \tag{40}$$

Thus, the general solution, equation (5) will be found by adding particular solution, equation (11) and homogeneous solution, equation (40):

$$C(x,t) = C_p(x,t) + C_h(x,t)$$

$$C(x,t) = C_0 - \frac{C_0}{L}x - \sum_{n=0}^{\infty} \frac{2C_0}{n\pi}\sin\left(\frac{n\pi x}{L}\right)e^{-\left(\frac{n\pi}{L}\right)^2 Dt} \tag{41}$$

NUMERICAL ANALYSIS

I. Simple System: Analytical Solution

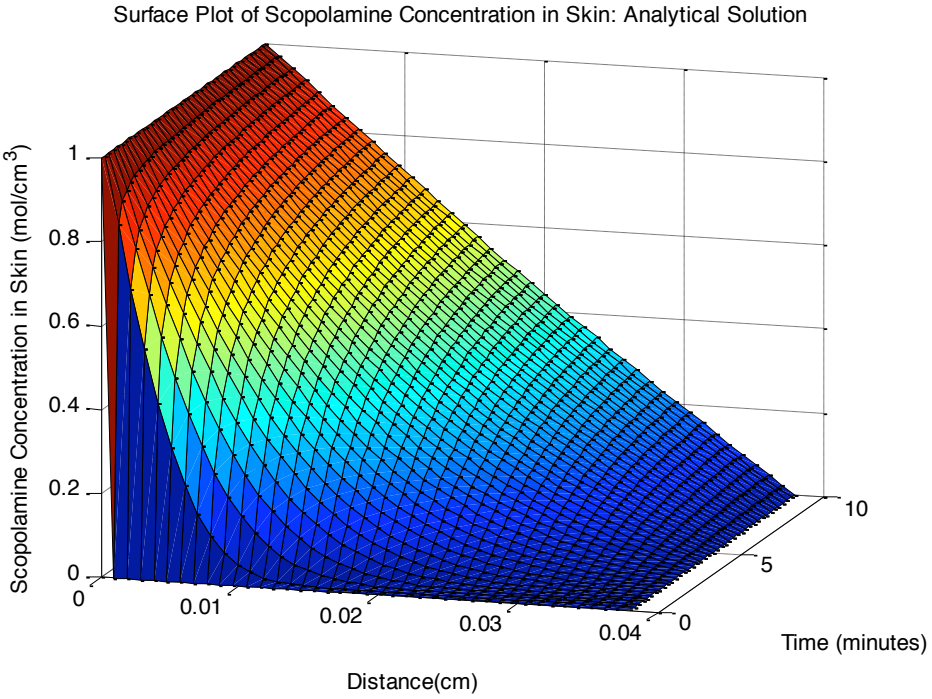


Figure 4. Surface plot of scopolamine concentration profile in skin based on analytical solution.

II. Simple System: PDEPE

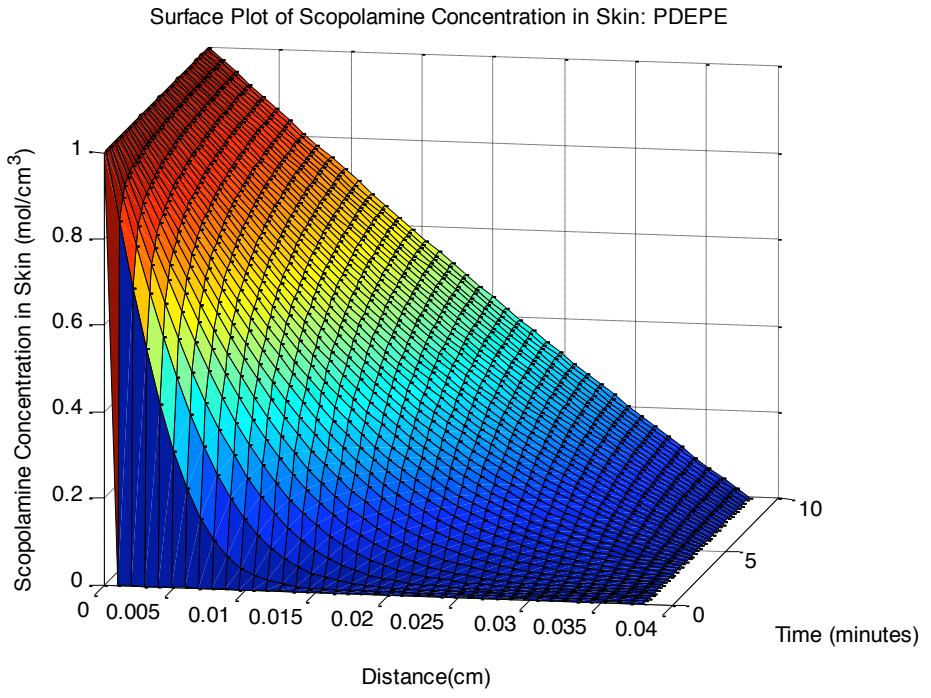
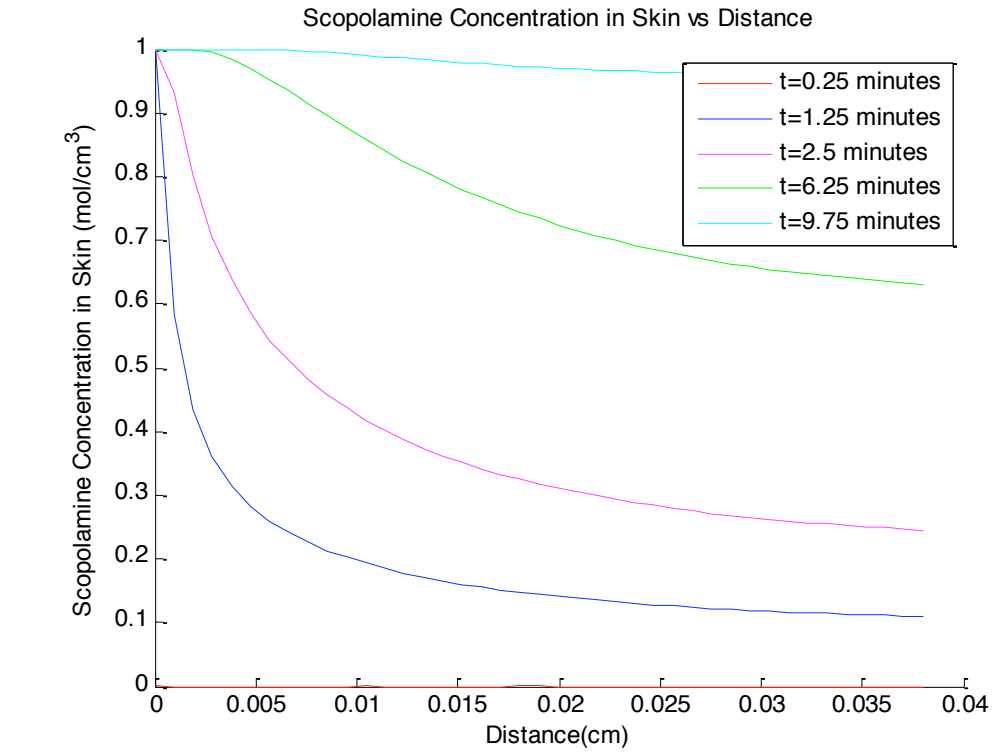
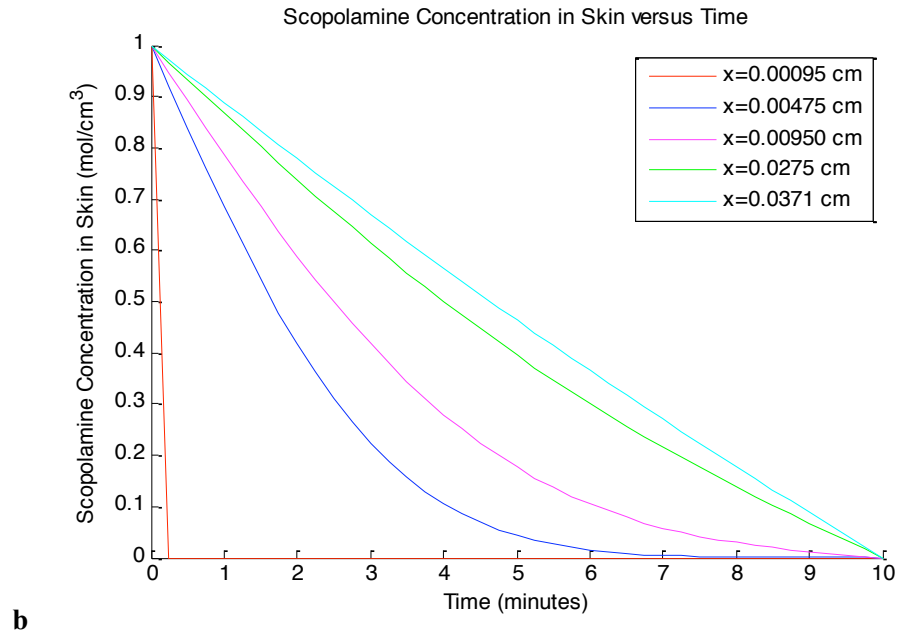


Figure 5. Surface plot of scopolamine concentration profile in skin using PDEPE.



a



b

Figure 6. Scopolamine concentration profile in skin in different (a) distances and (b) times.

In Figure 5, we can observe that the scopolamine concentration is maximal at $x = 0$, which is the interface between the patch and the skin. The concentration drops drastically to near zero around $x = 0.015$ cm. At different time points, the concentration of the drug varies in x-direction as shown in Figure 6(a). Figure 6(b) shows that at different positions in the skin, the concentration of scopolamine decreases over time.

II. More Complex System: Finite Element

We expanded the previous system to account for the patch and 2 different layers of skin as shown in Figure 7.

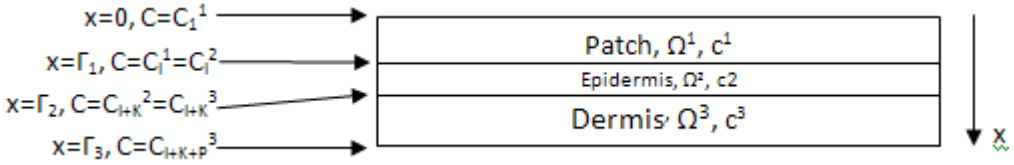


Figure 7. System diagram in which the drug is diffusing from the patch to the skin.

Our model now can be described by the following set of governing equations:

$\frac{\partial c^1}{\partial t} - D^1 \frac{\partial^2}{\partial x^2} c^1 = 0, \qquad 0 < x < \Gamma_1$

Within the patch, the drug diffuses out with diffusivity D^{A} and follows simple diffusion as described by Fick's second law.

$\frac{\partial c^2}{\partial t} - D^2 \frac{\partial^2}{\partial x^2} c^1 = 0, \qquad \Gamma_1 < x < \Gamma_2$

Within the epidermis, drug diffusion is also governed by Fick's second law with a diffusivity of D^{B1}.

$\frac{\partial c^3}{\partial t} - D^3 \frac{\partial^2}{\partial x^2} c^3 = -kc^3 \qquad \Gamma_2 < x < \Gamma_3$

Within the dermis, drug concentration changes due to both diffusion and perfusion into the circulatory system. Diffusion is again defined by Fick's law with constant D^{B2}, and the perfusion constant is $-k$.

Our model has the following initial and boundary conditions:

$$t = 0 \quad : \qquad C^1 = C_0, \qquad C^i = 0; \qquad i = 2,3$$

$$x = 0 \quad : \qquad \frac{\partial C^1}{\partial x} = 0, \qquad C_1^1 - C_2^1 = 0$$

$$x = \Gamma_1 : \begin{Bmatrix} D^1 \frac{\partial C^1}{\partial x} = D^2 \frac{\partial C^2}{\partial x} \\ C^1 = C^2 \end{Bmatrix}$$

$$x = \Gamma_2 : \qquad \begin{Bmatrix} D^2 \frac{\partial C^2}{\partial x} = D^3 \frac{\partial C^3}{\partial x} \\ C^2 = C^3 \end{Bmatrix}$$

$$x = \Gamma_3 \quad : \qquad C^3 = 0$$

We can assume that the concentration at the boundary between two compartments is equal since the concentration is continuous with position and time. The concentration of drug is 0 at the far boundary of the dermis because the drug is carried away by perfusion within the dermis layer.

The variables C, t, and x can be made dimensionless and expressed in the following forms:

$$\psi^i = \frac{C^i}{C_0}; \quad \tau = \frac{tD^1}{\Gamma_1^2}; \quad \xi = \frac{x}{\Gamma_1};$$

$$\frac{D^i}{D^1} = \beta^i, \quad \eta_k = \frac{\Gamma_k}{\Gamma_1}; \quad i = 1,2,3; \; k = 1,2,3$$

$$\alpha = \frac{k\Gamma_1^2}{D^1}$$

Inserting the above dimensionless variables into our governing equations gives the following set of dimensionless equations:

$$\frac{\partial \psi^1}{\partial \tau} = \frac{\partial^2 \psi^1}{\partial \xi^2} \qquad , \qquad 0 < \xi \le \eta_1 \qquad \eta_1 = 1$$

$$\frac{\partial \psi^2}{\partial \tau} = \beta^2 \frac{\partial^2 \psi^2}{\partial \xi^2} \qquad , \qquad \eta_1 < \xi \le \eta_2$$

$$\frac{\partial \psi^3}{\partial \tau} = \beta^3 \frac{\partial^2 \psi^3}{\partial \xi^2} - \alpha \psi^3 \qquad , \qquad \eta_2 < \xi \le \eta_3$$

The initial and boundary conditions in dimensionless form are expressed as:

$$\tau = 0 \; : \qquad \psi^1 = 1, \psi^2 = 0, \psi^3 = 0$$

$$\xi = 0 \; : \qquad \frac{\partial \psi^1}{\partial \xi} = 0$$

$$\xi = \eta_1 : \qquad \frac{\partial \psi^1}{\partial \xi} = \beta^2 \frac{\partial \psi^2}{\partial \xi} \; , \psi^1 = \psi^2$$

$$\xi = \eta_2 : \qquad \beta^2 \frac{\partial \psi^2}{\partial \xi} = \beta^3 \frac{\partial \psi^3}{\partial \xi} \; , \psi^2 = \psi^3$$

$$\xi = \eta_3 : \qquad \psi^3 = 0$$

The compartments fall under the following ranges of index values for concentration and their respective governing equations are as follows:

$$Patch: \psi_i \ : i = 2,3,4,...,x-2,\ x-1;$$

$$\frac{d\psi_i}{d\tau} = \frac{1}{\Delta\xi^2}\left(\psi_{i+1} - 2\psi_i + \psi_{i-1}\right)$$

$$Epidermis: \psi_i \ : i = x+1,\ x+2,...,\ x+y-2,\ x+y-1;$$

$$\frac{d\psi_i}{d\tau} = \frac{\beta^2}{\Delta\xi^2}\left(\psi_{i+1} - 2\psi_i + \psi_{i-1}\right)$$

$$Dermis: \psi_i \ : i = x+y+1,\ x+y+2,...,\ x+y+z-2,\ x+y+z-1;$$

$$\frac{d\psi_i}{d\tau} = \frac{\beta^3}{\Delta\xi^2}\left(\psi_{i+1} - 2\psi_i + \psi_{i-1}\right) - \alpha\psi_i$$

The above boundary conditions can be discretized in the following manner:

$$(\xi = 0)\ \ i = 1 : \psi_1 - \psi_2 = 0$$

$$(\xi = \eta_1) i = x : \psi_x^1 = \psi_x^2,\ \left(\psi_x^1 - \psi_{x-1}^1\right) = \beta^2\left(\psi_{x+1}^2 - \psi_x^2\right)$$

$$(\xi = \eta_2)\ i = x+y : \psi_{x+y}^2 = \psi_{x+y}^3,\quad \beta^2\left(\psi_{x+y}^2 - \psi_{x+y-1}^2\right) = \beta^3\left(\psi_{x+y+1}^3 - \psi_{x+y}^3\right)$$

$$(\xi = \eta_3)\ i = x+y+z : \psi_{x+y+z} = 0$$

These boundary conditions can be incorporated into the discretized governing equations to get the following distinctive equations:

Patch: $i = 2$

$$\psi_1 = \psi_2,\ \ \frac{d\psi_2}{d\tau} = \frac{1}{\Delta\xi^2}\left(\psi_3 - 2\psi_2 + \psi_1\right) \quad \Rightarrow \quad \frac{d\psi_2}{d\tau} = \frac{1}{\Delta\xi^2}\left(\psi_3 - \psi_2\right)$$

At the patch/epidermis interface:

$$\frac{d\psi_{x-1}}{d\tau} = \frac{1}{\Delta\xi^2}\left(\psi_{x-2} + \left(\frac{1}{1+\beta^2} - 2\right)\psi_{x-1} + \frac{\beta^2}{1+\beta^2}\psi_{x+1}\right)$$

$$\frac{d\psi_{x+1}}{d\tau} = \frac{1}{\Delta\xi^2}\left(\frac{1}{\left(1+\beta^2\right)}\psi_{x-1} + \left(\frac{\beta^2}{\left(1+\beta^2\right)} - 2\right)\psi_{x+1} + \psi_{x+2}\right)$$

At the epidermis/dermis interface:

$$\frac{d\psi_{x+y-1}}{d\tau} = \frac{\beta^2}{\Delta\xi^2}\left(\psi_{x+y-2} + \left(\frac{\beta^2}{\left(\beta^2+\beta^3\right)} - 2\right)\psi_{x+y-1} + \frac{\beta^3}{\beta^2+\beta^3}\psi_{x+y+1}\right)$$

$$\frac{d\psi_{x+y+1}}{d\tau} = \frac{\beta^2}{\Delta\xi^2}\left(\frac{\beta^2}{\left(\beta^2+\beta^3\right)}\psi_{x+y-1} + \left(\frac{\beta^3}{\left(\beta^2+\beta^3\right)} - 2\right)\psi_{x+y+1} + \psi_{x+y+2}\right)$$

At the dermis/hyperdermis interface:

$$\psi_{x+y+z} = 0, \qquad \frac{d\psi_{x+y+z-1}}{d\tau} = \frac{\beta^3}{\Delta\xi^2}\left(-2\psi_{x+y+z-1} + \psi_{x+y+z-2}\right) - \alpha\psi_{x+y+z-1}$$

We then renumbered the concentration variable so that:

$$\psi_2 : \psi_{x-1} = \phi_1 : \phi_k$$
$$\psi_{x+1} : \psi_{x+y-1} = \phi_{k+1} : \phi_l$$
$$\psi_{x+y+1} : \psi_{x+y+z-1} = \phi_{l+1} : \phi_m$$

The concentration across all three layers can be modeled by the following equation:

$$\frac{d\phi_j}{d\tau} = \bar{\bar{A}}\bar{x} + \bar{b}$$

$rows\, 1:k\ (j = 1:k)$

$$\frac{d\phi_j}{d\tau} = \frac{1}{\Delta\xi^2}\left[\begin{pmatrix} -2 & 1 & 0 & \text{L} & 0 & 0 \\ 1 & -2 & 1 & \text{O} & 0 & 0 \\ 0 & 1 & -2 & \text{O} & \text{M} & \text{M} \\ \text{M} & 0 & 1 & \text{O} & 1 & 0 \\ 0 & \text{M} & 0 & \text{O} & -2 & 1 \\ 0 & \text{L} & 0 & \text{O} & 1 & \dfrac{\beta^1}{\beta^1+\beta^2} - 2 \end{pmatrix} \begin{pmatrix} \phi_1 \\ \phi_2 \\ \text{M} \\ \text{M} \\ \phi_{k-1} \\ \phi_k \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ \text{M} \\ \text{M} \\ 0 \\ \dfrac{\beta^2}{\beta^1+\beta^2}\phi_{k+1} \end{pmatrix}\right]$$

$rows\, k+1:l\ (j = k+1:l)$

$$\frac{d\phi_j}{d\tau} = \frac{\beta^2}{\Delta\xi^2}\left[\begin{pmatrix} \dfrac{\beta^2}{\left(\beta^1+\beta^2\right)} - 2 & 1 & 0 & \text{L} & 0 & 0 \\ 1 & -2 & 1 & \text{O} & 0 & 0 \\ 0 & 1 & -2 & \text{O} & 0 & 0 \\ \text{M} & 0 & 1 & \text{O} & 1 & 0 \\ 0 & 0 & 0 & \text{O} & -2 & 1 \\ 0 & \text{L} & 0 & \text{O} & 1 & \dfrac{\beta^2}{\left(\beta^2+\beta^3\right)} - 2 \end{pmatrix} \begin{pmatrix} \phi_{k+1} \\ \phi_{k+2} \\ \text{M} \\ \text{M} \\ \phi_{l-1} \\ \phi_l \end{pmatrix} + \begin{pmatrix} \dfrac{\beta^1}{\left(\beta^1+\beta^2\right)}\phi_k \\ 0 \\ \text{M} \\ \text{M} \\ 0 \\ \dfrac{\beta^3}{\beta^2+\beta^3}\phi_{l+1} \end{pmatrix}\right]$$

$rows\, l+1:m\ (j = l+1:m)$

$$\frac{d\phi_j}{d\tau} = \frac{\beta^3}{\Delta\xi^2}\left[\begin{pmatrix} \dfrac{\beta^3}{\left(\beta^2+\beta^3\right)} - 2 - \dfrac{\Delta\xi^2\alpha}{\beta^3} & 1 & 0 & \cdots & 0 & 0 \\ 1 & -2 - \dfrac{\Delta\xi^2\alpha}{\beta^3} & 1 & \ddots & 0 & 0 \\ 0 & 1 & -2 - \dfrac{\Delta\xi^2\alpha}{\beta^3} & \ddots & 0 & 0 \\ \vdots & 0 & 1 & \ddots & 1 & 0 \\ 0 & 0 & 0 & \ddots & -2 - \dfrac{\Delta\xi^2\alpha}{\beta^3} & 1 \\ 0 & \cdots & 0 & \ddots & 1 & -2 - \dfrac{\Delta\xi^2\alpha}{\beta^3} \end{pmatrix} \begin{pmatrix} \phi_{l+1} \\ \phi_{l+2} \\ \vdots \\ \vdots \\ \phi_{m-1} \\ \phi_m \end{pmatrix} + \begin{pmatrix} \dfrac{\beta^2}{\left(\beta^2+\beta^3\right)}\phi_l \\ 0 \\ \vdots \\ \vdots \\ 0 \\ 0 \end{pmatrix}\right]$$

The following parameter values were chosen:

Dimensional	Dimensionless
$\Delta x = 3.75 * 10^{-4} cm$	$\Delta \xi = 0.005$
$D^A = 2 * 10^{-7} \frac{cm^2}{\sec}$	$\beta^1 = 1$
$D^{B1} = 3 * 10^{-10} \frac{cm^2}{\sec}$	$\beta^2 = 0.0015$
$D^{B2} = 5 * 10^{-10} \frac{cm^2}{\sec}$	$\beta^3 = 0.0025$
$k = 4 * 10^{-10} \frac{1}{\sec}$	$\alpha = 1.125 * 10^{-5}$
$\Gamma_1 = 0.075 cm$	$\eta_1 = 1$
$\Gamma_2 = 0.09 cm$	$\eta_2 = 1.2$
$\Gamma_3 = 0.12 cm$	$\eta_3 = 1.6$
	$x = 201$
	$y = 40$
	$z = 80$
	$k = 199$
	$l = 239$
	$m = 318$

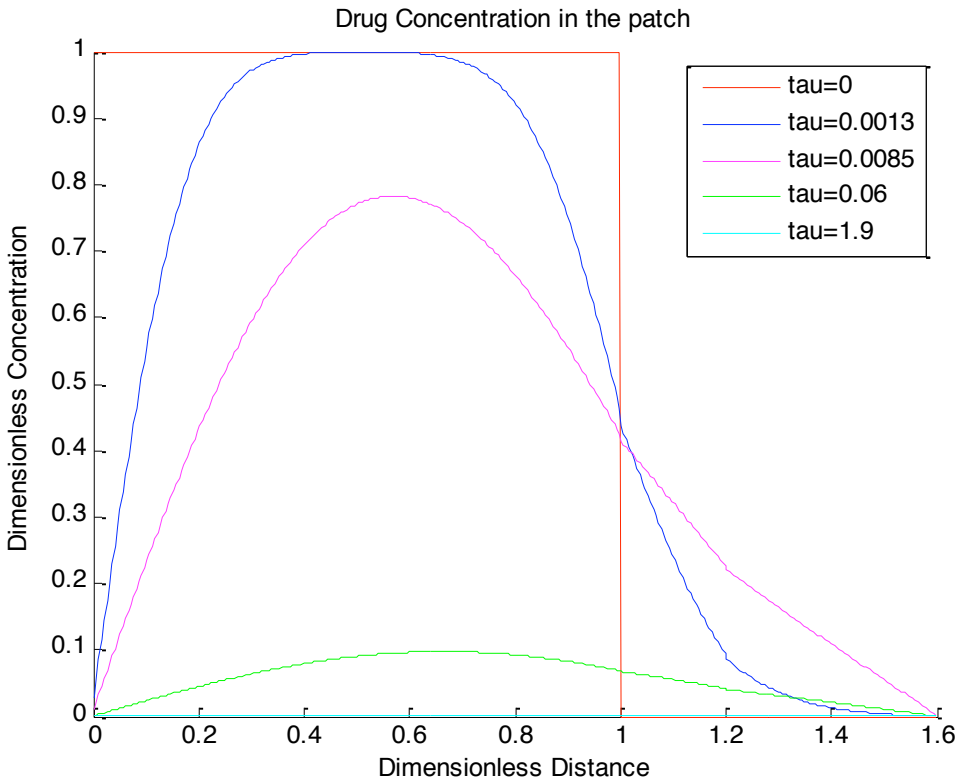


Figure 8. Scopolamine concentration profile in skin for a more complex system. The time points for the various taus correspond to: 0, 1 minute, 8 minutes, 50 minutes and 24 hours.

CONCLUSION

This report focused on two main components of modeling the delivery of scopolamine from a transdermal patch. In the first part of the report, a simple two-compartment model consisting of the patch and skin was established to study the concentration profile inside the skin. Several key assumptions were made in order to simplify our analytical solution. Based on the plots obtained, it appears that our analytical (Figure 4) and numerical (Figure 5) solutions correspond. The surface plots demonstrate expected results as the initial concentration at the boundary between the patch and the skin at $x = 0$ should be C_0, the uniform concentration of the patch based on our assumptions. Furthermore, as the concentration reaches the boundary of the skin that would be exposed to the body's vasculature, the concentration of the drug becomes zero as it is carried away by the blood. Lastly, the surface plots also indicate that the scopolamine concentration profile in the skin is depleted with time. This is expected because the concentration inside the skin would decrease with time as the drug is carried away by the microvasculature.

A similar pattern is observed in Figure 6(a), which shows the concentration profiles inside the skin at various times. The most gradual profiles appear to be at $t = 1.25$ and $t = 2.5$ minutes. In terms of practical applications, the desired profile would likely be around 2.5 minutes, where the concentration is slowly depleted by doesn't reach zero anywhere in the skin. Figure 6(b) shows how the concentrations change with respect to time at various locations in the skin. The results are expected as the skin moves the fastest away from the boundary of the patch and skin and toward the rest of the skin and hence, one would expect to observe a faster drop in the concentration profile. This pattern continues and at the boundary of the skin in contact with the vasculature, the concentration of the drug with respect to time is virtually linear because the drug is carried away from the right boundary of the skin quickly and, consequently, the

concentration is uniformly decreasing.

For the second part of our report, we investigated a slightly more complex 3-compartment model, which involved splitting the skin into the epidermis and dermis. We studied the concentration of the drug in the patch and how it changed with distance along the patch at various time points. This more complex model has a similar time scale for the release of scopolamine as we observed in the simple model, on the order of minutes. For practical applications, it seems as though the ideal release profile would correspond to $\tau = 0.0085$ (8 minutes) because the profile is rather uniform within the patch as compared to the other τ values. The graph shown in Figure 8 is slightly misleading in that it shows there is some leakage occurring from the patch as not all the plots start from the same point (dimensionless concentration 1) while our model does not account for that leakage. This could be a potential issue to investigate in our future work.

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APPENDIX

I. MATLAB Codes for Numerical Analysis of Simple System: Analytical & PDEPE

```
function SkinPatch

    %Declare variables
    global L C0 D;
    L = 0.038;%cm
    simulation_time = 10; %minutes
    D=4.4*10^-5;%cm^2/min
    C0=1; %1 mol/cm^3

    %Plotting Analytical Solution
    Cn = @(n) (-2*C0)/(n*pi);
    u=@(x,t,n) ((sin(n*pi*x./L).*exp(-1.*D.*((n.*pi/L)^2).*t)));

    %Defining time steps
```

```
    delta_x = 0.00095;
    delta_t = 0.25;
    x=0:delta_x:L;
    t=0:delta_t:simulation_time;
    [x, t] = meshgrid(0:delta_x:L, 0:delta_t:simulation_time);
    u_analytical = 0*x;

   for i=0:35
     u_analytical = u_analytical + u(x,t,i+1)*Cn(i+1);
 end
 figure(1)
 surf(x, t, u_analytical+C0-(C0/L).*x);
 xlabel('Distance(cm)');
ylabel('Time (minutes)');
zlabel('Oxygen Concentration (mol/cm^3)');
title('Surface Plot of Scopolamine Concentration in Skin: Analytical
Solution');
AXIS([0 0.04 0 10  0 1])
x_a = 0:delta_x:L;
 t_a = 0:delta_t:simulation_time;

%% pdepe part
%solving pde
x = 0:delta_x:L;
t = 0:delta_t:simulation_time;
sol = pdepe(0,@pdefunc, @icfunc, @bcfunc, x, t);
u_pdepe = sol(:, :, 1);
x_pdepe = x;
t_pdepe = t;
%Creating surface plot of numerical solution
figure(2)
surf(x, t, u_pdepe);
xlabel('Distance(cm)');
ylabel('Time (minutes)');
zlabel('Scopolamine Concentration in Skin (mol/cm^3)');
title('Surface Plot of Scopolamine Concentration in Skin: PDEPE');
x_pdepe = x;
t_pdepe = t;

%Creating plot of numerical solution versus distance at various times
figure(3)
hold on;
plot(x,C0-u_pdepe(:,1,:),'r');
plot(x,C0-u_pdepe(:,5,:),'b');
plot(x,C0-u_pdepe(:,10,:),'m');
plot(x,C0-u_pdepe(:,25,:),'g');
plot(x,C0-u_pdepe(:,39,:),'c');
hold off;
xlabel('Distance(cm)');
ylabel('Scopolamine Concentration in Skin (mol/cm^3)');
title('Scopolamine Concentration in Skin vs Distance');
```

```
legend('t=0.25 minutes','t=1.25 minutes','t=2.5 minutes','t=6.25
minutes','t=9.75 minutes');
x_pdepe = x;
t_pdepe = t;

%Creating plot of numerical solution versus time
figure(4)
hold on;
plot(t,u_pdepe(1,:),'r');
plot(t,u_pdepe(5,:),'b');
plot(t,u_pdepe(10,:),'m');
plot(t,u_pdepe(25,:),'g');
plot(t,u_pdepe(39,:),'c');
hold off;
xlabel('Time (minutes)');
ylabel('Scopolamine Concentration in Skin (mol/cm^3)');
title('Scopolamine Concentration in Skin versus Time');
legend('x=0.00095 cm','x=0.00475 cm','x=0.00950 cm','x=0.0275
cm','x=0.0371 cm');
x_pdepe = x;
t_pdepe = t;
end

 %%pdepe functions
    function [c,f,s] =pdefunc(x, t, u, ux)
        global D G;
        c = 1;
        f = D*ux;
        s = 0;
    end

 %Initial conditions
   function u =icfunc(x)
        global C0;
     u = 0;
   end

    %boundary conditions
   function [pl, ql, pr, qr] =bcfunc(xl, ul, xr, ur, t)
global C0;
pl = ul-C0;
ql = 0;
pr = ur;
qr = 0;
   end
```

II. MATLAB Codes for Numerical Analysis of More Complex System: Finite Element

```
function [T,S]=skin
clc;clear all;close all;
```

```
k=199;% Defines the number for the patch layer
l=40;% Defines the number for the epidermis layer
m=79;% Defines the number for the dermis layer

%Unitless layer thicknesses
g1=1;
g2=1.2;
g3=1.6;

delr=(g3-g1)/(k+l+m);%Defines step size for patch and 2 skin layers
%Position vectors for 3 layers
r1=linspace(delr/2,g1-delr/2,k);
r2=linspace(g1+delr/2,g2-delr/2,l);
r3=linspace(g2+delr/2,g3-delr/2,m);

r=[r1 r2 r3];%length of patch plus skin layers

tspan=linspace(0,10,600);
y0=zeros(length(r),1);
y0(1:length(r1))=1;

[T,Y] = ode15s(@odeskin,[0 2],y0);

% plot concentration in the device vs time
figure;
hold on;
plot(r,Y(1,:),'r');
plot(r,Y(100,:),'b');
plot(r,Y(120,:),'m');
plot(r,Y(140,:),'g');
plot(r,Y(192,:),'c');
hold off;
title('Drug Concentration in the Patch');
xlabel('Dimensionless Distance');
ylabel('Dimensionless Concentration');
legend('tau=0','tau=0.0013','tau=0.0085','tau=0.06','tau=1.9');

function [yprime]=odeskin(t,y)
%yprime are col vectors with the concentration of drug in the
%patch first followed by the discretized radial positions through the
%patch and skin layers.

k=199;% Defines the number for the patch layer
l=40;% Defines the number for the epidermis layer
m=79;% Defines the number for the dermis layer

%Unitless layer thicknesses
g1=1;
g2=1.2;
g3=1.6;
```

```
delr=(g3-g1)/(k+l+m);%Defines step size for the patch and 2 skin
layers
%constants
D_a=2*10^-10;%cm2/sec as obtained from the paper Chandrasekaran et al.
k1=4*10^-10; %perfusion constant in cm3/sec from the paper
Percutaneous drug penetration: Choosing candidates for transdermal
development
D_b1=3*10^-10;%cm2/sec as obtained from the paper Chandrasekaran et
al.
D_b2=5*10^-10;%cm2/sec as obtained from the paper Chandrasekaran et
al.

%Dimensionless constants
beta_B1=(D_a)/(D_a);
beta_B2=(D_b1)/(D_a);
beta_B3=(D_b2)/(D_a);
alpha=(k1*(g1)^2)/(D_a);

% Create Coefficient Matrix
A=zeros(k+l+m,k+l+m);

% Within the Patch:
A(1,1)=-2/delr^2;
A(1,2)=1/delr^2;
for n=2:k-1
    A(n,n)=-2/delr^2;
    A(n,n-1)=1/delr^2;
    A(n,n+1)=1/delr^2;
end
A(k,k-1)=1/delr^2;
A(k,k)=(beta_B1/(beta_B1+beta_B2)-2)/delr^2;
A(k,k+1)=beta_B2/(beta_B1+beta_B2)/delr^2;

%Within the Epidermis:
A(k+1,k)=beta_B1/(beta_B1+beta_B2)*(beta_B2/delr^2);
A(k+1,k+1)=(beta_B2/(beta_B1+beta_B2)-2)*(beta_B2/delr^2);
A(k+1,k+2)=1*(beta_B2/delr^2);
for n=k+2:k+l-1
    A(n,n)=-2*(beta_B2/delr^2);
    A(n,n-1)=1*(beta_B2/delr^2);
    A(n,n+1)=1*(beta_B2/delr^2);
end
A(k+l,k+l-1)=1*(beta_B2/delr^2);
A(k+l,k+l)=(beta_B2/(beta_B2+beta_B3)-2)*(beta_B2/delr^2);
A(k+l,k+l+1)=beta_B3/(beta_B2+beta_B3)*(beta_B2/delr^2);

%Within the Dermis:
A(k+l+1,k+l)=beta_B2/(beta_B3+beta_B2)*(beta_B3/delr^2);
A(k+l+1,k+l+1)=(beta_B3/(beta_B2+beta_B3)-2-
((delr^2)*alpha/beta_B3))*(beta_B3/delr^2);
A(k+l+1,k+l+2)=1*(beta_B3/delr^2);
```

```
for n=k+l+2:k+l+m-1
    A(n,n)=(-2-((delr^2)*alpha/beta_B3))*(beta_B3/delr^2);
    A(n,n-1)=1*(beta_B3/delr^2);
    A(n,n+1)=1*(beta_B3/delr^2);
end
A(k+l+m,k+l+m-1)=1*(beta_B3/delr^2);
A(k+l+m,k+l+m)=(-2-((delr^2)*alpha/beta_B3))*(beta_B3/delr^2);

yprime=A*y
```