DOI: 10.56511/JIPBS.2017.v4.i04.pp170-175

Journal of Innovations in Pharmaceutical and Biological Sciences (JIPBS)
ISSN: 2349-2759
Available online at www.jipbs.com

Research article

Drug distribution in sample of five layers of human skin

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Key words: Drug delivery through reservoir, Time dependent diffusion and finite element method.

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Abstract

The transdermal drug delivery is the delivery of drugs by using dermal layers. In medical sciences, it is an alternative to injections and oral drug delivery system. In this paper a mathematical model has been constructed to study the drugs concentration in the different layers of the skin through transdermal drug delivery system. The finite element method with linear shape functions has been used to obtain the solution of governing one-dimensional partial differential equation for unsteady state case. It is assumed that the drug is administered internally through reservoir. The dermal region under consideration is divided into five layers for the analysis.

Introduction

The suitable administration route for strong and low molecular weight drugs is transdermal drug delivery. It is an substitute to tablets and injections. This delivery system is mainly concerned with the delivery device and anatomy of dermal region, which consists of uppermost stratum corneum and underlying layers of stratum germinativum, dermis and subcutaneous tissue [1]. The transdermal drug delivery (TDD) is in suitable format is supplied externally either through a reservoir in contact with the outermost layer or through periodic application. The drug and the delivery system are designed in such a way that the drug reaches the targeted area in prescribed concentration.

Many researchers have studied drug absorption by two methods i.e. experimental and theoretical methods. These methods are considered for drug transport generally through the transdermal device and the skin. This type of transport of drug follows the Fick's law of diffusion by means of a simple homogeneous membrane. Kalia and Guy [2] have developed mathematical models based on the solution of Fick's Second law. These models described the drug release from various drug delivery systems and formulations. These models were based on only the different ways of drug transport and analytical solutions were found for the drug concentration that released from the transdermal device. They considered the dermal regions as boundary conditions only. "References [3, 4] were the first those have established the mathematical drug transport model for one-dimensional and single component drug penetration. The solutions were obtained by using finite difference methods. They have also considered the two pathways i.e. intercellular and transcellular for drug penetration in the skin. In these models the skin was divided into two sub layers as stratum corneum and epidermal layers. The drug diffusion model with partition of compounds in biological tissue was solved by Missel [5] by using finite element method. Chandrasekaren, Micharls, Compbell and J.E. Show [6] have examined the tendency of skin during the drug permeation process. They obtained the solution of transdermal diffusion of scopolamine for single component. A notable research work in the direction of heat distribution in human dermal region had carried out by Saxena and their co-researchers [7-9]. The finite element method has been used in most of the cases to study the distribution of temperature in the different layers of the skin. Gurung [10] studied the time dependent temperature distribution in human skin. The cold effect in human dermal layers is studied by Khandy and Saxena [11]. Using the same approach Khandy [12] computed the drug absorption at the nodal points of three dermal layers by taking the absorption as a function of field concentration. Sharma and Saxena [13-15] have established the drug distribution models in transdermal drug delivery systems by making use of FEM with different shape functions in epidermis, dermis and subcutaneous tissues. Also, they have studied the transdermal drug flow in radial and angular directions of human limbs.

In fact, the transport process of drugs in transdermal drug delivery systems involves the multi layers of the skin. In these systems the drug present in reservoir at outermost layer stratum cornenum, reaches to targeted region via different layers of the skin. Following the above approaches, this paper develops a five layered drug delivery model with the application of one dimensional

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variational finite element method to account for effect of the interfacial kinetics on the drug delivery process. This model is based on the diffusion for transport across a homogeneous medium. The present model involves the change in material properties, initial conditions and boundary conditions in only one dimension. There is no 'first pass metabolism' effect occurs in TDD therefore we ignore the presence of metabolic reactions in the skin.

Experimental

Material and Method

The transport of drugs in the skin is governed by the following differential equation taken by Crank [16]

$$\frac{\partial}{\partial x}\left(D\frac{\partial C}{\partial x}\right)-T-B=\frac{\partial C}{\partial t} \quad (1)$$

where D, C and t denote the diffusivity, concentration of drug and time respectively. Also, T represents absorption rate of drug by tissues, B is the drug intake rate by blood, both are different in each layer, and x is the space variable denoting depth below the skin surface.

The model under consideration, involves layers of the skin Figure 1 viz, stratum corneum, stratum germinativum, papillary, reticular and subcutaneous region with outer and internal boundaries equal to a_0 and a_5. It is also supposed that the applied drug has partitioned the uppermost layer stratum corneum and entered into the epidermis. The drug concentration is defined as a function of one space variable x and varies linearly in each layer.

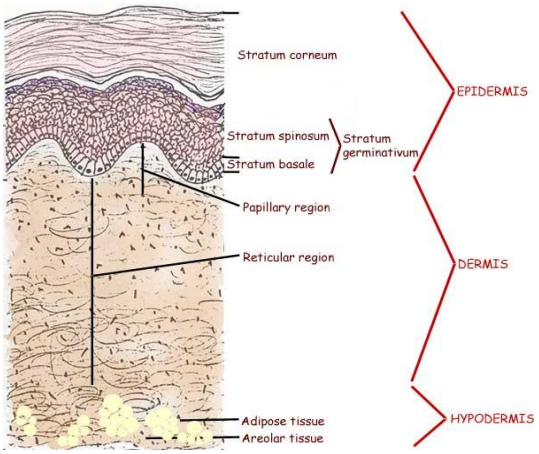


Figure. 1 General structure of the skin microscopic cross section) [17].

The concentration of drug varies linearly in each layer and is defined as a function of one space variable x. The parameters like diffusivity and absorption coefficients are assigned constant but different values in respective layers. The physiological barriers to the drug distribution at the interfaces are also considered. This partitioning of region and assignment of values to various quantities are based on the biological properties and on the geometrical details of the different skin layers.

In each layer field drug concentration $C^{(i)}$ $(i=1,2,3,4,5)$ is approximated by a linear shape function in x-direction only as

$$C^{(i)}=\alpha_i+\beta_i x \quad (2)$$

where the α_i and β_i co-efficient can be written as are given in terms of nodal concentration $C_i, (i=1, 2, 3, 4)$ as follows :

$$\begin{bmatrix}1 & a_0\\ 1 & a_1\end{bmatrix}\begin{bmatrix}\alpha_1\\ \beta_1\end{bmatrix}=\begin{bmatrix}C_0\\ C_1\end{bmatrix} \quad (3)$$

$$\begin{bmatrix}1 & a_{i-1}\\ 1 & a_i\end{bmatrix}\begin{bmatrix}\alpha_i\\ \beta_i\end{bmatrix}=\begin{bmatrix}C_{i-1}/\rho_{i-1}\\ C_i\end{bmatrix}, (i=2,3,4,5) \quad (4)$$

The drug concentration at the outer surface is known as C_0 and it is considered as the periodic function

$$C_0=\lambda(1+\sin\mu\pi t) \quad (5)$$

with initial conditions :

$$C_0(a_0, 0)=\lambda \quad (6)$$

$$C_i(a_i, 0)=0, \quad (i=1, 2, 3, 4, 5) \quad (7)$$

where all $C_i=(i=0, 1, 2, 3, 4)$ are the nodal concentrations. "Equation" (5) indicates the periodic administration of the drug at the skin surface. Also, λ and μ are known as control parameters which determine the periodicity and quantity of drug applied. "Equation (6)" and "(7)" show that initially the drug is in the reservoir, which is situated at the outer surface. At the innermost boundary the concentration

$$C_5=0$$

(8)

It is assumed that the applied drug is targeted to dermis only and it has negligible concentration beyond the subcutaneous region. This effect can be shown by "(8)". The concentration distributions $C^{(i)}, (i=1, 2, 3, 4, 5)$ are more or less matching at the interfaces due to mild barriers. However, the flux is generally incessant in many cases. For this reason, we have

$$C^{(i)}=\rho_i C^{(i+1)} \text{ at } x=a_i, \quad (i=1,2,3,4) \quad (9)$$

where ρ_i's are the skin partition coefficients for the drug at the respective interfaces. In most cases values of ρ_i $(i=1,2,3,4)$ are close to 1.

Solution

Many researchers solved such type of problem. The boundary value problem for various situations is solved by numerical methods because of non-availability of exact and analytical solutions. The finite element method is one of the most dependable methods in numerical

analysis. The usefulness of the method just because of its position dependent properties of parameters and their flexibility. As the problem involves irregular geometries, the method is suitable to understand the feasible diffusion. The variational integral

$$I = \int F(C, C', x)\, dx \tag{10}$$

in optimum form is equivalent to Euler-Lagrange differential equation given by Myer [18]

$$\frac{\partial F}{\partial C} - \frac{d}{dx}\left(\frac{\partial F}{\partial C'}\right) = 0 \quad ; \quad C' = \frac{\partial C}{\partial x} \tag{11}$$

On comparing "(1)" with Euler-Lagrange "(11)", we obtain the variational form

$$I = \int_{\Omega}\left[\frac{D}{2}\left(\frac{\partial C}{\partial x}\right)^2 + (B+T)C + \frac{1}{2}\frac{\partial C^2}{\partial t}\right]dx \tag{12}$$

where the region $'\Omega'$ is divided into five sub regions.

The integrals I_i ,$(i = 1, 2, 3, 4, 5)$ are evaluated for eachsubregion and are given as

$$I_i = \left[\frac{D_i\beta_i^2}{2} + \frac{(T_i + \mathrm{B}_i)}{\alpha_i}\right](a_i - a_{i-1}) + \frac{\beta_i}{2}(T_i + B_i)(a_i^2 - a_{i-1}^2) + \frac{1}{6}\frac{d}{dt}\left[3\alpha_i^2(a_i - a_{i-1}) + 3\alpha_i\beta_i(a_i^2 - a_{i-1}^2) + \beta_i^2(a_i^3 - a_{i-1}^3)\right] \tag{13}$$

On using the values of α_i and β_i, we get I_i in terms of nodal concentrations C_i, as follows:

$$I_1 = \frac{D_1(C_1 - C_0)^2}{2(a_1 - a_0)} + (T_1 + B_1)(C_0 a_1 - a_0 C_1) + \frac{1}{6(a_1 - a_0)}\frac{d}{dt}\left[3(C_0 a_1 - a_0 C_1)^2 + 3(C_1 - C_0)(C_0 a_1 - a_0 C_1)(a_1 - a_0)\right] + \frac{1}{2}(T_1 + B_1)(a_1 + a_0)(C_1 - C_0) + \frac{(C_1 - C_0)^2(a_1^2 + a_0^2 + a_1 a_0)}{(a_1 - a_0)} \tag{14}$$

$$I_i = \frac{D_i(C_i - C_{i-1})^2}{2(a_i - a_{i-1})} + (T_i + B_i)\left(\frac{C_{i-1}a_i}{\rho_{i-1}} - C_i a_{i-1}\right) + \frac{1}{2}(T_i + B_i)\left(C_i - \frac{C_{i-1}}{\rho_{i-1}}\right)(a_i + a_{i-1}) + \frac{1}{6(a_i - a_{i-1})}\frac{d}{dt}\left[3\left(\frac{C_{i-1}a_i}{\rho_{i-1}} - C_i a_{i-1}\right)^2\right] + \frac{3(a_i + a_{i-1})}{(a_i - a_{i-1})}\left(\frac{C_{i-1}a_i}{\rho_{i-1}} - C_i a_{i-1}\right)\left(C_i - \frac{C_{i-1}}{\rho_{i-1}}\right)^2 + \frac{\left(a_{i-1}^2 + a_i^2 + a_i a_{i-1}\right)}{(a_i - a_{i-1})}\left(C_i - \frac{C_{i-1}}{\rho_{i-1}}\right)^2, \quad (i = 2,3,4,5) \tag{15}$$

Thus integrals I_i ($i = 1, 2, 3, 4, 5$) are assembled to obtain

$$I = \sum_{i=1}^{5} I_i \tag{16}$$

Now 'I' in "(16)" is extermized with respect to each C_i ($i = 1, 2, 3, 4$) to given the following system of differentia equations:

$$\sum_{j=0}^{4}\left[p_{ij}C_j + q_{ij}\frac{dC_i}{dt}\right] = h_i \quad , (i = 1, 2, 3, 4) \tag{17}$$

where p_{ij} and q_{ij} ($i = 1, 2, 3, 4,\ j = 0, 1, 2, 3, 4$) are constants depending upon various physical and physiological parameters which are listed in Appendix. On taking Laplace transform of "(17)" we get

$$\begin{bmatrix} l_{11} & l_{12} & 0 & 0 \\ l_{21} & l_{22} & l_{23} & 0 \\ 0 & l_{32} & l_{33} & l_{34} \\ 0 & 0 & l_{43} & l_{44} \end{bmatrix}\begin{bmatrix} \overline{C}_1 \\ \overline{C}_2 \\ \overline{C}_3 \\ \overline{C}_4 \end{bmatrix} = \begin{bmatrix} m_1 \\ m_2 \\ m_3 \\ m_4 \end{bmatrix} \tag{18}$$

where $\overline{C}_i$ $(i = 1, 2, 3, 4)$ are the values of Laplace transform of C. The constant coefficients l_{ij} ($i = 1, 2, 3, 4,\ j = 1, 2, 3, 4$) and m_i $(i = 1, 2, 3, 4)$ are listed in Appendix.

On solving "(18)" we get the nodal concentrations as

$$\overline{C}_i = \frac{(F_{i1}s^3 + F_{i2}s^2 + F_{i3}s + F_{i4})}{s(N_1 s^4 + N_2 s^3 + N_3 s^2 + N_4 s + N_5)} + \frac{R_{i1}s^4 + R_{i2}s^3 + R_{i3}s^2 + R_{i4}s + R_{i5}}{(s^2 + \pi^2\mu^2)(N_1 s^4 + N_2 s^3 + N_3 s^2 + N_4 s + N_5)}, \quad (i = 1, 2, 3, 4) \tag{19}$$

$$L(C_i) = \overline{C_i} = \int_0^{\infty} e^{-st} C_i\, dt, \quad \mathrm{Re}(s) > 0, \quad (i = 1, 2, 3, 4)$$

where

Here 's' is the Laplace parameter and all F_{ij} and R_{ij}, ($i = 1, 2, 3, 4$ and $j = 1, 2, 3, 4$) are the constants depend upon the previously defined parameters. Applying the inverse Laplace transform on "(19)" and by making the use of Haviside Expansion theorem [19], we get all the nodal concentrations as follows:

$$C_i = \frac{F_{i4}}{N_5} + \sum_{i=1}^{4}\left[\frac{(F_{i1}r_i^3 + F_{i2}r_i^2 + F_{i3}r_i + F_{i4})}{(5N_1 r_i^4 + 4N_2 r_i^3 + 3N_3 r_i^2 + 2N_4 r_i + N_5)}\right]e^{r_i t} + \sum_{i=1}^{4}\left[\frac{(R_{i1}r_i^3 + R_{i2}r_i^2 + R_{i3}r_i + R_{i4})}{(G_1 r_i^5 + G_2 r_i^4 + G_3 r_i^3 + G_4 r_i^2 + G_5 r_i + G_6)}\right]e^{r_i t}, \quad (i = 1, 2, 3, 4) \tag{20}$$

where r_i's are the roots of equation

$N_1 S^4 + N_2 S^3 + N_3 S^2 + N_4 S + N_5 = 0$

where N_i, $(i = 1, 2, 3, 4, 5)$ are the constant coefficients.

Results and Discussion

For obtaining the drug concentration profile in the considered layers, we employ the following physical and physiological parameters which are practicable and fall within the acceptable ranges. We can allocate any value to the thickness of in-vivo tissues depending on the sample of the skin under study. Accordingly the set of values considered here are

$a_0 = 0.0\,\mu m.,\quad a_1 = 2.0\,\mu m.,\quad a_2 = 4.0\,\mu m,\quad a_3 = 8.0\,\mu m$,

$a_4 = 12.0\mu m\,m$, $a_5 = 16.0\,\mu m$, $\lambda = 100$, $\mu = 0.01$,

$\rho_i = 1,\quad (i = 1, 2, 3, 4)$.

The mathematical calculations have been carried out for different values of applied drug concentration, drug rate of absorptions and diffusivity. The terms T and B are taken equal to zero in upper most layer because this layer is free from active cells and blood vessels and have different values in other layers. The graphs for $C^{(i)}$, $(i = 1, 2, 3, 4, 5)$ versus thickness of the skin layer and time have been drawn using MATLAB software.

The present work is an attempt to estimate the drug concentration in human dermal layers. Firstly we have approximated the drug concentration at the nodal points of the layers of the skin with respect to time. It has been observed from the curves given in figure 2, 3 and 4, that the steepness of the curves decreases as the drug reaches to internal boundary. This effect is due to the boundary conditions where concentration decreases with raise in distance from the surface. The effect of change in the values of absorption coefficients and diffusivity can also be observed from these curves. The increase in absorption decreases the concentration. This effect is shown in figure 2 and 3.

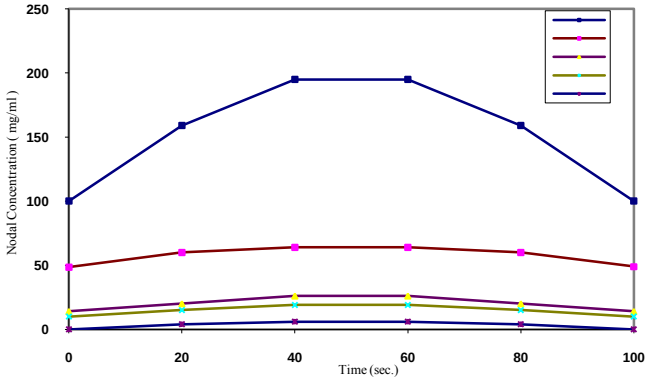


Fig. 2. Tissue absorption rate $T_2 = 2.0\times10^{-5}$, $T_3 = 1.0\times10^{-4}$, $T_4 = 1.0\times10^{-4}$, $T_5 = 3.0\times10^{-4}$, **Blood intake rate** $B_2 = 1.0\times10^{-5}$, $B_3 = 1.0\times10^{-4}$, $B_4 = 1.2\times10^{-4}$, $B_5 = 2.0\times10^{-4}$ **and Diffusivity** $D_1 = 1.0\times10^{-4}$, $D_2 = 2.0\times10^{-4}$, $D_3 = 3.0\times10^{-4}$, $D_4 = 5.0\times10^{-4}$, $D_5 = 9.0\times10^{-3}$.

Also, the increase in diffusion increases the concentration is shown in figure 3 and 4. Figure 5 to 7 are drawn between field concentration and depth for different values of time. The slop of these curves decreases at the interfaces. This result is due to the variation in properties of each sub section. The curves are linear within each element due to the linear shape functions, which are supposed in each element. Three-dimensional "Figure 8 to 10" are also drawn to show the variations in drug concentration with respect to time and thickness of dermal layers at the same time.

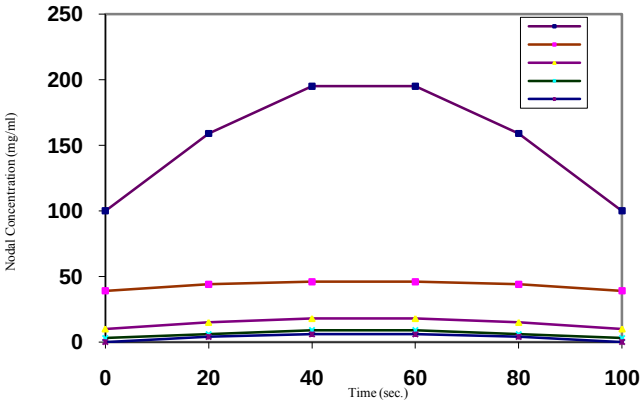


Figure 3. Tissue absorption rate $T_2 = 3.0\times10^{-5}$, $T_3 = 2.0\times10^{-4}$, $T_4 = 3.0\times10^{-4}$, $T_5 = 6.0\times10^{-4}$, **Blood intake rate** $B_2 = 4.0\times10^{-5}$, $B_3 = 4.0\times10^{-4}$, $B_4 = 5.0\times10^{-4}$, $B_5 = 4.0\times10^{-4}$ **and Diffusivity** $D_1 = 1.0\times10^{-4}$, $D_2 = 2.0\times10^{-4}$, $D_3 = 3.0\times10^{-4}$, $D_4 = 5.0\times10^{-4}$, $D_5 = 9.0\times10^{-3}$.

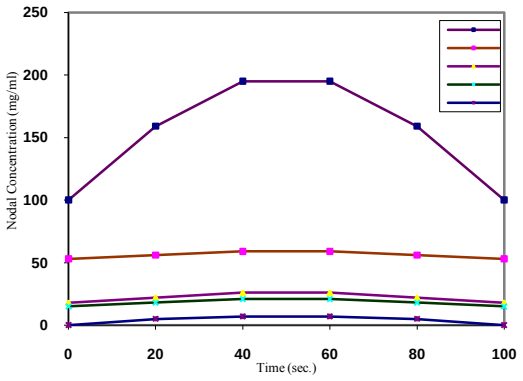


Figure 4. Tissue absorption rate $T_2 = 2.0\times10^{-5}$, $T_3 = 1.0\times10^{-4}$, $T_4 = 1.0\times10^{-4}$, $T_5 = 3.0\times10^{-4}$, **Blood intake rate** $B_2 = 1.0\times10^{-5}$, $B_3 = 1.0\times10^{-4}$, $B_4 = 1.2\times10^{-4}$, $B_5 = 2.0\times10^{-4}$ **and Diffusivity** $D_1 = 2.0\times10^{-4}$, $D_2 = 3.0\times10^{-4}$, $D_3 = 4.0\times10^{-4}$, $D_4 = 5.0\times10^{-4}$, $D_5 = 1.0\times10^{-2}$.

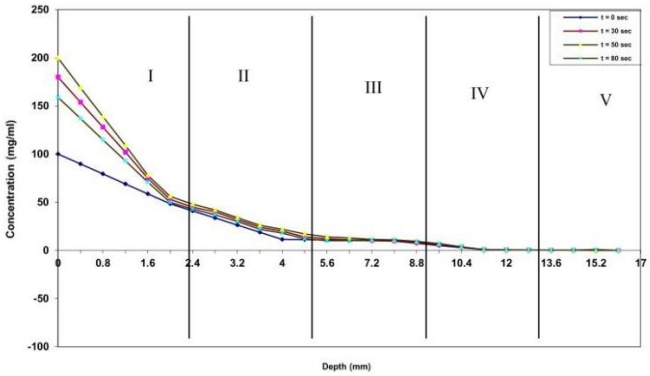


Figure 5. Tissue absorption rate $T_2 = 2.0\times10^{-5}$, $T_3 = 1.0\times10^{-4}$, $T_4 = 1.0\times10^{-4}$, $T_5 = 3.0\times10^{-4}$, **Blood intake rate** $B_2 = 1.0\times10^{-5}$, $B_3 = 1.0\times10^{-4}$, $B_4 = 1.2\times10^{-4}$, $B_5 = 2.0\times10^{-4}$ **and Diffusivity** $D_1 = 1.0\times10^{-4}$, $D_2 = 2.0\times10^{-4}$, $D_3 = 3.04\times10^{-4}$, $D_4 = 5.0\times10^{-4}$, $D_5 = 9.0\times10^{-3}$.

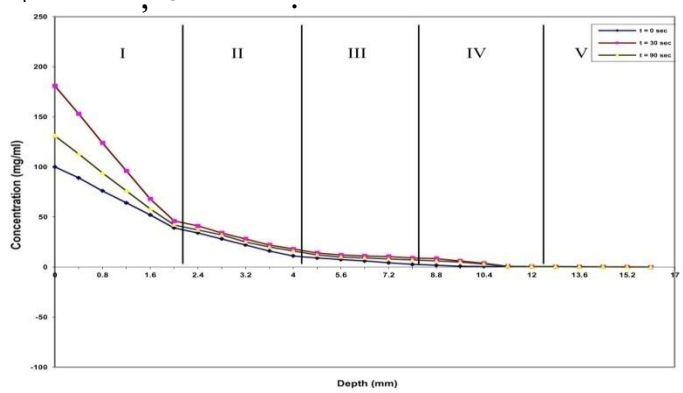


Figure 6. Tissue absorption rate $T_2 = 3.0\times10^{-5}$, $T_3 = 2.0\times10^{-4}$, $T_4 = 3.0\times10^{-4}$, $T_5 = 6.0\times10^{-4}$, **Blood intake rate** $B_2 = 4.0\times10^{-5}$, $B_3 = 4.0\times10^{-4}$, $B_4 = 5.0\times10^{-4}$, $B_5 = 8.0\times10^{-4}$ **and Diffusivity** $D_1 = 1.0\times10^{-4}$, $D_2 = 2.0\times10^{-4}$, $D_3 = 3.04\times10^{-4}$, $D_4 = 5.0\times10^{-4}$, $D_5 = 9.0\times10^{-3}$.

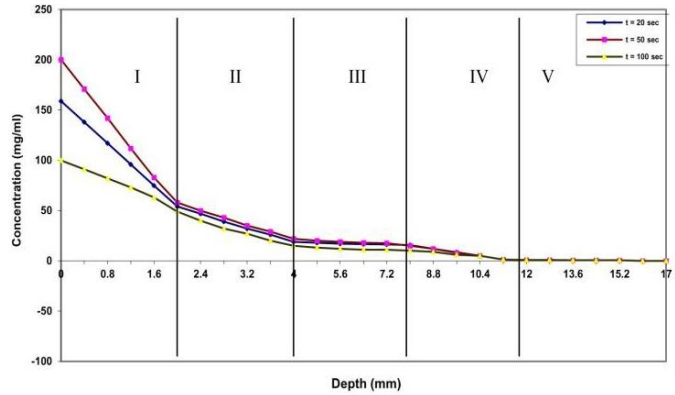


Figure 7. Tissue absorption rate $T_2 = 2.0\times10^{-5}$, $T_3 = 1.0\times10^{-4}$, $T_4 = 1.0\times10^{-4}$, $T_5 = 3.0\times10^{-4}$, **Blood intake rate** $B_2 = 1.0\times10^{-5}$, $B_3 = 1.0\times10^{-4}$, $B_4 = 1.2\times10^{-4}$, $B_5 = 2.0\times10^{-4}$ **and Diffusivity** $D_1 = 2.0\times10^{-4}$, $D_2 = 3.0\times10^{-4}$, $D_3 = 4.04\times10^{-4}$, $D_4 = 5.0\times10^{-4}$, $D_5 = 1.0\times10^{-2}$.

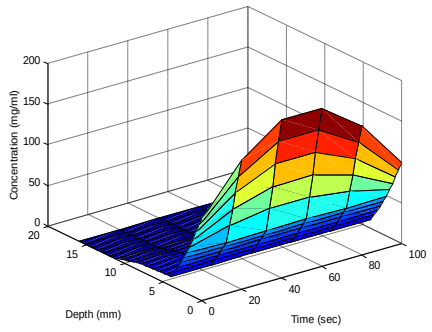


Figure 8. Tissue absorption rate $T_2 = 2.0\times10^{-5}$, $T_3 = 1.0\times10^{-4}$, $T_4 = 1.0\times10^{-4}$, $T_5 = 3.0\times10^{-4}$, **Blood intake rate** $B_2 = 1.0\times10^{-5}$, $B_3 = 1.0\times10^{-4}$, $B_4 = 1.2\times10^{-4}$, $B_5 = 2.0\times10^{-4}$ **and Diffusivity** $D_1 = 1.0\times10^{-4}$, $D_2 = 2.0\times10^{-4}$, $D_3 = 3.04\times10^{-4}$, $D_4 = 5.0\times10^{-4}$, $D_5 = 9.0\times10^{-3}$.

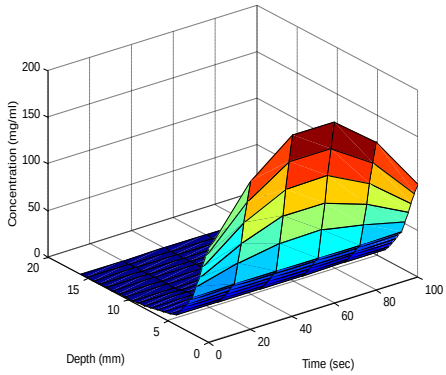


Figure 9. Tissue absorption rate $T_2 = 3.0\times10^{-5}$, $T_3 = 2.0\times10^{-4}$, $T_4 = 3.0\times10^{-4}$, $T_5 = 6.0\times10^{-4}$, **Blood intake rate** $B_2 = 4.0\times10^{-5}$, $B_3 = 4.0\times10^{-4}$, $B_4 = 5\times10^{-4}$, $B_5 = 8.0\times10^{-4}$ **and Diffusivity** $D_1 = 1.0\times10^{-4}$, $D_2 = 2.0\times10^{-4}$, $D_3 = 3.04\times10^{-4}$, $D_4 = 5.0\times10^{-4}$, $D_5 = 9.0\times10^{-3}$.

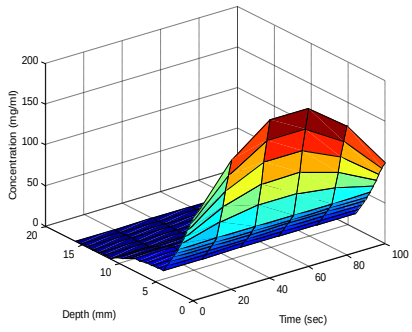


Figure 10. Tissue absorption rate $T_2 = 2.0\times10^{-5}$, $T_3 = 1.0\times10^{-4}$, $T_4 = 1.0\times10^{-4}$, $T_5 = 3.0\times10^{-4}$, **Blood intake rate** $B_2 = 1.0\times10^{-5}$, $B_3 = 1.0\times10^{-4}$, $B_4 = 1.2\times10^{-4}$, $B_5 = 2.0\times10^{-4}$ **and Diffusivity** $D_1 = 2.0\times10^{-4}$, $D_2 = 3.0\times10^{-4}$, $D_3 = 4.04\times10^{-4}$, $D_4 = 5.0\times10^{-4}$, $D_5 = 1.0\times10^{-2}$.

Conclusion

The solutions provided in this paper give better understanding of mechanisms of drug delivery in the five layers of the human skin. The results in this paper are stronger than the results obtained by Khandy and Rafiq. They have obtained the concentration only in three layers while as in our model, the drug concentration profiles has been studied for five layers as the drug flow in the skin is multi layered observable fact. Also, they have studied the drug distribution in-vivo tissues by applying the drug amount 5 grams while as the present work shows the drug distribution for different amount of applied drug i.e. 100 grams, 160 grams and 200grams. Hence our work gives modified results followed by the Khandy and Rafiq.
Moreover, our work shows the linear variation in each element. It is a justified approximation in view of small thickness of the layers. This assumption can always be enhanced by increasing the number of layers or by taking higher degree approximating polynomials. The developed model helps us in calculating the amount of drug concentration in different layers of the skin with the effect of change in diffusion constant and absorption coefficients. The model may be very helpful in formulation the effective transdermal drug delivery systems in various situation.

Appendix

$$p_{10}=0,\quad p_{12}=-\frac{D_2}{\rho_1(a_2-a_1)}=p_{21},\quad p_{13}=0=p_{14},\quad q_{10}=0,$$

$$q_{12}=(a_2-a_1)/6\rho_1,\ q_{13}=0=q_{14},\ p_{20}=0,$$

$$p_{23}=-\frac{D_3}{\rho_2(a_3-a_2)}=p_{32},\qquad p_{24}=0,\qquad q_{20}=0=q_{24},$$

$$q_{23}=\frac{(a_3-a_2)}{6\rho_2}=q_{32},\quad p_{30}=0=p_{31},$$

$$p_{34}=-\frac{D_4}{\rho_3(a_4-a_3)}=p_{43},\qquad p_{34}=-D_4/\rho_3(a_4-a_3)=p_{43},$$

$$q_{30}=0=q_{31},\quad q_{34}=\frac{(a_4-a_3)}{6\rho_3}=q_{43},\quad p_{40}=0=p_{41}=p_{42},$$

$$q_{40}=0=q_{41}=q_{42},\quad l_{13}=l_{14}=l_{24}=l_{31}=l_{41}=l_{42}=0,$$

$$l_{ij}=p_{ij}+s\,q_{ij},\qquad (i=1,2,3,4,\ j=1,2,3,4),$$

$$h_i=\frac{(T_i+B_i)(a_i-a_{i-1})}{2}+\frac{(T_{i+1}+B_{i+1})(a_i-a_{i+1})}{2\rho_i},$$

$$(i=2,3,4)$$

$$m_1=\frac{g_{11}}{s}+\frac{g_{13}}{(s^2+\pi^2\mu^2)},\qquad m_i=\frac{h_i}{s},\quad (i=2,3,4),$$

$$g_{11}=\frac{D_1\lambda}{(a_1-a_0)}+g_{12},$$

$$g_{12}=\frac{(T_1+B_1)(a_0-a_1)}{2}+\frac{(T_2+B_2)(a_1-a_2)}{2\rho_1}$$

$$g_{13}=\frac{D_1\lambda\,\pi\,\mu}{(a_1-a_0)},\qquad p_{ii}=\frac{D_i}{(a_i-a_{i-1})}+\frac{D_{i+1}}{\rho_i^2(a_{i+1}-a_i)},$$

$$(i=1,2,3,4)$$

$$q_{ii}=\frac{(a_i-a_{i-1})}{3}+\frac{(a_{i+1}-a_i)}{3\rho_i^2},\quad (i=1,2,3,4)$$

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