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An Analytical Approach To Study The Drug Diffusion Through Transdermal Drug Delivery System*

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Abstract

The transdermal drug-delivery (TDD) is an alternate route of drug transport through dermal regions with number of benefits over oral and parenteral routes. For this purpose, mathematical modelling of TDD can provide an efficient path-way of drug-diffusion through skin and subcutaneous tissues. A reaction-diffusion model has been formulated to discuss the dermal drug-diffusion with suitable initial and boundary conditions. The domain (dermal region) is discretized into seven compartments starting from stratum corneum to areolar tissue. For each compartment, the model equations were solved using an analytical eigenvalue-method together with the Fourier-expansion technique. The results obtained were simulated and interpreted graphically with the aid of Wolfram MATHEMATICA software. To strengthen the validity and accuracy of the proposed model, the results obtained were compared with the experimental data. The outcome of the model has applications in bioengineering research and biomedical sciences to investigate the drug delivery and its diffusion through TDDS.

1 Introduction

The transdermal drug delivery system (TDDS) consists of a medicative adhesive drug patch placed on a predetermined site of the skin to deliver a drug and to maintain clinically effective concentrations over a prolonged period of time through various layers of dermal region. TDDS can provide a controlled dose of medication from day one upto seven days. A typical transdermal patch is composed of an adhesive matrix, contains the drug in-between a backing layer and release liner. This system of drug application has several number of advantages over oral and parenteral dosing as it is simple to utilize, non-intrusive, more improved and helpful patient consistence, self medicine is conceivable, maintains a strategic distance from gastrointestinal disorders, prevents first pass digestion, limits bothersome symptoms and provides a substitute for oral drug dosage and prevents stomach reflex etc. Besides having these advantages, transdermal patches, on medication, result in local irritation, are uncomfortable to wear, have limited skin permeability and restricted to potent drugs only. The major obstacle in this type of drug-delivery is that this system can be formulated only for drugs with low molecular weights ($< 500\ amu$), low required doses ($< 2\ mg$) and having short half-life [3].

The historical backdrop of TDDS goes back when the primary glue TDDS was affirmed by Food and Drug Administration (FDA) in 1979. This technique for conveyance turned out to be broadly perceived when nicotine patches were presented in 1991 for smoking discontinuance. Scientific and mathematical models like Borchardt et al. [3] findings can give definite knowledge to such sort of medication conveyance. Specialists have built up the numerical establishments of controlled medication conveyance and prompted the cutting edge models [2, 14]. Peppas and Narsimhan have explained how mathematical models in drug delivery have shaped the way to design new drug delivery systems [14]. They have discussed the importance and mechanism of mathematical modeling for the drug release from drug-delivery devices. Many researchers

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studied how TDDS follow Fickian-type of diffusion and have developed mathematical models to describe the diffusion and drug-permeation in drug delivery processes. Lee et al., have studied the diffusion of drugs in skin by developing a multiple-pathway model [12]. They have solved their model for the steady state case only using the analytical approach. Manitz et al., have also discussed the mathematical approach to study dermal and transdermal drug delivery [13]. They have estimated the drug delivery process into the human skin by two types of extensions of the diffusion model, numerically. Fernandes et al., have also discussed the analysis and applications of transdermal drug-delivery systems by means of mathematical modeling [5]. They have used the Fickian diffusion equations in their model with appropriate boundary conditions and have obtained a closed-form mathematical solution to simulate their results using the Laplace transform methods. Rim et al., have used the finite element method to study the coupled diffusion with partioning in TDD [17]. Their formulation is based on the numerical approach of a general multi-compartment diffusion model, where they have descretized the skin into several compartments (corresponding layers of the skin). They have compared their model simulations with the clinical results to predict the efficiency of their model.

Later, Khanday and Rafiq also studied the drug absorption at the various dermal compartments through the TDDS, where they have explained a pattern of the drug diffusion in the human skin and its effective absorption rates at different interface points [6]. They have used the variational finite element method to simulate the drug kinetics through the TDDS. Khanday and his co-workers [7, 9, 10, 11] have also explained a detailed study of the drug absorption and fluid distribution in human skin through the TDDS. They have modified the basic reaction-diffusion model and used certain numerical methods to simulate their model results. A mathematical model was also developed by Sharma and Saxena to describe the drug distribution in five different layers of the skin through the TDDS [18]. They have also used the finite element technique to determine the drug concentrations in the corresponding layers of the skin. Compartment modeling of skin transport was also studied by Amarah et al., [1] and have explained the use of compartments to understand the transport process in skin using the basic diffusion model. They compared their model results using the numerical approaches with the practical data of water penetration profiles in the uppermost layer of the skin (stratum corneum). Khanday and Khalid [8] studied thermal challenges in cancerous tumors under local heat therapy using mathematical and numerical investigations.

In this work, we have developed a mathematical model based on basic reaction-diffusion equations to explain the drug absorption and its diffusion in the various layers of the skin as shown in Fig. (1). Suitable interface and initial conditions were coupled with the model equations. The skin and its underlying layers (domain of the study) is discretized into seven compartments as shown in Fig. (2). The analytical method has been employed to simulate the model results, which has not yet been done by researchers in TDD scheme. The outcome of the model generalizes other model results in several cases. As the analytical methods are more convenient than any numerical methods, the outcome in this case is more reasonable and efficient as compared to the numerical methods. The model outcome has been obtained by using the Wolfram MATHEMATICA software and the results were compared with the clinical data established by Rim et al. [17] to prove the accuracy and feasibility of the model.

2 Mathematical Model

The model construction is comprised of the following subsections:

2.1 Model Formulation

The model formulation given below is a modified version of the diffusion equation used by Khanday and Rafiq [7]

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x}(D\frac{\partial C}{\partial x}) - R(C,t) - B \tag{1}$$

where $C = C(x,t)$ is the concentration of the drug, x is the skin thickness, t is the time, D is the diffusion coefficient, R and B respectively denote the medication assimilation rate by the skin and drug utilization rate by the blood.

2.2 Discretization of the Domain

In order to calculate the drug diffusion in various layers of dermal region as shown in Fig. (1), the discretization of the domain into seven layers is given in Fig. (2). Each subdomain is considered as a compartment and based on the physiological parameters, the description of these compartments is defined as follows:

$$\begin{aligned}
\text{Stratum Corneum(SC)}: &\ 0 = p_0 \le x \le p_1,\\
\text{Stratum Spinosum}: &\ p_1 \le x \le p_2,\\
\text{Stratum Basale}: &\ p_2 \le x \le p_3,\\
\text{Papillary Region}: &\ p_3 \le x \le p_4,\\
\text{Reticular Region}: &\ p_4 \le x \le p_5,\\
\text{Adipose Tissue}: &\ p_5 \le x \le p_6,\\
\text{Areolar Tissue}: &\ p_6 \le x \le p_7 = l.
\end{aligned}$$

where l is the overall thickness of the skin and the relating interfaces joining the compartments are given as follows:
Interface 1: p_0 = Patch Release liner-Stratum Corneum($x = 0$)
Interface 2: p_1 = Stratum Corneum-Stratum Spinosum
Interface 3: p_2 = Stratum Spinosum-Stratum Basale
Interface 4: p_3 = Stratum Basale-Papillary Region
Interface 5: p_4 = Papillary Region-Reticular Region
Interface 6: p_5 = Reticular Region-Adipose Tissue
Interface 7: p_6 = Adipose Tissue-Areolar Tissue
Interface 8: p_7 = Areolar Tissue-Muscle

2.3 Initial and Interface Conditions

The diffusion coefficient D and other related parameters change due to heterogeneity of the dermal structure, were considered variables for the whole domain. However, in the subdomain elements (compartments), the behaviour of the various physiological parameters is almost uniform and as such these parameters were considered constants. Therefore, keeping this fact into consideration, Eqn. (1), at each compartment becomes

$$\frac{\partial C^{(i)}}{\partial t} = D_i \frac{\partial^2 C^{(i)}}{\partial x_i^2} - R_i(C^{(i)}, t) - B_i \tag{2}$$

where $p_{i-1} \le x_i \le p_i$ and $i = 1,\ 2,\ ...,7$ represent the corresponding compartments.

In the begining, when the medication is applied at the outermost skin layer stratum-corneum, the drugn concentration at differnt values of spatial variable x is expected to change[18], as

$$C^{(i)}(x, o) = \begin{cases} C_0 & \text{for } x = 0,\\ C_0 \prod_{j=0}^{i-1} \rho_j - \alpha x & \text{for } x > 0. \end{cases} \tag{3}$$

where $\alpha = \dfrac{C_0}{l}$, $\rho_0 = 1$, and the negative sign demonstrates that the drug concentration diminishes with the expansion in thickness of skin layers.

Further at the interfaces associating two compartments, the preservation of transition and Nernst's dispersion law must hold [7, 13], therefore the interface conditions are taken as

$$D_{i-1} \frac{\partial C^{(i-1)}}{\partial x}(x, 0) = D_i \frac{\partial C^{(i)}}{\partial x}(x, 0) \text{ at } x = l_i, \tag{4}$$

$$C^{(i)} = \rho_{i-1} C^{(i-1)} \text{ at } x = l_i, \tag{5}$$

for $i = 1, 2, ...6$, where $\rho_i' s$ are the corresponding partition coefficients.

Further to suppress the losses at the innermost interface, it must have zero flux [13]. Therefore by Fick's law

$$\left.\frac{\partial C^{(i)}}{\partial x_i}\right|_{x_i = p_7} = 0. \tag{6}$$

Also, the drug absorption rate by the skin depends on the initial concentration of the drug and decreases exponentially with respect to time as discussed in [6]-[10], we choose

$$R_i(C^{(i)}, t) = \mu_i C^{(i)} - \gamma_i e^{-\sigma_i t} \tag{7}$$

where μ_i, γ_i and σ_i (with $\mu_i \neq \sigma_i$) are the drug-simulation parameters in the compartment i such that

$$\gamma_i \begin{cases} = 0 & \text{for } t = 0, \\ > 0 & \text{for } t > 0. \end{cases}$$

3 Solution of the Model

To establish the solution of Eqn. (1), we take $D_{x_i} = \dfrac{\partial}{\partial x_i}$, $D_t = \dfrac{\partial}{\partial t}$. Substituting Eq. (7) in Eqn. (2) and on rearranging, we have

$$(D_i D_{x_i}^2 - D_t - \mu_i) C^{(i)}(x_i, t) = B_i - \gamma_i e^{-\sigma_i t}. \tag{8}$$

Eqn. (8) being a non-homogeneous partial differential equation, its solution is of the form [16]

$$C^{(i)}(x_i, t) = C_{C.F.}^{(i)}(x_i, t) + C_P^{(i)}(x_i, t) \tag{9}$$

where $C_{C.F.}^{(i)}(x_i, t)$ and $C_P^{(i)}(x_i, t)$ respectively represent the complementary function and the particular integral corresponding to Eq. (8). The complementary function $C_{C.F.}^{(i)}(x_i, t)$ is the solution of the following homogeneous part

$$(D_i D_{x_i}^2 - D_t - \mu_i) C_{C.F.}^{(i)}(x_i, t) = 0. \tag{10}$$

The solution of Eqn. (10) is of the form [2, 4, 16],

$$C_{C.F.}^{(i)}(x_i, t) = A^{(i)} e^{h x_i + k t} \tag{11}$$

where h and k are determined by using Eqn. (11) in Eqn. (10), and it is obtained that

$$D_i h^2 - k - \mu_i = 0$$

which is satisfied for $h = \pm i\lambda_n$, $k = -(D_i \lambda_n^2 + \mu_i)$.

On substituting these values in Eqn. (11), on application superposition principle yields

$$C_{C.F.}^{(i)}(x_i, t) = \sum_{n=0}^{\infty} A_n^{(i)} \cos(\lambda_n x_i) e^{-(D_i \lambda_n^2 + \mu_i) t} \tag{12}$$

where the coefficients $A_n^{(i)}$ and the eigenvalues λ_n are obtained using the corresponding initial and interface conditions as given by Eqns. (3)-(6), with the help of Fourier-series method [2, 4] and their values are given in the Appendix.

Also, the particular integral $C_P^{(i)}(x_i, t)$ is obtained as

$$C_P^{(i)}(x_i, t) = \frac{\gamma_i e^{-\sigma_i t}}{\mu_i - \sigma_i} - \frac{B_i}{\mu_i}. \tag{13}$$

Finally, using Eqn. (12) and Eqn. (13) in Eqn. (9), we get

$$C^{(i)}(x_i,t)=\sum_{n=0}^{\infty}A_n^{(i)}\cos(\lambda_n x_i)e^{-(D_i\lambda_n^2+\mu_i)t}+\frac{\gamma_i e^{-\sigma_i t}}{\mu_i-\sigma_i}-\frac{B_i}{\mu_i}. \tag{14}$$

Eqn. (14) gives the complete solution of Eqn. (2), which actually gives the concentration of the drug in the compartment i at any instant of time(t) and for any value of layer-size(x_i).

Moreover, summing up these $C^{(i)}$'s gives a complete solution of Eqn. (1) as

$$C(x,t)=\sum_{i=1}^{7}C^{(i)}(x_i,t) \tag{15}$$

which gives the drug concentration in the whole domain(skin) for any value of the skin thickness x at any instant of time t.

4 Numerical Computations

To determine the concentration profiles in various compartments, the numerical and physiological values of various parameters are used, given in Tables (1) and (2). The values of these parameters vary from person to person and organ to organ due to the morphological structure of various layers of the skin [10, 15]. The particular cases for these parameters used in our model are as follows:

Table 1: Sizes of different layers(compartments) of the skin [6, 7, 9, 10, 18].

S. No.	Compartment(skin-layer)	Layer-size(cm)	Total size from SC(cm)
1	Stratum Corneum	0.10	0.10
2	Stratum Spinosum	0.125	0.225
3	Stratum Basale	0.075	0.30
4	Papillary Region	0.15	0.45
5	Reticular Region	0.15	0.60
6	Adipose Tissue	0.075	0.675
7	Areolar Tissue	0.075	0.75

Table 2: Numerical and physiological values parameters for the corresponding compartments(layers) [6, 10, 13, 18].

Layer	$D_i(m^2/min)$	$B_i(mg/min)$	ρ_i	μ_i	σ_i	$\gamma_i(t>0)$
$i=1$	2.020×10^{-3}	0	1.55	0.08	0.05	0.03
$i=2$	2.021×10^{-3}	0	1.00	0.075	0.05	0.025
$i=3$	2.022×10^{-3}	0	1.00	0.075	0.05	0.025
$i=4$	2.038×10^{-3}	0.008	1.00	0.085	0.055	0.03
$i=5$	2.039×10^{-3}	0.008	1.00	0.085	0.055	0.035
$i=6$	2.045×10^{-3}	0.002	1.00	0.045	0.035	0.01
$i=7$	2.046×10^{-3}	0.002	1.00	0.045	0.035	0.01

Further, it is worth to mention here that as there are no blood vessels [10] in the uppermost layer of the skin(i.e; epidermis consisting of sub-layers (compartments): Stratum corneum, stratum spinosum and stratum basale), the value of the drug-consumption rate by the blood for these compartments(*i.e*; B_i for i=1, 2, 3) is taken as zero.

For the comparison of our model simulations, we considered the experimental data, mentioned in the work of Rim et al. [17].

5 Results

To determine the drug-concentration and diffusion profiles in each of the layers (compartments) of skin, Eqn. (14) was plotted with the different sets of parametric values given in Tables (1)–(2) for the corresponding compartments, using the Wolfram MATHEMATICA software, where the infinite series was truncated to fifty terms in each case, as shown in Figs. (3)–(7).

As shown in Fig. (3), the drug concentration decreases almost exponentially with time in stratum-corneum (represented by compartment $i = 1$), which is due to the presence of dry and dead cells in this layer, so there is slow diffusion. Almost same situation arises for the layers of stratum-spinosum ($i = 2$) and stratum-basale ($i = 3$), as shown in Fig. (5). Further, Fig. (4) shows that the drug concentration decreases rapidly with time in the areolar tissue (represented by compartment ($i = 7$)), because diffusion in this layer of skin is more rapid as there is a network of blood vessels in this region [15].

Now, as the drug enters into the dermis which itself is composed of the papillary and reticular regions, represented by compartments $i = 4$ and $i = 5$ respectively, where there are blood-vessels in each region, so besides the drug being absorbed by these types of tissues, its diffusion also takes place via the blood, so drug-concentration also decreases in these layers rapidly as shown in Fig. (6) and the decrease is more rapid in comparison to the other layers.

The drug-diffusion in the adipose-tissue(i.e; for compartment $i = 6$) is shown in Fig. (7), where it can be easily seen that the drug-concentration decreases rapidly in the beginning and then the decrease slows down as time increases. It is because with time, as the drug has to pass many layer-interfaces to reach this layer, its concentration decreases.

Finally, after determining the drug-distribution profiles, the experimental data of the scopolamine transdermal-drug(used to cure motion sickness) mentioned in the work of Rim et al., [17] was compared with our model simulations, with the parametric values given in Tables (1)–(2) and Rim et al. [17] to predict the efficiency of our model. Clearly, as shown in Fig. (8), the two simulations(model and experimental) are quite closer, which proves that our model is practically efficient to a larger extent.

Moreover, a steady-state drug concentration is plotted in Fig. (9), which shows a decreasing linear-dependence of drug-concentration on skin-thickness. Hence as the drug penetrates deeper into the skin, its diffusion decreases.

6 Discussion and Conclusion

The transdermal drug delivery is an adequate alternate route for other types of drug-delivery routes. Mathematical modeling plays a vital role to study such type of drug delivery systems. A mathematical model was formulated based on the basic reaction-diffusion model, with appropriate initial and boundary conditions. The domain of the problem (skin) was discretized into a number of compartments, where each compartment represent a layer of the skin. After discretization, the model was solved analytically for each compartment using the eigenvalue method. The solutions for each compartment and the whole domain are given by the Eqs. (14) and (15) respectively, which can be used to determine the concentration profiles in the corresponding compartment at any instant of time and for any thickness of the layer. The coefficients ($A'_n s$) occurring in Eq. (14) were calculated using the Fourier-series method and are given in the Appendix.

In order to determine the concentration profiles in each of the layers, numerical and physiological values of the parameters were used in Eqn. (14) and the solutions were simulated for every compartment as shown in Figs. (3)–(7), using the Wolfram MATHEMATICA software. As seen in Figs. (3)–(7), different layers have different concentration and diffusion profiles, due to the difference in their physical and morphological structures, from where it is quite evident that the drug-concentration decreases with time as the drug penetrates through different layers of the skin.

Further, the model simulations were compared with the experimental data as shown in Fig. (8), to guarantee the accuracy of our model. Clearly the model results being enough closer to the experimental ones, depict the extent of efficiency of our model. Finally a steady-state concentration profile was obtained as shown in Fig. (9) to study the variation of drug-concentration with respect to the skin thickness and it

was observed that the concentration decreases linearly as the drug penetrates deeper into the skin.

Moreover, the earlier results in this direction discussed in the models of Khanday et al., [6, 7, 9, 10] and Sharma et al., [18] were generalized in two ways: (*i*) In this work, the domain was discretized into seven compartments which was not done earlier, (*ii*) To study the drug-diffusion through the transdermal drug-delivery system more conveniently, the model was solved analytically. This approach too was not done in the above mentioned cases.

This work can help the researchers to study the drug dynamics, diffusion and concentration profiles through the transdermal drug-delivery system. Also, this model can be useful in various biomedical and biophysical situations. This work can further be extended by considering two/three dimensional diffusion-equations and to include the drug-excretion from the body via the blood vessels and some other factors which were not taken into account in this work.

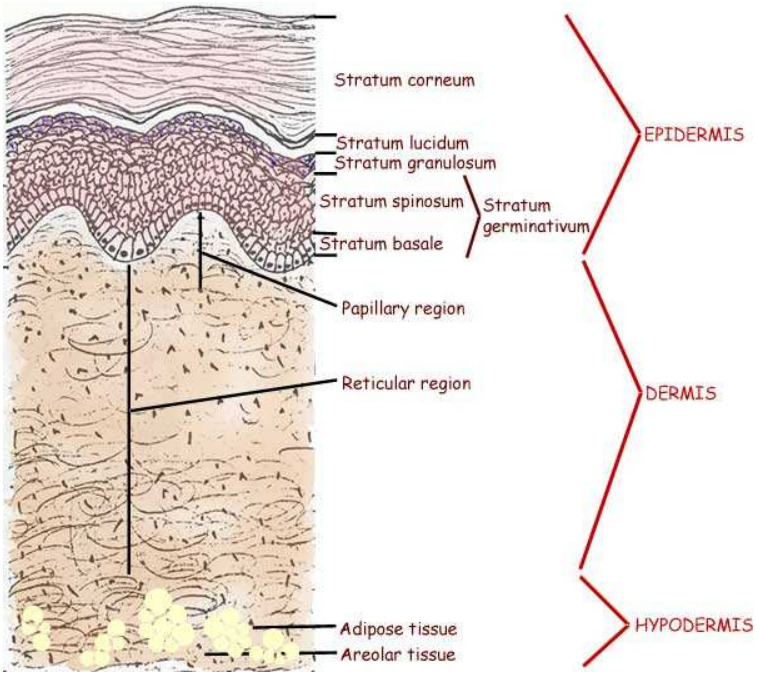

Figure 1: General structure of the skin and its various layers; a microscopic cross-section [18].

Appendix

$A_0^{(1)} = 2C_0 - \alpha l_1;\ A_n^{(1)} = \dfrac{2\alpha l_1}{n^2\pi^2}[1-(-1)^n]$ for $n \geq 1$,

$\lambda_n = \dfrac{n\pi}{l_1}$ for $i = 1;\ l_i = p_i - p_{i-1}\ \forall\ i,\ \sum_{i=1}^{7} l_i = l$,

$\beta_i = C_0 \prod_{j=0}^{i-1} \rho_j + \dfrac{\gamma_i}{\sigma_i - \mu_i} + \dfrac{B_i}{\mu_i}\ \forall\ i.$

For $i = 7$, $\lambda_n = \dfrac{n\pi}{l}$, $A_0^{(7)} = 2\beta_7 - \alpha l$,

$A_n^{(7)} = \dfrac{2\alpha l}{n^2\pi^2}[1-(-1)^n]$ for $n \geq 1$.

$A_0^{(i)} = 2\beta_i - \alpha l_i$ for $i = 2,\ 3,\ 4,\ 5,\ 6$.

$A_n^{(i)} = \dfrac{D_{i-1}}{D_i} A_n^{(i-1)},\ \lambda_n \approx \dfrac{n\pi}{l_i}$ for $n \geq 1$ and $i = 2,\ 3,\ 4,\ 5,\ 6$.

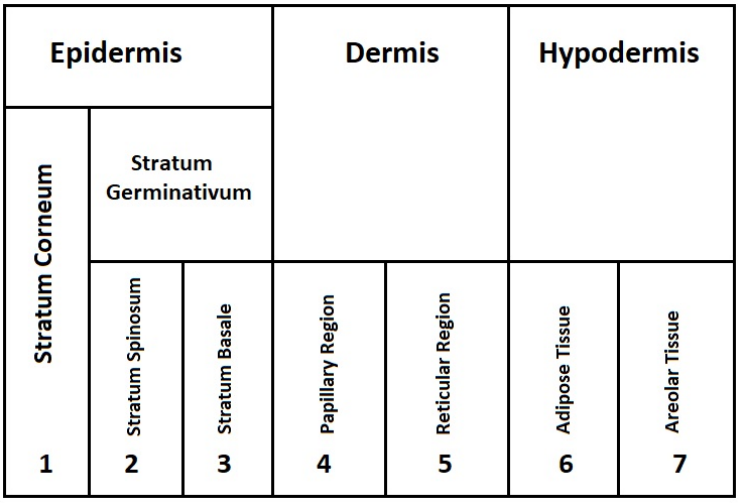

Figure 2: Shematic reprsentation of various layers of skin and descretisation into various compartments with respective compartment numbers.

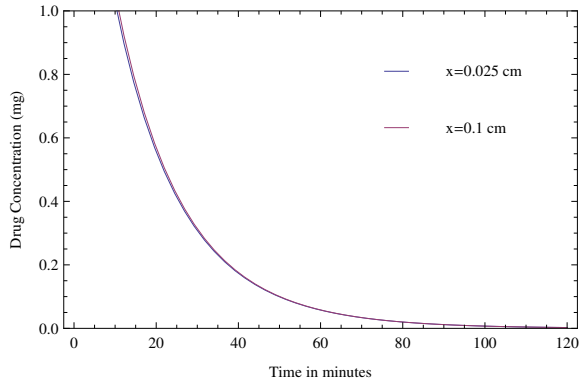

Figure 3: Drug concentration profile in Stratum Corneum with the set of values of parameters given in Tables (1) and (2) with $i = 1$ and $C_0 = 1\ mg$.

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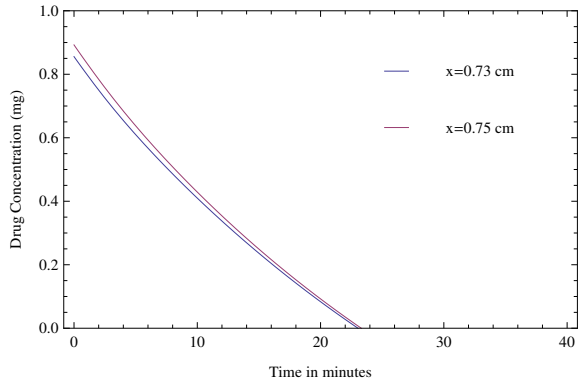

Figure 4: Drug distribution profile in Areolar Tissue with the set of values of parameters given in Tables (1) and (2) with $i = 7$ and $C_0 = 1\ mg$.

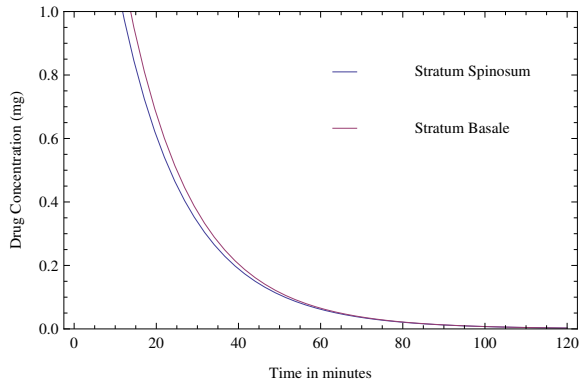

Figure 5: Drug concentration profiles for Stratum Spinosum and Stratum Basale with the set of values of parameters given in Tables (1) and (2) for $i = 2,\ 3$ respectively and $C_0 = 1\ mg$.

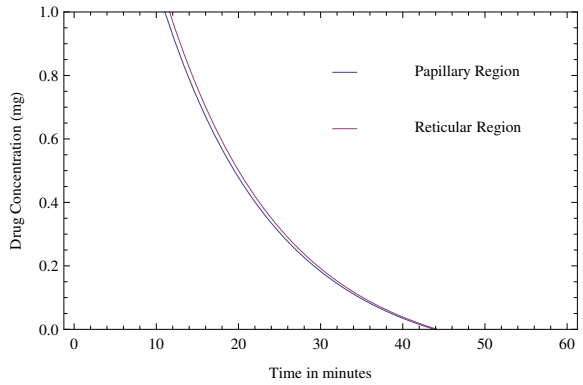

Figure 6: Drug concentration profiles for Papillary and Reticular regions with the set of values of parameters given in Tables (1) and (2) for $i = 4,\ 5$ respectively and $C_0 = 1\ mg$.

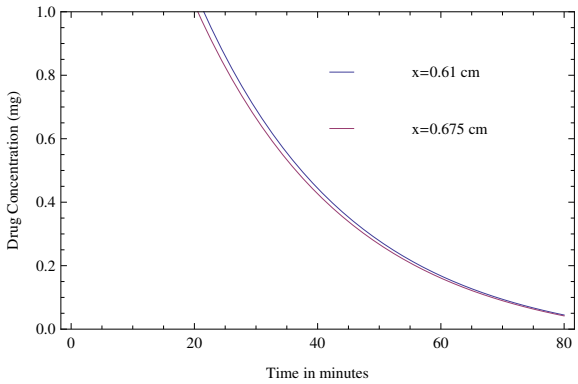

Figure 7: Drug concentration profile for Adipose tissue with the parametric set of values given in Tables (1) and (2) for $i = 6$ and $C_0 = 1\ mg$.

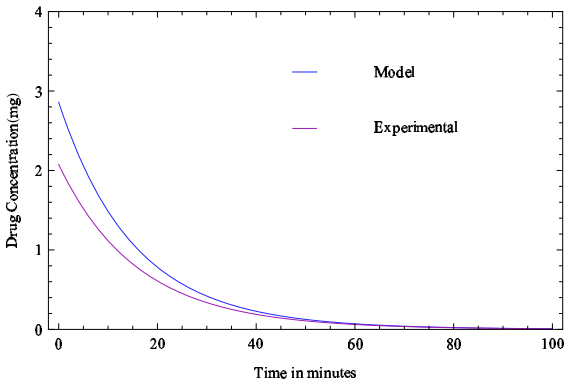

Figure 8: Comparison of model simulations with the parameter values given in Tables (1),(2), Rim et al., [17] and the experimental data of transdermal-drug(scopolamine) diffusion based on the model of Rim et al.,[17] with initial concentration $C_0 = 4.4$mg.

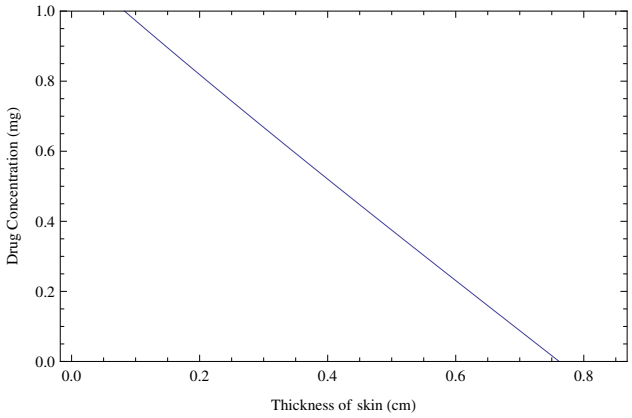

Figure 9: Variation of drug-concentration (Steady-state) with respect to skin thickness as a single compartment (i.e; when the whole domain is taken as a single compartment) with $C_0 = 1\ mg$, $D = 2.039 \times 10^{-2} m^2/min$, $B = 0.008\ mg/min$, $\mu = 0.085$.

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