Variational FEM Approach to the Study of Drug Distribution in Dermal Layers in Transdermal Drug Delivery System

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Abstract

Today about 75% of drugs are taken orally and are found not to be as effective as desired. To improve this, transdermal drug delivery system was emerged. Transdermal drug delivery is self-contained continuous dosage forms which, when applied to the intact skin, delivers the drug through the skin at controlled rate to the systemic circulation. The present model describes the diffusion of drugs in transdermal drug delivery system. The tissue absorption rate and drug intake rate by blood are taken in an account. The Finite Element Method (FEM) approach is used for the solution with four layers of skin which are taken as discretized elements. The numerical calculation and plotting graphs have been done by using MATLAB.

Keywords: *Transdermal drug delivery system (TDDS), Finite element method, linear shape function, diffusion equation, conservation equation.*

I. Introduction and preliminaries

A. Introduction

In the last 100 years, drug delivery system has enormously increased their performances, moving from simple pills to sustained/ controlled release. Nowadays, the drug delivery has become more specific from systemic to organ and cellular targeting [18].

The major sites of drug administration are [1]:

1. Oral: i) Buccal Cavity
   ii) Gastro-Intestinal Tract (GIT)
2. Eyes (Intraocular)
3. Nose (Nasal)
4. Lungs (Inhalation)
5. Skin (Topical/ Transdermal)
6. Rectum
7. Vagina
8. Injections (IV, IM, SC)

Here, we are concerned only about the drug delivery through skin: the transdermal drug delivery system. Oral delivery (tablets and capsules) has been considered as the most appropriate method of drug administration for many decades. The drugs that cannot be taken orally have been traditionally administered through hypodermic needles. However, the hypo-dermic injections have many disadvantages, such as the presence of pain, possibility of having infections, and necessity of medical expertise to complete the injection process.

These problems have therefore led to invention and development of new methods of drug delivery. So, transdermal drug delivery is an alternative route of drug administration.

B. Definition

Transdermal drug delivery is self-contained continuous dosage forms which when applied to the intact skin, delivers the drug through skin at controlled rate to the systemic circulation. It is a viable administration route for potent and low molecular weight therapeutic agent [2].

Drug can be delivered across the skin to have an effect on the tissue adjacent to the site of application (topical delivery) or to have an effect after distribution through the circulatory system (systemic delivery). There are many advantages in delivering drugs through skin; the barrier properties of the skin provide a significant challenge.

C. Structure of Skin

For development and optimization of effective transdermal formulation, it is important to understand the mechanism of drug permeation from the delivery device across the skin. The skin is the largest organ in the human body, highly organized structure consisting three main histological layers, called epidermis, dermis and hypodermis (subcutaneous tissues). The skin of an average adult body covers about $2m^2$ and receives about one third of the blood circulating through the body.

The epidermis is further subdivided into five anatomical layers [3]:

1) Stratum Corneum (SC)

2) Stratum Lucidum

3) Stratum Granulosum

4) Stratum Spinosum

5) Stratum Germinativum

The outermost layer stratum corneum consists of highly cornified (dead) cells.

The human skin surface is known to contain average 10-70 hair follicles and 200-250 sweat ducts on every square centimeter of the skin area.

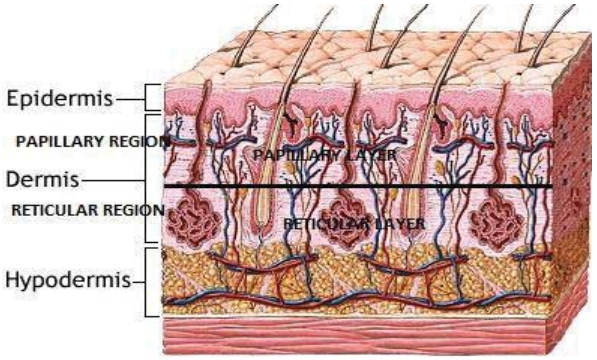

Fig. 1: Structure of the skin (Source:https://www.pinterest.com/pin/562738915914723926/)

Beneath the epidermis, the skin has another layer dermis consisting blood capillaries, sweat glands and sebaceous glands. This layer is again divided into two sub-layers: one is papillary region consisting networks of blood capillaries and another is reticular region consisting nexus of blood vessels, sweat glands and sebaceous glands. The third layer is hypodermis which attaches the skin to its underlying bones and muscles and contains blood vessels and the nerves [2].

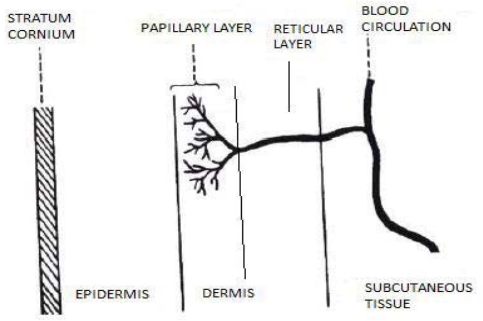

Fig. 2: Four layers of the model [2]

The skin is a readily accessible surface for drug delivery in human body. There is considerable interest in the skin as a site of drug application both topical and systemic effect. However, the outermost layer stratum corneum (SC) possess is very difficult barrier to drug penetration thereby limiting topical and transdermal bioavailability.

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D. Transdermal Patches

The skin penetration enhancement techniques have been developed to improve the bioavailability and increase the range of drug for which topical and transdermal delivery is viable option. Various types of patches with drugs and penetration enhancers have been developed nowadays. A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the blood stream. The main components of a transdermal patch are [2, 4]:

a) **Liner-** It protects the patch during storage. The liner is removed prior to use.
b) **Drug-** Drug solution in direct contact with releases liner.
c) **Adhesive-** It serves to adhere the components of the patch together along with adhering the patch to the skin.
d) **Membrane-** It controls the release of the drug from the reservoir and multilayered patches.

Some drugs have an inherent capacity to permeate skin without enhancers. However, when this is not a case, chemical or physical permeation enhancers may use in the TDDS.

II. Formulation of Mathematical Model

We present a finite element model for one dimensional steady state drug diffusion with partitioning through the interfaces between the different layers of the skin in the transdermal drug delivery system. In this model we take skin structure with four layers (shown in Figure 2):

1. Epidermis (Consisting dead cells and no blood capillaries)
2. Dermis with two sub layers:
   i) Papillary region (consisting fine blood capillaries)
   ii) Reticular region (consisting blood vessels, sweat glands and sebaceous glands)
3. Subcutaneous Tissue or Hypodermis (consisting blood vessels and nerves)

It is also assumed that the concentration of applied drug has varied linearly in each layer and is defined as a function of one space variable x, which denotes the depth below the skin surface, the partition coefficients, the diffusivity and the absorption coefficient in each layer are taken constant.

In 1855, Fick recognized that the equation of heat conduction developed by Fourier in 1822 could be applied to mass transfer. Fick gave the Fick's First law of diffusion which states that the flux is proportional to concentration gradient $\frac{dC}{dx}$. Hence,

$$J = -D\frac{dC}{dx} \qquad (1)$$

Where, D is diffusivity, C is concentration of drug and x is distance of movement normal to the surface of the barrier [5, 6, 7, 8].

In the most real situations, the concentration profile and the concentration gradient are changing with time. The change of the concentration profile is given by Fick's Second law, which is combination of Fick's First law (1) and the conservation equation $\frac{\partial C}{\partial t} = -\nabla . J$ i.e.,

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

This equation (2) was mostly employed to study heat diffusion in dermal region. Similar equations has also been widely used by Saxena and his coworkers (V.P. Saxena1983, Saxena and Ayra1981 and Saxena and Bindra1987)[9, 10, 11]. In most of the cases finite element method has been employed in other to study the temperature distribution. Gurung and Saxena, 2009[12] have used this approach to study one dimensional unsteady state temperature distribution in human dermal parts. Saxena and Sharma (2011)[13] used this approach to solve one dimensional drug distribution problem in three layered human dermal region by using quadratic shape function. Recently Gupta et.al (Vineeta Gupta, S.S. Pandey, V.P. Saxena, 2012)[7, 14] used the same approach using linear shape function as well as quadratic shape function in three layered human skin. In viewing this, an attempt has been made here to solve one dimensional steady state drug distribution problem in four layered human skin using finite element method.

When drug is diffused in dermal layers, it is mainly absorbed by tissues and blood but tissue absorption rate is decreasing function of drug concentration and the drug absorption by other factors, is almost negligible, hence the transport of drugs in the skin is governed by the following differential equation:

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial C}{\partial x}\right) - T(C) - B \qquad (3)$$

Where,

T(C) = Tissue absorption rate of drug depending on the concentration of drug C.

B = Drug intake rate by blood.

x = Depth below the skin surface.

The value of the parameters depend on time t and depth x where $a_{i-1} \le x \le a_i$. The thickness of four layers of the skin are respectively $a_1 - a_0$, $a_2 - a_1$, $a_3 - a_2$, and $a_4 - a_3$ (shown in Fig. 3).

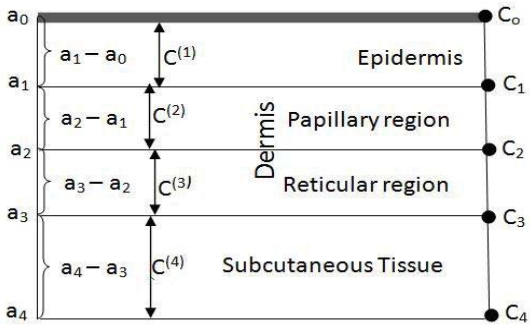

Fig. 3: Nodal concentration with field variables

The drug distribution has mild barrier effect at the interfaces. The flux of drug is generally continuous and hence,

$$C^{(i)} = \rho_i C^{(i)} \text{ at } a_i \text{ (i = 1, 2, 3)} \qquad (4)$$

where, ρ_i are the skin partition coefficients for drug at respective interfaces. In most cases $\rho_i = 1$.

The concentration of drug at outer surface (at x = a_0) is C_0 (is known). Drug is targeted up to subcutaneous tissue (Hypodermis) only and has negligible concentration beyond hypodermis. Therefore at the innermost boundary (x = a_4), the concentration is $C_4 = 0$.

The epidermis contains almost the dead cells and has no blood capillaries and vessels. So, the tissue absorption rate is very less in this layer and we consider negligible in this model. The drug intake rate by blood in this layer is also zero. After absorbing drug by tissues, the concentration of drug increases there and then the absorption rate of the tissues decreases, hence the tissue absorption rate is decreasing function of concentration. Therefore, we take

$$T_i(C) = e^{-ki}C^{(i)} \qquad (5)$$

where, k_i are absorption parameter in each layer which may be different for different drugs. Thus for marginally small concentrations i.e., $k_i \ll 1$, we can write

$$T_i(C) = 1 - kiC^{(i)} \qquad (6)$$

As the transdermal drug delivery is free from the first pass, metabolism effect, we ignore the metabolism in the skin tissues. In transdermal drug delivery system, the drug is released in the constant rate (controlled released) and hence concentration at a particular depth is always constant during the period of application of the patch. So, for this steady state case the equation (3) becomes

$$\frac{d}{dx}\left(D\frac{dC}{dx}\right) - T(C) - B = 0 \qquad (7)$$

For particular patch, the concentration of drug at the outer surface C_0 is known.

III. Solution of the Model

Comparing equation (7) with Euler-Lagrange equation, transforms to the variational form

$$I = \int_0^L \left[\frac{D}{2}\left(\frac{dC}{dx}\right)^2 + \left(B + \frac{1}{2}\right)C + \frac{T(C)}{2}C\right]dx \qquad (8)$$

where, L is total thickness of the skin ($a_4 - a_0$). For optimum value of I, L is divided into four layers of the thickness $a_1 - a_0$, $a_2 - a_1$, $a_3 - a_2$, and $a_4 - a_3$(as shown in Figure 3).

The parameters D, B, T are taken constant for each layer, then above variational form (8) can be written in the iterative form as

$$I_i = \int_{a_{i-1}}^{a_i} \left[\frac{D_i}{2} \left(\frac{dC^{(i)}}{dx} \right)^2 + \left(B_i + \frac{1}{2} \right) C^{(i)} + \frac{T(C)}{2} C^{(i)} \right] dx \quad (9)$$

The field variable $C^{(i)}$ for each layer is approximated by the linear shape function [15]

$$C^{(i)} = \frac{C_{i-1}a_i - C_i a_{i-1}}{a_i - a_{i-1}} + \frac{C_i - C_{i-1}}{a_i - a_{i-1}} x \quad (10)$$

of the one space variable x with $a_0 = 0$. Then the equation (9), for each layer is:

$$I_1 = \int_0^{a_1} \left[\frac{D_1}{2} \left(\frac{C_1 - C_0}{a_1} \right)^2 + \left(B_1 + \frac{1}{2} \right) \left(C_0 + \frac{C_1 - C_0}{a_1} x \right) + \frac{T_1}{2} \left(C_0 + \frac{C_1 - C_0}{a_1} x \right) \right] dx \quad (11)$$

$$I_2 = \int_{a_1}^{a_2} \left[\frac{D_2}{2} \left(\frac{C_2 - C_1}{a_2 - a_1} \right)^2 + \left(B_2 + \frac{1}{2} \right) \left(\frac{C_1 a_2 - C_2 a_1}{a_2 - a_1} + \frac{C_2 - C_1}{a_2 - a_1} x \right) + \frac{T_2}{2} \left(\frac{C_1 a_2 - C_2 a_1}{a_2 - a_1} + \frac{C_2 - C_1}{a_2 - a_1} x \right) \right] dx \quad (12)$$

$$I_3 = \int_{a_2}^{a_3} \left[\frac{D_3}{2} \left(\frac{C_3 - C_2}{a_3 - a_2} \right)^2 + \left(B_3 + \frac{1}{2} \right) \left(\frac{C_2 a_3 - C_3 a_2}{a_3 - a_2} + \frac{C_3 - C_2}{a_3 - a_2} x \right) + \frac{T_3}{2} \left(\frac{C_2 a_3 - C_3 a_2}{a_3 - a_2} + \frac{C_3 - C_2}{a_3 - a_2} x \right) \right] dx \quad (13)$$

$$I_4 = \int_{a_3}^{a_4} \left[\frac{D_4}{2} \left(\frac{C_4 - C_3}{a_4 - a_3} \right)^2 + \left(B_4 + \frac{1}{2} \right) \left(\frac{C_3 a_4 - C_4 a_3}{a_4 - a_3} + \frac{C_4 - C_3}{a_4 - a_3} x \right) + \frac{T_4}{2} \left(\frac{C_3 a_4 - C_4 a_3}{a_4 - a_3} + \frac{C_4 - C_3}{a_4 - a_3} x \right) \right] dx \quad (14)$$

Integrating I_1, I_2, I_3, and I_4, we get [17]

$$I_1 = \mathrm{G_1C_0} + \mathrm{G_1C_1} + \mathrm{F_1C_0^2} + \mathrm{F_1C_1^2} - 2\mathrm{F_1C_0C_1} \quad (15)$$
$$I_2 = \mathrm{G_2C_1} + \mathrm{G_2C_2} + \mathrm{F_2C_1^2} + \mathrm{F_2C_2^2} - 2\mathrm{F_2C_1C_2} \quad (16)$$
$$I_3 = \mathrm{G_3C_2} + \mathrm{G_3C_3} + \mathrm{F_3C_2^2} + \mathrm{F_3C_3^2} - 2\mathrm{F_3C_2C_3} \quad (17)$$
$$I_4 = \mathrm{G_4C_3} + \mathrm{F_4C_3^2} \quad (18)$$

Where,

$\mathrm{E_1} = \mathrm{B_1} + 1/2$ $\quad F_1 = \frac{D_1}{2a_1}$ $\quad G_1 = \frac{a_1}{4}(2E_1 - T_1)$

$\mathrm{E_2} = \mathrm{B_2} + 1/2$ $\quad F_2 = \frac{D_2}{2(a_2 - a_1)}$ $\quad G_2 = \frac{a_2 - a_1}{4}(2E_2 - T_2)$

$\mathrm{E_3} = \mathrm{B_3} + 1/2$ $\quad F_3 = \frac{D_3}{2(a_3 - a_2)}$ $\quad G_3 = \frac{a_3 - a_2}{4}(2E_3 - T_3)$

$\mathrm{E_4} = \mathrm{B_4} + 1/2$ $\quad F_4 = \frac{D_4}{2(a_4 - a_3)}$ $\quad G_4 = \frac{a_4 - a_3}{4}(2E_4 - T_4)$

Assembling these I_i, to obtain

$$I = I_1 + \mathrm{I_2} + \mathrm{I_3} + \mathrm{I_4}$$
$$= \mathrm{G_1C_0} + \mathrm{G_1C_1} + \mathrm{F_1C_0^2} + \mathrm{F_1C_1^2} - 2\mathrm{F_1C_0C_1} + \mathrm{G_2C_1} + \mathrm{G_2C_2} + \mathrm{F_2C_1^2} + \mathrm{F_2C_2^2} - 2\mathrm{F_2C_1C_2} + \mathrm{G_3C_2} + \mathrm{G_3C_3} + \mathrm{F_3C_2^2} + \mathrm{F_3C_3^2} - 2\mathrm{F_3C_2C_3} + \mathrm{G_4C_3} + \mathrm{F_4C_3^2} \quad (19)$$

To optimize I, we differentiate it with respect to each nodal concentration and equate them to zero.

i.e., $\frac{\partial I}{\partial C_i} = 0$ for i = 1, 2, 3 we get,

$$2(\mathrm{F_1} + \mathrm{F_2})\mathrm{C_1} - 2\mathrm{F_2C_2} = 2\mathrm{F_1C_0} - \mathrm{G_1} - \mathrm{G_2} \quad (20)$$
$$-2\mathrm{F_2C_2} + 2(\mathrm{F_2} + \mathrm{F_3})\mathrm{C_2} - 2\mathrm{F_3C_3} = -\mathrm{G_2} - \mathrm{G_3} \quad (21)$$
$$-\mathrm{F_3C_2} + 2(\mathrm{F_3} + \mathrm{F_4})\mathrm{C_3} = -\mathrm{G_3} - \mathrm{G_4} \quad (22)$$

This system of equation forms the tri-diagonal system

$$\mathrm{AC} = \mathrm{B} \quad (23)$$

Where, $A = \begin{bmatrix} 2(F_1 + F_2) & -2F_2 & 0 \\ -2F_2 & 2(F_2 + F_3) & -2F_3 \\ 0 & -2F_3 & 2(F_3 + F_4) \end{bmatrix}$, $C = \begin{bmatrix} C_1 \\ C_2 \\ C_3 \end{bmatrix}$ and $B = \begin{bmatrix} 2F_1C_0 - G_1 - G_2 \\ -G_2 - G_3 \\ -G_3 - G_4 \end{bmatrix}$

Solving the equation (23), we get the concentrations and then we can compute easily the field variables of the four layered human dermal parts.

IV. Numerical Results, Discussion and Conclusion

A. Numerical Results

On solving the system of linear equation (23), we get the nodal concentrations C_i (i = 1, 2, 3), which in turn are substituted in (10) to determine the values of the field variables $C^{(i)}$. The values of diffusivity D_i, tissue absorption rate $T_i(C)$ and drug intake by blood B_i varies according as the structure of the skin in this study. The following values of the physical and physiological parameters are, feasible and fall within the admissible range and, used for obtaining concentration profile in the region. [7, 12, 16]

Table 1: Drug absorption rates of tissue and blood according to skin thickness

	Interfaces from surface(cm)				$T_i(C)(\times 10^{-4}mg.cm^{-3}s^{-1})$			$B_i(\times 10^{-3}mg.cm^{-3}s^{-1})$		
SET	a_1	a_2	a_3	a_4	T_2	T_3	T_4	B_2	B_3	B_4
I	0.1	0.2	0.35	0.5	1.0	2.0	4.0	2.0	3.0	5.0
II	0.1	0.2	0.3	0.7	5.0	6.0	8.0	4.0	5.0	7.0
III	0.1	0.25	0.4	0.9	20.0	30.0	50.0	10.0	15.0	20.0

Table 2: Set of different values of diffusivity (cm^2s^{-1})

SET	D_1	D_2	D_3	D_4
I	1.83×10^{-2}	3.80×10^{-2}	4.52×10^{-2}	6.04×10^{-2}
II	5.83×10^{-2}	6.80×10^{-2}	52.83×10^{-2}	9.04×10^{-2}
III	4.00×10^{-1}	6.52×10^{-1}	7.58×10^{-1}	9.05×10^{-1}

The values of diffusivity D_i depend on the physicochemical properties of the substances and drugs used in the patch can be changed up to the desired level by using appropriate physical or chemical enhancers. The tissue absorption rate $T_i(C)$ and drug intake rate by blood B_i vary according to the structure of skin under study.

The graphs have been plotted between field concentration C(i) and thickness of the skin x for different sets of parameters for different thickness of skin layers..

The graphs in Fig. 4 and 5 show the concentration profile for various initial concentration C_0 and different thicknesses of dermal layers and corresponding parameters and different sets of diffusivity.

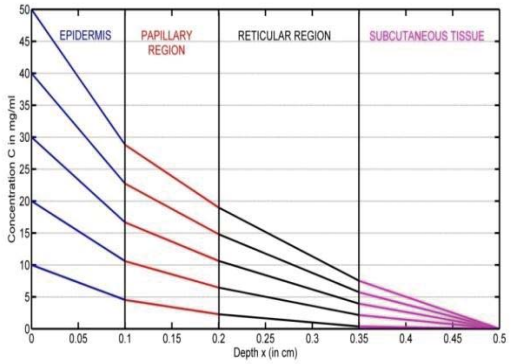

Fig.4: Concentration profile for parameters form SET I of table 1 and diffusivity SET 1 of table 2

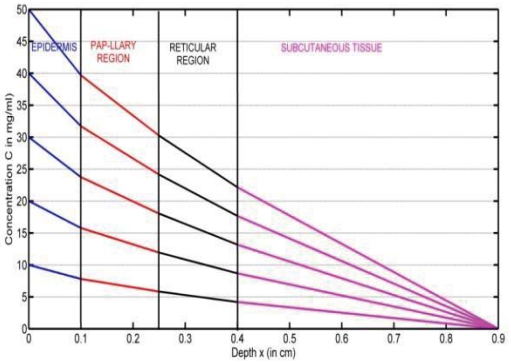

Fig.5: Concentration profile for parameters form SET III of table 1 and diffusivity SET III of table 2

The graphs in the Fig. 6 and 7 show the concentration profiles for the same initial concentration 50 mg/ml for same thickness of the dermal layers and different set of diffusivity from SET I and II of table 2.

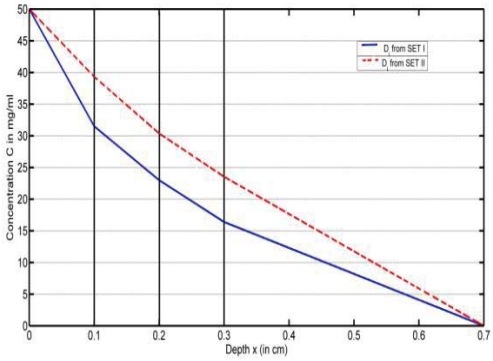

Fig.6: Concentration profile for C_0= 50mg/ml, parameters form SET II of table 1 and diffusivity SET 1 and II of table 2

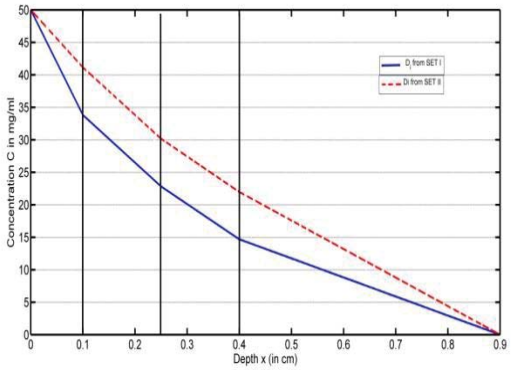

Fig.7: Concentration profile for C_0 = 50mg/ml, parameters form SET III of table 1 and diffusivity SET 1 and II of table 2

The graphs in the Fig. 8 and 9 show the concentration profiles for the different thicknesses of dermal layers but same Di from SET I of table 2

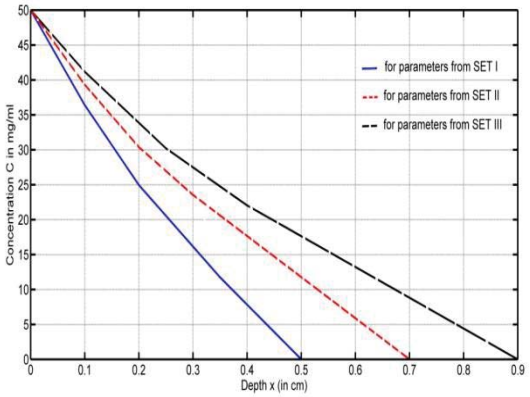

Fig. 8 : Concentration profile for C_0= 50mg/ml, parameters form SET I, II, and III of table 1 and D_i from SET I of table 2

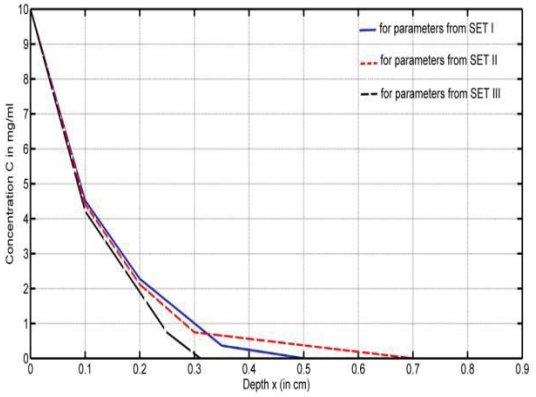

Fig. 9 : Concentration profile for C_0= 10mg/ml, parameters form SET I, II, and III of table 1 and D_i from SET I of table 2

The graphs in the Fig. 10 and 11 show the concentration profiles for the different thicknesses of dermal layers but same Di from SET III of table 2

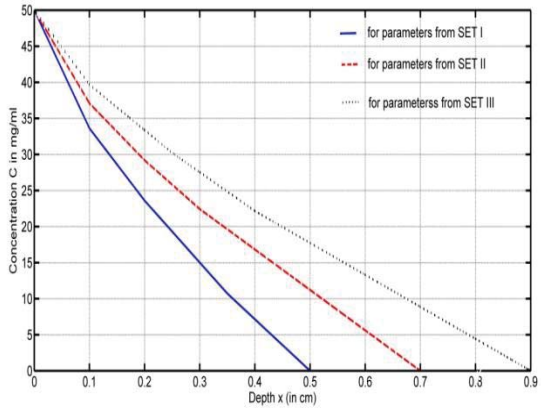

Fig. 10 : Concentration profile for C_0= 50mg/ml, parameters form SET I, II, and III of table 1 and D_i from SET III of table 2

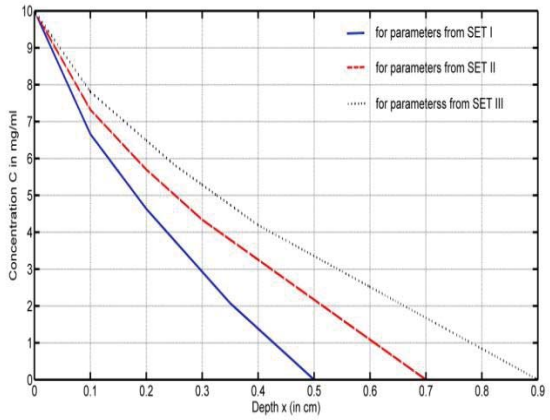

Fig. 11 : Concentration profile for C_0= 10mg/ml, parameters form SET I, II, and III of table 1 and D_i from SET III of table 2

B. Discussion

The graphs in Fig. 4 and 5 show that the increase in diffusion increases the concentration and decreases as we move towards the subcutaneous tissue from the outer surface of the skin. This is due to the effect of the absorption of the drug. The slop of the curve changes at the interfaces due to the change in properties of each sub-region.

The graphs in Fig. 6 and 7 individually show the effect of diffusivity in the concentration profile for the same thickness of the dermal layers and absorption coefficients i.e., at same part of the body. But, the simultaneous study of these two graphs show the effect of absorption coefficients (tissue and blood) in the concentration profile in the dermal layers for the same diffusivity. The rate of decrease of drug concentration in the dermal layers increases as absorption coefficient increases.

Also the graphs in Fig. 8 – 11 show the effect of different thickness of dermal layers i.e., at the different parts of the body for the same substance (drug) and same set of diffusivity. Fig. 8 and 10 show that the variation in thickness shows only slight variation in the concentration profile when the initial concentration C_0 is high. Fig. 11 shows that the variation in thickness again shows not significant effect in the concentration profile for high diffusivity but Fig. 9 shows that for low initial concentration C_0 and low diffusivity D_i, the variation of thickness shows the remarkable effect in the concentration profile.

That is, the variation of thickness shows the remarkable effect in concentration profile only in case of the small initial concentration and low diffusivity. In Fig. 9 the concentration C_0 = 10 mg/ml reduces to zero at the middle of reticular region in the skin of thickness 0.9 cm, while concentration reduces to zero only in subcutaneous tissue in the skin of thickness 0.5 cm. The presentation of the graphs plotted in Fig. 8 and 9 can be seen clearly in the thickness wise separate graphs as in the following figures:
.

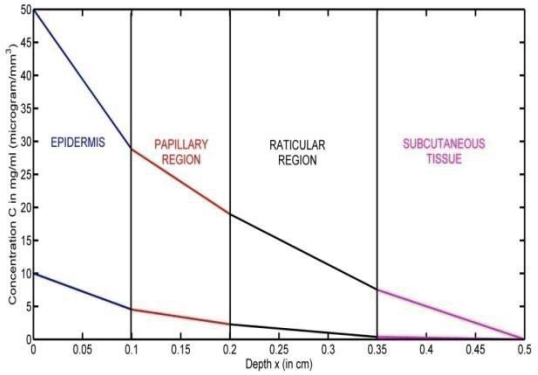

Fig.12: Concentration profile for thickness and other parameters from SET I of table 1 and diffusivity from SET I of table 2

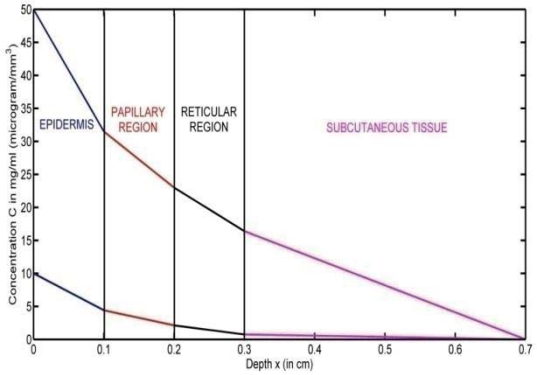

Fig.13: Concentration profile for thickness and other parameters from SET II of table 1 and diffusivity from SET I of table 2

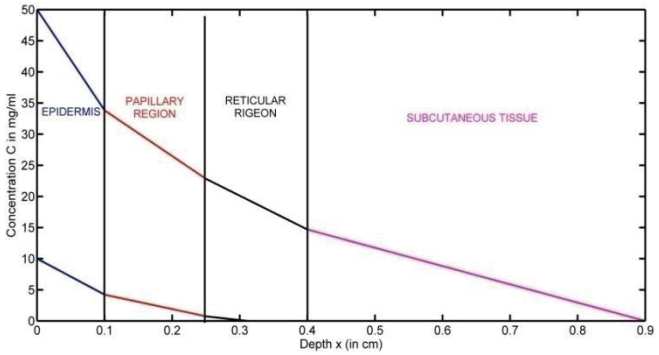

Fig. 14: Concentration profile for thickness and other parameters from SET III of table 1 and diffusivity from SET I of table 2

C. Conclusion

The exact amount of drug required depends on the physicochemical and biological properties of the compound. If these are known, the amount will be estimated. This solution predicts the amount of the drug release and individual concentration profiles in the skin. The model is useful to adjust various parameters, such as thickness, area, adhesive formulation of drug and enhancer concentrations to meet the several objectives: like drug dose, avoidance of irritation, dimension of patch to reduce cost etc. The appropriate combination of these parameters leads to develop the controlled drug delivery system. Without a precise knowledge of concentration and degree of storability of drugs, one cannot manufacture effective transdermal patch. The experiments using various combinations of parameters involve expensive clinical trials with potentially long evaluation period. This 1-D diffusion model of transdermal delivery predicts the delivery kinetics of transdermal patches and accelerates this process by enabling:

- rapid optimization of transdermal drug delivery parameters.
- insight into factors governing optimal delivery.
- reduction of number and duration of clinical experiments.
- knowledge for rapid development of transdermal drug delivery system.

This study is expected to provide a better understanding of the drug delivery mechanism and comprehend analysis of the effect of some physicochemical parameters on concentration

profile. This model will help to develop highly effective drug formulation and __accurate dosing regimens.

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