Chapter 3

Mathematical model on drug diffusion in human body using transdermal drug delivery system

3.1 Introduction

In medical sciences, various attempts have been made to search new drugs and to find the improved ways of drug delivery in the body. Oral drug delivery like pills has been considered as one of the most appropriate method of drug administration for decades worldwide. There are many drugs which cannot be taken orally so they are injected into the body by making use of hypodermic needles. However, the hypodermic injections have many disadvantages such as the presence of pain, the appearance of infections and the requirement of medical expertise to complete the process [45]. For the administration of drug and its absorption to target the desired compartment of the biological tissue; it is one of the challenging problems to control the adverse effects of the drug delivery through \textit{in-vivo} tissues. Thus, it is desirable to address this issue by using an alternate route of drug administration through dermal regions of the human body with minimal side effects. Transdermal drug delivery (TDD) is an alternate method of drug administration to pills and injections. This method operates by delivery of drugs into the human body tissues across the skin and subcutaneous layers. TDD system has the ability to overcome the problems associated with the
traditional delivery of drugs [3].

Transdermal drug delivery system has been in existence since last thirty years. Transdermal therapeutic systems are defined as self contained, continuous dosage forms which when applied to the skin deliver the drug through it at a controlled rate to the systemic circulation. TDD is a feasible administration route for potent and low molecular weight therapeutic agents. The choice of therapeutic agent is determined by the number of factors which include the physio-co-chemical properties of the drug and its interactions with the membrane. This is due to the barrier function of the skin represented by the outer layer- the stratum corneum, which generally allows diffusion of only small molecular weight solutes. To overcome this diffusion limitation at the stratum corneum, various methods have been developed the efficient procedure of drug delivery across stratum corneum which includes chemical enhancers or physical enhancer technique e.g. iontophoresis (a physical process in which ion flow diffusively in a medium driven by an applied electric field) and ultrasound [47].

Mathematical models of skin permeability are highly relevant to the fields of transdermal drug delivery systems. These models are helpful in developing fundamental understanding of bio-transport processes. The impact of such models on TDD has been particularly significant. The transport of drug through the device and skin follows the Fickian diffusion process by means of a simple homogeneous membrane. Kalia and Guy [21] have established the mathematical models on transport phenomena describing the release of drug from various delivery systems and formulations based on the solution of Fick’s second law. In these models, skin - outer layer was simply treated as a boundary condition and the main attention was focussed on the drug transport, also analytical expressions were found for the amount of drug released from the device. Qaliaf et al. [3] developed a mathematical model and carried numerical simulations to de-
scribe the pharmocokinetics of drug penetration into the skin regions from microneedle array. Missel [40] used finite element method for modelling of diffusion and partitioning in biological systems. One-dimensional mathematical models were developed by Lee et al. [34], [35] with a single component drug penetration via both intercellular and transcellular pathways of the skin. The dermal region of the human body was divided into stratum corneum and viable epidermal layers and diffusion of drug from the porous device into the multiple pathway model of skin was calculated using finite difference approximations. Sharma and Saxena [51] established one-dimensional steady state model on transdermal drug delivery distribution in human body using FEM with quadratic shape approximations. Most of the models have taken into consideration only the drug transport in the devices and did not discuss the flow of drug in the skin and subcutaneous tissues. In this chapter, a variational finite element approach with linear and quadratic shape functions are used to obtain the solution of diffusion equation taking into account the role of diffusion constant and the rate constants. The method has been used because of its applicability over the irregular geometries. Since the human skin and sub-cutaneous tissues have irregular geometry, therefore this method guarantees the reasonable outcome as compared to the other numerical methods.

3.2 Formulation of model

The transport of drugs in the biological tissues of human body through transdermal system is governed by the differential equation given in Crank [12]

\[
\frac{\partial}{\partial x} \left( D \frac{\partial C}{\partial x} \right) - A(C) - B = \frac{\partial C}{\partial t}
\]  

(3.2.1)

where \( C, D \) and \( t \) denote the drug concentration, mass diffusivity and time parameters respectively. Also, \( A(C) \) - the function of concentration represents the absorption rate of drug by the
tissues and $B$ represents the rate of drug intake by the blood.

The dermal system in this study has been discretized into stratum corneum, epidermis and dermis with concentration $C^{(i)}$ where $i = 1, 2, 3$, and the schematic diagram of dermal regions is given in Figure (3.1).

![Schematic diagram of dermal regions with nodal drug concentrations.](image)

By the law of mass action, the absorption rate of drug by the tissue decreases with changing time. Therefore, we assume the absorption rate of drug as a decreasing function of drug concentration as

$$A_i(C^{(i)}) = \exp(-k_i C^{(i)}) \text{ for } i = 1, 2, 3$$

$$\approx 1 - k_i C^{(i)}$$

(3.2.2)

where $k_i(<< 1)$ represents the rate constants.

The drug distribution processes through the interfaces of dermal layers with non-homogeneous character of tissues. Therefore, the drug flow due to the barrier coefficients of the interfaces can be approximated by

$$C^{(i)} = \sigma_i C^{(i+1)}$$

(3.2.3)
Also, the flux is generally continuous due to physiological structure of dermal regions, therefore, we have

\[ D_i \frac{\partial}{\partial x} C^{(i)} = D_{i+1} \frac{\partial}{\partial x} C^{(i+1)}; \quad \text{for} \ x = a_i \quad \text{where} \ i = 1, 2. \]

(3.2.4)

Here \( x \) and \( \sigma_i \) where \( i = 1, 2 \), represents the depth below the skin surface and the skin partition coefficients for the drug at the respective interfaces respectively. \( \sigma_i \approx 1 \) for most of the drugs [17].

### 3.3 Mathematical method

The solution of such type of problem has been carried out by various researchers and it is worthwhile to mention that the numerical solution of the boundary value problem is important for various situations due to the non-availability of the analytical and exact solutions. Among all the numerical methods, the finite element method is considered as one of the most reliable methods in numerical systems. The method has advantage over other methods due to position dependent properties of parameters and their flexibility. Moreover, the method is applicable to understand the feasible diffusion in irregular geometries.

The variational integral

\[ I = \int F(C, C', x)dx \]  

(3.3.1)

in optimum form is equivalent to Euler Lagrange’s differential equation (1.11.1).

On comparing equation (3.2.1) with Euler Lagrange’s equation (1.11.1), we obtain the variational integral

\[ I = \int_{a_0}^{a_3} \left[ \frac{D}{2} \left( \frac{\partial C}{\partial x} \right)^2 + (1 + B)C - \frac{k}{2}C^2 + \frac{1}{2} \frac{\partial C^2}{\partial t} \right] dx \]  

(3.3.2)
where $a_0$ to $a_3$ denotes the total thickness of the dermal tissues.

The solution $C(x)$ determining the drug concentration at various regions of dermal layers can be approximated using polynomial functions of higher degrees. Since the distance between the skin layers is of minute length, the higher order polynomial shape functions may not contribute a significant change in the drug diffusion, therefore the concentration of drug in each region is approximated by a lower degree polynomial. Two cases were considered and are discussed below:

(a) Linear shape function

Let the solution of the problem be established over each of the sub-domains using linear shape functions given as

$$C^{(i)} = \frac{a_i C_{i-1} - a_{i-1} C_i}{a_i - a_{i-1}} + \frac{C_i - C_{i-1}}{a_i - a_{i-1}} x; \quad (3.3.3)$$

where $i = 1, 2, 3$ and $\sigma_0 = 1$.

The variational integrals on each of the sub domains is given as

$$I_1 = \frac{1}{2} \int_{a_0}^{a_1} \left[ D_1 \left( \frac{\partial C^{(1)}}{\partial x} \right)^2 + 2(1 + B_1) C^{(1)} - k_1 (C^{(1)})^2 + \frac{\partial}{\partial t} (C^{(1)})^2 \right] dx ;$$

$$= \frac{1}{2} \int_{0}^{a_1} \left[ D_1 \left( \frac{C_1 - C_0}{a_1 - a_0} \right)^2 + 2(1 + B_1) \left( \frac{C_0 a_1 - C_1 a_0}{a_1 - a_0} + \frac{C_1 - C_0}{a_1 - a_0} x \right) \right. \left. - k_1 \left( \frac{C_0 a_1 - C_1 a_0}{a_1 - a_0} + \frac{C_1 - C_0}{a_1 - a_0} x \right)^2 + \frac{\partial}{\partial t} \left( \frac{C_0 a_1 - C_1 a_0}{a_1 - a_0} + \frac{C_1 - C_0}{a_1 - a_0} x \right)^2 \right] dx ;$$

$$= \frac{1}{2} \int_{0}^{a_3} \left[ D_1 \left( \frac{C_1 - C_0}{a_1 - a_0} \right)^2 + 2(1 + B_1) \left( \frac{C_0 a_1 - C_1 a_0}{a_1 - a_0} + \frac{C_1 - C_0}{a_1 - a_0} x \right) \right. \left. - k_1 \left( \frac{C_0 a_1 - C_1 a_0}{a_1 - a_0} + \frac{C_1 - C_0}{a_1 - a_0} x \right)^2 + \frac{\partial}{\partial t} \left( \frac{C_0 a_1 - C_1 a_0}{a_1 - a_0} + \frac{C_1 - C_0}{a_1 - a_0} x \right)^2 \right] dx ;$$

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\[- k_1 \left\{ C_0^2 + \frac{1}{a_1^2} (C_1 - C_0)^2 x^2 + \frac{2}{a_1} (C_0 C_1 - C_0^2) x \right\} \]

\[+ \frac{\partial}{\partial t} \left\{ C_0^2 + \frac{1}{a_1^2} (C_1 - C_0)^2 x^2 + \frac{2}{a_1} (C_0 C_1 - C_0^2) x \right\} \right\} \right] dx ;

\[- \frac{1}{2} \left[ \frac{D_1}{a_1} (C_1 - C_0)^2 + 2(1 + B_1) (C_0 a_1 + \frac{C_1 - C_0}{2} a_1) \right. \]

\[+ \left. k_1 \left\{ C_0^2 a_1 + \frac{a_1^2}{3} (C_1 - C_0)^2 + (C_0 C_1 - C_0^2) a_1 \right\} \right]

\[+ \frac{\partial}{\partial t} \left\{ C_0^2 a_1 + \frac{1}{3} (C_1 - C_0)^2 a_1 + (C_0 C_1 - C_0^2) a_1 \right\} \right] ;

\[- \frac{1}{2} \left[ \frac{D_1}{a_1} (C_1 - C_0)^2 + (1 + B_1) (C_0 + C_1) a_1 - \frac{k_1 a_1}{3} (C_0^2 + C_1^2 + C_0 C_1) \right. \]

\[+ \left. a_1 \left\{ 2 C_0 \dot{C}_0 + \frac{2}{3} (\dot{C}_1 - \dot{C}_0) (C_1 - C_0) + C_0 \dot{C}_1 + C_1 \dot{C}_0 - 2 C_0 \dot{C}_0 \right\} \right] ;

\[- \frac{1}{2} \left[ \frac{D_1}{a_1} (C_1 - C_0)^2 + (1 + B_1) (C_0 + C_1) a_1 - \frac{k_1 a_1}{3} (C_0^2 + C_1^2 + C_0 C_1) \right. \]

\[+ \left. \frac{a_1}{3} \left( 2 C_0 \dot{C}_0 + 2 C_1 \dot{C}_1 + \dot{C}_0 C_1 + C_0 \dot{C}_1 \right) \right] . \quad (3.3.4) \]

\[I_2 = \frac{1}{2} \int_{a_2}^{a_1} \left[ D_2 \left( \frac{\partial C^{(2)}}{\partial x} \right)^2 + 2 (1 + B_2) C^{(2)} - k_2 (C^{(2)})^2 + \frac{\partial}{\partial t} (C^{(2)})^2 \right] dx ;

\[- \frac{1}{2} \int_{a_2}^{a_1} \left[ D_2 \left( \frac{C_2 - \frac{C_1}{\sigma_1}}{a_2 - a_1} \right)^2 + 2 (1 + B_2) \left( \frac{\frac{C_1}{\sigma_1}}{a_2 - a_1} + \frac{C_2 - \frac{C_1}{\sigma_1}}{a_2 - a_1} x \right) \right] \]
\[-k_2 \left( \frac{C_1 a_2 - C_2 a_1}{a_2 - a_1} + \frac{C_2 - C_1 a_2}{a_2 - a_1} x \right)^2 + \frac{\partial}{\partial t} \left( \frac{C_1 a_2 - C_2 a_1}{a_2 - a_1} + \frac{C_2 - C_1 a_2}{a_2 - a_1} x \right)^2 \right] \, dx \; ;

\[= \frac{1}{2} \int_{a_1}^{a_2} \left[ D_2 \left( \frac{C_2 - C_1 a_2}{a_2 - a_1} \right)^2 + 2(1 + B_2) \left( \frac{C_1 a_2 - C_2 a_1}{a_2 - a_1} + \frac{C_2 - C_1 a_2}{a_2 - a_1} x \right) \right. \]
\[\left. - k_2 \left\{ \left( \frac{C_1 a_2 - C_2 a_1}{a_2 - a_1} \right)^2 + \left( \frac{C_2 - C_1 a_2}{a_2 - a_1} \right)^2 x^2 + \frac{2}{(a_2 - a_1)^2} \left( \frac{C_1 a_2 - C_2 a_1}{a_2 - a_1} \right) \right\} \right] \, dx \; ;

\[= \frac{1}{2} \left[ \frac{D_2}{a_2 - a_1} \left( \frac{C_2 - C_1 a_2}{a_2 - a_1} \right)^2 + 2(1 + B_2) \left\{ \frac{C_1 a_2 - C_2 a_1}{a_2 - a_1} \right. \right. \]
\[+ \frac{1}{2} \left( \frac{C_2 - C_1 a_2}{a_2 - a_1} \right)(a_2 + a_1) \right\} - k_2 \left\{ \left( \frac{C_1 a_2 - C_2 a_1}{a_2 - a_1} \right)^2 \right. \]
\[\left. + \frac{\left( C_2 - C_1 a_2 \right)^2}{3(a_2 - a_1)}(a_1^2 + a_2^2 + a_1 a_2) + \frac{1}{(a_2 - a_1)} \left( \frac{C_1 a_2 - C_2 a_1}{a_2 - a_1} \right) \right. \]
\[\left. (a_1 + a_2) \right\} + \frac{\partial}{\partial t} \left\{ \left( \frac{C_1 a_2 - C_2 a_1}{a_2 - a_1} \right)^2 \right. \]
\[\left. + \frac{\left( C_2 - C_1 a_2 \right)^2}{3(a_2 - a_1)}(a_1^2 + a_2^2 + a_1 a_2) + \frac{1}{(a_2 - a_1)} \left( \frac{C_1 a_2 - C_2 a_1}{a_2 - a_1} \right) \right. \]
\[\left. (a_1 + a_2) \right\} \right] \; ;

\[= \frac{1}{2} \left[ \frac{D_2}{a_2 - a_1} \left( \frac{C_2 - C_1 a_2}{a_2 - a_1} \right)^2 + (1 + B_2) \left( \frac{C_1 a_2 - C_2 a_1}{a_2 - a_1} \right)(a_2 - a_1) \right] \]
\[ -\frac{k_2}{3}(a_2 - a_1)\left(\frac{C_1^2}{\sigma_1^2} + C_2^2 + \frac{C_1C_2}{\sigma_1}\right) \]
\[ + \frac{(a_2 - a_1)}{3}\left(\frac{2C_1\dot{C}_1}{\sigma_1^2} + 2C_2\dot{C}_2 + \frac{\dot{C}_1C_2}{\sigma_1} + \frac{C_1\dot{C}_2}{\sigma_1}\right) \].

Similarly,
\[ I_3 = \frac{1}{2} \int_{a_2}^{a_3} \left[ D_3 \left(\frac{\partial C^{(3)}}{\partial x}\right)^2 + 2(1 + B_3)C^{(3)} - k_3(C^{(3)})^2 + \frac{\partial}{\partial t}(C^{(3)})^2 \right] dx; \]
\[ = \frac{1}{2} \left[ \frac{D_3}{(a_3 - a_2)}\left(C_3 - \frac{C_2}{\sigma_2}\right)^2 + (1 + B_3)\left(\frac{C_2}{\sigma_2} + C_3\right)(a_3 - a_2) \right. \]
\[ - \frac{k_3}{3}(a_3 - a_2)\left(\frac{C_2^2}{\sigma_2^2} + C_3^2 + \frac{C_2C_3}{\sigma_2}\right) \]
\[ + \frac{(a_3 - a_2)}{3}\left(2\frac{C_2\dot{C}_2}{\sigma_2^2} + 2C_3\dot{C}_3 + \frac{\dot{C}_2C_3}{\sigma_2} + \frac{C_2\dot{C}_3}{\sigma_2}\right) \];

In order to estimate the drug distribution among the entire dermal regions, we assemble variational integrals to obtain \( I = \sum_{i=1}^{3} I_i \) and optimising by taking the partial derivatives of \( I \) with respect to the nodal values \( C_i \) where \( i = 1, 2 \) and equating to zero.

i.e., \( \frac{\partial I}{\partial C_1} = 0 \)

which gives
\[ \frac{2D_1}{a_1}(C_1 - C_0) + a_1(1 + B_1) - \frac{k_1a_1}{3}(2C_1 + C_0) + \frac{a_1}{3}(2\dot{C}_1 + \dot{C}_0) \]
\[ + \frac{2D_2}{(a_2 - a_1)(-\sigma_1)}\left(C_2 - \frac{C_1}{\sigma_1}\right) + \frac{(a_2 - a_1)}{\sigma}(1 + B_2) \]
\[-\frac{k_2}{3}(a_2 - a_1)\left(\frac{2C_1}{\sigma_1^2} + \frac{2C_2}{\sigma_1}\right) + \frac{(a_2 - a_1)}{3}\left(\frac{\dot{C}_2}{\sigma_1} + \frac{2\dot{C}_1}{\sigma_1^2}\right) = 0;\]

or,

\[\alpha_{11}C_1 + \alpha_{12}C_2 + \beta_{11}\dot{C}_1 + \beta_{12}\dot{C}_2 = \gamma_{11}\]

(3.3.7)

where

\[\alpha_{11} = 2\left\{\frac{D_1}{a_1} + \frac{D_2}{\sigma_1^2(a_2 - a_1)} - \frac{1}{3}k_1a_1 - \frac{1}{3\sigma_1^2}k_2(a_2 - a_1)\right\};\]

\[\alpha_{12} = -\left\{\frac{2D_2}{\sigma_1(a_2 - a_1)} + \frac{k_2}{3\sigma_1}(a_2 - a_1)\right\};\]

\[\beta_{11} = \frac{2}{3}\left\{a_1 + \frac{1}{\sigma_1^2}(a_2 - a_1)\right\}; \quad \beta_{12} = \frac{1}{3\sigma_1}(a_2 - a_1);\]

\[\gamma_{11} = \left(\frac{2}{a_1}D_1 + \frac{1}{3}k_1a_1\right)C_0 - a_1(1 + B_1) - \frac{1}{\sigma_1}(a_2 - a_1)(1 + B_2).\]

Also,

\[\frac{\partial I}{\partial C_2} = 0\]

which gives

\[\frac{2D_2}{(a_2 - a_1)}\left(C_2 - \frac{C_1}{\sigma_1}\right) + (1 + B_2)(a_2 - a_1) - \frac{k_2}{3}(a_2 - a_1)\left(2C_2 + \frac{C_1}{\sigma_1}\right) + \frac{(a_2 - a_1)}{3}\left(\frac{\dot{C}_1}{\sigma_1} + 2\dot{C}_2\right) + \frac{2D_3}{(a_3 - a_2)(-\sigma_2)}\left(C_3 - \frac{C_2}{\sigma_2}\right) + \frac{1}{\sigma_2}(1 + B_3)(a_3 - a_2) - \frac{k_3}{3}(a_3 - a_2)\left(2\frac{C_2}{\sigma_2} + \frac{C_3}{\sigma_2}\right) + \frac{(a_3 - a_2)}{3}\left(\frac{\dot{C}_3}{\sigma_2} + 2\dot{C}_2\right) = 0;\]
or,

\[ \alpha_{12} C_1 + \alpha_{22} C_2 + \beta_{12} \dot{C}_1 + \beta_{22} \dot{C}_2 = \gamma_{22} \]  

(3.3.8)

where

\[ \alpha_{22} = 2 \left\{ \frac{D_2}{(a_2 - a_1)} + \frac{D_3}{\sigma_2^2 (a_3 - a_2)} - \frac{1}{3} k_2 (a_2 - a_1) - \frac{1}{3 \sigma_2^2} k_3 (a_3 - a_2) \right\}; \]

\[ \beta_{22} = \frac{2}{3} \left\{ (a_2 - a_1) + \frac{1}{\sigma_2^2} (a_3 - a_2) \right\}; \]

\[ \gamma_{22} = \frac{1}{\sigma_2} \left\{ \frac{2 D_3}{(a_3 - a_2)} + \frac{1}{3} k_3 (a_3 - a_2) \right\} C_3 \]

\[ - (a_2 - a_1) (1 + B_2) - \frac{1}{\sigma_2} (a_3 - a_2) (1 + B_3). \]

The equations (3.3.7) and (3.3.8) in the matrix form can be written as

\[ AC + B \dot{C} = Y \]

(3.3.9)

where

\[ A = \begin{pmatrix} \alpha_{11} & \alpha_{12} \\ \alpha_{12} & \alpha_{22} \end{pmatrix}; \quad B = \begin{pmatrix} \beta_{11} & \beta_{12} \\ \beta_{12} & \beta_{22} \end{pmatrix} \]

and

\[ Y = \begin{bmatrix} \gamma_{11} \\ \gamma_{22} \end{bmatrix}; \quad C = \begin{bmatrix} C_1 \\ C_2 \end{bmatrix}. \]

Case I: (Steady state)

Solving equation \( AC = Y \), we get the values of the concentration of the drug at the nodes \( a_1 \) and \( a_2 \) as

\[ C_1(a_1, 0) = \frac{\gamma_{22} \alpha_{12} - \gamma_{11} \alpha_{22}}{\alpha_{12}^2 - \alpha_{11} \alpha_{22}} \]  

(3.3.10)

\[ C_2(a_2, 0) = \frac{\gamma_{11} \alpha_{12} - \gamma_{22} \alpha_{11}}{\alpha_{12}^2 - \alpha_{11} \alpha_{22}} \]  

(3.3.11)
which in turn on substitution to equation (3.3.3) are used to determine the values of $C^{(i)}$ where $i = 1, 2, 3$.

**Case II: (Unsteady state)**

Applying the Laplace transform to the equation (3.3.9), we have

$$\mathcal{L} \left( AC + B\dot{C} \right) = \mathcal{L}(Y)$$

or,

$$A\mathcal{L}(C) + B\left\{ s\mathcal{L}(C) - C(x, 0) \right\} = \mathcal{L}(Y)$$

implies,

$$(A + Bs)\mathcal{L}(C) = \mathcal{L}(Y) + BC(x, 0)$$

which gives

$$(\alpha_{11} + \beta_{11}s)\dot{C}_1 + (\alpha_{12} + \beta_{12}s)\dot{C}_2 = \frac{\gamma_{11}}{s} + \beta_{11}C_1(a_1, 0) + \beta_{12}C_2(a_2, 0)$$

(3.3.12)

and

$$(\alpha_{12} + \beta_{12}s)\dot{C}_1 + (\alpha_{22} + \beta_{22}s)\dot{C}_2 = \frac{\gamma_{22}}{s} + \beta_{12}C_1(a_1, 0) + \beta_{22}C_2(a_2, 0).$$

(3.3.13)

On solving equations (3.3.12) and (3.3.13), we have

$$\dot{C}_1 = \frac{(\alpha_{22} + s\beta_{22})(m_1 + \frac{\gamma_{11}}{s}) - (\alpha_{12} + s\beta_{12})(m_2 + \frac{\gamma_{22}}{s})}{(s - \alpha)(s - \beta)}$$

(3.3.14)

and

$$\dot{C}_2 = \frac{(\alpha_{11} + s\beta_{11})(m_2 + \frac{\gamma_{22}}{s}) - (\alpha_{12} + s\beta_{12})(m_1 + \frac{\gamma_{11}}{s})}{(s - \alpha)(s - \beta)}$$

(3.3.15)

where $\alpha$ and $\beta$ are the roots of the equation

$$(\alpha_{22} + s\beta_{22})(\alpha_{11} + s\beta_{11}) - (\alpha_{12} + s\beta_{12})^2 = 0.$$  (3.3.16)
Also,

\[ m_1 = \beta_{11}C_1(a_1, 0) + \beta_{12}C_2(a_2, 0) \]

and

\[ m_2 = \beta_{12}C_1(a_1, 0) + \beta_{22}C_2(a_2, 0). \]

Applying the inverse Laplace transform and making use of Heaviside Expansion theorem (3), we get the value of \( C_i \) where \( i = 1, 2 \), which on substitution to equation (3.3.3) are used to determine the value of \( C^{(i)} \) where \( i = 1, 2, 3 \), at any instant of time.

The overall drug concentration can be formulated by assembling the linear variations of each region. This indicates polygonal variations of concentration with discontinuities of flux at the interfaces. In order to obtain the better approximations, the Lagrange’s interpolation method has been used. The method determines the drug concentration with continuous flux between the interfaces and within the region.

\[
C(x) = \frac{(x - a_1)(x - a_2)(x - a_3)}{(a_0 - a_1)(a_0 - a_2)(a_0 - a_3)} C_0 + \frac{(x - a_0)(x - a_2)(x - a_3)}{(a_1 - a_0)(a_1 - a_2)(a_1 - a_3)} C_1 \\
+ \frac{(x - a_0)(x - a_1)(x - a_3)}{(a_2 - a_0)(a_2 - a_1)(a_2 - a_3)} C_2 + \frac{(x - a_0)(x - a_1)(x - a_2)}{(a_3 - a_0)(a_3 - a_1)(a_3 - a_2)} C_3;
\]

\[
= \frac{x^3 - (a_1 + a_2 + a_3)x^2 + (a_1a_2 + a_1a_3 + a_2a_3)x - a_1a_2a_3}{(a_0 - a_1)(a_0 - a_2)(a_0 - a_3)} C_0 \\
+ \frac{x^3 - (a_0 + a_2 + a_3)x^2 + (a_0a_2 + a_0a_3 + a_2a_3)x - a_0a_2a_3}{(a_1 - a_0)(a_1 - a_2)(a_1 - a_3)} C_1 \\
+ \frac{x^3 - (a_0 + a_1 + a_3)x^2 + (a_0a_1 + a_0a_3 + a_1a_3)x - a_0a_1a_3}{(a_2 - a_0)(a_2 - a_1)(a_2 - a_3)} C_2 \\
+ \frac{x^3 - (a_0 + a_1 + a_2)x^2 + (a_0a_1 + a_0a_2 + a_1a_2)x - a_0a_1a_2}{(a_3 - a_0)(a_3 - a_1)(a_3 - a_2)} C_3; \\
= H_0x^3 - H_1x^2 + H_2x - H_3 \quad (3.3.17)
\]

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where the coefficients are given as

\[ H_0 = \sum_{i=0}^{3} \frac{C_i}{\Delta_i}; \quad \Delta_i = \prod_{i \neq j=0}^{3} (a_i - a_j); \quad H_1 = \sum_{i=0}^{3} H_{i1} \frac{C_i}{\Delta_i}; \]

\[ H_{i1} = \sum_{j=0}^{3} a_j; \quad H_2 = \sum_{i=0}^{3} H_{i2} \frac{C_i}{\Delta_i}; \]

\[ H_{02} = a_1 a_2 + a_1 a_3 + a_2 a_3; \quad H_{12} = a_0 a_2 + a_0 a_3 + a_2 a_3; \]

\[ H_{22} = a_0 a_1 + a_0 a_3 + a_1 a_3; \quad H_{32} = a_0 a_1 + a_0 a_2 + a_1 a_2; \]

\[ H_3 = \sum_{i=0}^{3} H_{i3} \frac{C_i}{\Delta_i}; \quad H_{i3} = \prod_{i \neq j=0}^{3} a_j. \]

(b) Quadratic shape function

Let the solution of the problem be established over each of the sub-domains using quadratic shape functions given as

\[ C^{(i)} = \alpha_i + \beta_i x + \gamma_i x^2 \quad (3.3.18) \]

With the help of heat flux continuities at the interfaces (equations (3.2.3) and (3.2.4)) and the nodal concentrations at \( x = a_i \) where \( i = 0, 1, 2, 3 \), the values of \( \alpha_1, \beta_1 \) and \( \gamma_1 \) in terms of the nodal concentrations are obtained as \( C_0, \frac{C_1 - C_0}{a_1} \) and 0 respectively, while the values of \( \alpha_i, \beta_i \) and \( \gamma_i \) where \( i = 2, 3 \), in terms of nodal concentrations are obtained from the following system of equations

\[
\begin{bmatrix}
1 & a_1 & a_1^2 & 0 & 0 & 0 \\
1 & a_2 & a_2^2 & 0 & 0 & 0 \\
0 & D_2 & 2a_1 D_2 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & a_2 & a_2^2 \\
0 & 0 & 0 & 1 & a_3 & a_3^2 \\
0 & -D_2 & -2a_2 & 0 & D_3 & 2a_2
\end{bmatrix}
\begin{bmatrix}
\alpha_2 \\
\beta_2 \\
\gamma_2 \\
\alpha_3 \\
\beta_3 \\
\gamma_3
\end{bmatrix}
= \begin{bmatrix}
\frac{C_1}{\sigma_1} \\
\frac{C_2}{\sigma_2} \\
\frac{C_3 - C_0}{a_1} \\
\frac{a_1}{\sigma_1} \\
\frac{a_2}{\sigma_2} \\
0
\end{bmatrix}
\quad (3.3.19)
\]
On solving equations (3.3.19), we have
\[ \alpha_i = r_{i0}C_0 + r_{i1}C_1 + r_{i2}C_2; \]
\[ \beta_i = s_{i0}C_0 + s_{i1}C_1 + s_{i2}C_2; \]
\[ \gamma_i = m_{i0}C_0 + m_{i1}C_1 + m_{i2}C_2; \]

where
\[ r_{20} = -a_2(s_{20} + 2a_2m_{20}); \quad r_{21} = -a_2(s_{21} + 2a_2m_{21}); \]
\[ r_{22} = 1 - a_2(s_{22} + 2a_2m_{22}); \quad s_{20} = -\left(\frac{D_1}{D_2a_1} + 2a_1m_{20}\right); \]
\[ s_{21} = \left(\frac{D_1}{D_2a_1} - 2a_1m_{21}\right); \quad s_{22} = -2a_1m_{22}; \quad m_{20} = \frac{D_1}{D_2a_1(a_2 - a_1)}; \]
\[ m_{21} = -\left\{\frac{1}{\sigma_1(a_2 - a_1)^2} + \frac{D_1}{D_2a_1(a_2 - a_1)}\right\}; \quad m_{22} = \frac{1}{(a_2 - a_1)^2}; \]
\[ r_{3j} = -a_3(s_{3j} + a_3m_{3j}) \text{ where } j = 0, 1, 2; \quad s_{3j} = z_{2j} - 2a_2m_{3j}; \]
\[ z_{2j} = \frac{D_2}{D_3}(s_{2j} + 2a_2m_{2j}); \quad m_{30} = \frac{z_{20}}{(a_3 - a_2)}; \quad m_{31} = \frac{z_{21}}{(a_3 - a_2)}; \]
\[ m_{32} = \frac{1}{(a_3 - a_2)^2}\left\{-\frac{1}{\sigma_2} + z_{22}(a_3 - a_2)\right\}. \]

The variational integral on each of the sub-domains is given as
\[ I_1 = \frac{1}{2} \int_{a_0=0}^{a_1} \left[ D_1 \left( \frac{\partial C^{(1)}}{\partial x} \right)^2 + 2(1 + B_1)C^{(1)} - k_1(C^{(1)})^2 + \frac{\partial}{\partial t}(C^{(1)})^2 \right] dx; \]
\[ = \frac{1}{2} \left[ \frac{D_1}{a_1}(C_1 - C_0)^2 + (1 + B_1)(C_0 + C_1)a_1 - \frac{k_1a_1}{3} \left( C_0^2 + C_1^2 + C_0C_1 \right) \right] \]
\[= \frac{1}{2} \left( \frac{1}{a_1} \left( \frac{D_1}{a_1} - \frac{k_1 a_1}{3} \right) \right) (2 C_1 \dot{C}_1 + C_0 \dot{C}_1) \] ;

\[= \frac{1}{2} \left[ M_{00} C_0^2 + M_{01} C_1^2 + M_{02} C_0 C_1 + a_1 (1 + B_1) (C_0 + C_1) + \frac{a_1}{3} (2 C_1 \dot{C}_1 + C_0 \dot{C}_1) \right] \quad (3.3.20) \]

where

\[M_{00} = M_{01} = \left( \frac{D_1}{a_1} - \frac{k_1 a_1}{3} \right) ; \quad M_{02} = -\left( \frac{2D_1}{a_1} + \frac{k_1 a_1}{3} \right)\]

Also, for \( i = 2, 3 \), we have

\[I_i = \frac{1}{2} \int_{a_{i-1}}^{a_i} \left[ D_i \left( \frac{\partial C^{(i)}}{\partial x} \right)^2 + 2(1 + B_i) C^{(i)} - k_i (C^{(i)})^2 + \frac{\partial}{\partial t} (C^{(i)})^2 \right] \, dx \]

\[= \frac{1}{2} \int_{a_{i-1}}^{a_i} \left[ D_i \left( \frac{\partial C^{(i)}}{\partial x} \right)^2 + 2(1 + B_i) (\alpha_i + \beta_i x + \gamma_i x^2) \right. \]

\[\left. - k_i (\alpha_i + \beta_i x + \gamma_i x^2)^2 + \frac{\partial}{\partial t} (\alpha_i + \beta_i x + \gamma_i x^2)^2 \right] \, dx ;\]

\[= \frac{1}{2} \int_{a_{i-1}}^{a_i} \left[ D_i \left( \beta_i^2 + 4 \gamma_i^2 x^2 + 2 \beta_i \gamma_i x \right) + 2(1 + B_i) (\alpha_i + \beta_i x + \gamma_i x^2) \right. \]

\[\left. - k_i (\alpha_i^2 + \beta_i^2 x^2 + \gamma_i^2 x^4 + 2 \alpha_i \beta_i x + 2 \alpha_i \gamma_i x^2 + 2 \beta_i \gamma_i x^3) \right. \]

\[+ \frac{\partial}{\partial t} \left( \alpha_i^2 + \beta_i^2 x^2 + \gamma_i^2 x^4 + 2 \alpha_i \beta_i x + 2 \alpha_i \gamma_i x^2 + 2 \beta_i \gamma_i x^3 \right) \, dx ;\]

\[= \frac{1}{2} \int_{a_{i-1}}^{a_i} \left\{ D_i \beta_i^2 + 2(1 + B_i) \alpha_i - k_i \alpha_i^2 \right\} + 2 \left\{ D_i \beta_i \gamma_i + (1 + B_i) \beta_i \right\} \]

\[\begin{align*}
+ \frac{1}{3} (2 C_1 \dot{C}_1 + C_0 \dot{C}_1) \right] ;
\end{align*}\]
\[-k_i \alpha_i \beta_i \} x + \{4D_i \gamma_i^2 + 2(1 + B_i) \gamma_i - k_i \beta_i^2 - 2k_i \alpha_i \gamma_i \} x^2 \\
-2k_i \beta_i \gamma_i x^3 - k_i \gamma_i^2 x^4 + \frac{\partial}{\partial t} (\alpha_i^2 + \beta_i^2 x^2 + \gamma_i^2 x^4 + 2 \alpha_i \beta_i x \\
+ 2 \alpha_i \gamma_i x^2 + 2 \beta_i \gamma_i x^3) \} dx ;
\]

\[
= \frac{1}{2} \left[ \{ D_i \beta_i^2 + 2(1 + B_i) \alpha_i - k_i \alpha_i^2 \} (a_i - a_{i-1}) \\
+ \{ D_i \beta_i \gamma_i + (1 + B_i) \beta_i - k_i \alpha_i \beta_i \} (a_i^2 - a_{i-1}^2) \\
+ \{ 4D_i \gamma_i^2 + 2(1 + B_i) \gamma_i - k_i \beta_i^2 - 2k_i \alpha_i \gamma_i \} \frac{(a_i^3 - a_{i-1}^3)}{3} \\
- \frac{k_i \beta_i \gamma_i}{2} (a_i^4 - a_{i-1}^4) - \frac{k_i \gamma_i^2}{5} (a_i^5 - a_{i-1}^5) \\
+ \frac{\partial}{\partial t} \left\{ \alpha_i^2 (a_i - a_{i-1}) + \alpha_i \beta_i (a_i^2 - a_{i-1}^2) \\
+ (2 \alpha_i \gamma_i + \beta_i^2) \frac{(a_i^3 - a_{i-1}^3)}{3} + \frac{\beta_i \gamma_i}{2} (a_i^4 - a_{i-1}^4) + \frac{\gamma_i^2}{5} (a_i^5 - a_{i-1}^5) \right\} \right].
\]

For \( i = 2, 3 \), we have

\[
\alpha_i^2 = (r_{i0}C_0 + r_{i1}C_1 + r_{i2}C_2)^2 \\
= n_{i0}C_0^2 + n_{i1}C_1^2 + n_{i2}C_2^2 + n_{i3}C_0C_1 + n_{i4}C_0C_2 + n_{i5}C_1C_2 \tag{3.3.22}
\]

where

\[
n_{i0} = r_{i0}^2; \ n_{i1} = r_{i1}^2; \ n_{i2} = r_{i2}^2; \\
n_{i3} = 2r_{i0}r_{i1}; \ n_{i4} = 2r_{i0}r_{i2}; \ n_{i5} = 2r_{i1}r_{i2}.
\]

\[
\beta_i^2 = (s_{i0}C_0 + s_{i1}C_1 + s_{i2}C_2)^2
\]
\[ p_{i0}C_0^2 + p_{i1}C_1^2 + p_{i2}C_2^2 + p_{i3}C_0C_1 + p_{i4}C_0C_2 + p_{i5}C_1C_2 \]
\[ \gamma_i = (m_{i0}C_0 + m_{i1}C_1 + m_{i2}C_2)^2 \]
\[ = q_{i0}C_0^2 + q_{i1}C_1^2 + q_{i2}C_2^2 + q_{i3}C_0C_1 + q_{i4}C_0C_2 + q_{i5}C_1C_2 \]
\[ \alpha_i \beta_i = (r_{i0}C_0 + r_{i1}C_1 + r_{i2}C_2)(s_{i0}C_0 + s_{i1}C_1 + s_{i2}C_2) \]
\[ = j_{i0}C_0^2 + j_{i1}C_1^2 + j_{i2}C_2^2 + j_{i3}C_0C_1 + j_{i4}C_0C_2 + j_{i5}C_1C_2 \]
\[ \alpha_i \gamma_i = (r_{i0}C_0 + r_{i1}C_1 + r_{i2}C_2)(m_{i0}C_0 + m_{i1}C_1 + m_{i2}C_2) \]
\[ = k_{i0}C_0^2 + k_{i1}C_1^2 + k_{i2}C_2^2 + k_{i3}C_0C_1 + k_{i4}C_0C_2 + k_{i5}C_1C_2 \]

where

\[ p_{i0} = s_{i0}^2; \quad p_{i1} = s_{i1}^2; \quad p_{i2} = s_{i2}^2; \]
\[ p_{i3} = 2s_{i0}s_{i1}; \quad p_{i4} = 2s_{i0}s_{i2}; \quad p_{i5} = 2s_{i1}s_{i2}. \]

\[ \gamma_i^2 = (m_{i0}C_0 + m_{i1}C_1 + m_{i2}C_2)^2 \]
\[ = q_{i0}C_0^2 + q_{i1}C_1^2 + q_{i2}C_2^2 + q_{i3}C_0C_1 + q_{i4}C_0C_2 + q_{i5}C_1C_2 \]
\[ \alpha_i \beta_i = (r_{i0}C_0 + r_{i1}C_1 + r_{i2}C_2)(s_{i0}C_0 + s_{i1}C_1 + s_{i2}C_2) \]
\[ = j_{i0}C_0^2 + j_{i1}C_1^2 + j_{i2}C_2^2 + j_{i3}C_0C_1 + j_{i4}C_0C_2 + j_{i5}C_1C_2 \]
\[ \alpha_i \gamma_i = (r_{i0}C_0 + r_{i1}C_1 + r_{i2}C_2)(m_{i0}C_0 + m_{i1}C_1 + m_{i2}C_2) \]
\[ = k_{i0}C_0^2 + k_{i1}C_1^2 + k_{i2}C_2^2 + k_{i3}C_0C_1 + k_{i4}C_0C_2 + k_{i5}C_1C_2 \]

where

\[ k_{i0} = r_{i0}m_{i0}; \quad k_{i1} = r_{i1}m_{i1}; \quad k_{i2} = r_{i2}m_{i2}; \]
\[ k_{i3} = r_{i0}m_{i1} + r_{i1}m_{i0}; \quad k_{i4} = r_{i0}m_{i2} + r_{i2}m_{i0}; \]
\[ k_{i5} = r_{i1}m_{i2} + r_{i2}m_{i1}. \]
\[ \beta_i \gamma_i = (s_{i0}C_0 + s_{i1}C_1 + s_{i2}C_2)(m_{i0}C_0 + m_{i1}C_1 + m_{i2}C_2) \]
\[ = l_{i0}C_0^2 + l_{i1}C_1^2 + l_{i2}C_2^2 + l_{i3}C_0C_1 + l_{i4}C_0C_2 + l_{i5}C_1C_2 \] \quad (3.3.27)

where
\[ l_{i0} = s_{i0}m_{i0}; \quad l_{i1} = s_{i1}m_{i1}; \quad l_{i2} = s_{i2}m_{i2}; \]
\[ l_{i3} = s_{i0}m_{i1} + s_{i1}m_{i0}; \quad l_{i4} = s_{i0}m_{i2} + s_{i2}m_{i0}; \]
\[ l_{i5} = s_{i1}m_{i2} + s_{i2}m_{i1}. \]

Using equations (3.3.22) to (3.3.27) in equation (3.3.21), we have
\[ I_i = \frac{1}{2} \left[ M_{i0}C_0^2 + M_{i1}C_1^2 + M_{i2}C_2^2 + M_{i3}C_0C_1 + M_{i4}C_0C_2 + M_{i5}C_1C_2 \right. \]
\[ + T_{i0}C_0 + T_{i1}C_1 + T_{i2}C_2 + \frac{\partial}{\partial t} \left\{ N_{i0}C_0^2 + N_{i1}C_1^2 + N_{i2}C_2^2 \right. \]
\[ \left. + N_{i3}C_0C_1 + N_{i4}C_0C_2 + N_{i5}C_1C_2 \right\} \right]; \]
\[ = \frac{1}{2} \left[ M_{i0}C_0^2 + M_{i1}C_1^2 + M_{i2}C_2^2 + M_{i3}C_0C_1 + M_{i4}C_0C_2 + M_{i5}C_1C_2 \right. \]
\[ + T_{i0}C_0 + T_{i1}C_1 + T_{i2}C_2 + 2N_{i1}C_1\dot{C}_1 + 2N_{i2}C_2\dot{C}_2 + N_{i3}C_0\dot{C}_1 \]
\[ \left. + N_{i4}C_0\dot{C}_2 + N_{i5}(C_2\dot{C}_1 + C_1\dot{C}_2) \right] \] \quad (3.3.28)

where
\[ M_{ii'} = (a_i - a_{i-1})(D_i p_{ii'} - k_i n_{ii'}) + (a_i^2 - a_{i-1}^2)(D_i l_{ii'} - k_i j_{ii'}) \]
\[ + \frac{1}{3} (a_i^3 - a_{i-1}^3)(4D_i q_{ii'} - k_i p_{ii'} - 2k_i k_{ii'}) - \frac{1}{4} (a_i^4 - a_{i-1}^4) k_i l_{ii'} \]
\[- \frac{1}{5}(a_i^5 - a_{i-1}^5)k_iq_{i^\prime}^{};\]

\[N_{i^\prime} = (a_i - a_{i-1})n_{i^\prime} + (a_i^2 - a_{i-1}^2)j_{i^\prime} + \frac{1}{3}(a_i^3 - a_{i-1}^3)(p_{i^\prime} + 2k_{i^\prime}) + \frac{1}{2}(a_i^4 - a_{i-1}^4)l_{i^\prime} + \frac{1}{5}(a_i^5 - a_{i-1}^5)q_{i^\prime}; \text{ where } i' = 0, 1, 2, 3, 4, 5;\]

\[T_{i^\prime} = (a_i - a_{i-1})(1 + B_i)\left\{2r_{i^\prime} + (a_i + a_{i-1})s_{i^\prime} + \frac{2}{3}(a_i^2 + a_ia_{i-1} + a_{i-1}^2)m_{i^\prime}\right\}; \text{ where } i' = 0, 1, 2.\]

Assembling the integrals \(I_j (j = 1, 2, 3)\) to obtain the integral \(I = \sum_{j=1}^{3} I_j\) and this \(I\) is extremised by establishing its derivatives with respect to \(C_j (j = 1, 2)\) to get the system of equations as

\[
\begin{align*}
Q_{11}C_1 + Q_{12}C_2 + R_{11}\overset{\cdot}{C}_1 + R_{12}\overset{\cdot}{C}_2 &= P_1 \\
Q_{21}C_1 + Q_{22}C_2 + R_{21}\overset{\cdot}{C}_1 + R_{22}\overset{\cdot}{C}_2 &= P_2
\end{align*}
\]

where

\[Q_{11} = 2(M_{01} + M_{21} + M_{31}); Q_{12} = Q_{21} = M_{25} + M_{35};\]

\[Q_{22} = 2(M_{22} + M_{32}); R_{11} = 2\left(\frac{a_1}{3} + N_2 + N_3\right);\]

\[R_{12} = R_{21} = N_{25} + N_{35}; R_{22} = 2(N_2 + N_3);\]

\[P_1 = -\left[(M_{02} + M_{23} + M_{33})C_0 + T_{21} + T_{31} + (1 + B_1)a_1\right];\]

\[P_2 = -\left[(M_{24} + M_{34})C_0 + T_{22} + T_{32}\right].\]
The above system of equations in matrix form can be written as

$$Q \dot{C} + RC = P$$  \hspace{1cm} (3.3.31)

where

$$Q = \begin{bmatrix} Q_{11} & Q_{12} \\ Q_{21} & Q_{22} \end{bmatrix}; \quad R = \begin{bmatrix} R_{11} & R_{12} \\ R_{21} & R_{22} \end{bmatrix}; \quad P = \begin{bmatrix} P_1 \\ P_2 \end{bmatrix};$$

$$C = \begin{bmatrix} C_1 \\ C_2 \end{bmatrix} \text{ and } \dot{C} = \begin{bmatrix} \dot{C}_1 \\ \dot{C}_2 \end{bmatrix}.$$

To solve the above system of ordinary differential equations (3.3.31), Crank-Nicolson method have been used. The solution of the system representing successive concentration in terms of time is given by the relation

$$\left( Q + \frac{\Delta t}{2} R \right) C^{(i+1)} = \left( Q - \frac{\Delta t}{2} R \right) C^{(i)} + \Delta t P$$  \hspace{1cm} (3.3.32)

where \( \Delta t \) is the time interval and \( C^{(0)} \) represents the \( 2 \times 1 \) matrix for the initial concentration of the drug.

### 3.4 Numerical calculations

To solve equations (3.3.9) and (3.3.32), we make use of the following hypothetical values of the unknown parameters [51] of the constants given in the Table (3.1).

**Table 3.1: Numerical values of the physiological parameters [51]**

<table>
<thead>
<tr>
<th></th>
<th>( \sigma_1 )</th>
<th>( \sigma_2 )</th>
<th>( k_1(\text{sec}^{-1}) )</th>
<th>( k_2 )</th>
<th>( k_3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Set-I</td>
<td>0.8</td>
<td>0.9</td>
<td>0.4</td>
<td>0.5</td>
<td>0.55</td>
</tr>
<tr>
<td>Set-II</td>
<td>0.98</td>
<td>1</td>
<td>0.5</td>
<td>0.7</td>
<td>0.8</td>
</tr>
</tbody>
</table>
We can assign different values to the constants $a_i$ where $i = 0, 1, 2, 3$ and $D_i$ where $i = 1, 2, 3$ depending on the sample of the skin under study.

The set of values considered here are

$$a_0 = 0 \mu m, \ a_1 = 0.3 \mu m, a_2 = 0.6 \mu m, \ a_3 = 1 \mu m$$

To solve equation (3.3.9), following values have been considered:

$$D_1 = 0.00068 \mu m^2 s^{-1}, \ D_2 = 0.0205 \mu m^2 s^{-1}, \ D_3 = 0.002 \mu m^2 s^{-1}$$

with two different values of $B_i$ where $i = 1, 2, 3$ as

<table>
<thead>
<tr>
<th>$B_1(\mu m^{-3})$</th>
<th>$B_2$</th>
<th>$B_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0.002</td>
<td>0.02</td>
</tr>
<tr>
<td>0.01</td>
<td>0.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

The numerical calculations have been carried out for 5mg of drug. The effect of the concentration of the drug diffusion at the dermal layers has been computed for $t = 0, 5$ and 10 seconds with respect to the thickness of the dermal layers.

To solve equations (3.3.32), the following values have been considered:

<table>
<thead>
<tr>
<th>$D_1(\mu m^2 s^{-1})$</th>
<th>$D_2$</th>
<th>$D_3$</th>
<th>$B_1(\mu m^{-3})$</th>
<th>$B_2$</th>
<th>$B_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00068</td>
<td>0.0205</td>
<td>0.0905</td>
<td>0.002</td>
<td>0.004</td>
<td>0.01</td>
</tr>
<tr>
<td>0.0062</td>
<td>0.0205</td>
<td>0.0905</td>
<td>0.01</td>
<td>0.002</td>
<td>0.01</td>
</tr>
</tbody>
</table>

### 3.5 Discussion and conclusion

The present work is an attempt to estimate the drug concentration at the human dermal layers through transdermal drug delivery mechanism. Initially, we have calculated the drug concentration at the nodal points of different dermal layers and graphs have been plotted using MATLAB software. The graphs given in Figure (3.2) and Figure (3.3) represent the drug concentration profiles at different time intervals established from
the formulated model using variational finite element method. It has been observed that the curves for the layer-wise drug concentration \( C^{(i)} \) where \( i = 1, 2, 3 \), fall more quickly in Set-II and reach the equilibrium state earlier than the Set-I. Analysing the concentration profiles, it seems that the concentration decreases with increase in the partition coefficient, absorption coefficient and rate constant parameters used in the model. The curves given in figures reflect that the drug absorption rate in the region of papillary and reticular layers is due to dense network of capillary bed.

Lagrange’s interpolation formula has been used and the

Figure 3.2: Concentration profile for Set-I at \( t = 0, 5 \) and 10 seconds.

curve describing the continuous drug pattern has been interpreted in Figure (3.4) and Figure (3.5). The results obtained appear to be realistic and are stronger than the results obtained by Sharma and Saxena [51]. Earlier, Sharma and Saxena [51] had taken the drug absorption rate and rate of drug intake by blood as constants; but keeping the physiological properties of the dermal layers into consideration, the absorption rate has
Figure 3.3: Concentration profile for Set-II at $t = 0, 5$ and 10 seconds.

Figure 3.4: Modified drug concentration based on Lagrange’s interpolation method for Set -I.
been taken as an exponentially decreasing function of the concentration. Also, they studied the drug distribution in TDD systems for steady state case while as the present work is time dependent problem and therefore their model is a special case of our model. Our work shows a close resemblance and gives modified outcome than the work carried out by Sharma and Saxena [51] for steady state case. Moreover, our model is time dependent and the time plays a key role in drug diffusion.

Figure (3.6) shows the effective and improved results shown in graphs as compared to the results obtained by Sharma and Saxena [51] for the steady state case. Figure (3.7) shows the distribution pattern of drug in viable epidermis region. The drug concentration in this region remains uniform initially and after sometime it shows sudden rise in its value and ultimately gets decreased. The decrease in the value assures that the drug has been absorbed by the tissue; or in other words, drug gets diffused in the surrounding tissue.

Figure (3.8) reveals the pattern of drug distribution in the
Figure 3.6: Distribution of drug concentration pattern at the steady state.

Figure 3.7: Behaviour of drug distribution in viable epidermis.

Figure 3.8: Behaviour of drug distribution in dermis.
dermis. The distribution pattern in this region shows that with the passage of time, the whole of the drug gets accumulated in this region. Since the drug concentration increases as such it gets absorbed by the tissue via capillary network. In the present study, we have taken a sample of 5mg of drug and from Figure (3.8), it is clear that the maximum value is slightly smaller than the input dosage which may be due to the excretion of some other antibodies from the body. Since two shape functions have been discussed in the present model; quadratic shape function gives the refinement of linear one as it takes into consideration the flux condition.

The developed model helps us in predicting the amount of the drug concentration in different tissues at different time intervals. Also, this model may be helpful in analysing the role of the diffusion constants and the absorption coefficients in drug delivery system. The study may be helpful in the medical sciences in various situations of medication.