



# Variational finite element method to study the absorption rate of drug at various compartments through transdermal drug delivery system



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## KEYWORDS

Transdermal drug delivery;  
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**Abstract** *Background:* The delivery of drugs through dermal layers known as transdermal drug delivery is one of the important contributions in medical practice. It represents an alternative to oral drug delivery and is poised to provide a substitute to hypodermic injections too. The diffusion of drug from the source to the target site is therefore an important issue to address.

*Aim:* This paper is an attempt to establish a mathematical model for the diffusion of drugs through the transdermal drug delivery system. The model identifies the pattern of drug diffusion in human body and its effective absorption rates at various compartments of skin and sub-cutaneous tissues.

*Methods:* The finite element method has been used to obtain the solution of the mass diffusion equation with appropriate boundary conditions. The tissue absorption rate of drug has been taken as the decreasing function of drug concentration from the skin surface towards the target site. The concentration at nodal points has been calculated which in turn determines the drug absorption at various layers.

*Conclusion:* The drug concentration at the nodal points of different dermal layers has been computed and the graphs were plotted between drug concentration and thickness of dermal layers using MATLAB software. It has been observed that due to dense network of connective tissues in dermal and sub-dermal parts, the drug absorption is maximum as compared to cutaneous tissues.

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## 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 mechanism delivery like pills has been considered as one of the most appropriate methods 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 hypoder-

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mic injections have many disadvantages such as the presence of pain, the appearance of infections and the requirement for medical expertise to complete the process.<sup>1</sup> 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 in-vivo tissues. Thus, it is desirable to address this issue by using an appropriate method of drug administration through dermal regions of the human body with minimal side effects. Transdermal drug delivery (TDD) is an alternate route of drug administration to pills and injections. This method operates by delivery of drugs into the human body across the skin and subcutaneous layers. TDD system has the ability to overcome the problems associated with the traditional delivery of drugs.

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 a number of factors which includes 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 to enhance drug delivery across stratum corneum which includes chemical enhancers or physical enhancer technique e.g. iontophoresis<sup>†</sup> and ultrasound.

The transport of drug through the device and skin follows the Fickian diffusion process by means of a simple homogeneous membrane. Kalia and Guy<sup>2</sup> have established the mathematical transport models describing the release of drug from various delivery systems and formulations based on the solution of Fick's second law. In these models, skin 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.<sup>3</sup> developed a mathematical model and carried numerical simulations to describe the pharmacokinetics of drug penetration into the skin from microneedle array. Missel<sup>4</sup> used FEM for modelling of diffusion and partitioning in biological systems. One-dimensional mathematical models were developed by Lee et al.<sup>5,6</sup> which considers a single component drug penetration via both intercellular and transcellular pathways of the skin. The skin 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 by finite difference approximations. Saxena, Pardasani and their co-workers<sup>7-9</sup> had carried out a notable research for the study of heat distribution in biological tissues. Khanday<sup>10</sup> studied the temperature distribution in multi-layered human skin and sub-cutaneous (SST) by assuming the thermal conductivity as a function of temperature. Khanday et al.<sup>11-14</sup> studied the diffusion of heat and mass in biological tissues particularly dermal regions and human head. Sharma and Saxena<sup>15</sup> used FEM to study the drug distribution in TDD

systems in steady state case by making use of quadratic shape function. 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 sub-cutaneous tissues. In this paper, a variational finite element approach with linear shape function is 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 has irregular geometry, therefore this method guarantees a reasonable outcome as compared to the other numerical methods.

## 2. Formulation of model

The transport of drugs through transdermal system is governed by the differential equation given in Crank<sup>16</sup>

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

where  $C$ ,  $D$  and  $t$  denote the drug concentration, mass diffusivity and time. Also,  $A(C)$  is the absorption rate of drug by the tissues, which is a function of concentration and  $B$  is the rate of drug intake by the blood.

Consider the domain consisting of three layers viz., epidermis, dermis and subcutaneous region with outer and inner boundaries as  $a_0$  and  $a_3$ . The concentration of the drug at the outer skin surface (epidermis) is known as  $C_0$  and it has negligible concentration beyond the subcutaneous tissue as the drug is absorbed through the subcutaneous tissue to reach the target site. Hence at the innermost boundary the concentration is  $C_3 = 0$ .

By the law of mass action, the absorption rate of drug by the tissue decreases with changing time, so we can say that absorption rate is decreasing function of drug concentration. Hence, we assume

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

where  $k_i (\ll 1)$  represents the rate constants. The drug distribution has a mild barrier at the interfaces due to non-homogeneous character of tissues in various layers of dermal regions. So,

$$C^{(i)} = \rho_i C^{(i+1)} \Big|_{x=a_i(i=1,2)} \quad (3)$$

Here  $x$  and  $\rho_i (i = 1, 2)$  represents the depth below the skin surface and the skin partition coefficients for the drug at the respective interfaces respectively.  $\rho_i \approx 1$  for most of the drugs<sup>17</sup>.

The solution  $C(x)$  of the problem can be approximated by polynomial functions of  $x$  of higher degrees. Since the distance between the skin layers is of minute length, the higher order shape functions may not contribute a significant change in the drug diffusion, therefore the concentration of drug in each region is approximated by a linear polynomial as

$$C^{(i)} = \phi_i + \varphi_i x, \quad (i = 1, 2, 3) \quad (4)$$

## 3. Mathematical method

The solution of such type of problem has been carried out by various researchers. The numerical solution of the boundary

<sup>†</sup> A physical process in which ion flow diffusively in a medium driven by an applied electric field.

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