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Analytic Solution for Hollow Microneedles Assisted Transdermal Drug Delivery Model

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Abstract

Microneedles is an alternative method to deliver drugs into the body via the skin. It has been proposed as a tool to by-pass the rate-limiting skin layer known as stratum corneum. By overcoming the stratum corneum, the diffusion of drug through the skin is more efficient. The study aims to predict the right amount of dosage for patient, having the right amount of dosage is crucial to avoid overdose or ineffectiveness. This model is presented by Fick's second law to imitate the movement of drug in skin. Most established model assumed infinite drug supply to simplify the solution of the model. In this model, finite drug supply was applied and has been solved analytically.

Keywords: Fick's second law; microneedles; drug diffusion; drug delivery

INTRODUCTION

The development of drug delivery method is an evidence that the conventional method such as drugs taken orally and injections are often not suitable for all types of drugs. In this research, only the transdermal drug delivery method is considered. The main obstacle in delivering drugs across the skin is the stratum corneum (SC). Despite being the thinnest layer of the skin which is between 10-20μm thick, SC is the main barrier and preventing drug molecules from penetrating the skin. SC only allows the diffusion of drug with small molecular weight of less than 500 Da and with certain oil soluble solutes (Jepps et al. 2013). In order to allow high molecular weight drug to penetrate through the skin, a method has been developed. The device was called microneedles and was proposed by (Henry et al. 1998) to assist in transdermal drug delivery. Microneedles could avoid the SC and the design which is painless will provide a faster pathway for drug delivery. Microneedles is an array of needles that is in micrometres dimension and has been fabricated for transdermal drug vehicle. To provide evidence that microneedles enhance skin permeation, (Ling Teo et al. 2005) have done *in vitro* experiment for various drugs in different molecular weight and indeed microneedles delivers drug much faster than the normal patch. Microneedles have width of a few human hairs and short, it penetrates the SC but does not go far enough to reach dermis therefore it would cause a little or no pain during injection (Henry et al. 1998)(Kaushik et al. 2001).

There are several types of microneedles design such as hollow microneedles and coated microneedles. A wide range of research has been made to improve the design of the microneedles because not all of them have the ability to optimize the drug concentration in the blood circulation and body tissues. Even then, there are very limited research that used mathematical model as a tool to analyse the movement of drug from microneedles into the skin. Therefore, different approaches have been made to assess the blood drug concentration respect to time. (Lv et al. 2006) developed a one-dimensional slab model with mass balance equation for the movement of drugs along the skin depth. In their model, the layer of skin is separated as saturated and unsaturated tissues. Results showed that by increasing initial injection velocity and accelerating the blood circulation in unsaturated tissue will boost the transdermal drug delivery. Later, (Zhang et al. 2010) proposed an improvised model by applying mixture theory as the drug concentration being absorbed by the blood circulation and cell tissues. This model is more accurate and comprehensive as it takes diffusion resistance into account as it was omitted by (Lv et al. 2006). (Al-Qallaf et al. 2007) presented a mathematical model on hollow microneedles that concentrated on the drug permeation across the skin until it reaches the blood circulation. This model was presented by Fick's second law and was solved numerically by finite difference method. In this study, we improvised the study done by (Al-Qallaf et al. 2007). This model is improved by using a more realistic approach of how drug is being supplied in the skin. Large number of publication used constant or infinite drug supply as a boundary condition. According to (Milewski et al. 2013), boundary condition is assumed to be constant due to the skin-controlled diffusion where flux is slower over the study duration. However, in this study we used a finite drug supply to imitate the real situation in transdermal drug delivery. Furthermore, this study investigate the release rate of drug from hollow microneedles and the effect of microneedles length and diffusion coefficient on drug release rate. Lastly, it is assumed that the patch has only single microneedle.

MATHEMATICAL MODEL

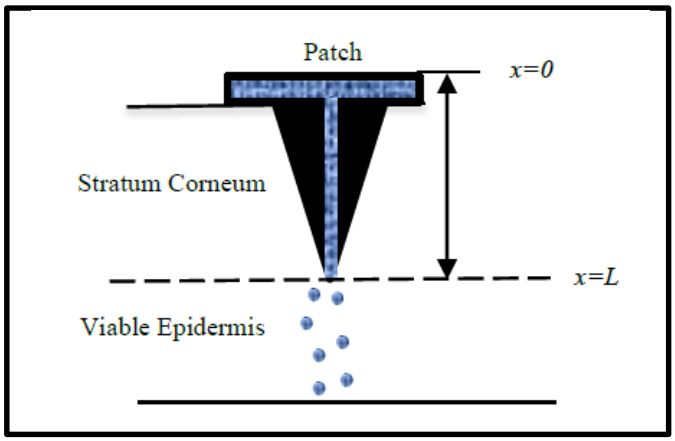

Figure 1. Schematic diagram for hollow microneedles array transdermal drug delivery.

Figure 1 below represents the mechanism of transdermal drug delivery across skin using patched hollow microneedle. The transdermal patch and the microneedle contained a homogeneous drug solution. Diffusion of drug solution starts as the transdermal patch is applied to the skin. As can be seen, the microneedle penetrates the skin and by-pass the SC which act as a rate- limiting barrier of the skin. Drug solution will directly be diffused into the viable epidemis where the drug will be taken up by the blood circulation. The behavior of the diffusion from the hollow microneedle patch is controlled by a few parameters such as length of needle, diffusion coefficient, time of application, etc. In this study, the maximum drug concentration will be able to predict and along with that the total mass release – time profile will be defined according to the parameters of interest which are the length of the microneedle and the diffusion coefficient of several type of drugs.

The mathematical model is based on a few assumptions. The first assumption defined that the skin metabolism follows first order kinetics ((Tojo 1983), (Guy & Hadgraft 1985)). Most of the mathematical models presented that during diffusion in skin, the concentration of drug is usually below the Michelis-Menten constant (K_m) which leads to first order kinetics (Higuchi 1960). The second assumption being that the distribution of enzyme in the viable epidermis is homogeneous (Al-Qallaf et al. 2009). (Tojo & Isowaki 2001) investigated and the outcome showed that there were no significant differences between the homogeneous enzyme distribution model and non-homogeneous enzyme distribution model. Hence, this assumption is applicable to present the drug diffusion across the skin. The third assumption assumed that all the drug is taken up by the blood circulation and this phenomena is known as sink condition. This assumption is applied as the boundary condition (Tojo 1983).

This model represents the drug penetration across the skin using hollow microneedle with attached patch. This diffusion problem is in one-dimensional where the spreading of drug in sideways is ignored because the study focuses only on the movement of drug along the x direction perpendicular to the skin surface. The fundamental equation that defines transient drug diffusion across the skin tissue is given by Fick's second law as

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \quad \text{at} \quad 0 < x < L, \qquad t > 0 \tag{1}$$

where C is the drug concentration at time t on depth x within the microneedle with D as the diffusion coefficient. Diffusion coefficient shows how fast drug penetrates the skin. At $t = 0$, the drug concentration is given by the following equation

$$C(x,0) = C_0 \quad \text{at} \quad 0 < x < L, \qquad \text{t= 0} \tag{2}$$

where L is the length of the microneedle and C_0 is the initial drug loading. Drug solution is available along the microneedle and in the patch even before application on the skin. Drug concentration at the upper inner slab of the patch is represent as $x = 0$ and is considered as the upper boundary condition for this model. Therefore, the upper boundary condition is given by the following equation

$$\frac{\partial C}{\partial x} = 0 \quad \text{at} \quad x = 0, \quad t > 0. \tag{3}$$

This shows that there is no flux from the outer slab and into the patch, hence the drug supply is finite. Whereas for the lower boundary condition, the equation is as follow

$$C(L,0) = 0 \quad \text{at} \quad x = L, \quad \text{t} > 0. \tag{4}$$

At the bottom of epidermis, the drug concentration is 0, it is assumed that drug concentration is taken up completely due to its fast clearance into the dermal blood circulation (sink condition) (Anissimov & Roberts 2011).

METHOD OF SOLUTION

Methods that had been used to solve the one dimensional diffusion model for hollow microneedle with the same initial and boundary equations are finite difference ((Al-Qallaf et al. 2007),(Al-Qallaf et al. 2009)).

In this study, separation of variables will be used to solve the governing equation (1)-(4). The idea behind finite difference method of solving partial difference equation is to replace spatial and time derivatives by suitable approximations and later on to solve the resulting difference equations numerically.

Firstly, the solution is assumed to be a function $C(x,t)$ and can be expressed as a product, $C(x,t) = X(x)T(t)$. X is a function of x alone and T is a function of t alone. Therefore, the diffusion equation as in (1) can be rewritten as

$$XT' = DX''T. \tag{5}$$

Both side are divided by DT and must be equal to the same constant, $-\lambda$. The constant is to ensure that both x and t could be held at a fixed value.

$$\frac{T'}{DT} = \frac{X''}{X} = -\lambda . \quad (6)$$

Next, eq. 6 are divided into two simultaneous system of ordinary differential equations as follow

$$X''+\lambda X = 0 \quad (7)$$

and

$$T'+\lambda DT = 0 . \quad (8)$$

Equation 7 is a second order homogeneous linear equation in term of x and can be solved by finding the eigenvalues λ with the stated boundary conditions as in eq. 3 and eq. 4. The general solution for eq. 7 when considering $\lambda > 0$ is as below

$$X(x) = C_1 \cos(\sqrt{\lambda}x) + C_2 \sin(\sqrt{\lambda}x) . \quad (9)$$

By applying the boundary conditions,

$$\begin{aligned} X'(0) = 0 &= -C_1\sqrt{\lambda}\sin(0) + C_2\sqrt{\lambda}\cos(0) = C_2 \\ X(L) = 0 &= C_1\sqrt{\lambda}\cos(\sqrt{\lambda}L) + C_2\sin(\sqrt{\lambda}L) = C_1\cos(\sqrt{\lambda}L) \end{aligned} \quad (10)$$

The second equation will resulted in having trivial solution if $C_1 = 0$. Therefore, by assuming $\cos(\sqrt{\lambda}L) = 0$, we will have $\sqrt{\lambda}L = \frac{\pi}{2}, \frac{3\pi}{2}, \frac{5\pi}{2}, \ldots, \frac{(2n-1)\pi}{2}, \ldots$. Moreover, there are infinitely many values $\sqrt{\lambda} = \frac{\pi}{2L}, \frac{3\pi}{2L}, \frac{5\pi}{2L}, \ldots, \frac{(2n-1)\pi}{2L}, \ldots$ such that there exists a nonzero solution of this boundary value problem. Hence, the eigenfunctions corresponding to the eigenvalues above is as given below,

$$X_n(x) = \sin\left(\frac{(2n-1)\pi x}{2L}\right), \quad n = 1, 2, 3, \ldots \quad (11)$$

The next step of the process is to solve eq. 8 and the solution is as

$$T_n(t) = A_n e^{-\lambda Dt}, \quad n = 1, 2, 3, \ldots \quad (12)$$

Substitute λ and the eq. 12 will be

$$T_n(t) = A_n e^{-\left(\frac{(2n-1)\pi}{2L}\right)^2 Dt} . \quad (13)$$

AThe result from eq.11 and eq.12 will be assembled into $C(x,t) = X(x)T(t)$. Therefore, the series solution for this model will be in the form of

$$C(x,t) = X_n(x)T_n(t) = \sum_{n=1}^{\infty} A_n \sin\left(\frac{(2n-1)\pi x}{2L}\right) e^{-\left(\frac{(2n-1)\pi}{2L}\right)^2 Dt}, \quad n = 1, 2, 3, \ldots \quad (14)$$

To determine A_n, the initial condition in eq. 2 will be set as $C(x,0) = f(x)$. Therefore, we will get

$$C(x,0) = \sum_{n=1}^{\infty} A_n \sin\left(\frac{(2n-1)\pi x}{2L}\right) e^{-\left(\frac{(2n-1)\pi}{2L}\right)^2 D(0)} = \sum_{n=1}^{\infty} A_n \sin\left(\frac{(2n-1)\pi x}{2L}\right) = f(x) \quad (15)$$

From eq. 15, it is known that the initial condition needs to be an odd periodic function of period $2L$, thus we expand the initial condition into

$$f(x) = \sum_{n=1}^{\infty} b_n \sin\left(\frac{(2n-1)\pi x}{2L}\right) . \quad (16)$$

By comparing eq. 15 and eq. 16, it can be seen that

$$C(x,0) = \sum_{n=1}^{\infty} A_n \sin\left(\frac{(2n-1)\pi x}{2L}\right) = f(x) = \sum_{n=1}^{\infty} b_n \sin\left(\frac{(2n-1)\pi x}{2L}\right) \quad (17)$$

In order to find the solution, all the coefficients are set to $A_n = b_n$, where b_n's are the Fourier sine coeffcients of the initial condition $f(x)$ as below

$$A_n = b_n = \frac{2}{L}\int_0^L f(x)\sin\left(\frac{(2n-1)\pi x}{2L}\right)dx . \quad (18)$$

After proving that $\left\{\sin\left(\frac{(2n-1)\pi x}{2L}\right)\right\}_{n=1}^{\infty}$ is orthogonal on $0 < x < L$ and that it can be written as

$$\int_0^L \sin\left(\frac{(2n-1)\pi x}{2L}\right).\sin\left(\frac{(2m-1)\pi x}{2L}\right)dx = \begin{cases} \frac{L}{2}, & m = n \\ 0, & m \neq n \end{cases} . \quad (19)$$

Thus, when $m = n$,

$$A_n = \frac{2}{L}\int_0^L C_0.\sin\left(\frac{(2n-1)\pi x}{2L}\right)dx = \frac{-4C_0}{(2n-1)\pi} \quad (20)$$

Plug in eq. 20 into eq. 14, the full solution for this model is as such

$$C(x,t)=\sum_{n=1}^{\infty}\frac{-4C_0}{(2n-1)\pi}\sin\left(\frac{(2n-1)\pi x}{2L}\right)e^{-\left(\frac{(2n-1)\pi}{2L}\right)^2 Dt},\quad n=1,2,3,\ldots \tag{14}$$

RESULTS AND DISCUSSION

The model is solved by using the input parameters as shown in Table 1 below.

Table 1. Input parameters used in this study for solving the model of blood concentration through the skin by hollow microneedles (Anon n.d.).

Parameters	Patch
Duration of application, t (hr)	96
Diffusion coefficient in viable skin, D (cm^2min^{-1})	5×10^{-8}
Device drug concentration, C_0 ($mgml^{-1}$)	15.8
Microneedles length, L (cm)	0.015

Drugs penetration across the human skin through the microneedles patch is associated with the length of the microneedles, *L.* The length of the microneedles is essential to have an optimum length, so that it is not too short to be ineffective or too long to cause pain. The length of the microneedles could cause pain if it is too long because it could touch the nerve endings. The results of the simulation done with different length of microneedles are shown in figure 2. Figure 2 shows the blood drug concentration in blood circulation for the duration of four hours. The distance for the penetration of the drug for the simulation is from the tip of the microneedles to the blood circulation. For the microneedles with the length of 0.01cm, the distance for the drug to penetrate into the blood circulation is 0.01cm because the skin thickness is 0.02cm. As the microneedles increased to 0.011cm, the distance from the tip of the microneedles to the blood circulation is reduced to 0.009cm and the blood drug concentration increased from 0.89×10^{-1}µg/ml to 1.07×10^{-1}µg/ml at fourth hour of application. On the other contrary, by decreasing the length of the microneedles, the blood drug concentration declined as the distance for the drug to diffuse into the blood circulation increased.

Skin thickness also plays a major role in delivering the drug into the body. The profile of drug delivery into the body or specifically in the tissues is presented in figure 3. The thickness of the skin is the distance from the skin surface to the blood circulation, l_s . In this study, the length of the needle is maintained at the same length as shown in table 1. There are three areas of skin taken into consideration following the previous research (Al-Qallaf et al. 2007). These areas such as cheek, back of forearm and back of leg are suitable for the application of microneedles patch.

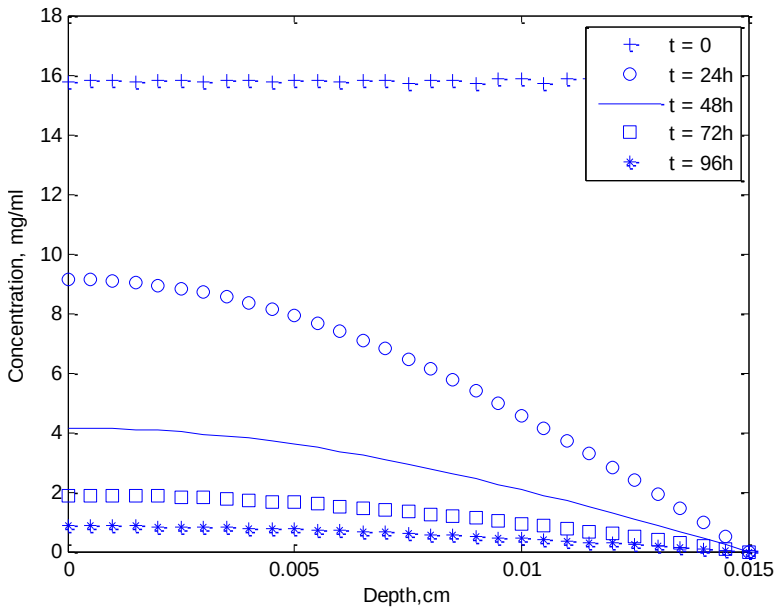

Figure 2. Effects of drug delivery into blood circulation for different lengths of microneedles.

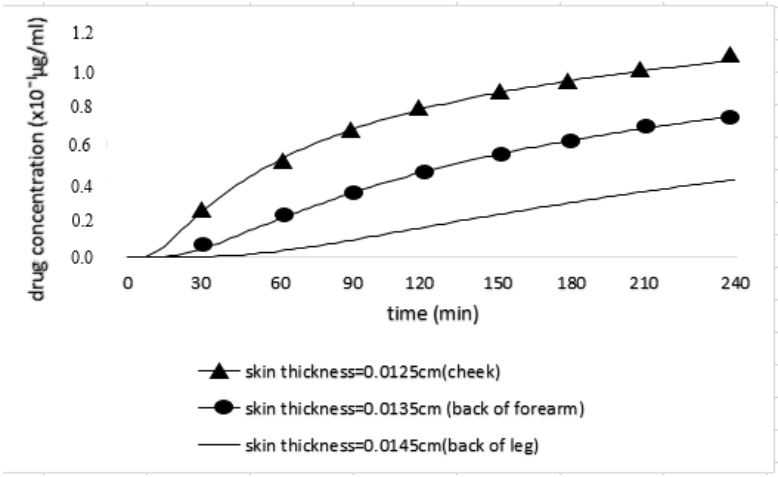

Figure 3. Effects of drug delivery into tissues for different skin thickness.

Thickness of the skin is an important parameter for the drug delivery using a microneedles patch as can be seen in figure 3. The drug concentration in tissues gave a significant difference with each area of skin. The thinnest skin is on the cheek with the thickness of 0.0125cm, the drug penetrates into the tissues after 10 seconds. At the fourth hour, the drug concentration is 1.11×10^{-1}µg/ml. Drug penetrates into the tissues at almost the exact time for the skin area at the back of forearm and at the back of leg. However, the delivery of drug on the back of the forearm with drug concentration of 0.77×10^{-1}µg/ml exceeds the drug concentration at the back of leg with the drug concentration of 0.40×10^{-1}µg/ml.

CONCLUSION

Drug delivery in skin using a microneedles patch is mathematically presented in this study. This paper contributed by adding another compartment to represent the tissues in the body. It is an effort to construct a model that is as close as the real-life situation in drug delivery phenomena. Furthermore, it is shown that the length of the microneedles and the skin thickness are important parameter in transdermal drug delivery. The length of the microneedles determines the distance for the drug to be diffused into the skin. The shorter the distance, the lesser time it takes for the drug to be delivered. It is important to include the thickness of the skin when designing the device as skin has various thickness all throughout the body. There are also other aspect of parameters that must be taken into consideration such as the surface area of the microneedles, the number of microneedles, duration of application, etc. These parameters are important especially in designing the optimum microneedles patch to enhance the drug delivery system. Future work could consider different situation for the boundary and initial conditions. In order to imitate the real situation, finite amount of drug in the microneedles patch has to be taken into account.

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