

Modelling transdermal delivery of high molecular weight drugs from microneedle systems

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In the past few years, a number of microneedle designs have been proposed for transdermal drug delivery of high molecular weight drugs. However, most of them do not increase the drug permeability in skin significantly. In other cases, designs developed based on certain criteria (e.g. strength of the microneedles) have failed to meet other criteria (e.g. drug permeability in skin, throughputs of the drugs, etc.). It is obvious therefore that in order to determine the ‘optimum’ design of these microneedles, the effect of different factors (e.g. length of the microneedle, surface area of the patch, etc.) along with various transport properties of drug transport behaviour using microneedles should be determined accurately. Appropriate mathematical models for drug transport from these systems into skin have the potential to resolve some of these issues. To address this, a parametric analysis for transdermal delivery of a high molecular weight drug from a microneedle is presented in this paper. The simulations have allowed us to identify the significance of various factors that influence the drug delivery while designing microneedle arrays. A scaling analysis is also done which shows the functional dependence of drug concentration on other variables of skin and microneedle arrays.

Keywords: microneedle systems; skin patch; transdermal drug delivery; pharmacokinetics; modelling; scaling relationship

1. Introduction

Oral delivery (e.g. pills) has been considered as the most appropriate method of drug administration for decades. Most of the drugs that cannot be taken by oral delivery have traditionally used injections by hypodermic needles. However, the hypodermic injections have many disadvantages, such as the presence of pain, the appearance of having infections and the requirement for medical expertise to complete the injection process (Park *et al.* 2005). These problems have therefore led to inventions and development of new methods of drug delivery. Transdermal drug delivery is an alternative route of drug administration to pills and injections. This method operates by delivering drugs into the human body across the skin

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using a patch. The transdermal patches have the ability to eliminate the problems mentioned above. They usually contain a drug reservoir that can maintain a steady drug flow up to about one week (Prausnitz *et al.* 2004). Although these patches have proven to be very successful, they depend on the characteristics of the drug, e.g. the size, charge and even some physiochemical properties (Naik *et al.* 2000). 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 (less than 500 Da) with the ability to allow penetration of certain oil-soluble solutes (Shah 2003). To circumvent this diffusion limitation, methods have been developed to more effectively deliver drugs across the stratum corneum, including chemical enhancers (Williams & Barry 2004) or physical enhancer techniques, e.g. iontophoresis (Kalia *et al.* 2004) and ultrasound (Prausnitz *et al.* 2004). However, the high cost, complexity and the difficulty in dealing with these methods at home pose problems for potential users.

A recent approach that combines the concepts of drug delivery across the skin using patches and hypodermic injections has been receiving significant attention in the field of transdermal drug delivery. Arrays of needles of micrometres in dimensions, called microneedles, have been fabricated for transdermal drug transport. The idea of applying the microneedles in transdermal drug delivery to increase the skin permeability was proposed by Henry *et al.* (1998), as far as the authors know. These microneedles have been shown experimentally to increase the skin permeability by orders of magnitude *in vitro* for a range of drugs varying in molecular size (Teo *et al.* 2005). The microneedle arrays penetrate the stratum corneum to reach the viable epidermis to deliver the drugs. At the same time, they increase the drug permeability in skin by causing no or little pain (Kaushik *et al.* 2001). A comparison of the usefulness and applicability of different transdermal drug delivery approaches has been carried out by Prausnitz *et al.* (2004).

Although different microneedle designs have been fabricated, not all of them have the ability to increase the blood drug concentration. Different approaches have been proposed to evaluate the influences of different parameters on the drug delivery process. Lv *et al.* (2006) proposed a theoretical model to determine the influence of injection velocity, blood perfusion rate and tissue porosity on the transdermal drug delivery process using microneedles. Teo *et al.* (2006) outlines different key parameters (e.g. sharpness, materials of microneedles, etc.) that may affect the design of microneedles. Further, there have been some discussions on how to determine the length of microneedle while designing these microneedle arrays. This is because the length is an important factor in determining whether the arrays touch the nerve endings and cause pain or not. Shikida *et al.* (2006) defined the length to be longer than 50 μm but shorter than 200 μm . Stoeber & Liepmann (2005) pointed out that the length of the microneedle must be longer than 100 μm . These differences in the microneedle length show the importance of determining the influence of the length of the microneedle in transdermal drug delivery with respect to obtaining the optimum concentration of drugs in blood.

Following the above discussions, the major focus in this study is to investigate the influences of a variety of variables related to the microneedles and their impacts on the drug transport in skin. Many relevant factors have been considered, including the length of the microneedle, the duration of application, the size of the patch, etc. Subsequently, we aim to determine the influence of microneedles on blood drug concentration during a drug delivery process. For our

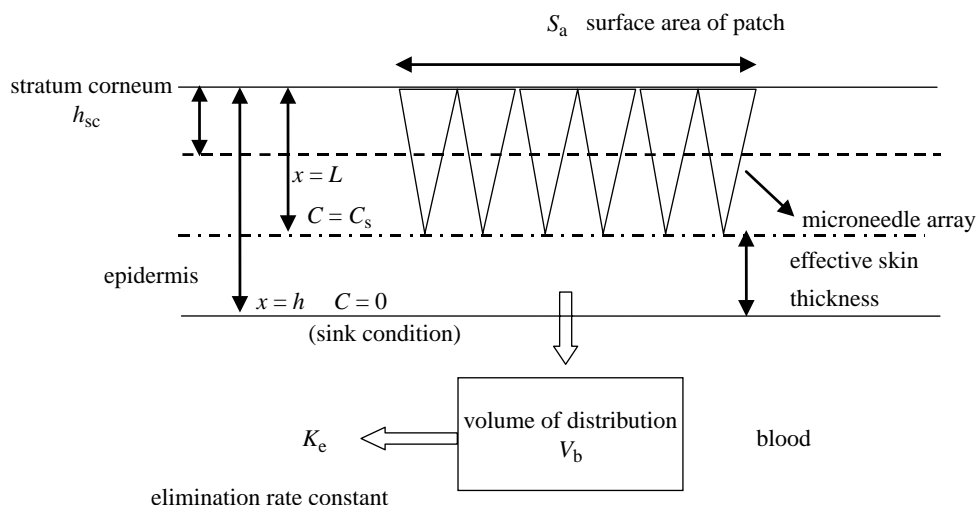


Figure 1. Schematic for microneedle array transdermal drug delivery.

purpose, a mathematical framework has been developed and numerical simulations have been carried out which describe the pharmacokinetics of drug penetration into skin from using a microneedle array. Finally, dimensional analysis has been carried out to obtain a scaling relationship between these parameters and the blood drug concentration.

2. Methods

(a) Mathematical model

The developed mathematical framework (figure 1) represents the phenomena of transdermal drug delivery across skin using hollow microneedles which contain a reservoir of drug on top. As shown in figure 1, the resistance of the stratum corneum is overcome by insertion of the microneedle and the rate-limiting barrier of skin is the viable skin. The drug concentration at the interface between the skin tissue and needle edge is defined to be the same as the drug concentration in the reservoir. The back diffusion of high molecular weight drugs from needle edge towards the stratum corneum is ignored because their diffusion coefficient in the stratum corneum is estimated to be too small (i.e. $10^{-17} \text{ cm}^2 \text{ s}^{-1}$ for human growth hormone (hGH), $MW = 22\,000$; Tojo 2005). The drug administered using microneedles diffuses across skin obeying Fick's second law until it reaches blood vessels. This transport behaviour is controlled by different parameters such as the diffusion coefficient, thickness of viable epidermis, length of microneedle, etc. In our case, we want to be able to predict blood drug concentration (C_b) at a given time from the time of drug injection. The drug permeated through the skin is absorbed into the bloodstream (blood compartment) and the body pharmacokinetics follows a one-compartment model which depicts the body as a simple homogeneous compartment (Xu & Weisel 2005). The one-compartment model is used because it is assumed that the drugs distribute rapidly between blood and tissue (short distribution half-life; Shiflet & Shiflet 2006).

The mass balance in the blood compartment is represented by equation (2.6), which includes the rate of bloodstream uptake under the assumption of 100% uptake (input into compartment) and elimination of drug from the blood compartment (output from compartment) as shown in figure 1.

The drug movement in skin tissue is expressed by Fick's second law as

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2}, \quad (2.1)$$

where C is the concentration; D is the diffusion coefficient; t is time; and x is the distance in a given skin layer. The initial boundary condition for solving equation (2.1) is given by the following equation, where the initial drug concentration in skin is set to 0

$$C = 0 \quad \text{at} \quad L < x < h \quad (t = 0). \quad (2.2)$$

The assumption of no back diffusion of the drugs is given as

$$-\frac{dC}{dx} = 0 \quad \text{at} \quad t > 0, \quad (2.3)$$

that is, the negative sign indicates that the back diffusion is from the bottom (tip of the microneedle) towards the top of the microneedle itself.

At the tip of the microneedle, the drug concentration is

$$C = C_s \quad \text{at} \quad x = L \quad (0 < t \leq t_a). \quad (2.4)$$

At the bottom of the skin epidermis, the concentration of the drug is

$$C = 0 \quad \text{at} \quad x = h \quad (0 < t), \quad (2.5)$$

where C_s is the drug concentration at the tip of microneedle; L is the microneedle length; t_a is the duration of application of the microneedle array; and h is the epidermis thickness (i.e. distance to blood vessel). At $x=h$, the concentration of the drug is assumed to be 0 (sink condition), as the drug has been taken up by dermal microcirculation (100% absorbed).

In our approach, the drug concentration in the blood after imposing the transdermal drug delivery is given by the one-compartmental pharmacokinetic model as

$$V_b \frac{dC_b}{dt} = \left(\frac{dQ}{dt} \right) S_a - K_e C_b V_b, \quad (2.6)$$

where K_e is the elimination rate constant from the blood compartment; dQ/dt is the penetration rate of drug through the skin; S_a is the surface area of the delivery system (i.e. patch of microneedles); V_b is the volume of distribution in the blood; and C_b is the drug concentration in the blood.

The rate of drug permeation and the cumulative amount of drug permeated per unit area of skin are given by equations (2.7) and (2.8), respectively, as

$$\left(\frac{dQ}{dt} \right) = -D \left(\frac{dC}{dx} \right)_{x=h}, \quad (2.7)$$

$$Q = \int_0^t \left(\frac{dQ}{dt} \right) dt = \int_0^t \left(-D \frac{dC}{dx} \right)_{x=h} dt. \quad (2.8)$$

(b) *Method of solution*

The governing equations (2.1)–(2.8) were implemented and solved using the software, SKIN-CAD (Biocom Systems 2006). SKIN-CAD employs the finite difference method to solve the partial differential equation, e.g. diffusion equation, subject to suitable initial and boundary conditions. In our case, the governing equations are discretized along all spatial coordinates using a central differencing scheme. Then the Runge–Kutta–Gill (Carver 1981) method is used for iterating and solving the discretized equations. It must be pointed out that SKIN-CAD is based on existing mathematical frameworks of mono- or bilayer diffusion models for skin penetration and a multicompartment model for body pharmacokinetics to calculate the permeability of any drug penetrating into the skin and the blood concentration profile by the input of different parameters (Tojo 2005). This model has been used to describe the pharmacokinetics of skin for transdermal drug delivery (Mori *et al.* 2003). SKIN-CAD has been used in this work to predict the drug penetration rate under microneedle delivery with the assumption that a monolayer diffusion model can be applied to the penetrating process of drug in the viable skin tissue from microneedle to dermal microcirculation.

(c) *Dimensional analysis for dependence of drug concentration in blood on parameters of microneedle, drug and skin*

As discussed earlier, a number of variables influence the process of drug delivery using microneedles. However, in most practical cases, the main variable of interest is the steady-state drug concentration in blood ($C_{b,ss}$) and its dependency on other variables. To address this issue, a scaling relationship is obtained using dimensional analysis. The dimensionless groups obtained in this can describe drug transport behaviour to a very good accuracy, as discussed later. Following the procedures of the Buckingham π theorem (Buckingham 1914), it can be shown that

$$\frac{C_{b,ss}}{C_s} = \phi \left[\frac{S_a}{L^2}, \frac{h}{L}, \frac{V_b}{L^3}, \frac{L^2 K_e}{D} \right], \quad (2.9)$$

where ϕ is an unknown function. This unknown function that appears in the dimensional analysis may need different approaches in order to identify its value. Although equation (2.9) provides the relationship of the dimensionless steady-state blood concentration, $C_{b,ss}/C_s$, with other individual dimensionless groups; in reality, however, the combined effects of all groups are more relevant to drug transport in skin. To address this issue, all groups have been combined by multiplication or division to form a new group. Then, the power law form is applied to convert the dimensionless groups, which are related to each other, with an unknown function as follows (Yahya & Manning 2004):

$$\frac{C_{b,ss}}{C_s} = K \left[\frac{S_a L^4 K_e}{V_b h D} \right]^n, \quad (2.10)$$

where K is a dimensionless constant and n is an unknown power. Ordinary regression is applied to determine the above dimensionless constant and the unknown power (Smith *et al.* 1992).

Table 1. The values of model parameters used in this work for analysing the blood concentration of Fentanyl penetrated through the skin with/without microneedle array patch, and hGH penetrated through the skin by the microneedle arrays (Tojo 2005).

parameters	Fentanyl	hGH
duration for medication (calculation): t_m (h)	8	8
duration of microneedle application: t_d (h)	4	4
surface area of microneedle array: S_a (cm ²)	2	2
thickness of stratum corneum: h_{sc} (cm)	0.002	—
distance to blood vessel: h (cm)	0.02	0.0125
effective skin thickness: h_e (cm)	0.012	variable
diffusion coefficient in stratum corneum: D_{sc} (cm ² s ⁻¹)	9.75×10^{-11}	—
diffusion coefficient in viable skin: D_{vs} (cm ² s ⁻¹)	9.75×10^{-8}	5.00×10^{-10}
volume of distribution: V_b (ml)	731 000	100
elimination rate constant: K_e (s ⁻¹)	2.840×10^{-5}	1.16×10^{-3}
skin surface concentration: C_s (µg ml ⁻¹)	15 800	4000
microneedle length: L (cm)	0.01	variable

3. Results and discussion

We begin our discussion by demonstrating the utility of microneedle systems for transdermal drug delivery. For this purpose, we compare this technique with a normal drug delivery such as a patch, which does not contain any microneedles. To make a logical comparison, the molecular weight of the candidate drug is chosen to be low as this overcomes the problem of the permeability of skin. Fentanyl (MW=336.5) is a good candidate for this comparison. The input parameters are shown in table 1. Figure 2 shows the difference between Fentanyl delivery without and with using the microneedle system. The results show clearly that the microneedle array enhances the transdermal drug delivery as the drug concentration and cumulative amount permeated are higher in this case. The blood concentration decreases after 4 hours because the duration of application is defined to be 4 hours.

Unless otherwise mentioned, in all our subsequent simulations, we use hGH (MW=22 000) as a model drug for microneedle systems. Injection of hGH has many benefits such as improving kidney function, improving skin quality (e.g. eliminating of wrinkles), increasing bone density, etc. (Rudman *et al.* 1990). Model parameters for our simulations are shown in table 1. In figure 3 we show the drug distribution profile of hGH across skin. This describes how the drug diffuses from the tip of the microneedle until it reaches the blood stream across a given skin thickness.

(a) Effect of duration of transdermal drug application and microneedle length

The insertion of microneedles has a significant ability to increase the permeability of the skin. For example, the permeability of calcein as a model drug was determined for different durations by Henry *et al.* (1998). By comparing two different intervals, one for 10 s and the other for 1 hour, the permeability increased by twofold for 1 hour insertion (Henry *et al.* 1998). This means that the duration of drug application is an important factor to be considered while designing

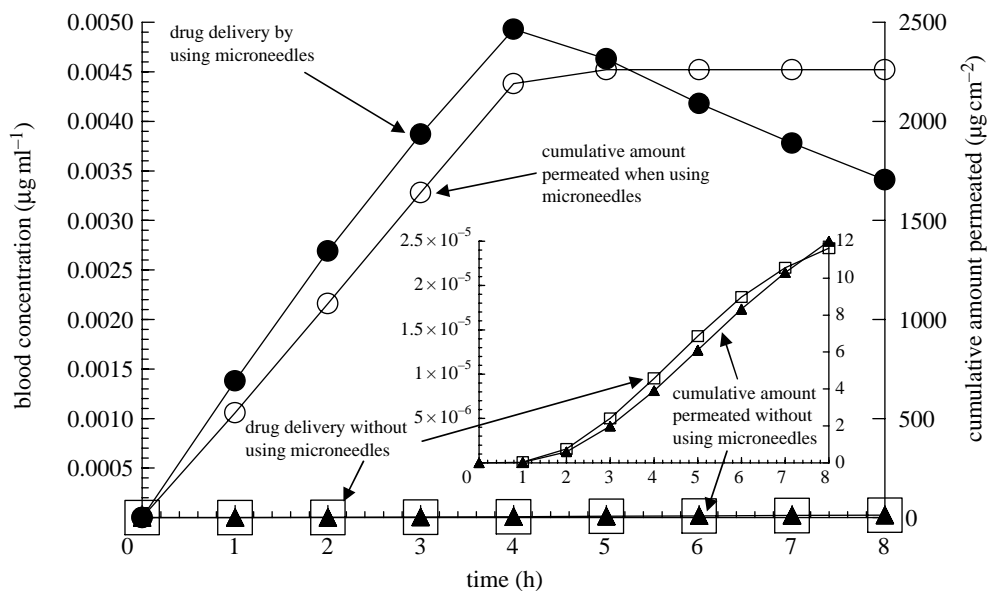


Figure 2. Effect of Fentanyl delivery in skin with/without microneedle array for the input parameters in table 1.

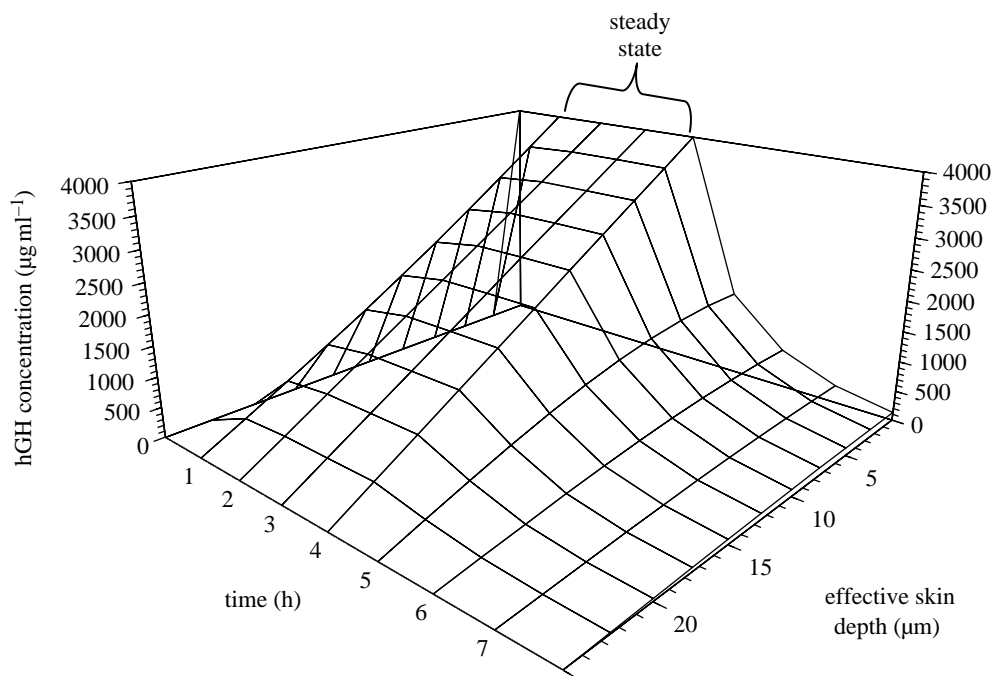


Figure 3. Transient drug distribution profile in skin for hGH ($L=0.01$ cm; all the remaining parameters are as shown in table 1).

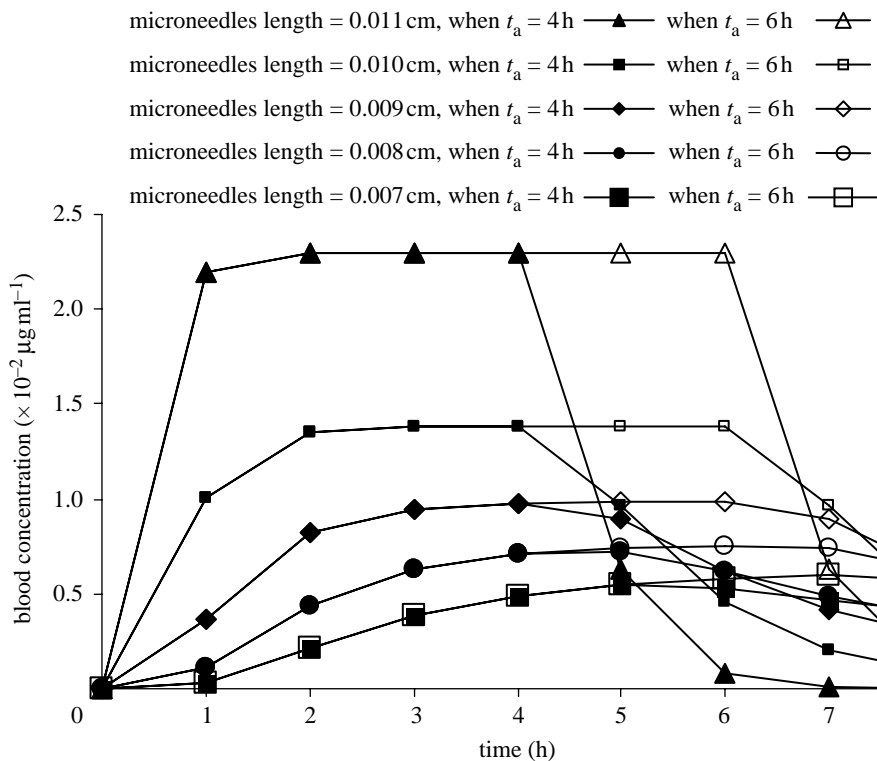


Figure 4. Influence of transdermal delivery of hGH for different lengths of microneedle and durations of application (t_a) for the input parameters in table 1.

microneedle arrays. Figure 4 shows the effects of the duration of application ranging from 4 to 6 hours for various lengths of microneedle and patch surface area of 2 cm^2 . The steady-state hGH concentration in blood ($C_{b,ss}$) does not change that much as there is a constant plateau concentration of approximately $0.023 \mu\text{g ml}^{-1}$ in the case of microneedle length $L=0.011$. However, the time duration within which the drug is active in skin varies depending on the duration of application. As expected, the results indicate that the duration of steady-state blood hGH concentration increases, as the duration of application increases.

The diffusion of drugs across human skin through the use of microneedle systems is also related to the length of the microneedles (L). This means that the lengths should be chosen so that they are not too short to be effective and not too long to touch the nerve endings embedded in the dermis. If the microneedles are too long, they contact the nerve endings and cause pain. Therefore, the amount of pain is also related to the microneedle lengths. The skin thickness chosen in our simulations represents the effective diffusion length from the needle tip to dermal microcirculation when the microneedle system is applied (figure 1). In other words, it is the distance from the microneedle tip to blood vessels. This has been calculated by knowing the difference between the distance from the skin surface to the dermal microcirculation and the length of the microneedles. In the results presented in figure 4, the length of the microneedles is 0.01 cm and the distance from skin surface to dermal microcirculation is 0.0125 cm. This means

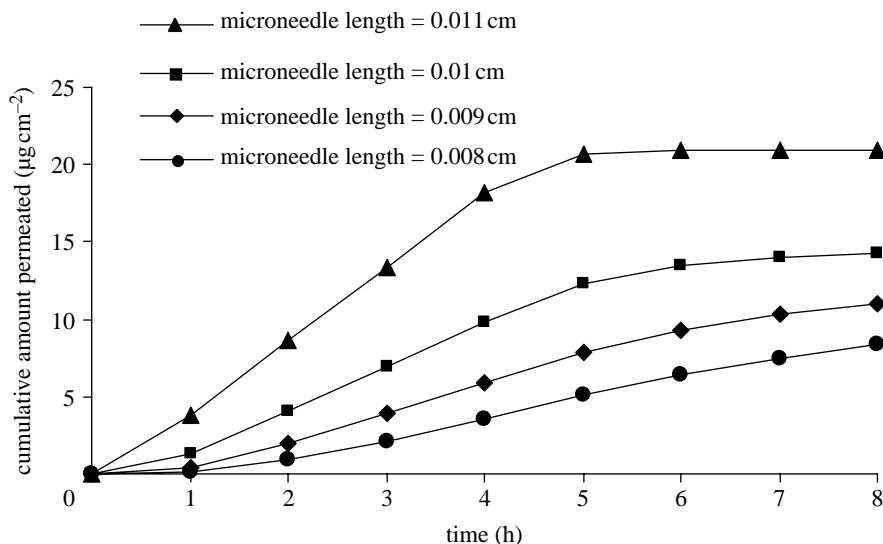


Figure 5. Cumulative amount of hGH permeated into blood per unit area of skin with various microneedle lengths for the input parameters in table 1.

that the effective diffusion length of the drug across the skin is 0.0025 cm. The duration of application is either 4 or 6 hours and the surface area of the patch is 2 cm². By increasing the length of the microneedles from 0.01 to 0.011 cm, the effective diffusion length of hGH is reduced to 0.0015 cm, which enhances the plasma drug concentration. On the other hand, by decreasing the length of the microneedles to 0.009 cm, the effective diffusion length is increased to 0.0035 cm, which drops the blood hGH concentration. In the cases we considered, the steady-state blood drug concentration h/L varies between 0.005 and 0.023 $\mu\text{g ml}^{-1}$ depending on the values of h/L , provided all other parameters remain the same. Figure 5 shows the cumulative amount permeated per unit area of skin for hGH with different microneedle lengths, which represents equation (2.8). The general functional dependency of h/L on $C_{b,ss}/C_s$ as shown in figure 6 (named, first curve) is given by the following relationship:

$$\frac{C_{b,ss}}{C_s} = 7.0 \times 10^{-6} \left(\frac{h}{L} \right)^{-3.2}; \quad 1.13 < \frac{h}{L} < 1.78; \quad h = 0.0125 \text{ cm}. \quad (3.1)$$

(b) Effect of patch surface area of microneedle

Since the first fabrication of the microneedles for drug delivery, there have been many different sizes of the microneedle surface areas. Some of them are relatively small with a surface area of 0.09 cm² (Kaushik *et al.* 2001), while others have a larger area of up to 0.81 cm² (Park *et al.* 2005). In this work we have carried out simulations to synthesize the effects of the patch size on drug delivery, as shown in figure 7. The surface area represents the perpendicular area of the direction of the drug diffusion for a patch with a uniform area. Therefore, $(dQ/dt)S_a$ in equation (2.6) represents the drug penetration rate into blood that passes an area inclined perpendicularly to the direction of diffusion per unit time. In figure 7, the duration

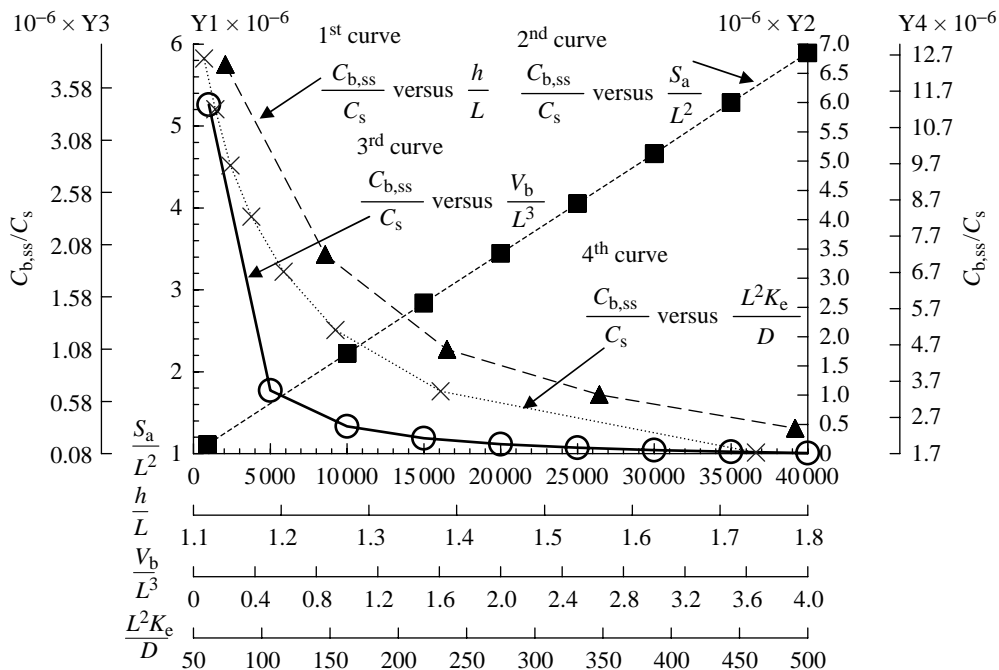
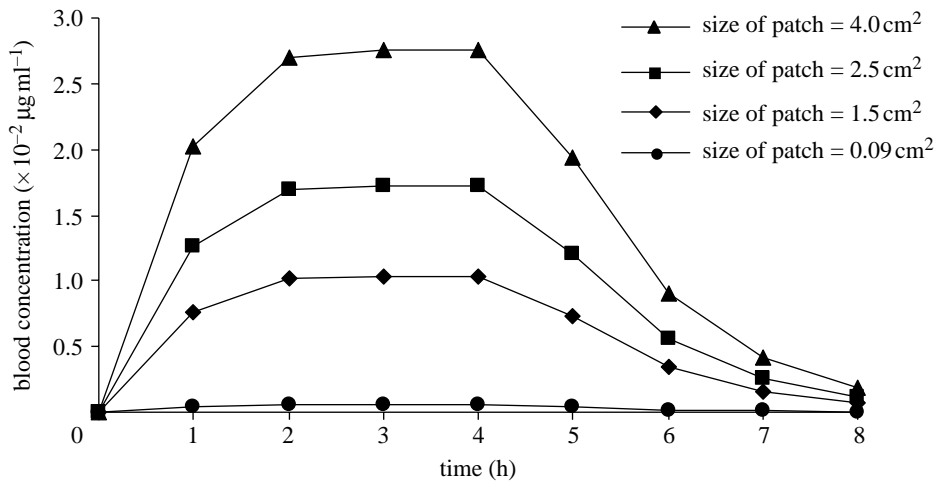


Figure 6. Scaling relationship of different dimensionless groups.

Figure 7. Transdermal delivery of hGH for various sizes of patches ($h=0.0125$ cm, $L=0.011$ cm, $h_e=0.0025$ cm), and all the remaining parameters are the same as shown in table 1.

of application is 4 hours and the effective skin thickness is 0.0025 cm while the size of the patch varies from 0.09 to 4 cm². We can see that the steady-state blood hGH concentration ($C_{b,ss}$) varies between 0.0006 and 0.027 $\mu\text{g ml}^{-1}$, and there is a steady-state concentration (the plateau) after a certain duration of application. This implies that there is a relationship between the size of the array (S_a) and the

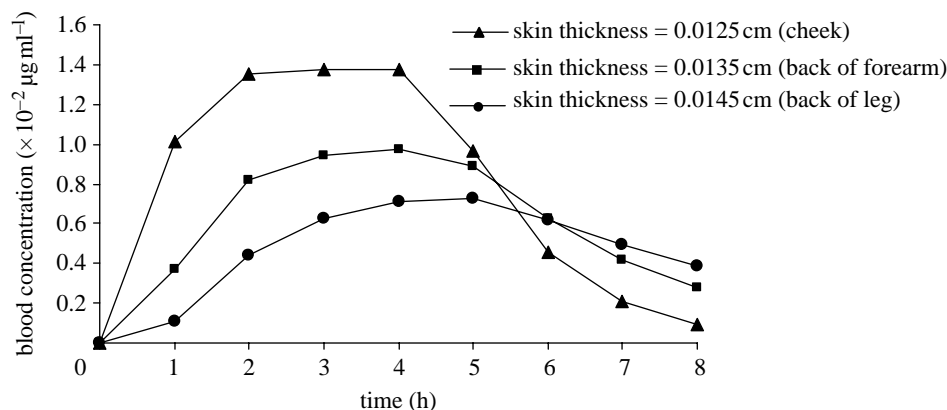


Figure 8. Transdermal delivery of hGH for typical skin thicknesses of various human anatomical regions (Lee & Hwang 2002; $L=0.01$ cm; all the remaining parameters are as shown in table 1).

blood hGH concentration. This relationship must be taken into account while designing microneedle array systems in practice. The functional dependency of S_a/L^2 on $C_{b,ss}/C_s$ is as shown in figure 6 (named, second curve) and given by the following relation, provided all other parameters remain the same:

$$\frac{C_{b,ss}}{C_s} = 2 \times 10^{-10} \left(\frac{S_a}{L^2} \right) + 7 \times 10^{-10}; \quad 900 < \frac{S_a}{L^2} < 40000. \quad (3.2)$$

This equation is valid for a given microneedle length (L), in this case $L=0.01$ cm corresponding to an epidermis skin thickness of 0.0125 cm.

(c) Effect of skin thickness

The distance from the skin surface to the dermal microcirculation represents the thickness of the epidermis. This can be a function of age, anatomical region, race and sex. If we change the skin thickness while maintaining the same length of the microneedles, then there will be a change in effective diffusion length, and hence plasma drug concentration. The implications of changing skin thickness while keeping a constant length of the microneedle are shown in figure 8. As expected, we find that the steady-state drug concentration in blood is a function of the number of variables for a given skin thickness. Such a dependency is given by the following scaling relationship for cases where $0.007 \text{ cm} < L < 0.011 \text{ cm}$:

$$\frac{C_{b,ss}}{C_s} = 1 \times 10^{-6} e^{32.1(S_a \times L^4 \times K_e)/(V_b \times h \times D)}; \quad (3.3)$$

$$1.31 \times 10^{-6} < \frac{S_a \times L^4 \times K_e}{V_b \times h \times D} < 5.75 \times 10^{-6}.$$

Such a scaling relationship is useful to determine the steady-state drug concentration in blood, where there are no modelling or experimental results, as shown in figure 9 for two different values of skin thickness (h). Figure 9 shows that the thickness of skin is an important parameter for the process of drug delivery using a microneedle array. In figure 10 we show a comparison of the effects of different variables on dimensionless drug concentration in blood at

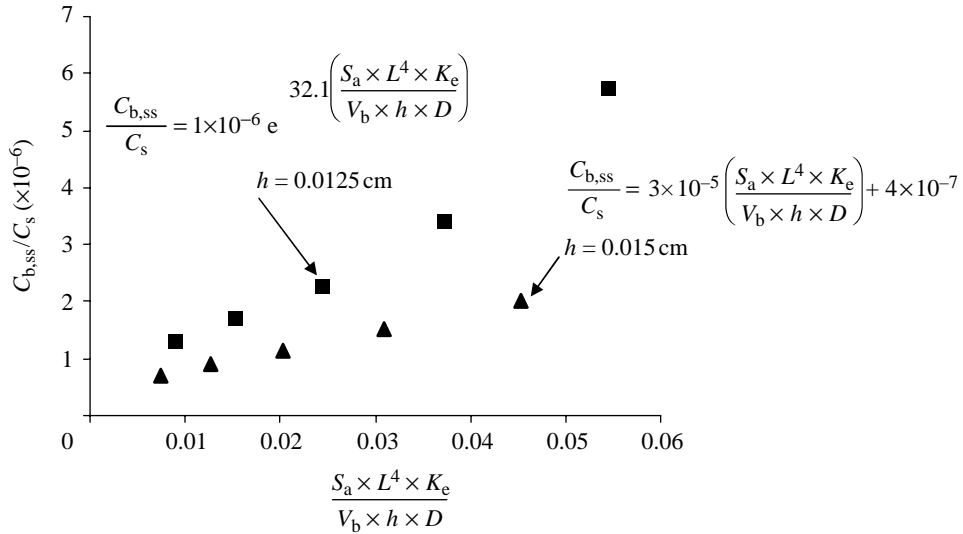


Figure 9. Scaling relationship for $(S_a \times L^4 \times K_e)/(V_b \times h \times D)$ versus $C_{b,ss}/C_s$ for injection of hGH in different skin thicknesses (h) using various microneedle lengths ($0.007 \text{ cm} < L < 0.011 \text{ cm}$) for the input parameters as shown in table 1.

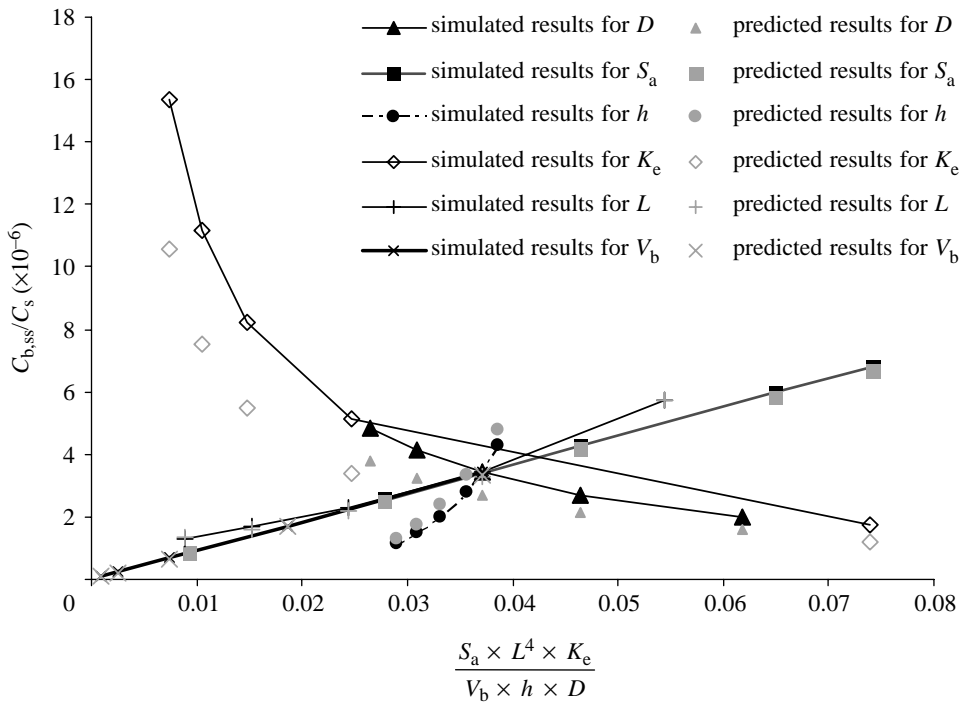


Figure 10. Scaling relationship for $(S_a \times L^4 \times K_e)/(V_b \times h \times D)$ versus $C_{b,ss}/C_s$ for predicted and simulated results for hGH for various D , K_e , V_b , L , h or S_a ($h = 0.0125 \text{ cm}$, $L = 0.01 \text{ cm}$, $h_e = 0.0025 \text{ cm}$; all the remaining parameters are as shown in table 1).

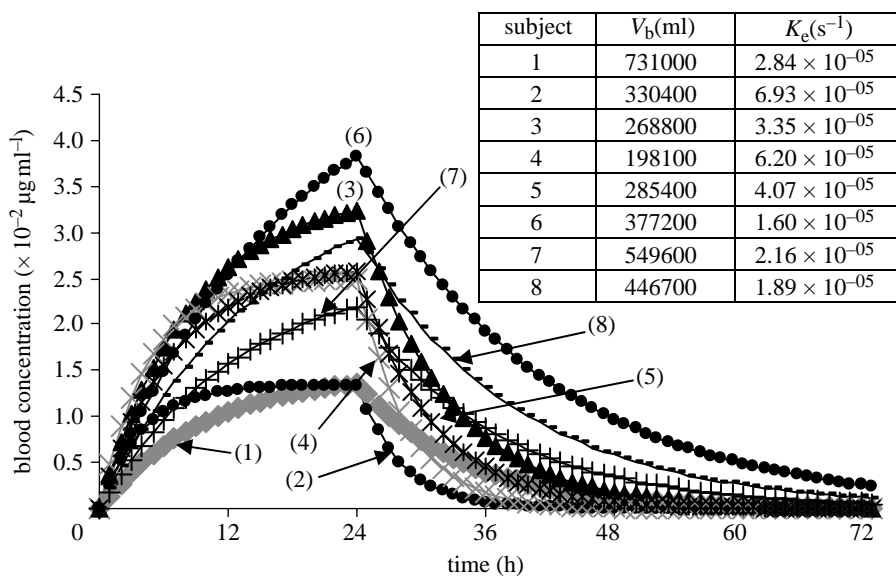


Figure 11. Effect of different pharmacokinetic parameters (Gupta *et al.* 1992) on blood concentration using microneedles for conditions (1–8) as shown above (total calculation length (t_m) = 72 hours, durations of application (t_a) = 24 hours, and all the remaining parameters are the same as shown in table 1).

steady state, which are calculated from both the scaling equation (3.3) and simulations. Figure 10 shows a good comparison, which gives confidence in equation (3.3).

(d) Effect of pharmacokinetic variables

To evaluate the effects of volume of distribution (V_b) and elimination rate constant (K_e) on the blood drug concentration, different values were chosen as shown in figure 11. These reflect the influences of different pharmacokinetics of V_b and K_e variables on blood Fentanyl concentration after applying the microneedle arrays. We chose Fentanyl as a model drug, as experimental values of V_b and K_e are available (Gupta *et al.* 1992). As expected, the blood Fentanyl concentration varies for different cases depending on the given input parameters. Although this profile has different distributions, it shows that pharmacokinetic variables have an effect on drug delivery using microneedles. This simulation is useful to predict the quantitative influence of pharmacokinetic variables on blood drug concentration. For given parameters, the functional dependency for volume of distribution, as shown in figure 6 (third curve), is governed by the following scaling relationship:

$$\frac{C_{b,ss}}{C_s} = 345.0 \left(\frac{L^3}{V_b} \right); \quad 5 \times 10^7 < \frac{V_b}{L^3} < 4 \times 10^8. \quad (3.4)$$

This scaling equation is valid for a given microneedle length, in this case $L = 0.01$ cm, assuming $100 \text{ ml} < V_b < 4000 \text{ ml}$. The range of V_b represents its typical values in animal (i.e. hairless guinea-pig with $V_p = 100 \text{ ml}$) and human ($V_p = 4000 \text{ ml}$) in body pharmacokinetics of hGH. The functional dependency of the elimination rate constant (K_e) for microneedle injection of hGH is shown in

figure 6 (curve four) which follows the scaling relationship as below:

$$\frac{C_{b,ss}}{C_s} = 6 \times 10^{-4} \left(\frac{L^2 K_e}{D} \right)^{-0.96}; \quad 57.8 < \frac{L^2 K_e}{D} < 462. \quad (3.5)$$

This scaling equation is also valid for a given microneedle length, in this case $L=0.01$ cm, assuming $2.13 \times 10^{-3} \text{ s}^{-1} < K_e < 2.31 \times 10^{-4} \text{ s}^{-1}$ corresponding to half-lifetime between 5 and 40 min. The other parameters D , h and C_s are assumed constant for both cases as shown in table 1. These relationships can be effective in terms of simulation time to determine the effects of both elimination rate constant and volume of distribution on blood drug concentration for real life problems. The more detailed evaluations should be performed with simultaneous consideration for the differences in skin structures and pharmacokinetic variables.

4. Conclusion

In this study a framework has been presented to mathematically describe the phenomena of drug delivery in skin tissues using a microneedle system. This paper provides quantitative evaluations of various parameters influencing the drug concentration in blood. For the purpose of this work, the blood drug concentration is adopted as the most important variable of interest, as is traditionally done in the field of transdermal drug delivery. Subsequently, its relations with various transport parameters are studied. It is shown that there are different parameters that must be considered in designing, and hence, optimizing any microneedle systems. These may include, e.g. the length of the microneedles, duration of the application, surface area of the array system, etc. This suggests that for the design of a microneedle system, evaluating various transport parameters as well as physical dimensions of the system enhances the efficiency of transdermal drug delivery techniques.

The skin/body pharmacokinetic model, as adopted in this work, has permitted us to study the blood drug concentration and determine its relation to different microneedle and skin tissue parameters. The parameters considered in this work have been used to generalize their effects through the development of scaling relationships. This is mainly because it is important to determine the general functional dependence of blood drug concentration on various parameters. This has been done by carrying out a dimensional analysis using Buckingham's π theorem. The developed relationships make the problem simpler to analyse and allow us to correlate multiscale behaviour of drug delivery using microneedles. These scaling relationships along with our simulations show how various parameters of microneedles, drug and skin determine the blood drug concentration. The results presented in this paper form the foundation for more detailed analysis to be carried out in the future.

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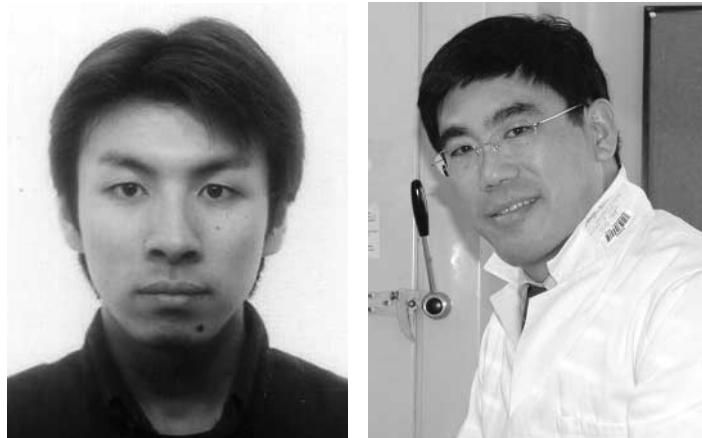


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