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MATHEMATICAL MODELING OF TRANSDERMAL DRUG DELIVERY

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A dynamic mathematical model for transdermal drug delivery is developed on the basis of the bi-layer skin/two-compartment body model. The effects of metabolism reaction in the viable skin, the drug binding and reservoir function in the stratum corneum, and the solubility and diffusivity of the drug in the skin on the permeation rate-time profile are extensively simulated. The effects of the pharmacokinetic parameters on the plasma concentration profile are also analyzed. The present model is useful not only for analyzing the rate of skin permeation but also for predicting the plasma concentration after transdermal drug delivery.

Introduction

For many years, drugs have been administered percutaneously to achieve localized pharmacological action. Recently, however, the skin has increasingly been used as a portal of entry for systemically active agents. In 1981, ALZA Corporation first introduced a product of transdermal therapeutic systems, Transderm-Scop[®], for medication of motion sickness. In 1982, three transdermal delivery systems for nitroglycerin, Nitro-Dur[®], Transderm-Nitro[®] and Nitrodisc, in the treatment of angina pectoris were introduced from Key Pharmaceuticals, Ciba Geigy and G.D. Searle, respectively. In 1985, the transdermal delivery system for clonidine, Catapres-TTS[®], was introduced in antihypertensive treatment by Boehringer Ingelheim. Other transdermal drug delivery systems are also in various stages of develop-

ment and testing. We can expect a significant force of transdermal drug delivery in the near future.

In spite of the great impact of transdermal drug delivery on pharmaceutical society, the mechanism of drug permeation across the skin is not clear due to the complicated structure of the skin. During the last decade, a number of researchers have extensively studied percutaneous absorption of drugs both experimentally and theoretically. They have made great efforts to understand the penetration of drugs through the skin. The permeation data, however, were frequently analyzed on simplistic assumptions such as a single layer skin, a constant diffusivity, a steady-state condition, a simplified boundary condition, a compartment model of skin, etc.^{1-3,6,8,9,12-14,18,21,23,37,43,44)} A more rigorous approach is needed, at this stage of transdermal drug delivery studies, to elucidate the mechanism of percutaneous absorption.

The main resistance to drug transport across the

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intact skin generally resides in drug diffusion through the stratum corneum, the outermost layer (dead keratinized) of the skin. In recent years, skin permeability of various drugs has been enhanced by physical,^{15,27,42)} electrical,²⁰⁾ and/or biochemical (prodrug) approaches.^{22,44)} As a result, drug permeation across the viable skin may play an important role in determining the overall rate of skin permeation. It is also well known that metabolism reaction takes place not in the stratum corneum but in the viable skin.²⁵⁾ Since the transdermal drug delivery system is usually applied to a specific site of the body for a long period of time, the metabolism reaction may be subject to the time-dependent activity of enzymes around the delivery system.

The present work is concerned with the dynamic mathematical modeling of transdermal drug delivery. The skin permeation of drugs is simulated by a combined model of bi-layer skin diffusion and two-compartment body elimination. The effects of physical-chemical properties, such as the diffusivity, solubility, partition coefficient, enzyme activity, drug binding and stratum corneum reservoir function, on drug permeation across the skin are extensively investigated. The effects of pharmacokinetic parameters, such as the elimination rate constant of the drug and the volume of distribution, on the plasma concentration-time profile are also discussed. A method for predicting the plasma concentration *in vivo* after transdermal drug delivery is proposed.

1. Model Formulation

A schematic diagram of the present diffusion/compartment model is illustrated in Fig. 1. The drug concentration on the surface of the stratum corneum is assumed to remain constant during the entire period of application of the transdermal drug delivery system. This is the usual case for skin-control transdermal drug delivery.^{28,31)} The skin is histologically a three-layer membrane which consists of the stratum corneum, viable epidermis and dermis. Schaefer *et al.* demonstrated a clear difference in drug distribution between the stratum corneum and the viable epidermis.²⁵⁾ They also found no discontinuity in the drug concentration profile between the viable epidermis and dermis.²⁵⁾ In addition, especially *in vivo*, the drug molecule permeated through the viable epidermis is absorbed rapidly through the microcirculation.⁴⁵⁾ In this study, therefore, the skin is assumed to be a bi-layer membrane which consists of the stratum corneum and the viable layer.

The drug, incorporated in the delivery system at a homogeneous concentration, is first partitioned and penetrates into the stratum corneum, in which the drug may partially be bound. The dual sorption model based on the Langmuir isotherm⁴⁰⁾ is assumed

Fig. 1. A diffusion/compartment model for transdermal drug delivery. Skin, bi-layer membrane (stratum corneum and viable skin); body, two-compartment open model. Drug elimination is restricted to central compartment. K_e , elimination rate constant; k_{12} and k_{21} , rate constants between the compartments; V_1 and V_2 are volumes of central and peripheral (tissue) compartments.

for this binding process.^{2,3)} The drug is then partitioned toward the viable skin, in which the drug is bioconverted to its metabolites. In this study, we assume the following scheme for the enzymatic reaction:

For the metabolism reaction of drug A, drugs B and C may be either active or nonactive metabolite, while for the transdermal delivery of prodrug A, drugs B and C are the active drug and the metabolite, respectively. The enzymatic reaction usually obeys Michaelis-Menten kinetics. The simple competitive inhibition of second reaction for drug A is also assumed.

The metabolites, B and C, generated in the viable skin, diffuse into the receptor compartment as well as into the stratum corneum based on Fick's equation (Fig. 1). In general, the rate of back-diffusion into the stratum corneum is quite low due to the substantially small diffusivity in the stratum corneum. However, the back-diffusion into the stratum corneum may not be neglected since the drug molecules in the stratum corneum play an important role in the reservoir function of the stratum corneum. The back diffusion of the metabolites into the donor compartment may also be important for the *in vitro* skin permeation experiment using a reservoir-type donor compartment. The drugs through the viable skin are absorbed into the body compartments (blood circulation and tissue compartment). In this study, a two-compartment model with first-order elimination kinetics (Fig. 1) is assumed to describe the drug concentrations in the plasma.

The mass balance of drugs, A, B and C, over a

differential volume element of the skin yields:

$$\left\{1 + \frac{p_a}{(1 + q_a C_a)^2}\right\} \frac{\partial C_a}{\partial t} = \frac{\partial}{\partial x} \left(D_a \frac{\partial C_a}{\partial x} \right) - \frac{M_a C_a}{B_a + C_a} \quad (1)$$

$$\left\{1 + \frac{p_b}{(1 + q_b C_b)^2}\right\} \frac{\partial C_b}{\partial t} = \frac{\partial}{\partial x} \left(D_b \frac{\partial C_b}{\partial x} \right) + \frac{M_a C_a}{B_a + C_a} - \frac{M_b C_b}{\left(1 + \frac{C_a}{K_i}\right) B_b + C_b} \quad (2)$$

$$\left\{1 + \frac{p_c}{(1 + q_c C_c)^2}\right\} \frac{\partial C_c}{\partial t} = \frac{\partial}{\partial x} \left(D_c \frac{\partial C_c}{\partial x} \right) + \frac{M_b C_b}{\left(1 + \frac{C_a}{K_i}\right) B_b + C_b} \quad (3)$$

where the notations are summarized in the Nomenclature. Equations (1) to (3) are applied to the stratum corneum ($0 \leq x \leq h$) without metabolism reaction and to the viable skin ($h < x \leq H$) without drug binding ($p = q = 0$).

At low concentration of drug A, Eqs. (1) to (3) reduce to:

$$\left\{1 + \frac{p_a}{(1 + q_a C_a)^2}\right\} \frac{\partial C_a}{\partial t} = \frac{\partial}{\partial x} \left(D_a \frac{\partial C_a}{\partial x} \right) - k_1 C_a \quad (1a)$$

$$\left\{1 + \frac{p_b}{(1 + q_b C_b)^2}\right\} \frac{\partial C_b}{\partial t} = \frac{\partial}{\partial x} \left(D_b \frac{\partial C_b}{\partial x} \right) + k_1 C_a - k_2 C_b \quad (2a)$$

$$\left\{1 + \frac{p_c}{(1 + q_c C_c)^2}\right\} \frac{\partial C_c}{\partial t} = \frac{\partial}{\partial x} \left(D_c \frac{\partial C_c}{\partial x} \right) + k_2 C_b \quad (3a)$$

Much of the present study was carried out by using the simplified governing equations (1a)–(3a). Recently, it was found that the bioconversion of estradiol diacetate followed first-order reaction kinetics.³⁵⁾

The appropriate boundary conditions are:

i) $x = 0$ (donor-side surface):

$$C_a = S \quad (0 < t \leq t_2) \quad (4)$$

or

$$dC_a/dx = 0 \quad (t > t_2) \quad (5)$$

$$dC_b/dx = 0 \quad (6)$$

$$dC_c/dx = 0 \quad (7)$$

where t_2 is the duration of the transdermal drug delivery system.

If the metabolites, B and C, diffuse back into the donor compartment (device), the following boundary conditions may be used instead of Eqs. (6) and (7):

$$C_b = 0 \quad (\text{sink condition}) \quad (8)$$

$$C_c = 0 \quad (\text{sink condition}) \quad (9)$$

ii) $x = h$ (stratum corneum/viable skin boundary):

$$D_i \frac{\partial C_i}{\partial x} \Big|_{h^-} = D_i \frac{\partial C_i}{\partial x} \Big|_{h^+} \quad (10)$$

$$C_i(h^-) = P_i C_i(h^+) \quad i = a, b, c \quad (11)$$

where P is the viable skin/stratum corneum partition coefficient. Kammerau *et al.* clearly demonstrated that the drug concentration changes discontinuously on the stratum corneum/viable skin boundary.¹⁶⁾ On the contrary, the concentration changes continuously on the boundary between the epidermis and the dermis.²⁴⁾ The diffusivity in the viable epidermis is of the same order of magnitude as that in the dermis.²⁶⁾

The initial conditions are:

$$t = 0; \quad C_i = 0 \quad (i = a, b, c) \quad (12)$$

The diffusivity of the drug across the skin is generally a function of the space coordinate (x), time (t) and concentration (C):

$$D = f(x, t, C) \quad (13)$$

In this study, the skin is assumed to be intact during the transdermal medication, and therefore the diffusivity is a function of the space coordinate only, as follows:

$$D_i = \begin{cases} D_{1i} & (0 \leq x \leq h; \text{stratum corneum}) \\ D_{2i} & (h < x \leq H; \text{viable skin}) \end{cases} \quad (14)$$

The diffusivity D_1 across the stratum corneum is an effective diffusivity,³³⁾ since the stratum corneum is a multicellular membrane which consists of flattened keratinized cells and lipid-rich intercellular material.¹¹⁾

The rate constants k_1 and k_2 of the enzymatic reaction, $A \rightarrow B \rightarrow C$, are generally time-dependent because the enzyme in the viable skin may be degraded due to skin aging. This inactivation process of enzymes is important especially in *in vitro* skin permeation. In the present study, the kinetics of the enzyme inactivation is assumed to obey a decreasing exponential law:^{5,35)}

$$k_i = Z_i \exp(-A_i t) \quad i = 1, 2 \quad (15)$$

where Z is the intrinsic rate constant and A is the decay rate constant of enzyme activity.

The rate of drug permeation across the skin can be calculated by

$$\left(\frac{dQ}{dt} \right)_i = -D_i \left(\frac{dC_i}{dx} \right)_{x=H} \quad (16)$$

The cumulative amount of drug permeated per unit

area is then

$$Q_i = \int_0^t \left(\frac{dQ}{dt} \right)_i dt = \int_0^t \left(-D_i \frac{dC_i}{dx} \right)_{x=H} dt \quad (17)$$

Assuming the two-compartment model as shown in Fig. 1, the drug concentrations in the plasma can be given by:

$$\frac{d(XV_1)}{dt} = \left(\frac{dQ}{dt} \right) S_a + k_{21} YV_2 - k_{12} XV_1 - K_e XV_1 \quad (18)$$

for the central compartment, and

$$\frac{d(YV_2)}{dt} = k_{12} XV_1 - k_{21} YV_2 \quad (19)$$

for the tissue (peripheral) compartment, where S_a is the surface area of drug delivery system. The other notations are given in the legend of Fig. 1. The rate of drug permeation across the skin, $(dQ/dt)_i$, can be calculated from Eq. (16).

2. Method of Solution

The so-called "Method of Lines"¹⁹⁾ is employed here to solve the partial differential equations. This method applied to the governing equations Eqs. (1) to (3) primarily involves discretizing the spatial coordinate and converting the partial differential equations into a set of ordinary differential equations.³⁰⁾ A numerical method (Runge-Kutta-Gill,⁴⁾ for ordinary differential equations is then used to solve the resulting equations to obtain numerical approximations to the original partial differential equations. Specifically, the formula of the second-order centered finite difference scheme is utilized for the present spatial discretization. The number of spatial meshes specified for this study is 41 for each skin layer. The use of mesh points greater than 41 yields essentially identical results for the present calculation.

To test the accuracy of numerical solution, it was compared with the analytical solution for a special case where no binding ($p=q=0$), first-order irreversible reaction ($k_2=0$) and unilayer membrane ($D_1=D_2=\text{constant}$, $P=1$) were assumed. It was found that the numerical solution agreed excellently with the analytical solution.³⁶⁾

3. Results and Discussion

The concentration profiles of drugs A, B and C in the stratum corneum and in the viable skin are plotted in Fig. 2 as a function of the dimensionless time. This calculation simulated steroid permeation across the hairless mouse skin.³⁴⁾ The concentration of drug A in the stratum corneum decreases rapidly along the depth of the stratum corneum, while the concentrations of its metabolites (B and C), bioconverted from drug A in the viable skin, increase with time in the stratum corneum. Since the diffusivity of drugs in

the viable skin is much greater than that in the stratum corneum (500–10,000 times,^{32,34)}, the effect of back-diffusion of the metabolites on the overall permeation rate may be neglected under normal skin permeation conditions. However, the back-diffusion may affect appreciably the dynamics of transdermal drug delivery because the concentrations in the stratum corneum play an important role in the reservoir function of the stratum corneum. In addition, if the resistance of the stratum corneum to permeation is minimized by an appropriate method such as the use of a skin enhancer, the effect of back-diffusion would become more significant.

The effect of the rate constants k_1 and k_2 of the enzymatic reaction in the skin on the cumulative amount of drug permeated is shown in Fig. 3. The rate constants were varied arbitrarily to demonstrate the effect of rate constants on permeation profile. The other parameters were the same as in Fig. 2. Recently, Valia *et al.*³⁸⁾ found that the estradiol diacetate was bioconverted into the estradiol by a consecutive first-order reaction in hairless mouse skin. They also reported that no estradiol diacetate was detected in the receptor solution during the entire period of their *in vitro* skin permeation studies (up to 48 hours) because k_1 is about 20 times k_2 .³⁸⁾

The effect of drug binding in the stratum corneum on the permeation profile is shown in Fig. 4. The values of the binding rate constant p , rate constant k and diffusivity ratio D_1/D_2 were varied arbitrarily to demonstrate the effect of these parameters. It can be seen that the time-lag, defined as the intercept on the time axis, increases with increasing binding rate constant. A similar result was reported by Chandrasekaran *et al.* assuming a single layer skin.²⁾ The steady-state rate of permeation of the drug is hardly influenced by the binding process. It is also found from Fig. 4 that the time-lag is significantly decreased by the first-order enzymatic reaction in the viable skin. This finding indicates that the time-lag method must carefully be applied to determine the diffusivity of drugs in the skin. If the membrane is a unilayer, the decrease in the time-lag caused by the enzymatic reaction can be explained analytically.³⁶⁾

Figure 5 shows the effects of partition coefficient P , defined as the ratio of the drug solubility in the stratum corneum to that in the viable skin, on the cumulative amount of the drug permeated. This calculation simulated the bioconversion of estradiol diacetate to estradiol in the hairless mouse skin. The steady-state rate of permeation decreases, while the time-lag increases as the partition coefficient increases. This is due to the decrease in drug solubility in the viable skin.

Figure 6 shows the effects of the system-on (system applied) and system-off (system removed) of the

Fig. 2. Concentration profile of drug in the skin as a function of time after application of transdermal drug delivery system. (a) stratum corneum, (b) viable skin. Parameter, dimensionless time ($= D_1 t/h^2$); $D_2/D_1 = 3000$; $P_1 = 5$; K_1 (dimensionless rate constant $= k_1 h^2/D_1$) $= K_2 = 10$; $h = 0.0010$ cm; $H = 0.0380$ cm.

Fig. 3. Effect of rate constants of metabolism reaction on cumulative amount of drug permeated. Parameter, dimensionless rate constant (K_1, K_2); $D_2/D_1 = 3000$; $P_1 = 5$; $h = 0.0010$ cm; $H = 0.0380$ cm: (-----), drug A; (---), drug B; (—), drug C.

Fig. 4. Effect of drug binding in stratum corneum based on dual sorption model on the cumulative amount of drug (A) permeated. $h = 0.0010$ cm; $H = 0.0380$ cm; $K_1 (= k_1 h^2/D_1) = K_2 (= k_2 h^2/D_1)$; $P_1 = 10$; $q = 0$. Parameters, ($p, K_1, D_2/D_1$); A, (0, 1, 10,000); B, (2, 1, 10,000); C, (0, 0, 1,000); D, (2, 0, 1,000); E, (0, 1, 1,000); F, (2, 1, 1,000); G, (0, 5, 1,000); H, (2, 5, 1,000).

transdermal drug delivery on the rate of drug permeation. In this simulation, a steady-state permeation was assumed at the system-off and system-on points. Under the steady-state condition without enzymatic

reaction and binding, the initial concentration profiles for the system-off and system-on are given, respectively, as follows:

$$t=0, \quad C=S \left\{ \frac{h-x}{h} + \frac{x}{h} \frac{1}{1 + (D_2/D_1)[h/(H-h)](1/P)} \right\} \quad (0 \leq x \leq h) \quad (20)$$

$$C=S \left\{ \frac{H-x}{H-h} \frac{1}{P + (D_2/D_1)[h/(H-h)]} \right\} \quad (h < x \leq H) \quad (21)$$

It is interesting to see that the permeation rate under the system-off condition changes more slowly than that under the system-on condition. This is due

to the reservoir function of the stratum corneum. As can be expected from Eq. (20), the reservoir function is influenced not only by the diffusivity ratio D_1/D_2 ,

Fig. 5. Effect of stratum corneum/viable skin partition coefficient P on the cumulative amount of drug permeated. Numbers on the curves are values of partition coefficient. $h=0.0010$ cm; $H=0.0380$ cm; (—), drug C; (---), drug B; $D_2/D_1=3000$; $P_1=P_2=P_3$; $K_1=170$; $K_2=10$; $p=q=0$.

Fig. 6. Effect of system-off and system-on of transdermal drug delivery on rate of drug permeation. (—), $D_2/D_1=10,000$; (---), $D_2/D_1=1,000$; (-·-), $D_2/D_1=500$; $P_1=10$; $K_1=0$; $p=q=0$; $h=0.0010$ cm; $H=0.0380$ cm.

but also by the solubility S or partition coefficient P . In this simulation, neither enzymatic reaction nor drug binding was assumed. Therefore, the reservoir effect appeared in Fig. 6 is due to the slow diffusion of drug accumulated in the stratum corneum. If the binding takes place in the stratum corneum, a more significant reservoir effect may appear. The stratum corneum reservoir function was first demonstrated by Vicker,³⁹⁾ who found that the hydration or occlusion of the stratum corneum noticeably influenced the reservoir function. His result indicated that the amount of drug accumulated in the stratum corneum played an important role in the reservoir function.

Figure 7 shows the effects of the enzyme activity on the cumulative amount of drug permeated as a parameter of the enzyme inactivation constant (Eq. 15). In this calculation, the rate constant k_1 was assumed to be much greater than k_2 , and therefore, drug A was completely bioconverted to drug B in the viable skin. The permeation rate of drug C gradually de-

Fig. 7. Effect of enzyme activity on cumulative amount of drug permeated. Numbers on the curves are dimensionless decay rate constant (Ah^2/D_1). (—), drug C; (---), drug B; no drug A appeared for initial 24 hours. $D_1=3.0 \times 10^{-11}$ cm²/s; $S=12.6$ mg/ml; $D_2/D_1=3.0 \times 10^3$; $Z_1=20$; $Z_2=340$; $P_1=5$; $h=0.0010$ cm; $H=0.0380$ cm.

creased as the time increased. On the contrary, the permeation rate of drug B slowly increased with time. Since the enzyme activity depends largely on animal species, *in vivo* or *in vitro* conditions as well as the site of skin, the enzyme activity in the viable skin must be carefully taken into account to establish a reliable *in vitro/in vivo* correlation. The enzyme inactivation is usually important in *in vitro* skin permeation study. For transdermal prodrug delivery, however, the skin permeation may be affected significantly by the time-dependent enzyme activity under *in vivo* conditions, because the enzymes in the skin underneath the delivery system may not be regenerated during a long period of the system application.

4. Plasma Concentration

The plasma concentration-time curve for transdermal drug delivery was calculated by solving the mass balance equations based on the two-compartment model (Eqs. 18 and 19). The thickness of the total skin was assumed to be 200 micrometers, since the distance from the skin surface to the microcirculation is reported to be about 200 micrometers.¹⁷⁾ The drug through the viable epidermis is uptaken almost entirely by the microcirculation system,⁴⁵⁾ although the resorption of drugs by this capillary system is not complete.

The effect of the stratum corneum thickness on the plasma concentration-time profile is shown in Fig. 8. This calculation simulated verapamil permeation across the human skin. It can be seen that the plasma concentration for thin skins (5 and 10 micrometers thick) reaches a steady state before the system-off point (24 hours). However, the concentration for the thicker skins (15 and 20 micrometers thick) continuously increases for a certain period after the

Fig. 8. Effect of stratum corneum thickness on dynamics of plasma concentration. Numbers on the curves are values of thickness in micrometers. $D_1 = 7.0 \times 10^{-11} \text{ cm}^2/\text{s}$; $D_2/D_1 = 1000$; $S = 344 \text{ mg/ml}$; $P = 8$; $K_1 = K_2 = 0$; $p = q = 0$; $V_1 = 3.65 \times 10^5 \text{ ml}$; $V_2 = 0$; device surface area = 80 cm^2 . Duration of TTS application (t_2) = 24 h; $K_e = 7.43 \times 10^{-5} (1/\text{s})$.

system-off point. This is due to the reservoir function of stratum corneum as mentioned earlier. Since the thickness of skin influences markedly not only the steady-state concentration but also the dynamics of the plasma concentration, the site of application of the skin-control transdermal drug delivery must be carefully determined.

The effect of the pharmacokinetic half-life $t_{1/2} (= 0.693/K_e)$ of the drug on the plasma concentration profile is simulated in Fig. 9. The time to reach a steady-state concentration in the plasma is markedly influenced by the half-life of the drug. If the half-life of the drug is very short, such as that of nitroglycerine, the dynamics of the plasma concentration is determined almost entirely by the skin permeation characteristics. On the contrary, if the drug has a very long half-life, such as that of clonidine, the body compartment determines the dynamics of the plasma concentration. Therefore, the optimum duration of the transdermal drug delivery system is a function of the physicochemical properties, such as diffusivity and solubility in the skin, as well as the pharmacokinetic parameters of the drug in the body compartment.

The dynamics of plasma concentration profile of nitroglycerin from a reservoir-type transdermal delivery system was simulated by the present model and compared with the clinical data reported by Good¹⁰⁾ in Fig. 10. The drug diffusivity and solubility in each skin layer were determined by bi-layer skin model²⁹⁾ with the time-lags and steady-state rates of permeation obtained in the *in vitro* permeation experiment using a hairless mouse skin. The pharmacokinetic properties of the two-compartment model (Fig. 1) were calculated from the intravenous infusion data for monkeys reported by Wester *et al.*⁴¹⁾ The body weight was assumed to be 60 kg. Therefore, all the parameters for simulating the human

Fig. 9. Effect of drug half-life on plasma concentration-time profile after application of transdermal drug delivery system. Numbers on the curves are values of drug half-life ($t_{1/2}$) ($= 0.693/K_e$). $D_1 = 7 \times 10^{-11} \text{ cm}^2/\text{s}$; $D_2/D_1 = 7.4 \times 10^3$; $h = 0.0010 \text{ cm}$; $S = 130 \text{ mg/ml}$; $P = 15$; $K_1 = K_2 = 0$; $p = q = 0$; $V_1 = 3.1 \times 10^5 \text{ ml}$; $V_2 = 0$; Surface area of TTS = 20 cm^2 . X_{ss} = steady-state plasma concentration.

plasma concentration of nitroglycerin were obtained from the animal models. It is interesting to see from Fig. 10 that not only the steady-state concentration in the plasma but also the dynamic response of the concentration profiles agree fairly well with the clinical data except under the system-off condition after 24 hours. This finding indicates that a hairless mouse and a monkey are good animal models for nitroglycerin to describe the skin permeation kinetics and to evaluate the pharmacokinetic parameters in human, respectively. It is also indicated that the present mathematical approach is useful for predicting the plasma concentration of nitroglycerin through transdermal administration. Under the system-off condition, the calculated profiles of plasma concentration show a typical reservoir effect of the stratum corneum because a considerable amount of nitroglycerin was accumulated in the stratum corneum under a steady-state condition. However, the experimental concentration decreases very rapidly after the removal of the transdermal delivery system (24 hours). Colfer *et al.*⁷⁾ reported a similar finding for their nitroglycerin delivery system. This is probably due to the fact that part of the stratum corneum was stripped when the delivery system was removed. For the transdermal nitroglycerin delivery system, the stratum corneum contains about 95% of total drug in the skin under a steady-state condition. In Fig. 10, the plasma concentration profile, assuming that the stratum corneum is completely removed together with the delivery system, is also plotted as a dashed line. The experimental data are found to fall between the two extreme cases. In general, the reservoir-function of stratum corneum is significant for a highly lipophilic drug. If the surface layer of stratum corneum may

Fig. 10. Comparison of dynamics of plasma concentration of nitroglycerin after transdermal drug delivery. (O), experimental (clinical data,⁶); (—), calculated by the present model. $D_1 = 1.93 \times 10^{-10} \text{ cm}^2/\text{s}$; $D_2/D_1 = 1090$; $h = 0.0020 \text{ cm}$; $H = 0.020 \text{ cm}$; $S = 5.19 \times 10^4 \text{ } \mu\text{g}/\text{ml}$; $P = 14.8$; $p = q = 0$; $K_i = 0$; $V_1 = 2.83 \times 10^4 \text{ ml}$; $V_2 = 1.35 \times 10^5 \text{ ml}$. Surface area = 10, 20 and 40 cm^2 . $K_e = 8.19 \times 10^{-3}/\text{s}$; $k_{12} = 5.3 \times 10^{-3}/\text{s}$; $k_{21} = 1.1 \times 10^{-3}/\text{s}$.

partly be stripped when the delivery system is removed, the effect of the reservoir function would be less significant than expected from simulation. Since each delivery system has its own characteristics with respect to adhesion to the skin surface, the system-off dynamics may be affected by the design of the delivery system as well as by the skin/drug interaction even if the system is the skin-control delivery system.

Conclusion

A combined bi-layer skin/two-compartment body model was proposed to predict the plasma concentration after transdermal drug delivery. The effects of drug binding in the stratum corneum, metabolism reaction in the viable skin, drug diffusivity and partition coefficient on the dynamics of the skin permeation were extensively simulated. The plasma concentration-time curve clinical data for a nitroglycerin delivery system was well explained by the present mathematical model.

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Nomenclature

A	= degradation rate constant of enzyme activity (Eq. 15)	$[\text{s}^{-1}]$
B	= Michaelis-Menten kinetics parameter	$[\text{g}/\text{l}]$
C	= drug concentration in skin	$[\text{g}/\text{l}]$
C_a	= drug concentration on the surface of stratum corneum	$[\text{g}/\text{l}]$
D	= drug diffusion coefficient in skin	$[\text{cm}^2/\text{s}]$
H	= thickness of intact skin	$[\text{cm}]$
h	= thickness of stratum corneum	$[\text{cm}]$
K	= intrinsic rate constant of enzymatic reaction	

K_e	= elimination rate constant (Fig. 1)	$[\text{s}^{-1}]$
K_i	= inhibition constant of the second reaction for drug A	$[\text{g}/\text{l}]$
k	= rate constant of enzymatic reaction in viable skin	$[\text{s}^{-1}]$
k_{12}	= transfer rate constant between compartments (Fig. 1)	$[\text{s}^{-1}]$
k_{21}	= transfer rate constant between compartments (Fig. 1)	$[\text{s}^{-1}]$
M	= Michaelis-Menten kinetics parameter	$[\text{g}/\text{s}]$
P	= drug partition coefficient from stratum corneum to viable skin	$[-]$
p	= binding rate constant based on dual sorption model	$[-]$
Q	= cumulative amount of drug permeated	$[\text{g}/\text{cm}^2]$
q	= binding rate constant based on dual sorption model	$[\text{l}/\text{g}]$
S	= drug solubility in the stratum corneum	$[\text{g}/\text{l}]$
S_a	= total surface area of transdermal drug delivery system	$[\text{cm}^2]$
t	= time	$[\text{s}]$
$t_{1/2}$	= pharmacokinetic half-life of drug ($= 0.693/K_e$)	$[\text{s}]$
t_2	= application time for transdermal drug delivery system	$[\text{s}]$
V_1	= volume of distribution of central compartment (plasma)	$[\text{l}]$
V_2	= volume of distribution of peripheral compartment (tissue)	$[\text{l}]$
X	= drug concentration in plasma	$[\text{g}/\text{l}]$
x	= distance from surface of skin	$[\text{cm}]$
Y	= drug concentration in tissue compartment	$[\text{g}/\text{l}]$
Z	= intrinsic rate constant	$[\text{s}^{-1}]$

<Subscripts>

a	= drug A
b	= drug B
c	= drug C
l	= stratum corneum

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