SKIN-CAD®: Pharmacokinetic Model for Transdermal Drug Delivery

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INTRODUCTION

Pharmacokinetic-pharmacodynamic (PK-PD) models for percutaneous absorption are useful in evaluating the clinical performance and optimizing the design of transdermal therapeutic systems [1, 2]. Diffusion models have been developed in order to analyze diffusivity and partitioning of drugs in the skin [3, 4]. However, there are few *in silico* approaches for predicting the clinical performance as well as the side effects following transdermal drug delivery.

We have developed a simulation software, SKIN-CAD®, for *in silico* PK-PD evaluation of transdermal drug delivery [5]. This includes the diffusion models for drug release from matrix device and drug permeation across the skin, the compartment model for the body elimination and distribution and the pharmacodynamic model. SKIN-CAD® can also analyze the effects of binding and metabolism in the skin, iontophoretic application and uptake by dermal blood flow. The PK-PD simulation using SKIN-CAD® requires the model parameters such as the thickness of stratum corneum, diffusion and partition coefficients in the skin, distribution volumes and rate constants for the compartment model and pharmacodynamic parameters. The model parameters can be determined independently from *in vitro* skin permeation study and intravenous administration study and can also be obtained from various literatures.

In this study, we propose a method for evaluating clinical performance of transdermal therapeutic systems by using SKIN-CAD® together with the model parameters under clinical conditions.

THEORETICAL

A general PK-PD model for transdermal drug delivery is illustrated in Fig. 1. In this figure, the model consists of the diffusion models for release of dispersed drug from matrix and permeation through the 2-layer skin, 2-compartment model for the whole body and the pharmacodynamic model. Each elemental model can be modified and adjusted depending on the target drug or device.

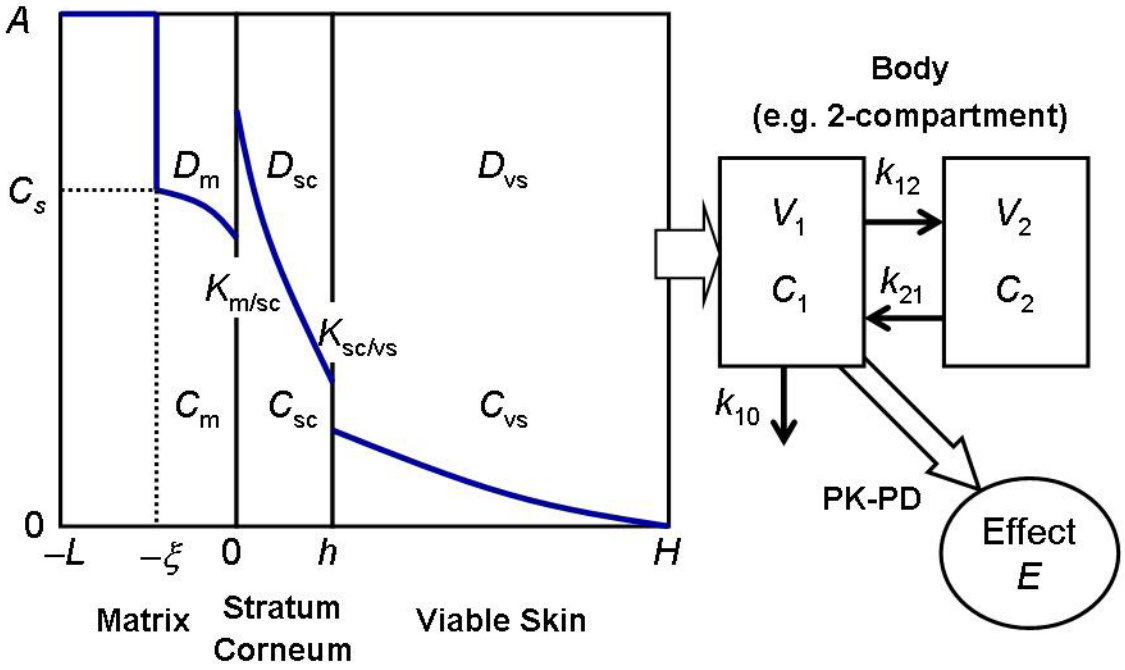

Fig.1. Schematic diagram of pharmacokinetic model for transdermal drug delivery.

Diffusion Model for Drug Release from Matrix

The diffusion process of drug dissolved in the matrix can be described by Fick's second law [6]:

$$\frac{\partial C_{\mathrm{m}}}{\partial t} = D_{\mathrm{m}} \frac{\partial^2 C_{\mathrm{m}}}{\partial x^2}, \quad -L < x < 0 \tag{1}$$

where D_{m} is the diffusion coefficient in the matrix and L is the thickness of the matrix. If the initial drug concentration, A, is lower than the solubility in the matrix, initial condition is:

$$C_{\mathrm{m}} = A, \quad -L \le x \le 0, \quad t = 0 \tag{2}$$

In the case of drug-dispersed matrix, the moving boundary problem should be considered because the diffusion front at $x = -\xi$, the boundary between dispersed zone and dissolved zone formed in the matrix, recedes to the backing layer side ($x = -L$).

$$\frac{\partial C_{\mathrm{m}}}{\partial t} = D_{\mathrm{m}} \frac{\partial^2 C_{\mathrm{m}}}{\partial x^2}, \quad -\xi < x < 0 \tag{3}$$

Initial and boundary conditions are as follows when the initial drug loading, A, is higher than the solubility:

$$C_{\mathrm{m}} = A, \quad -L \le x \le 0, \quad t = 0 \tag{4}$$

$$C_{\mathrm{m}} = C_s, \quad x = -\xi, \quad t > 0 \tag{5}$$

$$(A - C_s)\frac{\mathrm{d}\xi}{\mathrm{d}t} = D_{\mathrm{m}} \frac{\partial C_{\mathrm{m}}}{\partial x}, \quad x = -\xi, \quad t > 0 \tag{6}$$

where C_s is the drug solubility in the matrix.

Diffusion Model for Skin Permeation

The intact skin is assumed to be 2-layer membrane composed of stratum corneum and viable skin. Drug concentration in each layer can be expressed as follows based on diffusion equation with considering the skin binding by dual sorption model, the skin metabolism followed Michaelis-Menten kinetics and electrorepulsion and/or electroosmosis caused by the iontophoretic application [1, 7]:

$$\left\{1+\frac{p_{\mathrm{sc}}}{\left(1+q_{\mathrm{sc}}C_{\mathrm{sc}}\right)^2}\right\}\frac{\partial C_{\mathrm{sc}}}{\partial t}=D_{\mathrm{sc}}\frac{\partial^2 C_{\mathrm{sc}}}{\partial x^2}+\frac{zFD_{\mathrm{sc}}E}{RTh}\frac{\partial C_{\mathrm{sc}}}{\partial x}-u_{\mathrm{sc}}\frac{\partial C_{\mathrm{sc}}}{\partial x},\quad 0<x<h \tag{7}$$

$$\left\{1+\frac{p_{\mathrm{vs}}}{\left(1+q_{\mathrm{vs}}C_{\mathrm{vs}}\right)^2}\right\}\frac{\partial C_{\mathrm{vs}}}{\partial t}=D_{\mathrm{vs}}\frac{\partial^2 C_{\mathrm{vs}}}{\partial x^2}-\frac{V_{\max}C_{\mathrm{vs}}}{K_m+C_{\mathrm{vs}}}-u_{\mathrm{vs}}\frac{\partial C_{\mathrm{vs}}}{\partial x},\quad h<x<H \tag{8}$$

where D_{sc} and D_{vs} are the diffusion coefficients in the stratum corneum and the viable skin, respectively, h is the thickness of the stratum corneum, and H is the thickness of the whole skin and should be the distance to the dermal microcirculation under *in vivo* condition. The following initial and boundary conditions are applied:

$$C_{\mathrm{sc}}=0,\quad 0\le x\le h,\quad t=0 \tag{9}$$

$$C_{\mathrm{vs}}=0,\quad h\le x\le H,\quad t=0 \tag{10}$$

$$\frac{\mathrm{d}C_{\mathrm{sc}}}{\mathrm{d}x}=0,\quad x=0,\quad t>t_a \tag{11}$$

$$C_{\mathrm{sc}}=K_{\mathrm{sc/vs}}C_{\mathrm{vs}},\quad x=h,\quad t>0 \tag{12}$$

$$-D_{\mathrm{sc}}\frac{\mathrm{d}C_{\mathrm{sc}}}{\mathrm{d}x}+u_{\mathrm{sc}}C_{\mathrm{sc}}=-D_{\mathrm{vs}}\frac{\mathrm{d}C_{\mathrm{vs}}}{\mathrm{d}x}+u_{\mathrm{vs}}C_{\mathrm{vs}},\quad x=h,\quad t>0 \tag{13}$$

$$C_{\mathrm{vs}}=0,\quad x=H,\quad t>0 \tag{14}$$

$$C_{\mathrm{m}}=K_{\mathrm{m/sc}}C_{\mathrm{sc}},\quad x=0,\quad 0<t\le t_a \tag{15a}$$

$$C_{\mathrm{sc}}=\mathrm{const.},\quad x=0,\quad 0<t\le t_a \tag{15b}$$

where t_a is the duration of device application and $K_{\mathrm{m/sc}}$ is the partition coefficient between the polymer matrix and the stratum corneum. Eq. (15a) can be applied for the case of drug release from the matrix device and Eq. (15b) for infinite dose.

Compartment Model for Body Pharmacokinetics

The conventional multi-compartment model can be used for pharmacokinetics in the whole body. In the case of 2-compartment model which consists of blood compartment and tissue compartment, the mass balance in each compartment is described by:

$$V_1\frac{\mathrm{d}C_1}{\mathrm{d}t}=\left(\frac{\mathrm{d}Q}{\mathrm{d}t}\right)S_a+k_{21}C_2V_2-\left(k_{12}+k_{10}\right)C_1V_1 \tag{16}$$

$$V_2 \frac{dC_2}{dt} = k_{12} C_1 V_1 - k_{21} C_2 V_2 \quad (17)$$

where V_1 and V_2 are the distribution volumes of blood compartment and tissue compartment, respectively, k_{10} is the elimination rate constant, k_{12} and k_{21} are the transfer rate constants between compartments, S_a is the effective area applied and dQ/dt is the skin permeation rate determined by the above diffusion model:

$$\frac{dQ}{dt} = -D_{vs}\left(\frac{dC_{vs}}{dt}\right)_{x=H} \quad (18)$$

METHODS

Numerical Method

The diffusion equations or the partial differential equations are discretized with appropriate mesh points and converted into the ordinary differential equations using method of lines. The ordinary differential equations are numerically solved by Runge-Kutta-Gill method. The numerical solution was found to be precise compared with the analytical solution under the simplified condition.

Case Study

The PK-PD profiles following application of the transdermal fentanyl patch were evaluated by using SKIN-CAD®. Table 1 shows the model parameters obtained or determined from some literatures and estimated from the drug property.

The thickness of the stratum corneum and the distance to the dermal microcirculation were obtained from references [9, 10]. The diffusion coefficient in the stratum corneum was calculated from *in vitro* permeation data using human cadaver skin [11] and that in the viable skin was assumed to be 10000-fold. Stratum corneum/viable skin partition coefficient was estimated by correlation equation derived from *in vitro* permeation data using hairless mouse skin [12]:

$$K_{sc/vs} = 0.460 \times K_{o/w}^{\ 0.480} \quad (19)$$

where $K_{o/w}$ is octanol/wate partition coefficient (fentanyl: 860 [13]). The drug concentration on the skin surface was calculated from:

$$C_{sc,\,x=0} = J\left\{\frac{h}{D_{sc}} + \frac{(H-h)K_{sc/vs}}{D_{vs}}\right\} \quad (20)$$

where J is the *in vitro* flux across the intact skin (fentanyl patch: 2.5 μg/cm^2/h [14]). The distribution volumes and the rate constants following intravenous administration were obtained

from a reference [15]. In order to calculate pharmacologic or side effects using Eq. (21), the relationships between the serum fentanyl concentration and the VAS (visual analogue scale) score which is the estimation index for analgesic effect or the respiratory rate for evaluating the respiratory depressant effect by fentanyl were determined or obtained from clinical data [16, 17].

$$E = E_0 - \frac{E_{\max} C_1^n}{EC_{50}^n + C_1^n} \tag{21}$$

Table 1. Model parameters for PK-PD simulation of fentanyl patch.

Duration of TTS application	72 h	
System area	40, 30, 20 and 10 cm^2	
Diffusion model for skin permeation		
Thickness of stratum corneum	18.2 μm	
Distance to dermal microcirculation	200 μm	
Diffusion coefficient in the stratum corneum	2.44×10^{-11} cm^2/s	
Diffusion coefficient in the viable skin	2.44×10^{-7} cm^2/s	
Stratum corneum/viable skin partition coefficient	11.8	
Skin surface concentration	58.0 mg/cm^3	
Compartment model for body pharmacokinetics		
Distribution volume, V_1	26.8 L	
Distribution volume, V_2	48.2 L	
Distribution volume, V_3	189 L	
Elimination rate constant	0.0410 min^{-1}	
Transfer rate constant, k_{12}	0.185 min^{-1}	
Transfer rate constant, k_{21}	0.103 min^{-1}	
Transfer rate constant, k_{13}	0.141 min^{-1}	
Transfer rate constant, k_{31}	0.0200 min^{-1}	
Pharmacodynamic model (sigmoid E_{max} model)	*VAS score*	*respiratory rate*
Baseline, E_0	6.97	15.1 min^{-1}
Maximum effect, E_{max}	5.93	15.1 min^{-1}
Concentration producing 50% maximum effect, EC_{50}	0.346 ng/mL	3.5 ng/mL
Hill coefficient, n	2.62	1

RESULTS AND DISCUSSION

The time courses of the serum fentanyl concentration and pharmacologic or side effect were shown in Figs. 2 and 3.

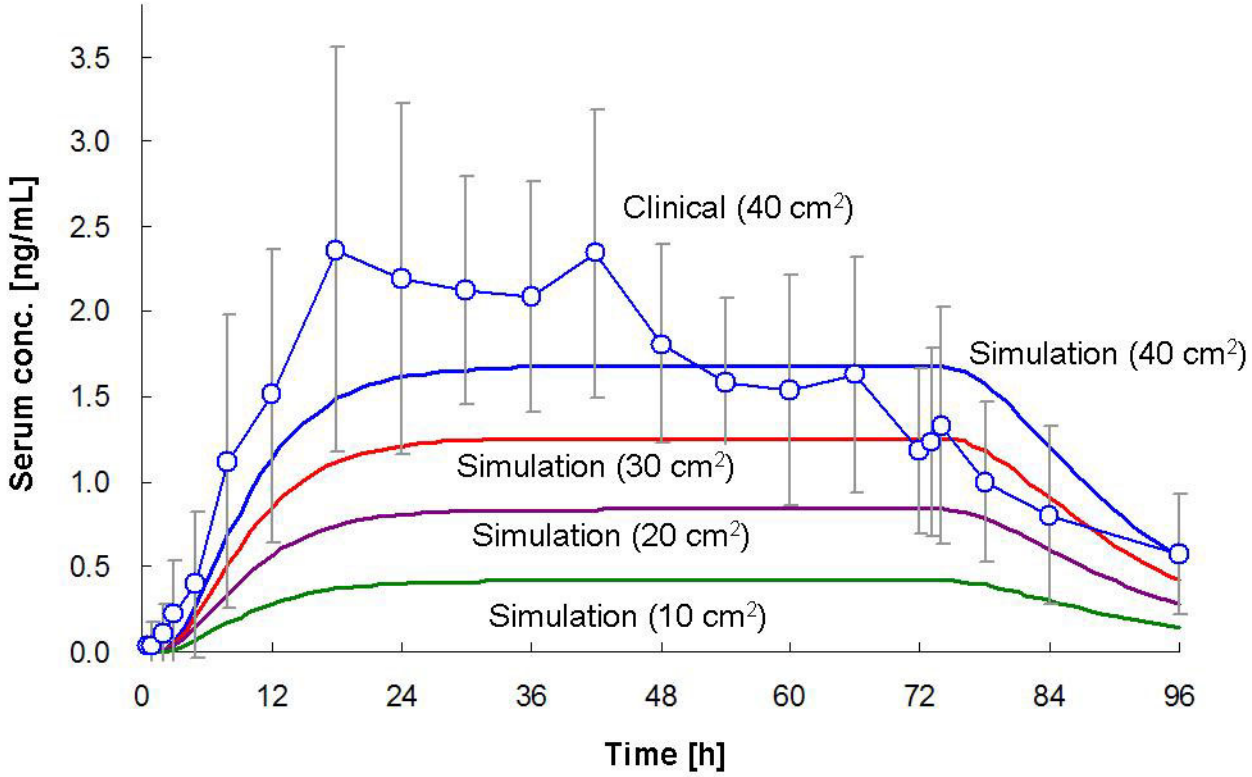

Fig. 2. Serum fentanyl concentration-time profiles following transdermal delivery. Comparison between simulated and clinical data [14].

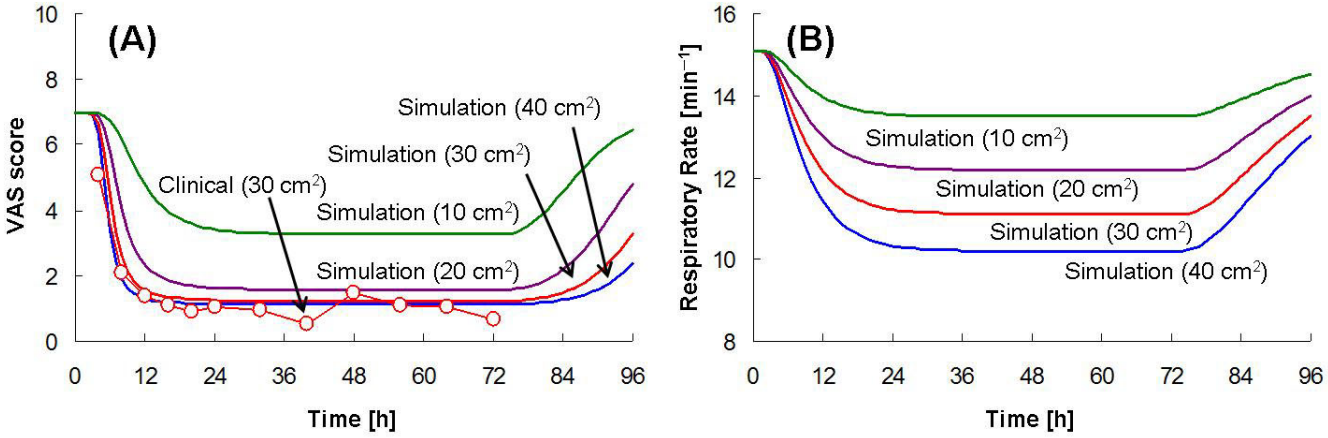

Fig. 3. Time courses of VAS score (A) and respiratory rate (B) following transdermal delivery. Comparison between simulated and clinical data [16].

The simulated profiles of the serum fentanyl concentration and the VAS score by SKIN-CAD® well agreed with the clinical data. The respiratory rate during transdermal fentanyl delivery was also found to be nearly equal to the clinical data for the application of 40-cm^2 system, 11.9 min^{-1} [18]. The simulation results may better duplicate the clinical data if the characteristics of release

from the matrix and permeation through the skin such as diffusion and partition coefficients are determined by *in vitro* studies.

CONCLUSIONS

The time courses of blood drug concentration and pharmacologic effects following transdermal drug delivery were well predicted by numerical simulation together with the model parameters and the given clinical conditions. SKIN-CAD® improved the development process of transdermal drug delivery systems. The *in silico* approach proposed in this study may be a substitute for doing both animal experiments and clinical trials.

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