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Concentration profile in plasma after transdermal drug delivery

K. Tojo

Department of Pharmaceutics, College of Pharmacy, Rutgers – The State University of New Jersey, Busch Campus, Piscataway, NJ 08855-0789 (U.S.A.)

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Summary

The plasma profile of the drug concentration after transdermal delivery was simulated on the basis of a dynamic mathematical model. The skin was assumed to be a bilayer membrane which consists of the stratum corneum and the viable epidermis. A conventional multi-compartment model was also assumed to describe the drug elimination/distribution in the body. The effects of the skin permeation kinetics as well as the body elimination/distribution on the plasma profile of the drug concentration were analyzed under various modes of application for the drug delivery system.

Introduction

Drug molecules released from a transdermal delivery system first partition into the stratum corneum, then diffuse into the lower layer of the skin and are finally transported away by the blood microcirculation. The drug concentration in the plasma after transdermal delivery is determined by the balance between the permeation rate across the skin (input) and the elimination/distribution rate in the body. Since the plasma profile for many drugs is controlled mainly by the skin permeation and/or the body elimination/distribution kinetics, it is important to understand the quantitative effect of the physicochemical properties for skin permeation as well as the pharmacokinetic parameters for the body elimination/distribution on the plasma profile after transdermal drug delivery.

In this communication, the plasma concentration profile after transdermal drug delivery is simulated on the basis of the diffusion/compartment model developed recently (Tojo, 1987). The effect of various modes of application on the plasma concentration profile is also discussed. The optimum design of the delivery system and its mode of application can be predicted by analyzing the effect of various parameters on the plasma concentration profile.

Theoretical model

A dynamic mathematical model of transdermal drug delivery was previously proposed (Tojo, 1987)

Correspondence: K. Tojo, Department of Pharmaceutics, College of Pharmacy, Rutgers University, Busch Campus, P.O. Box 789, Piscataway, NJ 08854-0789, U.S.A.

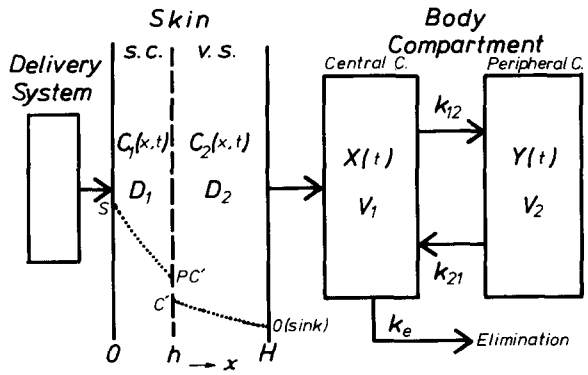

Fig. 1. Bilayer skin diffusion/multi-compartment body elimination model for pharmacokinetics of the transdermal drug delivery (two-compartment open model is shown as an example). s.c. = stratum corneum; v.s. = viable skin (epidermis); X = drug concentration in the central compartment; Y = drug concentration in the tissue compartment; V = volume of distribution; k_{12} and k_{21} = intercompartmental rate constants; k_e = elimination rate constant.

and is schematically illustrated in Fig. 1. This model consists of a bilayer diffusion barrier (stratum corneum and viable skin) and a multi-compartment for body distribution or elimination. In Fig. 1, a two-compartment open model is illustrated as an example.

Most drugs penetrate the skin approximately proportionally to the concentration gradient between the upper and the lower side of the skin (Schaefer et al., 1982). If the binding, metabolism and shunt diffusion in the skin are assumed to be negligible, the drug concentration in the skin can be described by the following Fick's law of diffusion (Crank, 1975):

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial C}\left(D\frac{\partial C}{\partial x}\right) \tag{1}$$

where C is the drug concentration in the skin, t is the time, x is the distance from the surface of the skin and the drug diffusivity D is given by:

$$D = \begin{cases} D_1 \ (0 \le x \le h\text{: stratum corneum}) \\ D_2 \ (h < x \le H\text{: viable skin}) \end{cases} \tag{2}$$

The drug diffusivity in the stratum corneum (layer 1 in Fig. 1) is usually about 1/1000 of that across the viable skin (layer 2 in Fig. 1) (Scheuplein and Blank, 1971; Tojo et al., 1987). The thickness of the human stratum corneum and the distance from the skin surface to the microcirculation are 10–20 μm and 150–200 μm, respectively (Schaefer et al., 1982). The drug molecules crossing the skin are efficiently transported away into the capillary layer (microcirculation). The sink condition can, therefore, be assumed to be on the front of the capillary layer (Fig. 1). The appropriate initial and boundary conditions of Eqn. 1 are summarized for various modes of applications in Table 1. The rate of drug permeation across the unit area of skin is computed by:

$$R = \frac{dQ}{dt} = -D_2\left(\frac{\partial C_2}{\partial x}\right)_{x=H} \tag{3}$$

The cumulative amount of drug permeated from one delivery system is then given by:

$$Q = \int_0^t R\,dt = \int_0^t \left(\frac{dQ}{dt}\right)dt \tag{4}$$

If a two-compartment open model as shown in Fig. 1 is assumed for the body elimination/distribution pharmacokinetics, the plasma concentration after the transdermal application of n systems is described by:

$$\frac{d(XV_1)}{dt} = \sum_{i=1}^{n}\left(\frac{dQ}{dt}\right)_i A_i + k_{21}YV_2 - k_{12}XV_1 - k_eXV_1 \tag{5}$$

for the central compartment, where A is the effective surface area and n is the number of the transdermal delivery systems applied, and

$$\frac{d(XV_2)}{dt} = k_{12}XV_1 - k_{21}YV_2 \tag{6}$$

for the tissue (peripheral) compartment.

Eqns. 1, 5 and 6 were solved simultaneously under appropriate boundary and initial conditions summarized in Table 1. To solve the partial differential equation, Eqn. 1, the Method of Lines procedure (Carver, 1981) was employed. A resultant set of ordinary differential equations were

TABLE 1

Initial and boundary conditions for Eqn. 1

Initial Conditions:
mode of application

system-on $C = 0 \ (0 \leq x \leq H)$ (7)

system-off ($t > t_a$)
after steady-state

$$C = \begin{cases} S\left\{\frac{h-x}{h} + \frac{x}{h}\frac{1}{1+(D_2/D_1)[h/(H-h)](1/P)}\right\} & (8) \\ 0 \leq x \leq h \\ S\left\{\frac{H-x}{H-h}\frac{1}{P+(D_2/D_1)[h/(H-h)]}\right\} & (9) \end{cases}$$

before steady-state $C = f(x, t_a)$ (10)

Boundary Conditions:

$x = 0$ (upper surface of the skin) $C = S \ (0 \leq t \leq t_a)$ (11)

$dX/dx = 0 \ (t > t_a$, system-off) (12)

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

$D_1(dC_1/dx) = D_2(dC_2/dx)$ (no accumulation) (13)

$C_1 = PC_2$ (partitioning) (14)

$x = H$ (lower surface of the skin) $C = 0$ (sink condition) (15)

t_a = duration of system application; $f(x,t_a)$ = concentration profile at time t_a after system-on; S = concentration on the surface of stratum corneum; Suffix: 1 = stratum corneum, and 2 = viable skin.

numerically solved by Runge-Kutta-Gill or Gear's Method (Gear, 1971). All simulations in this study were carried out using an IBM Personal Computer. Microsoft FORTRAN Optimizing Compiler (Version 4.0) was used for solving the computer programming written by FORTRAN77.

Results

Simulated profiles of the skin permeation rate and the plasma concentration after transdermal delivery are shown in Figs. 2 and 3 as a parameter of the duration (h) of application. Figs. 2 and 3 simulate the transdermal delivery of nitroglycerin and clonidine, respectively. The diffusion coefficient and the solubility of the drug for skin permeation were determined from an in vitro skin permeation experiment based on a bilayer skin model (Tojo et al., 1987). The pharmacokinetic parameters for body elimination/distribution were obtained previously (Tojo, 1987a and b). When the drug has a short elimination half-life (1.4 min) or a large elimination rate constant such as nitroglycerin in Fig. 2, the dynamic plasma profile of the drug concentration is almost identical to the rate profile of skin permeation. In this case, the plasma concentration profile is wholly controlled by the physicochemical properties of skin permeation. Therefore, it may be possible to control the plasma profile of the drug by the system design of the delivery system. On the other hand, when the drug has a long half-life (8.4 h) or a small elimination rate constant such as clonidine in Fig. 3, the plasma concentration profile (solid line) is mainly controlled by the pharmacokinetic parameters for the body elimination/distribution kinetics. In this case, the dynamic plasma profile under system-on

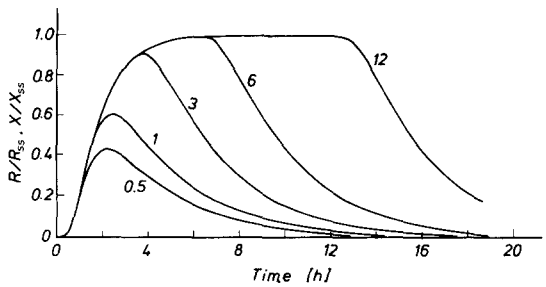

Fig. 2. Plasma concentration and skin permeation rate profiles after transdermal delivery of the drug with a large elimination rate constant k_e. The numbers on the curves are the duration (h) of the applications. Key: ———, plasma concentration profile; - - - - - -, skin permeation rate profile (almost identical to the plasma concentration profiles). Suffix ss = steady-state. $D_1 = 1.9\times10^{-10}$ cm^2/s; $D_2 = 2.1\times10^{-7}$ cm^2/s; $P = 14.8$; $h =$ 0.0020 cm; $H = 0.020$ cm; $V_1 = 2.8\times10^4$ ml; $V_2 = 1.4\times10^5$ ml; $k_e = 8.2\times10^{-3}$ s^{-1}; $k_{12} = 5.3\times10^{-3}$ s^{-1}; $k_{21} = 1.1\times 10^{-3}$ s^{-1}. These parameter values were determined previously (Tojo, 1987).

or system-off conditions cannot be optimized by the system design of the transdermal drug delivery, although the constant steady-state or zero level concentration is achieved after a remarkably long time lag.

It is possible for the drug with a short plasma half-life, such as nitroglycerin, to achieve a daily pulse delivery by applying another patch for an appropriate duration in addition to the regular

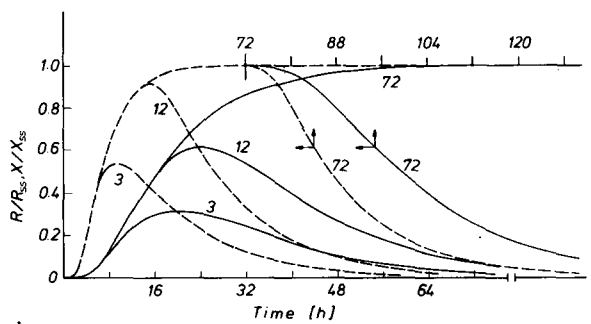

Fig. 3. Plasma concentration and skin permeation rate profiles after transdermal delivery of the drug with a small elimination rate constant k_e. The numbers on the curves are the duration (h) of application. Key: ———, plasma concentration profile; - - - - - -, skin permeation rate profile. Suffix ss = steady state. $D_1 = 3.9\times10^{-11}$ cm^2/s; $D_2 = 5.5\times10^{-8}$ cm^2/s; $P = 10$; $h = 0.0020$ cm; $H = 0.020$ cm; $V_1 = 2.1\times10^5$ ml; $V_2 = k_{12} = k_{21} = 0$; $k_e = 2.3\times10^{-5}$ s^{-1}.

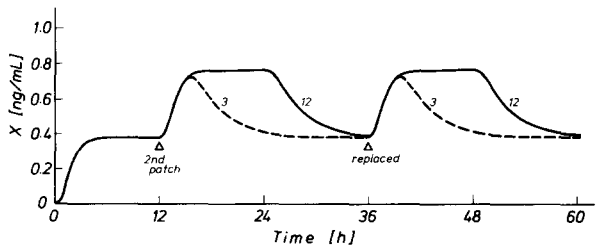

Fig. 4. Plasma profile of the drug concentration under multiple application ($A_1 = A_2$). Parameters are the same as in Fig. 2. Key: - - - - - -, 3 h application; ———, 12 h application.

long-term zero-order permeation system as shown in Fig. 4, where the duration of the second patch is 3 or 12 h. It can be seen from this figure that the daily pulsed concentration superimposed on the long-term zero-order concentration is achieved. The plasma concentration (peak value) and the duration for maintaining the effective plasma level can be controlled by the size of the delivery system and its duration for application. This approach may be useful to improve the efficacy of the transdermal delivery for drugs, whose optimum plasma concentration is not the conventional zero-order but rather pulsed pattern.

The plasma concentration profile of clonidine after transdermal delivery was simulated and compared with the clinical data reported by Arndts and Arndts (1984) in Fig. 5. It can be seen that the simulated profile agreed fairly well with the experimental profile not only in the initial start-up but under the system-replaced or system-removed conditions, as well.

The present mathematical model for transdermal drug delivery can be used for predicting a

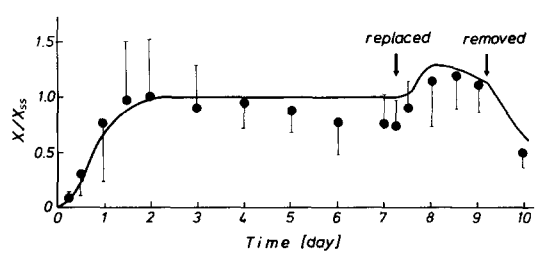

Fig. 5. Comparison of the plasma profile of clonidine after various modes of transdermal delivery. ●, human in vivo values (Arndts and Arndts, 1984); ———, simulated by the present model. Parameters are the same as in Fig. 3.

quantitative effect of various physicochemical and pharmacokinetic parameters on the plasma concentration profiles after transdermal drug delivery. The optimum design for the transdermal drug delivery and its mode of application may be predicted by solving the mathematical model under various initial and boundary conditions, if the physicochemical properties for skin permeation and the pharmacokinetic parameters are available in the literature or determined by conventional experimental procedures.

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