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Effect of Vehicles on Percutaneous Absorption. II.[1] Theory of Percutaneous Absorption

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Drug absorption across the skin has been interpreted as the diffusional mass transfer of the drug starting from the vehicle, travelling through the skin tissue, and terminating at the blood stream. There may be some non-diffusional resistance against the drug migration at the vehicle-skin interface and the skin-blood interface. Simulation calculation using an electronic computer can be applied to this simple model of the thickness of the administrated vehicle, that of the skin, the diffusion coefficient in the vehicle, that in the skin, the partition coefficient between these two phases, and the non-diffusional resistance at the vehicle-skin and the skin-blood interface. The present paper describes the method of simulation which has been applied to the experimental results detailed in the succeeding paper.

Drug absorption across the skin may simply be interpreted as the diffusional mass transfer starting from a liquid vehicle, travelling through the skin tissue, and terminating at the blood stream where the drug concentration is kept practically zero. The mathematical solution or even the formulation for this simple model is impracticable because the diffusion coefficient in the vehicle and the skin tissue are different to each other, the partition coefficient between these two phases is not equal to unity, and in addition, there may be some resistance against the drug migration at both the vehicle-skin interface and the skin-blood interface. Simulation calculation using an electronic computer[3] has been successfully applied to the above-mentioned model. The present paper describes the method of simulation.

Basic Principle of Diffusion

It is well known that the driving force of one-dimensional diffusion is the slope of chemical potential (μ) along the direction of diffusion (x), *i.e.* $-\partial\mu/\partial x$. The chemical potential can be approximately expressed as

$$\mu = \mu^\circ + \boldsymbol{R}T \ln C \tag{1}$$

where C is the concentration of solute and μ° stands for chemical potential at unit concentration. Notation $\boldsymbol{R}$ and T have their usual meanings. Equation (1) is sufficiently accurate in most cases, although C should be replaced by activity in a rigorous expression. When two phases, 1 and 2, containing a common solute are in equilibrium, the potentials in the two phases must be equal to each other.

$$\mu_1^\circ + \boldsymbol{R}T \ln C_{1eq} = \mu_2^\circ + \boldsymbol{R}T \ln C_{2eq} \tag{2}$$

$$\mu_1^\circ - \mu_2^\circ = \boldsymbol{R}T \ln (C_{2eq}/C_{1eq}) \tag{2'}$$

Consider the phase 1 as a reference phase ($\mu_1^\circ=0$), and let P_2 be the partition coefficient between the phase 2 and the reference phase, then one gets

1) Part I: H. Oishi, Y. Oshio, K. Narahara, and M. Takehara, *Chem. Pharm. Bull.* (Tokyo), 24, 1765 (1976). This work was presented at the 95 th Annual Meeting of the Pharmaceutical Society of Japan, Nishinomiya, April 1975.

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3) T. Nakagawa and H. Jizomoto, *J. Am. oil Chemists' Soc.*, 48, 571 (1971).

$$-\mu_2^\circ = \boldsymbol{R}T \ln P_2 \tag{3}$$

The subscript 2 may be omitted since Eq. (3) holds without regard to the kind of phase 2, and thus Eq. (4) is obtained by combining (1) and (2)

$$\mu = -\boldsymbol{R}T \ln P + \boldsymbol{R}T \ln C = \boldsymbol{R}T \ln (C/P) \tag{4}$$

The driving force acting on one mole of solute is given by

$$-\frac{\partial \mu}{\partial x} = -\boldsymbol{R}T \frac{\partial \ln (C/P)}{\partial x}$$

and the migration velocity of the solute molecules along x axis by

$$v = \left(-\frac{\partial \mu}{\partial x}\right) \Big/ \mathrm{Res} = -\frac{\boldsymbol{R}T}{\mathrm{Res}} \frac{\partial \ln (C/P)}{\partial x}$$

where Res is the frictional coefficient; frictional resistance acting on one mole of solute moving with unit velocity. Thus the flux I is expressed by

$$I = vC = -\frac{C\boldsymbol{R}T}{\mathrm{Res}} \frac{\partial (C/P)/\partial x}{(C/P)} = -\frac{P\boldsymbol{R}T}{\mathrm{Res}} \frac{\partial (C/P)}{\partial x} = -PD \frac{\partial C_{\mathrm{eff}}}{\partial x} \tag{5}$$

with the definitions of $D=RT/\mathrm{Res}$ and $C_{\mathrm{eff}}=C/P$. The first of them is concordant with the ordinary definition of diffusion coefficient and the second may be regarded as the effective concentration with respect to the diffusion. It should be noted that C_{eff} is a function of position x and time t whereas P and D are, substantially, functions of x only. Defining

$$G = PD \tag{6}$$

which is a function of x only, one gets

$$I = -G \frac{\partial C_{\mathrm{eff}}}{\partial x} \tag{7}$$

In a region where P does not change with x, Eq. (7) reduces to Fick's first law.

$$I = -D \frac{\partial C}{\partial x} \tag{7'}$$

Equation (7) reminds us of an electrodynamical relation having the same form

$$I = -\rho \frac{\partial E}{\partial x} \tag{8}$$

where I is the current density, E is the electrical potential, and ρ is the conductivity. We may call G "diffusibility" or "generalized diffusion coefficient" at position x. In a region x_1—x_2 where G varies along x axis, the average value of G in this region should be calculated by

$$G_{\mathrm{av}} = \frac{1}{\int_{x_1}^{x_2} \left(\frac{1}{G}\right) dx / (x_2 - x_1)} = \frac{x_2 - x_1}{\int_{x_1}^{x_2} \left(\frac{1}{G}\right) dx} \tag{9}$$

because the resistance obstructing the diffusion of solute, which corresponds to the reciprocal of G, is distributed in series along x axis. For the example shown in Fig. 1, G_{av} is given by

$$G_{\mathrm{av}} = \frac{\Delta x}{\frac{1}{G_{\mathrm{a}}} \frac{\Delta x}{2} + \frac{1}{G_{\mathrm{b}}} \frac{\Delta x}{2}} = \frac{2G_{\mathrm{a}}G_{\mathrm{b}}}{G_{\mathrm{a}} + G_{\mathrm{b}}} \tag{10}$$

Simulation Technique Applied

Our model is represented in Fig. 2. Drug diffusion in the blood stream must be very rapid ($D_{\mathrm{c}}=\infty$), and the partition coefficient in the skin tissue may be equated to unity by regarding the skin as the reference phase ($P_{\mathrm{b}}=1$). Both the vehicle and the skin are considered to be a pile consisting of many (n or m) thin layers whose thickness is $\Delta x = l_{\mathrm{a}}/\mathrm{n} = l_{\mathrm{b}}/\mathrm{m}$. Each layer is numbered from left to right (i=1—n for vehicle, n+1—n+m for skin), and the amounts

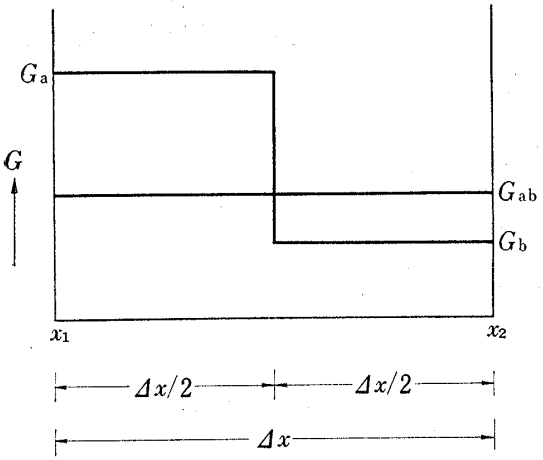

Fig. 1. An Example of Variation of G in a Region x_1—x_2

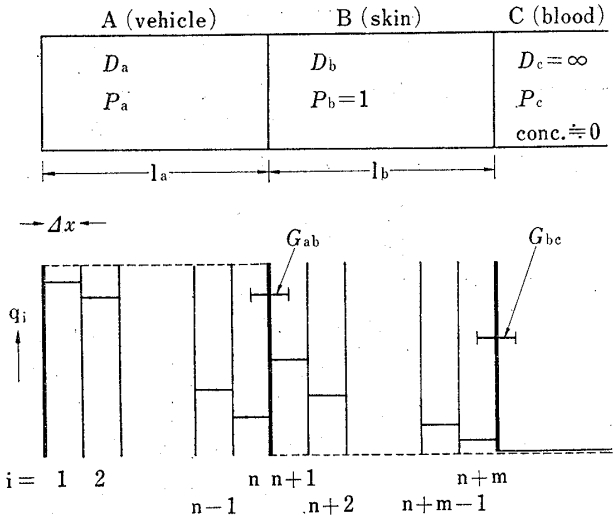

Fig. 2. A Simple Model of Drug Absorption

of drug present in these layers, q_1—q_{n+m}, are written in corresponding n+m memory fields of an electronic computer. The lapse of time t from the drug administration will cause the distribution profile to change from broken lines to solid lines. This change can be treated in the following manner.

Consider the i'th layer at any given time t. To the drug content q_i, add the quantity which flows in from the (i—1) th layer during an infinitesimal time interval Δt, and substract the quantity which flows out to the (i+1) th layer. The new q_i thus obtained shows the drug content at time $t+\Delta t$. Thus, the performance of the same procedure over all the n+m layers corresponds to the lapse of time Δt.

A series of renewals of all q_i values will be called a "process" hereafter. Repeating many processes, one can trace the drug diffusion step by step.

Equation (7) and (7′) will lead one to a rather intuitive idea that the quantity migrating from the i'th layer to the (i+1) th layer may be taken as

$$\Delta q = \alpha(q_i - q_{i+1}) \tag{11}$$

in the vehicle (i=1—(n−1))

$$\Delta q = \beta(q_i - q_{i+1}) \tag{12}$$

in the skin (i=(n+1)—(n+m−1))

$$\Delta q = \gamma(q_i/P_a - q_{i+1}) = \gamma(q_n/P_a - q_{n+1}) \tag{13}$$

at the vehicle–skin interface (i=n)

$$\Delta q = \delta(q_i - 0/P_c) = \delta q_{n+m} \tag{14}$$

at the skin–blood interface (i=n+m)

How to determine, then, the four constants α, β, γ, and δ?

Substituting $(C_{i+1}-C_i)/\Delta x$ for $\partial C/\partial x$ in (7′), one gets

$$I = -D\frac{C_{i+1}-C_i}{\Delta x} = D\frac{q_i - q_{i+1}}{(\Delta x)^2}$$

and accordingly

$$\Delta q = (I\cdot\Delta t =)\frac{D_a \Delta t}{(\Delta x)^2}(q_i - q_{i+1}) \tag{15}$$

for i=1—(n−1)

$$\Delta q = \frac{D_b \Delta t}{(\Delta x)^2}(q_i - q_{i+1}) \tag{16}$$

for i=(n+1)—(n+m−1)

The following two relations are derived from (7) in a similar way.

$$\Delta q = \frac{G_{ab}\Delta t}{(\Delta x)^2}\left(\frac{q_i}{P_a} - q_{i+1}\right) \quad (17)$$

for i=n

$$\Delta q = \frac{G_{bc}\Delta t}{(\Delta x)^2} q_i \quad (18)$$

for i=n+m

where G_{ab} and G_{bc} are the average values of G in the interfacial regions shown in Fig 2. Comparisons between two sets of equations, (11)—(14) and (15)—(18), shows the four constants to be

$$\alpha = \frac{\Delta t}{(\Delta x)^2} D_a, \quad \beta = \frac{\Delta t}{(\Delta x)^2} D_b, \quad \gamma = \frac{\Delta t}{(\Delta x)^2} G_{ab}, \quad \delta = \frac{\Delta t}{(\Delta x)^2} G_{bc} \quad (19)$$

Converting the first relation into the form of (20),

$$\Delta t = \frac{\alpha}{D_a}(\Delta x)^2 = \frac{\alpha}{D_a}\frac{l_a^2}{n^2} \quad (20)$$

one knows that a process corresponds to the lapse of time $\alpha l_a^2/D_a n^2$.

The values of α and n can be determined at our will whereas l_a and D_a have definite values specific to the system under examination. The larger the value of n and the smaller the value of α, the more accurate the simulation result but longer the calculation time required. Care should be exercised to satisfy the conditions

$$\alpha < 0.5, \ \beta = \frac{D_b}{D_a}\alpha < 0.5, \ \gamma = \frac{G_{ab}}{D_a}\alpha < \frac{P_a}{1+P_a}, \ \delta = \frac{G_{bc}}{D_a}\alpha < 1 \quad (21)$$

in order to keep the chemical potential of any layer being always higher than (or at least equal to) that of the neighbouring right layer.

If there is no special resistance against drug diffusion at the vehicle-skin and the skin-blood interface, G_{ab} and G_{bc} can be calculated to

$$G_{ab} = \frac{\Delta x}{\frac{1}{P_a D_a}\frac{\Delta x}{2} + \frac{1}{D_b}\frac{\Delta x}{2}} = \frac{2P_a D_a D_b}{P_a D_a + D_b} \quad (22)$$

$$G_{bc} = \frac{\Delta x}{\frac{1}{D_b}\frac{\Delta x}{2} + \frac{1}{P_c D_c}\frac{\Delta x}{2}} = 2D_b \quad (23)$$

by applying Eq. (10). The second term in the denominator of Eq. (23) equals zero unless $P_c=0$. If there is some non-diffusional resistance, its contribution must be taken into account by introducing X (or Y) term as shown in the following equations.

$$G_{ab} = \frac{\Delta x}{\frac{1}{P_a D_a}\frac{\Delta x}{2} + \frac{1}{D_b}\frac{\Delta x}{2} + X} = \frac{2P_a D_a D_b \Delta x}{(P_a D_a + D_b)\Delta x + 2P_a D_a D_b X} \quad (24)$$

$$G_{bc} = \frac{\Delta x}{\frac{1}{D_b}\frac{\Delta x}{2} + \frac{1}{P_c D_c}\frac{\Delta x}{2} + Y} = \frac{2D_b \Delta x}{\Delta x + 2D_b Y} \quad (25)$$

Note that the contribution is independent of the layer thickness Δx, and that a negative X means the promotion of drug migration.

Our experiments detailed in the succeeding paper have revealed the existence, *i.e.* a positive X, at the interface between the vehicle and the intact skin. The resistance disappeared when the skin is stripped of the honey layer.

To assist the understanding of simulation technique, a method for calculating the percentage of drug absorbed at one hour after the administration is exemplified here for a system in which $l_a=0.1$ cm, $l_b=0.01$ cm, $D_a=1\times10^{-6}$ cm^2/sec, $D_b=1\times10^{-7}$ cm^2/sec, $P_a=0.1$, $X=$

1×10^4 sec/cm, and $Y=0$ sec/cm. Taking n=100 and $\alpha=0.1$, one obtains m=10, $\Delta x=1\times10^{-3}$ cm, $\Delta t=0.1$ sec, $\beta=0.01$, $\gamma=0.005$, and $\delta=0.02$. Before beginning the first process, the drug content in the vehicle at $t=0$ is calculated by $Q_0=\sum_1^n q_i$. After completing 36000 processes, one calculates again the drug content $Q_{36000}=\sum_1^n q_i$ at t=3600 sec=1 hr. The requested percentage is given by $(Q_0-Q_{36000})/Q_0\times100$.