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Model Studies on Percutaneous Absorption and Transport in the Ointment. I. Theoretical Aspects[1]

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Mathematical models were defined that simulate the percutaneous absorption of drug and its transport in the ointment. Ointment and skin were, respectively, assumed as homogeneous phases through which drug diffuses according to Fick's law. Blood compartment and drug disposition were also taken into account.

When the ointment is applied to the surface of a living body, behavior of drug molecules follows a passive diffusional process, according to their activity gradients.

On this problem, Higuchi[3] divided the discussion into two parts. In the first situation, the rate-controlling step exists in the skin and in the other, the thermodynamic potential drop of the drug is largely in the applied phase. In more general case, however, neither phases are considered rate-limiting. Even if the skin, which itself is composed of dissimilar multilayers, is assumed as a physicochemically homogeneous single layer, we have to treat the diffusion in composite slabs with at least two phases, skin and ointment.

The purpose of the present paper is to define mathematical models that simulate the percutaneous absorption of drug molecules and their transport in the ointment, and to describe an algorithm with which numerical solutions of the models are obtained.

Theoretical

General Description of the Models

Fig. 1 shows a one-dimensional diffusion model. It is assumed that the ointment is a homogeneous phase through which drug molecules diffuse with effective diffusion constant D_o. Even though the ointment is emulsion type or heterogeneous system, transport of drug molecules is expressed with a single diffusion constant.[4] Concentration of the drug in ointment is expressed as C_o, and the thickness of ointment as L_o. At $x=-L_o$ (Fig. 1), there is no net transport of drug through the interface, *i.e.* it is insulated. The initial drug concentration in ointment is C_{in}, and the area of ointment application is A.

At $x=0$, skin-ointment interface, drug molecules distribute instantaneously with the partition coefficient P_o. Drug molecules are not accumulated at the interface. The skin is composed of morphologically dissimilar layers; epidermis, dermis, subcutaneous connective tissue *etc.*, which differ in drug permeability. Besides these, transepidermal and transfolicular routes of drug transport are quite different in permeability. In spite of these, in this study, it is assumed that the skin is a homogeneous layer of thickness L_s, in which drug diffusion is governed by a single diffusion constant D_s. At skin-blood interface ($x=L_s$), instantaneous drug distribution is reached with the partition coefficient P. Drug concentration in the

1) Partly presented at the 92nd Annual Meeting of Pharmaceutical Society of Japan, Osaka, April 1972.
2) Location: *3190 Gofuku, Toyama 930, Japan.*
3) T. Higuchi, *J. Soc. Cosm. Chem.*, **11**, 85 (1960).
4) W.I. Higuchi and T. Higuchi, *J. Am. Pharm. Assoc. Sci. Ed.*, **49**, 598 (1960); W.I. Higuchi, *J. Pharm. Sci.*, **51**, 802 (1962).

skin is expressed as C_s. Drug is eliminated from the blood compartment by first order rate process with rate constant k_{el}. Distribution volume of the blood compartment is V_d. At the moment when the ointment is applied, drug molecules exist only in the ointment, and blood and skin are free of drug.

When drug solution is applied on the skin instead of ointment, concentration gradient does not build up in the solution and drug concentration at any given time is expressed by a single value C. At skin-solution interface ($x=0$) and at skin-blood interface ($x=L_s$), drug molecules distribute instantaneously with the partition coefficient P.

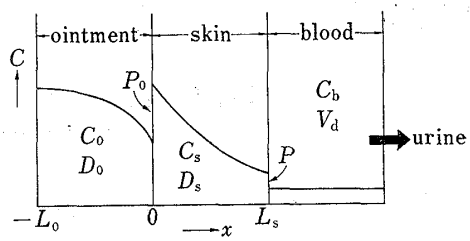

Fig. 1. General Model Consisting of an Ointment followed by Skin and a Blood Compartment

Mathematical interpretation of the models are as follows.

Model 1 (Case when drug solution is applied on the skin)

$$\frac{dC_s}{dt} = D_s\frac{d^2C_s}{dx^2} \quad (0\leq x\leq L_s) \qquad \text{Eq. 1}$$

$$C_s = P\cdot C \quad (x=0) \qquad \text{Eq. 2}$$

$$V\cdot\frac{dC}{dt} = A\cdot D_s\cdot\left(\frac{dC_s}{dx}\right)_{x=0} \qquad \text{Eq. 3}$$

$$C_s = P\cdot C_b \quad (x=L_s) \qquad \text{Eq. 4}$$

$$V_d\cdot\frac{dC_b}{dt} = -A\cdot D_s\cdot\left(\frac{dC_s}{dx}\right)_{x=L_s} - k_{el}\cdot C_b\cdot V_d \qquad \text{Eq. 5}$$

$$C = C_{in},\quad C_s = 0\ (0\leq x\leq L_s),\quad C_b = 0 \text{ at } t = 0 \qquad \text{Eq. 6}$$

Where V is the volume of the drug solution and C_b is blood concentration of the drug.

In the study of this and the succeeding report, experimental determination of P value was unsuccessful and introduction of the following variables was considered.

$$C_s^\circ = C_s/P,\quad D_s^\circ = P^2\cdot D_s,\quad x^\circ = P\cdot x \qquad \text{Eq. 7}$$

In terms of the variables of Eq. 7, Eq. 1 through Eq. 6 become

$$\frac{dC_s^\circ}{dt} = D_s^\circ\cdot\frac{d^2C_s^\circ}{dx^{\circ 2}} \quad (0\leq x^\circ\leq PL_s) \qquad \text{Eq. 8}$$

$$C_s^\circ = C \quad (x^\circ=0) \qquad \text{Eq. 9}$$

$$V\cdot\frac{dC}{dt} = A\cdot D_s^\circ\cdot\left(\frac{dC_s^\circ}{dx^\circ}\right)_{x^\circ=0} \qquad \text{Eq. 10}$$

$$C_s^\circ = C_b \quad (x^\circ=PL_s) \qquad \text{Eq. 11}$$

$$V_d\cdot\frac{dC_b}{dt} = -A\cdot D_s^\circ\cdot\left(\frac{dC_s^\circ}{dx^\circ}\right)_{x^\circ=PL_s} - k_{el}\cdot C_b\cdot V_d \qquad \text{Eq. 12}$$

$$C = C_{in},\quad C_s^\circ = 0\ (0\leq x^\circ\leq PL_s),\quad C_b = 0 \text{ at } t = 0 \qquad \text{Eq. 13}$$

Model 2 (Case when the ointment is applied on the skin)

$$\frac{dC_0}{dt} = D_0\cdot\frac{d^2C_0}{dx^2} \quad (-L_0\leq x\leq 0) \qquad \text{Eq. 14}$$

$$\frac{dC_s^\circ}{dt} = D_s^\circ\cdot\frac{d^2C_s^\circ}{dx^{\circ 2}} \quad (0\leq x^\circ\leq PL_s) \qquad \text{Eq. 15}$$

$$\left(\frac{dC_0}{dx}\right)_{x=L_0} = 0 \qquad \text{Eq. 16}$$

$$C_s^\circ = P^\circ\cdot C_0 \quad (x=0) \qquad \text{Eq. 17}$$

$$D_0\cdot\left(\frac{dC_0}{dx}\right)_{x=0} = D_s^\circ\cdot\left(\frac{dC_s^\circ}{dx^\circ}\right)_{x^\circ=0} \qquad \text{Eq. 18}$$

$$C_s^\circ = C_b \qquad (x^\circ = PL_s) \qquad \text{Eq. 19}$$

$$V_d \cdot \frac{dC_b}{dt} = -A \cdot D_s^\circ \cdot \left(\frac{dC_s^\circ}{dx^\circ}\right)_{x^\circ = PL_s} - k_{el} \cdot C_b \cdot V_d \qquad \text{Eq. 20}$$

$$C_0 = C_{in} \ (-L_0 \leqq x \leqq 0), \quad C_s^\circ = 0 \ (0 \leqq x^\circ \leqq PL_s), \quad C_b = 0 \text{ at } t = 0 \qquad \text{Eq. 21}$$

Where $P^\circ = P_o/P$.

Numerical Computation

To obtain the values of C_o, C°_s and C_b which satisfy each of the equations above, numerical calculation was examined by means of difference equations of Carslaw and Jaegar.[5]

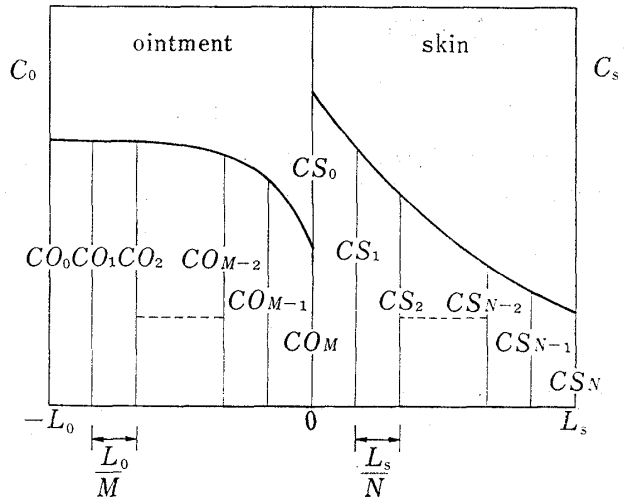

Fig. 2. Division into A Number of Equal Intervals for Finite-difference Approximation

a) Difference Equations——The thickness of ointment and skin L_o and L_s are divided into M and N parts, respectively (Fig. 2), and defined the concentrations at each position as CO_i $(i=O..M)$, CS_j $(j=O..N)$ at $t=T$ and CON_i and CSN_j at $t=T+DT$. Then Eq. 22 and Eq. 23 are obtained from Eq. 14 and Eq. 15.

$$CON_i = U \cdot (CO_{i+1} + CO_{i-1}) - (2 \cdot U - 1) \cdot CO_i$$
$$(i = 1 \cdots M-1) \qquad U = D_0 \cdot DT/(DX_0)^2$$
$$DX_0 = L_0/M \qquad \text{Eq. 22}$$

$$CSN_j = W \cdot (CS_{j+1} + CS_{j-1}) - (2 \cdot W - 1) \cdot CS_j$$
$$(j = 1 \cdots N-1) \qquad W = D_s \cdot DT/(DX_s)^2$$
$$DX_s = (PL_s)/N \qquad \text{Eq. 23}$$

It is known that the numerical solution is apt to diverge, if U and W are greater than 0.5,[5] therefore the value of DT should be chosen so as to satisfy Eq. 24.

$$DT < 0.5 \cdot (DX_0)^2/D_0 \text{ and } DT < 0.5 \cdot (DX_s)^2/D_s \qquad \text{Eq. 24}$$

Too small a value for DT increases the number of repetition and consequently the time of computation.

Eq. 17 and Eq. 18 give Eq. 25 and Eq. 26, respectively.

$$CSN_0 = P^\circ \cdot CON_M \qquad \text{Eq. 25}$$

$$D_0 \cdot \frac{CON_{M-1} - CON_M}{DX_0} = D_s^\circ \cdot \frac{CSN_0 - CSN_1}{DX_s} \qquad \text{Eq. 26}$$

Solving these equations for CON_M, Eq. 27 is obtained.

$$CON_M = \frac{DX_s \cdot D_0 \cdot CON_{M-1} + DX_0 \cdot D_s \cdot CSN_1}{P^\circ \cdot DX_0 \cdot D_s + DX_s \cdot D_0} \qquad \text{Eq. 27}$$

And CSN_o is calculated by Eq. 25.

Since $dC_o/dx_{x=o}$ is infinity at $t=0$, calculation by Eq. 18 is in danger of leading to noticeable error for small t values. Therefore, explicit equations for infinite system,[6] Eq. 28 and Eq. 29 are recommended for small t, for a few DT period.

$$C_0 = C_{in}\left[1 - \frac{P^\circ\sqrt{D_s^\circ}}{P^\circ\sqrt{D_s^\circ} + \sqrt{D_0}} \operatorname{erfc}\left(-\frac{x^\circ}{2\sqrt{D_0 t}}\right)\right] \qquad \text{Eq. 28}$$

5) H.S. Carslaw and J.C. Jaegar, "Conduction of Heat in Solids," Oxford University Press, London, 1959, pp. 466—478.
6) R.M. Barrer, "Diffusion in and through Solids," Cambridge University Press, Cambridge, 1951, pp. 10—12.

$$C_s = C_{in}\left[\frac{P^\circ\sqrt{D_0}}{P^\circ\sqrt{D_s^\circ}+\sqrt{D_0}}\ \mathrm{erfc}\left(\frac{x^\circ}{2\sqrt{D_s^\circ t}}\right)\right] \qquad \text{Eq. 29}$$

Where $\mathrm{erfc}(Z)=1-\sqrt{\frac{2}{\pi}}\int_0^z e^{-x^2}dx$.

CON_0 is calculated by Eq. 30, obtained from Eq. 16.

$$CON_0 = CON_1 \qquad \text{Eq. 30}$$

Eq. 19 and Eq. 20 are re-written as Eq. 31 and Eq. 32, respectively.

$$CSN_N = CBN \qquad \text{Eq. 31}$$

$$\frac{CBN-CB}{DT} = \frac{A\cdot D_s^\circ}{V_d}\cdot\frac{(CS_{N-1}+CSN_{N-1})\cdot 0.5-(CS_N+CSN_N)\cdot 0.5}{DX_s} - k_{el}\cdot(CB+CBN)\cdot 0.5 \qquad \text{Eq. 32}$$

Where $(C+CN)\cdot 0.5$ represents the average concentration during the time interval between T and $T+DT$. Solving these equations simultaneously for CBN, Eq. 33 is obtained.

$$CBN = \frac{B1\cdot(CSN_{N-1}+CS_{N-1}-CS_N)-(B2-V_d)\cdot CB}{V_d+B1+B2} \qquad \text{Eq. 33}$$

Where $B1=0.5\cdot A\cdot D_s^\circ\cdot DT/DX_s$ and $B2=0.5\cdot V_d\cdot k_{el}\cdot DT$.
CSN_N is calculated by Eq. 31.

For Model 1, CN and CSN_0 are calculated by Eq. 34 and Eq. 35 derived from Eq. 9 and Eq. 10.

$$CN = \frac{C\cdot V-B1\cdot(CS_0-CS_1-CSN_1)}{V+B1} \qquad \text{Eq. 34}$$

$$CSN_0 = CN \qquad \text{Eq. 35}$$

Where $B1$ is same as above.

For small T value (a few DT period), explicit equation for semi-infinite system,[7] Eq. 36 is recommended for the computation of CSN_j.

$$C_s^\circ = C_{in}\,\mathrm{erfc}\left(\frac{x^\circ}{2\sqrt{D_s^\circ t}}\right) \qquad \text{Eq. 36}$$

b) Algorithm for Numerical Computation——The following algorithm is used for numerical computation.

1) Define C_{in}, M, N, *etc.*
2) Set initial conditions, $C_b=0$ *etc.*
3) Evaluate DT so as to satisfy Eq. 24.
4) Compute CO_i and CS_j for small T by Eq. 28 and Eq. 29.
5) Compute CON_i ($i=1..M\text{-}1$) and CSN_j ($j=1..N\text{-}1$).
6) Compute CON_o.
7) Compute CBN and CSN_N.
8) Compute CON_M and CSN_o.
9) Replace CO_i and CS_j by the newly computed values of CON_i and CSN_j, and T is increased by DT. If T is the time for print out, control is transferred to step 10. If T is the time for end of computation, control is transferred to step 11, otherwise go to step 5.
10) Print out the values of CON_i, CSN_i, CBN *etc.* and go to step 5.
11) Stop computation.

7) J. Crank, "The Mathematics of Diffusion," Oxford University Press, London, 1957, p. 30.

TABLE I. Comparison of $C_s°/C_{in}$ Values calculated with the Explicit Equation (Eq. 37) and Those Simulated by Model 1
Input parameters were $PL_s=1.0$ cm, $D_s°=1.0$ cm²/sec, $A=1.0$ cm² and $N=10$.

t (sec)	$x°$ (cm) 0.2 explct.	0.2 simltd.	0.4 explct.	0.4 simltd.	0.6 explct.	0.6 simltd.	0.8 explct.	0.8 simltd.
0.020	0.31731	0.31524	0.04550	0.04605	0.00270	0.00299	0.00006	0.00008
0.040	0.47950	0.47815	0.15730	0.15685	0.03389	0.03423	0.00466	0.00488
0.060	0.56370	0.56283	0.24821	0.24757	0.08321	0.08322	0.02039	0.02059
0.080	0.61707	0.61645	0.31725	0.31663	0.13315	0.13295	0.04280	0.04285
0.100	0.65466	0.65420	0.37075	0.37019	0.17797	0.17765	0.06635	0.06626
0.120	0.68286	0.68248	0.41313	0.41262	0.21640	0.21603	0.08816	0.08800
0.140	0 70482	0.70450	0.44720	0.44674	0.24869	0.24830	0.10723	0.10702
0.160	0.72231	0.72204	0.47484	0.47443	0.27552	0.27514	0.12341	0.12319
0.180	0.73643	0.73619	0.49739	0.49701	0.29769	0.29734	0.13693	0.13671
0.200	0.74791	0.74769	0.51583	0.51548	0.31596	0.31563	0.14813	0.14793

Results and Discussion

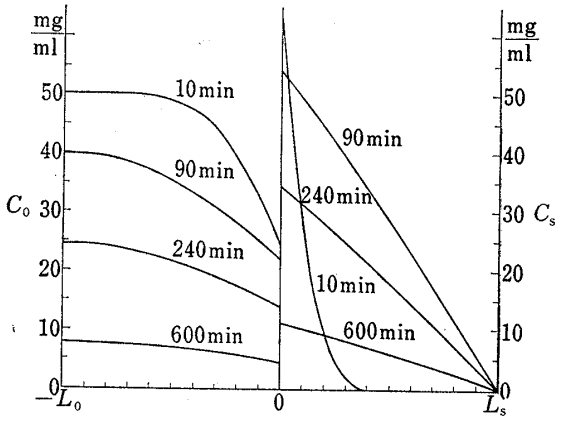

Fig. 3. Time-dependant Concentration Distribution Curves computed by Model 2

$C_{in}=50$ mg/ml, $A=20$ cm², $P°=2.5$, $L_0=0.2$ cm, $D_0=2.012\ 10^{-6}$ cm²/sec $L°_s=0.05117$ cm, $D°_s=3.459\ 10^{-7}$ cm²/sec, $k_{el}=0.04$ hr^{-1}, $N=M=10$

For Model 1, if V and V_d are sufficiently large, CS_0 and CS_n are fixed to C_{in} and O, respectively. Under such a special case, explicit solution is obtained as Eq. 37.[8]

$$C_s° = C_{in}\left[1-\frac{x°}{PL_s}-\frac{2}{\pi}\sum_{n=1}^{\infty}\frac{1}{n}\sin\left(\frac{nx°}{PL_s}\right)\exp\left(-\frac{D_s°n^2\pi^2t}{P^2L_s^2}\right)\right] \qquad \text{Eq. 37}$$

Comparison of the values calculated by the algorithm reported in this paper and that obtained by Eq. 37 are shown in Table I. Although N is as small as 10, coincidence of CS values are excellent. This results verify the algorithm of this report.

An example computation for Model 2 is shown in Fig. 3.

The algorithm described in this paper is used in the analysis of data in the study on percutaneous absorption of NaI which appear in the succeeding report.

8) J. Crank, "The Mathematics of Diffusion," Oxford University Press, London, 1957, p. 47.