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

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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 transfollicular 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 \(x=L_b\), instantaneous drug distribution is reached with the partition coefficient \(P\). Drug concentration in the

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2) Location: 3190 Gofuku, Toyama 930, Japan.
skin is expressed as $C_s$. Drug is eliminated from the blood compartment by first order rate process with rate constant $k_{ol}$. Distribution volume of the blood compartment is $V_b$. 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 $P$.

Mathematical interpretation of the models are as follows.

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

\[
\frac{dC_s}{dt} = D_s \frac{d^2C_s}{dx^2} \quad (0 \leq x \leq L_s)
\]

Eq. 1

\[C_s = P \cdot C \quad (x=0)\]

Eq. 2

\[V_s \frac{dC}{dt} = A \cdot D_s \left( \frac{dC_s}{dx} \right)_{x=0}\]

Eq. 3

\[C_s = P \cdot C_b \quad (x=L_s)\]

Eq. 4

\[V_d \frac{dC_b}{dt} = -A \cdot D_s \left( \frac{dC_s}{dx} \right)_{x=L_s} - k_{ol} \cdot C_b \cdot V_d\]

Eq. 5

\[C = C_{in}, \quad C_s = 0 \quad (0 \leq x \leq L_s), \quad C_b = 0 \quad at \quad t = 0\]

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.

\[C_s^o = C_s / P, \quad D_s^o = P^o \cdot D_s, \quad x^o = P \cdot x\]

Eq. 7

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

\[\frac{dC_s^o}{dt} = D_s^o \frac{d^2C_s^o}{dx^2} \quad (0 \leq x^o \leq PL_s)\]

Eq. 8

\[C_s^o = C \quad (x^o=0)\]

Eq. 9

\[V_s \frac{dC}{dt} = A \cdot D_s^o \left( \frac{dC_s^o}{dx^o} \right)_{x^o=0}\]

Eq. 10

\[C_s^o = C_b \quad (x^o=PL_s)\]

Eq. 11

\[V_s \frac{dC_b}{dt} = -A \cdot D_s^o \left( \frac{dC_s^o}{dx^o} \right)_{x^o=PL_s} - k_{ol} \cdot C_b \cdot V_d\]

Eq. 12

\[C = C_{in}, \quad C_s^o = 0 \quad (0 \leq x^o \leq PL_s), \quad C_b = 0 \quad at \quad t = 0\]

Eq. 13

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

\[\frac{dC_s}{dt} = D_s \frac{d^2C_s}{dx^2} \quad (-L_s \leq x \leq 0)\]

Eq. 14

\[\frac{dC_s^o}{dt} = D_s^o \frac{d^2C_s^o}{dx^o^2} \quad (0 \leq x^o \leq PL_s)\]

Eq. 15

\[\left( \frac{dC_s}{dx} \right)_{x=L_s} = 0\]

Eq. 16

\[C_s^o = P^o \cdot C_s \quad (x=0)\]

Eq. 17

\[D_s \frac{dC_s^o}{dx^o} \bigg|_{x=0} = D_s^o \frac{d^2C_s^o}{dx^o^2} \bigg|_{x^o=0}\]

Eq. 18
\[ C_0^o = C_b \quad (x^o = PL_o) \quad \text{Eq. 19} \]
\[ V_t \cdot \frac{dC_b}{dt} = -A \cdot D_x \left( \frac{dC_b}{dx} \right) x = PL_o \quad \text{Eq. 20} \]
\[ C_0^o = C_{in} \quad \left( -L_o \leq x \leq 0 \right) \quad C_0^o = 0 \quad \left( 0 \leq x \leq PL_o \right) \quad C_b = 0 \quad \text{at} \quad t = 0 \quad \text{Eq. 21} \]

Where \( P^o = P_0 / P \).

**Numerical Computation**

To obtain the values of \( C_o, C^o_3 \) and \( C_b \) which satisfy each of the equations above, numerical calculation was examined by means of difference equations of Carslaw and Jaeger.\(^5\)

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 \( CO_i \) \((i = \ldots M)\), \( CS_j \) \((j = \ldots N)\) 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.

\[
CON_i = U \cdot (CO_{i-1} + CO_{i+1}) - (2 \cdot U - 1) \cdot CO_i \quad (i = 1 \ldots M - 1) \quad U = D_0 \cdot DT / (DX_s)^3 \quad \text{Eq. 22}
\]
\[
DX_x = L_o / M \quad \text{Eq. 22}
\]
\[
CSN_j = W \cdot (CS_{j+1} + CS_{j-1}) - (2 \cdot W - 1) \cdot CS_j \quad (j = 1 \ldots N - 1) \quad W = D_s \cdot DT / (DX_s)^3 \quad \text{Eq. 23}
\]
\[
DX_s = (PL_o) / N \quad \text{Eq. 23}
\]

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.

\[
DT < 0.5 \cdot (DX_s)^3 / D_0 \quad \text{and} \quad DT < 0.5 \cdot (DX_s)^3 / D_s
\]

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.

\[
CSN_o = P^o \cdot CON_M
\]
\[
D_0 \cdot \frac{CON_{M-1} - CON_M}{DX_o} = D_0^2 \cdot CSN_o - CSN_1
\]

Solving these equations for \( CON_M \), Eq. 27 is obtained.

\[
CON_M = \frac{DX_x \cdot D_0 \cdot CON_{M-1} + DX_o \cdot D_0 \cdot CSN_1}{P^o \cdot DX_0 \cdot D_1 + DX_s \cdot D_0}
\]

And \( CSN_o \) is calculated by Eq. 25.

Since \( dC_0 / dx \) 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.

\[
C_0 = C_{in} \left[ 1 - \frac{P^o \cdot \sqrt{D^2}}{P^o \cdot D_0^2 + \sqrt{D_0}} \right] \cdot \text{erfc} \left( -\frac{x^o}{2 \sqrt{k \cdot DT}} \right)
\]

\[
\text{Eq. 28}
\]

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\[ C_s = C_{in} \left[ \frac{P_o\sqrt{D_b}}{P_o\sqrt{D_s^2} + \sqrt{D_b}} \text{erfc} \left( \frac{x^0}{2\sqrt{D_s^2}t} \right) \right] \]

Eq. 29

Where \( \text{erfc}(Z) = 1 - \frac{2}{\sqrt{\pi}} \int_{0}^{Z} e^{-x^2} dx \).

\( CON_s \) is calculated by Eq. 30, obtained from Eq. 16.

\[ CON_s = CON_1 \quad \text{Eq. 30} \]

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

\[ CSN_N = CBN \quad \text{Eq. 31} \]

\[ \frac{CBN-CB}{DT} = \frac{A \cdot D_o^0 \cdot (CS_{N-1}+CSN_{N-1}) \cdot 0.5 - (CS_N+CSN_N) \cdot 0.5}{V_s}DX_s \]

\[ -k_{at} \cdot (CB+CBN) \cdot 0.5 \quad \text{Eq. 32} \]

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.

\[ CBN = \frac{B1 \cdot (CS_{N-1}+CSN_{N-1} - CS_N) - (B2-V_s) \cdot CB}{V_s+B1+B2} \quad \text{Eq. 33} \]

Where \( B1 = 0.5 \cdot A \cdot D_o^0 \cdot DT/DX_s \) and \( B2 = 0.5 \cdot V_s \cdot k_{at} \cdot DT \).

\( CSN_N \) is calculated by Eq. 31.

For Model 1, \( CN \) and \( CSN_o \) are calculated by Eq. 34 and Eq. 35 derived from Eq. 9 and Eq. 10.

\[ CN = \frac{C \cdot V - B1 \cdot (CS_0 - CSN_0)}{V + B1} \quad \text{Eq. 34} \]

\[ CSN_0 = CN \quad \text{Eq. 35} \]

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 \( CSN_j \).

\[ C_i^o = C_{in} \text{erfc} \left( \frac{x^0}{2\sqrt{D_s^2}t} \right) \quad \text{Eq. 36} \]

\(^b\) 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 \( CON_i \) (\( i = 1 \ldots M-1 \)) and \( CSN_j \) (\( j = 1 \ldots N-1 \)).
6) Compute \( CON_o \).
7) Compute \( CBN \) and \( CSN_N \).
8) Compute \( CON_N \) and \( CSN_N \).
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 \( CON_o, CSN_o, CBN etc. \) and go to step 5.
11) Stop computation.

TABLE I. Comparison of $C_s^o/C_{in}$ Values calculated with the Explicit Equation (Eq. 37) and Those Simulated by Model 1

Input parameters were $PL_a=1.0$ cm, $D_a^o=1.0$ cm$^2$/sec, $A=1.0$ cm$^2$ and $N=10$.

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<th>0.2</th>
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<th>0.6</th>
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</tr>
</tbody>
</table>

Results and Discussion

For Model 1, if $V$ and $V_d$ are sufficiently large, $CS_h$ and $CS_n$ are fixed to $C_{in}$ and $O$, respectively. Under such a special case, explicit solution is obtained as Eq. 37.8)

$$C_s^o = C_{in} \left[ 1 - \frac{x^o}{PL_a^o} \right] \left[ 1 - \frac{L}{\sqrt{D_a^o}} \right] \exp \left( -\frac{D_a^o L}{P L_a^{0.5}} \right)$$

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.

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