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Finite dose transport of drugs in liquid formulations through stratum corneum: analytical solution to a diffusion model *

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Summary

Finite dose penetration of acetaminophen, through snake stratum corneum has been studied using modified Franz cells. The drug was formulated in a volatile : non-volatile vehicle system. Non-steady-state transport of the drug into the receptor compartment is observed. A diffusion model for the above situation is proposed. An analytical solution for this model has been obtained. This solution is used to obtain computer-simulated transport profiles. The experimental data is then fitted with the simulated profile to obtain a value for the apparent diffusion coefficient of the drug. Using steady-state experiments, an independent value of the diffusion coefficient is also obtained. The two values of the diffusion coefficient differ by a factor of 4.17.

Introduction

The main barrier to transport of drugs across the skin is thought to be the stratum corneum. Since this is dead tissue, transport of substances through it involves a process of passive diffusion down a concentration gradient. If the tissue is assumed to be homogeneous, then diffusion through it can be mathematically described by Fick's 1st and 2nd Laws as given below.

Fick's 1st Law:

$$J = -D\left[\frac{\delta C}{\delta x}\right]$$

Fick's 2nd Law:

$$\frac{\delta C}{\delta t} = D\left[\frac{\delta^2 C}{\delta x^2}\right]$$

where J = flux; D = diffusion coefficient of the drug in the stratum corneum; C = concentration of the drug in the stratum corneum, x = position within the stratum corneum, $0 \leq x \leq h$; h = thickness of the stratum corneum; t = time.

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Different situations to which the above relationships apply in describing the transport of drugs across the keratinized membrane have already been considered in some depth by many authors (Barrer, 1951; Crank, 1975; Jost, 1955). Carslaw and Jaeger (1948) have discussed these relationships for transport of heat. Mathematical solutions applicable to many situations have been discussed by Crank (1975). Gienger et al. (1986) modelled the transport of drug from a transdermal patch across the skin. They used a commercial software package (DISPL) to obtain a numerical solution to this model. In their model, they have assumed a reservoir of drug (patch) placed on the skin surface and a linear concentration gradient of the drug is assumed inside the skin layer. Scheuplein and Ross (1974) studied the flux of cortisone across human epidermis, in an in vitro situation, when the drug dissolved in acetone was placed on the membrane. Southwell and Barry (1984) have carried out similar studies with caffeine and aspirin using human stratum corneum.

We have studied the penetration of progesterone dissolved in acetone as well as acetaminophen dissolved in acetone, but no transport across the snake skin was observed when the samples were assayed for the drug using HPLC techniques. To increase skin penetration, Coldman et al. (1969) suggested the use of volatile : non-volatile system of vehicle for the drug. Shed snake skin was used as a model membrane because it is stratum corneum (Banerjee and Mittal, 1980). Also, the shed snake skin does not possess appendages like hair follicles or sweat glands so the route of penetration is directly through the stratum corneum. Both shed snake skin (Banerjee and Mittal, 1980) and human stratum corneum (Scheuplein and Blank, 1971) are composed of keratinized proteins and lipids. Water permeation characteristics of snake skin are very similar to those of human skin (Scheuplein and Ross, 1970; Roberts and Lillywhite, 1980). Acetaminophen was used as a marker substance.

The objectives of our work are: (a) to propose a diffusion model for the transport of drug through stratum corneum when the drug is formulated in a volatile : non-volatile solvent system; (b) to obtain an analytical solution to this model; (c) to use the solution to generate computer-simulated transport profiles; (d) to fit the non-steady-state transport data with simulated profiles and obtain a value for the diffusion coefficient of the drug; and (e) to get an independent measure of the diffusion coefficient and compare it to the value obtained in (d).

Materials and Methods

Chemicals and reagents

Acetaminophen and lauryl alcohol were obtained from Sigma Chemicals. HPLC grade methanol, propylene glycol and ACS grade buffer components were obtained from Fisher Scientific. Distilled deionized water was used throughout.

Apparatus

High-performance liquid chromatography (HPLC) was performed with a Perkin Elmer system consisting of a Series 410 LC pump, ISS-100 autoinjector, LC 90 UV variable wavelength spectrophotometric detector and a LCI-100 Laboratory Computing Integrator. A guard column (4.6 $\times$ 30 mm) along with an analytical column (4.6 $\times$ 100 mm) by Brownlee Labs. were used. Both were packed with RP-18 Spheri-5 particles.

Drug assay

Acetaminophen in the samples was analyzed by a reversed-phase HPLC procedure. A mobile phase system of 20% v/v methanol in water was used to obtain a retention time of approx. 3 min. The column effluent was monitored at 248 nm. Acetaminophen was quantitated by measuring the peak areas in relation to those of standards chromatographed under the same conditions.

Test formulation

Acetaminophen (1%), propylene glycol (5%), lauryl alcohol (5%) were taken by weight and dissolved in methanol and the final volume made up with methanol.

Transport simulations

BASIC language programs incorporating Eqn. 6 were written. These programs were run on a personal computer to obtain the data that were used to generate the simulated profiles.

Transport studies

Modified Franz cells (diffusional surface area 2.01 cm^2) were used for these studies. Snake (*Elaphe obsoleta obsoleta*) skin molts were used as a model membrane. The receptor compartment (volume approx. 8.5 ml) was filled with pH 7.2 isotonic phosphate buffer (USP XIX). The snake skin was hydrated by placing it in water at 30 °C for 30 min. It was then patted dry and placed between the donor and receptor cells and the assembly clamped together, 25 μl of the *test formulation* was placed on the skin surface. The cell assembly was then placed in a water bath maintained at 30 °C. The fluid in the receptor compartment was stirred magnetically. The receptor fluid was sampled at different times and acetaminophen present in the samples was analyzed by the HPLC technique. The experiment was run in duplicate.

Steady-state experiments

An independent measure of the diffusion coefficient was obtained by doing the transport experiment (in duplicate) at 30 °C using Side-bi-Side diffusion cells (Crown Glass) with the *test formulation* in the donor compartment and pH 7.2 isotonic phosphate buffer (USP XIX) on the receptor side. The diffusional surface area of this cell is 0.785 cm^2 and the volume of each compartment is 3.4 ml. The receptor fluid was sampled regularly and acetaminophen in the samples was analyzed by HPLC assay. The steady-state portion of the plot when extrapolated back gives an intercept on the abscissa. Knowing the value of h (measured by Scanning Electron Microscope), the value of D is calculated by the following equation (Barry 1983):

$$x\text{-intercept} = \frac{h^2}{6D}$$

Theoretical

In our experimental study, acetaminophen is dissolved in methanol along with propylene glycol and lauryl alcohol. When this formulation is applied onto the surface of the stratum corneum, the methanol will evaporate off. During the time methanol takes to evaporate, the drug has a chance to partition into the stratum corneum. Also, once all the methanol is gone, we have a thin layer of propylene glycol and lauryl alcohol (with some drug in solution) on the surface. The drug remaining in solution again has a chance to partition into the stratum corneum. The model we propose is shown in Fig. 1. It is assumed that all of the drug is initially present at the outer boundary of the stratum corneum as a very thin layer. The partitioning of the drug into the membrane is assumed to be a much faster process than the diffusional transport through the membrane. The drug is assumed to be non-volatile and there is no back-flux. Diffusion of the drug occurs through the skin into the receptor compartment. Sink conditions are assumed for the receptor compartment. The diffusion coefficient of the drug in the stratum corneum is assumed to be constant. The non-steady-state transport of the drug within the stratum corneum can be described by Fick's 2nd Law with the following boundary and initial conditions:

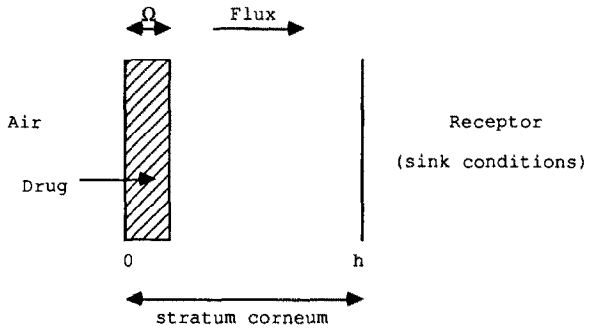

Fig. 1. Schematic diagram of the proposed model.

$$\frac{\delta C}{\delta t} = D\left[\frac{\delta^2 C}{\delta x^2}\right], \qquad 0 < x < h, 0 < t < \infty \tag{1}$$

$$\frac{\delta C}{\delta x}(0, t) = 0, \qquad 0 < t < \infty \tag{2}$$

$$C(h, t) = 0, \qquad 0 < t < \infty \tag{3}$$

$$C(x, 0) = f_\Omega(x), \qquad 0 < x < h \tag{4}$$

where:

$$f_\Omega(x) = \frac{A}{\Omega}, \qquad 0 < x < \Omega$$

$$= 0, \qquad \Omega < x < h$$

Here, "Ω" is a small positive number. A is the total amount of drug per unit area in the stratum corneum at time $t = 0$.

Let $C_\Omega(x, t)$ denote the solution to the above second-order differential equation. Solving Eqn. 1 by the method of separation of variables (Weinberger, 1965), we get:

$$C_\Omega(x, t)$$

$$= \sum_{k=1}^{\infty} \frac{2A}{h} \mathrm{Sinc}\left(\Omega\sqrt{\mu_k}\right) \mathrm{Cos}\left(x\sqrt{\mu_k}\right) e^{(-D t \mu_k)} \quad (5)$$

where

$$\mu_k = (2k-1)^2\left[\frac{\Pi}{2h}\right]^2 \qquad \text{and } \mathrm{Sinc}(z) = \frac{\mathrm{Sin}(z)}{z},$$

$$\Pi = 3.142\ldots$$

One can show that for $t > 0$, the series given by Eqn. 5 converges and defines a function $C_\Omega(x, t)$ on $0 \le x \le h$. The function $C_\Omega(x, t)$ has infinitely many continuous partial derivatives for $t > 0$, and satisfies equations 2, 3 and 4. Also, for any point $(x_0, 0)$, $x_0 \neq \Omega$,

$$C_\Omega(x, t) \Rightarrow f_\Omega(x_0) \quad \text{as} \quad (x, t) \Rightarrow (x_0, 0)$$

Next, we observe that

$$\mathrm{Sinc}\left(\Omega\sqrt{\mu_k}\right) \Rightarrow 1$$

as

$\Omega \Rightarrow 0$ via L'Hospital's Rule

This leads us to Eqn. 6.

$$C(x, t) = \sum_{k=1}^{\infty} \frac{2A}{h} \mathrm{Cos}\left(x\sqrt{\mu_k}\right) e^{(-D t \mu_k)} \quad (6)$$

The series in Eqn. 6 converges for $t > 0$, $0 \le x \le h$. We can think of the function $C(x, t)$ as defining the time history of the concentration for $t > 0$, when the initial concentration (for $t = 0$) is entirely based at the point $x = 0$. The series in Eqn. 6 can be evaluated easily when $t > 0$.

Results and Discussion

On evaluating Eqn. 6 at different values of x for a given value of time, we obtain a concentration profile of the drug within the stratum corneum. These profiles are shown in Figs. 2 and 3 for different values of time. It is seen that the concentration at the outer boundary of the stratum corneum decreases as we proceed towards larger values of time. The area under the curve for each profile is the amount of drug present within the stratum corneum at a particular time. Knowing the quantity A of the drug initially present at the outer boundary of the stratum corneum, we calculate the amount of drug that has come into the receptor phase at any time. Plots of percent of the drug into the receptor phase as a function of time are shown in Figs. 4 and 5. Fig. 4 shows the effect of varying the diffusion coefficient D of the drug on its transport through the stratum corneum

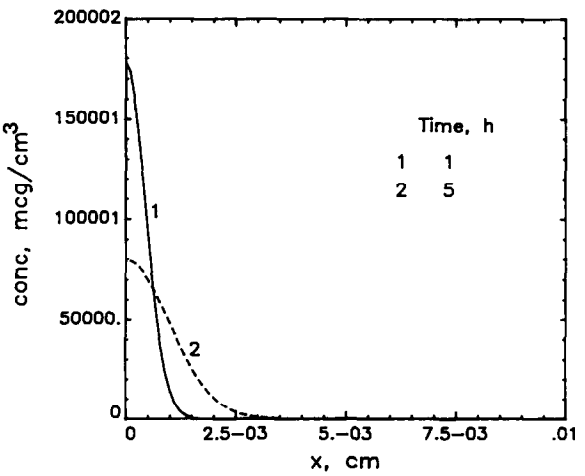

Fig. 2. Concentration of the drug as a function of distance within the stratum corneum at early times. $A = 100$ μg; $h = 0.01$ cm; $D = 1\text{E-}07$ cm^2/h.

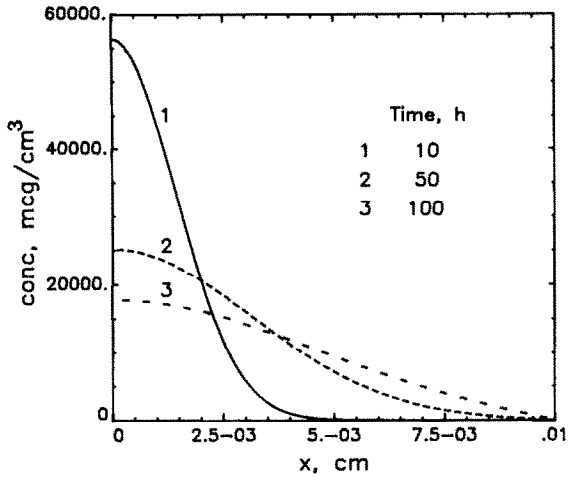

Fig. 3. Concentration of the drug as a function of distance within the stratum corneum at later times. $A = 100\ \mu g$; $h = 0.01$ cm; $D = 1E\text{-}07\ cm^2/h$.

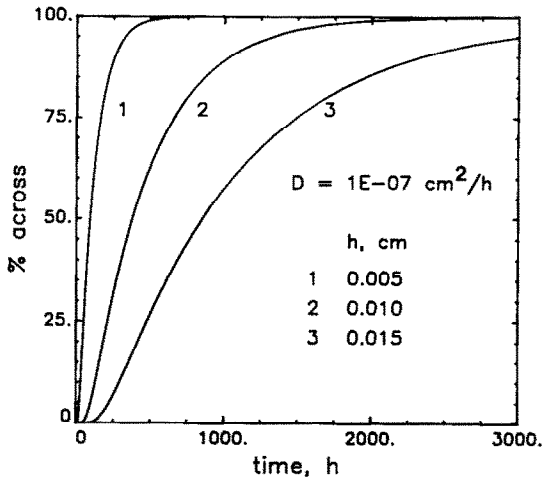

Fig. 5. Effect of changing the thickness of the stratum corneum on drug transport.

and Fig. 5 shows the effect of varying the thickness of the stratum corneum on drug transport.

Instead of getting many different curves for different values of D and h, we can get a single normalized plot (Fig. 6) by plotting the result in the form of percent of drug into the receptor phase as a function of T, where T is a unitless variable made up of D, h and t.

$$T = \frac{D \cdot t}{h^2}$$

The HPLC assay of acetaminophen was sensitive and accurate. The correlation coefficient for the standard curve was greater than 0.999. Linearity was observed in the range of 20–1000 ng of acetaminophen injected on the column. The transport experiments were carried out in duplicate as mentioned previously. The coefficient of variation ranged from 11% to 25% The results of the *Transport studies* are shown in Fig. 7 as circles. It is seen that the total amount (per cm^2 of skin) of acetaminophen transported into the receptor cell

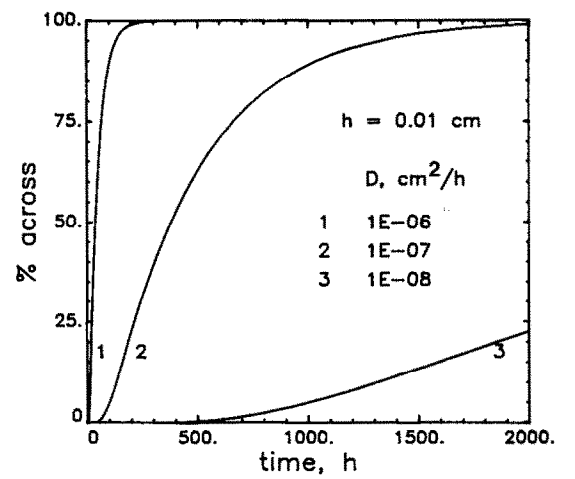

Fig. 4. Effect of changing the diffusion coefficient of the drug on its transport.

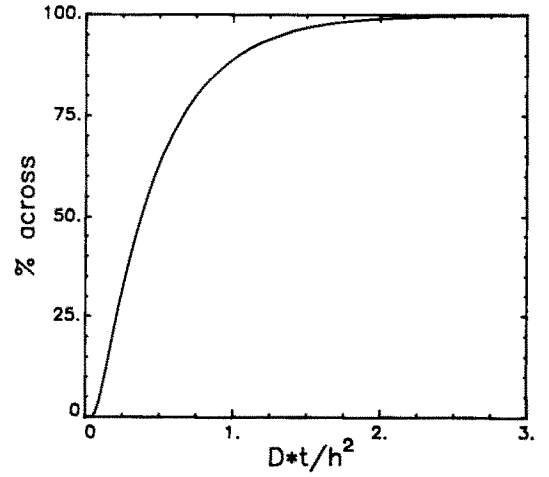

Fig. 6. A normalized plot of drug transport into the receptor phase.

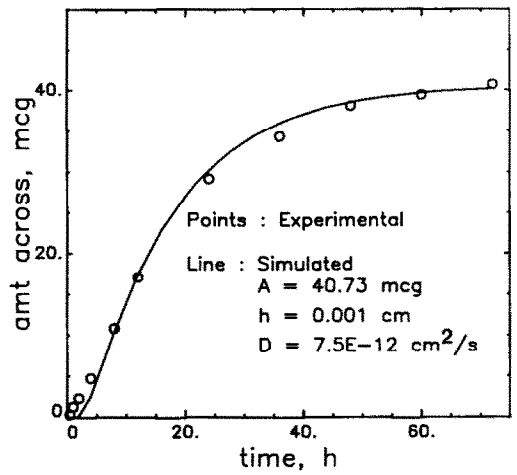

Fig. 7. Transport studies: amount of acetaminophen, per cm^2 of skin, into the receptor cell as a function of time.

reaches a plateau at 72 h. Considering this amount as the quantity A, a simulated profile is generated (based on Eqn. 6) to fit the experimental data. Such a fitted curve is shown in Fig. 7 as the solid line. The value of the diffusion coefficient used in generating this fit was 7.5×10^{-12} cm^2/s which we will call D_{app}.

Results of *steady-state experiments* are shown in Fig. 8. The ordinate shows the amount of acetaminophen transported into the receptor compartment per cm^2 of skin. Extrapolation of the steady-state portion (linear regression of last 3 points) gives us a x-intercept value of 25.69. Knowing the value of h (0.001 cm), the value of the diffusion coefficient was calculated to be 1.80×10^{-12} cm^2/s, which is denoted as D_{ss}. The values of D_{app} and D_{ss} differ by a factor of 4.17. We do not expect the value of D_{app} (obtained by computer-fitting of the data) to be exactly the same as D_{ss} because our model is an approximate situation of the complex process that diffusion through the stratum corneum really is. Taking this into consideration, we feel that the correlation between the two values is quite good.

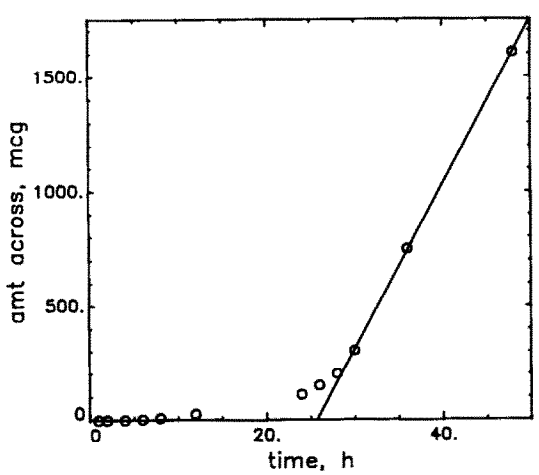

Fig. 8. Steady-state experiments: amount of acetaminophen, per cm^2 of skin, into the receptor cell as a function of time.

We have presented in this paper a model for the transport of drugs across the stratum corneum when the drug is formulated in a system of volatile : non-volatile vehicles. We have obtained an analytical solution to the model. The solution is used to obtain computer-simulated transport profiles which were used to fit experimental transport data. The value of the diffusion coefficient obtained from curve-fitting was found to be within an order of magnitude to the value of the diffusion coefficient obtained by *Steady-state experiments*.

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