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A Monte-Carlo model for the passive diffusion of drugs through the stratum corneum

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Summary

The diffusion of solute molecules through the stratum corneum has been described using a Monte-Carlo random walk model. The results obtained are in agreement with the solutions obtained from Fick's first and second laws. The method is computationally simple to apply, can handle time variation of the stratum corneum's thickness and diffusion coefficient, and provides physical insight into the process of diffusion on a molecular level.

Introduction

The skin consists principally of the stratum corneum, epidermal and dermal layers. Of these layers, the 10 μm stratum corneum layer has been shown to be the principal barrier to drug transport across the skin (Scheuplein and Blank, 1971). When a vehicle containing drug is placed on the surface of an excised piece of stratum corneum, the drug will eventually diffuse through the stratum corneum resulting in an output flux. This process can be described by using the one-dimensional forms of Fick's first and second laws:

$$J = -D\frac{dC}{dx} \tag{1}$$

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{2}$$

where J represents the flux, C the concentration, D the diffusion coefficient, x the distance, and t the time.

Analytical solutions for these equations have been given by Crank (1975); and with the advent of the computer, it has become feasible to solve such equations by numerical techniques employing difference equations (Gerald, 1980).

Alternatively, this one-dimensional diffusion process can be viewed as a one-dimensional random walk. Such an interpretation provides greater physical insight into the diffusional process on a molecular level. The physical basis for such an assumption is that molecules, which have thermal energy, undergo brownian motion. The random process can be described in terms of macroscopically measurable parameters by using the following relationship, developed by Einstein,

$$\overline{(\Delta x)^2} = 2D\Delta t \tag{3}$$

where $\overline{(\Delta x)^2}$ is the mean squared distance a molecule will move in a time Δt and D represents the diffusion coefficient. The appropriateness of such an approach can be illustrated by recognizing that the time and spatially dependent probability density function generated for such a random walk will lead to Fick's first and second laws if Eqn. 3 holds (Kac, 1954). Here it is assumed that molecules have equal probability of taking a forward or backward step of size $\sqrt{\overline{(\Delta x)^2}}$ (this step size will be called Δx throughout the remainder of the paper).

Materials and Methods

A section of the stratum corneum normal to the surface is represented by a one-dimensional array, where each element in the array is a unit cell having an area of 1 μm^2 and a height of Δx. Fig. 1 depicts the stratum corneum as consisting of m elements. An additional array element represents the vehicle phase (thickness equals Δx) while a second additional array element represents the sink at the stratum corneum–epidermis interface. If there are m elements in the stratum corneum array,

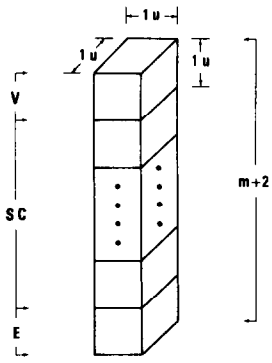

Fig. 1. A one-dimensional array model, consisting of m + 2 elements, of the stratum corneum; where V = vehicle, SC = stratum corneum, and E = epidermis.

then the stratum corneum thickness plus the vehicle phase thickness divided by $m + 1$ equals Δx. No additional array elements are necessary to represent the vehicle phase since this phase is considered to be homogeneously distributed with drug molecules, and because direct transfer of drug molecules across the vehicle–stratum corneum interface can only occur within a distance Δx of the interface. It should be noted that in this simple model the unstirred diffusion layer at the vehicle–stratum corneum interface has been ignored. This could be easily incorporated by adding an additional array element between the bulk vehicle phase and the stratum corneum which would represent the stagnant diffusion layer.

Let the operation of randomly determining the direction of molecular movement for each molecule, be referred to as one iteration. The time transpired during one iteration is equal to Δt and the total time elapsed after q iterations equals $q\Delta t$. At $t = 0$ (before any iterations), all drug molecules are in the vehicle phase. When $t = \Delta t$ (the first iterative step through the array), a random number (R) between zero and one is generated for each drug molecule available for transport from the vehicle phase. If $R > 0.5$, the drug molecule moves down into the first element of the stratum corneum array; otherwise, the molecule remains in the vehicle phase. Because there are no other molecules in the stratum corneum array, no further molecule movement can occur during the first Δt time period. At equilibrium, the molar free energy of the molecules on either side of the vehicle–stratum corneum interface must be equal. The required equilibrium amounts of drug molecules at the interface are set by the partition coefficient (K). For infinite dose conditions, the number of drug molecules available for transport from the vehicle phase to the stratum corneum (AMT) will therefore be:

$$AMT = (1\ \mu m^2)\Delta x K C_v \tag{4}$$

where C_v is the vehicle concentration in molecules per cubic micron. If a finite dose is applied, a conservation of mass constraint must be employed to determine the number of molecules available for transport from the vehicle phase. The number of drug molecules available for transport from the vehicle phase will be equal to AMT until the following difference (DIF) is less than AMT:

$$DIF = FD - SC - E \tag{5}$$

where FD is the finite dose, SC is the amount in the stratum corneum array, and E is the amount in the epidermis. This assumes that there is no loss of drug (e.g. degradation or evaporation from the vehicle phase). When AMT becomes greater than DIF, the number of molecules available for transport from the vehicle phase becomes equal to DIF.

For the next and subsequent iterations, the first element of the array (the vehicle phase) is treated as before. However, the next m array elements are sequentially treated as follows: a random number is generated for each drug molecule present in the i^{th} array element from the previous iterative step. If $R > 0.5$, the molecule moves to $i + 1$ element; otherwise, it moves to the $i - 1$ element. For the $m + 1$ array

element, if $R > 0.5$ the molecule moves to the $m + 2$ element (the stratum corneum–epidermis interface) and is counted as part of the amount released into the epidermis during the time interval $q\Delta t - (q\text{-}1)\Delta t$; otherwise, the molecule moves into the m^{th} array element,. Once the molecule arrives at the stratum corneum–epidermis interface it is not allowed to move back into the stratum corneum array. This corresponds to assuming sink conditions at the stratum corneum–epidermis interface. This assumption is reasonable since the diffusion coefficient of a drug in the epidermis is generally much greater than that of the stratum corneum (Scheuplein and Blank, 1971).

The vehicle concentration (molecules/μm^3) used and the fluxes (molecules/$\mu m^2 \cdot$ iteration) obtained from a simulation can be converted into moles/liter and moles/$cm^2 \cdot h$ by using the following conversion relationships:

$$C_v = \left(\frac{\text{molecules}/\mu m^2 \cdot \Delta x}{N_0} \right) \left(\frac{1 \times 10^{15} \mu m^3}{\text{liter}} \right) \tag{6}$$

$$J = \left(\frac{\text{molecules entering m + 2 element}/\Delta t \cdot \mu m^2}{N_0} \right) \left(\frac{1 \times 10^8 \mu m^2}{cm^2} \right) \left(\frac{3600\ s}{h} \right) \tag{7}$$

where Δx is measured in μm, Δt in s, and N_0 is Avogadro's constant. Here the density of the vehicle phase has been assumed to be unity.

Let the subscript "0" refer to the condition where the diffusion coefficient (D) and the stratum corneum thickness plus vehicle thickness (H) are fixed with respect to time. The output flux (J_0), obtained in time interval Δt_0, can be converted into an output flux (J) having a time varying stratum corneum thickness and diffusion coefficient by using the following conversion:

$$J = J_0 \left[\frac{\Delta t_0}{\Delta t(t)} \right] \left[\frac{\Delta x(t)}{\Delta x_0} \right] \tag{8}$$

where

$$\Delta t(t) = \frac{[\Delta x(t)]^2}{2D(t)} \text{ and } \Delta x(t) = \frac{H(t)}{m + 1}$$

Note that the factor $\Delta x(t)/\Delta x_0$ is required because as $\Delta x(t)$ changes, the amount of drug allowed to enter the stratum corneum from the vehicle phase (Eqn. 4) also changes.

All computer programs were written in BASIC and run on a VAX-11/780 at the Pharmacy Research Computing Facility. Simulations were run with AMT equalling 100,000 and m equalling 9. Increasing AMT will decrease the percent standard deviation and increasing m will provide more information about the spatial distribution of molecules in the stratum corneum (Fig. 4). However, both of these improvements result in longer computation times. The values of 9 for m and 100,000 for

AMT were chosen as a balance between an improved simulation versus an increase in computation time. For each test case, the fluxes from 5 runs were averaged, giving standard deviations which were less than $\pm 1\%$ of their associated mean values. Polynomial data fits for D(t) and H(t) were obtained by using a software package entitled CURVE FITTER from Interactive Microware (State College, PA). In this case, D(t) is interpreted as the mean diffusion coefficient (Wu, 1983) for the entire stratum corneum layer at time t. Hypothetical hand drawn curves of D and H vs time were fit using a third-order polynomial expansion. The curves were divided into two segments, each segment fit to the polynomial expansion with the value of the function continuous throughout the entire curve. Further improvement could be made, by using a cubic spline routine which would allow the function and its first and second derivatives to be continuous.

Results and Discussion

In Fig. 2, the fluxes and the drug distribution in the stratum corneum are identical (within the limits of the inherent random error associated with the

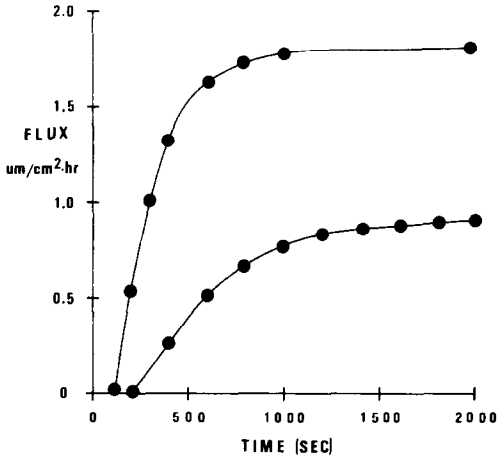

Fig. 2. A graph of flux versus time for the infinite dose case. $D_1 = 5 \times 10^{-10}$ cm^2/s, $D_2 = 2.5 \times 10^{-10}$ cm^2/s, H = 10 μm, $\Delta x = 1$ μm, K = 1, and $C_v = 100{,}000$ molecules/μm^3. The results were scaled up to where $C_v = 1$ mole/liter. The data plotted in this graph was obtained using the Monte-Carlo Model. The graph of the results obtained from the analytical solution is not plotted for clarity purposes because the plots are almost superimposable. The analytical equation used for comparison is:

$$Q_t^{out} = KHCv\left[\frac{Dt}{H^2} - \frac{1}{6} - \frac{2}{\pi^2}\sum_{n=1}^{\infty}\left(\frac{(-1)^n}{n^2}e^{-Dn^2\pi^2 t/H^2}\right)\right]$$

where Q_t^{out} is the amount per unit area at some time t leaving the stratum corneum into the epidermis (Scheuplein, R.J., 1983). Q_t^{out} was evaluated numerically and then the flux was obtained by numerical differentiation. Also, error bars are not shown for clarity because of their small size (standard deviation < $\pm 1\%$ of mean).

computation) to the results obtained from analytical solutions to Fick's first and second laws. That is, the time course and magnitude of flux, lag times, proportionality of flux to the diffusion coefficient at steady-state, and drug distribution are all in agreement. In terms of the random walk model, the lag time implies that the minimum time required for the drug molecule to move through the stratum corneum array is $(m + 1)\Delta t$. However, this is not absolutely correct since it has been assumed that all step sizes are equal. If the step size was allowed to have a Gaussian distribution, then a more accurate distribution would be obtained. The drug distribution obtained by the random walk model (Fig. 4), which assumes the diffusion coefficient is spatially independent, probably also lacks physical meaning, as would solutions obtained from Fick's first and second laws when a constant diffusion coefficient is assumed. For example, stratum corneum tissue which is closer to the epidermis or in close proximity to an occlusive bandage is more hydrated. Since the degree of hydration is correlated with the value of the diffusion coefficient (Wu, 1983), there would be a spatial variation in the diffusion coefficient which is not accounted for in this simulation.

The graph shown in Fig. 3 was generated assuming a 1 molar solution was applied to 1 cm^2 of stratum corneum. The thickness of the applied film was 1 μm. Situations where the finite dose changes as a function of time (such as with volatile substances or when drug degradation occurs in the vehicle phase) can be accounted for by incorporation of a loss term. For example, a first-order rate constant might be used to represent drug degradation.

The stratum corneum thickness can increase by 4-fold and the diffusion coefficient by 20-fold as the stratum corneum becomes fully hydrated (Scheuplein and Blank, 1971). Such changes can take place over a period of several hours. Figs. 5 and

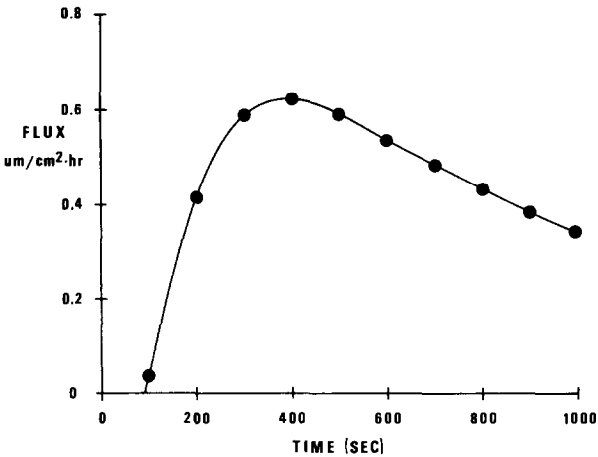

Fig. 3. A graph of flux versus time for the finite dose case. $D = 5 \times 10^{-10}$ cm^2/s, $H = 10$ μm, $\Delta x = 1$ μm, $K = 1$, $C_v = 100{,}000$ molecules/μm^3, and dose = 200,000 molecules. Results were scaled up so that $C_v = 1$ mole/liter and the dose = 1 μmole. Results were obtained by using the Monte-Carlo Model. Error bars were not shown for clarity because of their small size (standard deviation $< \pm 1\%$ of mean).

6 represent hypothetical time profiles for the diffusion coefficient and stratum corneum thickness. The initial and final values are consistent with experimental data (Scheuplein and Blank, 1971). Any graphical plot of the time fluctuation in the stratum corneum thickness and diffusion coefficient can be accommodated by the model by fitting the data to a best fit polynomial. This provides an analytical

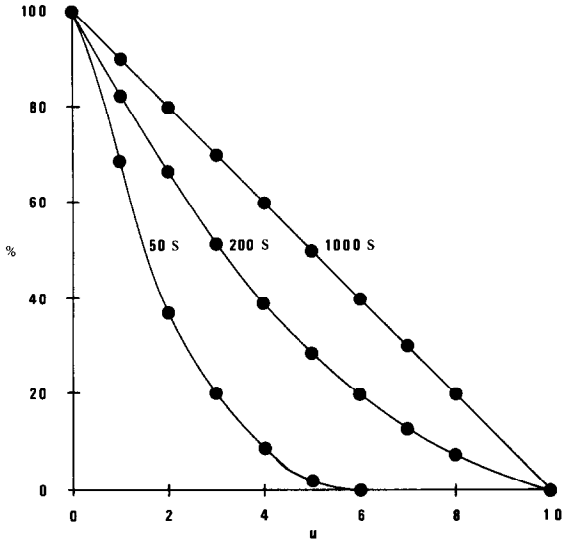

Fig. 4. % concentration of drug molecules, relative to C_v, in the stratum corneum as a function of position. Simulation run with $D = 5 \times 10^{-10}$ cm^2/s, $H = 10$ μm, $\Delta x = 1$ μm, $K = 1$, and $C_v = 100{,}000$ molecules/μm^3. Results obtained from Monte-Carlo Model. Error bars were not shown for clarity because of their small size (standard deviation $< \pm 1\%$ of mean).

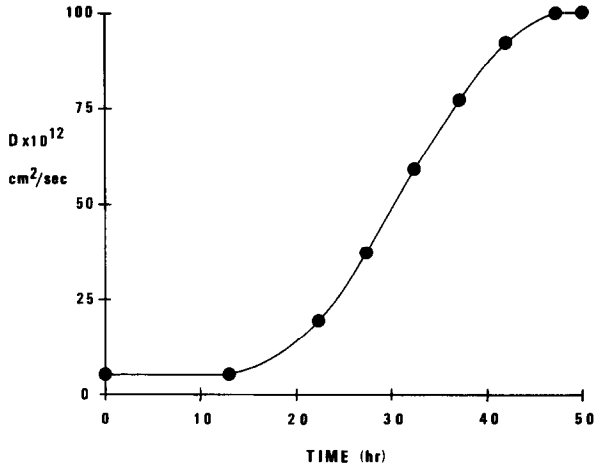

Fig. 5. Time variation of the diffusion coefficient. This graph was obtained by plotting the points generated from a third-order polynomial fit acquired from data derived from a hypothetical hand drawn curve of D(t) vs t.

expression for the diffusion coefficient and stratum corneum thickness which can be used in Eqn. 8. The resulting flux obtained is shown in Fig. 7.

The model can easily account for situations where there are other driving forces causing drug transport besides passive diffusion. Such an example would be the application of an external electric field, as in iontophoresis (Gangarosa, 1980). Here,

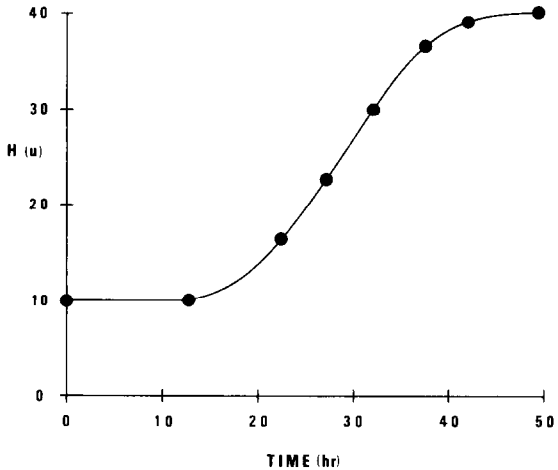

Fig. 6. Time variation of the stratum corneum thickness. This graph was obtained by plotting the points generated from a third-order polynomial fit acquired from a hypothetical hand drawn curve of H(t) vs t.

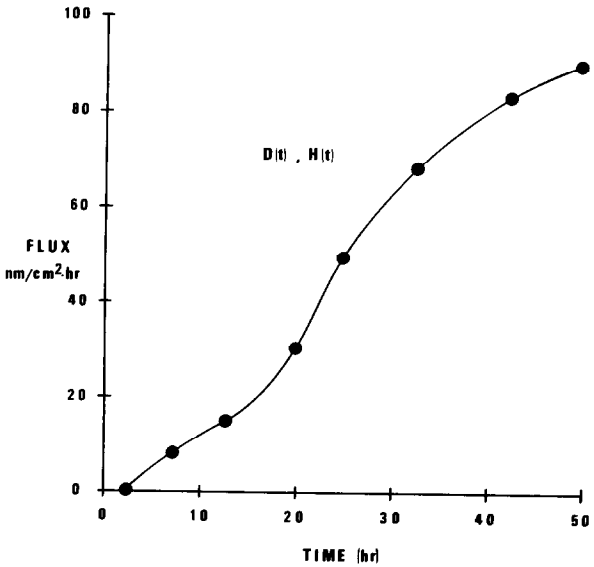

Fig. 7. Flux vs time derived using Eqn. 8 with D(t) and H(t) as depicted in Figs. 5 and 6, respectively. Results were obtained from the Monte-Carlo Model assuming an infinite dose. Error bars were not shown for clarity because of their small size (standard deviation $< \pm 1\%$ of mean).

as a first approximation, the probability of moving forward would be 0.5 + a and the probability of moving backward 0.5 − a, where 'a' is some constant less than 0.5 (Wax, 1954). In this context, diffusion can be viewed as an overall probability of moving in a given direction without requiring any detailed understanding of the transport process at the molecular level. In this sense, the random walk can be viewed as a model-independent approach to drug transport. However, as more information about the molecular pathway and mechanism of transport is obtained, it can easily be incorporated into the random walk formalism giving it more physical meaning. For example, as more detailed knowledge about the diffusional pathway of molecules through the stratum corneum is obtained, a three-dimensional random walk can be done. The advantage of using a random walk over other forms of solution becomes even more apparent in this case, since the complexity of solving a problem by a random walk method increases more slowly than solutions by other methods (King, 1951).

The random walk model thus provides a versatile, simple, and physically meaningful alternative for the solution of diffusional skin transport problems and modelling of the physical parameters and variables.

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