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Percutaneous absorption: theoretical description

W. JOHN ALBERY*‡ AND JONATHAN HADGRAFT†

Physical Chemistry Laboratory, South Parks Road, Oxford, OX1 3QZ, U.K.

Equations are derived to describe the percutaneous absorption of a substance through the epidermal barrier. The treatment includes interfacial barriers and allows for the depletion of the substance in the external phase. The equations are derived both for the continuous application and for pulse experiments where the drug is applied for a time, then removed, and the response occurs some time after the removal of the drug. Competition between the drug diffusing through the keratinized cells (transcellular route) and diffusing in the interstitial channels around the cells (intercellular route) is also considered.

In this paper we develop a theoretical model for the transport of a drug through the epidermis. The model includes diffusion and depletion in the external phase, diffusion through the epidermis and following the previous paper (Albery & Hadgraft 1979) the kinetics of the transfer reactions at the interfaces. We derive a complete set of equations describing how much of the drug has accumulated in the dermis as a function of time. By finding which equation best fits the experimental data, we can then determine which process is most rate limiting and obtain information about the diffusional path length in the epidermal barrier. Some parts of the problem have been treated previously (e.g. Kakemi et al 1975) but in this approach we include the interfacial barriers and we also derive analytical expressions wherever possible.

The model

The model together with the parameters and variables is shown in Scheme 1. For most substances the rate limiting region for diffusion across the epidermal barrier is the exterior stratum corneum (Loveday 1961; Scheuplein & Blank 1971). This layer is made up of dead cells separated by narrow channels containing a lipid phase. The next layer, the stratum granulosum, is more aqueous in nature; here the diffusion is more rapid and therefore this layer acts as a reservoir in which the drug accumulates. Since the stratum corneum is the rate limiting region, we assume that once the drug reaches the stratum granulosum it does not return. There is no back reaction at the internal barrier. This assumption may not be true for some drugs which are very soluble in the lipid phase (Scheuplein & Blank 1971). For these drugs the aqueous stratum granulosum will be the main barrier to percutaneous absorption and our treatment does not apply to these compounds.

In the model illustrated in Scheme 1 we have included an internal barrier as well as an external barrier. In order to simplify the algebra and in order not to introduce another parameter, we have assumed the same rate constant k_I for both barriers. It is possible that there is no barrier at all at this point. For instance the material in the interstitial channels may change gradually from a lipid-rich phase to an almost aqueous phase. We will therefore also report results for the simpler model without any internal barrier.

The concentration and distance variables are normalized respectively by the bulk concentrations (c_∞) and by the thickness (l) of the stratum corneum. We also define

$$\tau = tD_*/l^2 \quad .. \quad .. \quad .. \quad (1)$$

$$\kappa = k_I l/D_* \quad .. \quad .. \quad .. \quad (2)$$

$$p = D_0/D_* \quad .. \quad .. \quad .. \quad (3)$$

and

$$n' = \int_0^\tau \kappa u_1 \, d\tau = n/(lc_\infty) \quad .. \quad (4)$$

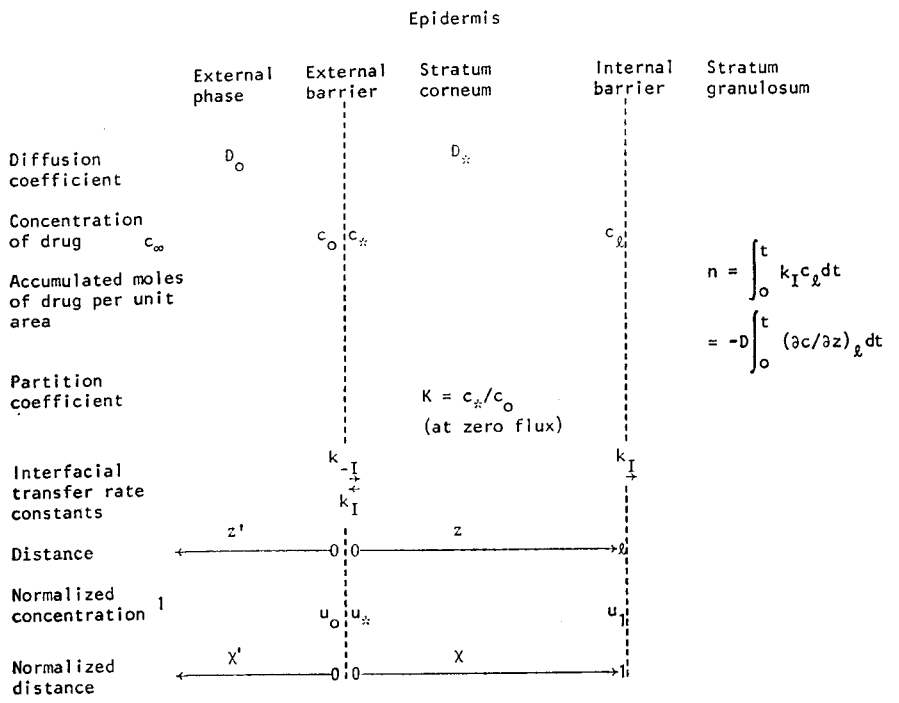
The equations

We assume that diffusion takes place in one dimension and then applying Fick's 2nd Law of Diffusion

Present addresses: *Department of Chemistry, Imperial College of Science & Technology, Prince Consort Road, London.

† Department of Pharmaceutical Chemistry, University of Strathclyde, 204 George Street, Glasgow.

‡ Correspondence.



Scheme 1

we obtain for the external phase

$$\frac{\partial u}{\partial \tau} = p\,\frac{\partial^2 u}{\partial \chi'^2} \quad .. \quad .. \quad (5)$$

and for the stratum corneum

$$\frac{\partial u}{\partial \tau} = \frac{\partial^2 u}{\partial \chi^2} \quad .. \quad .. \quad .. \quad (6)$$

At the external interface we have

$$p\left(\frac{\partial u}{\partial \chi}\right)_o = \kappa(Ku_o - u_*) = -\left(\frac{\partial u}{\partial \chi}\right)_o \quad .. \quad .. \quad (7)$$

and at the internal interface

$$(\partial u/\partial \chi)_1 = -\kappa u_1 \quad .. \quad .. \quad ..(8)$$

If there is no internal interface then $u_1 = 0$. This is because the more rapid diffusion in the stratum granulosum removes the drug. Equations (7) and (8) provide three boundary conditions to solve the differential equations (5) and (6). The remaining boundary condition is:

$$u \to 1 \quad \text{as} \quad \chi' \to \infty \quad ..(9)$$

The general solution

These equations are solved by Laplace transformation. Equation (5) with boundary condition (9) gives:

$$\bar{u}_o = \frac{1}{s} - \left(\frac{p}{s}\right)^{\frac{1}{2}}\left(\frac{\partial \bar{u}}{\partial \chi'}\right)_o \quad .. \quad .. \quad (10)$$

Equation (6) with boundary condition (8) gives

$$\left(\frac{\partial \bar{u}}{\partial \chi}\right)_o = -\frac{\bar{u}_*(\kappa + \sqrt{s}\tanh\sqrt{s})}{1 + \kappa\tanh\sqrt{s}/\sqrt{s}} \quad .. \quad (11)$$

and $\bar{u}_1 = \bar{u}_* \cosh\sqrt{s}_1$

$$+ (\partial\bar{u}/\partial\chi)_o \sinh\sqrt{s}_1/\sqrt{s}_1 \quad .. \quad ..(12)$$

Elimination between equations (7), (10) and (11) followed by substitution in equations (12) and (4) gives

$$\bar{n}' = \frac{\kappa\bar{u}_1}{s} = \bar{f} \quad .. \quad .. \quad .. \quad .. \quad (13)$$

where $\bar{f}$

$$= \frac{K}{s^{\frac{3}{2}} \sinh\sqrt{s}\ (1 + \frac{2\sqrt{s}}{\kappa \tanh\sqrt{s}} + \frac{s}{\kappa^2} + \frac{K}{\sqrt{p}\ \tanh\sqrt{s}} + \frac{K\sqrt{s}}{\kappa\sqrt{p}})} \quad .. \quad .. \quad (14)$$

This expression cannot be inverted but it is unlikely for any system that all the terms will be significant and we therefore derive a set of solutions which cover all cases where parameters differ by an order of magnitude or more; equation (14) can then be simplified by neglecting some of the terms.

The set of approximate solutions

The seven approximate solutions for f together with the appropriate conditions are given in Table 1. In order to facilitate discussion we have labelled the different solutions in the following systematic manner. First of all the solutions can be divided into those for which $\tau << 1$ and those for which $\tau >> 1$. The former are cases where there has not been enough time to establish a linear concentration profile across the stratum corneum. These solutions are labelled I. On the other hand when $\tau >> 1$ there is sufficient time for a linear concentration profile to be established and these solutions are labelled II. Secondly, depending on the size of either $\kappa\tau^{\frac{1}{2}}$ or of $\kappa\tau$ the solutions may be divided into two classes labelled A and B. The A solutions are found for smaller values of $\kappa\tau^n$ and correspond to those cases where the interfacial transfer kinetics are at least partly rate limiting. On the other hand, with one exception, the B solutions are independent of κ and the interfacial transfer kinetics are not rate limiting. The one exception is solution II A2 when $\kappa << 1$. For these conditions the kinetics of the transfer at the interfaces are always rate limiting. Thirdly, we can divide the solutions into classes 1 and 2 depending on whether depletion in the external phase is partly rate limiting or not. All the class 2 solutions contain p and depletion is partly rate limiting, whereas all the class 1 solutions are independent of p and depletion is not rate limiting. The rate limiting processes for the different solutions are summarized in Table 2.

Next we consider how any system will evolve with time through the different solutions. From the conditions for τ in Table 1 we conclude that all systems start with solution IA1. This corresponds to the non-linear concentration gradient in the stratum corneum (I), interfacial kinetics important (A), depletion unimportant (1). As τ increases the system will pass through one or two intermediate solutions and will eventually reach the other extreme solution IIB2. This final solution is the opposite of IA1 and corresponds to a linear concentration gradient (II),

Table 1. Approximate solutions for f from inverting equation (14).

	$\kappa^2\tau << 1$		$\kappa^2\tau >> 1$
	$\kappa^2\tau << p/K^2$	$\kappa^2\tau >> p/K^2$	
$\tau^2 << 1$	$\frac{32\kappa^2K\tau^{\frac{7}{2}}}{\pi^{\frac{1}{2}}} \exp(-\frac{1}{4\tau})$	$\frac{16\sqrt{p}\kappa\tau^{\frac{5}{2}}}{\pi^{\frac{1}{2}}} \exp(-\frac{1}{4\tau})$	$\frac{8K\tau^{\frac{3}{2}}}{\pi^{\frac{1}{2}}(1+K/\sqrt{p})} \exp(-\frac{1}{4\tau})$
	IA1	IA2	IB(1 & 2)[a]

	$\kappa^2\tau^2 << 1$		$\kappa^2\tau^2 >> 1$	
	$\kappa\tau << \frac{p}{K^2}$	$\kappa\tau >> \frac{p}{K^2}$	$\frac{\kappa^2\tau}{(2+\kappa)^2} << \frac{p}{K^2}$	$\frac{\kappa^2\tau}{(2+\kappa)^2} >> \frac{p}{K^2}$
$\tau^2 >>$	$\frac{\kappa^2K\tau^2}{2}$	$\frac{4\sqrt{p}\kappa\tau^{\frac{3}{2}}}{3\pi^{\frac{1}{2}}}$	$\frac{\kappa K\tau}{2+\kappa}$[b]	$\frac{2\sqrt{p}\tau^{\frac{1}{2}}}{\pi^{\frac{1}{2}}}$
	IIA1	IIA2	IIB1	IIB2

[a] IB1 is found for $p/K^2 \ll 1$ and IB2 for $p/K^2 \gg 1$.
[b] Reduces to $\frac{1}{2}\kappa K\tau$ for $\kappa^2 \ll 1$ and to $K\tau$ for $\kappa^2 \gg 1$.

Table 2. Rate limiting processes for the different solutions in Table 1.

		External phase	External interface	Stratum corneum	Internal interface
IA1		×	√	√	√
2		√	×	√	√
B1		×	×	√	×
2		√	×	√	×
IIA1		×	√	×	√
2		√	×	×	√
B1	$\kappa^2>>1$	×	×	√	×
	$\kappa^2<<1$	×	√	×	√
2		√	×	×	×

interfacial kinetics unimportant (B) but depletion important (2). Which intermediate solutions the system passes through depends on the size of κ, the normalized interfacial transfer rate constant, and on p/K^2, which compares transport in the external phase with that in the stratum corneum. Fig. 1 displays the information in Table 1 and shows the different possible sequences, the conditions under which they are found and the values of τ at which the system passes from one solution to another. At these values of τ reasonably good agreement is found for the corresponding values of f in Table 1 from the two merging solutions. Hence the set of solutions in Table 1 provides a reasonably complete description of the accumulation of drug by percutaneous absorption. In practice it may be that only one or two of the cases can actually be observed for any particular system. For instance the system may pass through the first case IA1 at times that are too short for any response to be detected, or the experiment may not last long enough for the system to reach the final solution IIB2. However, we believe, firstly that experimental data should be tested against all the different solutions in order to select the one that fits best, and secondly that the complete pattern of solutions aids our understanding of the evolution of the absorption process and the interplay of the various possible rate limiting processes.

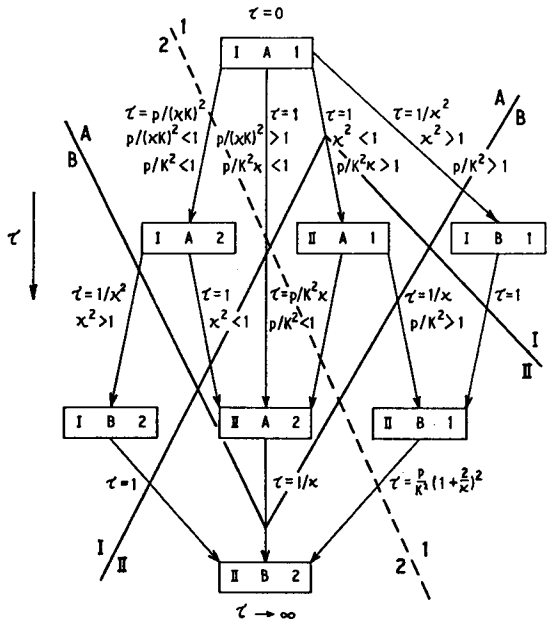


FIG. 1. Interrelation of solutions in Table 1. At $\tau = 0$ all systems start in solution IA1 and as $\tau \to \infty$ all systems would end in IIB2. Depending on the relative sizes of the parameters the system passes from IA1 to IIB2 through the intermediate solutions as shown.

For the case of the simpler model where there is no internal interface we obtain all the same solutions in class A except that the denominator in IIA2 is $(1 + \kappa)$ instead of $(2 + \kappa)$. There are no class B solutions except for solution IB2. Under these conditions we obtain

$$f = \frac{16K}{\sqrt{\pi}} \kappa \tau^{\frac{5}{2}} \exp\left(-\frac{1}{4\tau}\right) \quad .. \quad (15)$$

and the flux is controlled by the penetration of the external barrier followed by diffusion across the stratum corneum. From Table 2 we can see that the solutions that have been 'lost' are those where the internal interface was one of the main rate limiting terms.

Pulse experiments

In the simplest type of experiment, the drug is applied continuously. However, the different models for percutaneous absorption can be further tested if the drug is applied for a time t_1 and then removed. The response to the accumulated drug then occurs after a further period of time t_2. This type of experiment is particularly valuable for substances of low solubility where the concentration in the external phase cannot be varied over a wide range. The variation of t_1 provides an alternative experimental variable (Albery & Hadgraft 1979).

After the removal of the drug at time t_1 we need only describe the transport in the stratum corneum and the penetration across the internal interface. The differential equation is the same as equation (6) except that we define a new time scale which starts at t_1:

$$\frac{\partial u}{\partial \tau'} = \frac{\partial^2 u}{\partial x^2}$$

where $\tau' = (t - t_1)D_*/\ell^2$

The boundary conditions for this equation are equation (8) at the external interface,

$$(\partial u/\partial \chi)_o = 0,$$

and at $\tau' = 0$

$$u = \mathcal{L}^{-1}\bar{u}')_{\tau=\tau_1}$$

where $\bar{u}'$ is a function of s_1 and χ given by the solution of equations (5) and (6) as discussed below. The accumulated drug at time τ_2 is given by:

$$n' = \int_o^{\tau_1} \kappa u_1 d\tau + \int_o^{\tau_2'} \kappa u_1 d\tau'$$

$$= f(\tau_1) + T_2 \quad .. \quad .. \quad (16)$$

The first term describes the drug that accumulates before t_1 when the source of the drug is removed. The function f has been discussed above. The second term, T_2, describes the further accumulation of drug that had diffused into the stratum corneum before t_1 and which then subsequently penetrates the internal interface.

This term is found by taking the double Laplace transform of u with respect to both τ and τ'. We obtain

$$\bar{\bar{u}}_1 = \frac{\int_o^1 \cosh(\sqrt{s'}\chi)\bar{u}'d\chi}{\sqrt{s'}\sinh\sqrt{s'} + \kappa\cosh\sqrt{s'}}$$

.. .. (17)

where

$$\bar{u}' = A\cosh(\sqrt{s}\chi) + B\sinh(\sqrt{s}\chi),$$

from the definition of f

$$\frac{s\bar{f}}{\kappa} = A\cosh\sqrt{s} + B\sinh\sqrt{s}$$

and from eqn (11),

$$\frac{A}{B} = -\frac{\sqrt{s} + \kappa\tanh\sqrt{s}}{\kappa + \sqrt{s}\tanh\sqrt{s}}$$

Elimination of A and B, evaluation of the integral in equation (17) and substitution in equation (16) gives

$$\bar{\bar{n}}' = \left(\frac{\bar{f}}{s-s'}\right)\left(\frac{(\kappa\cosh\sqrt{s} + \sqrt{s}\sinh\sqrt{s})s}{(\kappa\cosh\sqrt{s'} + \sqrt{s'}\sinh\sqrt{s'})s'} - 1\right)$$

.. (18)

Again we cannot invert the double transform for all values of s and s' but in Table 3 we collect together a set of approximate solutions. The appropriate regions for the different solutions are shown in Fig. 2.

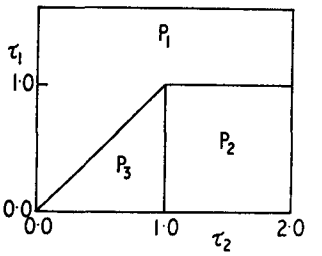


FIG. 2. The approximate solutions P1, P2 and P3 in Table 3 for the pulse experiments are applicable for the values of τ_1 and τ_2 shown in the diagram.

For most cases of solutions P1 and P2 the expression is dominated by the $f(\tau_1)$ term which describes the accumulation of the drug (in the stratum corneum) before its removal from the outside of the skin. In solution P1 the τ_2 term describes a small amount of accumulation immediately after the removal of the drug. In solution P2 when κ is large there is not much drug in the stratum corneum compared with that already accumulated. However when κ is small, then the drug may be trapped in the stratum corneum, and subsequently leak out during the t_2 period; for this case the τ_2 term may be significant. In solution P3, the drug is applied for a short time compared with the characteristic time for its diffusion across the stratum corneum. It therefore has to be 'stored' close to the external interface. This is described by the f'' function. For solution PI the rate-limiting process is either diffusion in the epidermis ($\sqrt{p}/K >> 1$) or diffusion and depletion in the external phase ($\sqrt{p}/K << 1$); for solution PII the rate-limiting process is the transfer reaction at the external interface. For solution P2 τ_2 is long enough for all the stored drug to reach the internal interface where its penetration is controlled by κ. For solution P3 τ_2 is small and only a small fraction of the stored drug has time to reach the internal interface.

Similar solutions are obtained for the model where there is no internal interface. In Table 3 for all solutions we take the limit where $\kappa \to \infty$; this of course corresponds to removing the barrier at the internal interface. The appropriate f must be used as discussed above and f'' in PI and PII is unchanged.

Multiple barriers

In the treatment so far our model has two interfaces. This will be approximately true if the drug penetrates through the intercellular channels. However, a different possible route involves diffusion straight through the dead cells in the stratum corneum. In this case there may be many interfacial barriers situated at the boundaries between the dead cells and

Table 3. Approximate solutions for pulse experiments from equation (18).

Condition	Solution	Label
$\tau_1^2 >> \tau_2^2$ or $\tau_2^2 >> \tau_1^2 >> 1$	$f(\tau_1) + (\frac{1}{2}+\frac{1}{\kappa})\left[1-\exp(-\frac{\tau_2}{\frac{1}{2}+\kappa^{-1}})\right] f'(\tau_1)$	P1
$\tau_2^2 >> 1 >> \tau_1^2$	$\{1-\exp(-\kappa\tau_2)\}\, f''(\tau_1)$	P2
$1 >> \tau_2^2 >> \tau_1^2$	$\{\frac{8\kappa\tau_2^{\frac{3}{2}}}{\sqrt{\pi}(1+2\kappa\tau_2)}\}\exp\,(-\frac{1}{4\tau_2})\, f''(\tau_1)$	P3

Solutions for

$f(\tau_1)$ are given in table 1

$f'(\tau_1) = \partial f(\tau_1)/\partial\tau_1$

$f''(\tau_1) \simeq \frac{2\sqrt{p}\tau_1^{\frac{1}{2}}}{\sqrt{\pi}(1+\sqrt{p}/K)}$ for $\kappa^2\tau_1 >> (1 + K/\sqrt{p})^{-2}$		PI
$\simeq K\kappa\tau_1$ for $\kappa^2\tau_1 << (1 + K/\sqrt{p})^{-2}$		PII

the interstitial channels containing lipid phase. In the appendix we show that, providing

$$t > k_I \ell^3 D_T^{-2}$$

passage across n such barriers, is described by the ordinary diffusion equation used above but instead of D_* we must use an effective diffusion coefficient $\bar{D}$ given by:

$$\frac{1}{\bar{D}} = \frac{1}{D_T} + \frac{n}{k_I \ell} \quad .. \quad .. \quad (19)$$

The effective diffusion coefficient is determined by the slower of the two processes the ordinary diffusion D_T or the 'diffusion' through the multiple barriers. But in either case the form of the equations derived above is not changed. This conclusion for interfacial barriers is similar to that reached by Higuchi (Higuchi & Higuchi 1960; Yotsuyanagi & Higuchi 1972) for diffusion in a two phase system.

Parallel routes

The model in Scheme 1 shows only one route for the penetration of the drug. It is possible that the drug penetrates simultaneously by diffusion through the dead cells and also through the intercellular channels. Furthermore Scheuplein & Blank (1971) have pointed out that there may be a change in the route of penetration with time. At short times routes with small cross sectional area but high values of D/l^2 are preferred. The drug therefore may start by penetrating through the channels but in the steady state the route may be through the dead cells. In this section we examine the factors that describe which route is preferred and whether such a change in mechanism is possible.

The model

The model is shown in Fig. 3. The epidermal barrier consists of n layers of dead cells. The route round the dead cells is of average length l_c, which we assume to be at least five times larger than the thickness of the barrier, l. The geometry of the barrier has been idealized as shown in Fig. 3. This idealized geometry is based on the model of Michaels et al (1975). In our model we have not included any cell stacking. However even if there was some cell stacking (Christophers & Kligman 1964), it is still likely that l_c/l is greater than 5. The diffusion coefficients are D_T and D_C for the cells and the channels respectively. We assume that there are no interfacial barriers and that the concentration of material in the channel is given by K'c where c is the concentration in the adjacent dead cells and K' is the partition coefficient for material between channels and cells. We make no assumptions about the size of K' or the relative sizes of D_T and D_C. We take the simple boundary conditions that c_0 the concentration of drug applied to the skin is constant and that c the concentration at

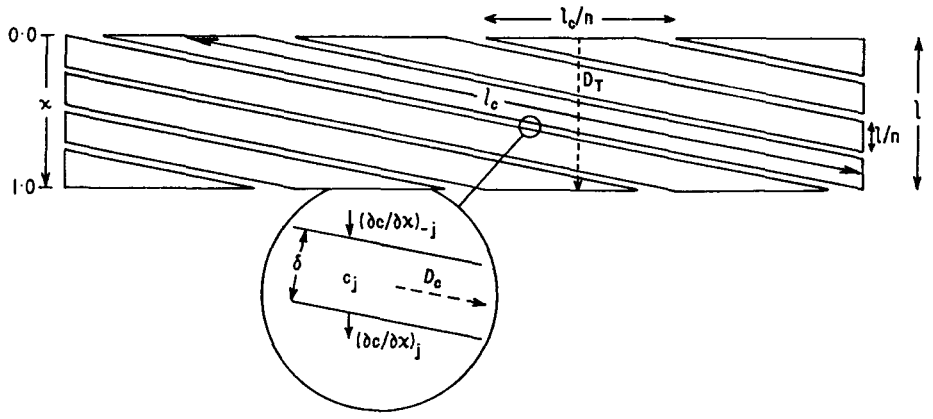


FIG. 3. Simplified model of the stratum corneum consisting of n layers of dead cells and with interstitial channels of length l_c. Parameters for the two different routes of penetration are shown.

the inside of the barrier is zero. We then calculate the flux.

The differential equations

The differential equation for diffusion in the cells is

$$\frac{\partial c}{\partial \tau} = \frac{\partial^2 c}{\partial \chi^2}$$

where τ and χ are the same as for Scheme 1 and equation 1 with $D_* = D_T$. We solve this differential equation for each layer of dead cells using the Laplace transformation and we obtain the following relations for the jth layer

$$\bar{c}_{j+1} = \bar{c}_j \cosh(\sqrt{s}/n) + s^{-\frac{1}{2}}(\partial\bar{c}/\partial\chi)_j \sinh(\sqrt{s}/n)$$

and

$$\bar{c}_{j-1} = \bar{c}_j \cosh(\sqrt{s}/n) - s^{-\frac{1}{2}}(\partial\bar{c}/\partial\chi)_{-j} \sinh(\sqrt{s}/n) \quad .. \; .. (21)$$

Because we have assumed there are no interfacial barriers the concentration of drug at the jth level is the same on both sides of the channel. However, the gradient $(\partial c/\partial\chi)$ may be different because material is supplied or lost to the transverse channel. Thus $(\partial c/\partial\chi)_{-j}$ and $(\partial c/\partial\chi)_{+j}$ are gradients on the external and internal faces of the channel respectively (see insert in Fig. 3).

Next we consider the concentration at a point j in a channel and we obtain

$$\delta K'\left(\frac{\partial c_j}{\partial t}\right) = \delta K' D_c \left(\frac{\partial^2 c_j}{\partial z_c^2}\right) - D_T \left[\left(\frac{\partial c}{\partial z}\right)_{-j} - \left(\frac{\partial c}{\partial z}\right)_{+j}\right]$$

The first term on the right-hand side describes diffusion along the channel and the second term the supply of material to and from the dead cells. We express this equation in dimensionless variables and obtain

$$\frac{\partial c_j}{\partial \tau} = \alpha\left(\frac{\partial^2 c_j}{\partial \chi_c^2}\right) - \beta n \left[\left(\frac{\partial c}{\partial \chi}\right)_{-j} - \left(\frac{\partial c}{\partial \chi}\right)_{+j}\right]$$

$$\text{where} \quad \alpha = \frac{D_c}{l_c^2}\frac{l^2}{D_T} \quad .. \; .. \; ..(22)$$

$$\beta = l/K'n\delta \quad .. \; .. \; ..(23)$$

$$\text{and} \quad \chi_c = z_c/l_c$$

We take the Laplace transform of this equation and substitute from equation (20) and (21) to obtain

$$\frac{\partial^2 \bar{c}_j}{\partial \chi_c^2}\left[\alpha + \frac{\beta(\sqrt{s}/n)}{\sinh(\sqrt{s}/n)}\right] = \bar{c}_j\left[s + \frac{2\beta n\sqrt{s}}{\sinh(\sqrt{s}/n)}\{\cosh(\sqrt{s}/n) - 1\}\right] \quad .. \; (24)$$

where we have written

$$\bar{c}_{j+1} + \bar{c}_{j-1} - 2\bar{c}_j \simeq \frac{1}{n^2}\frac{\partial^2 c_j}{\partial \chi_c^2}$$

The solution

Equation (24) is then solved for the boundary conditions to give

$$\bar{c}_o = \frac{c_*}{s}\left[\cosh(g^{\frac{1}{2}}\chi_c) - \frac{\sinh(g^{\frac{1}{2}}\chi_c)}{\tanh(g^{\frac{1}{2}})}\right]$$

where

$$g = \frac{s + \frac{2\beta n\sqrt{s}}{\sinh(\sqrt{s}/n)}\{\cosh(\sqrt{s}/n) - 1\}}{\alpha + \beta(\sqrt{s}/n)/\sinh(\sqrt{s}/n)} \quad .. (25)$$

The flux is given by

$$\text{Flux} = -D_T\left(\frac{\partial c}{\partial z}\right)_{z=\ell} - \frac{nD_c\delta K'}{\ell_c}\left(\frac{\partial c}{\partial z_c}\right)_{z_c=\ell_c}$$

The first term on the right-hand side describes the flux into the dermis through the dead cells and the second term the flux through the channels. In order to describe the flux we define the dimensionless quantity F where

$$\text{Flux} = FD_T c_*/\ell$$

and

$$c_*\bar{F} = -\left(\frac{\partial \bar{c}}{\partial \chi}\right)_{\chi=1} - \frac{\alpha}{\beta}\left(\frac{\partial c}{\partial \chi_c}\right)_{\chi_c=1} \quad .. (26)$$

From equation (21) with j = n

$$\left(\frac{\partial \bar{c}}{\partial \chi}\right)_{\chi=1} = -\frac{s^{\frac{1}{2}}}{\sinh(\sqrt{s}/n)}\bar{c}_{n-1}$$

$$\simeq \frac{s^{\frac{1}{2}}/n}{\sinh(\sqrt{s}/n)}\left(\frac{\partial \bar{c}}{\partial \chi_c}\right)_{\chi_c=1} \quad .. (27)$$

Combining equations (25) (26) and (27) we obtain

$$\bar{F} = -\frac{g^{\frac{1}{2}}}{s\sinh(g^{\frac{1}{2}})}\left[\frac{\alpha}{\beta} + \frac{s^{\frac{1}{2}}/n}{\sinh(\sqrt{s}/n)}\right] \quad .. (28)$$

The set of approximate solutions

Depending on the relative sizes of α,β and n we distinguish the different cases shown in Fig. 4. In Table 4 for each case we have listed approximate solutions for $\bar{F}$.

As t rises, in Laplace space the transformed variable s decreases. Therefore the approximations in s for the large values of s correspond to the transient behaviour whereas the approximations for s tending to zero describe the steady state. The solutions divide into two groups, the T group where the

Table 4. Approximate solutions for F (equation (28)) for the cases shown in Fig. 4.

Case	Transients		Steady state	
TI	$s^{-\frac{1}{2}}\,\text{cosech}\,s^{\frac{1}{2}}$		$\xrightarrow{s\ 1}$	s^{-1}
TII	$(\beta s)^{-\frac{1}{2}}\,\text{cosech}\,(s/\beta)^{\frac{1}{2}}$		$\xrightarrow{s\sim\beta}$	s^{-1}
CI	$\beta^{-1}(s/\alpha)^{-\frac{1}{2}}\text{cosech}(s/\alpha)^{\frac{1}{2}}$		$\xrightarrow{s\sim\alpha}$	$\alpha/\beta s$
CII	$\frac{\text{cosech}(s/\alpha)^{\frac{1}{2}}}{\beta(s/\alpha)^{\frac{1}{2}}}$	$\xrightarrow{s\sim\beta^2n^2}$ H*	$\xrightarrow{s\sim\alpha^2/\beta^2n^2}$	$\frac{\alpha}{\beta s}$
CIII	$\frac{\text{cosech}(s/\alpha)^{\frac{1}{2}}}{\beta(s/\alpha)^{\frac{1}{2}}}$	$\xrightarrow{s\sim\beta^2n^2}$ H* $\downarrow s\sim n^2$		
		$\frac{\text{cosech}(\beta s/\alpha)^{\frac{1}{2}}}{(\beta s/\alpha)^{\frac{1}{2}}}$	$\xrightarrow{s\sim\alpha/\beta}$	$\frac{\alpha}{\beta s}$

$$*H = \frac{\text{cosech}(2n\beta\sqrt{s/\alpha})^{\frac{1}{2}}}{(\beta/2n\alpha)^{\frac{1}{2}}s^{\frac{3}{4}}}$$

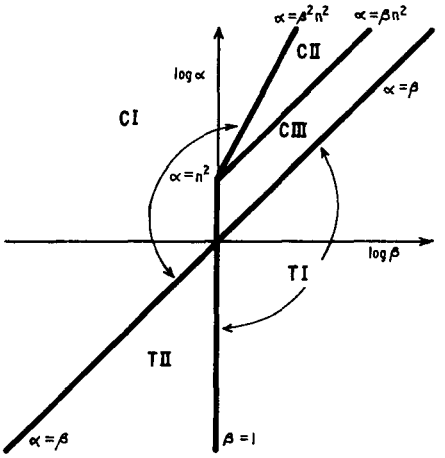


FIG. 4. The approximate solutions (TI, TII, CI, CII and CIII) in Table 4 for penetration through the model shown in Fig. 3 are applicable for the different values of α and β shown in the diagram. From equations (22) and (23), $\alpha = (D_c/l_c^2)/CD_T/l^2)$ and $\beta = l/K'n\delta$.

drug is transported by the trans-cellular route and the C group where the drug is transported through the channels. The dividing line between the two groups is $\alpha = \beta$ or from equations (22) and (23)

$$\frac{K'D_c\delta}{\ell_c} = \frac{D_T}{\ell}\,\frac{\ell_c}{n}$$

The left-hand side describes the steady state diffusion along the channels and the right-hand side the diffusion through the cells; there is one channel of width δ per length l_c/n of dead cells (See Fig. 3).

All the transient solutions in Table 4, except for H, have the form $s^{-\frac{1}{2}}$ cosech (constant x $s^{\frac{1}{2}}$). Equation (14) for $\bar{f}$ (where $\bar{F} = sK^{-1}\bar{f}$) reduces to the same form when the κ and p terms are neglected in the denominator. Thus except for H the transient behaviour is the same as discussed for case IA in Table 1 providing that the appropriate diffusion coefficient, partition coefficient and length are used. Taking each of the cases in turn we start with TI. In this case transport is through the dead cells and the channels are irrelevant. The normalization with D_T and l is correct and neither α nor β are found in the expression for $\bar{F}$. For case TII the parameter β is smaller than one. This parameter ($\beta = l/K'n$) compares the number of moles of drug in the cells and in the channels at equilibrium. In a unit area of epidermis the volume ratio is given by n channels of thickness δ in the total thickness l. Therefore if $\beta > 1$ more material accumulates in the cells and if $\beta < 1$ more material accumulates in the channels. For case TII (where $\beta < 1$) the transport is still through the cells but it is slowed down by having to saturate the channels.

In case CI transport is through the channels and the dead cells merely get in the way. The quantity α ($\alpha = D_C l^2/D_* l_C^2$) divides s because, instead of D_T and l, D_C and l_C should have been used for the normalization. Similarly β describes the correct partition coefficient and geometry for the channels. In Fig. 4 Case CI does include an area where $\alpha > 1$ and material accumulates in the dead cells. However the number of moles that accumulate in the dead cells is small at all times compared with the number that penetrate to the dermis and hence the dead cells have an insignificant effect on the rate of absorption. This is not true for cases CII and CIII. In these cases the function H in Table 4 describes the penetration of material through the channels to the dermis while at the same time significant quantities of the drug are being absorbed by the dead cells lining the route. The third transient approximation for CIII may be contrasted to TII. As in all the C solutions α changes the normalization to the channel parameters, and β describes the slower transient because material is accumulating in the cells while being transported through the channels. In CII and CIII the penetration is slower than CI because the channels feed the cells while in TII the penetration is slower than TI because the cells feed the channels.

An important conclusion can be drawn from the solutions in Table 4, and that is that *there is no change in the route of penetration with time*. For all the cases the same route is found for the transient expressions and for the steady state solution. This conclusion for the two routes through the epidermal barrier may be contrasted with the discussion of Scheuplein & Blank (1971). They showed that routes through the skin appendages (e.g. hair follicles and sweat ducts) may be preferred at short times although in the steady state penetration takes place through the whole of the epidermis. In this case the change in mechanism is possible because the follicles and ducts pass straight through the epidermal barrier. In our idealized geometry we have not included any cell stacking. For the perfect stacking of cells some channels will resemble pores and the treatment of Scheuplein & Blank (1971) would then be applicable. Any theoretical treatment requires an idealized geometry and our treatment therefore describes the opposite extreme to that of Scheuplein & Blank. In our case there is a continual exchange of material between that in the channels and that in the dead cells. This exchange ensures that the same route is preferred at all times.

	0	1	2	j	n
normalized distance	0	n^{-1}	$2n^{-1}$	jn^{-1}	1
normalized concentration	u_{-o} u_o	u_{-1} u_1	u_{-2} u_2	u_{-j} u_j	u_{-n} 0
concentration gradient	u'_o	u'_1	u'_2	u'_j	u'_n
Interfacial Transfer	κ κ	κ κ	κ κ	κ κ	κ

Scheme 2

APPENDIX

In this appendix we consider diffusion through the dead cells of the stratum corneum with the presence of interfacial barriers. The model and notation are shown in Scheme 2.

The definitions of μ, χ, κ and τ are the same as above. The flux, F′, is given by

$$F' = D_T c_\infty u'/\ell \quad .. \quad .. \quad (29)$$

The differential equation between the barriers is:-

$$\partial u/\partial \tau = \partial^2 u/\partial \chi^2$$

By Laplace transformation we obtain for any gap between the barriers:-

$$\bar{u}'_{j-1} = \bar{u}'_j\, C - \sqrt{s}\, \bar{u}_{-j} S \quad .. \quad .. \quad (30)$$

and

$$\bar{u}_{j-1} = \bar{u}_{-j}\, C - \bar{u}'_j\, S/\sqrt{s} \quad .. \quad .. \quad (31)$$

where $C = \cosh(\sqrt{s}/n)$ and $S = \sinh(\sqrt{s}/n)$

At any barrier

$$\bar{u}'_j = \kappa(\bar{u}_j - \bar{u}_{-j})$$

and elimination of $\bar{u}_j$ gives

$$\bar{u}_{-(j-1)} = \bar{u}_{-j}\,(C + \sqrt{s}S/\kappa) - \bar{u}'_j\,(S/\sqrt{s} + C/\kappa) \quad .. \quad .. \quad (32)$$

Equations (30) and (32) therefore describe the effect of each gap and barrier on $\bar{u}$ and $\bar{u}'$. By repeated application for the n barriers we can in principle obtain two relations between the flux into the stratum granulosum at n, given by u'_n and the boundary conditions, u_{-o} and u'_o on the surface at $\chi = 0$.

The general case is intractable, but, if we assume that $s < \kappa < n$, then the $\sqrt{s}S/\kappa$ term in equation (32) can be neglected. We can also write $C \simeq 1$ and $S \simeq \sqrt{s}/n$. With these approximations repeated application of equations (30) and (32) gives:

$$\bar{u}'_o = \frac{\bar{u}'_n}{2}\left[\left(1+\frac{\sqrt{s''}}{n}\right)^n + \left(1-\frac{\sqrt{s''}}{n}\right)^n\right] - \frac{\bar{u}_{-n}}{2}\,\frac{\sqrt{s''}}{(1+n/\kappa)}\left[\left(1+\frac{\sqrt{s''}}{n}\right)^n - \left(1-\frac{\sqrt{s''}}{n}\right)^n\right] \simeq \bar{u}'_n \cosh\sqrt{s''} - \frac{\bar{u}_{-n}\sqrt{s''}}{(1+n/\kappa)}\sinh\sqrt{s''} \quad .. \quad .. \quad (33)$$

and

$$\bar{u}_* = \frac{\bar{u}_{-n}}{2}\left[\left(1+\frac{\sqrt{s''}}{n}\right)^n + \left(1-\frac{\sqrt{s''}}{n}\right)^n\right] - \frac{\bar{u}'_n}{2}\,\frac{(1+n/\kappa)}{\sqrt{s''}}\left[\left(1+\frac{\sqrt{s''}}{n}\right)^n - \left(1-\frac{\sqrt{s''}}{n}\right)^n\right]$$

$$\simeq \bar{u}_{-n}\cosh\sqrt{s''} - \frac{\bar{u}'(1+n/\kappa)}{\sqrt{s''}}\sinh\sqrt{s''} \quad .. \quad .. \quad .. \quad (34)$$

where $s'' = s(1+n/\kappa)$

We now compare this pair of equations with the pair of equations (30) and (31) when in the latter pair we put $j = n = 1$. We see that the equations have the same form except that s is replaced with s'' and $\bar{u}'j$ with $\bar{u}'j(1 + n/\kappa)$. These two transformations are equivalent to replacing D_T by $D_T/(1 + n/\kappa)$. A change in D changes the relation between the flux and the concentration gradient given in equation (29) and (eqn (1)) it changes the definition of the dimensionless time τ and hence s. When $n = j = 1$ there are no barriers in the middle, and diffusion is the rate limiting process. With the multiple barriers the same relations between the fluxes and $\bar{u}_*$ are obtained except that the effective diffusion coefficient, $\overline{D}$, is given by

$$\frac{1}{\bar{D}} = \frac{1}{D_T} + \frac{n}{\kappa D_T}$$

$$= \frac{1}{D_T} + \frac{n}{k_I \ell}$$

The condition for this simplification is that

$$s < \kappa \text{ or } \tau > \kappa \quad \text{or} \quad t > k_I \ell^3 / D_T^2$$

It is interesting that when $s = \kappa$, $s'' \simeq n > 1$. Hence the diffusion kinetics not only describes the eventual steady state but also the approach to that steady state. If $n \simeq 10$, then, when $s'' \sim 10$ and this treatment breaks down, the hyperbolic terms in equations (33) and (34) are so large that very little material indeed will have penetrated. Thus this treatment covers the whole time period when significant quantities of drug are being accumulated.

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