Percutaneous absorption: in vivo experiments

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The percutaneous absorption of esters of nicotinic acid has been studied in vivo in man. The time for erythema to be produced has been measured both when the ester is applied continuously and in 'pulse' experiments when the ester is removed before the erythema develops. The results show that the erythema is produced long before steady state diffusion across the epidermis is established and the penetration of methyl nicotinate is characterized by $D/l^2 = 2\cdot3 \times 10^{-4}\,s^{-1}$ where D is the diffusion coefficient and l the thickness of the barrier. Results using glycerol water mixtures in the external phase show that the route of penetration for methyl nicotinate is through the interstitial channels and not through the keratinized cells. Data for absorption from various creams and ointments (Barrett et al 1964) show that the route is independent of the nature of the external phase. Steady state data for the absorption of salicylic acid and carbinoxamine through the abdominal skin of guinea-pigs (Arita et al 1970) show that the route of penetration does not change as the experiment proceeds. Data for the absorption of other substances (Michaels et al 1975) also fit the interstitial route.

In this paper we report the results of experiments in which the percutaneous absorption of three different esters of nicotinic acid were studied in vivo. These compounds readily penetrate the skin and after several minutes produce a noticeable erythema. Many workers (e.g. Stoughton et al 1960; Fountain et al 1969; Henschel & Jaminet 1972) have found that for the same conditions the time of onset of erythema is reproducible. The erythema is triggered by the direct action of the esters on the blood vessel walls at the junction between the dermis and the epidermis (Fulton et al 1959). We have conducted two types of experiment. In the first the ester is applied continuously and in the second it is applied for a shorter time and then removed before erythema has developed.

MATERIALS AND METHODS

All chemicals were supplied commercially except for butyl nicotinate which was prepared by esterifying nicotinic acid (Vogel 1951). Solutions of each of the esters were applied to the flexor aspect of the forearm of one subject (JH) using Astra Hewlitt A1 Test patches (Hadgraft et al 1972, 1973). In the first type of experiment (continuous experiment) the time for a pink halo to form round the patch is measured. In the second type of experiment (pulse experiment) the ester is applied for a time t_1 and then the time, t_2, for a distinct pink patch to form is measured. The onset of erythema is so rapid that the difference between the formation of the pink patch and the pink halo is negligible compared with experimental error.

RESULTS

In Table 1 we report the results for 208 continuous experiments on methyl nicotinate where the external solvent was water, 60% (w/v) glycerol–water or glycerol.

In Table 2 we report results for the pulse experiments for the three different esters. In these experiments the esters were dissolved in 40% (w/v) glycerol–water.

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Table 1. Times for the onset of erythema, t_E, for continuous experiments with methyl nicotinate (MeN).

Water [a] [MeN] (mM)	60% (w/v) glycerol/water [b]		Glycerol [c]	
	t_E/min	[MeN] (mM)	[MeN] (mM)	t_E/min
0·73	10·7 ± 0·2	0·88	13·7 ± 0·4	11·2	13·2 ± 0·1
3·65	6·5 ± 0·1	4·4	11·8 ± 0·2	56·2	8·8 ± 0·3
7·3	4·7 ± 0·1	8·8	6·8 ± 0·1	112	5·9 ± 0·1
36·5	4·1 ± 0·1	43·8	4·9 ± 0·1		

(a) Each value of t_E is the mean of 16 separate determinations.
(b) Each value of t_E is the mean of 24 separate determinations.
(c) Each value of t_E is the mean of 12 separate determinations except for the value of 5·9 which was the mean of 24 separate determinations.

Table 2. Results for the time interval t_2 between the removal of the patch and the onset of erythema as t_1, the application time of the patch, is varied.

Ester Concn (mM) t_1/s	Methyl nicotinate 75 t_2/s	Butyl nicotinate 5·3 t_2/s	Hexyl nicotinate 0·92 t_2/s
20	300	—	—
35	276	378	—
60	204	294	—
120	102	192	—
180	54	126	564
300	—	—	306
420	—	—	144
480	—	—	54

DISCUSSION

Experiments with continuous application

We start by considering the results for methyl nicotinate. Previously (Table 1 of Albery & Hadgraft 1979b) we presented seven different analytical expressions for experiments involving continuous application of a drug. The various expressions arise from different combinations of rate limiting processes. In terms of our previous notation all the class II solutions can be tested using the results in Table 1 together with the previous data (Hadgraft et al 1972, 1973) by plotting log([MeN]) against log t_E. This is done in Fig. 1. The points appear to lie on a curve; the line shown from least squares analysis has a gradient of $-4\cdot3$ but the minimum value of the gradient from the class II solutions is a gradient of -2. Hence all these solutions can be rejected. To test the class I solutions we plot in Fig. 2 log([MeN]$t^{m/2}$) where m = 3, 5 or 7 against t^{-1}. The correlation coefficients for the different plots are 0·92, 0·83, 0·55 for m = 3, 5, 7 respectively.
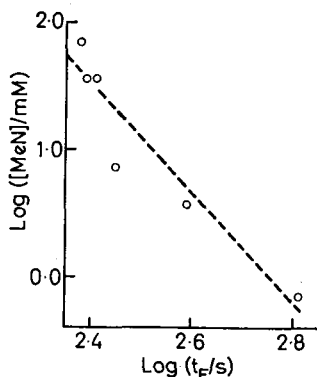

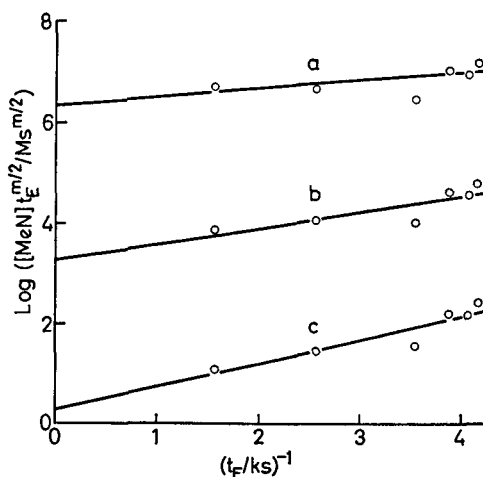FIG. 1. The results in Table 1 plotted according to the equations for the class II approximate solutions.

FIG. 2. The results in Table 1 plotted according to the equations for the class I approximate solutions. a, m = 7; b, m = 5; c,m = 3.

The line with m = 3 gives the best fit to the data. The fact that the class I solutions fit the data better than the class II, means that the amount of methyl nicotinate required to trigger erythema is so small, that enough drug reaches the dermis before a steady state concentration profile is established across the stratum corneum. The best fit with m = 3 means that the rate limiting processes are diffusion and depletion in the external phase and diffusion in the epidermis; interfacial transfer barriers are not rate limiting.

The equation for m = 3 (Albery & Hadgraft 1979b) may be written

$$\log\left(\frac{n_E}{\ell}\right) = \log(c_\infty t_E^{\frac{3}{2}}) + \log\left(\frac{K}{1+K/\sqrt{p}}\right)$$
$$+ \log\left[\frac{8}{\sqrt{\pi}}\left(\frac{D_*}{\ell^2}\right)^{\frac{3}{2}}\right] - \frac{\ell^2}{9.2D_* t_E} \quad .. (1)$$

where n_E/(mol m^{-2}) is the number of moles of drug accumulated per unit area that triggers erythema; l/m is the length of the diffusional path through the stratum corneum; c_∞/(mol m^{-3}) is the bulk concentration of drug in the external phase; $t_{E/s}$ is the time for the onset of erythema measured from the application of the drug; K is the partition coefficient between the stratum corneum (*) and the external phase (∞), K = [ ]$_*$/[ ]∞; D_* (m^2 s^{-1}) is the diffusion coefficient in the stratum corneum; and p = D∞/D$_*$ is the ratio of the diffusion coefficients.

From equation (1) and the gradient for the m = 3 plot in Fig. 1 we obtain:

$$D_*/l^2 = 2\cdot3 \times 10^{-4}\ s^{-1} \quad .. \qquad .. \quad (2)$$

Two routes can be considered for the diffusion of the drug through the stratum corneum. In the first route (transcellular) the drug diffuses through the dead cells. In this route the principal barrier is the low diffusion coefficient in the keratinized cell. We have shown (Albery & Hadgraft 1979b) that the existence of interfacial barriers at the interstitial channels will not change the form of the theoretical description but will lead to an even lower value of the observed diffusion coefficient. The average distance l across the stratum corneum is estimated to be (Katz & Poulsen 1971)

$$l = 1\cdot5 \times 10^{-5}\ m \quad .. \qquad .. \quad (3)$$

Using the value of D_*/l^2 in equation (2) we obtain for the diffusion coefficient for the transcellular route

$$D_T = 5\cdot3 \times 10^{-14}\ m^2\ s^{-1} \quad .. \qquad .. \quad (4)$$

This value is of the same order as those found by Scheuplein & Blank (1971) for a variety of different alcohols.

In the second route (intercellular) the drug diffuses in the interstitial channels around the dead cells. Using the model of Michaels et al (1975) and data for the cellular dimensions (Holbrook & Odland 1974) we estimate that the cross sectional area for diffusion, aA, is much smaller, being about $0\cdot7\%$ (a = 7×10^{-3}) of the total area (A) and the path length, l_c, is much longer with

$$l_c = 3\cdot4 \times 10^{-4}\ m.. \qquad .. \qquad .. \quad (5)$$

On the other hand the diffusion coefficient in the lipid phase may be considerably larger than that in the dead cells. Using the values of D_*/l^2 and l_c in equations (2) and (5) we obtain for the intercellular route

$$D_C = 2\cdot7 \times 10^{-11}\ m^2\ s^{-1} \quad .. \qquad .. \quad (6)$$

This value is also a reasonable value for diffusion in the lipid phase and hence we cannot decide between the routes from the values of D_C and D_T; both are possible values.

Results from similar experiments in which glycerol water mixtures were used in the external phase are plotted according to equation (1) in Fig. 3. The glycerol can only affect the term $K/(1 + K/\sqrt{p})$ which describes the depletion in the external phase. The gradients of the plots should all be the same since
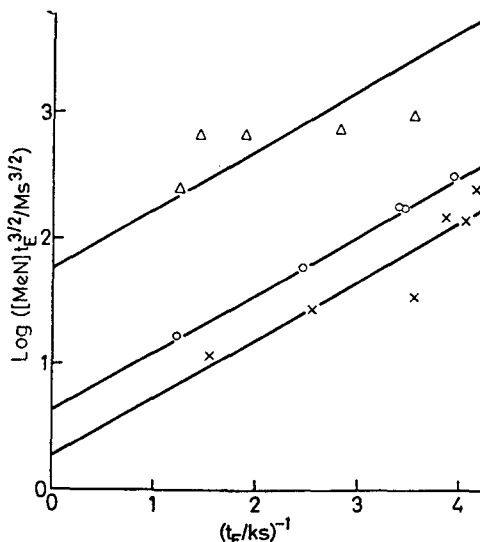

FIG. 3. Results for the percutaneous absorption of methyl nicotinate from water glycerol mixtures plotted according to equation (1). The composition of each mixture (w/v) was: 0%, ×, 60%, ○, 100%, △. The lines all have the same gradient as the aqueous solution.

l^2/D_* is a property of the epidermis and not the external phase. This is found to be so for 0% and 60% glycerol. The experiments with 100% glycerol were more difficult to carry out and the experimentally determined gradient is uncertain; the lines in Fig. 3 have all been drawn with a gradient of $0\cdot47\ ks^{-1}$ found for 0% glycerol. From equation (1) the intercepts I_x of the different plots, where x is the percentage of glycerol, can be written as

$$I_x = B + \log\left(\frac{1}{K} + \frac{1}{\sqrt{p}}\right)_x \quad .. \quad .. \quad .. \quad (7)$$

where

$$B = \log\left[\frac{\sqrt{\pi}}{8}\ \frac{l^2 n_E}{D_*^{\frac{3}{2}}}\right] \quad .. \quad .. \quad .. \quad (8)$$

From equation (7) we can see that the separation of the lines in Fig. 3 can be caused either by the difference in K or by the difference in diffusion coefficients described by $\sqrt{p}$ or possibly by a combination of both effects. The separation of the lines can be written

$$I_x - I_o \approx \log(K_o/K_x) \quad .. (9)$$

or

$$I_x - I_o \approx \tfrac{1}{2}\log(p_o/p_x) \approx \tfrac{1}{2}\log(\eta_x/\eta_o) \quad .. (10)$$

depending on which term is dominant. The partition coefficient ratio is determined by the partition of

Table 3. Values of intercepts from Fig. 3 and test of eqn[x](9) or (10).

	60% Glycerol	100% Glycerol
I_x-I_o[a]	0·36	~1·50
K_x[b]	2·76	1·07
$\log(K_o/K_x)$[c]	0·06	0·49
$\frac{1}{2}\log(\eta_x/\eta_o)$[d]	0·48	1·44

[a] From Intercepts of Fig. (3).
[b] Values of partition coefficients for methyl nicotinate between glycerol water mixtures and isopropyl myristate (Hadgraft et al 1972).
[c] Calculated from K_x and K_o. $K_o = 3\cdot28$.
[d] Calculated from data at $30° C$ (Handbook of Chemistry and Physics 1959).

methyl nicotinate between isopropyl myristate and glycerol water mixtures. Results are reported in Table 3. It can be seen that the separation of the lines in Fig. 4 is more nearly described by equation (10) rather than equation (9). This means we can conclude that

$$K_x > \sqrt{p_x} \qquad .. \qquad .. \qquad (11)$$

where for the transcellular route

$$\sqrt{p_o} \simeq 130 \qquad .. \qquad .. \qquad (12)$$

and for the intercellular route

$$\sqrt{p_o} \simeq 6 \qquad .. \qquad .. \qquad (13)$$

The values in equations (12) and (13) are calculated from the values in equation (4) and (6) and the value for the diffusion coefficient of methyl nicotinate in water at 25°C of $D_\infty = 8\cdot8 \times 10^{-10}$ m² s⁻¹ (Albery et al 1974). The partition coefficient for methyl nicotinate between water and isopropyl myristate (IPM) is close to unity. Considering the transcellular route it seems unlikely that K_x should be greater than 100; this implies that methyl nicotinate is over 100 times more soluble in the keratinized cells than in water. This seems to us to be unlikely. On the other hand considering the intercellular route equations (11) and (13) gives us a more reasonable condition for K_x. A value for K_o of ∼ 6 is similar to the value for K_o of 3 found for the partition of methyl nicotinate between water and IPM (Hadgraft et al 1972). This type of correspondence is what one might expect if IPM is a good model for skin lipids. Hence we conclude that in our experiments methyl nicotinate diffuses by the intercellular route.

We can now simplify eqn (7) to obtain

$$B \simeq I_o + \frac{1}{2}\log p_o$$

Substitution from equations (12) and (13) of the values for p_o for the two different routes gives transcellular route $B \simeq 5\cdot4$; intercellular route $B \simeq 4\cdot0$. Then using the appropriate values of l and D_* in equation (8) we can calculate n_E, the number of moles of drug accumulated per unit area that triggers erythema. For the intercellular route to obtain the accumulated drug per area of epidermis, n_E', we must multiply n_E by 7×10^{-3} the estimated fraction of the area occupied by the channels. The results are as follows: transcellular route $n_E = 6 \times 10^{-9}$ mol cm⁻²; intercellular route $n_E' = 4 \times 10^{-11}$ mol cm⁻². The value for the intercellular route is in reasonable agreement with a value of ∼10^{-11} mol cm⁻² found by the direct injection of methyl nicotinate (Stoughton et al 1960). The value for the transcellular route seems too large to be plausible.

Previous to our work, Barrett et al in 1964 studied the absorption of methyl nicotinate from a series of creams and ointments. Their data for these creams are plotted in Fig. 4 according to equation (1). The data fit a set of parallel lines which have been drawn with a gradient corresponding to our value of l^2/D_*. This shows firstly that the transient penetration of the epidermal barrier described by l^2/D_* is independent of the nature of the external phase. Secondly, as discussed above in Table 3, the dispersion of the lines probably arises from the different viscosities of the external phases rather than from differing partition coefficients.
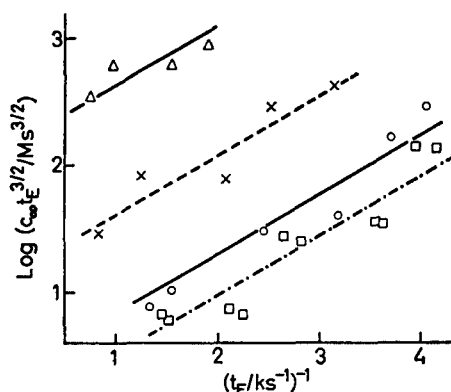

FIG. 4. Results for the percutaneous absorption of methyl nicotinate from various creams and ointments (Barrett et al 1964) plotted according to eqn (1). The gradient of each line is the same as the gradient in Fig. 3. The vehicles are as follows: □, aqueous cream B.P.; ○ oily cream B.P.; × white soft paraffin B.P.; △ macrogol ointment B.P.

Pulse experiments

We now turn to the results of the pulse experiments reported in Table 2. It can be seen that $t_1 \sim t_2$ and hence it is impossible to use the approximate solutions given in Table 3 of Albery & Hadgraft (1979b). Because we cannot obtain analytical expressions for the inverse transforms when $t_1 \sim t_2$, we compare our data with the theoretical model in Laplace space rather than in real time. Instead of proceeding by the route

Model $\rightarrow$ Laplace transform $\rightarrow$ Algebra in s_1 and s_2
$$\downarrow$$

Compare $\leftarrow$ Relation between $\leftarrow$ Invert transform
with t_1 and t_2
Experiment

we follow the alternative route:

Model $\rightarrow$ Laplace transform $\rightarrow$ relation between
                                              s_1 and s_2
                                                 $\downarrow$
                                              Compare
                                                 $\uparrow$
Experiment $\rightarrow$ Empirical relation $\rightarrow$ Laplace
           between t_1 and t_2 transform
                                   to relation between
                                         s_1 and s_2

The data in Table (2) can be fitted as shown in Fig. 5 to an empirical relation of the form:

$$t_1^{-1} = b_1 + b_2 t_2^m \quad .. \quad .. \quad (14)$$

where the values of b_1, b_2 and m are given in Table 4. Equation (14) can be expressed in terms of τ_1 and τ_2, where $\tau = D_* t / l^2$,
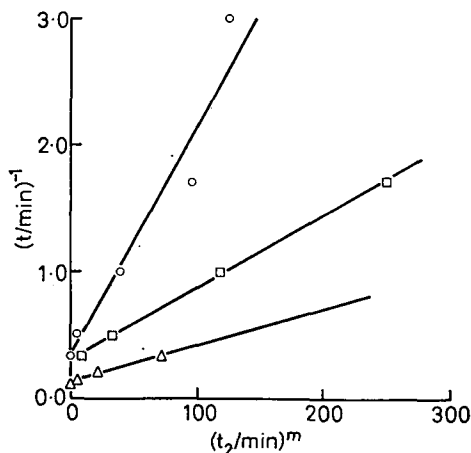

FIG. 5. Results in Table 2 for pulse experiments plotted according to equation (14). The three nicotinate esters are as follows: O, methyl; □, butyl; △, hexyl.

Table 4. Values of b_1, b_2 and m in equation (15) and n_E from Fig. 6.

Compound	$\dfrac{b_1}{\text{min}^{-1}}$	$\dfrac{b_2}{\text{min}^{-(m+1)}}$	m	$\dfrac{n_E}{\text{mol m}^{-2}}$
Methyl nicotinate	0·33	$1·8 \times 10^{-2}$	3·0	5×10^{-5}
Butyl nicotinate	0·30	$5·8 \times 10^{-3}$	3·0	8×10^{-6}
Hexyl nicotinate	0·13	$2·9 \times 10^{-2}$	1·9	8×10^{-6}

$$\frac{l^2}{D_* \tau_1} = b_1 + \frac{b_2 D_*^m \tau_2^m}{l^{2m}} \quad .. \quad .. \quad (15)$$

and then taking the Laplace transform with respect to both τ_1 and τ_2 we obtain the following empirical relation between s_1 and s_2:

$$s_1 = \frac{D_*}{l^2} \left[b_1 + \frac{b_2 D_*^m \, \Gamma(m+1)}{l^{2m} s_2^m} \right] \quad .. \quad .. \quad .. \quad (16)$$

From the discussion of the results in Table 1 it is clear that both τ_1 and τ_2 are smaller than unity which means that s_1 and s_2 are both greater than unity. Hence from equation (18) of Albery & Hadgraft (1979b) we can write

$$\overline{\overline{n}}_E = \frac{n_E}{s_1 s_2} \simeq \frac{2K l c_\infty \, s_1^{-\frac{1}{2}}}{\left(1 + \dfrac{s_1^{\frac{1}{2}}}{\kappa} + \dfrac{K}{\sqrt{p}}\right)(s_2 - s_1)}$$

$$\times \left(\frac{\exp(-s_1^{\frac{1}{2}})}{s_1(1 + s_1^{\frac{1}{2}}/\kappa)} - \frac{\exp(-s_2^{\frac{1}{2}})}{s_2(1 + s_2^{\frac{1}{2}}/\kappa)} \right)$$

$$.. \quad (17)$$

where $\kappa \simeq k_I l / D_*$
and k_I is the interfacial rate constant for transfer of the nicotinate ester from IPM to water (Albery & Hadgraft 1979a).

We now compare equations (16) and (17) by calculating $(n_E/l c_\infty)$ from the theoretical equation (17) for pairs of values of s_1 and s_2. These are given by the empirical equation (16) for ratios of s_1/s_2 comparable to the observed ratios of t_2/t_1. If the data fit the model then the calculated values of $(n_E/l_c \infty)$ should be constant. Fig. 6 shows the results using the values of (D_*/l^2) for the intercellular route in equation (16). For all the systems reasonably constant values are found and the values of n_E for all three esters are of the same order as that found from experiments using continuous application (eqn (1)).
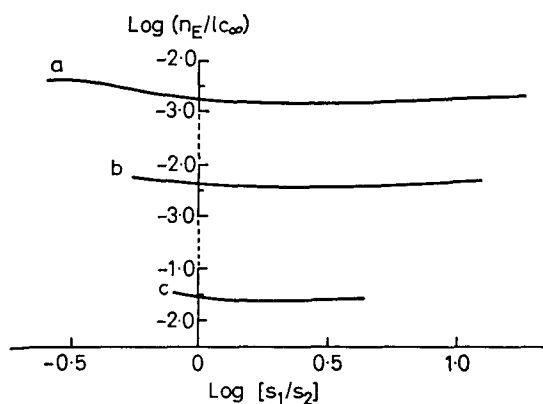
FIG. 6. Plot of equation (17) using equation (16), for the three nicotinate esters. The value of (n_E/lc_∞) should not vary with (s_1/s_2). a, methyl; b, n-butyl; c, n-hexyl.

An equally good fit to the data is found if the values of (D_*/l^2) for the transcellular route are used in equation (16). Thus the experiments do not distinguish between the two different routes. However, it is satisfactory that the same model fits the data for three esters that have different partition and diffusion coefficients. The pulse experiments are less accurate and the theory is more complicated than experiments with continuous application. However the solubility range available for the higher molecular weight esters is limited and this means that c_∞ cannot be easily varied to give the type of plot in Fig. 1. The pulse experiments are all carried out with a nearly saturated solution of the ester; for an insoluble ester this solution gives the best physiological response.

Parallel routes

In our previous paper (Albery & Hadgraft 1979b) we discussed the factors α and β that determined the route taken by the drug. The parameter α compared the diffusion characteristics of the two routes

$$\alpha = \frac{D_C}{l_C^2} \frac{l^2}{D_T}$$

where l_C is the length of the channel.

The parameter β described the number of moles of drug that accumulated in the cells compared to the number in the channels

$$\beta = \frac{l}{K'n\delta}$$

where K' is the partition coefficient; $K' = $ [Drug in

channel]/[Drug in cell]; n is the number of layers of dead cells and δ is the width of a channel.

We showed that if $\beta > \alpha$ then the diffusion at all times is transcellular and if $\alpha > \beta$ then again at all times it is intercellular. From the values of l and l_C in equations (3) and (5) we find

$$\alpha \sim 2 \times 10^{-3} \, D_C/D_T \qquad \cdot\cdot \quad (18)$$

but reasonable values for D_C/D_T would be $\sim 10^3$ and so we may expect $\alpha \sim 1$. Turning to β with the values for l and l_C in equations (3) and (5) and our previous estimate that the interstitial channels occupy 0·7% ($= n\delta/l_C$) of the total area we find $\beta \sim 6/K'$. Thus $\beta < \alpha$ if $K' > 6$. In our opinion it is probable that many substances will be at least ten times more soluble in the lipid phase than in the keratinized cells. Hence we expect to find these systems in the CI region of our previous treatment (Albery & Hadgraft 1979b). Experimentally as discussed above this expectation is confirmed for methyl nicotinate. Some substrates, for instance water soluble substances, may be more soluble in the keratinized cells than in the lipid phase. These substances will then absorb by the transcellular route.

Returning to methyl nicotinate the analysis of the data in Fig. 2 does not require the H function in Table 4 of Albery & Hadgraft (1979b) and this suggests that the system does not belong to cases CII or CIII. Furthermore the analysis of the data to obtain the plausible values for D_T and D_C in equation (4) and (6) did not include any β terms. These arise for solutions TII and CIII of Albery & Hadgraft (1979b), because for solution TII the drug accumulates in the channels while being transported through the cells, and for solution CIII the drug accumulates in the cells while being transported through the channels. Inclusion of values of β far removed from unity would lead to less plausible values of both D_T and D_C. These arguments therefore support our conclusion that methyl nicotinate lies in the CI region and that it diffuses round the cells.

The value of α in equation (18) depends on a ratio of diffusion coefficients; this ratio will not vary greatly for different solutes, and we may expect all solutes to have approximately the same value of α. Hence all solutes, which have $K' > 6$, will follow the same route as methyl nicotinate and absorb by the intercellular route. Exceptions will be firstly substances which have $K' < 6$ and secondly those substances for instance methanol (Scheuplein & Blank 1971) which actually damage and alter the structure of the epidermal barrier.

Comparison with previous results

Arita et al (1970) studied the in vivo diffusion of salicylic acid and carbinoxamine into the abdominal skin of guinea-pigs. Fig. 7 shows some of their results. For times greater than 1 h a steady state is established and an exponential decrease in the solute concentration in the external phase is observed. Before this time the decrease is faster than the extrapolated log plot. This faster decrease is caused by the transient behaviour before the steady state is established. From equation (11) of Albery & Hadgraft (1979b) we can show that once the steady state is established

$$\ln \frac{(c_\infty)_t}{(c_\infty)} = -\mathcal{L}^{-1} \frac{\ell_c aA/V}{s^2 \tanh(s^{\frac{1}{2}})}$$

$$\simeq -\frac{\ell_c aA}{V}(\tau + \tfrac{1}{3}) \quad .. \quad .. \quad .. (19)$$

where aA is the area of the channels and V is the volume of the applied solution.

The value of t corresponding to $\tau = -1/3$ can be found by extrapolation of the log plot to the point where the left-hand side of equation (19) equals zero. Values of D_*/l^2 are found to be about 3×10^{-5} s^{-1} which is about 6 times less than the value found by us for methyl nicotinate (eqn (2)). This type of variation is found for different human subjects. Scheuplein & Blank have suggested that the more rapid initial uptake of a drug compared to its steady

state absorption may be caused by a shift in the transport route. Initially the drug is absorbed through the follicles and/or sweat glands while in the steady state it is absorbed through the cells. While this shift may be possible, in our previous paper (1979b) we showed that it was unlikely for there to be a similar shift from the intercellular route to the transcellular route. This conclusion is supported by the values of D_*/l^2 being of similar magnitude whether they are measured in the initial few minutes as in our system or after several hours as in the work on the guinea-pigs (Arita et al 1970). We must expect that *for substances which do not alter the epidermal barrier at least 1 h must elapse before a steady state can be established.* Changes in the rate of absorption in this period are *not* evidence for a change in mechanism.

Our model can also be tested against the steady state data of Michaels et al (1975). We write

$$\frac{1}{k} = \frac{Ac_\infty}{J} = \frac{2}{ak_{-I}} + \frac{\ell}{a\gamma K_{mo}D_*} \quad .. \quad .. \quad .. (20)$$

where J is the flux, A is the area, a is the area fraction equalling unity for the transcellular route and 7×10^{-3} for the intercellular route, and the partition function K_{mo} describes the partition of the drug between mineral oil and water.

For the intercellular route we expect γ to be of the order of unity, providing that mineral oil is a good model for the skin lipids. For the transcellular route we expect γ to be approximately equal to K' and, as
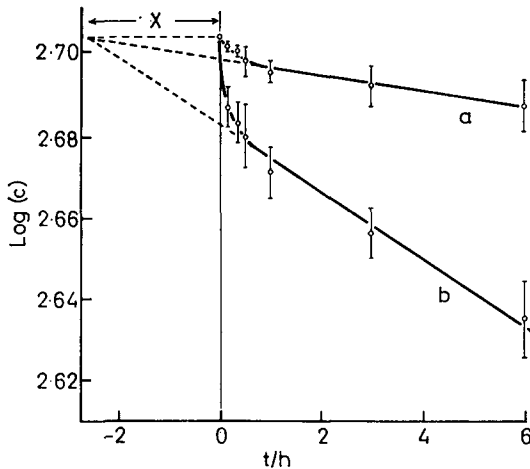

FIG. 7. Plots of data for the absorption of carbinoxamine at two different pH through the abdominal skin of guinea pigs (Arita et al 1970). From equation (11) extrapolation of the steady state part of the curve to the initial concentration gives the value of $-t$ for which $\tau = -1/3$ (x). a, pH 8; b, pH 9.
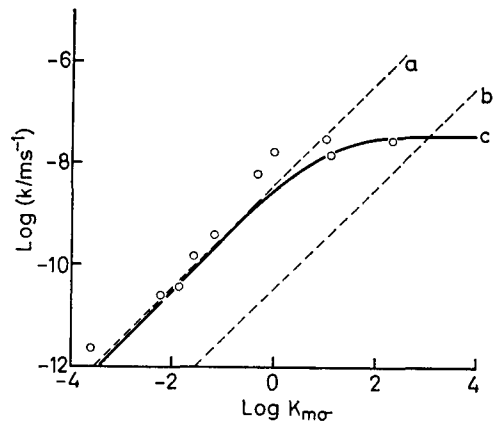

FIG. 8. Plot of data for steady state diffusion (Michaels et al 1975) according to equation (20). For the intercellular route the data can be fitted for $\gamma = 5$. For the transcellular route the data can be fitted for K' = 1 but this value is implausibly high. For comparison the line for K' = 10^{-2} is also plotted. a, K' = 1; b, K' = 10^{-2}; c, $\gamma = 5$.

discussed above, to be less than unity. The interfacial transfer rate constant, k_{-1}, (Albery & Hadgraft 1979a) describes the rate of transfer from the aqueous phase into the epidermal barrier and we put it equal to 10^{-5} m s^{-1}. Fig. 8 shows plots of equation (20) for the two different routes; for the transcellular route two values of K$'$ have been used. The plot for the intercellular route fits the data adequately. The plots for the transcellular route show once again that to fit the data the value of K$'$ has to be too high. The inclusion of the term describing interfacial transfer imposes a limit on k. This limitation is more important for the intercellular route but as yet there are insufficient data to see if this feature of our model is correct. The fact that the points for the different substances all lie close to one line confirms the conclusion, discussed above, that most solutes (with K$' > 6$) will follow the same route.

CONCLUSIONS

Finally we summarize our conclusions.
1. At short times the percutaneous absorption of methyl nicotinate takes place by the intercellular route.
2. The value of D_*/l^2 for this route is independent of the composition of the external phase.
3. There is no change in the route of penetration between the initial application and the establishment of a steady state.
4. The establishment of the steady state takes at least 1 h and during this time changes in the rate of absorption do not indicate a change in mechanism.
5. All solutes, which are more soluble in the lipid phase than in the keratinized cells (K$' > 6$), and which do not alter the epidermis, are likely to follow the same intercellular route as methyl nicotinate.

6. Interfacial transfer barriers are unlikely to be rate limiting unless the solute is very soluble in the lipid phase.

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