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Research Article

Physicochemical Aspects of Percutaneous Penetration and Its Enhancement

Richard H. Guy[1] and Jonathan Hadgraft[2,3]

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The classic diffusion model-based interpretation of percutaneous absorption is compared to a simple kinetic analysis. The physicochemical significance and the major deductions of the two approaches are shown to be in general agreement. In particular, the effect of penetrant oil/water partition coefficient on transdermal flux is consistently predicted by the two models. Diffusional and kinetic assessments of skin penetration enhancement are then shown to reveal similar dependencies upon penetrant physical chemistry. It is demonstrated that the requirements for successful promotion of a lipophilic drug's transdermal flux are quite different from those necessary for a hydrophilic penetrant. Finally, in light of published transport data and our increased comprehension of the stratum corneum barrier function, the evidence for (and significance of) different absorption paths across the stratum corneum is considered. In addition, the impact of penetrant "size" on transport is addressed. It is argued that currently held beliefs concerning (i) a putative "polar" route through the stratum corneum and (ii) the dependence of flux on molecular weight warrant considerable further attention before their unequivocal acceptance is appropriate.

KEY WORDS: percutaneous absorption; skin penetration; transport kinetics; permeation, skin enhancement, skin absorption.

INTRODUCTION

The absorption of chemicals across the skin has attracted considerable interest in the last decade. The advent of transdermal drug delivery, in particular, has led to the reconsideration of many aspects of the percutaneous penetration process. Most notably, the mechanism by which molecules penetrate the dermal barrier and the dependence of absorption kinetics and extent upon the physicochemical properties of the permeant have required particular attention. These important issues are now more amenable to discussion because of our improved understanding of the structure of the stratum corneum (the outermost layer of skin, primarily responsible for its barrier function). Further, a larger data base containing information on the absorption of a diverse range of chemicals is available to facilitate the physicochemical assessment and prediction of skin penetration.

In this paper, following a brief review of simple Fickian transport as it pertains to the skin, the relationship between permeation and penetrant physicochemical properties is examined. The effects of partitioning properties, molecular size, and diffusion pathways on the rate of absorption and on the location of the rate-determining step are illustrated. The results are also viewed in the context of approaches to enhance or promote chemical penetration across the skin. Overall, therefore, our aim is to establish a conceptual framework for the prospective assessment and optimization of transdermal transport.

INTERPRETATION OF TRANSPORT USING FICK'S LAWS OF DIFFUSION

In the simplest sense, the skin can be considered as a bilaminate membrane consisting of adjacent lipoidal and aqueous layers (see Fig. 1). Transport through this structure, assuming that the permeant exists at unit activity on the stratum corneum surface, is governed, therefore, by two diffusion coefficients (D_s, D_v), two associated diffusion path lengths (l_s, l_v), and a partition coefficient (K) of the penetrant between stratum corneum and viable tissue. Typically, skin permeation is characterized by the measurement of two experimentally determined parameters: the lag time (T) and the permeability coefficient (K_p) (1). The lag time is a descriptor of the non-steady-state portion of the transport process, while K_p represents permeation at steady state. Mathematically, expressions for T and K_p are derived (2), respectively, from Fick's second and first laws of diffusion, such that

$$T = \{R_s \cdot l_s(R_s/6K + R_v/2) + R_v \cdot l_v(R_s/2K + R_v/6)\}/[R_s/K + R_v] \quad (1)$$

where $R_s = l_s/D_s$ and $R_v = l_v/D_v$, and

$$K_p = D_v \cdot D_s/[K \cdot l_v \cdot D_s + l_s \cdot D_v]$$

[1] Departments of Pharmacy and Pharmaceutical Chemistry, University of California, San Francisco, San Francisco, California 94143.
[2] The Welsh School of Pharmacy, University of Wales, Cardiff, Cardiff, CF1 3XF Wales.
[3] To whom correspondence should be addressed.

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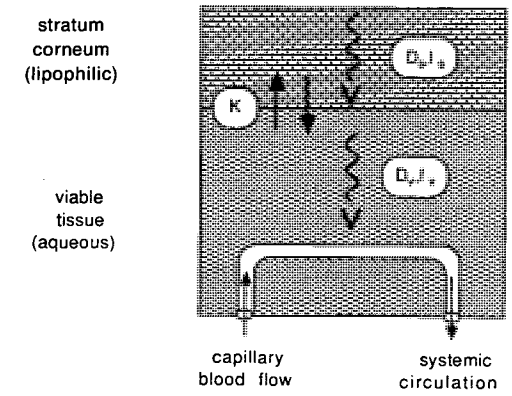

Fig. 1. Schematic representation of skin as a bilaminate membrane. Diffusion coefficients and diffusion path lengths through the adjacent layers are indicated; K is the penetrant's effective partition coefficient between the lipophilic stratum corneum and the more aqueous in nature viable tissue.

$$= (K \cdot R_v + R_s)^{-1} \quad (2)$$

These equations can be used to examine the influence of penetrant physicochemical properties on percutaneous absorption. In Fig. 2, T is plotted as a function of D_s and K. The calculations used fixed values for l_s, l_v, and D_v of 350 μm, 150 μm, and 10^{-7} cm²/sec, respectively. The value of l_s reflects the now generally accepted fact that molecules cross the stratum corneum by a tortuous, intercellular lipid pathway (3). The value for l_v is typical of the distance from the base of the stratum corneum to the upper dermal capillaries (4), and D_v is characteristic of diffusion through an aqueous protein gel (to which the viable tissue is often compared) (5). The ranges of D_s and K considered are 10^{-10}–10^{-7} cm²/sec and 0.01–100, respectively. It can be seen that T is insensitive to K but does depend on D_s. This can be demonstrated by considering approximations of Eq. (1) at small and large values of K:

small K, $l_s/D_sK \gg l_v/D_v$,

$$T = R_s \cdot l_s/6 + R_v \cdot l_v/2 \quad (3)$$

large K, $l_s/D_sK \ll l_v/D_v$

$$T = R_s \cdot l_s/2 + R_v \cdot l_v/6 \quad (4)$$

The insensitivity to K indicates that non-steady-state transport is not dependent upon an equilibrium parameter. It is the rate of diffusion, as determined by D_s, and D_v, which controls T, i.e., kinetic rather than thermodynamic control. The lag time is affected by the relative magnitude of D_s compared to D_v.

The dependence of the permeability coefficient on D_s and K is shown in Fig. 3. We observe that for slow diffusion across the stratum corneum, approximation of Eq. (2) ($K \cdot l_v \cdot D_s < l_s \cdot D_v$) yields

$$K_p = D_s/l_s \quad (5)$$

whereas for fast D_s ($K \cdot l_v \cdot D_s > l_s \cdot D_v$),

$$K_p = D_v/l_v \cdot K \quad (6)$$

Hence, in the former case, skin permeability is controlled by stratum corneum diffusion alone and the relative stratum corneum–viable tissue partition coefficient has no effect on K_p. In the latter situation, on the other hand, the slow partitioning process can exert influence on the overall transport rate. One may arrive at identical results and conclusions by considering the approximations to Eq. (2) in terms of small and large values of K. As K increases in magnitude, the stratum corneum to viable epidermis transport step becomes less favorable and slower. If the kinetics of this process are such that they become comparable to that of diffusion across the stratum corneum, then the "interfacial transfer" of permeant from horny layer to viable tissue can assume rate control.

KINETIC MODELING OF PERCUTANEOUS ABSORPTION AND PENETRATION ENHANCEMENT

In recent publications, a kinetic model (Fig. 4) for skin transport has been proposed (6,7). The simulation includes rate constants characterizing stratum corneum and viable tissue diffusion (k_1 and k_2, respectively) and a parameter (k_3), which on normalization with k_2 (i.e., k_3/k_2), describes the effective stratum corneum–viable tissue partition coefficient of the permeant. The model uses the penetrant's molecular weight (MW) to calculate k_1 and k_2 and the octanol–water partition coefficient (P) to estimate k_3. In Fig. 5, the maximum flux of permeant as a function of $P(=5K)$ is plotted assuming a constant MW of 250 daltons (Da) and a constant k_4 of 1 hr^{-1}. The relationship between K and P is

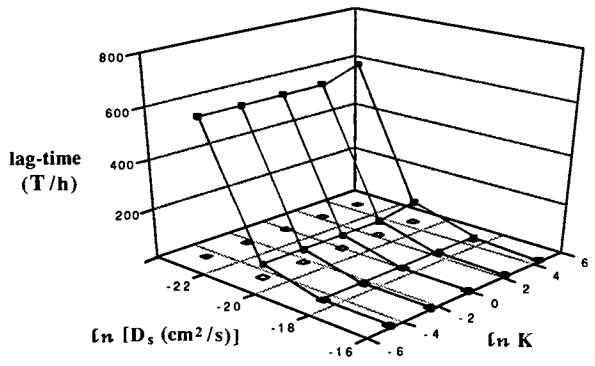

Fig. 2. The lag time (T) plotted as a function of D_s and K according to Eq. (1). Parameter values used in the calculations are given in the text.

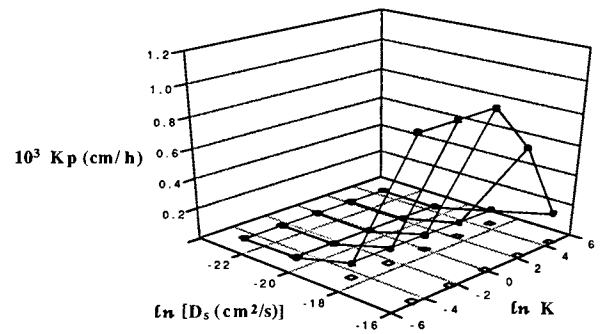

Fig. 3. The permeability coefficient (K_p) plotted as a function of D_s and K according to Eq. (2). Parameter values used in the calculations are given in the text.

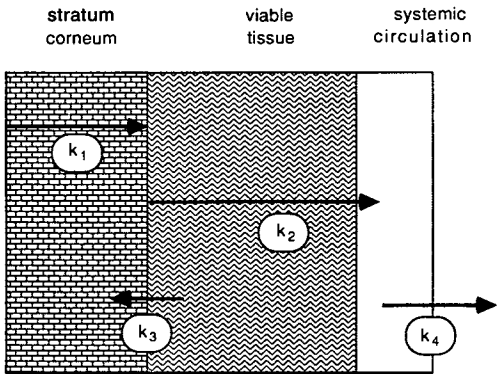

Fig. 4. Kinetic model for percutaneous absorption (6,7). The significance of the rate constants is described in the text.

empirical and has been derived by fitting published transdermal drug delivery data with the model (8–10). We again observe that, for large K, the partitioning of penetrant at the stratum corneum–viable epidermis interface is the transport rate-determining step.

In most practical situations, however, the attainment of unit penetrant activity at the stratum corneum surface is not possible. Typically, skin penetration experiments (particularly those conducted *in vitro*) involve topical delivery of the permeant in, for example, an aqueous vehicle. In these circumstances, the partitioning of penetrant into the skin is a crucial process and there is clear evidence in the literature to show that K_p increases (at least, for permeants of up to moderate lipophilicity) with the stratum corneum–water partition coefficient (Y) (11). It is expected, therefore, for penetrant delivery from aqueous solution, that maximum flux versus K (or P) will be parabolic. This is reasonable since K and Y are related; that is, they both reflect stratum corneum–aqueous phase partitioning. The parabolic relationship can be simulated with the kinetic model by compensating for the partitioning between the aqueous donor phase and the stratum corneum. This is achieved by a premultiplication factor, G:

$$G = Y/(1 + Y) \quad (7)$$

For large Y, $G = 1$, whereas for small Y, the function tends to Y. In Fig. 6, the maximum flux predicted by the model using Eq. (7) is plotted as a function of P; in these calculations, it was assumed that $Y = 5K = P$ and that, once again, MW = 250 Da and $k_4 = 1\ hr^{-1}$. Also shown in Fig. 6 are human *in vivo* data describing the minimum concentration (C) of nicotinic acid derivatives, as a function of P, necessary to elicit erythema following topical administration in water (12). A parabolic relationship is observed. However, the maximum in $1/C$ occurs at a higher log$P$ value than the simulated results for maximum flux described earlier. This is probably a reflection of the fact that the viable epidermal tissue, although aqueous in nature, is not identical to water. Hence, while the model can predict the general shape of the dependence of permeation on partition coefficient, it is not possible, at this time, to determine the location of the parabola on the log$P$ axis. It is likely that the positioning may be dependent upon the physicochemical properties of the group of penetrants considered. In addition, other oil–water partitioning systems may provide a better quantitative correspondence between theory and observation (13,14).

The kinetic model has been used to examine the effect of penetration enhancers on transdermal drug delivery (15). The majority of reported promoters of percutaneous absorption have their greatest effect on relatively hydrophilic (as opposed to lipophilic) nonelectrolytes (16). This can be understood in terms of the proposed mechanism of action of penetration enhancers, such as Azone and oleic acid, which are believed to fluidize the intercellular lipid lamella domains of the stratum corneum (17). These agents are expected to increase the diffusion coefficient of the penetrant in the stratum corneum and, in terms of the kinetic model, therefore, increase k_1. For lipophilic penetrants, percutaneous transport is controlled, at least in part, by the stratum corneum to viable epidermis partitioning step, which is more difficult to affect. In this case, the enhancer must act so as to decrease the k_3 parameter of the kinetic model. It is possible to show, using the simulation, that increasing k_1 for lipophilic penetrants does not significantly improve transdermal delivery (15). To illustrate these points, Figs. 7 and 8 depict transder-

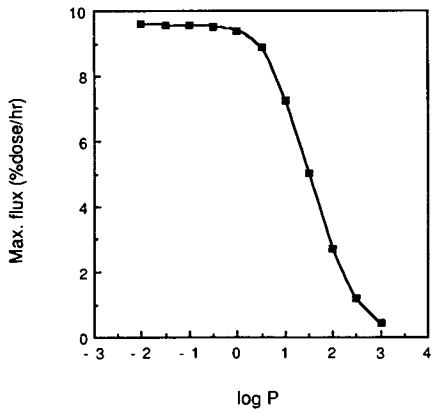

Fig. 5. Maximum penetrant flux, as a function of octanol–water partition coefficient ($P = 5K$), predicted by the kinetic model depicted in Fig. 4. The calculations hold penetrant molecular weight constant at 250 Da and set k_4 to be $1\ hr^{-1}$.

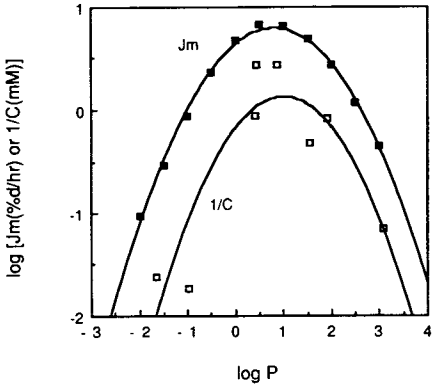

Fig. 6. Maximum penetrant flux [Jm (% dose/hr)], as a function of P, predicted by the kinetic model (Fig. 4) with the correction factor (G) defined in Eq. (7). Also shown are *in vivo* results describing the minimum concentration (C) of nicotinic acid derivatives required to cause local vasodilatation following transdermal delivery from aqueous solution (12).

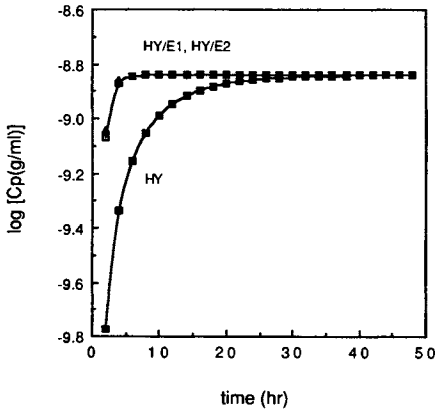

Fig. 7. Simulated plasma concentration versus time profiles following transdermal delivery of a hypothetical hydrophilic compound (HY). The effects of two putative enhancers (E1 and E2; see text) are illustrated. It is assumed that HY has MW = 250 Da, log$P$ = 0, $t_{1/2}$ = 0.5 hr. Further, the calculations are based on the zero-order delivery of HY from a 10-cm^2 device at 20 μg/cm^2/hr (15).

mal delivery simulations for two hypothetical drugs that differ only in the log$P$ values. Figure 7 shows the simulation for a hydrophilic compound (HY) with log$P$ = 0 in the absence and then in the presence of two putative enhancers, E1 and E2: E1 increases k_1 by 10-fold; E2 also increases k_1 to $10k_1$ but, in addition, reduces k_3 by an order of magnitude. Data very similar to those in Fig. 7 are observed if the penetrant lipophilicity is further lowered (e.g., log$P$ = −1). Figure 8 presents parallel simulations, assuming the same theoretical enhancers, for a lipophilic drug (LI) with log$P$ = 3. As expected, E1 has a significant effect on HY but alters the penetration of LI very little. On the other hand, for L1, E2 provides substantial promotion, whereas it is no more effectual than E1 on the penetration of HY. It follows that the achievement of successful penetration enhancement will require appropriate matching of the enhancer and drug. In some circumstances, a combination of agents which can affect both the k_1 and the k_3 processes [e.g., Azone and propylene glycol, respectively (18)] may prove most efficacious.

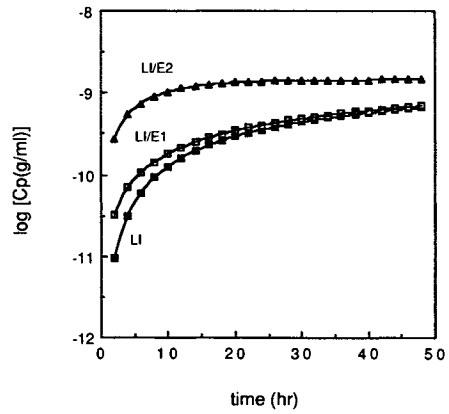

Fig. 8. Simulated plasma concentration versus time profiles following transdermal delivery of a hypothetical lipophilic compound (LI). The effects of two putative enhancers (E1 and E2; see text) are illustrated. It is assumed that LI has MW = 250 Da, log$P$ = 3, and $t_{1/2}$ = 0.5 hr. Again, the calculations are based on the zero-order delivery of HY from a 10-cm^2 device at 20 μg/cm^2/hr (15).

Consideration of the Fick's laws solutions for T and K_p is also appropriate in light of this discussion of penetration enhancement. Figure 2 shows that the value of T is affected only by changes in D_s and is unaltered by the value of K. Therefore, the measurement of a lag time in the presence and absence of a penetration enhancer can reveal its mechanism of action. Further insight can be obtained by considering how K_p alters in conjunction with T. If the lag time shortens in the presence of an enhancer but K_p does not change, then the promoter must have acted on D_s alone. On the other hand, if K_p increases with the enhancer but T does not change, then the promoter is affecting K. Finally, if the enhancer decreases T and increases K_p, then D_s is definitely facilitated but the effect on K is indeterminable. These simplistic deductions require, of course, that the enhancer have no effect on the diffusion path lengths of the penetrant across the stratum corneum and viable tissue (in particular, on l_s). An aggressive enhancer may create new "shortcuts" across the stratum corneum and thereby lower T and increase K_p without necessarily impacting on K and/or D_s.

ROUTES OF STRATUM CORNEUM PENETRATION

The classic work of Scheuplein (19) identified three possible pathways of transport across the stratum corneum:

(a) transcellular,

(b) intercellular, and

(c) appendageal (primarily, follicular).

Although the transcellular route was initially considered most likely, it now appears that, for most compounds, the intercellular route predominates. In man, appendageal transport has not been shown to contribute significantly to the total percutaneous flux. There is a poor correlation between appendageal density and absorption when different anatomic sites are compared (20). The transcellular path requires that transport occurs through the densely packed keratin-filled corneocytes and that multiple transfers between these cells and the lipid-filled intercellular channels take place. A range of experiments, however, has demonstrated that access to the corneocytes is limited or precluded and the evidence points strongly to the intercellular route as the predominant pathway. For example, *in situ* precipitation of butanol during its passage across the stratum corneum shows that the chemical is concentrated in the intercellular lipid domains and is excluded from the interior of the corneocytes (21). This experiment confirmed an indirect deduction of the intercellular route from an analysis of the *in vivo* absorption of nicotinic acid esters (22). Lately, increased knowledge of the fine structure and composition of the intercellular lipid (23), coupled with sensitive biophysical characterization, has firmly established the role of these domains in barrier function (24). Fluidization of the lipid "mortar" can be directly correlated with facilitated stratum corneum transport (25). Interference of the packing of the intercellular lipid lamellae is seen, therefore, as a molecular mechanism by which the diffusion resistance of the stratum corneum can be reduced.

Thus, current evidence strongly supports the notion of the stratum corneum as a lipid-rich barrier. Nevertheless, there have been references to, and justifications of, a parallel

"polar" pathway across the stratum corneum. The existence of such a route is based primarily on observations of the type: "The flux (at constant concentration) of polar molecules is independent of [oil/water] partition coefficient" (26). Graphically, data documenting this thesis are shown in Fig. 9 as a plot of the chemical permeability coefficient through hairless mouse skin versus the corresponding ether/water partition coefficient (27). A linear regression of the points gives the following relationship:

$$\log K_p = -2.76 + 0.45 \log K_{e/w} \quad (8)$$

with a correlation coefficient of 0.89. It follows that 79% of the variation in K_p can be explained in terms of $K_{e/w}$. Given that coefficients of variation in percutaneous absorption data, intra- and interspecimen, are minimally 30% (28), it seems to us that the results in Fig. 9 provide only tenuous evidence for an alternative transport path across stratum corneum. A further ramification of this conclusion is that it calls into question the hypothesis that certain penetration enhancers act on the polar route, as opposed to the lipid pathway (29). While there is no doubt that lipids exist in lamellae within the stratum corneum and that there must be water associated with the head-group regions, current experimental evidence is not sufficiently detailed or specific to allow inference of anything more than the predominance of the lipid nature of the stratum corneum transport pathway. Parenthetically, in this context, one might ask why hydration of the stratum corneum enhances the percutaneous absorption of lipophilic compounds, sometimes to a greater extent than more polar materials (30). Within the intercellular domains, water is expected to be associated with the head-group regions and the spaces between adjacent head groups. It is conceivable that increasing the water concentration here could loosen the packing constraints on the lipids (i.e., increase the surface area occupied per lipid molecule in the bilayer) and hence increase the hydrocarbon chain fluidity. However, this mechanism has not yet been substantiated spectroscopically (e.g., by Fourier transform infrared). Alternatively, an increased level of water in the stratum corneum will cause the stratum corneum–viable epidermis partition coefficient of a lipophilic penetrant to decrease (since the affinity of the drug for the horny layer will be less relative to that in the unhydrated state). It follows that the partitioning of penetrant from stratum corneum to viable tissue will proceed more rapidly when the skin is occluded; if the latter process determines, in part or completely, the observed rate of penetration, then a mechanism exists for the occlusion-enhanced absorption of lipophilic drugs.

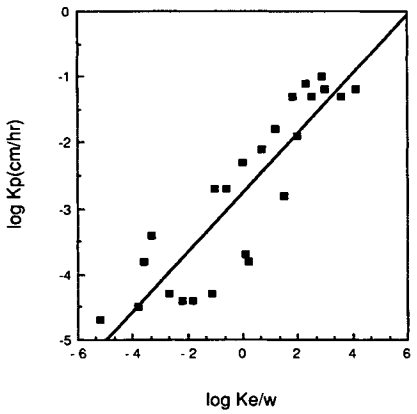

Fig. 9. The permeability coefficients of various chemicals across full-thickness hairless mouse skin plotted as a function of the ether/water partition coefficient (data redrawn from Ref. 27). The compounds represented in the graph are *n*-alkanols (C1 through C8), hydrocortisone and its acetate through heptanoate 21-esters, ara-A and its acetate, pentanoate, and octanoate 5′-esters, urea, thiourea, glycerol, glucose, and neomycin B.

Recent investigations of penetration enhancer effects on the stratum corneum have shown that fluidization of the hydrocarbon regions is a mechanism by which increased transport occurs (17,25). These observations raise questions about the diffusion medium, provided by the stratum corneum, and the likely dependence of D_s on penetrant molecular size. The latter issue has been confused by the fact that most of the quoted values for D_s are underestimates of the true figures. The reason for this is that the path length of diffusion across the stratum corneum has been assumed to be the thickness of the membrane (typically 15 μm) rather the actual, much longer, value [ca. 350 μm (31)] which results from the tortuosity of the intercellular route. Thus, whereas Albery and Hadgraft (22) (who deduced the intercellular path) determined the D_s for methyl nicotinate to be approximately 10^{-8} cm^2/sec, most values quoted in the literature for comparable molecules are two orders of magnitude smaller. In turn, this has led to the supposition that the stratum corneum provides a diffusion environment similar to that of a polymeric membrane (32). As a result, a strong exponential dependency of permeation on penetrant molecular size has been proposed. It has then been shown (32), on the basis of this model, that, for a series of 36 chemicals, 21% of the variation in steady-state flux can be accounted for by the variation in molecular volume (or molecular weight). A less severe dependency invokes the Stokes–Einstein relation and argues that D_s will vary with the cube root of molecular weight (6,7,10). This assumption implies that the diffusion environment of the stratum corneum is much more fluid than that of a polymeric network. If one takes the data in Fig. 9 and performs a least-squares fit of K_p on $K_{e/w}$ and molecular weight (MW), then one obtains the relationship

$$\log K_p = -0.38 + 0.50 \log K_{e/w} - 1.05 \log MW \quad (9)$$

with a correlation coefficient of 0.94. In this case, therefore, the inclusion of MW has allowed a further 9% of the variability in K_p to be assigned. The coefficient premultiplying MW is greater than the figure of 0.33, which would be predicted by the simple Stokes–Einstein relation (33). On the other hand, the dependency is not as great as that expected from free volume theory (34). One might tentatively conclude, therefore, that the diffusion pathway through the stratum corneum resembles neither a liquid nor a polymeric membrane but is somewhat between the two. It also follows that, for the passive diffusion of relatively small molecules (MW <700 Da), on which all observations are based at this time, it is the penetrant's solubility in the stratum corneum which exercises the most significant control over K_p. In most circumstances, it is probably true to say that the MW variable provides a correction which is less than the vari-

ability of the flux measurement. One should note, however, that this situation may change when the penetration of larger molecular species is considered. Additionally, absorption under the influence of (for example) an electric current may also alter the sensitivity of flux to the molecular size variable.

SUMMARY

The overall intent of this paper has been to examine key aspects of the percutaneous absorption process in terms of the underlying physical chemistry. A comparison between the classical "steady-state" interpretation of skin penetration and a simple kinetic analysis has been presented and the coincidence between the conclusions of the models demonstrated. The agreement has been further illustrated with reference to the mechanism of action of penetration enhancers. Finally, pathways of diffusion across the stratum corneum have been addressed and the effect of molecular weight on percutaneous absorption considered. We suggest that certain strongly held beliefs with respect to the existence of a "polar" route, and with respect to the sensitivity of flux to MW, require closer scrutiny and testing.

ACKNOWLEDGMENTS

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