Percutaneous Absorption: A New Physicochemical Predictive Model for Maximum Human *In Vivo* Penetration Rates

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Abstract □ A diffusion model for stratum corneum-limited percutaneous absorption based on the interaction of the diffusate with the stratum corneum was derived. Two types of interactions were proposed, ion-dipole and lipid-lipid, based on current knowledge of the stratum corneum and on irreversible thermodynamic arguments. The resulting flux equations predict a linear dependence of flux on the dipole moment and ln X of the diffusates, where X is the mole fraction solubility. These flux equations were tested on 21 different diffusates whose human percutaneous absorption rates *in vivo* had been previously determined. A solubility method was used to classify the interaction pathway for each diffusate. Correlation of the maximum absorption rate for the lipid and polar pathways give correlation coefficients of 0.946 and 0.998, respectively. It is believed that these studies provide a starting point for the ultimate goal of percutaneous absorption research: to be able to bypass *in vivo* and *in vitro* studies and to predict absorption solely on the basis of the physicochemical properties of the diffusates.

Keyphrases □ Absorption, percutaneous—maximum *in vivo* penetration rates, humans, physicochemical predictive model □ Penetration rates—maximum, *in vivo* percutaneous absorption in humans, physicochemical predictive model □ Diffusion model—physicochemical, predictive, stratum corneum-limited percutaneous absorption, maximum *in vivo* penetration rates in humans

The ultimate goal of percutaneous penetration research is to predict the permeability of structurally unrelated compounds from physical properties, thereby eliminating the need for studies in humans or animals (1). Stoughton *et al.* (2) examined a series of nicotinic acid esters and correlated absorption with the oil-water partition coefficient of the molecules. Similar studies were carried out by Katz and Shaikh (3), Durrheim *et al.* (4), and Roberts *et al.* (5) for a series of corticosteroids, alcohols, and phenols, respectively. Lien and Tong (6) attempted to use multiple regression analysis to correlate absorption with steric factors, molar refraction, Taft's polar substituent constant, and molecular weight. In all of these studies, the correlation had to be limited to a series of closely related compounds. The goal of this study is to develop a model that can be used to predict human percutaneous absorption of any molecule from only its physicochemical properties.

THEORETICAL

Diffusion - In 1855, Fick (7) formulated a set of diffusion equations by direct analogy with the equations of heat conduction, which have come to be known as Fick's First and Second Laws, respectively:

$$J = -D \text{ grad } C \qquad \text{(Eq. 1)}$$

$$\partial C/\partial t = D \text{ div grad } C \qquad \text{(Eq. 2)}$$

where J is the flux in mol/cm^2/s, D is the diffusion coefficient in cm^2/s, and C is the molar concentration of the diffusate. Equations 1 and 2 only describe ideal diffusion. In most real systems, the driving force for diffusion is the gradient of the chemical potential, μ, and not the gradient of the concentration. Thus, the most general forms of the diffusion equations are (8):

$$J = -(C \cdot u/N) \text{ grad } \mu \qquad \text{(Eq. 3)}$$

$$\partial C/\partial t = \text{div } [(C \cdot u/N) \text{ grad } \mu] \qquad \text{(Eq. 4)}$$

where u is the mobility and N is Avogadro's number. Because Eqs. 2 and 4 are not invariant with respect to time inversion, one characteristic of diffusion so described is that it is an irreversible process in which chemical equilibrium is approached in such a way that free energy is minimized and entropy is maximized. Classical thermodynamics deals mainly with closed systems at equilibrium; irreversible thermodynamics copes with open systems that are not at equilibrium.

Irreversible Thermodynamics - This discipline is almost exclusively concerned with the analysis of entropy production, entropy flow, and the possible coupling of entropy production between different processes. In Fig. 1, a model irreversible system applied to percutaneous absorption is shown. System I is composed of the stratum corneum, which is generally considered the rate-limiting skin barrier for passive diffusion. System II contains system I and the applied drug, the rest of the organism, and its excretory products. In this model, system I is *open* to exchange mass with system II. The global system containing I and II is isolated.

For a continuous open system, such as system I, in which the only change in entropy is due to exchange of matter by diffusion, entropy is a function of the spatial coordinates. If s denotes entropy per unit volume for system I, then (9):

$$\partial s/\partial t = -\text{div } \Phi + \sigma \qquad \text{(Eq. 5)}$$

where Φ is the flow of entropy due to the interactions of system I with system II and σ is the entropy production per unit volume and time due to changes within system I. One of the fundamental postulates of irreversible thermodynamics is that:

$$\sigma > 0 \qquad \text{(Eq. 6)}$$

for irreversible processes like diffusion.

For a multicomponent system of γ elements with no temperature gradients, σ is given by (9):

$$\sigma = \sum_{\gamma} \sum_{i} \frac{1}{T}\left[F^i - T\frac{\partial \mu/T}{\partial x^i}\right] \rho_\gamma u_\gamma{}^i + \frac{A \cdot v}{T} \qquad \text{(Eq. 7)}$$

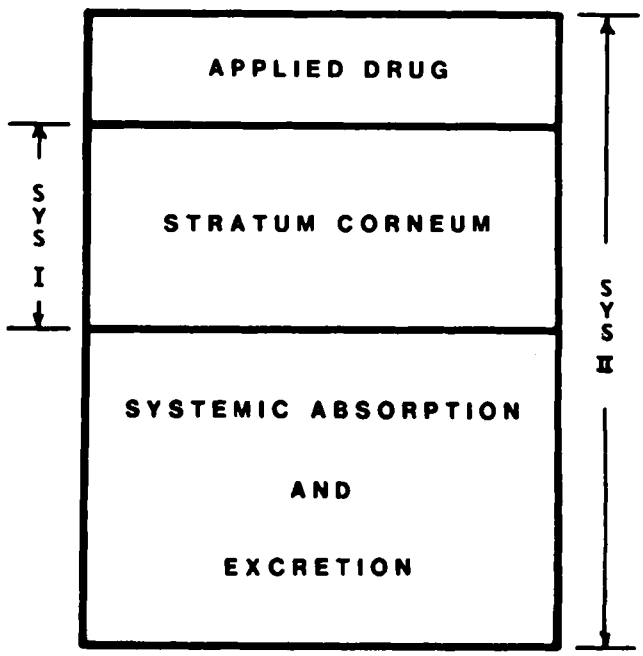

Figure 1—*A model thermodynamic system for percutaneous absorption.*

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where F is the force/mass acting on the component γ; μ is the free energy/mass for the component γ; ρ_γ is the density of component γ; u_γ is the diffusion velocity of component γ; A is the affinity of chemical reaction; v is the rate of chemical reaction/unit volume; and i is the index for spacial coordinates. If consideration is limited to a two-component system in which a diffusing chemical ($\gamma = 2$) moves in the x direction through a stratum corneum ($\gamma = 1$) stationary with respect to the coordinate system, then σ becomes:

$$\sigma = (F_2 - \text{grad } \mu_2)\frac{\rho_2\Delta_2}{T} + \frac{A \cdot v}{T} \qquad \text{(Eq. 8)}$$

where Δ_2 is the diffusion velocity with respect to the velocity of the center of gravity. The first term represents the diffusion contribution to σ, the second, the chemical reaction.

When:

$$A \cdot v < 0, \textit{ i.e.}, \text{ an endothermic reaction} \qquad \text{(Eq. 9)}$$

$$A \cdot v > 0, \textit{ i.e.}, \text{ an exothermic reaction} \qquad \text{(Eq. 10)}$$

where A is the affinity of the reaction (9) and v is the rate of the reaction per unit volume. The chemical potential, μ_2, can be written as:

$$\mu_2 = \mu_2^\circ + RT \cdot ln\ \gamma_2^\circ C_2 \qquad \text{(Eq. 11)}$$

$$\mu_2 = RT \cdot \ln \gamma_2 C_2 \qquad \text{(Eq. 12)}$$

where:

$$RT \cdot \ln \gamma_2 = \mu_2^\circ + RT \cdot \ln \gamma_2^\circ \qquad \text{(Eq. 13)}$$

Using Eq. 12, we can rewrite Eq. 8 as:

$$\sigma = \sigma_d + \sigma_f + \sigma_i + \sigma_x \qquad \text{(Eq. 14)}$$

where:

$$\sigma_d = -(\rho_2\Delta_2/T)RT \text{ grad ln } C_2 \qquad \text{(Eq. 15)}$$

$$\sigma_f = (\rho_2\Delta_2 F_2)/T \qquad \text{(Eq. 16)}$$

$$\sigma_i = -(\rho_2\Delta_2/T)RT \text{ grad ln } \gamma_2 \qquad \text{(Eq. 17)}$$

$$\sigma_x = A \cdot v/T \qquad \text{(Eq. 18)}$$

Equation 14 expresses the fact that the local entropy production rate within system I can be attributed to at least four additive factors. The first factor is due to ideal diffusion as described by Fick's Law, while the third factor accounts for the interaction of the diffusate within the stratum corneum. These terms will be the subject of further discussion in the next section.

With regard to the σ_f and the σ_x terms, it is possible that under some circumstances they might be important in understanding *in vivo* percutaneous absorption. Since there is a sizable electric potential across the stratum corneum of ~−30 mV (10), certain highly polar diffusates might be affected by this force field; σ_f is the predicted manifestation of this effect. Such an effect would not be expected *in vitro* since the skin potential disappears when the animal dies. At this time, it is not clear how large or significant this effect might be. However, it was noted by Anjo *et al.* (11) that while the correlation between *in vivo* and *in vitro* penetration is good, any individual component may deviate significantly. With regard to σ_x, if a substance reacts within the stratum corneum, σ_x will be altered. There are many enzymes in the stratum corneum which might facilitate this process. This would affect σ_i and σ_d since the character of the diffusing substance would be changed.

The total entropy production rate, σ, must be positive in every macroscopic region of system I. This local formulation of the second law is the fundamental postulate of irreversible thermodynamics. This does not mean, however, that each individual term in Eq. 14 must be positive. Since the concentration gradient for passive diffusion is always negative, σ_d must always be positive. The other two terms that are of most interest are σ_i and σ_x. For σ_i, the gradient of the activity coefficient could be positive or negative; the same is true for σ_x. Therefore, the type of gradient and the kind of chemical reaction can influence whether these terms increase or decrease the total entropy production rate.

Physicochemical Predictive Model—Equation 1 has been used to confirm the passive diffusion properties of the stratum corneum (12). It implies, however, that the activity coefficient of the diffusate in the stratum corneum is unity. This is not likely. Higuchi (13) has written Eq. 1 in a form equivalent to:

$$J = -(D/\gamma) \text{ grad } a \qquad \text{(Eq. 19)}$$

where γ and a are the activity coefficient and the activity, respectively, in the stratum corneum. Although Eq. 18 formally appears more correct than Eq. 1, it is difficult to experimentally distinguish D from D/γ. This equation also assumes that grad γ is zero, *i.e.*, it is not a function of the space coordinates.

To account for the contribution of activity gradients in our model, Eq. 3 will be used as the description of diffusion in which the driving force is the gradient of the chemical potential, μ. The stationary component (stratum corneum) will be denoted by the subscript 1 in this model; the diffusate, by the subscript 2. Since Eq. 12 can be written as:

$$\mu_2 = RT \cdot \ln C_2 + RT \cdot \ln \gamma_2 \qquad \text{(Eq. 20)}$$

Eq. 3 can be written as:

$$J_2 = J_2^i - J_{21} \qquad \text{(Eq. 21)}$$

where:

$$J_2^i = -(C_2u_2/N)RT \text{ grad ln } C_2 \qquad \text{(Eq. 22)}$$

$$J_{21} = (C_2u_2/N)RT \text{ grad ln } \gamma_2 \qquad \text{(Eq. 23)}$$

and N is Avogadro's number.

Equation 21 is the fundamental equation in our model. It says that the flux of a diffusate through the stratum corneum is dependent on two terms. The first term, J_2^i, is a restatement of Fick's Law for ideal diffusion since Eq. 22 is identical to Eq. 1 where:

$$D = u_2RT/N \qquad \text{(Eq. 24)}$$

The second term, J_{21}, depends on the interaction between the stratum corneum and the diffusing molecules. This interaction is expressed in the γ_2 factor. If biological gradients exist in the stratum corneum with respect to keratin hydration of the fixed amino acid ions and with respect to lipid composition, γ_2 would be expected to be a function of the spacial coordinate in the direction of diffusion, chosen here to be x.

Polar Gradients—Consider first the interaction of the fixed ions of the amino acids in the stratum corneum keratin with *polar* diffusants: ln γ_2 can be expressed as (14):

$$\ln \gamma_2 = (A/RT)(w_{11} + w_{22} - 2w_{21}) \qquad \text{(Eq. 25)}$$

where A is constant, w_{11} and w_{22} are the cohesive energies of the stratum corneum and the diffusate, respectively, and w_{21} is the interaction energy of the stratum corneum and the diffusate.

The simplest interpretation of w_{11} and w_{22} is in terms of the solubility parameters δ_1 and δ_2 (15) where $\delta_1 = (w_{11})^{1/2}$ and $\delta_2 = (w_{22})^{1/2}$. For the lipoidal barrier model, in the absence of a gradient, the closer δ_2 matches δ_1, the faster the diffusate permeates through the membrane (16). The gradient of w_{21} accounts for a deviation from this ideality. The interpretation of δ_1 for the ion–dipole interaction could be made in terms of cross-linkings of keratin by disulfide and ϵ-(γ-glutamyl)lysine bonds (17).

If constant cohesive energies are assumed, then Eq. 23 can be written as:

$$J_{21} = -L_{21} \text{ grad } w_{21} \qquad \text{(Eq. 26)}$$

where $L_{21} = 2C_2u_2A/N$. For the percutaneous absorption, the positive x coordinate direction will be chosen as increasing from the skin surface into the deeper layers of the skin.

Water gradients in fixed-charge systems of proteins have been proposed by Ling (18, 19) as a mechanism for the selective permeability of nonelectrolytes into the cells. Such multilayer gradients can exist when fixed negative charges alternate with positive charges in a checkerboard-like arrangement of the right dimension (19). More recently, Flagg-Newton and Loewenstein (20) have argued that the directional "permselectivity" channels that they found between asymmetric cell junctions of two different cell types could only result from an interaction of the permeating species with the channel. The effects of the interaction of the stratum corneum with a diffusate in terms of irreversible thermodynamics have been discussed. For a continuous system, the total entropy production per unit volume per unit time is given by Eq. 14. The importance of activity gradients can be seen from Eq. 17.

From skin resistance data, a linear hydration gradient of the stratum corneum keratin with respect to depth has been shown to exist, the innermost layer being the most hydrated (21). Water adsorption occurs at the polarized amino acid fixed ions of the polypeptide chain in keratin, which are then surrounded by a maximum of four water molecules (22). A linear increase of the dielectric isotherm up to 8% water suggests that there is a well-defined contribution for each newly added water molecule to the total polarization. For increasing positive values of x, such a reduction of the effective charge of the z_ith ion due to increasing hydration with depth can be expressed as $Z_{ix}e = Z_ie(1 - x/b)$,

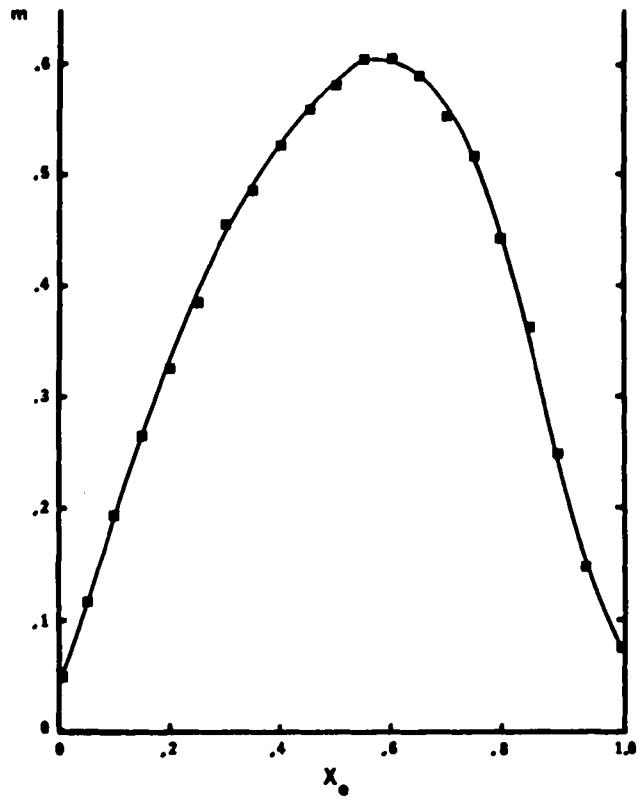

Figure 2—*Determination of the maximum solubility for cholesterol in the* n-*heptane-ethanol cosolvent system. Key:* (m) *molal solubility;* (X_e) *mole fraction ethanol.* m_{max} *occurs at* $X_e = 0.575$.

where b is the thickness of the stratum corneum. Therefore, replacing $Z_i e$ by $Z_{ix} e$ in the ion-dipole interaction energy expression (23) gives:

$$w_{21} = \sum_i (Z_i e \cos\theta\, \mu_2 / r_i^2)(1/D_s - (x/b)/D_s) \qquad \text{(Eq. 27)}$$

for $x \leq b$, where $Z_i e$ is the charge on the ions in the stratum corneum a distance r_i from the diffusate of dipole moment μ_2, D_s is the aqueous dielectric saturation value (24, 25), and b is the asymptotic value of r_i when the dielectric constant equals that of liquid water. Equation 26 can now be written as:

$$J_{21} = \Delta_p \mu_2 \qquad \text{(Eq. 28)}$$

where:

$$\Delta_p = L_{21} \sum_i (Z_i e \cos\theta)/(D_s b \cdot r_i^2) \qquad \text{(Eq. 29)}$$

Using Eq. 28, Eq. 21 can be written for ion-dipole interactions as:

$$J_2 = J_2^i - \Delta_2 \mu_2 \qquad \text{(Eq. 30)}$$

For the polar diffusing species in our study, it will be shown that a plot of J_2 *versus* μ_2 is linear.

Lipid Gradients—Recent freeze-fracture electron microscopic studies by Elias *et al.* (26) have shown that within the stratum corneum there is a gradient of lipid coalescence from the innermost layer to the surface. Odland bodies (membrane-coating granules), which are extruded into the intercellular spaces of the stratum granulosum, aggregate in the lower reaches of the stratum corneum. However, in the middle and upper reaches, all membrane-associated particles are absent. Studies with essential fatty acid-deficient mice (27) have shown that when these particles fail to coalesce into normal neutral lipid-rich sheets in the upper stratum corneum, a defective barrier results. Recent studies in humans stress the importance of these lipids as a major determinant of percutaneous absorption (28). Onken and Moyer made similar observations many years ago (29).

At this time, the exact profile of the lipid gradient is not known. However, it is likely that it will have exponential character for the following reasons. For phospholipid membranes, like the Odland bodies, the bimolecular leaflet is thermodynamically the most stable configuration (30, 31). Such membranes do not coalesce under normal conditions; according to Lucy (32), coalescence will only occur when two adjoining membranes both take on micellar character. In the micellar configuration, coalescence can occur when adjacent micelles mutually interdigitate.

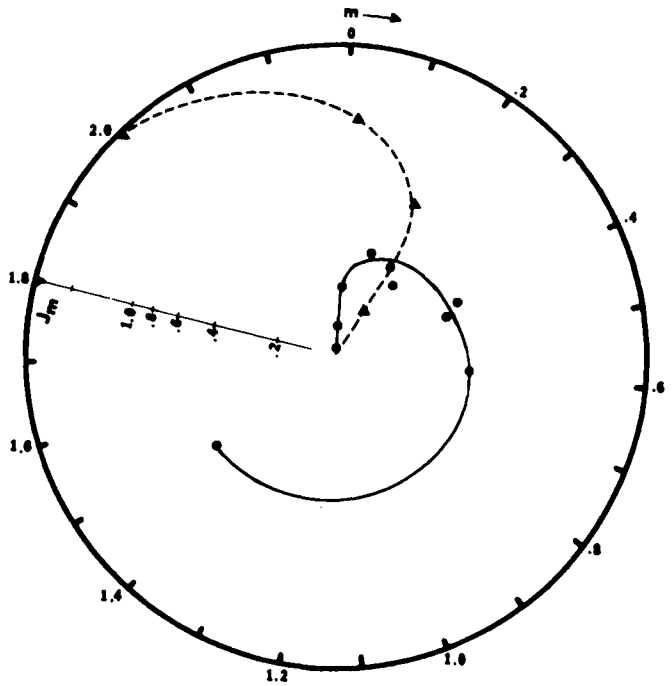

Figure 3—*Absorption patterns for proposed dipole and lipid pathway. Key:* (J_m) *maximum percutaneous absorption rate (%/h) (46);* (m) *molal solubility in the* n-*heptane-ethanol cosolvent,* $X_e = 0.575$; *(---) proposed polar pathway for* ▲ *diffusates; (—) proposed lipid pathway for* ● *diffusates.*

Certain agents cause micellar configurations in membranes, including the biologically significant lysolecithin (33). In the stratum corneum, lysolecithin is released when the phospholipase A enzymes decompose phospholipids (34). This byproduct of enzyme metabolism is an excellent detergent (35), which, because of its wedge shape, easily forms micelles (32). Studies have shown that treatment of whole cells with lysolecithin causes membrane fusion and disintegration (33). The action of phospholipase A on red blood cells (36) and rat liver cells (37) *in vitro* is the same as its action on lipid extracts, except higher concentrations of the enzyme are required for extracts (37). Evidently, surface phospholipids are more available to the enzyme. Whole cells, therefore, have a higher effective enzyme/phospholipid molar ratio. For the release of lysolecithin in the stratum corneum from the Odland bodies, this means that enzyme kinetics is most likely carried out in the linear Michaelis-Menten region. Since the release of lysolecithin would be expected to be the rate-limiting step in initiating coalescence of the Odland bodies, coalescence would be expected to have an exponential time dependence. The gradient would also be expected to have an exponential dependence, since the stratum corneum squames are shed at a uniform rate from the innermost layer to the surface (38, 39).

For diffusates with lipid-like character, interaction with the lipid stratum corneum gradient would be expected to occur through dispersion or van der Waals forces (40). Using Hildebrand's thermodynamic interpretation of such interactions in terms of solubility parameters (40), Khalil and Martin (41) have argued that permeation is optimal when the solubility parameter of the diffusate, δ_2, is as close to the solubility parameter of the lipid barrier, δ_1. Therefore, ln γ_2 in Eq. 25 would be expressed as (14):

$$-\ln \gamma_2 = (A/RT)(\delta_1 - \delta_2)^2 \qquad \text{(Eq. 31)}$$

where δ_1 and δ_2 are the solubility parameters of the barrier and the diffusate, respectively. Therefore:

$$\text{grad} \ln \gamma_2 = -(2A/RT)(\delta_1 - \delta_2)\, \text{grad}\, (\delta_1 - \delta_2) \qquad \text{(Eq. 32)}$$

From our discussion above, if the lipid gradient has the general exponential character:

$$\delta_1 - \delta_2 = E\text{-}\exp\,(g_{np} x) \qquad \text{(Eq. 33)}$$

then:

$$\text{grad} \ln \gamma_2 = 2g_{np}(A/RT)(\delta_1 - \delta_2)^2 \qquad \text{(Eq. 34)}$$

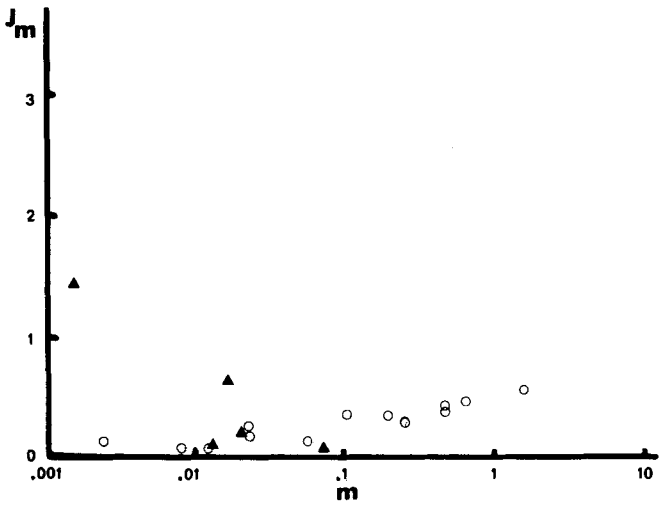

Figure 4—*Log-linear plot of absorption patterns for proposed dipole and lipid pathway. Key: (J_m) maximum percutaneous absorption rate (%/h) (46); (m) molal solubility in the* n*-heptane–ethanol cosolvent, X_e = 0.575; (▲) proposed polar pathway diffusates; (○) proposed lipid pathway diffusates.*

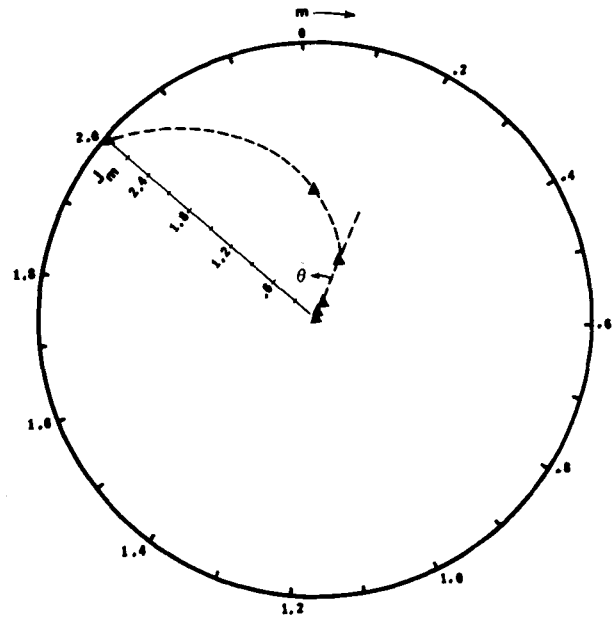

Figure 5—*Absorption pattern for proposed dipole pathway. Key: (J_m) maximum percutaneous absorption rate (%/h) (46); (m) molal solubility in the* n*-heptane–ethanol cosolvent, X_e = 0.575; (θ) positive azimuthal angle in the counterclockwise direction from m = 0.16; (▲) diffusate outward along the spiral: thiourea, urea, nicotinamide,* p*-aminobenzoic acid, caffeine, and benzoic acid.*

But from regular solution theory (13):

$$(A/RT)(\delta_1 - \delta_2)^2 = ln\, X_2^i - \ln X_2 \qquad \text{(Eq. 35)}$$

where X_2^i and X_2 are the ideal and the measured solubilities of the diffusates. Therefore, Eq. 21 can be expressed as:

$$J_2 = J_2^i - \Delta_{np}(\ln X_2^i - \ln X_2) \qquad \text{(Eq. 36)}$$

where $\Delta_{np} = 2C_2u_2RTg_{np}/N_2$ and the ideal solubility, X_2^i, can be determined from (18):

$$\ln X_2^i = (\Delta H_f/RT)[(T_m - T)/T_m] \qquad \text{(Eq. 37)}$$

where ΔH_f is the molar heat of fusion of the diffusate and T_m is the melting point in degrees Kelvin. Equation 36 is the lipid–lipid interactional diffusion equation that is analogous to Eq. 30 for the polar gradient. This equation can also be expressed as:

$$J_2 = J_2^i - \frac{\Delta_{np} \cdot A}{RT}(\delta_1 - \delta_2)^2 \qquad \text{(Eq. 38)}$$

Resolution of Diffusional Pathways—In the stratum corneum, both lipid and protein interactional pathways have been hypothesized by Higuchi (13) and Scheuplein (42). The nonideal portion of Eq. 21 (Eq. 23) has, therefore, been expressed in a form which reflects such pathways. Equation 30 is based on an ion–dipole interaction, Eq. 36, on van der Waals interaction. To experimentally identify those solutes that might interact with the stratum corneum lipids by van der Waals forces during diffusion, a plot of flux *versus* the molal solubility of the diffusate in a cosolvent system in which the polarity could be varied over a wide range was proposed. Since the cholesterol/phospholipid (C/P) molar ratio increases 1700-fold from the basal layer to the stratum corneum (43) due to the near complete catabolism of the phospholipids, cholesterol was hypothesized to be the major lipid which interacts with the diffusing solutes. The proposed composition of the cosolvent, therefore, was chosen to be that in which cholesterol has a maximum solubility. At this composition, $w_{11} = w_{22}$, *i.e.* the difference in solubility parameters of the solvent and the lipid approaches zero (44, 45).

EXPERIMENTAL

Solutes—The following solutes were used as provided by the manufacturer: acetylsalicylic acid[1], androstenedione[1], benzoic acid[1], caffeine[1], corticosterone[1], cortisone[1], dehydroepiandrosterone[1], estradiol[1], hydrocortisone[1], hydrocortisone acetate[1], nicotinamide[1], *p*-aminobenzoic acid[1], progesterone[1], testosterone[1], testosterone acetate[1], testosterone propionate[1], salicylic acid[1], thiourea[1], urea[1], 17-hydroxyprogesterone[2], deoxycorticosterone[2], and cholesterol[3].

Solubility Determination—All solubility determinations were carried out in cosolvent mixtures of absolute ethanol[4] and *n*-heptane[3], which were miscible in all proportions. To obtain a saturated solution, 5 mL of solvent was added to a 7-mL liquid scintillation vial[5] containing an excess amount of solute and a 6-mm glass bead. The bead ensured good mixing of the solute and the solvent when the vials were placed on a linear reciprocating agitator[6]. A temperature of 27°C was maintained during agitation by placing a plastic heating pad[7] underneath the vial holders. Dissolution studies showed that agitation at 180 cpm for 48 h was sufficient to ensure that a saturated solution was formed for the most insoluble solute–solvent combinations: that of caffeine or thiourea in *n*-heptane. These agitation conditions, therefore, were used for all solutes.

After agitation, the vials were centrifuged in a clinical centrifuge[8] at 4000 rpm for 5 min. During this centrifugation, a hair dryer[9] was used to maintain the temperature of the vials >27°C. The vials were then allowed to equilibrate at 25°C in a water bath for 24 h before solubility determinations of the saturated supernatant were carried out gravimetrically in aluminum foil planchets[10]

RESULTS

Diffusional Pathways—The molal solubility of cholesterol in an *n*-heptane–ethanol cosolvent system is shown in Fig. 2. These data show that the maximum solubility occurs at an ethanol mole fraction (X_e) of 0.575. Since cholesterol was chosen as our model stratum corneum interactional lipid, all subsequent solubility determinations were carried out at X_e = 0.575. Such data were used, first, to discriminate the lipid and polar pathways.

In Fig. 3, the molal solubilities of the solutes that were studied are plotted as the azimuthal coordinate in a polar coordinate system. The maximum percutaneous absorption rates, J_m, for these solutes determined by Feldmann and Maibach (1, 46) are plotted as the radial coordinate on a logarithmic scale. Two distinct trends for these data are depicted by the dotted and solid lines. The dotted line describes a curve that spirals out from the origin in the positive azimuthal direction (counterclockwise) from the initial ray, m = 0.19. The solid line, on the other hand, describes a curve that spirals out from the initial ray, m = 0, in the negative azimuthal direction. In the strictest sense, these logarithmic curves are not true spirals. However, it will be shown presently that each curve, plotted with respect to a rectilinear radial coordinate, can

[1] Sigma Chemical Co., St. Louis, Mo.
[2] Research Plus Steroid Laboratory, Bayonne, N.Y.
[3] Fisher Scientific, Fair Lawn, N.J.
[4] Publicker Industries, Linfield, Pa.
[5] Kimble, Toledo, Ohio.
[6] Eberbach, Ann Arbor, Mich.
[7] Walker Co., Middleboro, Mass.
[8] Model CL, IEC, Needham Heights, Mass.
[9] Osler Corp., Milwaukee, Wis.
[10] A. H. Thomas, Philadelphia, Pa.

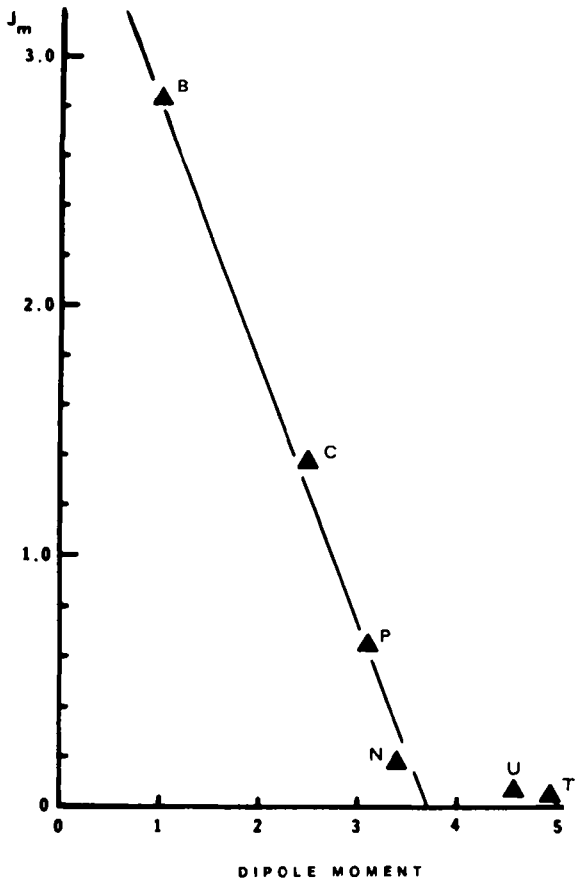

Figure 6—*Regression of dipole moment* versus *absorption rate. Key: (J_m) maximum percutaneous absorption rate (%/h)(46); (B) benzoic acid dipole moment (47); (C) caffeine dipole moment (51); (P)* p*-aminobenzoic acid dipole moment (48); (N) nicotinamide dipole moment (52); (U) urea dipole moment (49); (T) thiourea dipole moment (50).*

be represented by a modified Archimedean spiral[11] and that each spiral is consistent with one of the proposed mechanisms. Figure 4 shows how a similar pathway designation on a log-linear plot would be much more difficult to ascertain for the solid triangles. These points are the same as the triangles on the counterclockwise spiral in Fig. 3.

Polar Mechanism—In Fig. 5, J_m for the diffusates along the dotted line of Fig. 3 are plotted on a rectilinear scale. The diffusates lie on a path described by a modified Archimedean spiral:

$$J_m = J_i + a \cdot \theta \qquad \text{(Eq. 39)}$$

where the initial ray is defined by:

$$J_i = 1.1; \qquad m = 0.16 \qquad \text{(Eq. 40)}$$

θ is the angular molal increment in the positive azimuthal direction from the initial ray, and the slope a is given by:

$$a = 8.3 \qquad \text{(Eq. 41)}$$

This spiral is defined as a modified Archimedean spiral since some of the diffusates lie on the initial ray before θ evolves. Thus, for $\theta = 0$, thiourea, urea, nicotinamide, and *p*-aminobenzoic acid (from the origin outward) lie on the initial ray. For increasing values of θ (counterclockwise direction), the radial component of each diffusing species is located on the spiral by adding a times θ to J_i. Caffeine and then benzoic acid lie on the spiral as θ increases.

Figure 6 shows a plot of J_m *versus* μ_2, the dipole moment of the diffusates (47–52) in Fig. 4. The first four points agree with the linear relationship

[11] Archimedes described in his book *On Spirals* a plane spiral as the locus of points described by the polar coordinate equation $\rho = a \cdot \theta$, where θ = angular (azimuthal) coordinate and ρ = radial coordinate. Such a spiral could be formed, mechanically, in the following way. Imagine a machine that could move a pen along a straight line at a uniform rate. If the pen were placed at the center of a rotating turntable and pulled outward along this line, the curve that would be traced out on the turntable would be an Archimedean spiral. The line would be called the initial line; the center, the origin. The modified Archimedean spiral we defined spirals out from some point along the initial line rather than from the origin.

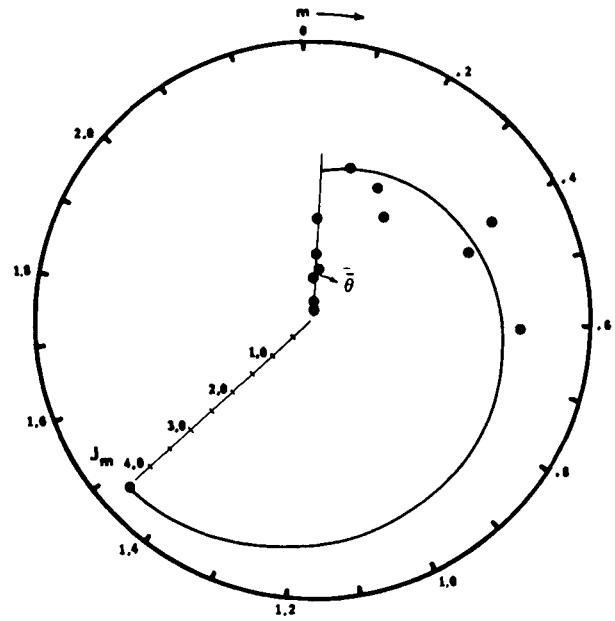

Figure 7—*Absorption pattern for proposed lipid pathway. Key: (J_m) maximum percutaneous absorption rate (%/h) (46); (*m*) molal solubility in the* n*-heptane–ethanol cosolvent. $X_e = 0.575$; ($\bar{\theta}$) negative azimuthal angle from* m *= 0.03; (●) diffusates outward along the spiral: hydrocortisone, cortisone, hydrocortisone acetate, estradiol, corticosterone, 17-hydroxyprogesterone, androstenedione, deoxycorticosterone, progesterone, acetylsalicylic acid, testosterone, dehydroepiandrosterone, salicylic acid.*

predicted by the polar pathway of Eq. 30. The linear regression equation for J_m *versus* μ_2 is:

$$J_m = 4.25 - 1.18 \cdot \mu_2 \qquad \text{(Eq. 42)}$$

with a linear regression coefficient of −0.998. It is also evident from Fig. 6 that there is a limit beyond which further increases in the dipole moment, μ_2, cannot continue to cause a linear reduction in J_m. This, evidently, is the situation with urea and thiourea.

Nonpolar Mechanism—The data along the solid line spiral are plotted in Fig. 7 on a rectilinear radial scale. This modified Archimedean spiral can be described by:

$$J_m = J_i + a \cdot \bar{\theta} \qquad \text{(Eq. 43)}$$

where the initial ray is defined as:

$$J_i = 2.7; \qquad m = 0.3, \qquad \text{(Eq. 44)}$$

$\bar{\theta}$ is the angular molal increment in the negative azimuthal direction from the initial ray, and the slope a is given by:

$$a = 1.22 \qquad \text{(Eq. 45)}$$

Along the initial ray of this spiral, from the origin outward, are hydrocortisone, cortisone, hydrocortisone acetate, estradiol, corticosterone, and 17-hydroxyprogesterone. For increasing values of $\bar{\theta}$ (clockwise direction), androstenedione, deoxycorticosterone, progesterone, acetylsalicylic acid, testosterone, dehydroepiandrosterone, and salicylic acid are found on the spiral. In Fig. 8, J_m *versus* $-\ln X$ is plotted assuming that the nonpolar mechanism of Eq. 36 would describe this spiral, since all of the diffusates are steroids except for salicylic acid. The linear regression equation for this plot is:

$$J_m = 0.73 + (9.3 \times 10^{-2}) \cdot \ln X_2 \qquad \text{(Eq. 46)}$$

with a linear regression coefficient of −0.945.

DISCUSSION

The existence of gradients in the stratum corneum were suspected over 17 years ago. Kligman (53) argued that even though the stratum corneum appears to be a homogeneous structure from its innermost layer to its outer surface, there must be a stratification of the keratinization process within the structure, at least at the chemical level. Believing that biochemical and biophysical events of this magnitude could take place so abruptly, in Kligman's opinion, is tantamount to believing in a biological miracle. It has been only recently, however, that experimental evidence for such gradients has been

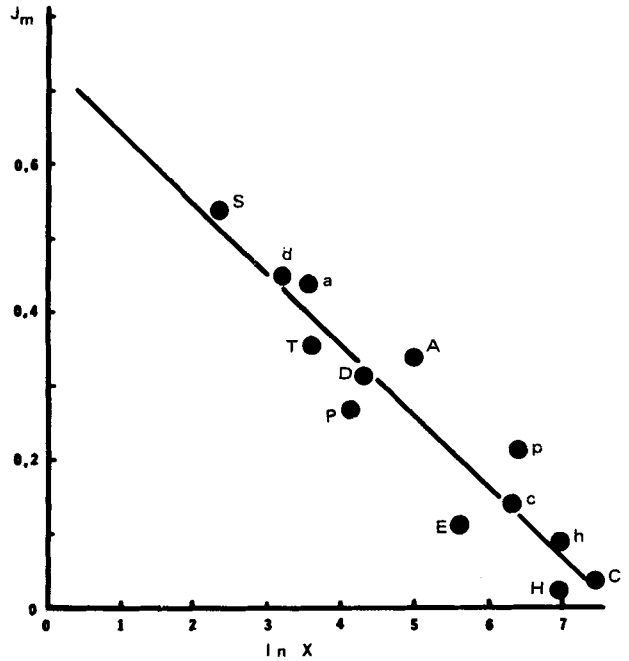

Figure 8—*Regression of ln* X versus *absorption rate. Key: (X) mole fraction solubility; (J_m) maximum absorption rate (%/h.) (46); (S) salicylic acid; (d) dehydroepiandrosterone; (T) testosterone; (a) acetylsalicylic acid; (P) progesterone; (D) deoxycorticosterone; (A) androstenedione; (E) estradiol, (p) 17-hydroxyprogesterone; (c) corticosterone; (h) hydrocortisone acetate; (H) hydrocortisone; (C) cortisone.*

confirmed. Elias *et al.* (26) have demonstrated a lipid gradient of coalescence and Tagami *et al.* (21, 54), a hydration gradient of the stratum corneum keratin. Based on reasonable physical assumptions concerning the mathematical form of these gradients, a physical model predicting the dependence of solute transport through the stratum corneum on the dipole moment, μ_2, and the logarithm of the mole fraction solubility, ln X_2, have been derived.

To test this model, a solubility method, using a polar coordinate plot, has been developed to separate those diffusates that would be most affected by the lipophilicity of the stratum corneum from those that would be more affected by its ionic components. However, it is not clear what the "effective" lipophilicity of the stratum corneum might be. Most likely it is different between different animal species. This may be the reason why human penetration data often differ from animal data, even after corrections are made for the stratum corneum thickness (55).

Classically, the oil–water partition coefficient has been used as a measure of lipophilicity. The relationship of octanol–water partition coefficients to biological activity has proven to be of value in predicting quantitative structure–activity relationships (56). However, application of this approach to percutaneous absorption has not been completely successful, we believe, because lipophilicity differs from tissue to tissue depending on the relative composition of neutral to polar lipids. One reason diffusion in nervous tissue is slower than in liver tissue is because the cholesterol/phospholipid molar ratio of nerve cell plasma membranes is much higher than in liver cells. Mammalian cells appear to control membrane permeability by varying the relative amounts of cholesterol and phospholipids in their membranes (57, 58).

For these reasons, use of 1-octanol which has a solubility parameter of 10.3 and the 1-octanol–water partition coefficient may not accurately represent the lipophilicity of the stratum corneum. In these studies, an *n*-heptane–ethanol cosolvent system that spans a solubility parameter range from 7.5 to 13 was used. Since cholesterol is one of the dominant neutral lipids in the stratum corneum (59), the cosolvent composition (or solubility parameter) at which cholesterol had an optimum was chosen to represent the lipophilicity of the stratum corneum, other lipids such as ceramide not being readily available in sufficient quantities. In this sense, then, these studies should be viewed only as a first attempt to evaluate stratum corneum lipophilicity. Conceptually a distribution function, $X(\delta)$, could be determined for each compound by determining its mole fraction solubility, X, over a range of solvent polarities. Chertkoff and Martin (44) and others have shown that $X(\delta)$ will have a maximum value when δ for the solute equals δ for the cosolvent. Experimental data for these bell-shaped distribution functions could then be fitted by nonlinear regression to a mathematical function so that for each solute $X_j(\delta_i)$ for any δ_i could be generated. For a given δ_i, ln X_j for all of the diffusates in the van der Waal group could then be determined. The linear regression coefficient r_i for the regression over j of ln X *versus* the percutaneous absorption rate for the jth drug, J_j, would then be possible. δ_i could then be varied to optimize r_i. The value of δ, δ_{pa}, which corresponds to the largest value of r_i might then be designated the "effective" lipophilicity for percutaneous absorption. If such studies should come to pass, it is possible that separate δ_{pa} values for humans and animals could be determined, thus providing a quantitative parameter for human–animal correlations.

The penetration data of Feldmann and Maibach (1, 46) was used because these data represent the most complete set of human *in vivo* studies ever attempted using a common methodology and have provided the human *in vivo* comparison for most animal models (60–63). Maximum absorption rates were chosen because they are the only unique characteristics of these absorption curves, since half-lives or absorption constants could not be determined due to the sampling intervals.

A classification based on modified Archimedean spiral pattern formation was used to determine which regression expression should be used. To date, 21 different diffusates have been studied. Nineteen of these solutes correlate with one of the two mechanisms developed in the *Theoretical* section. The permeability of two solutes, testosterone acetate and testosterone propionate, cannot be explained on the basis of either mechanism. Parenthetically, these solutes were not predicted to correlate with either mechanism, *i.e.*, they did not fall on either the polar or nonpolar spirals. On the other hand, it was extremely gratifying that the percutaneous absorption of diffusates of such differing structure could be explained in terms of two physical properties.

Since the net flux in Eq. 21 is a function of the ideal flux and the interaction flux, the good correlation between the net flux and μ_2 or ln X_2 may indicate that the ideal fluxes of the different solutes within the stratum corneum are of the same order of magnitude. This would differ from diffusion in liquids, where the mobility is a function of the reciprocal of the frictional resistance, which is in turn a function of the viscosity of the media and the size of the molecule (64). In the stratum corneum, specific physical interactions may control diffusion.

Finally, this physicochemical model does not attempt to explain percutaneous absorption in terms of different structural components of the epidermis. Michaels *et al.* (65) have described one such model in which the stratum corneum is conceived of as proteinaceous bricks held together by interstitial lipid mortar. For the model developed here, only the properties of the physical components are accounted for, because it is extremely difficult to unambiguously discriminate structural pathways. On the other hand, the parameters that have been chosen are open to future verification. If on further testing, deviations from the predicted model expressions are found, an analysis can be carried out to determine whether the form of the gradient or the polarity of the solvent system that has been chosen to represent the stratum corneum can explain this deviation. In some situations, neither approach may suffice because the stratum corneum may not be rate limiting. In summary, the physicochemical model presented here is only meant to represent the current state of knowledge; it may need modifications in the future based on new evidence. It is hoped, however, that it provides a measurable framework for the future testing of its validity.

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