As mentioned above, with a proper damping of the signals, C_h can also be measured. This is the information needed in making numerical computations of oxygen transfer rates by using Equations (6) and (7).

ACKNOWLEDGMENT

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NOTATION

a = surface area of small particles (microbial cells) per unit volume of particles
A = gas-liquid interface per unit volume of liquid
C = concentration of the transferring solute
C_h = C at $x = h$
C^* = C at $x = 0$
D = solute diffusivity
D_s = D in the surface zone
D_L = D in the liquid bulk
e = enzyme concentration or microbial cell concentration
e_o = e in the surface zone
h = thickness of the surface zone
k_L = liquid side mass transfer coefficient
r = rate of interfacial mass transfer
$\bar{r}$ = time average of r
s = concentration of microbial cells and also Danckwerts surface renewal rate
R = rate of solute uptake by the microbial cells
t = time
x = distance from the interface
w = $w = x - h$

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Drug Permeation Through Human Skin: Theory and in Vitro Experimental Measurement

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The penetration of drugs and other micromolecules through intact human skin can be regarded as a process of dissolution and molecular diffusion through a composite, multilayer membrane, whose principal barrier to transport is localized within the stratum corneum. A mathematical model of the stratum corneum as a two-phase protein-lipid heterogeneous membrane (in which the lipid phase is continuous) correlates the permeability of the membrane to a specific penetrant with the water solubility of the penetrant and with its lipid-protein partition coefficient.

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Experimentally measured permeabilities of human skin to a variety of drugs have been found to conform to this model. The extraordinarily low permeability of skin to most micromolecules appears to arise from the very low diffusivity of such molecules in the intercellular lipid phase.

SCOPE

The skin is one of the most extensive and readily accessible organs of the human body; only a fraction of a millimeter of tissue separates the skin surface from the underlying capillary network. Yet, despite the proximity of the external surface of the skin to the circulating blood, we are superbly protected against damage by micro and macromolecular substances in our hostile environment (as well as against uncontrolled loss of vital biological substances such as water) by virtue of the astonishingly low permeability of skin to such substances.

An understanding of the nature and origin of the barrier properties of skin, and of the physicochemical characteristics of substances which determine their ability to permeate the skin and enter the circulation, would have great value to toxicologists and environmentalists concerned with the hazards of topical exposure to air and water pollutants and industrial chemicals, and to physicians and pharmacologists interested in the use of skin as a route of entry of drugs for the treatment of systemic or dermatologic diseases.

In this paper, we have reexamined and attempted to reconcile the barrier characteristics of skin in terms not only of its composition and microstructure, but also of present understanding of membrane permeability and permselectivity. The resulting model of the skin permeation process appears to be reasonable and useful for explaining and predicting the rates of penetration of various substances through intact skin.

CONCLUSIONS AND SIGNIFICANCE

The principal resistance to penetration of drugs and other small molecules through intact human skin resides within the *stratum corneum*, or "horny layer," which is comprised of dead, keratinized, partially desiccated epidermal cells. A simplistic two-phase model of the stratum corneum, which describes the tissue as a dispersion of hydrophilic protein in a continuous lipid matrix through which penetrant molecules migrate by dissolution and Fickian diffusion, predicts a dependence of the permeability of the membrane upon water solubility of the drug and upon its lipid-protein partition coefficient. The actual permeability of excised human skin to a number of drugs (as determined by controlled *in vitro* transport measurements) is quite satisfactorily correlated with the water solubility and mineral oil/water partition coefficient of the drug, as the model predicts. When the permeating substance exists in aqueous solution as both a nonionic and ionic species, the nonionic (more lipophilic) form is decidedly the more skin permeable; hence, for such compounds, skin permeability is strongly pH dependent.

Drug diffusivities in the lipid phase of stratum corneum are two to four orders of magnitude smaller than the values expected for an isotropic oil phase, an observation which accounts for the anomalously low permeability of skin to most micromolecular penetrants. Such low diffusivities are postulated to be a consequence of a high degree of molecular order on the intracellular lipid.

The results of this work provide a rationale for quantitative prediction of the rate of absorption of drugs and other low molecular weight compounds through skin from a knowledge of readily determined physicochemical properties of those compounds. Of particular medical significance is the conclusion that drugs of high water and oil solubility can be expected to be quite skin permeable and, if sufficiently potent, can be administered at therapeutically effective rates through a relatively small skin area.

ANATOMY AND MORPHOLOGY OF SKIN AND ITS GENERAL PERMEATION PROPERTIES

The skin of humans, as well as that of most land dwelling mammals (shown cross sectionally in Figure 1), is anatomically characterized as a bilayer membrane laminate, the outer layer of which (the epidermis) is about 100 μm thick and unvascularized, while the inner layer (the dermis) is several hundreds of microns in thickness and interlaced with capillaries (Hunter, 1973). As a general rule, the capillary loops within the dermis extend to within 100 μm or so of the dermis/epidermis junction, so that the thickness of the membrane which lies between the external skin surface and the capillary bed is of the order of 200 to 400 μm. This membrane may be regarded as an effective barrier to the penetration into the circulation of substances deposited on the skin surface.

Originating deep within the dermis and terminating at the external surface of the epidermis are two specialized organs: the hair follicles and sweat ducts. These organs ostensibly provide channels for passage of substances between the external environment and the capillary bed; however, the fraction of the total skin surface which is occupied by these structures is very small (of the order of 1% in total), and their contribution to the total permeability of skin to most substances can be shown to be negligible.

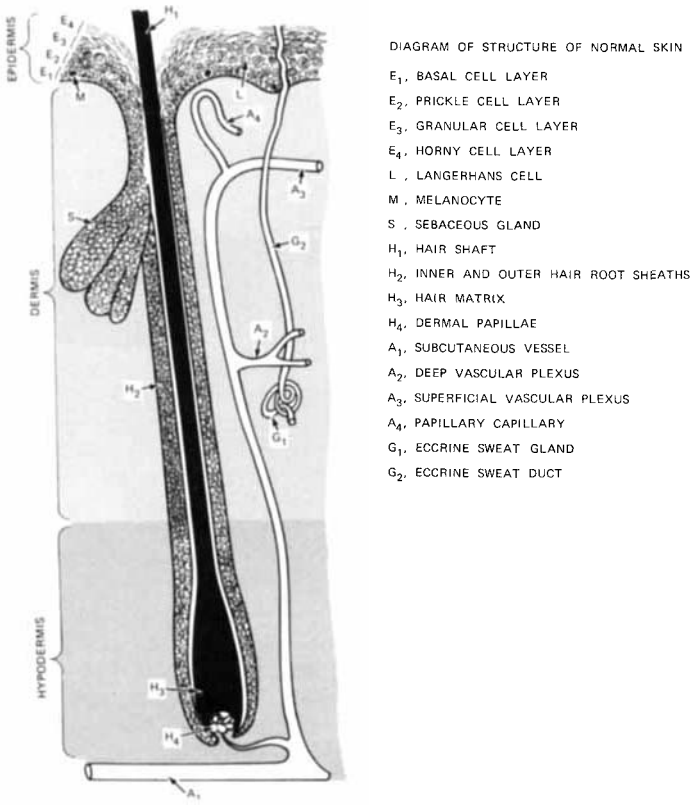

Fig. 1

Microscopic and histologic examinations of skin reveal that it should more properly be regarded as a trilayer laminate: the outermost layer of the epidermis (the so-called *horny layer*, or *stratum corneum*) is of the order of 10 to 50 μm thick, and is composed of dead, partially desiccated, keratinized epidermal cells; below the stratum corneum lies the living epidermis, a layer of rapidly proliferating, nucleated cells (about 50 to 100 μm) which generates about one new cell layer per day (Holbrook and Odland, 1974; Montagna and Parakkal, 1974; Rothman, 1965); the deepest layer of skin is the virtually noncellular, collagenous hydrous dermis. In the normal human, the stratum corneum is shed regularly at a rate equal to the rate of epidermal cell regeneration, thereby maintaining a stratum corneum of virtually constant thickness. Hence, the stratum corneum can be expected to be replaced in its entirety once every 1 to 3 wk.

Direct experimental measurement of the rates of permeation of substances through skin in vivo is very difficult, both because of the unusually low permeability of the skin to most compounds and because of the formidable analytical problems of measuring, and correlating with transdermal penetration rates, the concentrations of skin transported substances in blood and other tissues. It has, however, been long recognized that certain substances of high toxicity (for example, nicotine, chlorinated hydrocarbons, etc.) or of distinctive taste and odor (for example, mercaptans, dimethyl sulfoxide) do penetrate skin with rapidity, as evidenced by their pharmacological effects following topical application. For a long time, it was speculated that active transport processes occurring within skin were responsible for its unique barrier properties, an argument difficult to refute without experimental evidence to the contrary. Rein (1924) postulated that the principal permeation barrier in the skin resided in the layer of cells joining the stratum corneum to the living epidermis; much later, Blank (1964) appeared to confirm this postulate by showing that as cellular layers of stratum corneum were stripped one by one from the skin surface, the rate of water loss from the skin underwent a very sudden and large increase as the last cellular layer of stratum corneum was removed.

It was, however, the work of Scheuplein and his collaborators (1965 to 1973) that has ultimately clarified the locus and origin of the molecular impermeability of skin and established it to be a passive rather than biologically active property. Through their studies of the permeability of excised human skin in vitro to a large number of substances, they were able to show conclusively that the principal barrier to permeation is provided by the stratum corneum per se. By separating epidermis from the underlying dermis, by enzymatically removing the (unkeratinized) live epidermal layer, and then by measuring the permeabilities of the stratum corneum and dermis independently, it was shown that the stratum corneum is at least three, and frequently as much as five, orders of magnitude less permeable to most substances as the dermis. Moreover, the permeability of the entire epidermis was found to be indistinguishable from that of the stratum corneum alone. This prompted Scheuplein to model the skin as a three layer laminate of stratum corneum, epidermis, and dermis, with permeation occurring by Fickian diffusion of the penetrating species through the three layers in series array. Since the dominant resistance to permeation of most compounds is offered by the stratum corneum, the gradient in penetrant concentration across the entire skin is, for all practical purposes, localized within the stratum corneum.

By treating the stratum corneum as a passive, homogeneous membrane of known thickness, by measuring permeation flux as a function of concentration difference of penetrant across the membrane, and by measuring the partition coefficient of the penetrant between the tissue and contacting solution, Scheuplein (1967, 1971) was able to compute apparent permeability coefficients and diffusion coefficients for the various penetrants studied. Diffusivities so computed vary from about 10^{-9} to 10^{-13} cm^2/s, compared to values of 10^{-5} to 10^{-6} cm^2/s for the same compounds in water. For the homologous series of aliphatic alcohols in aqueous solution, partition coefficients into stratum corneum increased with molecular weight (as did permeability coefficients), while the apparent diffusivities were virtually constant and molecular weight independent. For water itself, the most rapidly permeating species studied, which is present in high concentration in stratum corneum, the apparent diffusivity was about 6×10^{-10} cm^2/s. For gases such as oxygen and carbon dioxide, diffusion coefficients of the order of 10^{-7} cm^2/s are reported, values in the same range as the diffusivities of these gases in many polymers.

The extraordinary low diffusivity of water and other low molecular weight penetrants in stratum corneum is particularly surprising: this tissue is composed predominantly of hydrous protein, and while all other body tissues are similarly constituted, they are orders of magnitude more permeable than stratum corneum to these substances. A more detailed examination of the composition and microstructure of stratum corneum, and certain other properties it displays, has thrown considerable light on its unique transport behavior.

The stratum corneum is a heterogeneous structure containing about 40% protein (mainly keratin, a disulfide cross-linked linear polypeptide), about 40% water, and about 15 to 20% lipids (principally, triglycerides, free

HAMSTER CHEEK-POUCH EPITHELIUM AFTER EXPANSION

(MACKENZIE, I.C. AND LINDER, J.E.
J. INVEST. DERMATOL. 61, 245 (1973))

Fig. 2

fatty acids, cholesterol, and phospholipids) (Andersen and Cassidy, 1973; Katz and Poulson, 1971). Structurally, as shown in Figure 2, it is comprised of a layered, close-packed array of flattened, interdigitated cells whose major axes lie parallel to the plane of the membrane; the intercellular phase is clearly distinguishable from the intracellular material and serves to cement the structure together into a coherent mass (Mackenzie and Linder, 1973). Protein is present in both the extra and intracellular phases; lipid is largely concentrated in the extracellular phase and forms in large measure the membranes surrounding the cells (Andersen and Cassidy, 1973; Rothman, 1965).

The normal water content of the stratum corneum is widely variable, depending upon both the moisture content of the environment and the body location from which it is derived. The value of 40% by weight is a representative value for exposed skin in vivo in contact with air of 30 to 50% relative humidity. If the surface of skin is occluded with a water impermeable barrier (or excised skin is immersed in liquid water), the stratum corneum slowly imbibes water and will ultimately absorb upwards of five to six times its dry weight. In its fully hydrated state, the permeability of the stratum corneum to water and other low molecular weight penetrants is substantially higher than during its normal state of hydration; Wurster (1964) and Scheuplein (1967, 1971) have reported increases in permeability to various substances of two to fivefold as stratum corneum passes from its anhydrous to its fully hydrated state. Since, in the hydration process, the thickness of the stratum corneum increases about fourfold, the specific permeability of the layer must increase between eight and twentyfold.

Of particular significance is the role played by the lipid components of the stratum corneum in determining the permeability of small molecules. If this tissue is extracted with a suitable fat solvent (a chloroform/methanol mixture is frequently used), a substantial fraction of lipid material (representing 20 to 30% by weight of the tissue) is selectively removed without detectable mechanical or morphological alteration of the membrane. Once so extracted and rehydrated, the water permeability of the stratum corneum is found to be about three to four orders of magnitude larger than that of the normal tissue, while its permeability to larger molecules may be increased four to six orders of magnitude as a consequence of lipid removal (Scheuplien, 1967, 1971). Indeed, the permeability of delipidized, hydrated stratum corneum to various micromolecular substances is within the same range as that of typical synthetic hydrogels of comparable water content. While it is difficult to be certain that the delipidizing process does not cause structural changes in the skeletal protein of the stratum corneum which results in the observed permeability increases, the inference is strong that the lipid components of stratum corneum are directly responsible for its uniquely low permeability. This inference is supported by observations showing marked changes in stratum corneum permeability over narrow temperature intervals, which coincide with reversible thermal transitions observed by differential scanning calorimetry that are attributed to transitions in lipid structure (Blank Scheuplein and MacFarlane 1967; Scheuplein and Blank, 1971).

In order for a minor phase component of a heterogeneous membrane to function as a major transport barrier, that phase must be deployed in a manner which requires all (or virtually all) penetrating molecules to transit that phase by the permeation process. Presented below is a model of the stratum corneum which conforms with this requirement; however, before developing this model, we think it important to describe the skin permeation process and to define carefully the parameters which govern permeation kinetics.

MATHEMATICAL TREATMENT OF SKIN PERMEATION MEASUREMENTS

In a typical in vitro skin permeation experiment, a sample of skin of essentially uniform thickness is contacted on its external (stratum corneum) surface with a solution of penetrant of known concentration, on its internal (dermis) surface with water, physiological saline, or Ringers solution, and the steady state rate of transport of penetrant across the tissue is measured by appropriate means. In this manner, the transdermal flux of penetrant J, in (say) $\mu g/cm^2$ hr., can be computed with little ambiguity. If the tissue layer is assumed to be homogeneous, and to permeate the penetrant by simple molecular diffusion, then the flux J can be represented by Fick's equation:

$$J = -D_M \frac{dC_M}{dx} \cong D_M \frac{\Delta C_M}{t} \tag{1}$$

where D_M is the penetrant diffusivity in the membrane, ΔC_M is the penetrant concentration decrement across the membrane, and t is the membrane thickness. In most cases, the penetrant concentration at the downstream boundary is maintained at or close to zero, whereupon

$$J \cong D_M \frac{C_{M(1)}}{t} \tag{2}$$

where $C_{M(1)}$ is the concentration of penetrant in the tissue contacting the source of the penetrant. Since the direct determination of $C_{M(1)}$ is usually difficult, it is common practice to express (2) in the form

$$J = \overline{P} \left(\frac{C_1}{t} \right) \tag{3}$$

where $\overline{P}$ is the specific permeability of the membrane to the penetrant, and C_1 is the penetrant concentration in the solution contacting the membrane. Simultaneous solution of (2) and (3) yields

$$\overline{P} = D_M \frac{C_{M(1)}}{C_1} = k_M D_M \tag{4}$$

where k_M is the partition coefficient of the penetrant between membrane and contacting solution. If both k_M and D_M are independent of penetrant concentration, then it is obvious from (3) that the transmembrane flux will be directly proportional to the penetrant concentration in the contacting solution.

The use of $\overline{P}$ as defined in Equation (4) to characterize the permeability of skin (or any membrane) to a specific penetrant, while of customary practice among researchers in skin permeation, is confusing and ambiguous since its magnitude is determined not only by the properties of the penetrant and its interaction with the tissue, but also by the solvent used in preparing the penetrant solution. This is true even if the solvent has no influence on the transport processes occurring within the membrane. Since most drugs of interest in skin penetration are solids or liquids of finite water solubility, and since the permeability of skin when in saturation equilibrium with liquid water is of primary importance, we can define a more useful term for characterizing skin permeability:

$$J_{max} = \overline{P}\frac{C^*}{t} = D_M\frac{C^*_M}{t} \tag{5}$$

where J_{max} is the maximum flux of penetrant through the skin when contacted with a saturated aqueous penetrant solution of concentration C^*. Since C^*_M is the penetrant concentration within the membrane when in saturation equilibrium with unit activity penetrant, this value is solvent independent (so long as the solvent does not solvate the membrane), and thus the product $[J_{max}\ (t)]$ is truly descriptive of the permeability of the membrane to a specific penetrant.

If, furthermore, it can be assumed that, for any penetrant or solvent

$$a = C/C^* \tag{6}$$

and

$$C_M = a\,C^*_M \tag{7}$$

where a is the activity of the penetrant in solution when its concentration is C, then Equation (5) can be rewritten as

$$J = J_{max}\frac{C}{C^*} = \overline{P}\frac{C}{t} = D_M\frac{C^*_M C}{C^* t} \tag{8}$$

We can now define the term $\overline{J}$ as the normalized flux

$$\overline{J} = \frac{J}{C} = \frac{J_{max}}{C^*} = \frac{\overline{P}}{t} \tag{9}$$

whence, it is clear that the permeation flux will be proportional to the penetrant concentration in the contacting solution up to the saturation limit. The term $[J_{max}\ t]$ may be regarded as the intrinsic permeability of the membrane to a given penetrant.

In dealing with steady state permeation through whole skin, Scheuplein (1967, 1971) and others have treated the tissue as a trilayer laminate, each layer of which transmits penetrant by normal Fickian diffusion, with partition equilibrium of penetrant being maintained at the interlayer boundaries. Under these assumptions, the flux across the tissue is given simply by

$$\frac{Jt_0}{C} = \overline{P}_0 = \frac{t_0}{\frac{t_1}{P_1} + \frac{t_2}{P_2} + \frac{t_3}{P_3}} \tag{10}$$

or

$$J_{max(0)} = \frac{1}{\frac{1}{J_{max(1)}} + \frac{1}{J_{max(2)}} + \frac{1}{J_{max(3)}}} \tag{11}$$

where the subscripts (1), (2), (3) refer to the individual layers (stratum corneum, epidermis, dermis) of the laminate and (0) to the entire laminate. Since, as pointed out above, the permeation barrier imposed by the stratum corneum is by far the greatest, Equations (10) and (11) reduce to

$$\frac{Jt_0}{C} = \overline{P}_0 = \overline{P}_S\frac{t_0}{t_S} \tag{12}$$

and

$$J_{max(0)} = J_{max(S)} \tag{13}$$

where S refers to the stratum corneum. Hence, measurement of the permeability of whole skin to specific penetrants yields for all practical purposes the rate of penetration of the stratum corneum alone. It is therefore appropriate to attempt to characterize the stratum corneum per se in an effort to explain and predict drug and other penetrant transport through intact skin.

A HETEROGENEOUS STRUCTURAL MODEL OF THE STRATUM CORNEUM

The observations that the stratum corneum is comprised of flattened, interdigitated, keratinized epidermal cells, that it is capable of sorbing up to six times its dry weight of water without exceedingly great increase in permeability, and that it undergoes a catastrophic increase in permeability upon lipid extraction favor an idealized model of this membrane shown in Figure 3. We postulate the tissue to consist of an essentially parallel array of thin plates, each consisting substantially of protein, which are separated from one another by thin layers of interstitial lipoidal material. This interstitial lipid is the residue of the membrane surrounding each epidermal cell when it became embodied into the stratum corneum. According to the model, the interstitial lipid rich phase (designated L) is the continuous phase of the matrix, whereas the proteinaceous phase (the cell cytoplasm, designated P, and by far the larger volume fraction of the tissue) is discontinuous. The interstitial lipid phase is, of course, in reality anything but homogeneous, since it must be comprised of organized lipid/phospholipid bilayer structures characteristic of virtually all cell membranes and an interpenetrating protein/polysaccharide network which evidently serves as an intercellular cement. For our purpose here, however, we will treat the L and P phases of the structure as if each were both homogeneous and isotropic. For any permeating species, there are only two routes for penetration of the barrier: one requires alternate transit through protein and lipid phases and the other transit solely through the continuous lipid phase. Within each phase, the permeating species is assumed to have a characteristic solubility (proportional to its local thermodynamic activity) and diffusivity.

The overall permeability of the composite barrier can be quantitatively related to the specific transport properties of the two phases and to their geometric configuration as follows:

IDEALIZED MODEL OF THE STRATUM CORNEUM

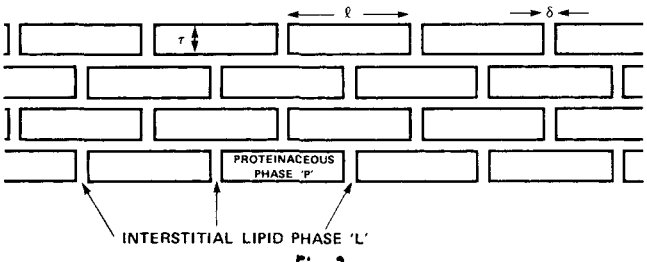

Fig. 3

If each plate element is assumed to be square, of side length (l) and thickness (τ), and if each plate is separated equidistantly from its nearest neighbors by an interstitial layer of thickness (δ), it can be readily shown that

$$\frac{\phi_L}{\phi_P} = \frac{\beta}{\alpha}(\alpha + 2) \tag{14}$$

For molecules which penetrate the structure by permeation through the two phases in series, we can write

$$R_L = \frac{t_L}{k_L D_L} \tag{15}$$

$$R_P = \frac{t_P}{k_P D_P} \tag{16}$$

$$R_S = \frac{t_S}{k_S D_S} = R_L + R_P = \frac{t_L}{k_L D_L} + \frac{t_P}{k_P D_P} \tag{17}$$

where t_L and t_P are the thicknesses of the lipid and protein layers in the membrane of total thickness t_S. Since $\delta/\tau = t_L/t_P = \beta$

$$R_S = \frac{t_S}{1+\beta}\left(\frac{\beta}{k_L D_L} + \frac{1}{k_P D_P}\right) \tag{18}$$

or

$$\frac{1}{k_S D_S} = \frac{1}{1+\beta}\left(\frac{\beta}{k_L D_L} + \frac{1}{k_P D_P}\right) \tag{19}$$

Let us define the ratio

$$\frac{k_L}{k_P} = \sigma \tag{20}$$

Since $k_S D_S = J'_S\, t_S / C_{Aq}$, from (19)

$$\frac{J'_S t_S}{C_{Aq}} = \frac{(\beta+1)\, k_P D_P}{\left(\frac{\beta}{\sigma}\frac{D_P}{D_L} + 1\right)} \tag{21}$$

An alternate permeation pathway consists of transport solely through the lipid phase. In this case, the flux of permeate through the membrane via this route is given approximately by

$$\frac{J''_S t_S}{C_{Aq}} = \frac{k_L D_L\left(\frac{2\delta}{l}\right)}{\left(1 + \frac{\alpha+\beta}{2(1+\beta)}\right)} = \frac{k_L D_L\left(\frac{2\beta}{\alpha}\right)}{\left(1 + \frac{\alpha+\beta}{2(1+\beta)}\right)} \tag{22}$$

The term $(2\beta/\alpha)$ is the fraction of the total surface area of the membrane normal to the flow direction which is lipid, while the term in the denominator of (22) is the effective path length for transport via tortuous lipid channels. On the assumption that the total traffic of penetrant through the tissue is the sum of the two contributions, we find, by adding (21) and (22), that

$$\frac{(J'_S + J''_S)t_S}{C_{Aq}} = \frac{J_{S(max)}\, t_S}{C^*_{Aq}} = k_P D_P\left[\left[\frac{\beta+1}{\frac{\beta}{\sigma}\frac{D_P}{D_L}+1}\right] + \sigma\frac{D_L}{D_P}\left[\frac{2\beta/\alpha}{1+\frac{\alpha+\beta}{2(1+\beta)}}\right]\right] \tag{23}$$

Examination of (23) indicates that the permeability of stratum corneum to any specific penetrant should be determined by only two physicochemical parameters: one is the quantity $[k_P D_P]$, which is the specific permeability of the protein phase of the tissue; the other is the quantity $[\sigma\, D_L/D_P]$, which is the product of the partition coefficient of the penetrant between the lipid and protein phases and the ratio of the diffusivities of the penetrant in the two phases. The remaining parameters in (23) are determined by the geometry of the protein and lipid elements.

The geometric parameters α and β can be approximated with reasonable accuracy from micrographs of the stratum corneum and its macroscopic composition. Thus, the cellular axial ratio α is approximately 20, and since the lipid content of stratum corneum is about 15% by volume, from Equation (14), β is computed to be

$$\beta = \frac{\alpha}{\alpha+2}\frac{\phi_L}{\phi_P} = \frac{20}{22}\frac{15}{85} \cong 0.16$$

whereupon Equation (23) reduces to

$$\bar{J}\, t_S \cong k_P D_P\left[\frac{1.16}{0.16\frac{D_P}{\sigma D_L}+1} + 0.0017\left(\frac{\sigma D_L}{D_P}\right)\right] \tag{23a}$$

where

$$\bar{J} = \frac{J_{S(max)}}{C^*_{Aq}}$$

The permeability of highly hydrated protein gels to relatively small molecules (of molecular weight 1000 or less) can be approximated with fair accuracy if the permeating species does not specifically bind to or associate with the protein. Under these circumstances, k_P, the distribution coefficient of solute between the protein gel, and its equilibrium aqueous solution will be about equal to the volume fraction of water in the gel. The diffusivity of the solute in the gel D_P is typically about one-tenth of its diffusivity in water; for gels containing 75 to 90% water by volume and for solutes in the molecular weight range of 300 to 500, a value of $D_p \cong 2 \times 10^{-7}$ cm²/s is a reasonable approximation (Scheuplein, 1967). With these assumptions, we further reduce (23*a*) to

$$\bar{J}\, t_S \cong 1.5 \times 10^{-7}\left[\frac{1.16}{0.16\frac{D_P}{\sigma D_L}+1} + 0.0017\left(\frac{\sigma D_L}{D_P}\right)\right] \tag{24}$$

If we accept an average stratum corneum thickness t_S of 40 μm, express flux in micrograms per square centimeter hour and concentration in micrograms per milliliter, (24) reduces to

$$\bar{J} = 0.135\,\sigma\frac{D_L}{D_P}\left[\frac{1.16 + .0017(\sigma D_L/D_P)}{0.16 + (\sigma D_L/D_P)}\right] \tag{24a}$$

Equation (24*a*) can be further simplified as follows:
Case 1: $\sigma\, D_L/D_P$ very small

$$\bar{J} \simeq 0.98\,\sigma\frac{D_L}{D_P} \tag{24b}$$

Case 2: $\sigma\, D_L/D_P$ very large

THEORETICAL VARIATION OF NORMALIZED TRANSDERMAL FLUX WITH $\sigma D_L/D_P$

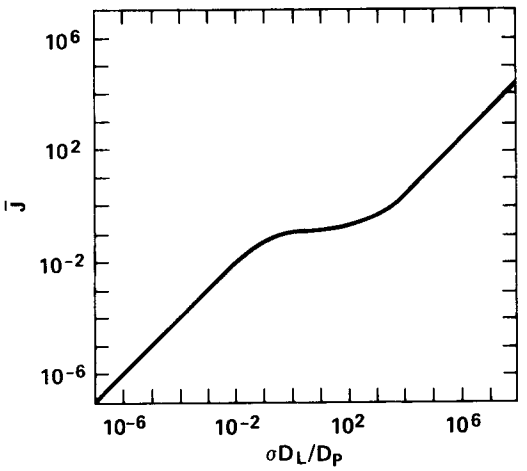

Fig. 4

$$\bar{J} \simeq 2.3 \times 10^{-4}\, \sigma \frac{D_L}{D_P} \qquad (24c)$$

The theoretical plot of Equation (24*a*) depicting the variation of the normalized drug flux $\bar{J}$ with $\sigma\ D_L/D_P$ is shown in Figure 4.

The quantity σ can, for most skin penetrants, be approximated by the experimentally determined oil/water partition coefficient for the compound in question, so long as the oil phase used in the measurement is of cohesive energy density not unlike that of the lipid phase in the tissue. Thus, substances which are either exceedingly insoluble in water and/or have very low oil solubility will display low rates of skin permeation. Conversely, compounds which are both highly water soluble and have a strong tendency to partition into oils will display relatively high permeation rates through skin.

DRUG SOLUTION PROPERTIES AND SKIN PERMEATION

The preceding analysis leads to the prediction that the maximum attainable rate of permeation of a specific drug through intact skin will depend primarily upon (1) the water solubility of the drug (which basically determines the magnitude of the chemical potential gradient which can be established across the skin, and which is the driving force for permeation) and (2) the oil/water partition coefficient of the drug, which largely governs the specific permeability of the skin to that compound. For nonionogenic organic compounds, one might therefore expect to find a monotonic decline in skin permeation rate, and increase in specific permeability, with increasing lipophilicity.

For ionogenic drug compounds (which constitute a large fraction of the pharmacopeia), the process of skin permeation is likely to be complicated by the simultaneous presence of both ionized and nonionic species in solution, each of which permeates through the skin at different rates. If, however, it can be assumed that each species migrates through skin by simple diffusion at a rate governed solely by its own concentration gradient and unaltered by the presence of other species, we can correlate the total flux of drug in terms of the sum of the fluxes of the species present and their respective concentrations and concentration gradients.

If a drug is a weak base, its behavior in (aqueous) solution can be represented by

$$BH^+ \leftrightarrows B + H^+$$

where BH^+ is the protonated, ionized form of the compound, and B is the unionized, free base form.

The relative concentrations of ionized and unionized forms in solution are, of course, governed by the equilibrium relationship

$$\frac{(C_B)\,(C_{H^+})}{(C_{BH^+})} = K_A \qquad (25)$$

If we define $C_{B(O)}$ as the total concentration of the compound present in solution in all forms, then Equation (25) can be written as

$$\frac{(C_B)}{(C_{BH^+})} = \frac{(C_B)}{(C_{B(O)} - C_B)} = \frac{K_A}{(C_{H^+})} \qquad (25a)$$

or

$$\frac{C_B}{C_{B(O)}} = \frac{K_A/(C_{H^+})}{1 + K_A/C_{H^+})} \qquad (25b)$$

Whereupon the absolute and relative concentrations of the drug in the two forms can be computed by knowing the total drug concentration, the acid ionization constant of the compound K_A, and the pH of the solution.

If we assume that the transdermal flux of each species is determined by

$$\frac{J_B\, t_S}{C_B} = \bar{P}_B \qquad (26)$$

$$\frac{J_{BH^+}\, t_S}{C_{BH^+}} = \bar{P}_{BH^+} \qquad (27)$$

then

$$J_{B(O)} = J_B + J_{BH^+} = \frac{\bar{P}_B\, C_B + \bar{P}_{BH^+} + C_{BH^+}}{t_S} \qquad (28)$$

or

$$\frac{J_{B(O)}\, t_S}{C_{B(O)}} = \bar{P}_B \frac{C_B}{C_{B(O)}} + \bar{P}_{BH^+} \frac{C_{BH^+}}{C_{B(O)}} \qquad (29)$$

or

$$\frac{J_{B(O)}\, t_S}{C_{B(O)}} = \frac{\bar{P}_B + \bar{P}_{BH^+}\ (C_{H^+}/K_A)}{(1 + C_{H^+}/K_A)} \qquad (30)$$

From (30), it is evident that

if $(K_A/C_{H^+}) >> 1$,

$$\frac{J_{B(O)}\, t_S}{C_{B(O)}} \to \bar{P}_B$$

and if $(K_A/C_{H^+}) \to 0$,

$$\frac{J_{B(O)}\, t_S}{C_{B(O)}} \to \bar{P}_{BH^+}$$

and if $C_{H^+} = K_A$,

$$\frac{J_{B(O)}\, t_S}{C_{B(O)}} = \frac{\bar{P}_B + \bar{P}_{BH^+}}{2}$$

It is also clear from (30) that at constant solution pH, the transdermal permeation rate should be proportional to the total drug concentration in the contacting solution.

The quantities $\bar{P}_B$ and $\bar{P}_{BH^+}$ in Equation (30) should, from Equation (24*b*), be equivalent to

$$\frac{\bar{P}_B}{t_S} = \sigma_B \frac{D_{L(B)}}{D_{P(B)}} \qquad (31)$$

and

$$\frac{\bar{P}_{BH^+}}{t_S} = \sigma_{BH^+} \frac{D_{L(BH^+)}}{D_{P(BH^+)}} \qquad (32)$$

If it is assumed that the diffusion coefficients of the drug in the protein and lipid phases of the stratum corneum are the same for the ionized and unionized forms, then it follows that

$$\frac{\overline{P}_B}{P_{BH^+}} \cong \frac{\sigma_B}{\sigma_{BH^+}} \tag{33}$$

This indicates that the specific permeabilities of the skin to the ionized and unionized forms of the drug are in the ratio of their oil/water partition coefficients. Since the free energy change associated with the transfer of an ion pair from an aqueous (high dielectric constant) to an oil (low dielectric constant) phase is invariably greater than that for transfer of a neutral molecule, one should expect that $\sigma_B >> \sigma_{BH^+}$, whereupon $\overline{P}_B >> \overline{P}_{BH^+}$. Hence, one should also expect the specific permeability of skin to the unionized form of a drug to be substantially greater than that of the ionized form. However, the maximum rate of permeation is also determined by the maximum achievable concentration of the species in water; hence

$$\frac{J_{\max(B)}}{J_{(\max)BH^+}} = \frac{\overline{P}_B C^*_{Aq(B)}}{P_{BH^+}\, C^*_{Aq(BH^+)}} \cong \frac{\sigma_B}{\sigma_{BH^+}} \frac{C^*_{Aq(B)}}{C^*_{Aq(BH^+)}} \tag{34}$$

Thus, if the water solubility of the free base, unionized form of the drug is much less than that of its ionized salt, its rate of permeation in unionized form may be lower than that of its salt, even though the intrinsic permeability of the skin to the free base may be much greater.

EXPERIMENTAL

Permeation Apparatus

Skin permeabilities were measured in glass premeation cells as shown in Figure 5; a piece of skin separated two aqueous solution filled compartments, one containing concentrated drug solution and the other virtually drug free solution. The stratum corneum surface of the skin was always exposed to the concentrated upstream compartment. Each compartment was about 13 ml in volume, with a port for removal of solution samples and a port for the removal of any air bubbles that may form on the skin surface; the solutions were stirred by Teflon impellers powered by 400 rev./min. synchronous motors. Sixteen cells were placed in a water bath assembly, the temperature of which was controlled to 30.0 ± 0.1°C.

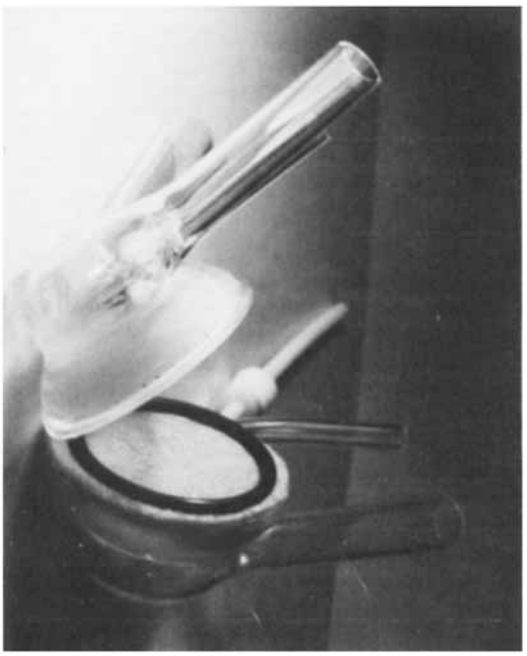

Fig. 5. Typical Permeation Cell.

Table 1. List of Drugs Studied

Drug	Formula	Molecular weight
Atropine	$C_{17}H_{23}NO_3$	289
Chlorpheniramine	$C_{16}H_{19}ClN_2$	275
Diethylcarbamazine	$C_{10}H_{21}N_3O$	199
Digitoxin	$C_{41}H_{64}O_{13}$	765
Ephedrine	$C_{10}H_{15}NO$	165
Estradiol	$C_{18}H_{24}O_2$	272
Fentanyl	$C_{22}H_{28}N_2O$	337
Nitroglycerin	$C_3H_5N_3O_9$	227
Ouabain	$C_{29}H_{44}O_{12}$	585
Scopolamine	$C_{17}H_{21}NO_4$	303

Chemicals

Permeation studies were conducted with ten USP grade drugs (Table 1). Radiolabeled forms of these drugs were obtained from New England Nuclear Corporation, Amersham/Searle, or International Chemical and Nuclear Corporation. Their radio-purity was determined by thin layer chromatography and, defined as the percentage of the total radioactive label associated with the parent drug moiety, was found to be greater than 99% in all cases. These drugs were chosen because they represent both a wide range in chemical structure/molecular weight and in oil/water solubility characteristics. Each drug was dissolved in distilled water to produce solutions of concentration varying from 1 to 100% of saturation at 30°C.

Analytical Methods

The analysis of nonradioactive drugs in aqueous solutions was performed by gas phase chromatography with a Hewlett-Packard No. 5711A chromatograph equipped with a flame ionization detector. The column was 4 ft. × ⅛ in. I.D., packed with 3% OV225 on gas chrom Q. The column temperature was held at 230°C with the injector and detector temperatures of 250° and 300°C, respectively. The carrier gas was pure helium, and purified hydrogen and breathing quality compressed air were used for the detector flame. A Hewlett-Packard No. 7123A recorder was used.

Concentrations of solutions of radiolabeled drugs were determined by adding aliquots to a dioxane base scintillation fluor and by counting the mixture with a Packard Tricarb 3375 refrigerated scintillation counter.

Permeation Measurements

Skin was obtained from Caucasian cadavers, in most instances excised from the inner surface of the thigh; samples were preserved in heat sealed plastic bags, stored at 4°C prior to use, and discarded if not used within 2 wk. Skin samples could also be safely preserved for periods up to 4 wk. if refrigerated (4°C) in a suspension of saline human blood plasma containing Neomycin sulfate. The morning preceding the permeation experiment, the skin was cut and mounted in the permeation cell with a rubber O-ring placed on the stratum corneum side of the skin; the exposed area of the skin approximated 7.85 cm^2. A drug solution of known concentration and *p*H was placed in the upstream side, and Ringer's solution (*p*H about 6.5) was added to the downstream compartment.

Samples were periodically withdrawn from the downstream compartment and subsequently analyzed for drug concentration, either by chromatography or by scintillation counting. A volume of drug free Ringer's solution equal to the amount removed was always replaced in the cell. As a rule, during the experiment the decrease in the upstream drug concentration was small and did not warrant periodic concentration measurements.

Transdermal permeation rates measured with either distilled water (*p*H 5.0), isotonic saline USP (*p*H 5.5), or Ringer's solution as the downstream compartment vehicle were found to be equal within experimental accuracy, indicating that *p*H or simple electrolyte gradients across skin do not significantly affect drug permeability.

TABLE 2. SUMMARY OF EXPERIMENTAL RESULTS

Drug	Source of radiolabel drug*	Radiolabel	Water solubility mg/ml at 30°C	Mineral oil/water partition coefficient at 30°C	pK	Solution pH	No. of skin donors	Number of permeation experiments	Range of $J_{S(max)}$ $\mu g/cm^2$ hr. at 30°C	$J_{S(max)}$ avg $\mu g/cm^2$ hr. at 30°C	$\bar{J}$ avg cm/hr. $\times 10^3$ at 30°C
Ephedrine	NEN	Carbon[14]	50	1.0	9.65	10.8	3	8	250 to 400	300	6.0
Diethylcarbamazine			800	0.064		10.0	2	6	83 to 120	100	0.13
Nitroglycerin			1.3	10		—	2	4	10 to 25	13	11
Scopolamine	ICN	Tritium	75	0.026	7.35	9.6	5	10	2.0 to 8.0	3.8	0.05
Chlorpheniramine	ICN	Tritium	1.6	0.46	9.1	10.3	4	8	2.9 to 3.9	3.5	2.2
Fentanyl	McNeill	Tritium	0.2	200		8.0	5	10	0.8 to 3.8	2.0	10
Atropine	A/S	Tritium	2.4	0.006		8.0	2	5	0.01 to 0.05	0.02	0.0086
Estradiol	NEN	Tritium	0.003	12		7.0	4	8	0.01 to 0.03	0.016	5.2
Ouabain	NEN	Tritium	10	0.00026		7.0	2	4	0.005 to 0.02	0.008	0.00078
Digitoxin	NEN	Tritium	0.01	0.014		7.0	1	2	0.00012 to 0.00014	0.00013	0.013

* A/S = Amersham/Searle; NEN = New England Nuclear Corporation; ICN = International Chemical & Nuclear Corp.

Solubility Determinations

Solubilities of the various drugs in water and mineral oil were experimentally measured at 30°C. An excess quantity of drug was placed in a known volume of either water or mineral oil (usually 10 ml) and allowed to equilibrate with stirring for 24 hr. at 30°C. Drug concentrations were subsequently analyzed by scintillation counting. An apparent mineral oil/water partition coefficient of the drug was then computed from the ratio of the drug solubility in mineral oil to that in water.

RESULTS

The experimentally determined maximum skin permeation fluxes [$J_{S(max)}$] for the ten drugs studied are documented in Table 2, in order of decreasing skin permeation rate. Also tabulated are drug water solubilities (30°C), mineral oil/water partition coefficients, pK values (where applicable), donor solution pH's, and computed values of normalized flux ($\bar{J}$).

Permeation measurements for each drug were usually performed on skin samples from several different subjects; the reported range of values of $J_{S(max)}$ thus reflects the variability in skin permeability between individuals. (As a rule, there is greater variability of skin permeability between individuals than between locations in the same individual.)

Simultaneous determination of permeant concentration in the downstream compartment by radiochemical and gas chromatographic analysis confirmed that for scopolamine, ephedrine, and estradiol, the species permeating the skin was in all cases unmodified drug; hence, it is concluded that enzymatic modification of drug during in vitro skin permeation does not take place to a significant extent.

The measured rate of skin permeation of ephedrine was found to be virtually independent of the rate of stirring of the solutions in the diffusion cells for stirrer rotation rates between 120 to 800 rev./min. Accordingly, it was concluded that the liquid phase boundary layer resistance to mass transfer was negligibly small relative to the skin transport resistance. Since ephedrine was by far the most skin permeable drug studied, it could be safely assumed that liquid boundary layer resistances were small enough to be neglected in all permeation experiments. A constant stirrer speed of 400 rev./min. was then selected for all subsequent measurements.

As is evident from Table 2, the differences in maximum skin transport rates between drugs are enormous, the highest (about 300 $\mu g/cm^2hr.$) being observed for ephedrine and the lowest (about 1.3×10^{-4} $\mu g/cm^2hr.$) for digitoxin. Variations of permeability between drugs are so much greater than those between skin samples that the latter can, for all practical purposes, be neglected in efforts to analyze or correlate skin permeability with drug properties. Also, the variability of stratum corneum thickness between skin samples (whether obtained from the same subject or different subjects) was experimentally determined on about 25% of all skin samples studied and was found to vary from about 25 to 50 μm. Thus, skin permeability variation due to stratum corneum thickness variability probably does not exceed a factor of two, or about one-half the range of permeability observed between subjects for a given drug. The use of an average value of stratum corneum thickness of 40 μm in Equation (24) thus seems reasonable.

For scopolamine, ephedrine, and chlorpheniramine, considerably more extensive skin permeation measurements were performed (on skin samples from a limited number of donors) to determine the effects of drug donor solution concentration and pH upon drug permeation rate.

TABLE 3. EFFECT OF DRUG CONCENTRATION ON FLUX (30°C)

Drug	Solution pH	Solution concentration mg/ml	Skin donor	Number of permeation experiments	J_S avg μg/cm^2 hr. at 30°C
Chlorpheniramine	10.0	2.1*	A	2	2.9
($pK = 9.1$)	10.0	1.1	A	2	1.5
	10.0	0.6	A	2	0.5
Ephedrine	10.85	50*	B	3	300
($pK = 9.65$)	10.45	10	B	3	60
	8.85	1.0	B	3	1.7
Scopolamine	4.0	520*	C	2	1.3
($pK = 7.35$)	4.0	52	C	2	0.13
	4.0	5.2	C	2	0.016
	6.6	470*	C	2	2.2
	6.6	47	C	2	0.19
	6.6	4.7	C	2	0.03
	9.6	110*	D	2	3.6
	9.6	11	D	2	0.15
	9.6	1.1	D	2	0.025

* Saturated solution.

EFFECT OF CONCENTRATION AND pH ON SCOPOLAMINE FLUX THROUGH HUMAN SKIN

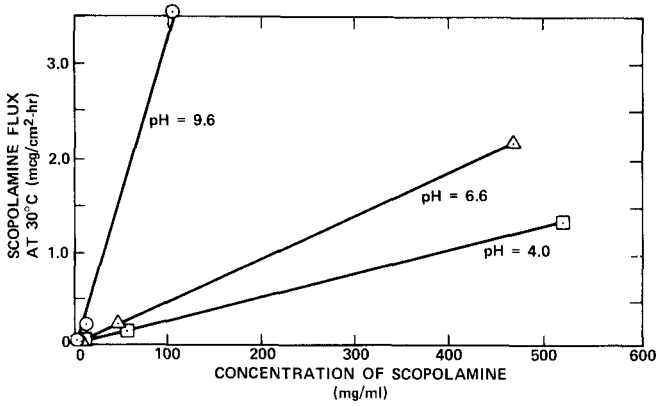

Fig. 6

EFFECT OF CONCENTRATION ON TRANSDERMAL FLUX THROUGH HUMAN SKIN IN VITRO

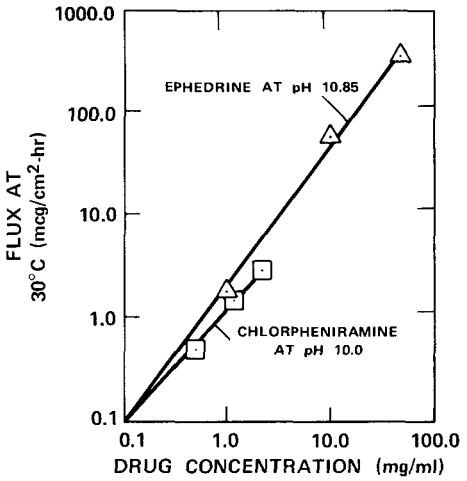

Fig. 7

Results of these measurements are summarized in Table 3 and Figures 6 and 7.

Scopolamine is a belladonna alkaloid with a pK of 7.35; the water solubility at 30°C of the base is about 75 mg/ml and of the hydrobromide salt 520 mg/ml. In Figure 6, the transdermal flux of scopolamine is shown as a function of concentration and pH of the aqueous drug solution contacting the stratum corneum surface of the skin; the highest concentration of scopolamine at each pH corresponds to a saturated aqueous solution. The in vitro flux of scopolamine at constant pH shows a linear increase with increasing concentration. Under saturation conditions, at pH 4 (where the drug is virtually 100% in the salt form), the in vitro flux of scopolamine is about 1 mcg/cm^{2}hr., whereas at pH 9.6 (where the drug is present almost entirely as free base), the flux approximates 4 mcg/cm^{2}hr.

Ephedrine (N, methyl phenyl propanolamine) has a pK of 9.65 and chlorpheniramine [N,N dimethyl, 1(p-chlorophenyl), 1(1-pyridyl) propylamine] a pK of 9.1. In Figure 7, the in vitro fluxes of these two drugs are plotted as functions of drug concentration on the (aqueous) solution contacting the stratum corneum surface of the skin. Since the pH of these solutions was about 1 pH unit greater than the drug pK values, the drugs were in solution virtually completely in the base form. The highest concentration of each drug corresponds to a saturated solution in water. As with scopolamine, the fluxes of both ephedrine and chlorpheniramine increase linearly with increasing concentration.

Scopolamine and chlorpheniramine have maximum in vitro fluxes of about 3 to 5 μg/cm^{2}hr., whereas that of ephedrine approximates 300 μg/cm^{2}hr. From the pK's of these three drugs and by applying Equation (30), normalized fluxes of the base and ionic forms of the drugs were computed. These are presented in Table 4. The base normalized flux values increase in the order scopolamine < chlorpheniramine < ephedrine, which are in the ratio 1:~40:~120, while the ionized form values are at least an order of magnitude smaller and in the ratio 1:3:100. (The fact that the maximum transdermal fluxes of chlorpheniramine and scopolamine are nearly equal is attributable to the fact that the latter compound is about fifty times more water soluble than the former.) These calculations confirm that for these three drugs, the base form is by far the more skin permeable than the ionized salt form.

Table 4. Normalized Drug Fluxes through Human Skin In Vitro

Drug	Normalized flux (cm/hr. × 10^4) Base form ($\overline{P}_B/t_S$)	Ionized form ($\overline{P}_{BH^+}/t_S$)
Ephedrine	60	3.3
Scopolamine	0.5	0.03
Chlorpheniramine	22	0.08

In Figure 8, the normalized transdermal fluxes for all drugs studied (for amino drugs, the values are those for the free bases) are plotted against the respective mineral oil/water partition coefficients. Vertical bars represent the scatter of the permeability values between individual skin samples. Also plotted on Figure 8 are two numerical solutions to Equation (24*a*), on the assumption that σ, the lipid/protein partition coefficient, is equal to the measured mineral oil/water partition coefficient for each drug, and for values of D_L/D_P of 10^{-2} and 10^{-3}. The region between these two solid lines envelops most of the experimentally obtained data points; the best theoretical fit through the data is obtained for a value of D_L/D_P of about 2.0×10^{-3}. Based on this agreement between theory and experimental results, we can conclude that if the lipid/protein partition coefficient σ can be approximated by the mineral oil/water partition coefficient for the base or unionized form of the drug, then the diffusion coefficient of the base form of each drug in the lipid phase is about 500 times lower than its diffusion coefficient in the protein phase.

If the normalized flux values for the ionized forms of ephedrine, scopolamine, and chlorpheniramine (Table 4) are made to fit the correlation of Figure 8 for the free base forms, the predicted mineral oil/water partition coefficients for the ionic forms would be only one to two orders of magnitude smaller than those of the corresponding free bases. Experimentally, it is observed that the mineral oil solubility of the ionic forms of these drugs is in the parts-per-million range, from which partition coefficients are estimated to be three to five orders of magnitude lower than the values observed for the free bases. This suggests that for ionized forms of drugs, mineral oil does not accurately model the lipid phase of the stratum corneum. This is perhaps not unexpected, since the phospholipid bilayer, which is comprised largely of fatty zwitterion, should be able to solubilize organic electrolytes much more easily than any pure hydrocarbon or nonionic lipid.

DISCUSSION

The exceedingly low apparent diffusivity of most substances through the interstitial lipid phase of the stratum corneum is an anomaly of considerable note, for therein lies the origin of the skin's remarkable impermeability. If this lipid phase were a truly homogeneous and isotropic oil, penetrant diffusion coefficients of 10^{-7} to 10^{-8} cm²/s (corresponding to bulk oil viscosities of 10 to 100 centipoises) would be expected. Scheuplein's (1965, 1967) and other measurements of the temperature dependency of skin permeability to various substances are informative and suggestive of an explanation for the anomalous results. Arrhenius plots of permeability vs. temperature have been used to compute activation energies for permeation, which are found to be substantially larger than expected for

VARIATION OF NORMALIZED TRANSDERMAL FLUX WITH PARTITION COEFFICIENT

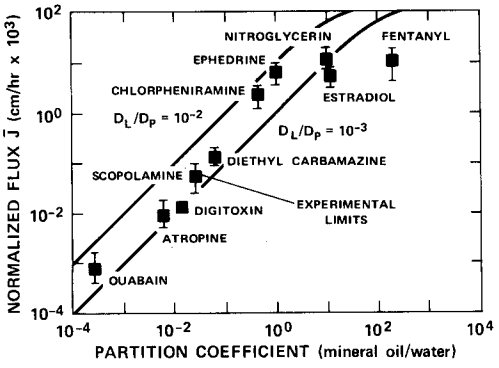

Fig. 8

normal activated diffusion in liquids (which, to a first approximation, should be equal to the viscous flow activation energy). We eschew and advise others to avoid any inferences about the micromechanics of diffusion from these apparent activation energies, since particularly in complex heterogeneous structures such as skin many morphologic changes (reversible or irreversible) which can occur with temperature changes can profoundly alter permeation rates and mechanisms. To attempt to attach thermodynamic significance to these apparent activation energies is thus likely to be idle, if not misleading. Of particular interest, however, is that these apparent activation energies for permeation are nearly constant (at about 17 to 20 kcal/mole) and independent of size, shape, or chemical constitution of the penetrating molecule. This observation suggests a temperature dependent microstructural change in the lipid phase of the tissue as responsible for the observed permeability/temperature variations.

We choose to propose that the interstitial lipid barrier to permeation in the stratum corneum is comprised of two-dimensionally ordered, lipid bilayer membrane, which has first been compressed by partial dehydration of the epidermal cell cytoplasm after cell death, and subsequently becomes stabilized in this compressed state during the protein keratinization process. If this hypothesis is correct, the permeation of substances through stratum corneum should approximate in rate and kind the permeation of small molecules through isolated crystalline monomolecular and lipid bilayer membranes. With these structures, diffusion coefficients for small molecules (oxygen, water, etc.) have been found to lie in the range of 10^{-8} to 10^{-11} cm²/s, and to increase several orders of magnitude over narrow temperature ranges which can be correlated with two-dimensional solid-liquid transitions in the membrane. When apparent activation energies are computed for these permeability changes, values ranging from 20 to 40 kcal/mole are obtained. True diffusion activation energies of this magnitude would hardly be expected in an isotropic lipid phase; hence, migration of penetrants through defects in a two-dimensional crystal lattice is often regarded as the transport mechanism in such membranes.

If, indeed, organized lipid bilayer membranes are largely responsible for the impermeability of stratum corneum, the lipid/protein phase partition coefficient σ for a particular penetrant need not be directly related to the oil/water partition coefficient of that substance, since the penetration of the permeating substance into the lipid bilayer may require alteration of its structure. Hence, compounds which may be highly lipophilic, yet which are poorly accommodated into the organized lipid phase, will display low skin permeability despite predictions to the

contrary, while substances of relatively low oil affinity but which penetrate readily into and disorder the lipid microcrystalline structure may display exceedingly high skin permeability. Such substances should be able to cause marked increases in D_L, not only for themselves, but also for other concurrently permeating species. Indeed, it seems probable that universal solvents such as dimethyl sulfoxide and hexamethyl phosphortriamide, which permeate through intact skin at phenomenally rapid rates and substantially enhance the permeation of other substances, may operate by creating controlled disorder in organized lipid membranes.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Patricia Campbell, Tyler Watanabe, Lina Taskovitch, and Anna Reuter for conducting the experimental part of this study.

NOTATIONS

a = activity
C = concentration
D = diffusion coefficient
J = flux
k = partition coefficient
K = ionization constant
l = length
P = permeability
R = resistance
t = thickness
x = distance

Greek Letters

Δ = difference operator
τ = thickness of plate element
δ = thickness of interstitial layer
α = l/τ = plate axial ratio
β = δ/τ
ϕ = volume fraction
σ = lipid phase/protein phase partition coefficient

Subscripts

Aq = aqueous phase
B = unionized base form
BH^+ = ionized form
H^+ = hydrogen ion
L = lipid phase
M = membrane
max = maximum
P = protein phase
S = stratum corneum

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Breakup of a Turbulent Liquid Jet in a Low-Pressure Atmosphere

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Breakup length measurements were made of turbulent liquid jets in a low-pressure atmosphere. As a result of these experiments, it was found that the jets obey a pseudo laminar analogy only at low exit velocity. The nondimensional breakup length correlates with the jet Weber number through the complete range.