Increased Skin Permeability for Lipophilic Molecules

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Abstract □ Treatment of the epidermis with surfactants can markedly increase the transport of polar molecules but only marginally increases the transport of nonpolar (lipophilic) molecules. Thus, other vehicle systems are needed to increase the transport of lipophilic molecules. One method to accomplish this increased transport is to add small quantities of polar lipids to a base vehicle containing propylene glycol. The transport of nonpolar materials such as salicylic acid can be increased by an order of magnitude by the addition of small amounts of fatty acids or alcohols to a formulation. The effect of this mixed system is much greater than the effect of any of the agents alone.

Keyphrases □ Transport systems—increased skin permeability, lipophilic molecules □ Lipophilic molecules—transport systems, increased skin permeability

The stratum corneum, which is the main barrier to cutaneous transport (1), is structurally a complex membrane, and thus, transport probably takes place through a variety of pathways. It has been suggested in a study of the effect of temperature on the penetration of alcohols (2) that there are at least two pathways for transport across the skin: a polar pathway and a nonpolar pathway. The polar pathway is associated with the protein component of the stratum corneum and might be envisioned as aqueous channels in the protein; the nonpolar pathway is associated with the lipid component.

In recent studies (3), the attempt has been made to clarify and support the hypothesis that there are at least two parallel pathways for transport by using surfactant treatment, which greatly increases the transport of polar molecules but only slightly increases the transport of nonpolar molecules. For example, it has been found that treatment of the human epidermis with decylmethyl sulfoxide greatly increases the transport of salicylic acid at pH 9.9 (ionized or polar form) but only slightly increases salicylic acid transport at pH 2.65 (un-ionized or nonpolar form). Other studies have shown that the transport of 1-propanol is greater than that of propylene glycol or glycerol. That is, even though propylene glycol has a much higher oil–water partition coefficient than glycerol (4), its cutaneous flux from aqueous solution is only slightly greater than that of glycerol but much less than that of 1-propanol. Thus, as the polarity of a molecule is increased, *i.e.*, its oil–water partition coefficient decreases, a polarity exists for which the oil–water partition coefficient is not related to transport. These results differ noticeably from those obtained previously (2), in which even 1-pentanol is claimed to transport *via* a polar pathway.

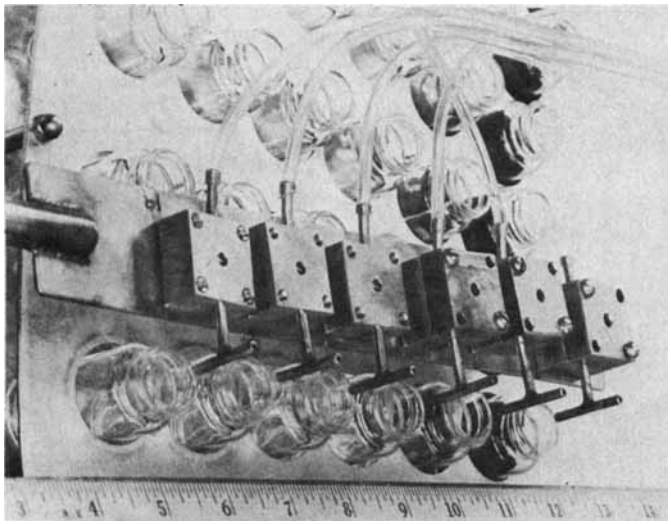

Figure 1—*Diffusion cell.*

The existence of multiple transport pathways in skin points to the possibility for design of vehicles to alter the permeability of the skin *via* the different pathways, as the surfactants seem to uniquely alter the polar pathway. Certain two-component systems have been found which alter transport differently from the way the components behave individually. The purpose of this report is to describe the effects of these vehicle systems on the transport of nonpolar molecules across skin. Salicylic acid was used as a prototype nonpolar compound, but similar results were obtained on many other nonpolar compounds. A model is proposed to interpret these findings, but the mechanism by which these vehicles alter transport is still unknown.

EXPERIMENTAL SECTION

Materials—Salicylic acid[1], [^{14}C-carboxylate]salicylic acid[2], the fatty acids and alcohols[3], propylene glycol[4], diethylene glycol[5], and the polyethylene glycols[6] were obtained commercially. The sulfoxides (purity >95%) were synthesized[7], and the dimethyl polysiloxane[8] rubber membranes were cast on a large stainless steel plate. All other chemicals used were of reagent grade.

Diffusion Studies—*Epidermis Preparation*—Full-thickness human ab-

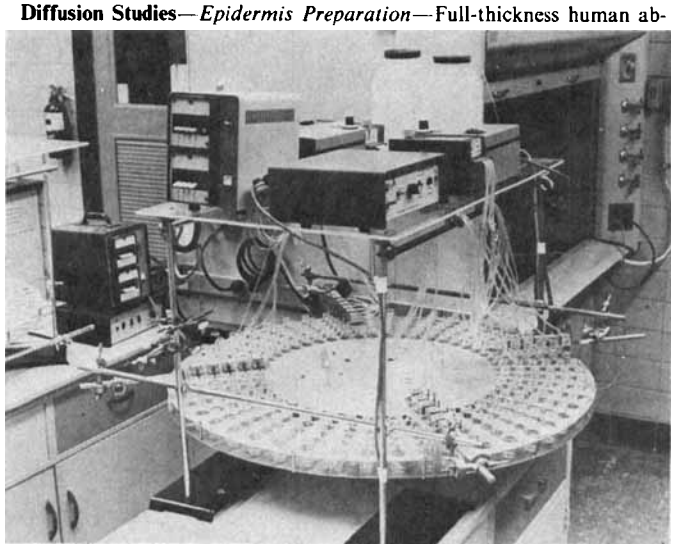

Figure 2—*Diffusion Apparatus.*

[1] Fisher Scientific Co., Cincinnati, Ohio.
[2] ICN Chemicals, Radioisotope Division, Irvine, Calif.
[3] Nu-Chek Prep, Inc., Elysian, Minn.
[4] J. T. Baker Chemical Co., Phillipsburg, N.J.
[5] Aldrich Chemical Co., Inc., Metuchen, N.J.
[6] Ventron Corp., Danvers. Mass.
[7] Miami Valley Laboratories.
[8] MDX-4-4210 elastomer and MDX-4-4210 curing agent; Dow Corning, Midland, Mich.

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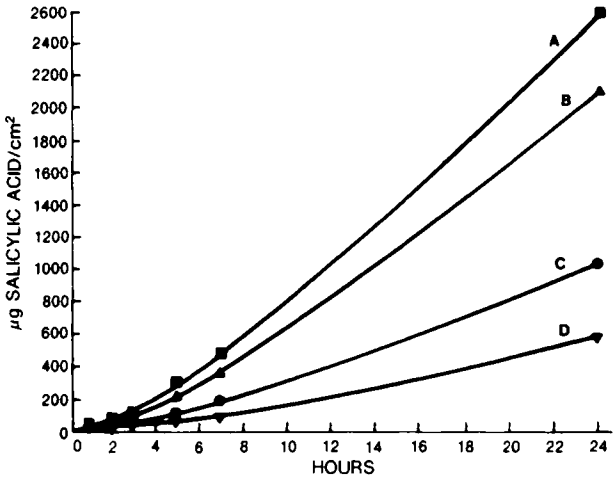

Figure 3—*Effect of polar solvents on salicylic acid transport across human epidermis. Key: (A) 24% salicylic acid in diethylene glycol; (B) 19% salicylic acid in propylene glycol; (C) 30% salicylic acid in tetraethylene glycol; (D) 27% salicylic acid in pentaethylene glycol.*

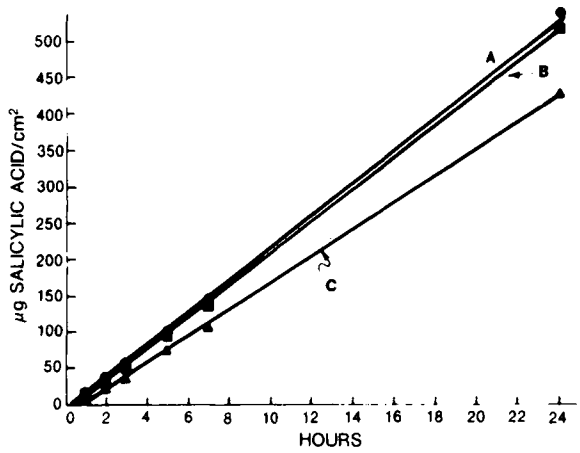

Figure 4—*Effect of polar solvents on salicylic acid transport across silicone rubber. Key: (A) 30% salicylic acid in tetraethylene glycol; (B) 19% salicylic acid in propylene glycol and 24% salicylic acid in diethylene glycol; (C) 27% salicylic acid in pentaethylene glycol.*

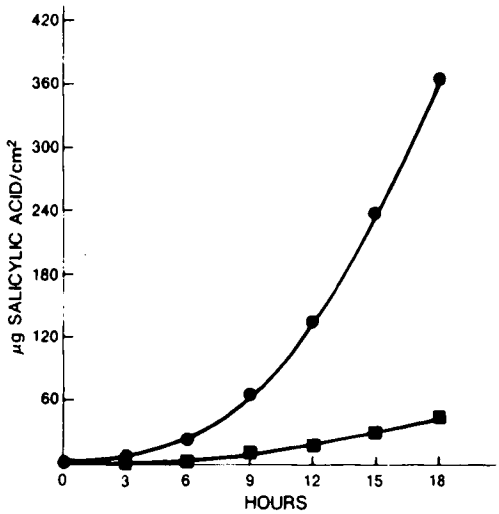

Figure 5—*Penetration of 1% salicylic acid across human epidermis. Key: (●) 0.1 M oleic acid in propylene glycol; (■) propylene glycol.*

dominal skin was obtained at autopsy and frozen until ready for use. The subcutaneous fat was removed with a scalpel, and the skin was placed in water at 60°C for 80 s. The epidermis was carefully removed and mounted (outer surface up) on aluminum foil before rinsing in 0°C hexane for 10 s to remove

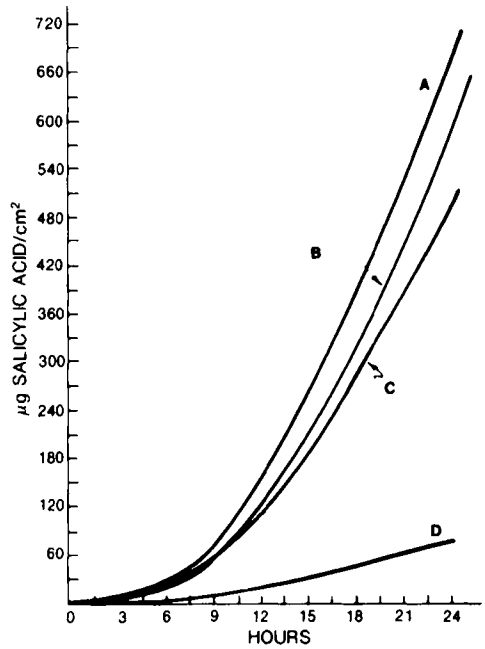

Figure 6—*Effect of the addition of* cis*-unsaturated fatty acids on the penetration of 1% salicylic acid in propylene glycol across human epidermis. Key: (A) 0.1 M myristoleic acid; 0.1 M palmitoleic acid; (C) 0.1 M oleic acid; (D) propylene glycol.*

any fat contamination. The epidermis was either used immediately or wrapped in a plastic sheet[9] and frozen.

Experimental Apparatus—The epidermis was mounted in diffusion cells as pictured in Fig. 1. The flat surfaces of the cell provide a pressure seal after the epidermis is placed between the two compartments, which are bolted together. Up to 100 µL of solution can be placed in the chamber above the skin. The area for transport is 0.122 cm². Water was pumped *via* a multichannel peristaltic pump through the lower compartment at 3.5 mL/h and collected in scintillation vials placed in a programmable rotating fraction collector. Figure 2 shows the entire assembly. The volume of water in the chamber beneath the skin is ~5 µL, so the volume beneath the skin is replaced ~100 times/h. The temperature of the experiments was that of the laboratory, 22 ± 1°C.

Assay for Penetration—Approximately 1 µCi of radioactive tracer was used for each diffusion cell. The quantity of radioactive tracer transported

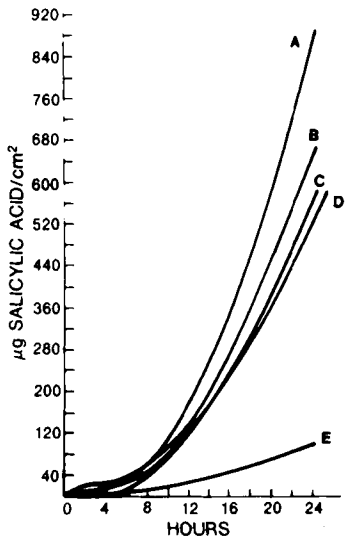

Figure 7—*Effect of the addition of* cis*-unsaturated fatty acids on the penetration of 1% salicylic acid in propylene glycol across human epidermis. Key: (A) 0.1 M vaccenic acid; (B) 0.1 M 10-heptadecanoic acid; (C) 0.1 M petroselenic acid; (D) 0.1 M eicosenoic acid; (E) propylene glycol.*

[9] Saran Wrap.

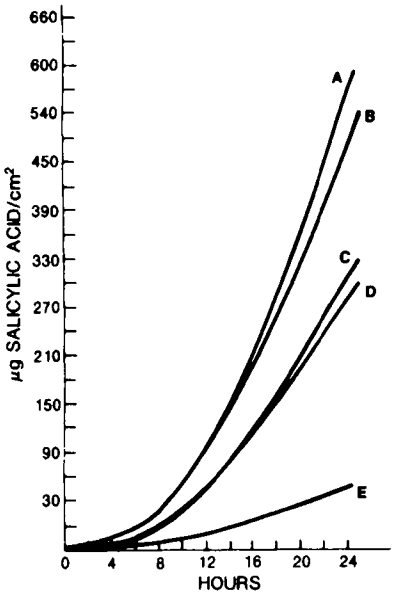

Figure 8—*Effect of the addition of polyunsaturated fatty acids on the penetration of 1% salicylic acid in propylene glycol across human epidermis. Key: (A) 0.1 M linolenic acid; (B) 0.1 M linoleic acid; (C) 0.1 M vaccenic acid; (D) 0.1 M linoelaidic acid; (E) propylene glycol.*

across the skin and collected in the scintillation vials was determined by liquid scintillation counting. The scintillation counting solution (10 mL), added to each 7-mL sample, consisted of cocktail stock solution. The latter consisted of 2,5-diphenyloxazole (8 g) and 1,4-bis(4-methyl-5-phenyloxazol-2-yl) benzene (0.16 g) per liter of toluene.

Variation in Data—The epidermal transport from each vehicle was determined in quadruplicate, and the variation in the data was ±25%. Data on each graph represent separate experiments run on different days with different epidermal samples.

RESULTS AND DISCUSSION

The vehicles described in this paper are two-component systems consisting of a polar solvent, such as propylene glycol, and a lipid, such as oleic acid. The choice of polar solvent is important, since there is a wide range in the effects of polar solvents. For example, it can be seen in Fig. 3 that propylene glycol and diethylene glycol support a high rate of transport of salicylic acid but that the flux drops off some as the number of ethylene oxide groups is increased. (Note that comparisons are made among saturated solutions to ensure equal thermodynamic activity.) Transport of salicylic acid across a dimethyl polysiloxane membrane (Fig. 4) was essentially the same from each of these

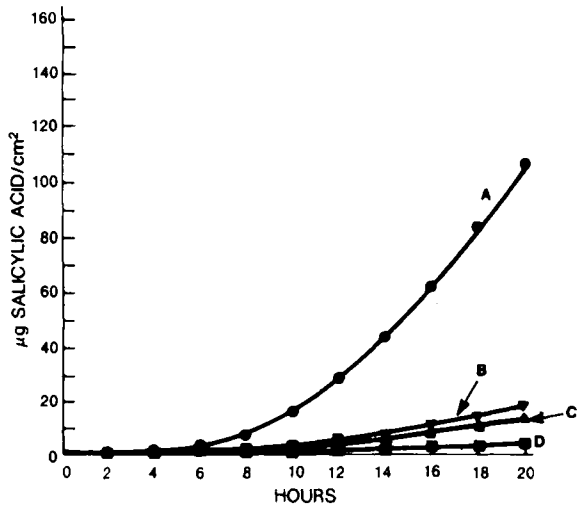

Figure 9—*Effect of the addition of fatty acids on the penetration of 1% salicylic acid in propylene glycol across human epidermis. Key: (A) 0.1 M oleic acid in propylene glycol; (B) 0.1 M lauric acid in propylene glycol; (C) 0.1 M decanoic acid in propylene glycol; (D) propylene glycol (control).*

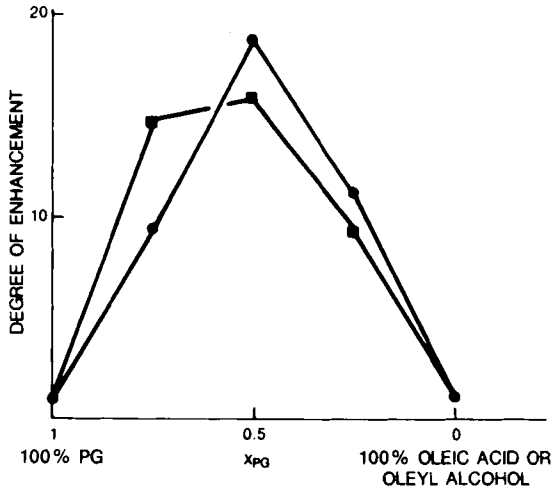

Figure 10—*Degree of enhancement of salicylic acid steady-state flux as a function of propylene glycol mole fraction ($X_{propylene\ glycol}$) from saturated solutions. Key: (■) oleyl alcohol; (●) oleic acid.*

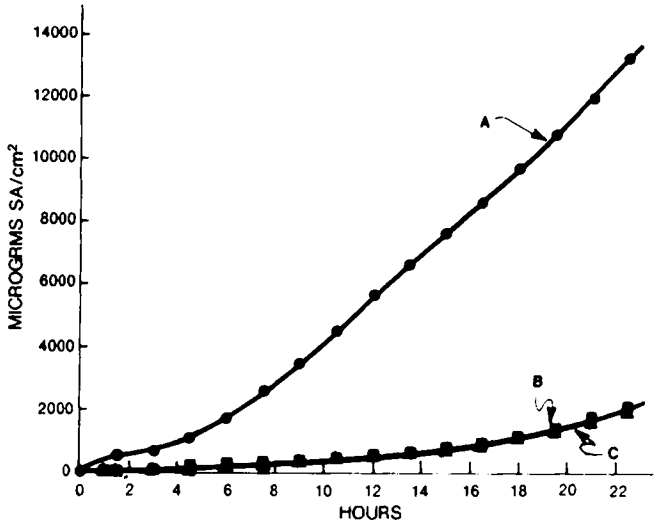

Figure 11—*Effect of sulfoxides on salicylic acid transport across human epidermis. Key: (A) 24% salicylic acid in propylene glycol plus 0.1 M oleyl methyl sulfoxide; (B) 21% salicylic acid in propylene glycol; (C) 22% salicylic acid in propylene glycol plus 1 M decyl methyl sulfoxide.*

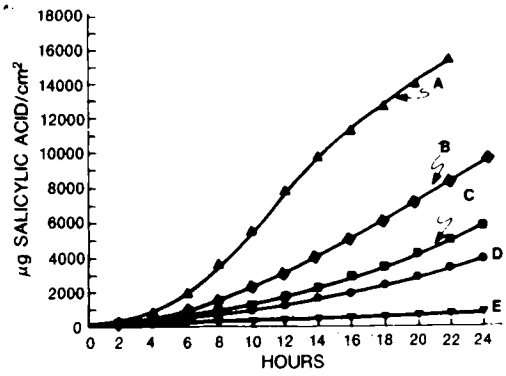

Figure 12—*Penetration of salicylic acid at saturation from propylene glycol–alcohol vehicles across human epidermis. Key: (A) 21% salicylic acid in 0.25 mole fraction decanol–propylene glycol; (B) 22% salicylic acid in 0.25 mole fraction hexanol–propylene glycol; (C) 22% salicylic acid in 0.25 mole fraction octanol–propylene glycol; (D) 22% salicylic acid in 0.25 mole fraction butanol–propylene glycol; (E) 20% salicylic acid in propylene glycol.*

solvents. This result indicates that polar solvents interact differently with skin and that the variations in transport are not due to solution phenomena.

The addition of a small amount of oleic acid to propylene glycol provides for a rather large increase in salicylic acid transport (Fig. 5). (Similar increases

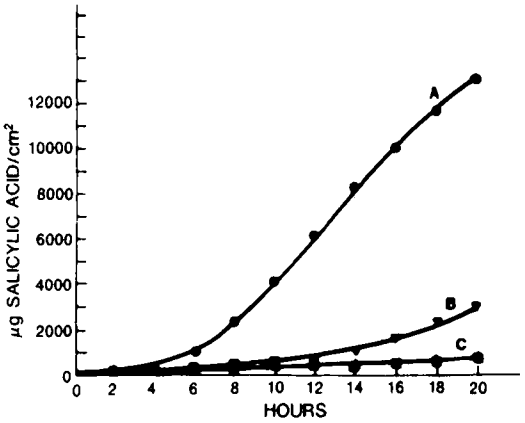

Figure 13—*Penetration of salicylic acid at saturation from oleic acid–propylene glycol or –1,2-butanediol vehicles across human epidermis. Key: (A) 15% salicylic acid in 0.25 mole fraction oleic acid–propylene glycol; (B) 15% salicylic acid in 0.25 mole fraction oleic acid–1,2-butanediol; (C) 23% salicylic acid in propylene glycol or 1,2-butanediol.*

in transport were also observed for the other polar solvents, but only the results for propylene glycol are presented.) Other unsaturated fatty acids give a similar result. Figures 6–8 show the effects of chain length and number and type of double bonds. The effect is reduced for saturated fatty acids (Fig. 9). Long-chain saturated fatty acids are too insoluble in propylene glycol for any effect on transport to be observed.

As the concentration of oleic acid (or oleyl alcohol) is increased, the transport of salicylic acid is also increased, up to a point. As the concentration of lipid is further increased, the flux of salicylic acid decreases (Fig. 10). Here, as mentioned above, transport from saturated solutions is compared to ensure equal driving force (chemical potential). The transport of salicylic acid from saturated solutions of propylene glycol (~22%) and oleic acid (~4%) [or water (0.2%)] are the same. However, use of a mixture of the two materials gives a ~20-fold increase in the transport rate.

The hydrocarbon chain seems to be the important factor as to whether a lipid will increase transport. For example, it can be seen (Fig. 11) that only the unsaturated methyl sulfoxide increases transport. Stearyl methyl sulfoxide also had no effect on transport. However, for alcohols, even the saturated chains can increase transport (Fig. 12). Here, the longer chains are more effective at increasing transport until the length of the chain exceeds 14. At this point, solubility of the alcohol becomes too small for an effect on transport to be observed. Other diols also exhibit this synergism with lipids, but the effect is less pronounced as the chain length is increased (Figs. 13 and 14).

The mechanism by which the epidermal barrier properties are altered is

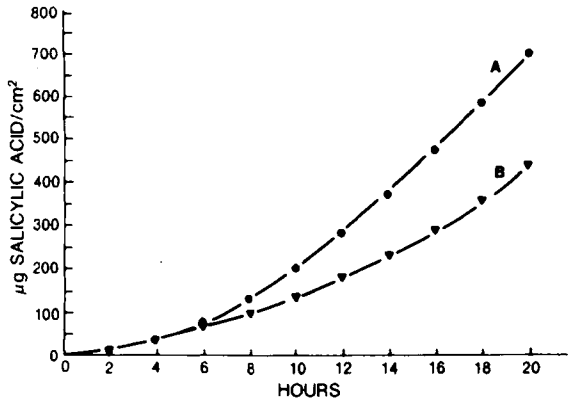

Figure 14—*Penetration of salicylic acid at saturation from oleic acid–1,2-hexanediol vehicles across human epidermis. Key: (A) 24% salicylic acid in 0.25 mole fraction oleic acid–1,2-hexanediol; (B) 14% salicylic acid in 1,2-hexanediol.*

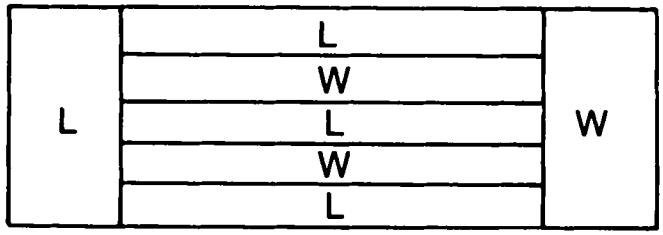

Figure 15—*Model for skin transport.*

not known, but differential scanning calorimetry studies of the stratum corneum[10] indicate that the two-component systems result in an increased fluidization of the stratum corneum lipids. This effect could then result in more rapid diffusion of the molecules across skin. The use of two different solvents to increase solute solubility has been known for some time as "cosolvency" and "blending" (5), and there might be a connection between cosolvency and the effects observed in this study on skin transport.

Regardless of the detailed mechanism by which these vehicles act, the results presented here open the door to the investigation of multicomponent systems to alter the barrier properties of skin. The penetration-aid guidelines obtained from this study and an earlier report (3) indicate that, for polar molecules, the head groups dominate (ionic > zwitterionic > nonionic) and for nonpolar molecules (polar solvent plus lipid), the hydrocarbon chains dominate. It was predicted that branched-chain lipids would be as effective as unsaturated lipids; this was, indeed, the case for isostearic acid.

A general way to categorize the pathways for transport in skin is depicted in Fig. 15, in which no attempt was made to assign a pathway to a particular morphological structure. J_s, the flux at steady state, can be written as:

$$J_s = a_w J_w + a_{Lw} J_{Lw} + (1 - a_w - a_{Lw}) J_L$$

where a_w is the area fraction of the aqueous pathway, a_{Lw} is the area function of the lipid–water pathway, J_w is the flux across the aqueous pathway, J_{Lw} is the flux across the lipid–water pathway, and J_L is the flux across the lipid pathway. It seems clear that there exists a continuous polar pathway, because the flux (at constant concentration) levels off with a decreasing oil–water partition coefficient and because surfactants act primarily to increase the transport of polar molecules. The pathway with the largest area fraction is probably the lipid–water pathway because molecules that have high solubility in both oil and water have the greatest transport. The lipid continuous pathway is included to account for the transport of very lipophilic molecules (such as benzyl salicylate), for which water becomes a major barrier to transport. The two-component systems described in this report act primarily on the lipid barriers, but they may have some effect on the polar pathway.

REFERENCES

(1) R. J. Scheuplein and I. H. Blank, *Physiol. Rev.*, **51**, 702 (1971).

(2) I. H. Blank, R. J. Scheuplein, and D. J. MacFarlane, *J. Invest. Derm.*, **49**, 582 (1967).

(3) E. R. Cooper, in "Solution Behavior of Surfactants: Theoretical and Applied Aspects," K. L. Mittal and E. J. Fendler, Eds., Plenum, New York, N.Y., 1982.

(4) E. M. Wright and J. R. Diamond, *Proc. R. Soc. B.*, **172**, 227 (1969).

(5) K. Shinoda, "Principles of Solution and Solubility," Dekker, New York, N.Y., 1978, chap. 10.

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[10] Experiments were performed in collaboration with Randy Wickett at the Miami Valley Laboratories.