(11). Cosmetics applied to skin previously exposed to solvents may be expected to penetrate more readily and possibly cause irritation. Depilatory creams and cold-wave solutions may be alkaline; only if their pH is greater than 11.5 will the barrier be sufficiently damaged to alter permeability.

REFERENCES

(1) Griesemer, R. D., "Protection Against the Transfer of Matter Through the Skin," In *The Human Integument*, Am. Assoc. Advance. Sci. Pub. No. 54 (1959), pp. 25–46.
(2) Mali, J. W. H., *J. Invest. Dermatol.*, **27**, 451 (1956).
(3) Blank, I. H., *Ibid.*, **18**, 433 (1952).
(4) Higuchi, T., *J. Soc Cosmetic Chemists*, **11**, 85 (1960).
(5) Blank, I. H., and Gould, E., "Penetration of Anionic Surfactants into Skin. I. Penetration of Sodium Laurate and Sodium Dodecyl Sulfate into Excised Human Skin," *J. Invest. Dermatol.*, **33**, 327 (1959).
(6) Szakall, A., *Fette, Seifen, Anstrichmittel*, **53**, 399 (1951).
(7) Stoughton, R. B., "Relation of the Anatomy of Normal and Abnormal Skin to its Protective Function," In *The Human Integument*, Am. Assoc. Advance. Sci. Pub. No. 54 (1959), pp. 3–24.
(8) Selby, C. C., *J. Invest. Dermatol.*, **29**, 131 (1957).
(9) Treherne, J. E., *J. Physiol. (London)*, **133**, 171 (1956).
(10) Blank, I. H., Personal communication.
(11) Blank, I. H., Personal communication.

PHYSICAL CHEMICAL ANALYSIS OF PERCUTANEOUS ABSORPTION PROCESS FROM CREAMS AND OINTMENTS

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PROBLEMS ASSOCIATED with penetration of intact skin are, of course, of great interest to both pharmaceutical and cosmetic chemists. Not only are we concerned with maximizing the rate of penetration of beneficial drugs from ointments and lotions but also in minimizing the rate of entry of toxic chemicals, as such, or from drug and cosmetic preparations. In this brief discussion I hope to review from the viewpoint of a physical chemist some of the factors which may govern the rate of the penetration process.

Despite the large amount of work already carried out in this field, there is very little agreement on the basis process which is largely responsible for percutaneous absorption through the intact skin. Many workers feel that essentially all penetration occurs through the transfollicular route. Other equally recognized investigators support the view that the major pathway of entry is transepidermal through the intact cornified and transition

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layers. A third and growing group is inclined to accept both routes, relative importance depending on the chemical nature of the penetrating agent. In this treatment little attempt will be made to resolve this controversy. Rather, general aspects of the problem which embrace largely both mechanisms will be presented based on laws of thermodynamics and diffusion, the only restriction being that the absorption process is not energetically coupled to any biological process.

Despite the dissimilarity in the two modes of drug movement through the skin structure (shown schematically in Fig. 1) there are relationships which are valid irrespective of the correct absolute mechanism. The rate

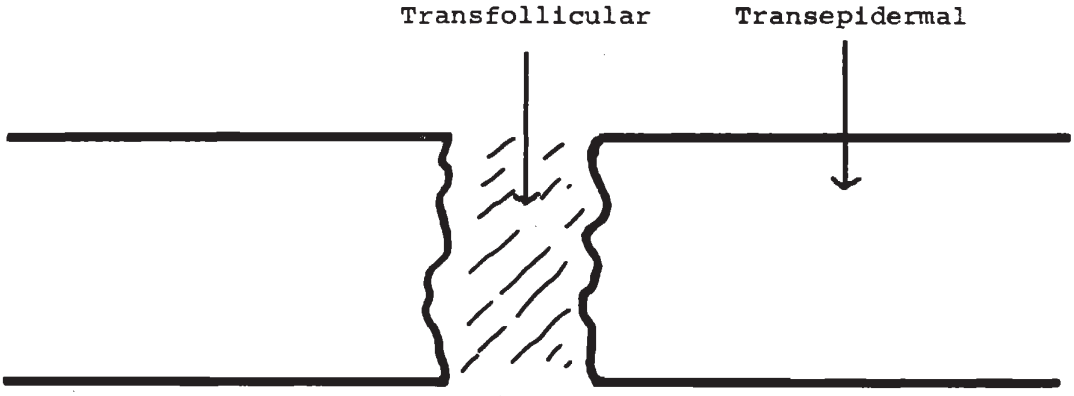


Figure 1.—Schematic diagram of two routes of percutaneous penetration.

of penetration by both pathways can be set up mathematically by employing as a model the diffusional process through a passive membrane. Resulting relationships, which appear to have received only partial attention in pharmaceutical and dermatological literature, should prove useful guides to those entrusted with development of new medicinal and cosmetic preparations.

Because of the nature and the complexity of the problem, it is convenient to divide the discussion into two parts. In the first we will analyze situations where the rate-controlling step or steps are in the skin. In the second part we will consider those cases where the thermodynamic potential drop of the percutaneously absorbed materials is largely in the applied phase such as an ointment base.

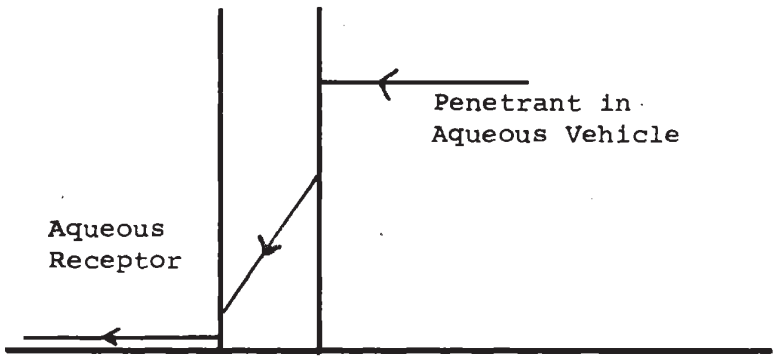
Relationships for Systems Where the Rate Controlling Barrier Is in the Skin

The majority of the cases of interest to us fall into this category. The skin is a wonderfully resistant cover and it is penetrated only with difficulty by most noncaustic substances. In our discussion of this aspect of the problem of percutaneous absorption, we will treat it initially in its simplest aspects, then attempt to see what additions and modifications must be made in our formulation to better fit the real systems.

Simplest Model. If it is assumed that the vehicle containing the penetrating chemical does not appreciably affect the skin, we can set up the following approximate relationship for an idealized system, such as shown in Fig. 2, between the steady state rate of penetration (dq/dt) and various properties of a fairly water soluble drug:

$$\frac{dq}{dt} = (P.C.)\,\frac{(\text{Conc. of Drug})\,DA}{L} \tag{1}$$

where ($P.C.$) is the effective distribution coefficient of the penetration agent between the vehicle and the barrier of the skin, (Conc. of Drug), the concentration of the agent in the vehicle, D, the effective average diffusivity of the agent in the barrier phase, A, the effective cross section area, and L, the effective thickness of the barrier phase.



$$\frac{dq}{dt} = D[PC]A\,\frac{[CONC]}{L} = A\,\frac{D}{\delta}\,\frac{a}{L}$$

Figure 2.—Schematic plot showing simple steady state diffusion across a barrier layer of thickness L.

The main characteristics of the penetrating agent which determine its rate of entry through the skin, according to this equation, are its effective partition coefficient and diffusivity in the barrier phase. The product of these two

$$(P.C.)\,(D)$$

is often spoken of as the permeability constant. If the barrier phase were available in the form of a film, the two constants can be separated and individually determined by a technique known as the lag time method. Actually the important variable in the permeability constant is the ($P.C.$) factor since diffusivity of a substance of similar molecular weight and shape usually differ only slightly. According to the Stokes-Einstein equation, D varies approximately only as the cube root of molecular weight. The partition coefficient, on the other hand, is an extremely sensitive function of molecular structure and size.

Another useful but equivalent form expresses the same equation in terms

of the thermodynamic activity of the penetrating agent in its vehicle:

$$\frac{dq}{dt} = \frac{a}{\gamma}\frac{DA}{L} \qquad (2)$$

where a is the thermodynamic activity of the drug in its vehicle and γ is the effective activity coefficient of the agent in the skin barrier phase.

The significance of the second relationship is apparent in Fig. 3 where both activity and concentration under steady state conditions of a hypothetical penetrating drug having a partition coefficient of $^1/_2$ and 2 have been plotted as a function of depth.

In the activity plot there is a discontinuity in the slope but not in the absolute value at the interphase. Whereas in the concentration plot there are usually sharp breaks in both. Since the driving force behind the drug movement is the difference in the thermodynamic potential between the vehicle and the deeper tissues, activity plots always show a decrease with depth. This is not necessarily true with concentration plots since favorable partition coefficients may result in an increase as shown in one of the examples in Fig. 3.

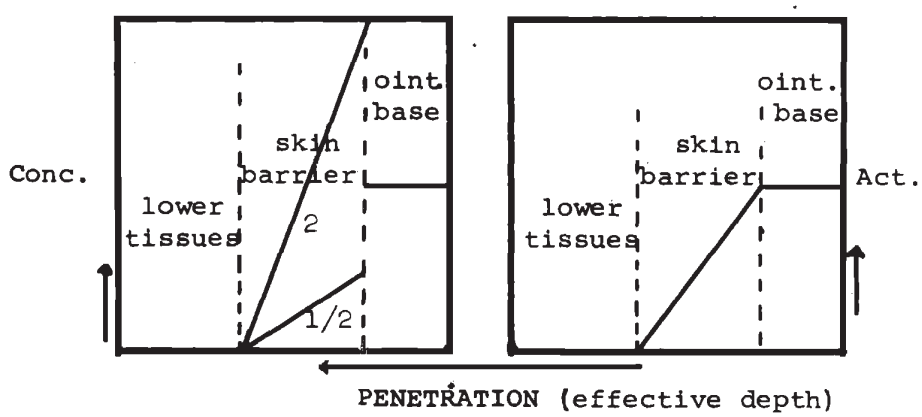


Figure 3.—Plots showing schematically the changes in concentration and activity with effective depth of penetration.

Although for thermodynamic reasons the direction of flow is always in the direction of negative concentration gradient for passive systems, one may conceivably obtain a net flow against the gradient if there exists an energy transfer mechanism. If Buettner's contention that water is readily absorbed through human skin from highly hypertonic solutions is correct, there must be a pump mechanism which will push water molecules against the gradient into body fluid.

Thermodynamic Activity and Rate of Penetration. In equation 2 only the activity of the drug in its vehicle appears, the properties of the base itself seem to play no part. For such systems the rate of percutaneous penetration measured for different ointment bases would be approximately constant provided the thermodynamic activity of the drug in the vehicles

was maintained constant. Thus all ointments containing finely ground suspensions of the drug (thermodynamic activity equal to that of the solid drug) will produce the same rate of penetration. This again presupposes that the rate determinining step is essentially in the passage of the barrier phase. For highly insoluble systems this would not be true as we will see later.

In order to obtain the maximum rate of penetration it is evident that the highest thermodynamic potential possible for the penetrating substances must be used. For simple organic compounds the activity of the pure form of the material at environmental temperature places, however, an upper limit on the available thermodynamics activity. Any higher activity would represent supersaturation with respect to the form. With more complex compounds, however, different crystalline modifications may exist having different free energies, thus different thermodynamic activities, at room temperature. In such instances the selection of the most energetic species will result in fastest penetration. These systems are, however, metastable and may show a gradual change in properties.

TABLE 1—LIMITING ACTIVITY COEFFICIENTS OF SARIN IN ORGANIC SOLVENTS AND WATER

Perfluorotributylamine	66.6	Diisooctyl adipate	1.84
Hexadecane	15.6	Methyl salicylate	1.74
Water	14	N-methylacetamide	1.44
Tributylamine	10.4	Dibutyl phthalate	1.42
Tetralin	4.3	Butryolactone	1.31
2-Pyrrolidone	2.8	Isoamyl alcohol	1.07
Diethylene glycol	2.4	Ethyl lactate	0.536
Carbon tetrachloride	2.4	Benzyl alcohol	0.446
Phenyl ether	2.38	*m*-Cresol	0.044

Since activities are important rather than any absolute concentration, it is obvious that, for a given concentration of the penetrating substance, vehicles which have lower affinity (poorer solvent power) will normally produce faster penetration. It is not commonly realized how dependent such activity coefficients are on solvents. In Table 1, I have listed values in some solvents for sarin, a nerve gas, which we determined a few years ago. It is evident that these values encompass three orders of magnitude. It is to be expected that the same degree of difference will be found in the rates of absorption of the fluorophosphate from these solutions.

In practical language one might say that solutes held firmly by the vehicle will exhibit low activity coefficients and slow rates of penetration. Good pharmaceutical examples of this behavior are the relative rates of release (penetration) of phenols from mineral oil or petrolatum bases and from camphor or polypropylene glycol bases. The latter preparations are mild and bland whereas the former are quite corrosive at equal concentrations. This is due to the reduction in the thermodynamic activity of the phenols caused by the ketone or the polyethers. Such complex formations usually

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