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Biophysical Factors in Skin Penetration

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Synopsis—The factors that affect rates and extent of PENETRATION of agents into the SKIN are dependent primarily on the physical-chemical properties of the penetrant and secondarily on pH, concentration, particle size, and vehicles. PHYSIOLOGICAL VARIABLES exerting penetrant influence are the intact or injured condition of the skin, the skin age, area of skin involved, and blood flow to that area. PHYSICO-CHEMICAL FACTORS involve the hydration and temperature of the skin and the concentration, solubility, and molecular characteristics of the penetrant. VEHICLES, under specialized conditions, can materially affect skin penetration.

Introduction

The skin is under constant assault by a huge variety of noxious chemicals as well as from substances applied to the skin as cosmetics or medicinals. The degree of penetration is dependent primarily on physiologic factors of the skin and physical-chemical factors due to the penetrant and somewhat secondarily on the vehicle or formulation. Generally, localized action is desired for cosmetics and medicinals. A maximum of agent should be concentrated at a particular epidermal site. Subsequent systemic absorption should be kept to a minimum to both prolong the contact of the drug with the skin tissues and reduce undesirable systemic side-effects. This review attempts to draw together the more significant work on these biophysical and formulation factors in the hope of improved correlative understanding.

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Physiological Factors in Skin Penetration

Skin Condition

The intact skin presents a formidable barrier to skin penetration. In diseases characterized by a defective horny layer, percutaneous absorption is increased (1–6). Removal of the skin barrier by cellophane tape stripping will enhance the absorption of almost any substance (7–10). Chemical agents such as acids, alkalies, or mustard gas injure barrier cells and increase water loss.

Solvents, other than water, appear to cause varied alteration in the resistance of the skin barrier (11–15). Tregear (16) has reviewed the permeability of the skin to aqueous solutes, organic liquids, and solutes in organic liquids and solids. Treatment with ether does not alter the penetration rate of salicylates or surfactants (14), while the polar solvents, acetone, alcohol, and hexane increase the penetration of water into the skin (17). Excised stratum corneum is virtually "opened" by delipidization of the stratum concern by holding it in a mixture of a polar and a nonpolar solvent, such as chloroform-methanol. Removal of the lipid fraction of the stratum corneum can be considered to make "holes" or "artificial shunts" in the membrane (18).

Skin Age

Relationship of age to skin permeability has rarely been investigated. Fetal and infant skin appears more permeable than adult skin (19). Percutaneous absorption of topical steroids occurs more readily in children than adults (20). The significant dermal atrophy and gross epidermal changes in the elderly denote absorption influence (21).

Regional Skin Sites

There are relatively few references in the literature to the variations in absorption from one skin site to another, and much of it is conflicting (22–36). In different "normal" individuals, there are wide variations in the absorption rate of a given substance through the same skin site, and penetration rates for the most permeable regions (posterior auricular skin) in some subjects are comparable to rates for the least permeable regions (plantar skin) in others (26). Variations in penetration rates have been demonstrated for full thickness cadaver skin, isolated from different sites. These permeations may be in direct proportion to the thickness of the area, for the penetration across skin, the flux, is inversely proportional to the thickness.

Cronin and Stoughton (37), using the erythema reaction produced by vasodilators such as ethyl nicotinate and histamine, demonstrated that the forehead, presternal area, and back showed a greater response than the limbs, and the arm was more reactive than the leg. They concluded that the presence of more follicles in the forehead indicated increased penetration through sebaceous glands. A similar conclusion was reached by Feldmann and Maibach (38), in studies of hydrocortisone. Measurable absorption occurred through all regions of human skin except the heel. Absorption seemed greater in areas where follicles are large or more numerous, such as the forehead and scalp, and decreased where the stratum corneum is thicker, such as the foot. Tregear (39), on the other hand, from studies of rapidly absorbed tributyl phosphate, concluded that hair follicles do not increase penetration. Smith *et al.* (36) observed a difference between the times taken for local anesthesia to develop on scrotal and abdominal skin after the topical application of lidocaine. With *in vitro* experiments they also found differences in the penetrability of skin between these two areas.

Blood Flow

If blood flow through the dermal vessels increases, the rate of clearance of materials should also increase as the concentration decreases. This is particularly true of gas permeation (40). Whether the rate of passage through the barrier layer is altered is not quite so clear, although it seems possible that this may occur as the more rapid removal of material that has penetrated must alter the perfusion gradient across this area. Clinically, erythematous skin is usually diseased, and this may alter the rate of absorption, at least partially due to increased vascular flow (21).

Species Variation

Human and animal skins display wide differences in physical characteristics such as the number of appendageal openings per unit area and the thickness of the stratum corneum, thus affecting the penetration pathways and the penetration resistance of skin (41). In spite of limitations, animals must be used in studies of percutaneous absorption because biologically dangerous substances, including radioactive compounds, are under many restrictions as to the application to human subjects.

The skin of rabbits, rats, and mice lacks sweat glands and abounds in hair and hair-follicles, in contrast to that of man. The relationship between species is not consistent for different substances, but the average

permeability order is rabbit, rat, guinea pig, and man in descending sequence (16). The largest deviation from the average is that human skin is very much less permeable to ions than rabbit or pig skin. While penetrability through rabbit skin is rapid, its structure of epidermis or appendages does not appear to differ significantly from that of other animals which are more resistant to penetration (40, 42, 43).

Physico-Chemical Factors in Skin Penetration

Hydration

Hydration of the stratum corneum is possibly the most important factor in skin penetration, increasing the rate of passage of all substances which penetrate the skin. Hydration results from water diffusing from underlying epidermal layers or from perspiration that accumulates after application of an occlusive vehicle or covering on the surface. Under occlusive conditions, the stratum corneum is changed from a tissue which normally contains very little water (5–15%) to one which may contain as much as 50% water.

The importance of hydration can be found in those investigations employing occlusive plastic film in steroid therapy. Here, the prevention of water loss from the stratum corneum and the subsequent increased water concentration in this skin layer enhances the penetration of the steroid (44–48). McKenzie and Stoughton (45) have shown that penetration of corticosteroids may be increased 100-fold by occluding the site of application, and thus hydrating the stratum corneum.

Wurster and Kramer (49) measured the rate of penetration of esters of salicyclic acid through skin with dry and hydrated stratum corneum. They found that when the tissue was hydrated the rate of penetration of the most water-soluble ester increased more than that of the other esters studied. Working with aspirin in a temperature-humidity chamber, Fritsch and Stoughton (13, 50) showed the dual importance of these factors on the penetration of excised skin. Full hydration of the keratin, accomplished by layering water over acetylsalicyclic acid on the epidermal surface, dramatically increased the penetration when compared to conditions of lower humidity at the same temperature.

The mechanism of transport of a drug through hydrated stratum corneum may be quite different from that through normal stratum corneum. The low diffusion constant and high activation energy obtained for water and polar alcohol, as well as the selective diffusion exhibited by molecules of varying polar character, suggest that extensive

hydration does not drastically affect the "barrier" function of the stratum corneum (24). The more important point to consider is the thermodynamic activity of water in the barrier phase, not just the amount there.

The efficiency of varied type vehicles in aiding penetration can be reasonably predicted on the basis of their effect on hydration of the stratum corneum or how the vehicle alters the activity of water in the stratum corneum and influences the stratum corneum/vehicle partition coefficient. Greases and oils are the most occlusive vehicles and induce the greatest hydration through sweat accumulation at the skin-vehicle interface (51). This is accentuated by covering with occlusive bandages or plastic. Emulsions of the water-in-oil type are less occlusive than greases. Substances in the vehicle, such as humectants, which have a high affinity for water, would act in proportion to the relative humidity of the environment. If the latter is low, the humectant would tend to dehydrate the stratum corneum and decrease penetration. Similarly, powders increase surface area, increase the rate of evaporation of water, and so decrease the extent of hydration (51).

Temperature

Under normal *in vivo* conditions, substances penetrate the skin only within a very narrow temperature range. Clinical variations derive chiefly from occlusion. *In vitro* experiments, on the other hand, may be conducted over a much wider range.

Blank and Scheuplein (25) studied the rates of penetration of ethanol and 1-pentanol within the range of 0 and 55°C. The flux, or the amount of alcohol penetrating per unit area in unit time, was an exponential function of the temperature. The energies of activation were determined by Arrhenius plots of the log of the permeability constant against the reciprocal of the temperature. The activation energies of the two alcohols differ measurably from one another and are higher than those obtained for diffusion of the same substances in solutions. The magnitude of the activation energies for the penetration of the low molecular weight alcohols through the skin indicates that penetration is a more complex process than diffusion through vehicle-filled channels. The same authors observed little alteration of the permeability of the barrier by exposure for several hours to temperatures as high as 60°C. However, Allenby *et al.* (52) showed that the stratum corneum undergoes irreversible structural changes when heated above 65°C or incubated in aqueous media at pH <3 or >9.

Concentration of Penetrant

The amount of penetrant percutaneously absorbed per unit surface area per time interval will usually increase as the concentration of the drug in the vehicle is increased. Diffusion through the skin is virtually always a passive process, governed by Fick's general law of diffusion:

$$\frac{Q}{At} = J_s = k_p \Delta C_s \quad (1)$$

where Q is the amount of the solute which penetrates; A is the area of the membrane; t is the time; J_s is the flux or the amount which penetrates per unit area in unit time; k_p is the permeability constant, and ΔC_s is the difference in concentration of the solute on the two sides of the membrane.

In essence, the driving force or rate of transfer across the membrane is the concentration of the applied drug. The permeability constant is of utmost importance, for by varying the concentration of the penetrant and observing the consistency of k_p, one can determine the extent to which Fick's law is applicable under the experimental conditions. When Fick's law is indeed applicable, the k_p value provides a satisfactory basis for comparing penetration rates obtained in different laboratories with different concentrations and techniques.

Thermodynamically, the activity of the drug in the vehicle is the product of the concentration of drug and the activity coefficient of the drug in the vehicle. For most substances, the rate of penetration is limited by the impermeability of the skin and, in such cases, the highest thermodynamic potential in the applied phase is necessary to obtain the maximum rate of penetration. For a given concentration of drug in certain vehicles, the activity coefficient of the drug, and consequently the thermodynamic activity of the drug in the vehicle at that concentration, may vary by a factor as much as a thousandfold from one vehicle to the next. Solutes held firmly by the vehicle, such as when the drug forms a soluble complex with the vehicle, exhibit low activity coefficients; hence, the rate of release from such drug-vehicle combinations will be slow. Solutes held "loosely" by the vehicle (less affinity of the vehicle for the drug or solute) exhibit high activity coefficients; therefore, the rate of release from such drug-vehicle combinations will be faster (11).

Higuchi (11) initiated the basic equations describing the variables affecting the rate of release of solid drugs suspended in vehicles. He

pointed out that the driving force behind the drug movement is the difference in the thermodynamic potential between the vehicle and the deeper tissues, and the direction of flow for systems is always from higher thermodynamic potential to lower thermodynamic potential. Wagner (53) has reviewed the thermodynamic considerations involved in vehicle-drug relationships.

The positive penetrative effects of increased concentration have been particularly demonstrated using varied steroids (53–56). Skog and Wahlberg (57) have shown a definite increase in the absorption of various compounds with increasing concentration in guinea pigs. They noted increasing penetration up to a certain point at which a plateau was reached. This may indicate that the barrier layer may not be primarily influenced by diffusion gradients, but act by limiting the total amount of any substance passing through in unit time. When true steady-state diffusion is reached, the permeability constants are independent of concentration.

Dimethyl sulfoxide (DMSO) has an unusual concentration dependence. Low concentrations are virtually without effect. As the concentration is increased, there is a rapid enhancement of percutaneous penetration (58). A direct relationship was obtained between the concentration of dimethyl sulfoxide and the rate of penetration of potassium methylsulfate (59).

Solubility Characteristics of the Penetrant

The aqueous solubility of a drug determines the concentration presented to the absorption site, and the partition coefficient strongly influences the rate of transport across the absorption site. Katz and Shaikh (60) indicate that the efficiency of percutaneous absorption may be a function of the product of the partition coefficient and the square root of the aqueous solubility, in agreement with theoretical considerations developed by Higuchi (11).

The lipid/water partition coefficient *per se* is not as significant as the stratum corneum/vehicle partition coefficient (11, 28). If a substance is much more soluble in the stratum corneum than in the vehicle in which it is dissolved, the concentration in the first layers of the stratum corneum at equilibrium may be much higher than the concentration in the presenting solvent. The concentration in the lower layers of the stratum corneum will remain near zero, since these layers are in contact with a fluid which is being continuously replaced, or through which diffusion is relatively rapid. The flux, therefore, is more accurately related to the

difference in concentration in the top and bottom layers of the stratum corneum. The concentration in the top layer of the stratum corneum will be determined by the relative solubility of the penetrant in the stratum corneum and the vehicle, i.e., the partition coefficient (K_m), as shown in the expansion of Fick's law:

$$J_s = \frac{K_m D_m}{\delta} \Delta C_s \tag{2}$$

where D_m is the diffusion constant, and the permeability constant (k_p) now becomes:

$$k_p = \frac{K_m D_m}{\delta} \tag{3}$$

When k_p and K_m have been determined experimentally, and δ is known, D_m can be calculated. The nonhomogeneous nature of the stratum corneum and the complications and uncertainties attendant upon an accurate determination of K_m and δ pose serious limitations in developing a satisfactory diffusion constant (61).

Main factors in the physico-chemical relationship of the penetrant to vehicle appear to be the solubility of penetrant in the vehicles or a constituent of the vehicle, the rate of diffusion of penetrant within the vehicle, the rate of release of penetrant from the vehicle, and the possible release of penetrant in solubilized form together with a constituent of the vehicle. Blank and Scheuplein (25) consider that differences in penetration from vehicles can be explained by differences in stratum corneum/vehicle partition coefficient without assuming that one vehicle penetrates more readily than another. From the "model" work using receptor phases, it should be possible, with suitable models, to predict *in vivo* effects (62).

Minato *et al.* (63) have reviewed the literature on the percutaneous absorption of various lipid-soluble substances. Tregear (16) has reviewed the permeability of the skin to water, electrolytes, and organic solvents. Treherne (64) has related the permeability constants of a series of compounds to their ether/water partition coefficients and suggested that a partition coefficient of unity might favor skin penetration. A similar relationship between the vasodilator activity and lipid/water partition coefficient was demonstrated for a series of esters of nicotinic acid by Stoughton *et al.* (65). They also found a similar correlation between the benzene/water partition coefficients and the penetration of the epidermis by a series of closely related boronic acid derivatives.

Cronin and Stoughton (66), studying the penetration of nicotinic acid and ethyl nicotinate, were able to show a very dramatic difference (37,000-fold) between the penetration rates of the two materials. They postulated that the differing ether/water partition coefficients of the two compounds were at least in part responsible for the difference. Aprotic molecules such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and dimethylacetamide (DMA), with high lipid and water solubility and the capacity to form strong hydrogen bonds, penetrate skin themselves and aid in the penetration of other agents.

The positive permeation effects of solubility and partition coefficient characteristics are perhaps best illustrated with the corticosteroids. Triamcinolone possesses five times the systemic activity of hydrocortisone but only one-tenth its topical activity. Conversion of triamcinolone to its acetonide yields a more favorable lipid/water partition coefficient and enhances the topical activity one-thousandfold (67). Similarly, betamethasone has 30 times the systemic activity of hydrocortisone, but only ten times its topical activity. Conversion to betamethasone-17-valerate, with a more balanced lipid/water coefficient, increased topical activity over tenfold (68). The effects of steroid solubility are also major factors in penetration from varied vehicles (60, 69–71).

Molecular Characteristics of Penetrant

An inverse relationship appears to exist between absorption rate and molecular weight (16, 25, 65, 72–74). Small molecules penetrate more rapidly than large molecules, but within a narrow range of molecular size there is little correlation between size and penetration rate. Diffusion constants through hydrated stratum corneum for many low molecular weight compounds appear approximately the same (75). Yet, when Feldmann and Maibach (19) determined the human urinary excretion of a series of topically applied molecules of relatively similar molecular weight (*ca.* 200), there was a large difference in penetration of the compounds tested.

The specific effect on penetration rate of the size and shape of the penetrating molecules can be determined only if the effect of size and shape can be separated from the effect of solubility characteristics. Blank and Scheuplein (25), in studies of homologous alcohols from methanol to octanol, noted that water solubility decreases and lipid solubility increases with increasing molecular weight, and the rate of penetration increases as the molecular weight increases.

Higher molecular weight materials also show variable penetration. Very large molecules such as proteins and polysaccharides go through very poorly, if at all. The use of DMSO as a penetration carrier indicated that substances which have molecular weights of 3000 or more cannot be transported into the skin (76). There are few published reports in which permeability coefficients are correlated with the size of penetrating molecules. Virtually nothing is known of the effect of molecular shape.

Miscellaneous Physical Factors

Other drug-vehicle factors of importance are the particle size of poorly suspended drugs, the viscosity of the vehicle, and the drug concentration in the vehicle. A reduction in the particle size of fluocinolone acetonide has been shown to enhance its penetration (77, 78). Where a drug exists in more than one crystalline form, the one with the highest thermodynamic activity would be expected to penetrate most rapidly, provided it is stable (11, 53).

VEHICLES

Factors in Release of Penetrant

The literature on the influence of vehicles on skin penetration is confusing and often contradictory. The variety of experimental animals and methods of estimating penetration renders correlation of results tenuous. A lack of awareness of possible drug-vehicle interactions and of the functions of different vehicles (18, 79, 80), as well as a lack of consideration of the thermodynamics involved in the interpretation of results (11, 18, 53, 81), has added to the difficulties. In general, the emphasis in developing vehicles has generally been placed on the compatibility, stability, and appearance of the product, rather than on the influence which the components in the vehicle had on enhancing or hindering the movement of the drug through the skin (82). Rothman (83) reviewed the literature on vehicles up to 1954, and Barr (84) to 1962. More recent reviews are those of Malkinson (1, 2), Vickers (21), Barrett *et al.* (79, 80), Busse *et al.* (62), Munro (85), and Sarkany and Hadgraft (86).

Physiological availability of a topically applied drug depends on both the rate of release from the vehicle and the permeability through the skin. The drug, incorporated in the vehicle, should reach the skin surface at an adequate rate and in sufficient amounts. Earlier belief held that the primary factor influencing penetration through the skin was the

vehicle itself. The bulk of evidence now indicates that unless an applied material is capable of passage either through the skin barrier or follicles the vehicle is of subsidiary importance. However, experimental and clinical evidence is now appearing which points the way to vehicles which may materially affect skin penetration (54, 56, 60, 62, 69–71, 87, 88).

The previous physico-chemical discussion of solubility and partition coefficients, as well as *in vivo* (54) and *in vitro* (25) studies, has supported the postulate that the release of a substance will be favored by the selection of vehicles having a low affinity for the penetrant, or in which the drug is least soluble. This is consistent with the view that the rate of release is governed by the vehicle to receptor phase (stratum corneum) partition coefficient.

For a given concentration of drug in certain vehicles, the activity coefficient of the drug, and consequently the thermodynamic activity of the drug in the vehicle at that concentration, may vary by a factor as much as a thousandfold from one vehicle to the next. Solutes held firmly by the vehicle, such as when the drug forms a soluble complex with the vehicle, exhibit low activity coefficients; hence, the rate of release from such drug-vehicle combinations will be slow. Solutes held "loosely" by the vehicle (less affinity of the vehicle for the drug or solute) exhibit high activity coefficients; therefore, the rate of release from such drug-vehicle combinations will be faster (11). This was shown by Blank and Scheuplein (24, 25) in a study of the penetration of polar ethanol and nonpolar heptanol from water and lipid solvents. Ethanol penetrates better from oils than from water, but the reverse is true for heptanol. The polar alcohol tends to stay in the polar vehicle and not be transferred to the skin, but it is transferred from oily vehicles; the reverse occurs for the nonpolar alcohol.

Dempski *et al.* (71) noted that dexamethasone was released more rapidly from gelled isopropyl myristate than from petrolatum and two other nonaqueous vehicles. Their studies demonstrated that the *in vitro* release of a medicinal agent is a function of the degree of solubility of that agent in both the base and its surrounding media. The medicinal must be sufficiently soluble in a nonaqueous base to allow for its release into an aqueous medium but not so soluble to preferentially remain in that base. If the drug is insoluble in its vehicle, it appears that only the drug particles available at the surface of the vehicle will dissolve into an aqueous medium. If the drug is partly soluble in the vehicle, it seems to dissolve and diffuse throughout the medium as it dissolves

from the surface, and then returns to the surface for release into the surrounding medium.

All the studies cited deal with the use of a skin membrane either *in vitro* or *in vivo*. Recently, solvents have been used to act as receptor phases to simulate the skin. Chloroform (54, 62) and isopropyl myristate (62, 69) have served as "sinks." Since they are immiscible with the alcohol-water it is not necessary to introduce an artificial membrane to separate them from the vehicles.

Poulsen and coworkers (69) measured the release of fluocinolone acetonide and its acetate ester into an isopropyl myristate phase. The vehicles used were mixtures of propylene glycol and water gelled with Carbopol 934 and diisopropanolamine. The studies showed that optimal release was obtained from vehicles containing the minimum concentration of propylene glycol required for complete solubilization of the corticosteroid. The poorest release rates were obtained with very high concentrations of propylene glycol. The results indicated that the important factors influencing the release into the receptor phase were the solubility in the vehicle and the partition coefficient of the steroid between the vehicle and the receptor phase. The findings appear to indicate that each compound requires individual formulation based on its solubility characteristics and the formulation may also need modification for different concentrations of the agent to obtain maximal release rates. Busse *et al.* (62) used both chloroform and isopropyl myristate (IPM) as separate receptor phases in studies of betamethasone valerate in ointment bases. The rate of release of the steroid into the chloroform phase from a paraffin ointment was about 4.5 times that from a similar ointment containing 10% hydrogenated lanolin. Conversely, in the IPM system, the reverse occurred. The *in vitro* results suggest the IPM system more adequately represents the skin.

"Accelerant" Solvents

In the past ten years attention has focused on methods of increasing the rate of absorption of topically applied drugs. So far, the one method that has come into everyday use is the application of topical corticosteroids under thin plastic film (46, 47, 89, 90). This method of treatment now has widespread application in the treatment of recalcitrant psoriasis. The other method is to add materials which can combine with, or dissolve in the structures of, substances which make up the barrier. These agents have come to be known as "accelerants." To increase permeability the

accelerant causes the keratin to swell and leaches out essential structural material from the stratum corneum, thus reducing the diffusional resistance and increasing the permeability (31, 58, 91–93). Varied agents have been reported to have accelerant action, particularly propylene glycol, surface active agents, and aprotic materials such as urea, DMSO, DMF, and DMA.

The evidence for the effect of propylene glycol in skin penetration is conflicting (56, 62, 69, 77, 88, 94–100). In combination with surface active agents, propylene glycol was claimed by MacKee and coworkers (94) to promote the penetration of water-soluble substances *via* the transfollicular route. A concentration of 1% 5-fluorouracil in propylene glycol has been found to be as effective clinically in certain skin carcinomas, as opposed to a minimum concentration of 5% in an ointment (100). Enhanced effects were noted in absorption of varied steroids (56, 62, 77, 96, 98, 99).

The most effective of the "accelerants" are DMSO, DMF, and DMA. On application to the skin, DMSO passes rapidly through the stratum corneum (52, 101–104) and can aid in the penetration of a wide range of substances. The role of DMSO in enhancing percutaneous migration is well documented (13, 91, 101, 105–110). DMF and DMA enhance cutaneous penetration to a lesser degree than DMSO. Work with these solvents is contributing greater understanding of the chemical nature of the skin barrier in relation to a specified penetrant and the transport mechanisms of various compounds across skin.

The mechanism of action of these penetrant accelerants needs greater definition. DMSO, DMF, and DMA are all strongly hygroscopic and it is likely that the presence of these substances in the stratum corneum increases the hydration of the tissue and therefore its permeability. There are possible reversible configuration changes in skin protein structure brought about by substitution of integral water molecules by DMSO (111), with resultant swelling. This may explain, in part, the sometimes observed variable role of DMSO. Swelling may induce the formation of channels within the matrix of the stratum corneum which either favor the passage of varied compounds (59) or lower the diffusional resistance of the stratum corneum. DMSO can extract soluble components from the stratum corneum, suggesting ultrastructural modifications consistent with an increase in permeability. DMSO exhibits an unusual concentration dependence (15, 52, 58, 59, 112). At least 60% DMSO is required for a measurable penetration rate. The rate rises to a maximum at

about 3 hours and then declines, and this is true for both the pure liquid and for DMSO-water mixtures containing >70% DMSO. The continued increase in the penetration rate of pure DMSO with increase in the applied quantity is probably a consequence of progressive barrier impairment. The decline in the peak rate after 3 hours is probably due to the back-diffusion of water with consequent dilution of the DMSO (52).

Surface active agents appear to play a major role in promoting transappendageal absorption. The influence, particularly of anionic type materials, seems related to their ability to increase the permeability of the skin to water by altering the physical state of water in the skin in such a way as to permit greater freedom to the passage of charged hydrophylic substances (73). The irritant action of anionic materials, such as, e.g., "soap" or sodium lauryl sulfate, suggests that they must penetrate to susceptible tissue. The role of surfactants in percutaneous absorption has been reviewed by Barr (84), Sprott (73), Ritschel (107), Scala *et al.* (113), and Minato *et al.* (63).

Penetration of certain antimicrobial substances appears enhanced by addition of surface active agents. Washing with sodium dodecyl sulfate enhanced the amount of hexachlorophene and tetrachlorosalicylanilide which penetrated rat skin (73). However, the bulk of evidence indicates that the stratum corneum is an effective barrier (12, 14, 59, 112–116). When penetration occurs, anionics penetrate best (12, 14, 113, 115–117), followed by cationics and nonionic surfactants (118, 119). Among anionic substances the laurate ion is reported to have the greater penetration and the most effect on the penetration of other solutes (117, 120). Soaps of different fatty acids have this property in varying degrees (117, 119), with penetration more significant for salts of fatty acids with chain length of 10 carbon chains or less (14, 73, 115). The penetration of fatty acid soaps varies inversely with pH (14, 73, 115). At higher pH (*ca.* 11), the action of the anionic surfactant appears to be attenuated or overshadowed by the influence of the more alkaline pH itself. Interpretation of surfactant action upon the skin must deal separately with these two phenomena, i.e., pH on the one hand and surfactant effect on the other. Possible mechanisms whereby the skin is able to restrict the percutaneous migration of synthetic anionic surfactants have been reviewed by Blank and Gould (14).

Scala and his colleagues (113) calculated permeability constants for a wide variety of materials, including surfactants. The nonlinearity of diffusion curves (permeability constants *vs.* time) for an anionic surfac-

tant (sodium tetrapropylenebenzenesulfonate), a cationic (dodecyltrimethylammonium chloride), and soap probably means that the barrier to these surfactants is being altered by the surfactants themselves as they diffuse into and through the skin. Decrease in the barrier properties allows an increased diffusion, which in turn results in a greater alteration of the barrier. Removal of the surfactant causes the process to stop at the stage of barrier alteration to which it had progressed.

Conclusion

While conflicting ideas and contrary evidence exist in elucidating skin barrier properties and mechanisms of skin penetration, it is becoming increasingly evident that main channels for understanding rest in well-defined studies of the physical-chemical properties of the agents and correlation with skin variables. Hopefully, chemical structures may be manipulated to effect selective permeability. The role of vehicles or formulation is likely to remain of subsidiary importance. However, there is need to pursue studies to resolve much conflicting evidence and elucidate further the mechanism of action of vehicles which enhance penetration of varied materials.

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