Chapter 11

Skin Penetration

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Contents

11.1 Introduction

Penetration of the skin is a key element in cutaneous reactions, be it to xenobiotics, to drugs, or to other compounds. The major difficulties in accurately describing percutaneous absorption are related to the size of the compartments. A topical application of a cream or ointment, for example, is routinely spread to a thickness corresponding to no greater than 10 µm.

The stratum corneum is also approximately 10 µm thick, whereas the viable epidermis, dermis, and to a greater extent the systemic compartment represent an effective large sink where absorbed substances undergo dilution to levels that often remain undetectable to all but the most sensitive techniques. Sampling the time-dependent changes in the concentration of a compound in individual compartments is thus technically challenging. Following application:

- Topical formulations may undergo radical changes in composition and structure.
- Xenobiotics are in general not evenly distributed on the skin surface.
- The effectiveness of the skin barrier often changes with time.
- The skin barrier is influenced by the type and progression of a disease.
- There is regional variation in the barrier properties of the skin.
- The viable tissues themselves respond to topical contact with xenobiotics in manners that may either enhance or retard percutaneous absorption.
- Drugs influence all of these processes in a more-or-less specific manner.

In view of these facts, the description of the kinetics of penetration after topical contact with a xenobiotic is a complex affair. A number of mathematical models have been developed to describe or define the relative importance of these processes in determining the bioavailability of compounds in a target tissue [1–6].

11.2 Diffusion

Any passage into and through the skin is governed by diffusion processes. In other words, active transport mechanisms play no role in penetration. Compounds that come into contact with the skin surface migrate down concentration gradients according to well-described laws governing diffusion of solutes in solutions and across membranes. For a more complete derivation of relevant equations, interested readers are referred to comprehensive reviews [7, 8].

11.2.1 Fick's Laws

Diffusion of uncharged compounds across a membrane or any homogeneous barrier is described by Fick's first and second laws. The first law states that the steady-state flux of a compound (J, mol/cm per second) per unit path length (δ, cm) is proportional to the concentration gradient (ΔC) and the diffusion coefficient (D, cm²/s):

$$J = -D(\Delta C/\Delta\delta) \qquad (11.1)$$

The negative sign indicates that the net flux is in the direction of the lower concentration. This equation holds for diffusion-mediated processes in isotropic solutions under steady-state conditions. Fick's second law predicts the flux of compounds under non-steady-state conditions. The solution to these equations depends upon defining appropriate boundary conditions [6–10]. However, regardless of whether diffusion occurs in a system under steady-state or non-steady-state conditions, the principal factors that determine the flux of a compound between two points in an isotropic medium are the concentration gradient, the path length, and the diffusion coefficient [11].

It is worthwhile pointing out that diffusion is a very effective transport mechanism over very short distances but not over long ones. The relationship between the time (Δt) it takes for a molecule to transverse a path length (x) and its diffusion coefficient is governed by:

$$\Delta t = x^2/2D \qquad (11.2)$$

For example, the diffusion coefficient for water in an aqueous solution is 2.5×10^{-5} cm²/s, suggesting that a water molecule would traverse a 10-µm path (the equivalent of the width of the stratum corneum) in 0.4 ms. However, since diffusion depends upon the square of the distance, longer pathlengths are not efficiently traversed: a 100-µm path would take 40 ms.

This explains why xenobiotics attain high concentrations in the upper layers of the skin, i.e., in the epidermis, while serum levels after cutaneous exposure remain low. The diffusional nature of percutaneous absorption also explains the exclusion of large molecules by the intact barrier: only a small number of such molecules per square centimeter can be brought into contact with the skin surface, which then encounter multilayers consisting of low-molecular-weight lipids with corresponding narrow intermolecular spaces (see below). As a rule of thumb, the passage of proteins and polymers >50,000 Da through the horny layer barrier becomes imperceptible.

Core Message

- Penetration is based on passive diffusion. There is no mechanism of active transport through the horny layer barrier.

11.3 Three-Compartment Model

Although pharmacokinetic analysis of topical applications may require the description of a relatively large number of compartments, this discussion is confined to three compartments: the skin surface, the stratum corneum, and the viable tissue. In order to undergo percutaneous absorption, a compound must be released from its formulation, particulate state, solvent, etc., encounter the skin surface, penetrate the stratum corneum, diffuse through the viable epidermis into the dermis, and finally gain access to the systemic compartment through the vascular system. In addition, it may diffuse through the dermal and hypodermal layers to reach underlying muscular tissues. Within each compartment, the compound may diffuse down its concentration gradient, bind to specific compound, or be metabolized.

11.4 The Skin Surface

11.4.1 Surface Contact

The physical forms of contact with the skin surface, that is dust, powders, solutions, and formulations, all differ in their physicochemical properties, and, as discussed below, this influences the kinetics of release and/or absorption. However, the principal consideration is that topical contacts represent a physically small phenomenon, significantly limited by the amount of compound that is applied to the skin surface. When a patient applies, for example, a dermatologic preparation, the layer of a semisolid formulation covering the skin is very thin, corresponding to a volume of between 0.5 and 2 mg/cm². Thicker layers are felt as "undesirable" and consciously or subconsciously rubbed or spread to larger surfaces. This restricts the amount of compound that can effectively come into contact with the skin surface to approximately 0.5–2 µg/cm² for a 1% (wt/wt) topical formulation and other contact forms.

However, even after being rubbed in, material on the skin surface does not remain homogeneous over the time frame of penetration [15]. Topical applica-

tions undergo evaporation, such that even relatively nonvolatile substances such as water are rapidly lost [16, 17]. This phenomenon is readily recognized by patients as a cooling sensation. The evaporation results in rapid concentration of nonvolatile substances on the skin surface, which may result in the formation of supersaturated "solutions" or precipitation of active ingredients. Any material also mixes with skin-surface lipids and undergoes time-dependent changes in chemical composition, as their carrier undergoes absorption. Taken together, these considerations suggest that dramatic changes in the composition and structure of form occur following surface application, which determines the subsequent bioavailability.

An additional consideration is that topical contact does not result in an even distribution over the skin surface, but material will be deposited in crevices and appendages. This may result in a relative increase in absorption through appendages. This phenomenon may be accentuated in forms that contain particles or precipitates, since there is evidence that appropriately sized particles can rapidly penetrate along the shafts of hair follicles to a depth of up to 100–500 µm [18, 19]. Such deposits might be an important element in allergic reactions to airborne allergens such as house dust, pollen, etc.

11.5 The Skin Barrier

The primary compartment that limits the percutaneous absorption of compounds is the stratum corneum. This thin (10–20 µm) layer effectively surrounding the body represents a highly differentiated structure that determines the diffusion of compounds across the skin. The physical description of the stratum corneum has now been well documented [20], and it can be accurately characterized as 'bricks", i.e., cornified cells consisting of bundled, water-insoluble proteins, embedded in a "mortar" of intercellular lipid.

The general consensus today is that the stratum corneum is a highly organized, differentiated structure. In order to participate fully in forming an effective barrier to diffusion, the biogenesis of the corneocytes as well as the synthesis and processing of the intercellular lipid must proceed in an orderly manner. Recent evidence suggests that disruption in the kinetics of skin barrier formation by accelerating the division of the keratinocytes found in the underlying layers will lead to a disruption in the barrier properties of the skin [16, 17]. Thus the concept of dead or dying skin forming a passive barrier to diffusion is now replaced by a model of the stratum corneum as a highly differentiated structure that has unique properties particularly suited to its role in forming the skin barrier.

11.5.1 Corneocytes

Fully 85% of the stratum corneum is protein (as a percentage of dry mass), mostly associated with cornified cells, i.e., the corneocytes. These structures contain a core of keratins surrounded by an envelope made up of cross-linked proteins [21]. The keratins may account for up to 80% of the total dry mass of the corneocytes and thus represent the most important constituents. In addition to these fibrous proteins, the core contains low-molecular-weight polar compounds such as amino acids, urocanic and pyrrolidone carboxylic acid. These compounds play a role in maintaining the hydration properties of the stratum corneum.

11.5.2 Intercellular Lipid

Interspersed between corneocytes, the intercellular lipid is organized into sheets, which provide the primary barrier to diffusion across the stratum corneum [22]. This lipid is located in an extracellular domain and thus is not morphologically equivalent to a cellular membrane. The lipid accounts for approximately 15% of the dry weight of the stratum corneum or 20% of the volume. It is composed of roughly equimolar mixtures of ceramides, cholesterol, and long-chain free fatty acids. There is now substantial evidence that these lipids form structures [23, 24] wherein diffusion of the lipidic substances is more than 1,000-fold less than that found in cellular membranes [25, 26]. This material property of the intercellular lipid is particularly suited to play a role as a barrier to diffusion [20].

Core Message

- It is the complex structure of the thin stratum corneum that limits the penetration of compounds through the horny layer barrier.

11.5.3 Appendages

A variety of appendages penetrate the stratum corneum and epidermis, facilitating thermal control and providing a protective covering. Appendages are potential sites of discontinuity in the integrity of the skin barrier. Appendages account for 0.1% to 1% of the area of the skin and 0.01% to 0.1% of the total skin volume. It can be concluded that in order to significantly influence the flux of compounds across the skin, the diffusion coefficient has to be considerably higher than that across the intercellular lipid domains or corneocytes. For this reason, it is likely that "shunt" pathways are relatively more important for molecules exhibiting relatively slow rates of percutaneous absorption and are of primary importance during early stages after topical contact. There is unequivocal proof that solid material can enter the lower lumen of the hair follicle [27]. Follicular penetration was clearly demonstrated for titanium dioxide particles [28]. Thus one has to assume that any allergenic material associated with or presented as particles can take this route, thereby bypassing the horny layer barrier. The extent to which such a passage contributes to the allergic and irritant reaction to airborne xenobiotics (pollen allergens, etc.) and to bulky proteins in general merits further investigation.

Core Message

- Hair follicles present sites of imperfection in the skin protection afforded by the barrier function of the horny layer. They have to be taken into consideration as a port of entry for large molecules (proteins, etc.) as well as particles carrying adsorbed allergens.

11.5.4 Pathways Across the Stratum Corneum

The relevance of the intercellular lipid domain to permeation of compounds across the stratum corneum (Fig. 1) is inferred from the striking relationship between the hydrophobicity of compounds and their permeability coefficients across the skin [28, 29]. This suggests that the rate-limiting step for permeation includes a hydrophobic barrier, i.e., the intercellular lipid. The observation that small polar molecules such as urea exhibit higher permeability coefficients than expected on the basis of their partition coefficient between *n*-octanol and water has been interpreted to support the presence of polar and apolar pathways [29, 30]. However, alternative single-pathway models indicate that this observation can be accounted for by considering the influence of molecular volume on the relative diffusivity of compounds in membranes [30–32]. In addition, available evidence suggests that the only continuous domain within the stratum corneum is formed by the intercellular lipid space [32, 33]. This implies that compounds penetrating the stratum corneum must pass through intercellular lipid, although it does not exclude the possibility that compounds can also enter the inner lumen of corneocytes.

There are several studies that have directly visualized penetration pathways across the stratum corneum with electron microscopy. Osmium tetroxide vapor can be used to precipitate *n*-butanol that has penetrated the stratum corneum [32, 33]. Following a brief (5- or 60-s) exposure of murine or human stratum corneum, the alcohol was found enriched in the intercellular spaces (threefold), though significant levels were also found in the corneocytes. Using a different approach involving rapid freezing, water, ethanol, and cholesterol were also found preferentially concentrated in the intercellular lipid spaces [33, 34].

However, in most of these investigations there was also significant localization of compounds in the corneocytes, more prevalent in the upper layers (stratum disjunctum). Thus, corneocytes undergoing desquamation appear to be relatively permeable, even to rather bulky ions such as mercury. There is additional evidence that other compounds can and do penetrate the corneocytes. It is well established, for example, that occlusion or immersion of skin in a bath leads to swelling of the corneocytes, consistent with the entry of water. Other compounds have also been localized to corneocytes, including the binding of anionic surfactants to keratins. Low-molecular-weight moisturizers such as glycerol are likely to partition into the corneocytes and alter their water-binding capacity. Thus, the penetration of corneocytes cannot be excluded when considering percutaneous absorption pathways.

11.5.5 Inter- and Intra-individual Variation in Skin-Barrier Function

Finally, it is worthwhile considering the level of inter- and intra-individual variation in skin. The most ac-

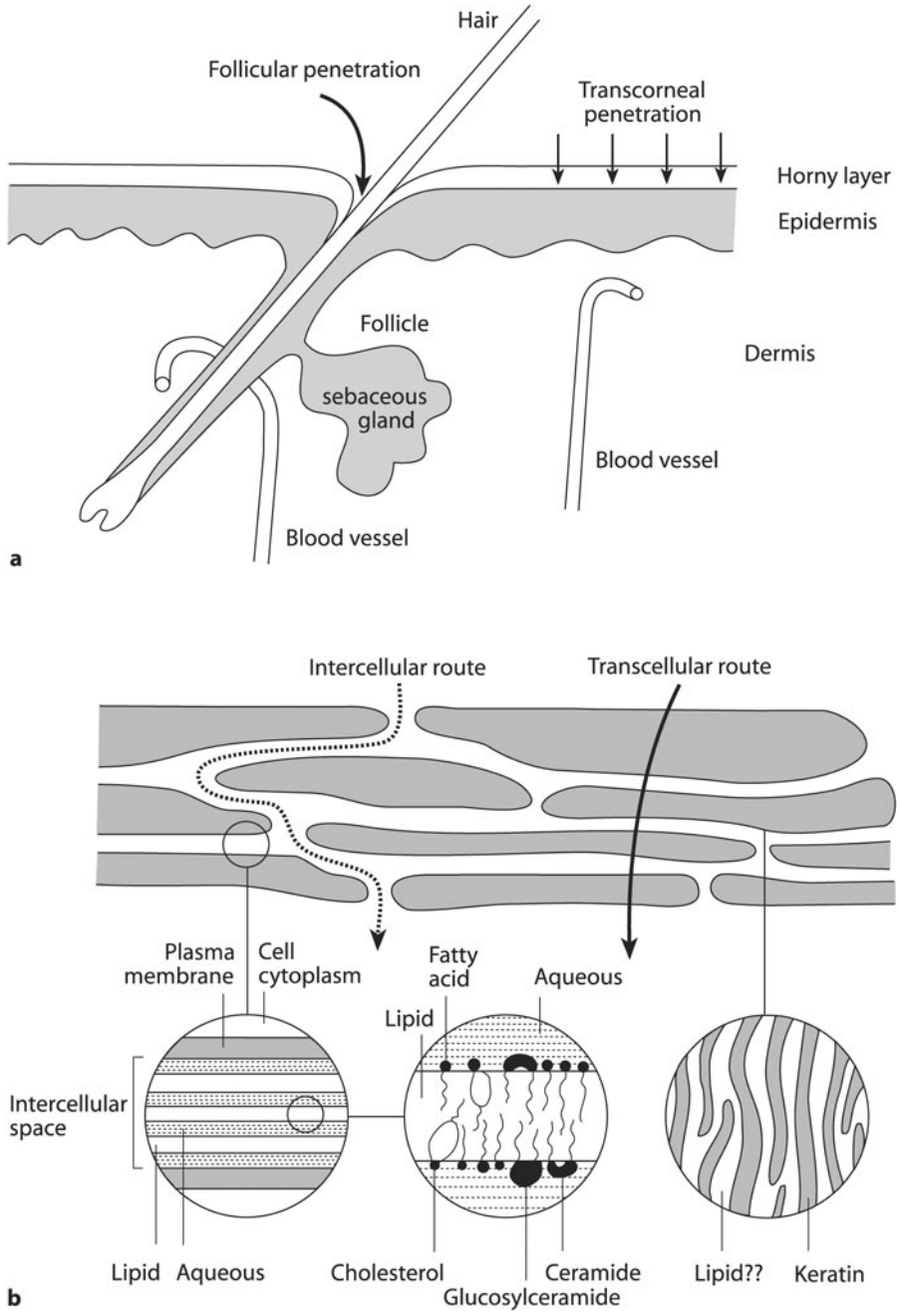

Fig. 1a, b. Model of penetration pathways. **a** Penetration occurs via appendages that exhibit a reduced barrier to diffusion but occupy a relatively small surface area. **b** Permeation through the stratum corneum (transcorneal permeation) may be considered to occur through the intercellular lipid domain or through the corneocytes (transcellular route). (From [20])

curate and reproducible method of measuring barrier activity is to follow transepidermal water loss (TEWL) [34–37]. The extent of within-individual variation in this parameter has been estimated to be 8% by site and 21% from day to day. The variations between individuals are reported to be somewhat larger, ranging from 35% to 48% [37, 38]. There appears to be no significant sex- or race-dependent differences in skin-barrier activity. The skin-barrier activity of premature infants (delivered more than 3 weeks premature) has been demonstrated to be markedly impaired, whereas skin-barrier function

appears normal for full-term infants. There seems to be no significant alteration in skin-barrier activity as a function of age. Better-defined differences in skin barrier activity between different sites are observed; barrier function can be ranked as arm > abdomen > postauricular > forehead [34–37]. Undoubtedly contact sensitization and elicitation depend on threshold concentrations in the viable tissue, which however depend on quite a number of factors (surface concentration, size of contact area, antigenic potency of the allergen, number of exposures, effect of draining lymph node, vehicle, occlusion, eczematous conditions), as well as the degree and route of penetration [39, 40].

Core Message

- Thresholds for sensitization and elicitation depend on many things including the degree of penetration by allergens: potency overrules penetration.

11.6 Viable Tissue

Although the primary barrier to percutaneous absorption lies within the stratum corneum (Fig. 2), diffusion within the viable tissue as well as metabolism and resorption will also influence the bioavailability of compounds in, and passage through, specific skin compartments. These processes are interrelated, and factors that increase the rate of one of these processes inevitably influence the others.

The passage of compounds from the stratum corneum into the viable epidermis results in a substantial dilution (Fig. 3). This reflects not only the relatively larger size of the epidermis as compared with the stratum corneum, but also the lower resistance to diffusion within viable tissues, corresponding approximately to that on an aqueous protein gel [37, 38]. Concentrations of 10^{-4}–10^{-6} M may be attained in the epidermis and dermis for substances that permeate readily (Fig. 3). Although the actual concentration gradient of a compound is influenced by both its physicochemical properties and the time of contact, the presence of a concentration gradient is visible at

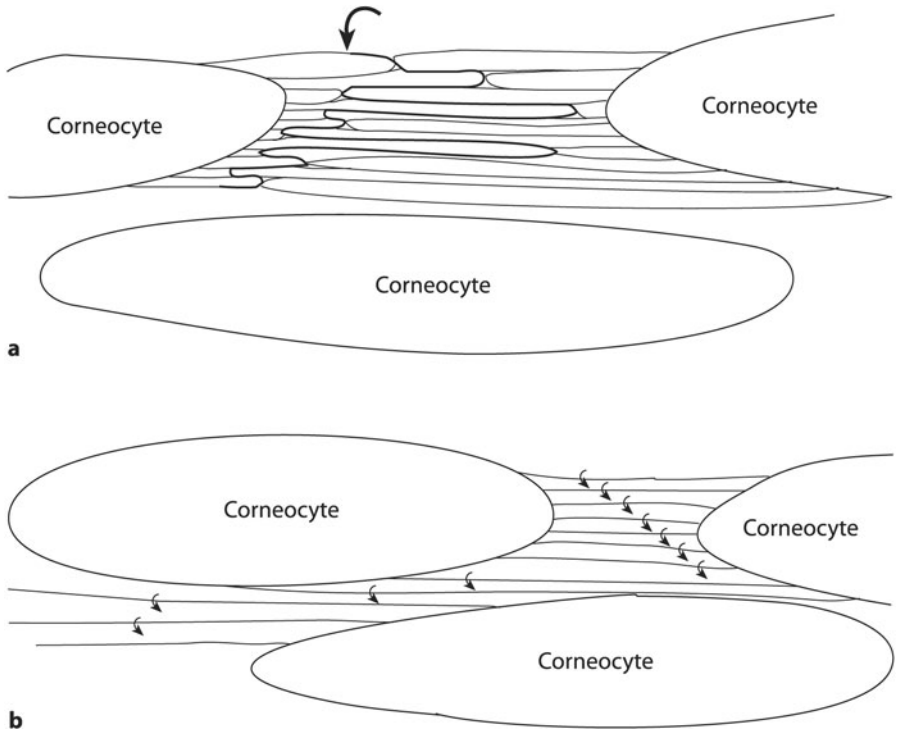

Fig. 2a, b. Schematic of possible penetration pathways through the intercellular lipid domain. **a** Diffusion of compounds may occur along lipid lamellae (*single line*), which occasionally penetrate the stratum corneum, or **b** diffusion occurs across the lamellae in a mechanism that is analogous to diffusion across lipid bilayers. **a** The pathway is indicated by a *heavy line*; **b** the pathway is denoted by an *arrow* to indicate translamellar diffusion and *lines* to denote lateral-lamellar diffusion. (From [20])

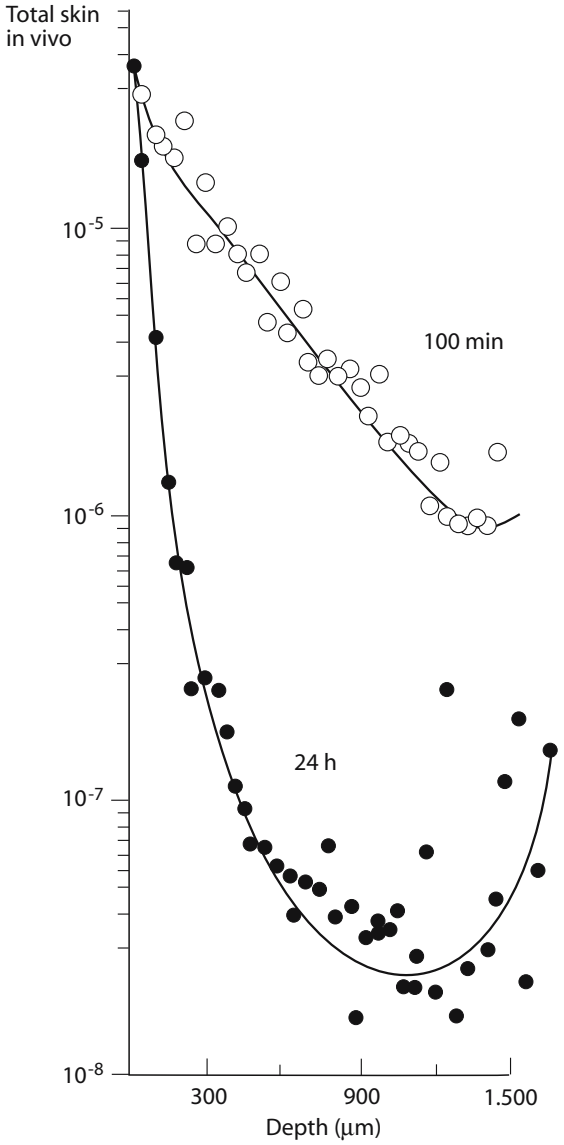

Fig. 3. Distribution of 8-methoxypsoralen (*8-MOP*) in the skin at the indicated time after application. At early time points, a steep nonlinear gradient is observed across the whole of the skin. At later periods, the concentration in the dermis has begun to level off. (From [20])

all times. In other words, strategies to enhance or decrease percutaneous absorption generally result in a relatively even increase or decrease in the concentration of compounds in all compartments.

11.6.1 Skin Metabolism

The skin contains a wide range of enzymatic activities, including phase-I oxidative, reductive, hydrolytic, and phase-II conjugative reactions as well as a full complement of metabolizing enzymes [38, 39, 41,42]. Metabolic activity is a primary consideration in the design of prodrugs and may influence the bioavailability of drugs delivered via dermatologic or transdermal formulations.

Alterations in skin metabolism have been implicated in a range of diseases including hirsutism and acne, and they may be relevant to risk assessment of carcinogens. Metabolic processing of antigens by Langerhans cells is involved in the presentation of allergens to the immune system. Thus, metabolism in the skin compartments plays a significant role in determining the fate of a topically applied compound.

Significant cutaneous metabolism has been demonstrated for a wide variety of compounds of differing physicochemical properties, including the steroid hormones estrone, estradiol, and estriol as well as glucocorticoids, prostaglandins, retinoids, benzoyl peroxide, aldrin, anthralin, 5-fluorouracil, nitroglycerin, theophylline, and propranolol [38, 41]. It is convenient to classify metabolic reactions in terms of their cofactor dependence. Processes that require cofactors are likely to be energy-dependent and thus to be located within viable tissues. Among the best-studied examples are the interconversion of steroids (e.g., estrone and estradiol), and the oxidation of polycyclic aromatic hydrocarbons with mixed-function mono-oxygenases. Cinnamic aldehyde and cinnamic alcohol are known allergens, cinnamic aldehyde being the more potent sensitizer. It has been assumed that cinnamic alcohol is a "prohapten" that requires metabolic activation, presumably by oxidoreductase enzymes such as alcohol dehydrogenase or cytochrome P450 2E1, to the protein reactive cinnamaldehyde as hapten. In fact such bioconversion could be demonstrated in human skin [43]. In contrast, cofactor-independent processes involve catabolism and may be located outside of viable tissues, i.e., in the transition region between the stratum corneum and stratum granulosum. The best characterized of these involve hydrolytic reactions such as those described for nonspecific ester hydrolysis. Furthermore activation can take place outside the tissue: ethoxylated nonionic surfactants were shown to be susceptible to oxidation on air exposure and to form allergenic hydroxyaldehydes. More importantly irritant components present in the oxidation mixture facilitated the penetration [44].

Metabolic activity is found in: (1) skin-surface microorganisms, (2) appendages, (3) the stratum corneum, (4) the viable epidermis, and (5) the dermis. In considering the site of the most significant metabolism, one has to take into account the relevant enzymes and their specific activity as well as their ca-

pacity relative to the size of the compartment. Thus, though the level of many enzymes is highest in the epidermis, the relatively large size of the dermal compartment may play a significant role in determining the site of metabolism. A further consideration is that enzymes involved in cutaneous metabolism may be induced upon exposure to xenobiotics. This has been well described for various mixed-function mono-oxygenases [39, 42]. Finally, the quantitative extrapolation of results from animal models to humans is hazardous owing to the significant species differences in the metabolism of compounds.

However, despite the variety of skin-associated metabolic processes, the extent of metabolism is normally relatively modest, perhaps 2% to 5% of the absorbed compounds. Metabolism is limited not only by the relatively short period of time that a compound spends in the viable layers of the skin, but also by the overall level of enzyme activity. Thus, under many circumstances, the available enzymes are saturated by the level of compound undergoing percutaneous absorption [38, 41].

Core Message

- Pure compounds are not necessarily capable of eliciting allergic reactions: metabolism before and during penetration of the skin may activate compounds to potent allergens.

11.6.2 Resorption

Resorption, defined as the uptake of compounds by the cutaneous microvasculature, is directly related to the surface area of the exchanging capillaries as well as their blood flow. Total blood flow to the skin may vary up to 100-fold, a process primarily regulated by vascular shunts as well as by recruitment of new capillary beds [40, 41, 45, 46]. It has been estimated that, under resting conditions, only 40% of the blood flow passes via exchanging capillaries capable of acting as a sink for absorbed compounds. However, this value demonstrates considerable variation between body sites, individuals, and species [42, 47], and is influenced by disease states and environmental conditions. In particular, changes in temperature and humidity as well as the presence of vasoactive compounds may directly influence skin blood flow [43, 48].

11.6.3 The Influence of Pathologic Processes on Skin Barrier

It has been argued that the molecular weight of a compound must be under 500 Da to allow absorption through the skin [49]. This assumption is however based on a "macrophysiological" view of penetration kinetics, considering transcorneal diffusion to be the only route of entry into and through the skin. This view is contradicted by the very experience that proteins can be allergenic [39]. Two possible routes for protein penetration have to be taken into account: First, large molecules, and in fact particulate material, can enter deep into the lumen of hair follicles, as mentioned above [29]. Thereby they reach an area that is devoid of protection by a barrier [50], and which is surrounded by a dense population of immune-competent dendritic cells. Second, irritation is known to provoke barrier defects, thereby allowing proteins to enter into direct contact with the viable epidermis and its immune-competent Langerhans cells [20, 39, 44, 51, 52]. Environmental factors such as low humidity are suggested to increase the number of Langerhans cells as well as favor penetration by trinitrochlorobenzene [53]. Depending on the vehicle, occlusion may increase or decrease the response when testing the allergenic potency of parabens [54].

Reduced skin-barrier function is observed for a number of pathologic conditions including ichthyosis [44–46, 55–57], psoriasis [47, 48, 58, 59], atopic dermatitis [49, 50, 60, 61] and contact dermatitis [51, 62] (Tables 1 and 2). It is generally accepted that this can be attributed to structural alterations in the stratum corneum [20]. Structural deficiencies may arise from abrasion, from the extraction of lipids by solvents or strong detergents, by exposure to potent alkaline or acidic fluids and dusts, by the absence of an enzyme or structural protein in the underlying viable tissues, or they may be related to the improper formation of the stratum corneum resulting from an increase in keratinocyte proliferation [52, 63], as in the case of psoriasis. A consequence of poor barrier function is a further increase in penetration by xenobiotics, which

Table 1. Excretion of triamcinolone acetonide in the urine after topical application to normal and psoriatic skin

Skin area	Applied preparation	Excretion (%)	Time (h)
Uninvolved skin	0.1% cream	0.4	72
Psoriatic skin	0.1% cream	4.3	72
Healthy skin	0.1% cream	1.4	72

Table 2. Barrier function as measured by transepidermal water loss (*TEWL*) for normal, uninvolved, and involved psoriatic skin [20]. (*NS* Not significant)

Condition	TEWL (g/m^2 per h)	Student's *t* test
Healthy individual	4.3±1.2	NS
Uninvolved skin	6.3±1.8	n.a.
Psoriatic plaque	11.5±6.3	$p<0.05$
After scale removal	29.1±9.8	$p<0.05$
Fissured plaque	20.9±8.0	$p<0.05$

Student's *t* test is in comparison with uninvolved skin

may accentuate the problem. Thus in individuals predisposed to a defective barrier, a minor perturbation may become amplified as the skin attempts to compensate by increasing keratinocyte proliferation [52, 63]. As a rule of thumb in areas devoid of a functional horny layer, the penetration by a compound is increased by a factor of 3- to up to 15-fold. A further consideration is that the homeostatic mechanisms responsible for recovery of barrier activity after perturbation may be altered in some diseases or physiologic states. For example, whereas the skin of elderly people exhibits normal barrier function, the recovery of barrier activity after perturbation is markedly reduced [53, 64]. This kinetic basis for reduced barrier function may also account for inter-individual variation in barrier function and/or an apparently increased susceptibility of certain individuals to contact dermatitis [51, 62]. It follows that, on the one hand, in skin areas with pathologically disturbed barrier function the entrance of topical substances is accelerated and increased relative to the surrounding normal skin (targeting to the disease). On the other hand, once an irritant has overcome the barrier it facilitates its own penetration, thereby amplifying the damage [54, 65].

Core Message

- Any disturbance or disorder of the barrier function facilitates penetration by allergens. This is particularly true for eczematous conditions such as atopy, psoriasis, etc.

11.6.4 Allergens

Surprisingly little work has been published on penetration by allergens. Nickel penetrates through rubber gloves [55, 66]. However, its penetration of the skin is relatively minimal [56, 67] and depends on the vehicle [57, 68]. Occlusion enhances its penetration [58, 69]. Differences in higher penetration by squaric acid esters as compared to low penetration by squaric acid explain why the latter is a less-effective sensitizer in the sensitization therapy of alopecia areata [59, 70].

Pre-treatment with topical cyclosporin appears to provoke a perturbation of the horny layer barrier and thereby enhances penetration by allergens rather than inhibiting the allergic reaction by immunosuppression [60, 71].

One has to suppose that the elicitation of allergic reactions depends largely on the individual patient's barrier function, and thus on the influence of the site of elicitation, moisture, temperature, season, and environmental and endogenous factors on the penetration by the allergen in question.

Much more work is needed to address the prevention of elicitation by restricting allergen penetration: a hypothetical reduction of such penetration by a factor of three would lower the titer, and hence the frequency and severity of allergic reactions by a factor of three as well.

Several papers address the efficiency of barrier creams in reducing penetration by allergens and irritants [61–66, 72–77], demonstrating moderate to good protective capacity.

11.7 Vehicles

The influence of a carrier medium on percutaneous absorption of an incorporated substance is very complex [20]. It depends on the physicochemical interaction between a compound and its carrier as well as between the carrier and the skin surface. In very general terms the primary factor governing the passage of a compound is its own physicochemical property, that is its molecular size, polarity and lipophilicity: small nonpolar and moderately lipophilic substances penetrate best; highly polar water soluble compounds, least. The influence of classical vehicles on the passage of these two extremes is limited. The most prominent "vehicle effect" is reached either by pushing the concentration of a compound close to its solubility limits in a given carrier (thereby increasing its thermodynamic potential in favor of diffusion out of the vehicle and into the skin) or by dis-

turbing the barrier function. However, the potential of so-called penetration enhancers is limited in practical terms, since the disturbance of the barrier function challenges the homeostatic equilibrium in the stratum corneum and provokes a counteraction in the sense of a strengthening of the barrier.

Core Message

- The carrier acts on the barrier – it can increase or decrease exposure to allergens.

11.8 Conclusions

The principal factors determining the kinetics of the diffusion into the skin of a xenobiotic are the physiochemical properties of the molecule. Hydrophobicity, molecular weight, and ionic charge determine the feasibility of transdermal delivery for any particular compound. Form of contact influences the kinetics largely from considerations of the thermodynamic activity of the compound. However, one should not exclude the impact of changes in the physical forms that occur following topical application. Evaporation, and changes in the structure of emulsion, dissolution in sebum, entry into the follicle, etc. may bring dramatic changes in the thermodynamic activity of the compound. Under some circumstances, this may lead to the retention of the drug on the skin surface.

The rate-limiting step for percutaneous absorption of most compounds is its penetration through the stratum corneum. There is substantial evidence that this is related to diffusion through a tortuous path around the corneocytes within the highly structured intercellular lipid, the constituents of which exhibit diffusional properties consistent with their role in the skin barrier. For skin diseases exhibiting reduced skin-barrier function, the absence of these critical structures may account for the decreased barrier activity. The progression of a disease and the inherent biological variability make predictions of percutaneous absorption for diseased skin inherently difficult. This contributes significantly to the challenges of developing topical applications of drugs as well as to that of barrier creams.

Processes occurring in viable tissues can have a significant though generally less-important influence on the bioavailability of compounds undergoing percutaneous absorption. It has been difficult to establish in vivo the level of skin-related metabolism of drugs undergoing percutaneous absorption.

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