Part One

Current Science, Skin Permeation, and Enhancement Approaches
Chapter 1

Skin Structure, Function, and Permeation

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INTRODUCTION

The skin is the largest organ of the body, covering about 1.7 m² and comprising approximately 10% of the total body mass of an average person. The primary function of the skin is to provide a barrier between the body and the external environment. This barrier protects against the permeation of ultraviolet (UV) radiation, chemicals, allergens and microorganisms, and the loss of moisture and body nutrients. In addition, the skin has a role in homeostasis, regulating body temperature and blood pressure. The skin also functions as an important sensory organ in touch with the environment, sensing stimulation in the form of temperature, pressure, and pain.

While the skin provides an ideal site for administration of therapeutic compounds for local and systemic effects, it presents a formidable barrier to the permeation of most compounds. The mechanisms by which compounds permeate the skin are discussed later in this chapter, and methods to enhance permeation are described in Chapters 2–4. An understanding of the structure and function of human skin is fundamental to the design of optimal topical and transdermal dosage forms. The structure and function of healthy human skin is the main focus of this chapter. Physiological factors that can compromise the skin barrier function, including age-related changes and skin disease, are also reviewed. Chapter 19 describes the current and future trends in the treatment of these and other skin diseases.

HEALTHY HUMAN SKIN: STRUCTURE AND FUNCTION

Human skin is composed of four main regions: the stratum corneum, the viable epidermis, dermis, and subcutaneous tissues (Fig. 1.1). A number of appendages are
associated with the skin: hair follicles and eccrine and apocrine sweat glands. From a skin permeation viewpoint, the stratum corneum provides the main barrier and therefore the structure of this layer will be discussed in most detail. The other layers and appendages contribute important functions and are important target sites for drug delivery.

**Epidermis**

The epidermis is a multilayered region that varies in thickness from about 0.06 mm on the eyelids to about 0.8 mm on the palms of the hands and soles of the feet. There are no blood vessels in the epidermis, therefore epidermal cells must source nutrients and remove waste by diffusion across the epidermal–dermal layer to the cutaneous circulation in the dermis. Consequently, cells lose viability with increasing distance from the basal layer of the epidermis. The term “viable epidermis” is often used for the epidermal layers below the stratum corneum, but this terminology is questionable, particularly for cells in the outer layers. The epidermis is in a constant state of renewal, with the formation of a new cell layer of keratinocytes at the stratum basale, and the loss of their nucleus and other organelles to form desiccated, proteinaceous corneocytes on their journey toward desquamation, which in normal skin occurs from the skin surface at the same rate as formation. Thus the structure of the epidermal cells changes from the stratum basale, through the stratum spinosum, stratum granulosum, and stratum lucidum to the outermost stratum corneum (Fig. 1.2). The skin possesses many enzymes capable of metabolizing topically applied compounds. These are involved in the keratinocyte maturation and desquamation process,\(^1\) formation of natural moisturizing factor (NMF) and general homeostasis.\(^2\)

While the stratum corneum provides an efficient physical barrier, when damaged, environmental contaminants can access the epidermis to initiate an immunological response. This includes (1) epithelial defense as characterized by antimicrobial
peptides (AMP) produced by keratinocytes—both constitutively expressed (e.g., human beta defensin 1 [hBD1], RNAse 7, and psoriasin) and inducible (e.g., hBD 2-4 and LL-37); (2) innate-inflammatory immunity, involving expression of pro-inflammatory cytokines and interferons; and (3) adaptive immunity based on antigen presenting cells, such as epidermal Langerhans and dendritic cells, mediating a T cell response. An understanding of these systems is important as they can be involved in skin disease and may also be therapeutic targets for the management of skin disease. The importance of these systems as therapeutic targets is highlighted in Chapter 19.

**Stratum Basale**

The stratum basale is also referred to as the stratum germinativum or basal layer. This layer contains Langerhans cells, melanocytes, Merkel cells, and the only cells within the epidermis that undergo cell division, namely keratinocytes. The keratinocytes of the basal lamina are attached to the basement membrane by hemidesmosomes, which are proteinaceous anchors. The absence of this effective adhesion results in rare chronic blistering diseases such as pemphigus and epidermolysis bullosa. Within the epidermis, desmosomes act as molecular rivets, interconnecting the keratin of adjacent cells, thereby ensuring the structural integrity of the skin.

Langerhans cells are dendritic cells and the major antigen presenting cells in the skin. They are generated in the bone marrow, and migrate to and localize in the stratum basale region of the epidermis. When activated by the binding of antigen to the cell surface, they migrate from the epidermis to the dermis and on to the regional lymph nodes, where they sensitize T cells to generate an immune response.
Langerhans cells are implicated in allergic dermatitis and are also a target for the mediation of enhanced immune responses in skin-applied vaccine delivery.

Melanocytes produce melanins, high molecular weight polymers that provide the pigmentation of the skin, hair, and eyes. The main function of melanin is to protect the skin by absorbing potentially harmful UV radiation, thus minimizing the liberation of free-radicals in the basal layer. Melanin is present in two forms: eumelans are brown-black, whereas pheomelanins are yellow-red. Melanin is synthesized from tyrosine in the melanosomes, which are membrane-bound organelles that are associated with the keratinocytes and widely distributed to ensure an even distribution of pigmentation. Regulation of melanogenesis involves over 80 genes, many of which have now been characterized and cloned. Mutations in these genes can result in conditions such as albinism and vitiligo, production of melanin with reduced photoprotective effects, and they may offer immune targets for the management of malignant melanoma.

Merkel cells are associated with the nerve endings and are concentrated in the touch-sensitive sites of the body such as the fingertips and lips. Their location suggests that their primary function is in cutaneous sensation.

**Stratum Spinosum**

The stratum spinosum or prickle cell layer consists of the two to six rows of keratinocytes immediately above the basal layer (Fig. 1.3). Their morphology changes from columnar to polygonal, and they have an enlarged cytoplasm containing many organelles and filaments. The cells contain keratin tonofilaments and are interconnected by desmosomes.

**Stratum Granulosum**

Keratinocytes in the stratum granulosum or granular layer continue to differentiate. Present are intracellular keratohyalin granules and membrane-coating granules containing lamellar subunits arranged in parallel stacks, which are believed to be the precursors of the intercellular lipid lamellae of the stratum corneum. The lamellar granules also contain hydrolytic enzymes including stratum corneum chymotryptic enzyme (SCCE), a serine protease that has been associated with the desquamation process. Overexpression of SCCE has been implicated in psoriasis and dermatitis. As the cells approach the upper layers of the stratum granulosum, the lamellar granules are extruded into the intercellular spaces.

**Stratum Lucidum**

Within the stratum lucidum the cell nuclei and other organelles disintegrate, keratinization increases, and the cells are flattened and compacted. This layer takes on the typical structure common also to the stratum corneum of intracellular protein matrix and intercellular lipid lamellae, which is fundamentally important to the permeability barrier characteristics of the skin.
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Stratum Corneum

The outermost layer, the stratum corneum (or horny layer), consists of 10–20 μm of high density (1.4 g/cm³ in the dry state) and low hydration (10%–20% compared with about 70% in other body tissues) cell layers. Although this layer is only 10–15 cells in depth, it serves as the primary barrier of the skin, regulating water loss from the body and preventing permeation of potentially harmful substances and microorganisms from the skin surface. The stratum corneum has been described as a brick wall-like structure of corneocytes as “bricks” in a matrix (or “mortar”) of intercellular lipids, with desmosomes acting as molecular rivets between the corneocytes.\textsuperscript{14,15} While this is a useful analogy, it is important to recognize that the corneocytes are elongated and flattened, often up to 50 μm in length while only 1.5 μm thick and is more like a brick wall built by an amateur. The corneocytes lack a nucleus and are composed of about 70%–80% keratin and 20% lipid within a cornified cell envelope (\textasciitilde 10 nm thick). The cornified cell envelope is a protein/lipid polymer structure formed just below the cytoplasmic membrane that subsequently resides on the exterior of the corneocytes.\textsuperscript{16} It consists of two parts: a protein envelope and a lipid envelope. The protein envelope is thought to contribute to the biomechanical properties of the cornified envelope due to cross-linking of specialized structural proteins by both disulfide bonds and N-(γ-glutamyl) lysine isopeptide bonds formed by transglutaminases. Some of the structural proteins involved include involucrin, loricrin, small proline-rich proteins, keratin intermediate filaments, elafin, cystatin A, and desmosomal proteins. It has been proposed that the corneocyte envelope plays an important role in the assembly of the intercellular lipid lamellae of the stratum corneum. The lipid envelope comprised of N-ω-hydroxyceramides, which is covalently bound to the protein matrix of the cornified envelope,\textsuperscript{17} has been shown to be essential for the formation of normal stratum corneum intercellular lipid lamellae, and in its absence, the barrier function of the skin is disrupted.\textsuperscript{18} Thus, the anchoring of the intercellular lipids to the corneocyte protein envelope is important in providing the structure and barrier function of the stratum corneum.

The unique composition of the stratum corneum intercellular lipids and their structural arrangement in multiple lamellar layers within a continuous lipid domain...
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is critical to the barrier function of the stratum corneum. In recent years, our knowledge of the structure and organization of the stratum corneum lipids has been greatly enhanced by a range of sophisticated visualization techniques. The major components of the lipid domains are ceramides, cholesterol, free fatty acids, cholesterol esters, and cholesterol sulfate, with the notable absence of phospholipids. The lipid content varies between individuals and with anatomical site. Ceramide structures are based on sphingolipids (Fig. 1.4) and have been classified based on their polarity, with ceramide 1 being the least polar. New ceramide species continue to be identified using increasingly sophisticated analytical techniques.

The free fatty acids in the stratum corneum consist of a number of saturated long-chain acids, the most abundant being lignoceric acid (C24) and hexacosanoic acid (C26), with trace amounts of very long-chain (C32-C36) saturated and monounsaturated free fatty acids. The presence of cholesterol and cholesterol esters is likely to reduce the fluidity of the intercellular lipid lamellae in the same way as incorporation of cholesterol into other lipid membranes, such as liposomes, provides a stabilizing effect.

An increasing understanding of the biophysics of the stratum corneum intercellular lipid lamellae has been developed in recent years. It is clear that the intercellular

Figure 1.4 Molecular structure of ceramides (CER) in human stratum corneum. CER1, CER4 and CER9 have an ω-hydroxy acyl chain to which a linoleic acid is chemically linked.
lipid lamellae that are oriented parallel to the corneocytes cell wall are highly structured yet exhibit heterogeneous phase behavior with multiple states of lipid organization. Using X-ray diffraction, Bouwstra et al. identified two lamellar phases with periodicities of 6.4 (short periodicity phase, SPP) and 13.4 nm (long periodicity phase, LPP), together with a fluid phase. They proposed a “sandwich model” consisting of three lipid layers: one narrow central lipid layer with fluid domains on both sides of a broad layer with a crystalline structure as most representative of the lamellar phase (Fig. 1.5). The lattice spacing within these layers has been measured and lipid packing identified as orthorhombic (crystalline), hexagonal (gel-like), and liquid (Fig. 1.5). These packing lattices correspond with low, medium, and high permeability, respectively. Within human stratum corneum, the orthorhombic lattice predominates, thus providing the main contribution to the permeability barrier function, while a transition to the less tightly packed hexagonal lattice structure increases toward the skin surface and is thought to be induced by sebum lipids. An in-depth review of the structural organization of the stratum corneum in healthy and diseased skin has been provided by Bouwstra and Ponec.

The stratum corneum contains about 15%–20% water that is primarily associated with the keratin in the corneocytes. Only small amounts of water are present in the intercellular polar head group regions. The presence of water is essential to maintain the suppleness and integrity of the skin. NMF acts as a humectant and

Figure 1.5 Lateral packing (a) and molecular arrangement (b) of stratum corneum lipids domains in the long periodicity phase (LPP) as determined from X-ray diffraction patterns. The presence of a broad–narrow–broad sequence in the repeating unit of the LPP (arrows) (left panel) is in agreement with the broad–narrow–broad pattern found in RuO$_4$-fixed stratum corneum (right panel). CER1 plays an important role in dictating the broad–narrow–broad sequence: fluid phase in the central narrow band and crystallinity gradually increasing from the central layer. Bouwstra-proposed “sandwich model”: permits deformation as a consequence of shear stresses (skin elasticity) while barrier function is retained.
plasticizer in the stratum corneum, binding water to aid swelling of the corneocytes. Hydration within the stratum corneum is controlled by the conversion of filaggrin to NMF: conversion occurs only at high water activity, with low NMF levels present in corneocytes under occlusive conditions. Rawlings and Matts have reviewed the role of hydration and moisturization in healthy and diseased skin states.\textsuperscript{30} Water is known to enhance skin permeability yet it has only a small presence and does not directly alter the organization of the intercellular lipid lamellae.\textsuperscript{29} Walters and Roberts proposed that water-induced swelling of the corneocytes acts in a similar way to how the swelling of bricks in a wall could loosen the mortar, thus increasing permeability by loosening the lipid chains without exerting a direct effect on the lipid ordering.\textsuperscript{31}

### Dermis and Appendages

The dermis is about 2–5 mm in thickness and consists of collagen fibrils that provide support, and elastic connective tissue that provides elasticity and flexibility, embedded within a mucopolysaccharide matrix. Within this matrix is a sparse cell population, including fibroblasts that produce the components of the connective tissue (collagen, laminin, fibronectin, vitronectin), mast cells involved in immune and inflammatory response, and melanocytes responsible for pigment production. Due to this structure, the dermis provides little barrier to the permeation of most drugs, but may reduce the permeation to deeper tissues of very lipophilic drugs. A number of structures and appendages are contained or originate within the dermis, including blood and lymph vessels, nerve endings, hair follicles, sebaceous glands, and sweat glands.

Contained within the dermis is an extensive vascular network that acts to regulate body temperature, provides oxygen and nutrients to and removes toxins and waste products from tissues, and facilitates immune response and wound repair. In addition to fine capillaries, arteriovenous anastomoses are present throughout the skin. They permit direct shunting of up to 60\% of the skin blood flow between the arteries and veins, thus permitting the rapid blood flow required in heat regulation.\textsuperscript{32} This extensive blood supply ensures that most permeating molecules are removed from the dermo–epidermal junction to the systemic blood supply, thus establishing a concentration gradient between the applied chemical on the skin surface and the dermis.

Lymph vessels within the dermis play important roles in regulating interstitial pressure, mobilizing immune response and waste removal. As they also extend to the dermo–epidermal junction, they can also remove permeated molecules from the skin. While small molecule permeants such as water are primarily removed via the blood flow, it has been shown that clearance by the lymph vessels is important for large molecules such as interferon.\textsuperscript{33}

There are three appendages that originate in the dermis: the hair follicles and associated sebaceous glands, eccrine, and apocrine sweat glands. Hair follicles are present at a fractional area of about 1/1000 of the skin surface, except on the lips, palms of the hands, and soles of the feet. The sebaceous gland associated with each
hair follicle secretes sebum, which is composed of free fatty acids, triglycerides, and waxes. Sebum protects and lubricates the skin, and maintains the skin surface at pH of about 5. The erector pilorum muscle attaches the follicle to the dermis and allows the hair to respond to cold and fear. Eccrine glands, present at a fractional area of about 1 in 10,000 of the skin surface, secrete sweat (dilute salt solution of pH about 5) in response to exercise, high environmental temperature, and emotional stress. Apocrine glands are present in the axillae, nipples, and anogenital areas, and are about 10 times the size of eccrine glands. Their secretion consists of “milk” protein, lipoproteins, and lipids.

**Subcutaneous Tissue**

The subcutaneous tissue or hypodermis consists of a layer of fat cells arranged as lobules with interconnecting collagen and elastin fibers. Its primary functions are heat insulation and protection against physical shock, while also providing energy storage that can be made available when required. Blood vessels and nerves connect to the skin via the hypodermis.

**Physiological Factors Affecting the Skin Barrier**

There are a number of physiological factors that affect the skin barrier and hence skin permeability.

**Age**

It is clear from visual inspection that the skin structure changes as the skin ages. It is important to recognize that while there are intrinsic aging processes, environmental factors such as exposure to solar radiation and chemicals, including cosmetics and soaps, will also influence skin structure and function over time. Intrinsic aging causes the epidermis to become thinner and the corneocytes less adherent to one another. There is flattening of the dermoepidermal interface and a decrease in the number of melanocytes and Langerhans cells. The dermis becomes atrophic and relatively acellular and avascular, with alternations in collagen, elastin, and glycosaminoglycans. The subcutaneous tissue is diminished in some areas, especially the face, shins, hands, and feet, but increased in other areas, particularly the abdomen in men and the thighs in women. As the stratum corneum constitutes the skin barrier function, it is important to understand age-related changes to this structure. While epidermal thickness alters with age, stratum corneum thickness has been shown not to significantly change. However, the lipid composition did alter with age and also with seasons, as demonstrated from stratum corneum tape strips taken from three body sites (face, hand, leg) of female Caucasians of different age groups in winter, spring, and summer. There were significantly decreased levels of all major lipid species (ceramides, ceramide 1 subtypes, cholesterol, and fatty acids), in particular
ceramides, with increasing age. In addition, stratum corneum lipid levels were substantially depleted in winter compared with spring and summer.

Do these age-related changes alter skin barrier function? Studies of barrier function with age cohorts have generally involved biophysical measures such as transepidermal water loss (TEWL) and skin conductance (as a measure of stratum corneum hydration) in vivo or direct measurement of permeation in vitro. A number of studies have shown a decrease in TEWL with age. However, aging has not been shown to significantly effect the skin permeation of compounds such as estradiol, caffeine, aspirin, nicotinates, or water. These studies have been conducted in adults ranging from young adult (twenties) to aged (seventies to eighties). In contrast, skin barrier function in young children may be significantly reduced, particularly in newborn and neonatal (preterm) children. This needs to be taken into account in topical therapy.

**Anatomical Site**

Skin permeability at different body sites has been widely studied over age range from neonates to adults. Feldman and Maibach first described regional variation of 14C-labeled hydrocortisone skin permeation and subsequent elimination in human volunteers over 40 years ago. Highest absorption was seen for the scrotal areas (42 times greater than the ventral forearm) and lowest absorption was observed on the heel. Rougier et al. conducted a similar experiment with 14C-labeled benzoic acid application, measuring elimination and amount in stratum corneum tape strip at 30 minutes, at six body sites on male volunteers. They reported that the 30-minute tape strip samples correlated well with skin absorption, and a similar regional variation with head and neck showing three times the permeability as back skin. Based on a number of studies, the regional variation in skin barrier function is in the following order:

Genitals > head and neck > trunk > arm and leg.

Transdermal patches are generally applied to the trunk where there is intermediate skin permeability, though there are examples of patches applied to areas where permeability is higher, such as the scopolamine patch to the postauricular region (behind the ear) and a testosterone patch to the scrotal region.

There is also variability within body regions as demonstrated by Marrakchi and Maibach for the face. Basal TEWL measurements taken to map the skin barrier function on the face of 20 volunteers showed a twofold difference between nasolabial and forehead areas, with the following rank order:

Nasolabial > perioral > chin > nose > cheek > forehead > neck > forearm.

**Ethnicity**

Ethnic differences in skin barrier function have been extensively investigated in recent years, with the majority of studies reporting no significant difference across
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ethnic groups. Some differences have been reported but these are inconsistent, suggesting that ethnic differences are much less profound than inter-individual differences within the ethnic groups. Differences in skin lipid composition across ethnic groups have been reported and it is suggested that these may influence the prevalence of skin disease and sensitivity. A comprehensive review of the literature on skin barrier function and ethnicity is provided by Hillebrand and Wickett.

Gender

There is little if any difference in skin barrier function as determined by basal TEWL between male and female skin. Differences in corneocytes size between pre- and postmenopausal women have been reported, but this did not correlate with any change in basal TEWL in this study. Other groups have investigated skin barrier function during the menstrual cycle, reporting that skin barrier function is reduced in the days before the onset of menses.

Skin Disorders

The clinical symptoms and pathophysiology of skin disorders has been extensively reviewed in dermatological textbooks. The focus here is on the effect of skin disorders on barrier function, and thus on topical and transdermal drug delivery. A number of common skin disorders compromise barrier function, including eczema (dermatitis), ichthyosis, psoriasis, and acne vulgaris. Skin infections that cause eruptions at the skin surface such as impetigo, Herpes simplex infections (“cold sores”), and fungal infections (such as “athlete’s foot”) reduce the barrier, but the effect is self-limiting and resolves as the infection is treated.

Atopic dermatitis is common in children and often associated with other atopic disorders such as asthma and hay fever. It is characterized by papules (solid, raised spot), itching, and thickened and hyperkeratotic (thickened, scaly stratum corneum) skin with reduced barrier function as demonstrated by elevated TEWL and hydrocortisone penetration compared to uninvolved skin on atopic patients, which is also higher than normal skin. Contact or allergic dermatitis is characterized by erythema (skin reddening), papules, vesicles, and hyperkeratosis, which occurs in response to skin contact with allergenic substances. Sodium lauryl sulfate (SLS) has been used to experimentally generate contact dermatitis and the barrier reduction caused is dose dependent. Benfeldt et al. reported a 46-fold and 146-fold increase in salicylic acid skin permeation in mild dermatitis (1% SLS) and severe dermatitis (2% SLS), respectively, relative to normal skin, as measured by microdialysis of skin tissue levels. This correlated with other measures of barrier perturbation (TEWL and erythema) in each individual.

Psoriasis is a chronic autoimmune disease characterized by red lesions and plaques (epidermal hyperproliferation), particularly at the knee, elbow, and scalp. Elevated TEWL and permeation of a range of compounds including electrolytes,
steroids, and macromolecules in psoriatic skin relative to normal skin has been reported.

**SKIN PERMEATION**

Compounds have been applied to the skin for thousands of years to enhance beauty and treat local conditions. More recently, transdermal delivery devices, primarily patches, have been successfully developed for a range of disorders. These include scopolamine for travel sickness, nitroglycerin for cardiovascular disorders, estradiol and testosterone for hormone replacement, fentanyl for pain management, nicotine for smoking cessation, rivastigmine for Alzheimer’s disease, and methylphenidate for attention deficit hyperactivity disorder (ADHD). Transdermal delivery offers significant advantages over oral administration due to minimal first-pass metabolism, avoidance of the adverse gastrointestinal environment, and the ability to provide controlled and prolonged drug release. Despite these obvious advantages, the range of compounds that can be delivered transdermally is limited because permeability sufficient to provide effective therapeutic levels often cannot be achieved.

The outermost layer of the skin, the stratum corneum, is generally considered to be the main barrier to permeation of externally applied chemicals and loss of moisture (TEWL). Removal of the stratum corneum by tape stripping and reduced stratum corneum barrier integrity in psoriatic skin have been shown to provide significantly increased permeability. This region therefore provides the primary protection of the body from external contaminants and limits the potential therapeutic effectiveness of topically applied compounds.

The therapeutic target sites within the skin must be considered. While for most applications this will involve permeation to the deeper skin tissues (e.g., antihistamines, anesthetics, anti-inflammatories, antimitotics) or systemic uptake, other applications may necessitate targeting the skin surface (e.g., sunscreens, cosmetics, barrier products) or appendages (e.g., antiperspirants, hair growth promoters, anti-acne products). Thus the following consideration of skin permeation pathways must be viewed within the context of the therapeutic target site.

**SKIN PERMEATION PATHWAYS**

A penetrant applied to the skin surface has three potential pathways across the epidermis: through sweat ducts, via hair follicles and associated sebaceous glands, or across the continuous stratum corneum (Fig. 1.1). These pathways are not mutually exclusive, with most compounds possibly permeating the skin by a combination of pathways and the relative contribution of each being related to the physicochemical properties of the permeating molecule.

**Permeation via Appendages**

While it is generally accepted that the predominant permeation route is across the continuous stratum corneum, Scheuplein suggested that the appendageal route
dominates during the lag phase of the diffusional process. While the appendages have been considered as low resistance shunts, this is an overly simplistic view, as the sweat glands are filled with aqueous sweat and the follicular glands with lipoidal sebum. In addition, the appendages represent only 0.1%–1% of the total skin surface area, varying from the forearm to the forehead. 

In recent years, there has been renewed interest in targeting the skin appendages, in particular targeted follicular delivery. This can be achieved by either manipulating the formulation or modifying the target molecule to target delivery, as recently reviewed by Lu et al. 

Formulation approaches have included particle-/vesicle-based dosage forms and the use of sebum-miscible excipients, while molecular modification involves optimizing physicochemical properties such as size, lipophilicity, solubility parameter, and charge.

**Permeation via the Stratum Corneum: Transcellular Route**

The transcellular route (Fig. 1.6) has been regarded by some as a polar route through the stratum corneum. While the corneocytes contain an intracellular keratin matrix that is relatively hydrated and thus polar in nature, permeation requires repeated partitioning between this polar environment and the lipophilic domains surrounding

![Figure 1.6](image-url)
the corneocytes. Based on the large body of permeation data, the view of most skin scientists is that transport through the stratum corneum is predominantly by the intercellular route.

**Permeation via the Stratum Corneum: Intercellular Route**

While the intercellular lipid bilayers occupy only a small area of the stratum corneum, they provide the only continuous route through the stratum corneum (Fig. 1.6). Evidence of the importance of the intercellular route has been generated over many years. This includes studies investigating the effects of solvents capable of delipidizing the stratum corneum bilayers and microscopic studies providing direct evidence of the histological localization of topically applied compounds.

The structure of the stratum corneum lipids contributes to the barrier properties of the skin. Within the intercellular lipid domains, transport can take place via both lipid (diffusion via the lipid core) and polar (diffusion via the polar head groups) pathways. The diffusional rate-limiting region of very polar permeants is the polar pathway of the stratum corneum, which is fairly independent of their partition coefficient, while less polar permeants probably diffuse via the lipid pathway, and their permeation increases with increase in lipophilicity.

Clearly the relative contribution of these three pathways to skin permeation will depend on the physicochemical characteristics of the permeant.

**SKIN PERMEATION AND THE INFLUENCE OF PERMEANT PHYSICOCHEMICAL CHARACTERISTICS**

The permeation process involves a series of processes starting with release of the permeant from the dosage form, followed by diffusion into and through the stratum corneum, then partitioning to the more aqueous epidermal environment and diffusion to deeper tissues or uptake into the cutaneous circulation. These processes are highly dependent on the solubility and diffusivity of the permeant within each environment. Release of the permeant from the dosage form vehicle and uptake into the stratum corneum is dependent on the relative solubility in each environment, and hence the stratum corneum–vehicle partition coefficient. The diffusion coefficient or speed at which the permeant moves within each environment is dependent on the permeant properties including the molecular size, solubility and melting point, ionization and potential for binding within the environment, and factors related to the environment such as its viscosity and tortuosity or diffusional path length. Although the thickness of the stratum corneum is only 10–15 μm, the intercellular route is highly tortuous and may be in excess of 150 μm. Given that the intercellular pathway is predominant, factors that influence movement into and within this environment are of greatest importance.

The permeation of an infinite dose of a molecule applied to the skin surface in an *in vitro* experiment can be measured over time and plotted as cumulative amount
permeating \( (Q) \) versus time. Steady-state permeation or flux \((J)\) can be viewed fairly simplistically based on Fick’s laws of diffusion:

\[
J = \frac{dQ}{dt} = \frac{DPC_v}{h},
\]

(1.1)

where \( Q \) is the amount permeating a unit area of skin, \( D \) is the diffusion coefficient of the permeant in the skin, \( P \) is the partition coefficient between the stratum corneum and the vehicle, \( C_v \) is the applied concentration of permeant, and \( h \) is the diffusional path length. As the stratum corneum is the main barrier for most permeants, diffusion coefficient within and the path length of the intercellular route through the stratum corneum are most relevant.

A number of groups have developed more complex mathematical approaches to describe and/or predict skin permeation under a range of conditions and readers are referred to some of the more recent reviews of this area. \(^{78-81}\) These models take into account key parameters such as partition coefficient, molecular size and aqueous solubility, and other factors such as ionization and permeant binding \(^{82,83}\) within the stratum corneum.

**Partition Coefficient**

The first step in the skin transport process is partitioning of the permeant from the applied vehicle to the intercellular lipid domains of the stratum corneum, followed by diffusion within this relatively lipophilic environment. Many studies have demonstrated that increasing lipophilicity increases skin permeation \(^{84-87}\) with \( \log P(o/w) \) of 2–3 being optimal. It is likely that these molecules with intermediate lipophilicity can permeate via both the lipid and polar microenvironments within the intercellular route. Very lipophilic molecules will have high solubility in the intercellular lipids but will not readily partition from the stratum corneum to the more aqueous viable epidermis, thus limiting their skin permeation rate.

**Molecular Size**

The size and shape of the permeant will influence the diffusivity within the stratum corneum. It has been shown that there is an inverse relationship between permeant size and skin permeation. \(^{82,83,88-91}\) As a general rule, permeants selected for topical and transdermal delivery tend to be less than 500 Da, as larger molecules permeate poorly. Consequently, although molecular size is important and is incorporated as a parameter in many mathematical models, when considering the physicochemical factors influencing permeation of the molecules that tend to be applied to the skin (generally in the sub 500 Da range), other factors such as partition coefficient and ionization are more influential. It is important to note that large molecules such as proteins and peptides are not good candidates for topical and transdermal delivery unless their transport can be facilitated (usually by physical disruption of the barrier), as discussed in later chapters.
Solubility

The solubility of the permeant in the intercellular pathway will influence the diffusion coefficient within the stratum corneum. Lipophilic compounds have increased solubility in the intercellular domains and thus increased flux. However, the skin permeation rate is also dependent on the concentration of soluble permeant in the applied vehicle. Thus if a lipophilic compound has limited solubility in a topical vehicle, the compound may readily partition into the stratum corneum, resulting in depletion in the vehicle and thus reducing permeant flux. Therefore, the ideal permeant requires lipid solubility (high diffusion coefficient) but also reasonable aqueous solubility (high donor concentration) to maximize flux. In mathematical models, melting point is frequently used as a predictor of aqueous solubility.

Hydration

Increasing stratum corneum hydration increases skin permeability. Indeed, water is considered to be a natural skin penetration enhancer in topical formulation. This has been applied in the use of transdermal patches, occlusive dressings (e.g., Tegaderm dressing with EMLA™ cream; Tegaderm, 3M, Maplewood, MN; EMLA, AstraZeneca, Wilmington, DE), and occlusive or hydrating topical formulations. The formulation of topical and transdermal products, and their influence on skin hydration and permeability, is considered later in this book. In addition, the reader is referred to reviews on skin hydration and moisturization available in the literature.92–95

CONCLUSION

The successful development of products for topical and transdermal drug delivery relies on understanding skin permeation and designing a solute and/or formulation appropriately. Methods to assess and enhance skin permeation are discussed in the following chapters in Part One of this text.

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REFERENCES

References


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