Skin Barrier and Transdermal Drug Delivery

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Chapter Contents

The skin provides the largest interface between the human body and the external environment. Therefore, one of its most important functions is to regulate what enters the body via the skin, as well as what exits. In general, the skin is designed to let very little enter, since other tissues, such as the permeable epithelia of the gastrointestinal tract and lung, provide the primary means of regulated entry into the body. Likewise, the skin must prevent excessive loss of water and other bodily constituents.

The skin's remarkable barrier properties are due in large part to the stratum corneum, which represents the thin outer layer of the epidermis[1]. In contrast to other tissues in the body, the stratum corneum consists of corneocytes (composed primarily of aggregated keratin filaments encased in a cornified envelope) that are surrounded by an extracellular milieu of lipids organized as multiple lamellar bilayers. These structured lipids prevent excessive loss of water from the body and likewise block entry of most topically applied drugs, other than those that are lipid-soluble and of low molecular weight. This poses a significant challenge to administering medications via the skin either for local cutaneous effects or as systemic therapy following their entry into superficial dermal capillaries.

STRUCTURE AND ORIGIN OF THE SKIN BARRIER

Stratum Corneum Structure and Organization

The stratum corneum is a composite material made of proteins and lipids structurally organized as "bricks and mortar" (Fig. 124.1; Table 124.1)[2]. Instead of being uniformly dispersed, the highly hydrophobic lipids in normal stratum corneum are sequestered within the extracellular spaces, where this lipid-enriched matrix is organized into lamellar membranes that surround the corneocytes[3]. Hence, rather than stratum corneum thickness, variations in number of lamellar membranes (= lipid weight %), membrane structure, and/or lipid composition provide the structural and biochemical basis for site-related variations

FEATURES OF THE STRATUM CORNEUM
• Primary barrier to drug absorption into skin
• Two-compartment organization: "bricks and mortar"
• Microheterogeneity within extracellular spaces: "There's more to the mortar than lipid"
• Persistent metabolic activity: dynamic changes in cytosol, cornified envelope, and interstices from inner to outer stratum corneum
• Homeostatic links to the nucleated cell layers: barrier function regulates epidermal DNA and lipid synthesis
• Pathophysiologic links to deeper skin layers: barrier abrogation and/or epidermal injury initiates epidermal hyperplasia and inflammation
• Stratum corneum as a biosensor: changes in external humidity alone regulate proteolysis of filaggrin, epidermal DNA/lipid synthesis, and initiation of inflammation

Table 124.1 Features of the stratum corneum.

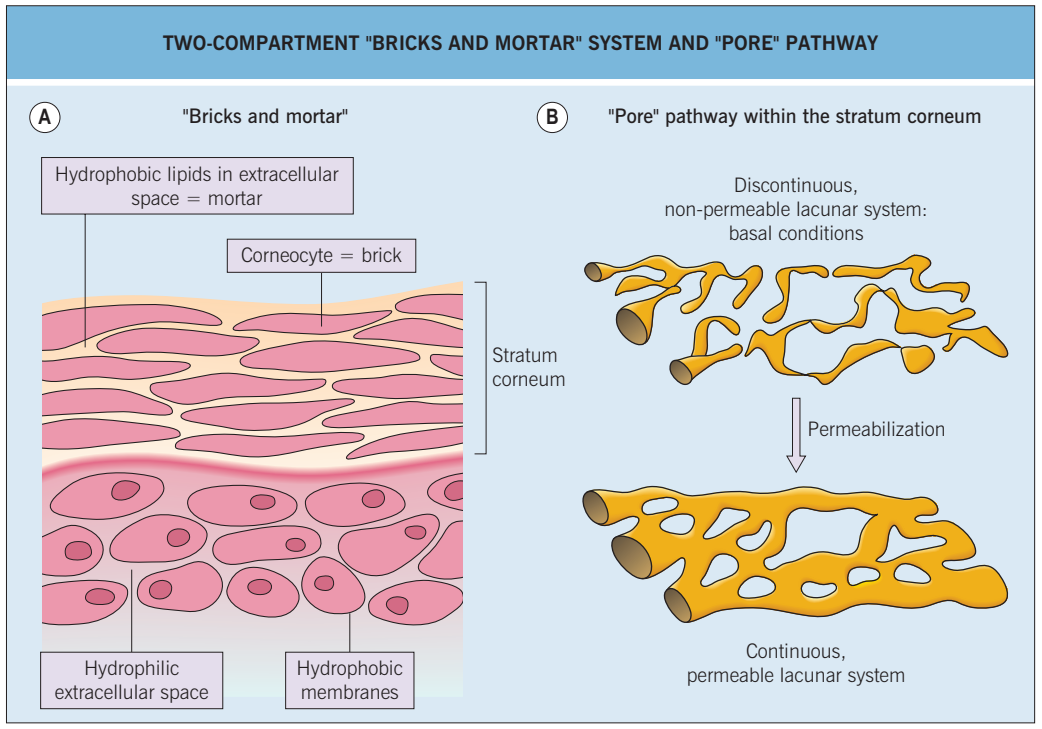

Fig. 124.1 Two-compartment "bricks and mortar" system and "pore" pathway. A The stratum corneum is a unique two-compartment system, analogous to a brick wall. Whereas lipids are sequestered extracellularly within the stratum corneum, the corneocyte is lipid-depleted but protein-enriched. **B** The degradation of corneodesmosomes results in discontinuous lacunar domains, which represent the likely aqueous "pore" pathway. These lacunae can enlarge and extend, forming a continuous but collapsible network under certain conditions, e.g. occlusion, prolonged hydration, sonophoresis.

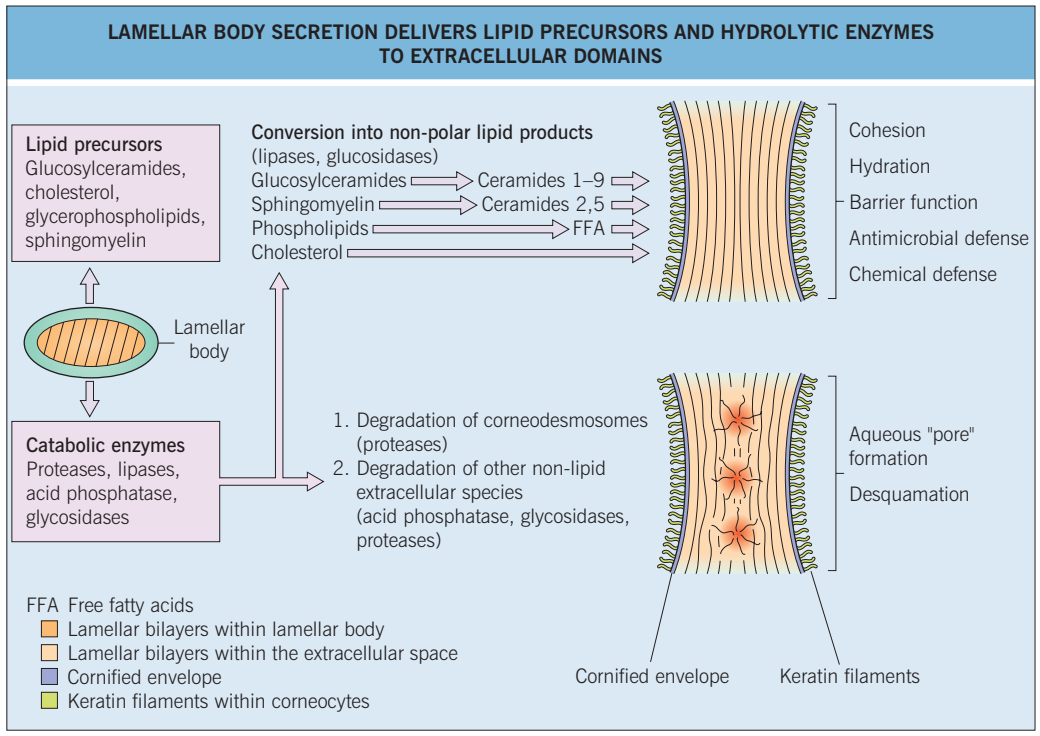

Fig. 124.2 Lamellar body secretion delivers not only lipid precursors, but also several hydrolytic enzymes to extracellular domains. These organelles also release antimicrobial peptides, including human β-defensin 2 and LL-37 (the carboxy-terminal fragment of human cathelicidin). As a result, the antimicrobial barrier is intimately linked to the permeability barrier. In atopic dermatitis, for example, there is both an impaired permeability barrier and reduced expression of antimicrobial peptides, explaining in part the predisposition to colonization with *Staphylococcus aureus*.

FACTORS AFFECTING HOW STRATUM CORNEUM LIPIDS MEDIATE BARRIER FUNCTION
• Extracellular localization: only intercellular lipids play a role
• Amount of lipid (lipid weight %)
• Elongated, tortuous pathway: increases diffusion length
• Organization into lamellar membrane structures
• Hydrophobic composition: absence of polar lipids and presence of very-long-chain saturated fatty acids
• Correct molar ratio: approximately 1 : 1 : 1 of three key lipids: ceramides, cholesterol and free fatty acids
• Unique molecular structures (e.g. acylceramides)

Table 124.2 Factors affecting how stratum corneum lipids mediate barrier function.

in permeability[4]. It follows, then, that the extracellular, lipid-enriched matrix of the stratum corneum comprises not only the structure that limits transdermal delivery of hydrophilic drugs, but also the so-called stratum corneum "reservoir"[5], within which lipid-soluble drugs, such as topical corticosteroids, can accumulate and be slowly released.

Human stratum corneum is typically comprised of about 20 corneocyte cell layers, which differ in their thickness, packing of keratin filaments, filaggrin content, and number of corneodesmosomes, depending on body site. Corneocytes are surrounded by a highly cross-linked, resilient sheath, the cornified envelope, while the cell interior is packed with keratin filaments embedded in a matrix composed mainly of filaggrin and its breakdown products (the latter are also referred to as "natural moisturizing factors"). As noted above, individual corneocytes, in turn, are surrounded by a lipid-enriched extracellular matrix, organized largely into lamellar membranes, which derive from secreted lamellar body precursor lipids (Fig. 124.2). Following secretion, lamellar body contents fuse end-to-end, forming progressively elongated membrane sheets[3], a sequence requiring the action of a battery of lipolytic "processing" enzymes (see below). Although corneocytes play a role both as spacers and as a scaffold for the extracellular matrix, transdermal drug delivery strategies have focused primarily on manipulations of the extracellular lipid milieu[6,7]. Lastly, the existence of aqueous pores within the extracellular matrix[8] not only adds further complexity to the extracellular pathway (see Fig. 124.1), but also provides additional opportunities for novel delivery strategies.

The exceptionally low permeability of normal stratum corneum to water-soluble drugs is the consequence of several characteristics of the lipid-enriched, extracellular matrix (Table 124.2), including its organization into a highly convoluted and tortuous extracellular pathway imposed by geometrically arrayed corneocyte "spacers"[9]. Moreover, not only the paired-bilayer arrangement of extracellular lipids, but also their extreme hydrophobicity and the composition and distribution of the three key species (ceramides, cholesterol and free fatty acids) in a critical (1 : 1 : 1) molar ratio are further characteristics that provide for barrier function.

Ceramides account for approximately 50% of the total stratum corneum lipid mass[10,11], and are crucial for the lamellar organization of the stratum corneum barrier[12]. Of the nine ceramide classes, acylceramides or ceramides 1, 4 and 7 (which contain ω-hydroxy-linked, essential fatty acids in an ester linkage) are epidermis-unique compounds, known to be important for the barrier[13]. *Cholesterol*, the second most abundant lipid by weight in the stratum corneum, promotes the intermixing of different lipid species and regulates its "phase" behavior[14]. *Free fatty acids*, which account for 10–15% of stratum corneum lipids, consist predominantly of very-long-chain, saturated species with ≥18 carbon atoms[10]. A decrease in the concentrations of any of these critical lipid species compromises barrier integrity, by altering the molar ratio of the membranes that mediate normal barrier function.

The "domain-mosaic model" advocates a meandering, polar (pore) pathway for water transport through lamellar boundaries within the lipid mosaic[15], adding potential complexity to the already tortuous, extracellular pathway. An alternative model is based upon the presence of lacunar domains embedded within the lipid bilayers[8] (see Fig. 124.1). These lacunae correspond to sites of subjacent corneodesmosome degradation (see Fig. 124.2), and presumably they contain the hydrophobic degradation products of corneodesmosomes[16]. Whereas these lacunae are scattered and discontinuous under basal conditions, following certain types of permeabilization (e.g. occlusion, prolonged hydration, sonophoresis, iontophoresis), they are thought to expand until they interconnect, forming a continuous "pore pathway" (see Fig. 124.1). The pore pathway can revert back to its original, discontinuous state once the permeabilizing stimulus disappears.

Epidermal Lipid Metabolism and the Skin Barrier

Biosynthetic activities

Epidermal differentiation is a vectorial process that is accompanied by dramatic changes in lipid composition, including loss of phospholipids with the emergence of ceramides, cholesterol and free fatty acids in the stratum corneum[11,13] (see Fig. 124.2). Although epidermal lipid synthesis is both highly active and largely autonomous from

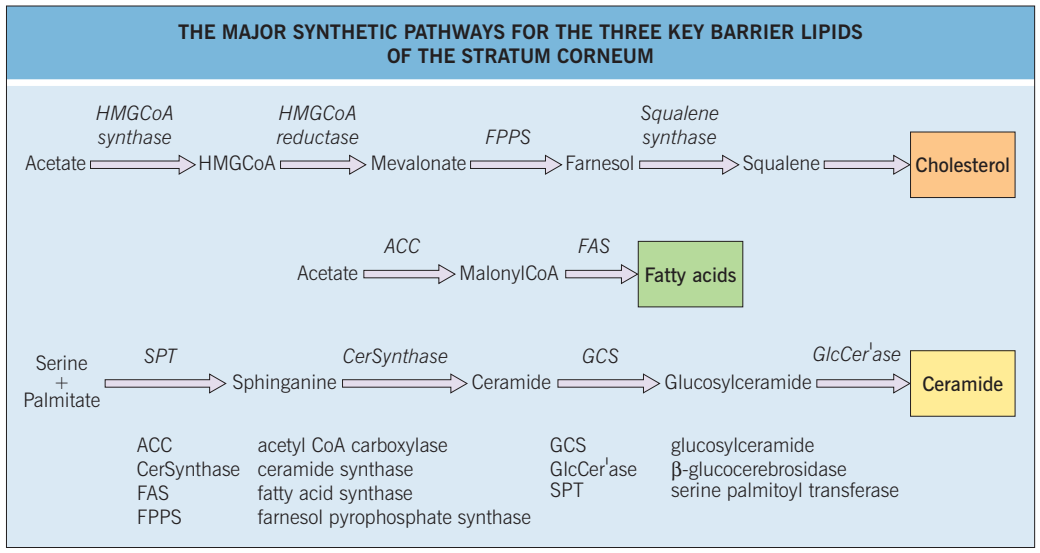

Fig. 124.3 The major synthetic pathways that lead to the generation of the three key barrier lipids of the stratum corneum. The rate-limiting enzymes in each pathway are shown. Applications of specific, conduritol-type inhibitors of β-glucocerebrosidase to intact skin lead to a progressive abnormality in barrier function. In both a transgenic murine model of Gaucher disease (GD) (produced by targeted disruption of the β-glucocerebrosidase gene) and in the severe, type 2 neuronopathic form of GD, infants present with a barrier abnormality. This was attributable to accumulation of glucosylceramides, depletion of ceramides, and persistence of immature lamellar bodies within the interstices of the stratum corneum.

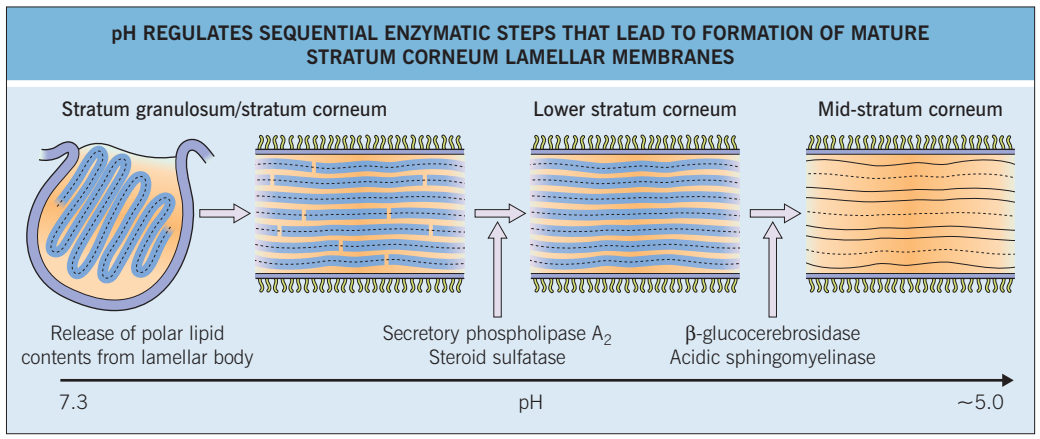

Fig. 124.4 pH regulates sequential enzymatic steps that lead to formation of mature stratum corneum lamellar membranes. The process begins at the stratum granulosum–stratum corneum interface. Of note, in atopic dermatitis, a higher pH is observed.

systemic influences, it can be regulated by external influences, i.e. changes in the status of the permeability barrier[17]. Acute perturbations of the permeability barrier stimulate a characteristic recovery sequence that leads to restoration of normal function over about 72 hours in young skin (the cutaneous stress test). This sequence includes an increase in cholesterol, free fatty acid and ceramide synthesis that is restricted to the underlying epidermis, and attributable to a prior increase in mRNA and enzyme activity/mass for each of the key synthetic enzymes (Fig. 124.3). Furthermore, synthesis of each of the three key lipids is required for normal barrier homeostasis, i.e. topically applied inhibitors of the key enzymes in each pathway produce abnormalities in permeability barrier homeostasis[17].

Lamellar body secretion

The unique two-compartment organization of the stratum corneum is attributable to the secretion of lamellar body-derived lipids and co-localized hydrolases at the stratum granulosum–stratum corneum interface[3]. Under basal conditions, lamellar body secretion is slow, but sufficient to provide for barrier integrity. Following acute barrier disruption, calcium is lost from the outer epidermis, and much of the preformed pool of lamellar bodies in the outermost cells of the stratum granulosum is quickly secreted[18–20]. Calcium is an important regulator of lamellar body secretion, with the high levels of Ca^{2+} in the stratum granulosum restricting lamellar body secretion to low, maintenance levels[21].

Extracellular processing

Extrusion of the polar lipid contents of lamellar bodies at the stratum granulosum–stratum corneum interface is followed by the processing of those lipids into more hydrophobic species that form mature, lamellar membranes[8] (Fig. 124.4). The extracellular processing of glucosylceramides, phospholipids and cholesterol sulfate with accumulation of ceramides, free fatty acids and cholesterol in the stratum corneum is attributable to the co-secretion of a set of hydrolytic enzymes[3] (see Fig 124.2).

Extracellular processing of *glucosylceramides* plays a key role in barrier homeostasis (see legend to Fig. 124.3). In addition, phospholipid hydrolysis, catalyzed by one or more secretory phospholipases (e.g. $sPLA_2$), generates a family of non-essential free fatty acids, which are required for barrier homeostasis[22–24]. Since applications of either bromphenacylbromide or MJ33 (chemically unrelated $sPLA_2$ inhibitors) modulate barrier function in intact skin, $sPLA_2$ appears to play a critical role in barrier homeostasis[22–24]. Moreover, applications of either inhibitor to perturbed skin sites delay barrier recovery.

Sphingomyelin hydrolysis by acidic sphingomyelinase generates two of the nine ceramides required for normal barrier homeostasis (see Fig 124.2). Moreover, patients with mutations in the gene encoding acidic sphingomyelinase (Niemann–Pick, Type A) that lead to low enzyme activity display an ichthyosiform dermatosis, and transgenic mice with an absence of acidic sphingomyelinase also demonstrate a barrier abnormality. Finally, applications of nonspecific inhibitors of acidic sphingomyelinase to perturbed skin sites lead to a delay in barrier recovery[25].

Just as with glucosylceramides and sphingomyelin, *cholesterol sulfate* content increases during epidermal differentiation, and then decreases progressively as the latter is desulfated during passage from the inner to the outer stratum corneum[26]. Both cholesterol sulfate and its processing enzyme, steroid sulfatase, are concentrated in membrane domains of the stratum corneum. Of note, the content of cholesterol sulfate in these sites increases by approximately 10-fold[26] in recessive X-linked ichthyosis (see Ch. 57). Not only is recessive X-linked ichthyosis characterized by a barrier defect[27], but also repeated applications of cholesterol sulfate to intact skin produce a barrier abnormality[28]. In both cases, the barrier abnormality is attributable to cholesterol sulfate-induced phase separation in lamellar membrane domains[27]. But the barrier defect may also be, in part, attributed to a reduction in

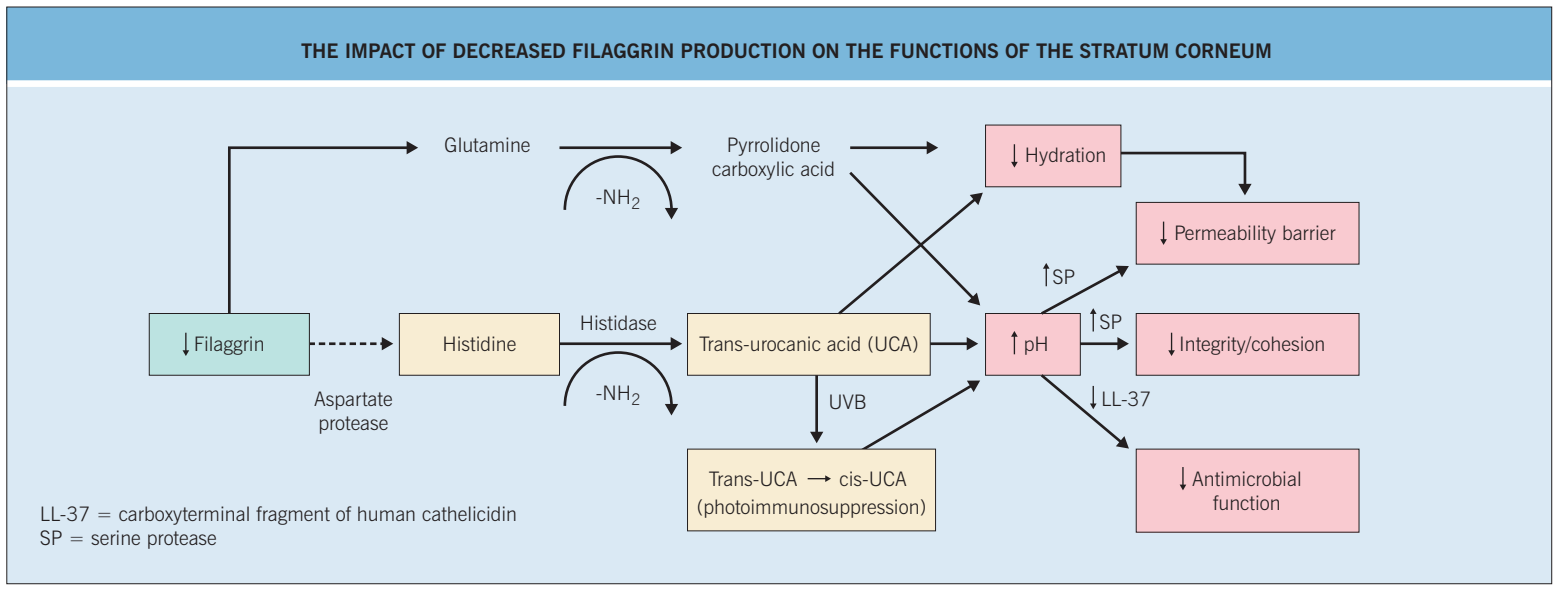

Fig. 124.5 The impact of decreased filaggrin production on the functions of the stratum corneum. UVB, ultraviolet B.

cholesterol content, since cholesterol sulfate is a potent inhibitor of HMG-CoA reductase (see Fig. 124.3).

In addition to lipid precursors and hydrolytic enzymes (e.g. steroid sulfatase, acidic sphingomyelinase), lamellar bodies contain proteases and antiproteases that orchestrate the orderly digestion of corneodesmosomes, allowing corneocyte shedding. These organelles also release antimicrobial peptides, including human β-defensin 2 and LL-37 (the carboxy-terminal fragment of human cathelicidin). As a result, the antimicrobial barrier is intimately linked to the permeability barrier. In atopic dermatitis, for example, there is both an impaired permeability barrier and reduced expression of antimicrobial peptides, explaining in part the predisposition to colonization with *Staphylococcus aureus* (see Table. 12.3). Inherited abnormalities in serine protease/antiprotease expression and filaggrin production are also observed in patients with atopic dermatitis and the impact of reduced filaggrin production on various functions of the stratum corneum is depicted in Figure 124.5.

Acidification

The fact that the stratum corneum displays an acidic external pH ("acid mantle") is well documented, but its origin is not fully understood. Extraepidermal mechanisms (including surface deposits of eccrine- and sebaceous gland-derived products as well as metabolites of microbial metabolism), endogenous catabolic processes (e.g. phospholipid-to-free fatty acid hydrolysis, deamination of histidine to urocanic acid; see Fig. 124.5), and local generation of protons within the lower stratum corneum (by sodium-proton antiporters [NHE_1] inserted into the plasma membrane[29,30]) could actively acidify the extracellular space. These mechanisms would explain not only the pH gradient across the interstices of the stratum corneum (see Fig. 124.4), but also selective acidification of membrane microdomains within the lower stratum corneum.

The concept that acidification is required for permeability barrier homeostasis is supported by the observation that barrier recovery is delayed when acutely perturbed skin sites are immersed in neutral pH buffers[31], or when either the sodium–proton exchanger/antiporter or $sPLA_2$-mediated phospholipid catabolism to free fatty acids is blocked[29]. Acidification appears to impact barrier homeostasis through regulation of enzymes involved in extracellular processing, such as β-glucocerebrosidase and acidic sphingomyelinase, which exhibit acidic pH optima (see Fig. 124.4).

PARAMETERS AFFECTING SKIN PERMEABILITY

As discussed in greater detail in the following sections, the skin is an attractive site for drug delivery[6,7]. However, normal skin provides a significant barrier to drug absorption. Understanding the parameters that affect the permeability of this barrier is essential for achieving successful drug therapy via the skin. While local cutaneous effects are generally achieved by dissolving or suspending the drug in a vehicle that is applied topically as a semi-solid formulation (e.g. cream or ointment)[32], administration of systemic therapy via the skin is typically accomplished through the use of a patch. In either situation, drug is supplied at the surface of the skin for diffusion across the stratum corneum, with the goal of reaching therapeutic targets within the skin and/or systemic uptake via superficial dermal capillaries.

Parameters Controlling Absorption

Conventional transdermal drug delivery is a passive process governed by Fick's law, that is, the rate of absorption or flux (J) of any substance across a barrier is proportional to its concentration difference across that barrier[33,34]. For topically applied drugs, the concentration difference can be simplified as the concentration of drug in the vehicle, C_v, and the proportionality constant relating flux to concentration is the permeability coefficient, K_p (equation 1). K_p is composed of factors that relate to both drug and barrier, as well as their interaction. These factors are: K_m, the partition coefficient; D, the diffusion coefficient; and L, the length of the diffusion pathway (equation 2). Thus, four factors control the kinetics of percutaneous drug absorption (equation 2); however, it is of great practical importance that two of the four (C_v, K_m) are highly dependent on one additional factor, the vehicle.

$$J = K_p C_v \tag{1}$$

$$J = \left(\frac{DK_m}{L}\right) C_v \tag{2}$$

Role of the Vehicle

The vehicle is an important link between drug potency and therapeutic effectiveness, since extensive pharmaceutical research has shown that the composition of the vehicle can profoundly influence the rate and extent of absorption (bioavailability). As illustrated by the potency ranking scale for glucocorticoids[35], the same drug appears in different potency classes when formulated in different vehicles (Table 124.3). It was once axiomatic that ointments were more potent than creams. Though true for the early glucocorticoid products, it is no longer generally applicable. Greater understanding of the science underlying topical formulations has allowed creams, gels, solutions and foams to be specifically formulated equipotent to ointments (see Table 124.3).

In the rational design of dermatologic vehicles that maximize bioavailability, two factors are of critical importance: (1) solubilizing the drug in the vehicle (C_v); and (2) maximizing movement (partitioning) of drug from vehicle to stratum corneum (K_m). The partition

EFFECT OF VEHICLE ON POTENCY	
Corticosteroid*	**Potency class**
BETAMETHASONE DIPROPIONATE	
• Diprolene ointment 0.05%	1
• Diprolene gel 0.05%	1
• Diprolene cream AF 0.05%	2
• Diprosone ointment 0.05%	2
• Diprosone cream 0.05%	3
• Diprosone lotion 0.05%	5
CLOBETASOL PROPIONATE	
• Temovate ointment 0.05%	1
• Temovate cream 0.05%	1
• Temovate gel 0.05%	1
• Temovate E cream 0.05%	1
• Olux foam 0.05%	1
• Temovate Scalp Application 0.05%	2
FLUOCINONIDE	
• Lidex ointment 0.05%	2
• Lidex cream 0.05%	2
• Lidex gel 0.05%	2
• Lidex solution 0.05%	2
• Lidex E cream 0.05%	3
TRIAMCINOLONE ACETONIDE	
• Aristocort A ointment 0.1%	3
• Kenalog cream 0.1%	4
• Kenalog lotion 0.1%	5
• Aristocort cream 0.1%	6

Table 124.3 Effect of vehicle on potency. *Generic name in header, followed by trade names.

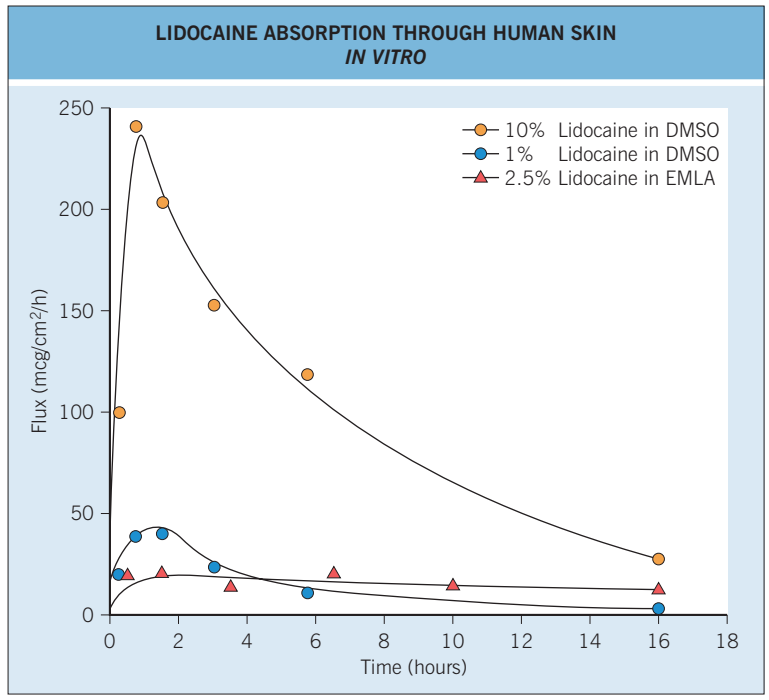

Fig. 124.6 Lidocaine absorption through human skin *in vitro*. Incorporation of DMSO as a co-solvent with ethanol results in both increased drug solubility (C_v) and partitioning (K_m). At 10% drug concentration, the maximum flux is 10-fold greater than that achieved in an emulsion formulation (eutectic mixture of lidocaine 2.5% and prilocaine 2.5% [EMLA]). At 1% drug concentration in DMSO the maximum flux is twofold greater than 2.5% drug in EMLA. *Reproduced from Mallory SB, et al. Topical lidocaine for anesthesia in patients undergoing pulsed dye laser treatment for vascular malformations. Pediatr Dermatol. 1993;10:370–5.*

coefficient describes the ability of a drug to escape from the vehicle and move into the outermost layer of the stratum corneum. It is defined as the equilibrium solubility of drug in the stratum corneum (sc) relative to its solubility in the vehicle ($K_m = C_{sc}/C_v$).

Drug Concentration

The driving force for percutaneous absorption is the concentration of *soluble* drug in the vehicle. Many older topical drug products were marketed with the expectation that higher concentrations were more potent. Although true for some products, e.g. tretinoin gels and creams (0.01–0.1%) in which the drug is completely solubilized at all concentrations, for others it is not. Hydrocortisone 1% and 2.5% in a cream formulation have been shown to be of equal potency, as have triamcinolone acetonide 0.025%, 0.1% and 0.5% creams[35]. One of the major advances in formulating glucocorticoids, as first shown with fluocinonide, came when it was discovered that the addition of propylene glycol to the vehicle could completely solubilize the drug. This led to corticosteroid products with greater potency, as demonstrated in the vasoconstrictor assay. Newer products are now tested during the development process to ensure that increased drug concentration results in increased bioavailability. However, excess non-dissolved drug can sometimes be advantageous, especially in transdermal patches worn for prolonged periods of time (e.g. up to a week). In this situation, as dissolved drug is absorbed into the body, non-dissolved drug can then become dissolved in order to maintain an equilibrium, thereby maintaining a constant dissolved drug concentration over time and providing a constant rate of delivery[36].

Partition Coefficient

In general, topically applied drugs are poorly absorbed because only a small fraction partitions into the stratum corneum. Most of the drug remains on the skin surface, subject to loss from a multitude of factors (exfoliation, sweating, wash-off, rub-off, adsorption onto clothing, and chemical or photochemical degradation). Even 10–12 hours following dosing, a drug that has not been lost by exfoliation or rub-off remains largely on the skin surface, and it is easily removed by a simple soap and water wash[37]. In the case of patches worn for several days, as much as half of the original amount of drug may still be present in the patch when it is removed, and this can pose a safety hazard upon disposal, especially with potentially dangerous drugs such as fentanyl[38].

A number of physical and chemical factors can improve partitioning. Hydration of the skin due to occlusion, either from a topical formulation or a patch, expands the reservoir volume available to drugs within the stratum corneum; this can increase absorption as much as five- to tenfold[39]. Common excipients such as ethanol and propylene glycol can also alter barrier structure so as to increase partitioning[40]. In addition, many excipients have good solvent properties and, as a result, positively affect C_v as well as K_m. The use of high concentrations of propylene glycol to maximize bioavailability has become pervasive among the super- and high-potency corticosteroids, but at a price. Adverse events such as burning and stinging are common when such preparations are applied to fissured or eroded skin, and contact dermatitis may occur.

A number of other compounds have been identified as enhancers. Dimethylsulfoxide (DMSO), the archetypical enhancer, exemplifies the effects that can be achieved (Fig. 124.6). As with ethanol and propylene glycol, both C_v and K_m are affected. Because DMSO is a superb solvent, higher drug concentrations can be achieved than with other solvents, but it also expands the stratum corneum barrier, permitting increased drug uptake and possibly an increased rate of diffusion (D) through the barrier. However, the use of powerful enhancers such as DMSO is constrained by excessive skin irritation or toxicity[41].

Regional Variation

All body sites are not equally permeable[42]. Variations in stratum corneum thickness, the number of sebaceous glands, and hydration status can all affect absorption. Current data and clinical experience suggest that one can crudely rank regional permeability as follows: nail < < palm/sole < trunk/extremities < face/scalp < < scrotum.

STRATEGIES TO ENHANCE TRANSDERMAL DRUG DELIVERY

Despite the significant permeability barrier of the stratum corneum, drug delivery via the skin is a very attractive option and is widely employed for both local and systemic therapy (Table 124.4; Fig. 124.7)[6,7]. Topical treatment of cutaneous disorders obviously targets the site of disease, thereby minimizing adverse side effects elsewhere within the body. Delivery of systemic therapies via the skin avoids degradation of the medication within the gastrointestinal tract and first-pass metabolism by the liver, both of which are associated with oral administration of drugs, in addition to evading the pain and safety issues associated with injections. Transdermal delivery of drugs, especially via long-acting patches, enables infrequent dosing and maintenance of steady-state drug levels.

Many dermatologic medications can be applied topically to the skin because the required dosage is often exceedingly small and therefore they can be effective even in the setting of highly inefficient absorption. In addition, a number of skin disorders are associated with compromised barrier function, which leads to enhanced drug uptake in sites of involvement[43].

In contrast, systemic drug delivery via the skin typically requires administration of larger doses through normal skin. As a result, at the time of writing, only ~20 drugs have been FDA-approved for transdermal administration. The drugs contained within these patches share several characteristics – they are low molecular weight (<400 Da), lipophilic (octanol–water partition coefficient up to 10 000), and relatively low dose (typically <10 mg per day)[44] (Table 124.5).

Significant efforts have been expended on the development of new approaches to enhance transdermal drug delivery and thereby increase the number of drugs administered via this route (Fig. 124.8). These strategies can be broadly subdivided into chemical, biochemical and physical approaches (Table 124.6).

TRANSDERMAL DRUG DELIVERY: THEORETICAL ADVANTAGES
• Improved patient compliance
• Improved efficacy, i.e. continuous release
• Reduced toxicity: (a) no "peaks" and (b) lower total absorbed dose
• Bypass hepatic first-pass metabolism
• Avoid local GI side effects/metabolism
• Decreased dosing frequency
• Avoid painful injections
• Decreased costs to patient due to decreased: (a) total dose and (b) dosing frequency (increased efficiency)

Table 124.4 Transdermal drug delivery: theoretical advantages.
GI, gastrointestinal.

THEORETICAL ADVANTAGES OF TRANSDERMAL DELIVERY INCLUDE LESS TOXICITY AND IMPROVED EFFICACY

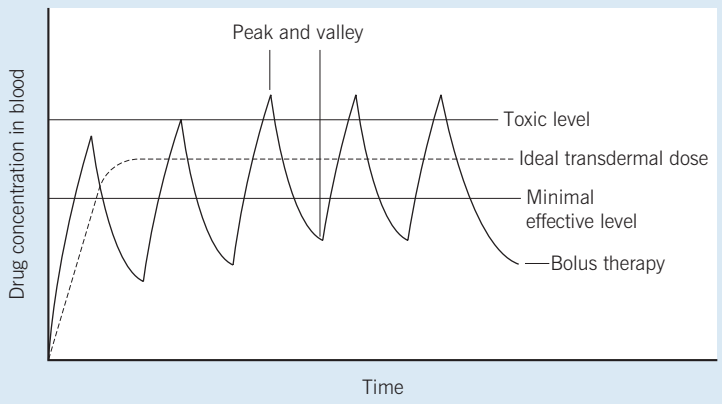

Fig. 124.7 Theoretical advantages of transdermal delivery include less toxicity and improved efficacy. This is due to a reduction in the "peaks" and "valleys" associated with bolus therapy.

Chemical Enhancement

Chemical enhancers include compounds that interact with the lipid matrix of the stratum corneum to alter its nanostructure and thereby increase permeability[7,40]. The major advantages of chemical enhancers are that they are typically low cost, can be incorporated into a conventional patch or topical formulation, and do not require the complexity of a battery-powered device. The primary disadvantage of chemical enhancers is that they are often associated with skin irritation or toxicity when present at high concentrations and with long exposure times[41]. Thus, chemical enhancers have been employed principally to increase permeability to compounds that already cross the skin reasonably well, but they have generally been unable to significantly impact delivery of new classes of molecules (e.g. highly water-soluble drugs) or macromolecules such as proteins, gene-based medicines and vaccines.

The most common chemical enhancer is water, which leads to hydration of the stratum corneum when it accumulates during prolonged occlusion; the occlusion can result from a topical formulation or a patch[39,45]. Following 24–48 hours of occlusion, corneocytes swell, the intercellular spaces become distended, and the lacunar network becomes dilated. Distention of lacunae is thought to eventually lead to connections within an otherwise discontinuous system, creating "pores" in the stratum corneum interstices through which polar and non-polar substances can penetrate more readily (see Fig. 124.1).

Solvents, such as ethanol, methanol, chloroform and acetone, as well as detergents can extract barrier lipids and/or disrupt their bilayer structures, which then permeabilizes the stratum corneum[7,40,41]. Morphologic changes in human stratum corneum following exposure

CONVENTIONAL TRANSDERMAL DRUG DELIVERY UTILIZING PATCHES
IDEAL DRUG CHARACTERISTICS
• Low dosage (<10 mg/day) • Low molecular weight (<400 Da) • Moderately lipophilic
EXAMPLES OF DRUGS AVAILABLE IN TRANSDERMAL PATCHES
Clonidine, estradiol*, ethinyl estradiol*, fentanyl, granisetron, levonorgestrel*, methylphenidate, nicotine, nitroglycerin, norelgestromin*, norethindrone*, oxybutynin, rivastigmine, rotigotine, scopolamine, selegiline, testosterone*
*Hormones.

Table 124.5 Conventional transdermal drug delivery utilizing patches.

PATHWAYS INTO THE SKIN FOR TRANSDERMAL DRUG DELIVERY

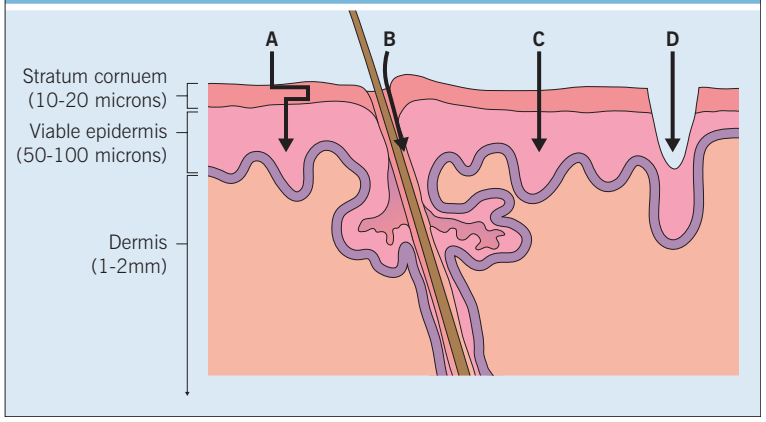

Fig. 124.8 Pathways into the skin for transdermal drug delivery.
A Transdermal transport via a tortuous pathway largely within extracellular lipids. This pathway is utilized during drug absorption in association with chemical, biochemical and some physical enhancers. **B** Transport through hair follicles and sweat ducts can be enhanced by iontophoresis and certain particulate formulations. **C** Transport directly across the stratum corneum is enabled by electroporation. **D** Stripping, ablation, abrasion and microneedles remove stratum corneum to make micron-scale (or larger) pathways into the skin. *Reproduced with permission from Prausnitz MR, et al. Current status and future potential of transdermal drug delivery. Nat Rev Drug Discov. 2004;3:115–24.*

to solvents[46] include phase separation and disruption of lamellar bilayers in addition to the creation of defects in corneocyte membranes (with detergents). Moreover, surfactants, such as sodium dodecyl (lauryl) sulfate, and vehicles (e.g. propylene glycol) extract lipids and create extensive expansion of pre-existing lacunar domains. Furthermore, solvent-based penetration enhancers, such as azone, sulfoxides, urea and free fatty acids, not only extract extracellular lipids, but they also alter stratum corneum lipid organization (phase behavior), thereby increasing transdermal delivery and expanding intercellular domains (Fig. 124.9; see Fig. 124.6). Recent work suggests that combinations of particular chemical enhancers that adhere to specific, narrow-range compositions can be especially effective[47].

Finally, *liposomes* represent yet another "chemical" method frequently employed to enhance delivery into the skin, especially in the case of cosmetics and moisturizers[48]. While intact liposomes probably do not penetrate the stratum corneum[49], they can be used to increase effective drug solubility in a vehicle (C_v) and facilitate partitioning into the skin (K_m).

STRATEGIES TO ENHANCE TRANSDERMAL DRUG DELIVERY
CHEMICAL
• Water • Solvents • Surfactants • Liposomes
BIOCHEMICAL
• Peptides • Metabolic inhibitors
PHYSICAL
• Stripping • Iontophoresis • Electroporation • Ultrasound (thermal) • Ultrasound (cavitational) • Thermal ablation • Mechanical abrasion • Microneedles

Table 124.6 Strategies to enhance transdermal drug delivery.

Fig. 124.9 Lipophilic agents (e.g. *n*-butanol) penetrate across the stratum corneum (SC) via the intercellular spaces. Note huge volume expansion of extracellular domains in this electron photomicrograph, representing the putative SC reservoir. *Method: n*-butanol precipitation *in situ* with osmium vapors.

Biochemical Enhancement

Biochemical methods have been developed to *directly* increase permeability of the stratum corneum lipid matrix as well as to *indirectly* affect skin permeability via alteration of lipid metabolism. Much of the work in this area has focused on peptides that are believed to disrupt or penetrate stratum corneum lipids. For example, polyarginine has been shown to ferry molecules attached to it across the stratum corneum and into the viable epidermis and dermis[50] (Fig. 124.10). Other peptides, identified by phage-display screening, appeared to target transfollicular pathways and did not require the drug to be attached[51]. Magainin, a naturally occurring pore-forming peptide, has been shown to increase skin permeability by direct interaction with and disruption of stratum corneum lipids[52].

In a related strategy, metabolically based approaches aim to enhance the efficacy of standard enhancers by biochemically inhibiting the repair (metabolic) response *in vivo* and thereby delaying barrier recovery[53]. This can be accomplished by altering the critical molar ratio of the three key stratum corneum lipids or by inducing discontinuities in the lamellar bilayer system. Both lipid synthesis inhibitors and agents that interfere with the assembly, secretion or extracellular processing of lamellar bodies have been examined, including brefeldin A, monensin, chloroquine, high Ca^{2+}/K^{+} levels and neutral pH buffers. Overall, biochemical enhancement methods are relatively new and to date they have not been used much in clinical drug delivery.

Physical Enhancement

There are a number of physical methods to increase drug delivery via the skin, many of which require the use of devices and some of which hold the promise to significantly expand the spectrum of drugs that can be administered transdermally to include water-soluble molecules and macromolecules[54,55].

Stripping is a simple technique used in research protocols to remove stratum corneum by sequential application of adhesive tape or cyanoacrylate glue[53,56]. Tape stripping removes both corneocytes and extracellular lipids, thereby reducing the elongated path length that drugs otherwise need to traverse, and it mechanically disrupts lamellar bilayers, even in the retained lower stratum corneum layers. Barrier disruption of human skin requires multiple strippings, which can lead to inflammation. More strippings are required to disrupt the barrier in skin phototypes V and VI (darkly pigmented) than in phototypes I and II (lightly pigmented) subjects[57].

Iontophoresis and electroporation represent electrically assisted, physical approaches to enhance delivery of drugs/macromolecules across the stratum corneum[58]. *Iontophoresis* uses low currents applied

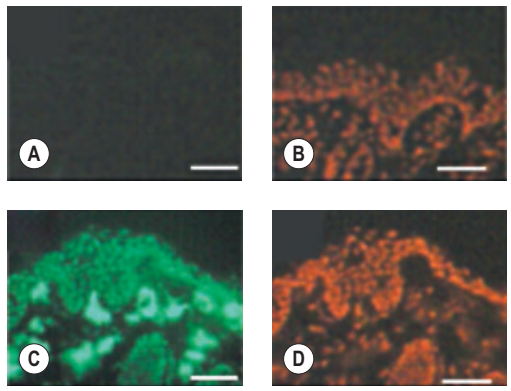

Fig. 124.10 Biochemical enhancement of drug delivery to the skin in mice. **A** Fluorescein does not penetrate intact skin. **C** Fluorescein conjugated to a heptamer of D-arginine penetrates extensively across the stratum corneum and localizes within viable epidermis and dermis. **B,D** Propidium iodide counter-staining shows tissue architecture in the same tissue sections as **A** and **C**. Scale bars are 20 microns. *Reproduced with permission from Rothbard JB, et al. Conjugation of arginine oligomers to cyclosporin A facilitates topical delivery and inhibition of inflammation. Nat Med. 2000;6:1253–7.*

for minutes to hours from an externally placed electrode (with the same charge as the drug) in order to drive these molecules across the stratum corneum, primarily by electrophoresis[59]. As the rate of drug delivery is generally proportional to the applied current, iontophoresis offers an opportunity for programmable drug delivery, especially with the recent development of miniaturized microprocessor systems. Clinically, iontophoresis has been employed to deliver: fentanyl and lidocaine for pain relief[60], pilocarpine to induce sweating (as a diagnostic test)[61], and tap water to treat hyperhidrosis[62]. Reverse iontophoresis has been used to extract glucose from the skin as a means of monitoring glucose levels in diabetic patients[63].

Electroporation (electropermeabilization) utilizes very short (microsecond to millisecond) and relatively high voltage (~100 V) electrical pulses to induce structural rearrangement of stratum corneum lipids, leading to pore formation[64,65]. Properly designed systems can minimize sensations from the pulses and facilitate delivery, especially of hydrophilic and charged molecules into the skin. Although only at the research stage with regard to transdermal delivery, electroporation is currently being used to drive chemotherapeutic agents into superficial skin tumors by applying surface or penetrating electrodes[66].

While *ultrasound* is widely and safely employed in both medical diagnostics and physical therapy, this technology can also be used to enhance transdermal delivery. When ultrasound is utilized in a manner that resembles medical imaging, it is not very effective at increasing skin permeability. However, ultrasound administered in the context of heating deep tissues, for example during physical therapy, has been shown to increase drug penetration into the skin, and this technique is actually used to increase local delivery of anti-inflammatory agents at the time of physical therapy[67]. With still different settings (in particular low frequencies such as <1 MHz), ultrasound can be used to generate bubble activity, referred to as "*cavitation*". Cavitation bubbles oscillating and imploding in the medium between the ultrasound transducer and the skin surface generate shockwaves that mechanically impact the skin, creating submicroscopic defects in stratum corneum structure. These defects increase skin permeability to water-soluble molecules and some macromolecules[68]. In a related approach, pulsed laser beams have also been used to generate photomechanical shockwaves at the skin surface, which also increase skin permeability[69]. Cavitational ultrasound of the skin has been approved as a pretreatment prior to the application of lidocaine as a means of accelerating local anesthesia.

In addition to the methods described above that disrupt stratum corneum structure on a nanometer scale, there are methods for producing micron-scale holes within the stratum corneum. This enables delivery of much larger molecules with much greater fluxes into the skin. With *thermal ablation*, microsecond- to millisecond-long pulses of heat are applied utilizing electrical filaments, radiofrequency electrodes or lasers which lead to micron-sized holes in the stratum corneum[70,71]. Because the pulses are so short, there is not enough time for heat to propagate deeply into the tissue, thereby localizing the ablation to the epidermis and minimizing pain; these latter effects have been demonstrated in clinical trials. An at least partial removal of the stratum corneum and an increase in skin permeability can also be accomplished via sandpaper abrasion and microdermabrasion[72,73].

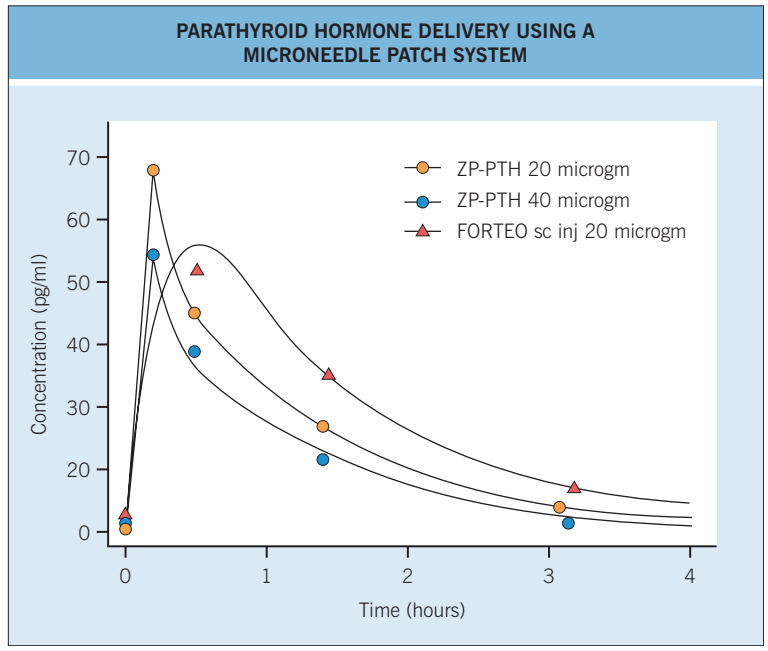

Fig. 124.11 Parathyroid hormone delivery to human subjects using a microneedle patch system. Subcutaneous (sc) injection of synthetic human parathyroid hormone 1-34 (FORTEO) achieved a peak drug concentration (T_{max}) at 23 min, whereas application of a microneedle patch coated with the same drug achieved a T_{max} of 8 min (ZP-PTH). *Reproduced with permission from Daddona PE, et al. Parathyroid hormone (1-34)-coated microneedle patch system: clinical pharmacokinetics and pharmacodynamics for treatment of osteoporosis. Pharm Res. 2011;28:159–65.*

Finally, *microneedles* represent another micron-scale approach to drug delivery via the skin[74]. Microneedles typically measure 0.1–1 mm in length; they can be solid or hollow and are manufactured by microfabrication tools similar to those used in the microelectronics industry. When solid, microneedles can be incorporated into patches that are applied to the skin and possibly worn for some time. In clinical trials, microneedles have been used to punch microscopic holes into the skin prior to the application of drug-loaded patches such as those containing naltrexone[75]. Drug-coated solid microneedles, designed to undergo dissolution upon insertion into the skin, have also been tested, and the efficacy of parathyroid hormone delivered in this manner for the treatment of osteoporosis has been demonstrated[76] (Fig. 124.11).

In contrast to the Mantoux technique, which requires clinical training to ensure an intradermal location for the needle injection[77], hollow microneedles enable simple and reliable intradermal injections. Clinical trials in patients with diabetes have shown accelerated pharmacokinetics of insulin after microneedle injections into the skin, when compared to conventional subcutaneous infusions[78]. Influenza vaccine that is approved for injection into the skin using a microneedle demonstrated increased immunogenicity in the elderly and a lower dose was effective in non-elderly adults[79]. This increased effectiveness of the vaccine is due to the highly immunoresponsive environment in the skin compared to muscle, the conventional site of vaccination.

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