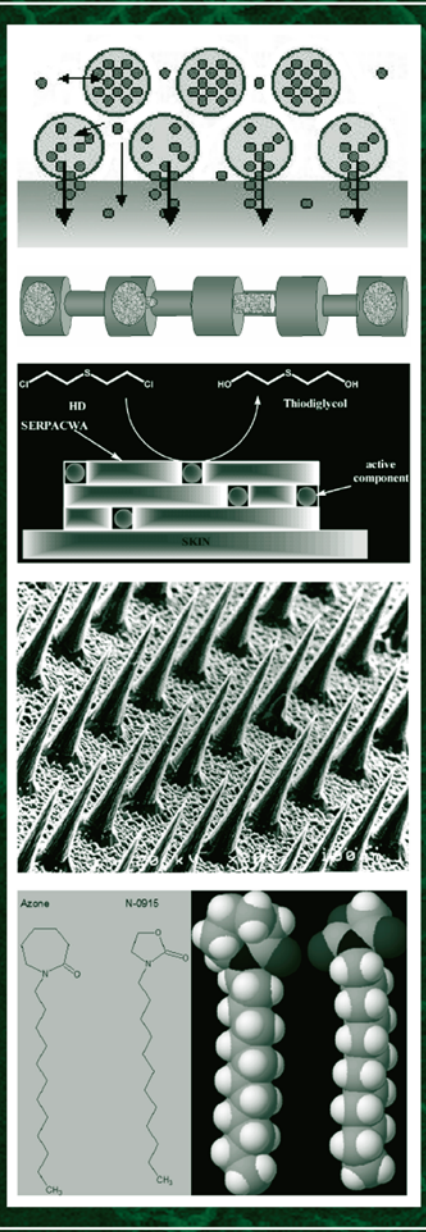
# Percutaneous Penetration Enhancers




*Second Edition*

*Edited by*

Eric W. Smith
Howard I. Maibach

CRC Taylor & Francis
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**Howard I. Maibach, M.D.,** is a professor of dermatology at the University of California, San Francisco, and has been a long-term contributor to experimental research in dermatopharmacology and to clinical research on contact dermatitis, contact urticaria, and other skin conditions.

# Preface

It has been ten years since the first edition of *Percutaneous Penetration Enhancers* was published. At that time we expected to see an explosion in the number of chemical enhancers researched and developed for commercial formulations. Surprisingly, this has not been the case; at this point there are still only a handful of chemical entities that are close to realizing this goal. In the first edition we suggested that the full impact of penetration enhancer species on transdermal delivery may not become evident simply because of the costs associated with regulatory registration formalities. It now appears that this suggestion may have held more validity than we initially believed. This theory may be corroborated by the evidence of dramatic growth and innovation in the field of physical (rather than chemical) penetration enhancement systems. Several commercial units utilizing physical enhancement mechanisms, spanning the full spectrum from iontophoresis to microneedle devices, are in the final stages of development and testing. On the other hand, there is some renewed interest in transdermal penetration retardation to limit the absorption of chemicals through the skin. These retardation systems are based on the biochemical groundwork established by enhancer studies in the past. To assist with all these research efforts, our analytical, bioengineering, and predictive systems continue to become ever more sophisticated to the point that much laboratory wet-work can now be replaced by computer-assisted systems. The field is clearly evolving and redefining itself, and it is therefore timely to attempt to summarize our current knowledge. To this end we have assembled a list of researchers who are authorities in their respective disciplines — this volume is an elegant summary of their recent research efforts in the ever-broadening fields of topical penetration, enhancement, and retardation. We are thankful to each author for their individual contributions to this volume. We hope that readers will find these chapters useful in establishing the broad framework for the topic and a stimulant for continued research in the diverse areas of percutaneous penetration enhancement.

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# INTRODUCTION 1

# *Chapter 1*

# Penetration Enhancer Classification

**Brian W. Barry**

## CONTENTS

## Introduction

This chapter presents a brief overview of the topics dealt with in more detail in subsequent contributions to this book, that is, the major ways by which scientists attempt to overcome the highly impermeable nature of human skin so as to deliver drugs at clinically active body concentrations. The organization of the material essentially follows the review published in 2001.[1] To conserve space, most of the 200 references from that work will not be repeated here, nor those listed in subsequent chapters in this book.

## Drug Transport Routes through Human Skin

Human skin selectively and effectively inhibits chemical penetration.[2] The most important control element is generally the stratum corneum and accelerant techniques usually try to reduce this barrier's hindrance so as to maximize drug flux, although occasionally the follicular route may also be relevant.

At the skin surface, a molecule has three possible routes to reach the viable tissue: via hair follicles with their sebaceous glands, through eccrine sweat ducts, or across the continuous horny layer (Figure 1.1). Because of the low fractional appendageal area (about 0.1%), except for ions and highly polar molecules that struggle to cross intact stratum corneum, this pathway usually adds little to *steady-state* drug flux. However, appendages may function as shunts, which may be important at short times prior to steady-state diffusion. Additionally, polymers and colloidal particles can target the follicle.

The main barrier is thus the intact horny layer with its "brick and mortar" structure[3] (Figure 1.2). The "bricks" of hydrated keratin in the corneocytes distribute in a "mortar,"

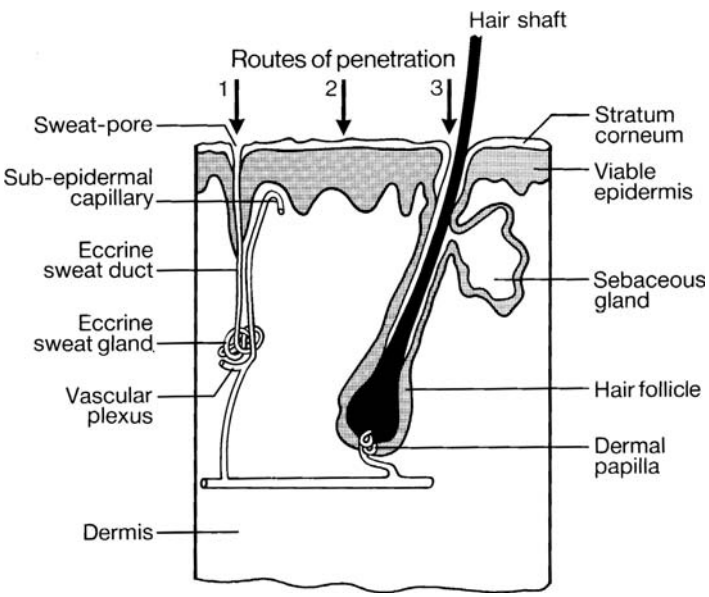



**Figure 1.1 Simplified diagram of skin structure and macroroutes of drug penetration: (1) via the sweat ducts, (2) across the continuous stratum corneum, or (3) through the hair follicles with their associated sebaceous glands.**

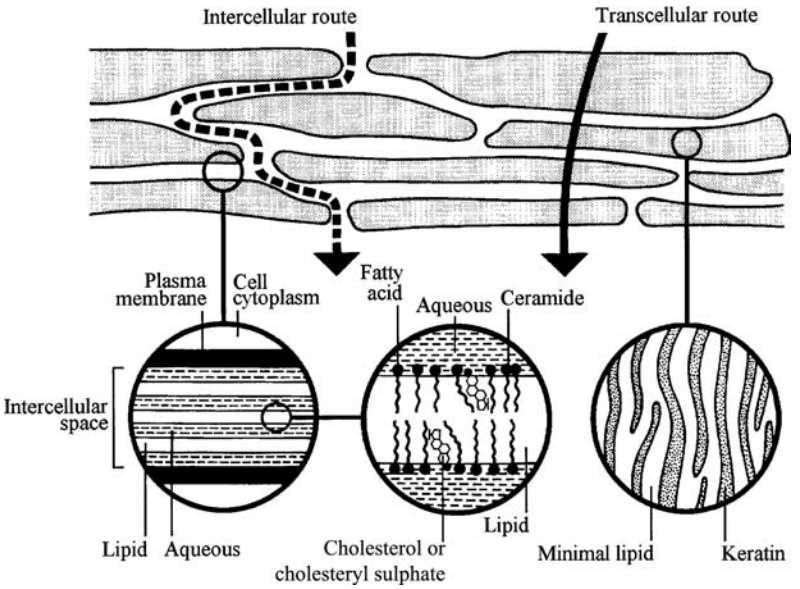



**Figure 1.2 Simplified diagram of stratum corneum and two microroutes of drug penetration.**

consisting of lipid bilayers of ceramides, fatty acids, cholesterol, and cholesterol esters. Most transdermal molecules penetrate through this intercellular microroute and therefore many accelerant methods disrupt or bypass these crystalline, semicrystalline, gel, and liquid crystal domains.

## Enhancing Transdermal Drug Delivery

Figure 1.3 summarizes some techniques for overcoming the barricade offered by an intact stratum corneum.

### *Interactions between Drug and Vehicle*

#### *Selection of Correct Drug or Prodrug*

If at all possible, we choose a drug possessing the optimal physicochemical properties to translocate well across skin, and our transdermal problems essentially evaporate. The simple equation for steady-state flux is useful when considering factors controlling stratum corneum permeation rates (Equation (1.1)). When we plot the cumulative mass of diffusant, $m$, passing per unit area through a membrane, at long times the graph approaches linearity and its slope yields the steady flux, $dm/dt$, as in the following Equation:

$$\frac{dm}{dt} = \frac{DC_0K}{h} \tag{1.1}$$

where $C_0$ represents the constant donor drug concentration; $K$, the partition coefficient of solute between membrane and bathing solution; $D$, the diffusion coefficient; and $h$, the membrane thickness.

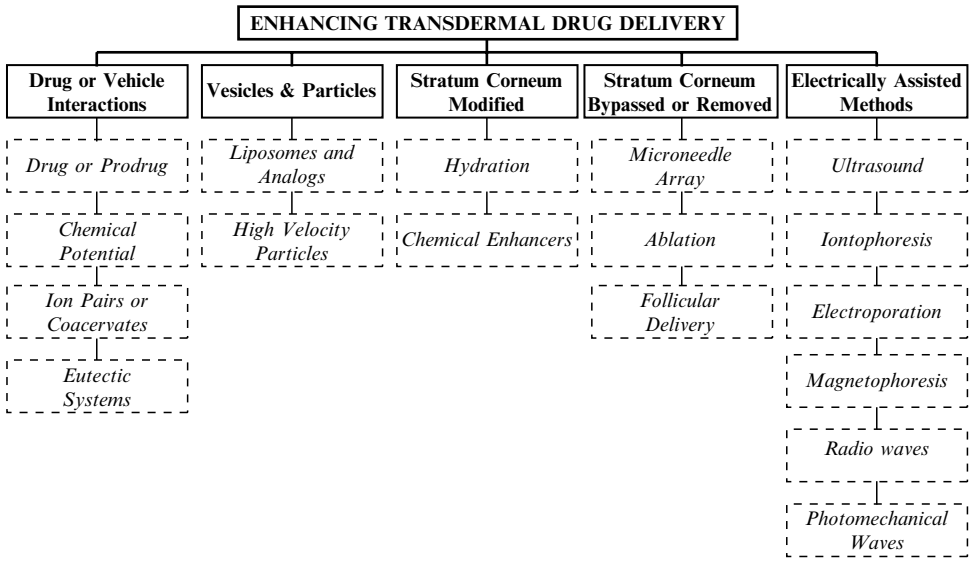



**Figure 1.3 Some methods for enhancing transdermal drug therapy.**

From Equation (1.1), we can assess the ideal properties needed for a molecule to penetrate stratum corneum well. These are: low molecular mass, solubility in oil and water, high but balanced (optimal) partition coefficient, and a low melting point, correlating with good solubility as predicted by ideal solubility theory.

However, saturated systems of most drugs fail to provide adequate topical bioavailabilities, and then we must have recourse to other approaches.

## Chemical Potential Adjustment

An alternative form of Equation (1.1) uses thermodynamic activities[4]

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \frac{aD}{\gamma h} \tag{1.2}$$

where $a$ is the thermodynamic activity of penetrant in its vehicle and $\gamma$ is its effective activity coefficient in the skin membrane. For the greatest flux, the drug should operate at its maximum thermodynamic activity. Dissolved molecules in saturated solution equilibrate with pure solid (defined as maximum activity for an equilibrated system) and they are also thus at maximum activity. Therefore, all vehicles containing drug as a finely ground suspension should produce the same penetration rate, provided that the systems behave ideally, that is, $D$, $\gamma$, and $h$ remain constant.

*Supersaturated* solutions may form, either by design or by uncontrolled evaporation on the skin; in either situation, the theoretical maximum stratum corneum uptake and flux may increase many-fold compared to a stable system.[5] The practical problem with using this approach is, of course, how do we maintain a suitable period of metastability on storage?

### Ion Pairs and Complex Coacervates

Charged species do not readily penetrate lipid membranes. One enhancement approach uses an oppositely charged species to form a lipophilic ion pair. As charges temporarily neutralize, the complex partitions into the stratum corneum lipids. The ion pair diffuses in to the interface between the horny layer and viable epidermis, dissociates into its charged species, which partition into the aqueous epidermis and diffuse onward. A similar process, complex coacervation, is the phenomenon whereby oppositely charged ions separate into an oil phase, rich in ionic complex. The coacervate partitions into horny layer, where it behaves as ion pairs, diffusing, dissociating, and passing into viable tissues. Generally, for either process, any enhancement derived is rather modest.

### Eutectic Systems

The eutectic mixture of lidocaine and prilocaine in EMLA cream provided formulation advantages[6] for a successful product that encouraged the study of such systems for other drugs, such as ibuprofen and propranolol (as well as lidocaine) interacting with terpenes.

## Vesicles and Particles

### Liposomes and Analogs

Most early reports on traditional liposomes when applied to skin propose a localizing effect; the vesicles deposit their enclosed drugs in the upper layers of the stratum corneum or pilosebaceous unit. Generally, liposomes were not expected to penetrate into viable skin. How well vesicles transport drugs *through* the skin is still the subject of considerable debate.

The introduction by Cevc of *Transfersomes*® (recently reviewed[7]) that incorporate "edge activators" excited much interest. Their inventor argues that such ultradeformable vesicles squeeze through pores in stratum corneum that are less than one-tenth the liposome's diameter. Two features are claimed to be important. Transfersomes require a hydration gradient to encourage skin penetration (nonoccluded conditions); the gradient operating from the (relatively) dry skin surface towards waterlogged viable tissues drives Transfersomes through the horny layer (Figure 1.4). They also work best under *in vivo* conditions. Data indicate that as much as 50% of a topical dose of a protein or peptide (such as insulin) penetrate skin *in vivo* in 30 min.

Other investigators, such as Barry and his colleagues, investigated drug delivery from ultradeformable liposomes and traditional vesicles, using open and occluded conditions *in vitro*. Both types raised maximum flux and skin deposition compared to saturated aqueous drug solution (maximum thermodynamic control) under a nonoccluded environment, but results were not as dramatic as detailed in earlier work. Five potential mechanisms of action of these liposomes were assessed:

1. A free drug process — the liposome releases the drug, which independently permeates skin.
2. Vesicles release their lipids which then act as penetration enhancers with respect to the skin lipids.
3. Improved skin uptake of drug.

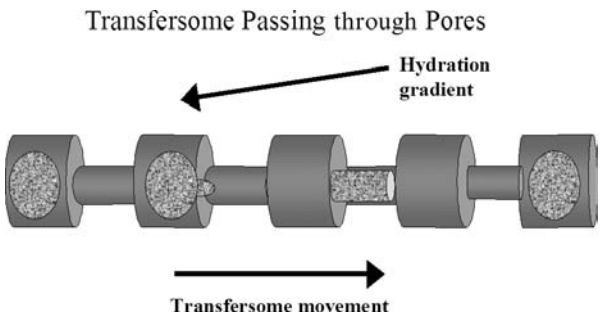



**Figure 1.4 Ultradeformable *Transfersome* squeezing through minute pores in the stratum corneum, driven by the water concentration gradient. The liposome with edge-activator thus penetrates from the horny layer surface (relatively dry) to the aqueous viable tissues.**

4. The different entrapment efficiencies of the liposomes control drug input.
5. Deep penetration of stratum corneum by intact liposomes.

As developed by Touitou, *ethosomes* (liposomes with a high ethanol content) penetrate and deliver compounds into the skin as the alcohol fluidizes both ethosomal lipids and those in the intercellular bilayers (Figure 1.2). The soft, malleable vesicles then penetrate through the disorganized lipid bilayers.

*Niosomes* use nonionic surfactants to form vesicles. Flexible ones, as investigated by the Bouwstra group, consist of a mixture of a bilayer-forming molecule (stabilizer) and a micelle-forming component (destabilizer) and penetrate to the deeper layers of the stratum corneum.

### *High-Velocity Particles*

The PowderJect system fires solid nanoparticles through the horny layer into viable tissues, driven by a supersonic shock wave of helium. Although many advantages were claimed for this delivery system (e.g., freedom from pain and needle phobia, improved efficacy and bioavailability, targeting, controlled release, accurate dosing, and safety), there have been problems with bruising and particles bouncing off skin surfaces. Regulatory authorities may be concerned by the damage caused by high-velocity particles breaking through the horny layer (Figure 1.2) and also allowing extraneous contaminants such as bacteria to enter into living tissues. Commercial work is now concentrating on vaccine delivery.[8]

The Intraject is a development of the vaccine gun designed to deliver liquids through skin without using needles.[9] It is surprising that, after the intensive use of similar devices for vaccination, such as by the U.S. military during the Vietnam conflict, it was not earlier developed for drug delivery.

## *Stratum Corneum Modified*

### *Hydration*

Most (but not all) substances penetrate better through hydrated stratum corneum; water opens up its compact structure of horny layer. Moisturizing factors, occlusive films, and patches, together with hydrophobic ointments, all enhance topical bioavailability.

## Chemical Enhancers

Substances that temporarily reduce skin resistance (also known as *accelerants* or *sorption promoters*) thereby enhance drug passage. Examples include water, hydrocarbons, sulfoxides (especially dimethylsulfoxide [DMSO]) and their analogs, pyrrolidones, fatty acids, esters and alcohols, azone and its derivatives, surfactants (anionic, cationic, and nonionic), amides (including urea and its derivatives), polyols, essential oils, terpenes and derivatives, oxazolidines, epidermal enzymes, polymers, lipid synthesis inhibitors, biodegradable enhancers, and synergistic mixtures.

For safety, effectiveness, and cheapness, the best penetration enhancer is water. Any chemical that is nondamaging, pharmacologically inactive, and which promotes stratum corneum hydration is a penetration enhancer. Examples include the natural moisturizing factor and urea.

One simple classification of enhancers is through the lipid–protein partitioning (LPP) concept that provides an easy way both to categorize chemical accelerants and to rationalize their different modes of action.[10,11] This hypothesis proposes that promoters operate in one or more of three main ways (see Figure 1.5).

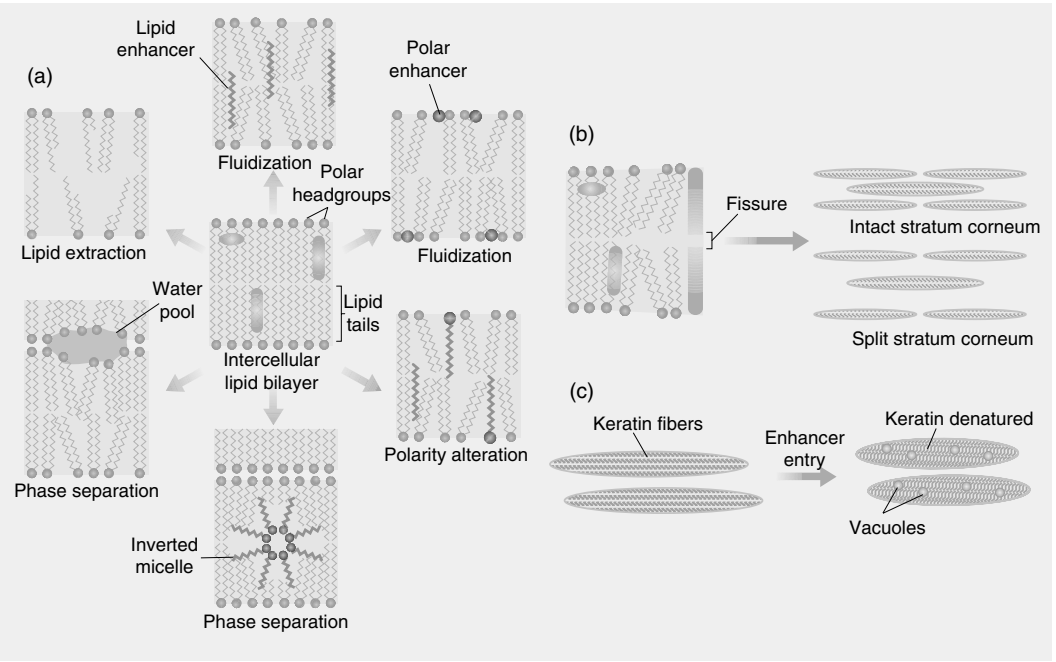



**Figure 1.5 Some actions of penetration enhancers on human stratum corneum: (a) *Action at intercellular lipids.* Some of the ways by which chemical penetration enhancers attack and modify the structured intercellular lipid domain of the stratum corneum. (b) *Action at desmosomes and protein structures.* Such dramatic disruption by accelerants (particularly potent solvents) as they split the stratum corneum into additional squames and individual cells would be clinically inappropriate. (c) *Action within corneocytes.* Swelling, further keratin denaturation, and vacuolation within individual horny layer cells would not be so drastic but would usually be cosmetically challenging. (Reprinted with permission from Barry, B.W., *Nature Biotechnology,* 22, 165, 2004.)**

*Lipid action*. The enhancer disrupts lipid organization within the stratum corneum, making it more permeable and increasing the penetrant's diffusion coefficient (Equation (1.1)). Many enhancers operate mainly in this fashion (e.g., azone, terpenes, fatty acids, DMSO, and alcohols). They may or may not mix homogeneously with the endogenous lipids.

Good solvents such as DMSO and ethanol, as well as micellar solutions, may also extract lipids, making the horny layer more permeable as aqueous channels form.

*Protein alteration*. Compounds such as ionic surfactants, decylmethylsulfoxide, and DMSO can open up the dense keratin structure in corneocytes, increasing its permeability by again raising the appropriate diffusion coefficient (Equation (1.1)). Such molecules may also modify peptide or protein material in the bilayer domain, and even split the stratum corneum, a clinically unacceptable process (Figure 1.5).

*Partitioning promotion*. The entry of solvent into the stratum corneum alters the chemical environment and thus may increase partitioning of a companion molecule (drug, coenhancer, or cosolvent) into the horny layer (i.e., raise $K$ in Equation (1.1)).

Many chemical enhancers combine these three LPP mechanisms. Thus, DMSO (above 60%) disturbs intercellular organization, extracts lipids, interacts with keratin, and promotes partitioning of lipid drugs.

As for other routes of drug delivery, researchers have investigated structure–activity relationships. Terpenes and sesquiterpenes have been investigated and other attempts were based on factors such as chain length, polarity, unsaturation, and the presence of special groups. Another technique uses a conceptual diagram of three areas based on the accelerants' organic and inorganic characteristics — first region for solvents, the second for hydrophilic drugs, and the third for lipophilic compounds.

Unfortunately, despite various *in silico* attempts, we still cannot predict theoretically what safe enhancer to use with a particular drug to achieve a satisfactory clinical result. Many potent enhancers irritate tissues as they interfere with viable cell membranes. Formulators therefore often limit their choice of a suitable enhancer to materials known to be gentle to the skin, for example, generally regarded as safe (GRAS) substances. The metered-dose transdermal spray adopts this approach while incorporating sunscreens as enhancers in a volatile:nonvolatile vehicle that provides accurate and precise dosing.[12] However, multiple time-consuming skin experiments are still necessary to develop suitable formulations that will satisfy drug regulatory bodies. The challenge then is: how can we screen many possibilities within a reasonable time? We do know that, in general, enhancer mixtures are more efficient than single chemicals. Karande and coworkers[13] therefore recently introduced the concept of an *in vitro* process for skin impedance high-throughput screening. The technique claims to be more than 100-fold more efficient than current screening methods; it provides what the authors term as synergistic combinations of penetration enhancers (SCOPE) formulations. They selected 32 enhancers from 100 chemicals reported in the literature. They then assessed 5040 binary formulations in 50% ethanol/buffer, four times each, using conductivity measurements *in vitro* with porcine skin, yielding more than 20,000 measurements. (Note that ethanol itself can be an enhancer,[14] but this was allowed for in the control.) The leading hits were then evaluated for their irritation potential using Epiderm cell culture. Potent and safe enhancer mixtures (SCOPE formulations) were selected for flux measurements with candidate drugs. Finally, the best formulations were assessed for bioavailability and safety *in vivo* in hairless rats.

Ninety-eight percent of candidate formulations were eliminated based on poor potency, 99.5% were discarded after irritation studies, the remaining 0.5% was tested for flux

enhancement, and 0.02% was finally assessed for bioavailability. The investigators discovered rare mixtures of enhancers that increased the skin permeability to macromolecules, such as heparin, leutenizing hormone releasing hormone, and an oligonucleotide, by up to 100-fold, without irritating the skin. The two most successful SCOPE formulations were a mixture of sodium laureth sulfate with phenyl piperazine and a combination of *N*-lauroyl sarcosine with sorbitan monolaurate (Figure 1.6a and b).

A challenge for the future would be to elucidate why the areas of potency hot spots were so restricted, and the fundamental molecular mechanisms producing the enhancement. Examination of the molecular structures of the most successful SCOPE mixtures, as illustrated in Figure 1.6, suggests that surface-active phenomena may play a crucial role.

In recent years, investigators have combined chemical enhancers with other promoting techniques, such as ultrasound, iontophoresis, and electroporation.

Metabolic interventions use strategies that interfere with barrier homeostasis.[15,16] They attack the processes of synthesis, assembly, secretion, activation, processing, or assembling or disassembling of the extracellular lamellar membranes in the stratum corneum. However, the idea of challenging barrier homeostasis for a significant time brings in many clinical considerations and possible regulatory problems, as stratum corneum is a "smart" material that responds to the environment.[17]

## *Stratum Corneum Bypassed or Removed*

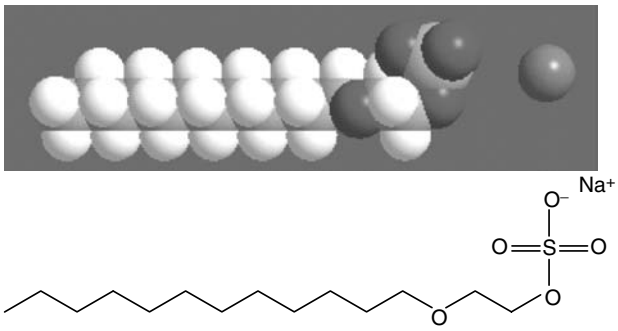
### *Microneedle Array*

The stratum corneum can be bypassed by injection, and many years ago attempts were made to develop devices based on multiple tiny needles, but these were abandoned because of breakage in the skin. More recently, as fabrication techniques and materials have improved, a similar approach has developed a device of 400 microneedles that insert drug just below the horny layer. The solid silicon needles (coated with drug) or hollow metal needles (filled with drug solution) penetrate the stratum corneum; the feeling is rather like sharkskin, or a cat's tongue, rubbing against the skin. Drug flux increases up to 100,000-fold are claimed. The Macroflux® technology of the Alza Corporation similarly uses a thin titanium screen with precise microprojections (approximately 200 μm long) to transport macromolecules into the skin; the technique may also be combined with electrotransport. Microneedles have been used to insert molecules such as oligonucleotides, insulin, and protein and DNA vaccines.[18]

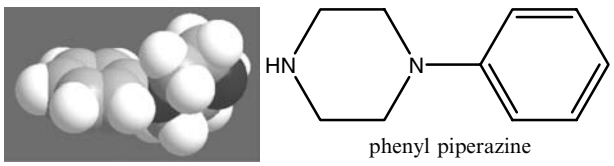
### *Stratum Corneum Ablated*

We could consider simply removing the horny layer. Chemical peels operate at different tissue layers, dermabrasion employs a motor-driven abrasive fraise or cylinder and microdermabrasion uses a stream of aluminum oxide crystals. A new development of this technique (termed microscission) drives the aluminum oxide crystals in a stream of nitrogen into the stratum corneum through a mask, to form microconduits that are 100 to 250 μm in diameter and between 50 and 200 μm deep.[19] A somewhat different approach employs high-powered laser pulses to vaporize sections of the horny layer, producing permeable regions.

Adhesive tape can remove stratum corneum prior to drug application. Tape stripping is also now popular for assessing bioavailability by measuring drug uptake into skin.



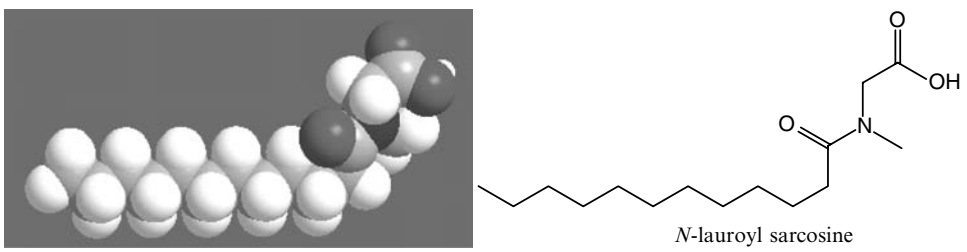

sodium laureth (1 mol) sulfate



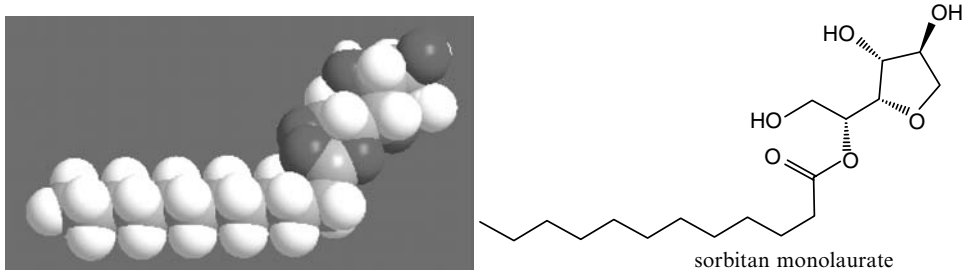

phenyl piperazine

**SCOPE formulation: sodium laureth sulfate + phenyl piperazine**

(a)




*N*-lauroyl sarcosine




sorbitan monolaurate

**SCOPE formulation: *N*-lauroyl sarcosine + sorbitan monolaurate**

(b)

**Figure 1.6 The two most successful SCOPE formulations[13]: (a) a mixture of sodium laureth sulfate with phenyl piperazine and (b) a combination of *N*-lauroyl sarcosine with sorbitan monolaurate.**

A microinfusor device has been proposed to deliver peptides, proteins, and other macromolecules. Another method forms a suction blister, an epidermatome removes the raised tissue, and then a morphine solution delivered directly to the exposed dermis quickly relieves pain.

### Follicular Delivery

The pilosebaceous unit provides a route that bypasses the intact horny layer, representing a target for drug delivery. Even topical application of a macromolecule such as "naked" DNA can immunize, and the employment of the hair follicle as a gene therapy target seems promising. Colloidal particles, such as liposomes and analogs, together with small crystals, may target the follicle. In general, particles greater than 10 μm remain on the skin surface, those that are approximately 3 to 10 μm concentrate in the follicle and those lesser than 3 μm, penetrate follicles and stratum corneum alike.

## Electrically Assisted Techniques

### Ultrasound (Phonophoresis, Sonophoresis)

This technique, used originally in physiotherapy and sports medicine, massages a topical preparation with an ultrasound source. The low-frequency ultrasonic energy (~20 kHz) disrupts the lipid packing in stratum corneum (see Figure 1.2) by cavitation. Shock waves of collapsing vacuum cavities increase free volume space in bimolecular leaflets and thus enhance drug penetration into the horny layer by a thousand-fold.[20,21]

Investigations have probed many aspects: a possible deactivation of skin enzymes by ultrasound, effects of pulsed delivery, synergistic cooperation of ultrasound with iontophoresis, penetration enhancers, and electroporation, phonophoresis used to probe the relative contribution of the follicular route to the penetration of hydrophilic permeants, and its potential for the transdermal extraction of blood and tissue analytes.

### Iontophoresis

Iontophoresis passes a small direct current (approximately 0.5 mA/cm$^2$) through a drug-containing electrode in contact with the skin; a grounding electrode completes the circuit. Three main mechanisms promote drug entry: (a) charged species are driven mainly by electrical repulsion from the driving electrode; (b) the electric current may increase the permeability of skin; and (c) electroosmosis may promote passage of uncharged molecules and large polar peptides. Efficiency of transport depends mainly on polarity, valency, and mobility of the charged species, as well as electrical duty cycles and formulation components.

Considerable interest is now being shown in transdermal delivery of therapeutic peptides, proteins, and oligonucleotides, as well as many other drugs such as lidocaine and fentanyl.

A lidocaine–epinephrine (adrenaline) device for local anaesthesia is now available (the Vyteris system[22]) and work proceeds on the development of iontophoretic patch systems, such as the E-Trans® technology of Alza.[23]

An interesting development is reverse iontophoresis for clinical sampling. A molecule in the systemic circulation (such as glucose) can be extracted at the skin surface using the electroosmotic effect; thus the GlucoWatch Biographer monitors blood glucose concentrations in diabetics using this procedure.

### Electroporation

Skin electroporation or electropermeabilization applies short (micro to millisecond) electrical pulses of approximately 100 to 1000 V/cm to generate transient aqueous

pores in the lipid bilayers (Figure 1.2). These pores travel straight through the stratum corneum, providing pathways for drug delivery. Molecules transport via iontophoresis or electroosmosis or both while the pulse is on. Between pulses, simple diffusion can allow additional movement as relatively persistent changes in the stratum corneum lower its resistance. The *in vivo* application of electroporation is claimed to be well tolerated, although the process usually induces muscle contractions.[24,25]

Fluxes can increase 10- to 10,000-fold for neutral and highly charged molecules of up to 40 kDa. The process may also transport vaccines, liposomes, nanoparticles, and microspheres. Macromolecules and small molecules may sterically stabilize pores created in skin, and thus enhance electroporation flux.

Electroporation may combine with iontophoresis to enhance the penetration of peptides such as vasopressin, neurotensin, calcitonin, and LHRH. The combination has recently been applied to ultradeformable liposomes.[26] Electroporation has also been combined with ultrasound.

### Magnetophoresis

Magnetic fields can move diamagnetic materials through skin, and some work has investigated this process.

### Radio Waves

A recent technique (the Viaderm device) uses the energy of radiofrequency waves to form micro-channels through the stratum corneum, with the possibility of feedback control.[27] A densely spaced array of microelectrodes takes microseconds to form the holes; applied drug then easily passes into the skin.

### Photomechanical Wave

In this procedure, a laser pulse irradiates a black polystyrene target on the skin covering a drug solution. The resulting photomechanical wave stresses the horny layer and promotes drug delivery. A single pressure wave can permeabilize the stratum corneum so that macromolecules can penetrate into the deeper skin tissues.[28]

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# *Chapter 2*

# Structure–Activity Relationship of Chemical Penetration Enhancers

**Narayanasamy Kanikkannan, R. J. Babu, and Mandip Singh**

## CONTENTS



## Introduction

Transdermal drug delivery offers many advantages over the conventional routes of administration. Elimination of hepatic first-pass effects, reduced side effects through

optimization of the blood concentration profile, and extended duration of activity are some of the advantages of transdermal delivery. However, the highly organized structure of the stratum corneum forms an effective barrier to the penetration of a diverse range of agents, which must be modified if poorly penetrating drugs are to be administered. The stratum corneum consists of dead, anucleate, keratinized cells embedded in a lipid matrix. The drug molecules have two major routes of passage through the stratum corneum, passage between the cells (intercellular route) and passage across the corneocytes (transcellular route).

The use of chemical penetration enhancers would significantly enhance the number of candidates suitable for transdermal delivery. According to the lipid protein partitioning (LPP) theory,[1] chemical penetration enhancers would act by one or more of three major mechanisms: (a) disruption of the stratum corneum lipid matrix; (b) interaction with intracellular protein; (c) improvement in partitioning of a drug or solvent into the stratum corneum. The LPP theory was recently extended to recognize: (d) disruption of the corneocyte envelope by compounds such as phenol, in high concentrations and in some vehicles and hydrocarbons; (e) effects on proteic junctions, such as desmosomes; (f) change in the partitioning between stratum corneum components and the lipid in the diffusion pathway.[2,3]

Compounds with a wide variety of chemical structures have been evaluated as skin penetration enhancers. These compounds include fatty acids, fatty alcohols, terpenes, pyrrolidones, surfactants, amides, azone and its derivatives, urea and its derivatives, sulfoxides, alkanes, esters, and cyclodextrins. The differences in the structure and physicochemical properties among each class of the enhancers accounted for their penetration enhancement potencies. Structure–activity relationship (SAR) represents an attempt to correlate the structure or physicochemical property of a compound with its enhancement activity. The physicochemical descriptors include molecular shape, size, lipophilicity, hydrophilicity, molecular geometry, and electronic and steric effects, which have strong influence in the biological activity of the compounds. SAR is currently being applied in many disciplines pertaining to drug design, proteomics, and environmental risk assessment. In this chapter, the relationship between the chemical structure and skin permeation enhancement effect of some of the extensively studied chemical penetration enhancers such as fatty acids, fatty alcohols, terpenes, pyrrolidones, and surfactants has been discussed.

## Fatty Acids

Saturated and unsaturated fatty acids have been established as effective enhancers for transdermal permeation of drugs.[4–7] The SAR of fatty acids is covered in detail in this section.

### *Effect of Carbon Chain Length*

There are several reports on the effect of carbon chain length of fatty acids on the percutaneous permeation enhancement of drugs. Aungst et al.[4] investigated the effect of carbon chain length of saturated fatty acids (C7–C18) on the penetration of naloxone through human skin. As the carbon chain length increased from C7 to C12, there was an increase in the permeation of naloxone. An increase in the carbon chain length

beyond C12 decreased the flux of naloxone. Maximum permeation was observed with C9–C12.

Ogiso and shintani[8] studied the effect of a series of saturated fatty acids on the permeation of propranolol through rabbit skin using gel formulations. Lauric acid and myristic acid were the most effective agents among the fatty acids used in increasing the permeation of propranolol and the enhancement was significantly larger than those in short and long chain fatty acids. Lee et al.[9] investigated the effect of a series of saturated fatty acids (C6–C18) and unsaturated fatty acids (oleic and linoleic acid) on the permeation of Tegafur across hairless mouse skin. These enhancers were studied using Ethanol/Panasate 800 (40/60) and Ethanol/Water (60/40) systems as vehicles. The fatty acids enhanced the skin permeation of Tegafur in the Ethanol/Panasate 800 (60:40) binary vehicle in the following order: oleic acid > C12 > linoleic acid > C10 > C8 > C6 > no fatty acid > C14 > C16 > C18. All fatty acids increased the skin permeation of Tegafur in the Ethanol/Water (60:40) binary vehicle. The skin permeation of Tegafur decreased in the following order: C12 > C10 > linoleic acid > oleic acid > C8 > C6 > no fatty acid. These results suggest that vehicle plays an important role in the skin permeation enhancement effect of fatty acids.

The skin permeation enhancement and the skin perturbation effects of a number of fatty acids, namely, straight chain saturated, monounsaturated and polyunsaturated acids, were evaluated using human stratum corneum.[5] Saturated fatty acids with 6 to 12 carbons showed a parabolic correlation between enhancement effect and chain length, with a maximum at nonanoic–decanoic acids (with 9 and 10 carbons). A parabolic relationship between carbon chain length of fatty acids and skin permeation enhancement was also observed with thiamine disulfide,[10] testosterone,[11] and indomethacin.[12]

Kandimalla et al.[13] investigated the effect of saturated fatty acids (C9–C14) on the permeation of melatonin across excised rat skin. A sharp increase in the permeation of melatonin was observed, as the fatty acid chain length increased from 9 to 10 carbons (Figure 2.1). A further increase in the permeation of melatonin was observed when the chain length was increased to 11. However, the permeation of melatonin decreased when the chain length was increased beyond 11 carbons. It can be observed that the permeation of melatonin has a parabolic relationship with the chain length of the saturated fatty acids. In general, medium chain fatty acids have showed greater permeation enhancement effect compared to short or long chain fatty acids.

It has been proposed that acids with a certain chain length, that is, around 12 carbons, possess an optimal balance between partition coefficient or solubility parameter and affinity to skin.[8] Shorter chain fatty acids would have insufficient lipophilicity for skin permeation, whereas longer chain fatty acids would have much higher affinity to lipids in stratum corneum and thereby retard their own permeation and that of other permeants. The parallel effect with the permeation enhancement suggests that the mode of action of saturated fatty acids as enhancers is dependent on their own permeation across the stratum corneum or skin.[5]

The mechanism by which fatty acids increase skin permeability appears to involve disruption of the densely packed lipids that fill the extracellular spaces of the stratum corneum.[14,15] The change in the physical structure of stratum corneum lipids has been assessed using differential scanning calorimetric (DSC) and infrared spectroscopic techniques.[16,17] Treatment of rabbit stratum corneum with various unsaturated fatty acids resulted in a shift to higher frequency for the CH asymmetric stretch peak near 2920 $cm^{-1}$ on FTIR Spectra, which primarily results from the acyl chains of intercellular lipid in the stratum corneum lipid.[17]

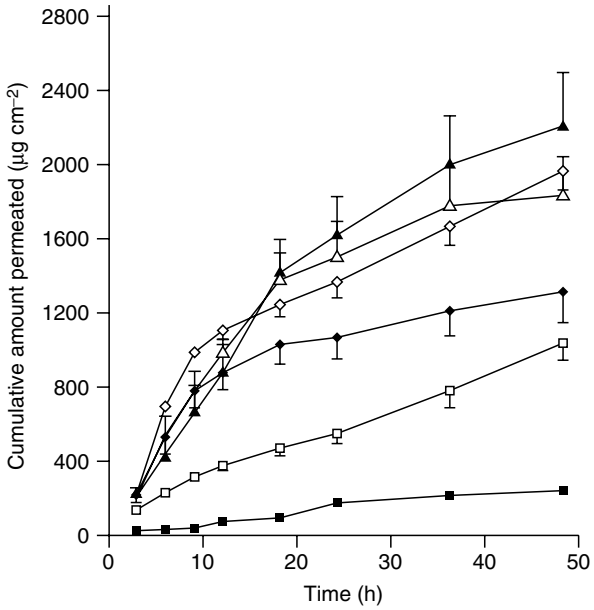


**Figure 2.1 Effect of saturated fatty acids (5% w/v) on the permeation profile of melatonin through rat skin. ■ Control, ◆ nonanoic acid, Δ decanoic acid, ▲ undecanoic acid, ◇ lauric acid, □ myristic acid. Control is the permeation profile of melatonin from the vehicle without enhancer. Data are means ± SE ($n = 3$). (From Kandimalla, K., Kanikannan, N., Ardega, S., and Singh, M., *J. Pharm. Pharmacol.*, 51, 783, 1999. With permission.)**

## Saturated and Unsaturated Fatty Acids

The application of saturated long chain fatty acids (stearic acid [C18], myristic acid [C14], and lauric acid [C12]) as enhancers was studied on the percutaneous transport of thiamine disulphide from propylene glycol through excised rat skin.[10] The permeation of thiamine disulphide was enhanced 31 times by C12 and 1.4 times by C14 and suppressed to 80% of its original value by C18. However, with unsaturated fatty acids, the permeation of indomethacin was enhanced in the following order: C20 > C22 > C18 = C16 > C14 and the flux values were correlated well with the uptake of these compounds into the stratum corneum.[17] Oleic acid (C18, unsaturated) has been shown in several studies to be an effective skin permeation enhancer, whereas stearic acid (C18, saturated) is not a good skin permeation enhancer. Chi et al.[18] reported an increase of 6.5- to 17.5-fold in the permeation rate of flurbiprofen by unsaturated fatty acids, while no significant increase was observed with saturated fatty acids. Thus saturated and unsaturated fatty acids behave differently on the skin permeation enhancement.

## Branched versus Unbranched Fatty Acids

Aungst[14] reported that maximum flux of naloxone was observed with C9–C12-branched and unbranched fatty acids across human skin. The branched and unbranched isomers of C5–C14 fatty acids showed similar effects. However, isostearic acid [$(CH_3)_2CH(CH_2)_{14}$ COOH] was a more effective permeation enhancer than stearic acid. The higher

permeation enhancement effect of isostearic acid than stearic acid was attributed to its lower melting point and greater solubility in propylene glycol.[19]

## Position of Double Bond

Tanojo et al.[5] investigated the effect of position of double bond on the percutaneous absorption of para amino benzoic acid with human stratum corneum using *cis*-octadecenoic acid with a double bond at 6th, 9th, 11th, or 13th position counted from the carboxyl head group. There was no significant difference in the effect of these acids on the permeation of para amino benzoic acid. Morimoto et al.[17] studied the effect of double bond positions of unsaturated fatty acids (C18) on the permeation of indomethacin through rat skin. The permeation of indomethacin with oleic acid (*cis*-9), asclepic acid (*cis*-11), petroselinic acid (*cis*-6) was not affected by the position of the double bonds.

## Geometric Isomers

The effect of geometric isomers of unsaturated fatty acids on the permeation of indomethacin through rat skin was investigated.[17] The indomethacin flux with elaidic acid (*trans*-9-octadecenoic acid) was significantly lower than that of oleic acid (*cis*-9-octadecenoic acid). The flux of salicylic acid enhanced by *trans*-isomers of 9-octadecenoic acid was lower than that of their *cis*-isomers.[20] However, there was no significant difference between *cis*- and *trans*- unsaturated C16–C18 fatty acid isomers in their effects on naloxone flux across human skin.[14] The discrepancy in these results may be due to the difference in the properties of drugs employed and the variation in the skin species used for the studies.

## Number of Double Bonds

As the number of double bonds in the C18 fatty acid increased from one (oleic acid) to two (linoleic acid), a significant increase in the flux of naloxone was observed.[4] An increase in the number of double bonds to three (linolenic acid), however, did not increase the flux further. Tanojo et al.[5] investigated the effect of number of double bonds (in *cis*-conformation) in straight chain polyunsaturated acids on the permeation of para amino benzoic acid in human stratum corneum. Polyunsaturated fatty acids such as linoleic, linolenic, and arachidonic acid with, respectively, two, three, and four double bonds produced a significantly higher permeation of para amino benzoic acid than the monounsaturated fatty acid. However, there was no significant difference in the permeation enhancement effects among the polyunsaturated fatty acids. Carelli et al.[21] also reported that the enhancement of flux of alprazolam by linoleic acid was greater than that of oleic acid through hairless mouse skin. However, the flux of indomethacin was not affected by the number of double bonds.[17]

Kandimalla et al.[13] studied the effect of oleic acid, linoleic, and linolenic acid on the permeation of melatonin across excised rat skin (Figure 2.2). As the number of double bonds increased, there was a slight increase in the permeation of melatonin. The flux of melatonin with linolenic acid was significantly higher than that of oleic acid ($P < 0.05$). However, there was no significant difference in the flux values of linoleic acid and linolenic acid ($P > 0.05$). Recently, Fang et al.[22] studied the effect of oleic acid, linoleic

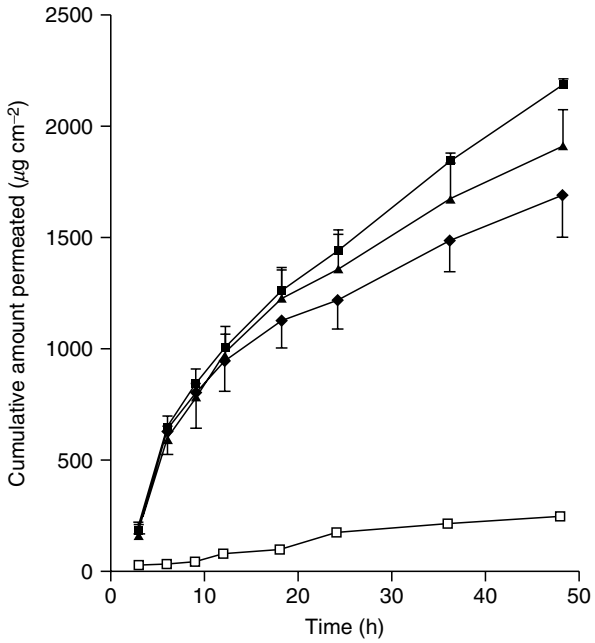


**Figure 2.2 Effect of unsaturated fatty acids (5% w/v) on the permeation profile of melatonin through rat skin. □ Control, ◆ oleic acid, ▲ linoleic acid, ■ linolenic acid. Control is the permeation profile of melatonin from the vehicle without enhancer. Data are means ± SE ($n = 3$). (From Kandimalla, K., Kanikannan, N., Ardega, S., and Singh, M., *J. Pharm. Pharmacol.* 51, 783, 1999. With permission.)**

acid, and linolenic acid on the permeation of flurbiprofen through mouse skin. The permeation of flurbiprofen increased with an increase in the number of double bonds in the fatty acid.

Oleic acid has been reported to be an effective skin penetration enhancer for polar and nonpolar drugs.[23–26] *Cis*-unsaturated fatty acids (e.g., oleic acid, linoleic acid, and linolenic acid) have been reported to form separate domains within stratum corneum lipids that effectively decrease the diffusional path length or the resistance.[27,28] The formation of separate domains would provide permeability defects within the bilayer lipids and facilitate the permeation of hydrophilic permeants. The presence of double bonds in the structure has been proposed to cause the formation of kinks in the lipid matrix to allow water permeation across the skin.[29] An increase in the number of double bonds increases the flux of drugs, possibly by causing more kinks in the lipid structure of skin.

## Fatty Alcohols

The effect of saturated alcohols (C8-OH to C18-OH) on the flux of naloxone in propylene glycol was studied through human skin.[4] A parabolic effect of alkyl chain length was observed with C10-OH and C12-OH being most effective. The effect of a series of straight chain alkanols on the transdermal delivery of levonorgestrel through excised rat and human cadaver skin was investigated by Friend et al.[30] The flux of levonorgestrel increased as the alkyl chain increased from C2 to C4, but decreased as the chain length increased above 1-butanol.

Lee et al.[9] studied the effect of a series of fatty alcohols in Ethanol/Panasate 800 and Ethanol/Water on the permeation of Tegafur across hairless mouse skin. All fatty alcohols, except the C18-OH, increased the skin permeation of Tegafur in the Ethanol/Panasate 800 (60:40) binary vehicle. The degree of permeation percentage of Tegafur obtained was same at 12 h (64.1 to 67.9% of dose) in all cases, and no significant difference between them was observed. However, all fatty alcohols significantly enhanced the skin permeation of Tegafur with Ethanol/Water (60:40) binary vehicle. The flux of Tegafur increased with an increase in alkyl chain length, reached a maximum permeation in C12-OH, then decreased as the alkyl chain length increased further. The skin permeability of Tegafur was in the following order: C12-OH > C10-OH > C9-OH > C8-OH > C14-OH > C16-OH > C18-OH > no fatty alcohol. Fatty alcohols with 9, 10, and 12 carbon atoms showed the greatest permeation percentage of Tegafur at 12 h in the Ethanol/Water (60:40) binary vehicle. These results suggest that vehicle plays an important role in the permeation enhancement effect of fatty alcohols.

The effect of *n*-alkanols on the permeation of a polar, nonelectrolyte penetrant, nicotinamide through hairless mouse skin was studied by Kai et al.[31] The enhancement versus alkanol chain length profile was parabolic, C6-OH being the maximum. The alkanol flux after a 6-h contact period, versus carbon number, was also a parabolic function. Alkanol uptake on the other hand increased with increasing chain length. The authors suggested that the primary mechanism by which alkanols increase percutaneous absorption is extraction of stratum corneum intercellular lipids. Sloan et al.[32] studied the fluxes of theophylline through hairless mouse skin from suspensions in straight alkyl chain alkanols. The flux of theophylline was the lowest from methanol (C1-OH), increased by almost 100-fold from pentanol (C5-OH), hexanol (C6-OH), heptanol (C7-OH), octanol (C8-OH) and nonanol (C9-OH), then decreased tenfold from undecanol (C11-OH).

In our laboratory, we studied the effect of saturated fatty alcohols (C8-OH to C14-OH) on the permeation of melatonin across excised hairless rat skin.[33] All saturated fatty alcohols increased the permeation of melatonin through hairless rat skin and the permeation of melatonin was found to be related to the carbon chain length of the fatty alcohols. An increase in the flux of melatonin was observed when the fatty alcohol chain length increased from 8 to 10 carbons. However, the flux of melatonin decreased when the chain length was increased beyond ten carbons. The maximum permeation of melatonin was observed with decanol. The parabolic relationship between carbon chain length of fatty alcohol and skin permeation enhancement was also observed for testosterone[11] and indomethacin.[12]

The effect of number of double bonds in the C18 fatty alcohol on the permeation of naloxone across human skin was investigated.[4] The permeation of naloxone was increased with an increase in the number of double bonds. Like fatty acids, fatty alcohols also act by disrupting the stratum corneum lipid matrix.[15] Recently, the influence of hydrocarbon chain branching on the effectiveness of alkanol skin permeation enhancers has been investigated using corticosterone as a model drug across hairless mouse skin.[34] The branched-chain alkanols showed lower enhancer potency than the 1-alkanols of the same molecular formula; the potency decreases as the hydroxyl group moves from the end of the chain towards the center of the enhancer alkyl chain. The authors also reported that the intrinsic potencies of the 1-alkyl enhancers (1-alkanols, 1-alkyl-2-pyrrolidones, and 1-alkyl-2-azacycloheptanones) are essentially the same and independent of their alkyl chain length at their isoenhancement concentrations.[34–36]

It has been reported that the most effective chain lengths (C10–C12) correspond to the length of the steroid nucleus of cholesterol, suggesting that these may act by

disrupting ceramide–cholesterol or cholesterol–cholesterol interaction.[37] Ackermann et al.[38] studied the permeation of a series of alkanols (C1-OH to C8-OH) across the nude mouse skin. The permeability coefficients of alkanols increased linearly as the chain length increases. Further, the permeability coefficients of *n*-alkanols correlated well with their ether–water partition coefficients. These results could be used to explain the permeation enhancement effect of different alkanols. The increase in the enhancement effect of lower alkanols with increase in the alkyl chain length may be attributed to the increased permeation of alkanols through the skin.

### *Fatty Acids versus Fatty Alcohols*

Fatty acids have a higher melting point than their corresponding fatty alcohols, but lower solubility parameters. If the enhancement by these fatty acids and alcohols was solely due to solubility effects, then it would be expected that the alcohols would be more effective than the acids, whereas the reverse is true for alkyl chains up to C18. This suggests that more specific interactions must occur.[37] Introduction of double bonds into long alkyl chains modifies the effect significantly and, for the C18 compounds, there was little difference between the corresponding fatty acids and alcohols. There was a greater concentration dependence of permeation enhancement for lauric acid than lauryl alcohol.[4]

## Terpenes

Terpenes are naturally occurring compounds, which consist of isoprene ($C_5H_8$) units. Terpenes are classified according to the number of isoprene units they contain: monoterpenes ($C_{10}$) have two isoprene units, sesquiterpenes ($C_{15}$) have three, and diterpenes ($C_{20}$) have four. The structural formulae of different types of terpenes (hydrocarbon, ketone, alcohol, oxide, and cyclic ether terpenes) evaluated as skin penetration enhancers are shown in Figure 2.3.

Terpenes have been widely studied as skin penetration enhancers for various drugs.[1,39–41] Okabe et al.[39] studied ten cyclic monoterpenes as penetration enhancers for lipophilic drug indomethacin in rats. The absorption of indomethacin from gel ointment was substantially enhanced by hydrocarbon terpenes such as *d*-limonene. However, the oxygen containing terpenes did not affect the permeation of indomethacin. The authors concluded that cyclic monoterpenes with lipophilic indices greater than 0 were most effective for indomethacin. But the alcohol and ketone terpenes were less effective for lipophilic drugs such as diazepam[42] and estradiol.[43]

Williams and Barry[1] evaluated a series of terpenes as skin penetration enhancers for the hydrophilic drug 5-fluorouracil in human skin. Cyclic terpenes were chosen from the chemical classes of hydrocarbons, alcohols, ketones, and oxides. Of the terpenes studied, hydrocarbons were poor enhancers and alcohols and ketones were more effective. The epoxides showed mild enhancing activity, whereas the cyclic ethers were very effective; ascaridole, 7-oxabicyclo[2.2.1]heptane, and 1,8-cineole all induce a near 90-fold increase in the permeability coefficient of 5-fluorouracil. The five-membered cyclopentene oxide showed higher enhancing activity than the six-membered cyclohexene oxide.

The effect of 12 sesquiterpenes on the permeation of 5-fluorouracil was evaluated across human skin.[44] Pretreatment of epidermal membranes with sesquiterpene oils or

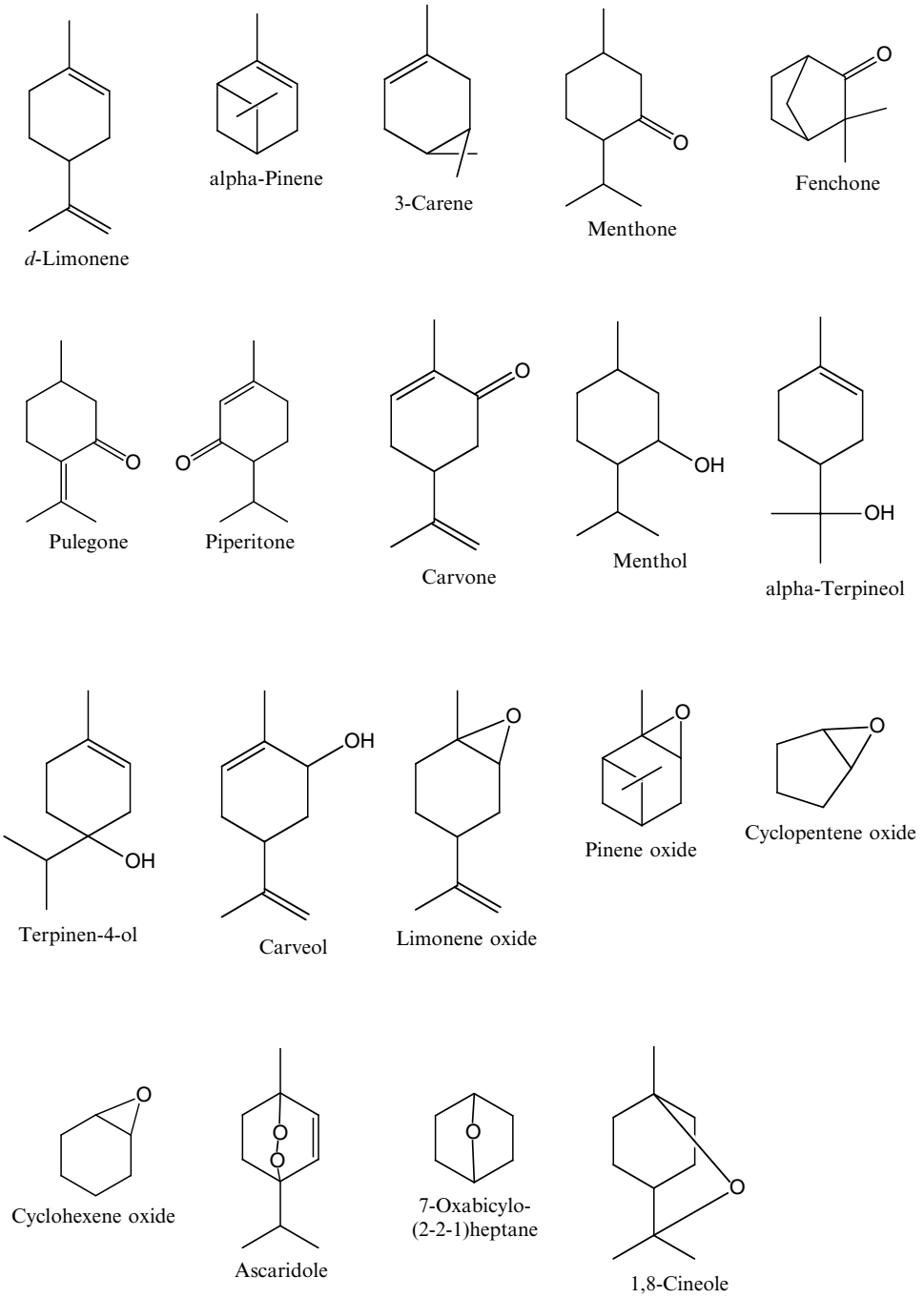


**Figure 2.3 Structural formulae of various types of terpenes (hydrocarbon, ketone, alcohol, oxide, and cyclic ether terpenes) assessed as skin penetration enhancers.**

using solid sesquiterpenes saturated in dimethyl isosorbide enhanced the absorption of 5-fluorouracil. Enhancers containing polar functional groups were generally more effective than pure hydrocarbons and enhancers with the least "bunched" structures were the most active.

Obata et al.[45] reported that percutaneous absorption of hydrophilic diclofenac sodium was substantially enhanced in the presence of *l*-menthol and *dl*-menthone, while it was little enhanced by *d*-limonene and *p*-menthane. Overall, the skin permeation enhancing effect of terpenes depends on the physicochemical properties of the drugs. In general, hydrocarbon terpenes are effective for lipophilic drugs and oxygen containing terpenes are effective for hydrophilic drugs.

Okamoto et al.[46,47] evaluated the compounds containing azacyclo ring and acyclic terpene hydrocarbon chains as enhancers for a variety of drugs. These studies demonstrated that azacyclo ring size has little effect on the potency of the enhancers, whereas the length of hydrophobic terpene chain has a significant effect; a chain length of 12 carbons provided maximum effect.

El-Kattan et al.[48] investigated the effect of terpene lipophilicity (log *P* 1.06 to 5.36) (terpene-4-ol, verbenone, fenchone, carvone, menthone, alpha-terpineol, cineole, geraniol, thymol, cymene, *d*-limonene, and nerolidol) on the percutaneous absorption of hydrocortisone from hydroxypropyl methyl cellulose gel formulations using hairless mouse skin *in vitro*. A linear relationship was found between the log *P* of terpene and the cumulative amount of hydrocortisone in the receptor compartment after 24 h. An increase in terpene lipophilicity was associated with an increase in the cumulative amount of hydrocortisone transported.

The effects of terpene enhancers (fenchone, thymol, *d*-limonene, and nerolidol) on the percutaneous absorption of drugs with different lipophilicities (nicardipine hydrochloride, hydrocortisone, carbamazepine, and tamoxifen) were studied.[49] Nerolidol (highest lipophilicity) provided the highest increase in the flux of the model drugs. The lowest increase in the flux was observed with fenchone (lowest lipophilicity). The results indicated that these four enhancers were more effective at enhancing the penetration of hydrophilic drugs rather than lipophilic drugs.

The synergism of ethyl alcohol and limonene on the permeation enhancement of indomethacin was examined and it was found to be significant.[50] The combined effect of menthol and ethanol as skin penetration enhancers was also studied by Kobayashi et al.[51] Addition of ethyl alcohol to water and 5% menthol enhanced the drug solubility in the vehicle, decreased skin polarity, and increased the role of pore pathway to whole skin permeation. Synergistic action was also observed with terpene or propylene glycol mixture as evaluated by DSC and x-ray diffraction.[52,53] The terpenes act mainly by disrupting the lipid matrix of the stratum corneum.[1] Spectroscopic studies have also suggested that terpenes could exist within separate domains in stratum corneum lipids.[52]

## Pyrrolidones

Pyrrolidones and their derivatives have been investigated as potential skin penetration enhancers.[54–56] 2-Pyrrolidone and *N*-methyl-2-pyrrolidone (NMP) have been evaluated as penetration enhancers for a variety of drugs.[57–59] Figure 2.4 presents the chemical structures of some pyrrolidones, which have been evaluated as skin penetration enhancers. Aoyagi et al.[60] synthesized a new group of 2-pyrrolidone enhancers containing a short alkyl group, such as methyl, ethyl, propyl, or butyl group, at the 1-position and a dodecyl group at the 3-position of a 2-pyrrolidone ring. The enhancing effect of these compounds was studied using indomethacin as a model drug. The length of the short alkyl group at the 1-position greatly impacted the enhancing activity of the

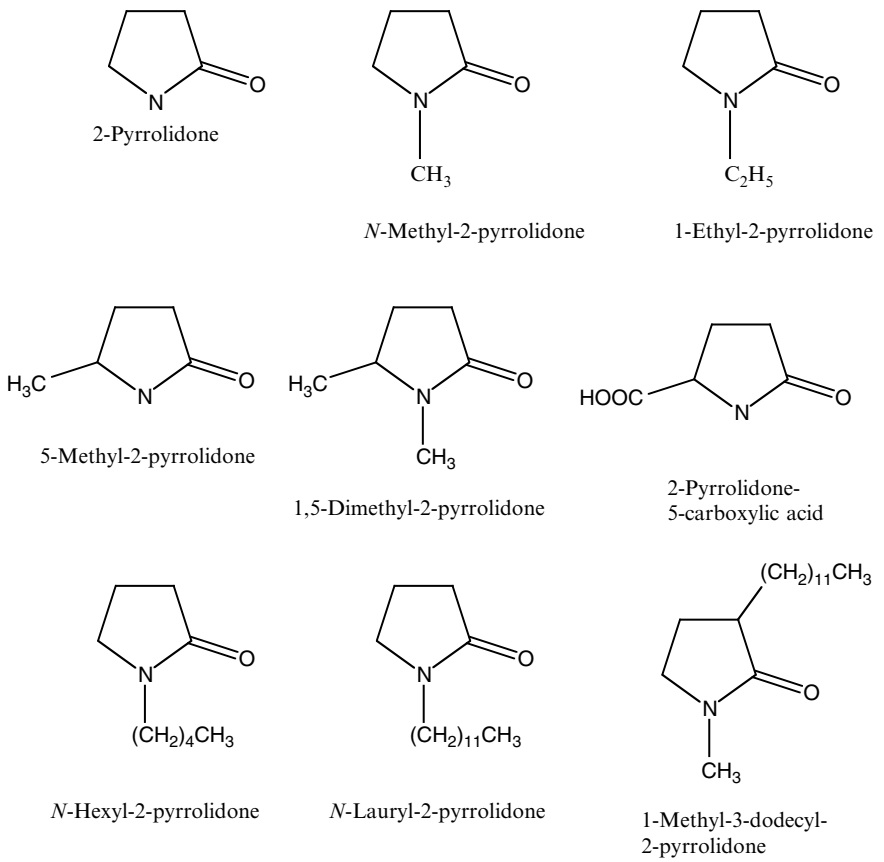


**Figure 2.4 Structural formulae of pyrrolidone enhancers.**

2-pyrrolidone derivatives. 1-Propyl and 1-butyl-3-dodecyl-2-pyrrolidone showed the greatest permeation enhancement effect of indomethacin through the skin.

The skin permeation enhancement activity of a series of alkyl substituted pyrrolidones was studied using phenol red as a model drug across rat skin *in vitro* and *in vivo*.[61–64] A correlation between the flux of phenol red and partition coefficient of the pyrrolidones was observed. The percutaneous penetration enhancement of 6-mercaptopurine by nine azacycloalkanone derivatives with an alkyl or terpene chain was studied using excised guinea pig skin.[47] The number of carbonyl groups in the chain influenced the enhancing activity more effectively than the ring size.

It has been reported that pyrrolidone derivatives alter the liposomal membrane made with stratum corneum lipid.[65] Yoneto et al.[66] studied the effects of 1-ethyl, 1-butyl, 1-hexyl, 1-octyl-2-pyrrolidones on the transport of beta-estradiol, hydrocortisone, and corticosterone across hairless mouse skin. The results showed a 3.5-fold increase in enhancement potency per methylene group introduced at the 1-N position. The authors reported that the 1-alkyl-2-pyrrolidones may act via the intercalation of the alkyl group of the enhancer into the highly ordered interfacial region of the lipid bilayers, inducing significant disorder and enhancing microenvironmental fluidity. The authors studied the fluidizing effects of alkyl pyrrolidones upon the stratum corneum lipid liposome bilayer using steady-state anisotropy and fluorescence lifetime studies.[67] The results suggested that the alkyl pyrrolidones might induce a general fluidizing effect upon the lipid bilayer.

As a continuing effort to understand the mechanism of action, the authors studied the influence of the alkyl pyrrolidones on permeant partitioning into hairless mouse stratum corneum under the isoenhancement concentration conditions using beta-estradiol as the model drug.[68] The results suggested that inducing a higher partitioning tendency for beta-estradiol into the lipoidal pathway of hairless mouse stratum corneum is a principal mechanism of action of the alkyl pyrrolidones in enhancing percutaneous absorption.

## Surfactants

Surfactants generally consist of a lipophilic alkyl or aryl chain with a hydrophilic head group. Surfactants may be classified according to the nature of the head group as anionic, cationic, nonionic, or zwitterionic. Surfactants have been used as skin permeation enhancers in several studies.[69–72] In general, cationic surfactants cause greater increase in the flux of drugs than anionic surfactants, which, in turn, produce greater increases in flux than nonionic surfactants. Ashton et al.[73] compared the effects of dodecyltrimethylammonium bromide (DTAB), sodium lauryl sulfate (SLS), and polyoxyethylene fatty ether (Brij 36T™) on the *in vitro* flux of methyl nicotinamide across excised human skin. The permeation enhancement of methyl nicotinamide was in the following order: DTAB > SLS > Brij 36T. However, Brij 36T exhibited a smaller but more immediate effect on the permeation of methyl nicotinate, resulting in the highest degree of flux enhancement over the first 24-h period.

The effects of various cationic surfactants (alkyl trimethylammonium halides, alkyl dimethylbenzylammonium halides, and alkyl pyridinium halides) on the permeation of radiolabeled water and lidocaine through excised human epidermis have been studied.[74] All surfactants increased the mean steady-state flux of water and lidocaine by two to fourfold compared to the initial control period. However, there was no significant difference in the enhancing effects of these three hexadecyl derivatives. The maximum flux enhancement was observed from those derivatives with an alkyl chain length of 12 to 14 carbons. Cooper and Berner[75] reported that the optimal chain length for skin barrier impairment might be attributed to the factors such as solubility of the surfactant in the donor vehicle, the critical micellar concentration, the stratum corneum–hyphen;vehicle partition coefficient, and the binding affinity of the surfactant for epidermal keratin. An optimum chain length of 12 to 14 carbons may represent compromise between water solubility and lipophilic character. Furthermore, stratum corneum keratin may bind preferentially with carbon chains of specific length.

Cappel and Kreuter[76] compared the enhancement potential of polysorbates 20, 21, 80, and 81. The results of these studies showed that polysorbates had a lesser effect on the transdermal permeation of methanol. Maximum permeation enhancement was achieved in the presence of polysorbates 21 and 81 enhanced the permeation of methanol of two to threefold, indicating that the more lipophilic polysorbates alter the barrier properties of the skin to a greater extent than their hydrophilic analogs.

Lopez et al.[76] studied the influence of the polar functional group on the skin permeation enhancement effects of nonionic surfactants. Their results indicated that the nature of the enhancer head group greatly influences cutaneous barrier impairment. Span®20 showed greater permeation enhancement of all compounds compared to Tween®20. Ionic surfactants interact well with keratin filaments in the corneocytes and make it more permeable and increase the diffusion coefficient of the drug.[15] Surfactants may also modify peptide or protein material in the bilayer domain.[1]

## Conclusions

Extensive research has been undertaken to study the effects of a variety of chemical compounds as skin penetration enhancers. The list of potential drugs that can be effectively delivered via transdermal route is increasing. Structure–permeation enhancement relationship studies have increased our understanding of the effect of penetration enhancers for different types of drugs. The chemical structures and physicochemical properties of penetration enhancers play an important role in their permeation enhancement effects. In general, a parabolic relationship between the carbon chain length of fatty acids and fatty alcohols and skin permeation enhancement has been observed. The unsaturated fatty acids have shown a greater permeation enhancement effect compared to their corresponding saturated fatty acids. The hydrocarbon terpenes have been found to be more effective for lipophilic drugs and oxygen containing terpenes are more effective for hydrophilic drugs. The chain length of the alkyl pyrrolidone enhancers plays an important role in their skin permeation enhancement potencies. In general, ionic surfactants showed a greater flux of drugs than nonionic surfactants. The permeation enhancement effect of enhancers is also greatly influenced by the physicochemical properties of the drug. Unfortunately, many of the chemical penetration enhancers that showed good permeation enhancement effect also cause skin irritation.[33,77] The practical use of chemical penetration enhancers requires careful balancing of their benefits and risks, that is, penetration rates and irritation. Further studies are needed in the areas of evaluation of skin permeation enhancement *vis-à-vis* skin irritation in order to choose penetration enhancers, which possess optimum enhancement effect with no skin irritation. Further studies are also needed to understand the mechanism of action of chemical penetration enhancers.

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