chapter six

*Transdermal drug delivery**

Contents

I. Introduction

Although some drugs have inherent side effects that cannot be eliminated in any dosage form, many drugs exhibit undesirable behavior that is specifically related to a particular route of administration. One recent effort at eliminating some of the problems of traditional dosage forms is the development of transdermal delivery systems.

Oral administration of drugs has been practiced for centuries and, most recently, through tablets and capsules. Injectables came into being approxi-

* Adapted from Ranade, V.V., Drug delivery systems. 6. Transdermal drug delivery, *J. Clin. Pharmacol.*, 31, 401, 1991. With permission of *J. Clin. Pharmacol.* and J.B. Lippincott Publishing Company, Philadelphia, PA.

mately 130 years ago, but have only become acceptable since the development of a better understanding of sterilization. Topical application has also been used for centuries, predominantly in the treatment of localized skin diseases. Local treatment requires only that the drug permeate the outer layers of the skin to treat the diseased state, with the hope that this occurs with little or no systemic accumulation.[1]

Transdermal delivery systems, on the other hand, are specifically designed to obtain systemic blood levels and have been used in the U.S. since the 1950s. Transdermal permeation, or percutaneous absorption, can be defined as the passage of a substance, such as a drug, from the outside of the skin through its various layers into the bloodstream. Any time there is systemic access of a drug, unwanted side effects or toxic effects can occur. Certainly, each dosage form has its unique place in medicine, but some attributes of the transdermal delivery system provide distinct advantages over traditional methods. Cleary[1] has listed important advantages and disadvantages of transdermal delivery systems. The advantages are: the system avoids the chemically hostile gastrointestinal (GI) environment; no GI distress or other physiological contraindications of the oral route exist; the system can provide adequate absorption of certain drugs; there is increased patient compliance; the system avoids the first-pass effect; the system allows for the effective use of drugs with short biological half-lives; the system allows for the administration of drugs with narrow therapeutic windows; the system provides controlled plasma levels of highly potent drugs; drug input can be promptly interrupted should toxicity occur. Disadvantages of this system include: drugs that require high blood levels cannot be administered; the adhesive used may not adhere well to all types of skin; drug or drug formulation may cause skin irritation or sensitization; the patches can be uncomfortable to wear; and this system may not be economical for some patients.[1,2]

In the development of transdermal delivery systems, a series of interrelated elements must be taken into consideration. These elements can be classified into five basic areas: bioactivity of the drug, skin characteristics, formulation, adhesion, and system design. The transport of drugs through the skin is complex since many factors influence their permeation. To simplify the situation somewhat, one should consider the following: skin structure and its properties, the penetrating molecule and its physical–chemical relationship to the skin and the delivery platform, the platform or delivery system carrying the penetrant, and the combination of skin, penetrant, and delivery system as a whole. The major emphasis of this chapter is on discussing each of these factors, their complexities, and their interdependencies in the development of transdermal delivery systems.[3,4]

II. Structure of human skin

As has been discussed by Barry et al.,[5] human skin consists of two distinct layers: the stratified avascular cellular epidermis and an underlying dermis of connective tissue. A fatty subcutaneous layer resides beneath the dermis.

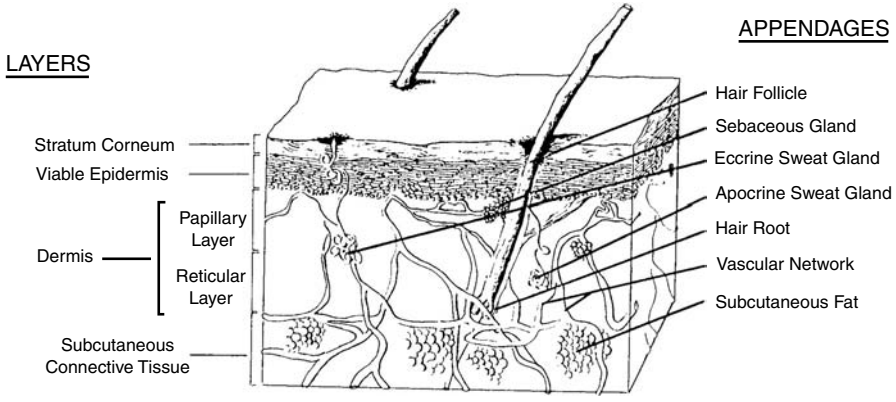


Figure 6.1 Basic diagram of skin structure. (From Langer and Wise, Eds., *Medical Applications of Controlled Release*, CRC Press, Boca Raton, FL, 1984, 207.)

Hairy skin develops hair follicles and sebaceous glands, and the highly vascularized dermis supports the apocrine and eccrine sweat glands, which pass through pores in the epidermis to reach the skin surface. With respect to drug permeation, the most important component in this complex membrane is the stratum corneum, or horny layer, which usually provides the rate-limiting or slowest step in the penetration process.

The transport mechanisms by which drugs cross the intact skin have not yet been completely elucidated. However, possible macro-routes may comprise the transepidermal pathway (across the horny layer either intra- or intercellularly) or via the hair follicles and sweat glands (the appendageal route). The appendageal route may be of significance for short diffusional times and for polar molecules. Until recently, it was believed that, for polar molecules, the probable route was via the hydrated keratin of the corneocyte. However, it now seems more probable that the dominant pathway is via the polar region of intercellular lipid, with the lipid chains providing the non-polar routes[6–10] (see Figure 6.1).

The relative importance of these routes depends upon numerous factors, such as the time-scale of permeation (steady-state vs. transient diffusion), the physicochemical properties of the penetrant (e.g., pKa, molecular size, stability, binding affinity, solubility, and partition coefficient), integrity and thickness of the stratum corneum, density of sweat glands and follicles, skin hydration, metabolism, and vehicle effects.

In order to develop a topical system, there is a definite need for a stable preparation of the drug with a correct partition coefficient relative to the drug reservoir, device membrane, and skin layers. For the type of transdermal delivery device that incorporates a rate-controlling membrane, the flux across this barrier should be low enough so that the underlying skin acts as a sink. This could be a severe restriction because of the general impermeability of the stratum corneum. If the horny layer cannot be utilized as a sink, then the individual patient's skin will control drug input, and variable

consequences can ensue due to the significant biological variability existing between people and from different skin sites.

Many pharmacologically active drugs have inappropriate physiochemical properties to partition into the skin. An important effort in the future will undoubtedly be devoted to synthesizing suitable pro-drugs to optimize the partition coefficient, stratum corneum penetration, and vehicle. In developing new drug entities, more attention will have to be paid to producing chemicals with low melting points (preferably liquids at biological temperatures) and to include penetration-enhancing substances.

In traversing the skin, the drug must partition into the stratum corneum and diffuse through this nearly impermeable barrier. Following this pathway, the molecules will have to interact with many potential binding sites, possibly forming a reservoir operating for days or even weeks. Free drug will eventually reach the interface between the stratum corneum and the epidermis, where the drug will have to partition into this water-rich tissue. There is a potential problem here in that a drug or pro-drug designed to partition from a vehicle into the horny layer may then have difficulty leaving the stratum corneum to enter the epidermis. For drugs that are lipid-soluble, clearance from the living tissue may replace diffusion through the stratum corneum, and this could be the rate-limiting step.[11–15]

Light, oxygen, and bacteria can influence the microenvironment of the skin surface. For example, skin microflora can destroy nitroglycerin and steroid esters. Occlusive systems, such as transdermal devices, when applied for several days, may cause problems with changes in skin flora, as well as with maceration and irritation of the skin, since prolonged application can make sweat glands ineffective.[16] In addition, the skin is a storehouse of enzymes which can have activities 80 to 90% as efficient as those present in the liver. Hydrolytic, oxidative, reductive, and conjugative reactions can all take place in the skin. One possible reason why activities approach those in the liver is the extreme dilution at which molecules cross the epidermis. As a result, the process renders them subject to attack. However, this is counterbalanced by the much greater permeation rates compared with those operating within the stratum corneum. Metabolism can alter permeation pharmacokinetics, activating pro-drugs and destroying active drugs, while generating active and inactive metabolites.

A future possibility may be to incorporate enzyme inhibitors into the devices to protect the drugs. In the epidermis, the drug comes in contact with pharmacological receptors as it approaches the epidermal/dermal boundary, where it then partitions into the dermis. Since both tissues consist mainly of water, it is preferable that the partition coefficient be approximately 1, provided that no different binding sites are in close proximity on either side of the interface. It is possible that, over time, sensitization reactions can occur in a small percentage of the patient population when any chemical is delivered via an unusual route (i.e., one to which the body is not accustomed). This phenomenon of sensitization has been observed with clonidine,

and it may occur with other drugs, enhancers, enzyme inhibitors, adhesives, and vehicle components.[17,18]

After the penetrating drug partitions into the dermis, metabolic and depot sites may intervene as the drug gradually moves to a blood capillary, partitions into the wall, and then exits into the blood. The lymph system can also aid in drug removal. A portion of the drug may also partition into subcutaneous fat and underlying muscle to form further depots, even though this finding would appear insignificant based on theoretical considerations.[19,20]

III. Theoretical advantages of the transdermal route

It is customary to compare the percutaneous route with oral delivery since the latter provides the most popular way for delivering drugs. Transdermal delivery of a drug may eliminate several variables associated with oral intake since it bypasses GI absorption. In the GI tract, changes occur in pH as a molecule moves from gastric acid, with a pH as low as 1, to the intestine, with a pH of up to 8. Other variables that may be obviated include gastric emptying, intestinal motility and transit times, the activity of human and bacterial enzymes, and the influence of food.

In transdermal delivery, the drug enters the systemic circulation without first passing into the hepatic portal system and traversing the liver. This route, therefore, avoids the first-pass phenomenon by which the liver can significantly reduce the amount of intact drug. Additionally, the drug avoids the enzymes present in the gut wall. However, as has been emphasized earlier, the skin itself possesses some metabolic capability for biotransformation.

Percutaneous administration of a drug can control administration and limit pharmacological action, while the corresponding oral or injectable formulation may well elicit several effects, including toxic reactions. Patient compliance may be achieved by the continuity of delivery of drugs with short half-lives (see Figure 6.2).

Transdermal administration, under suitable rate control, may minimize pulse entry of a drug into the bloodstream. However, it is difficult to deliberately provide a controlled on/off action because intact skin membranes are intrinsically slow-response systems with prolonged lag times, at least when shunt diffusion via the appendageal route is negligible.

IV. Optimization of percutaneous absorption

Two main strategies for the formulation of dermatological preparations have been described.[5] In the first strategy, a vehicle or device is utilized in order to maximize drug partition into the skin without significantly affecting the physicochemical properties of the stratum corneum. Thus, the vehicle in this instance promotes drug release by optimizing the absorption potential of the drug. However, if hydration occurs, even the most innocuous of vehicles tends to change the nature of the stratum corneum.

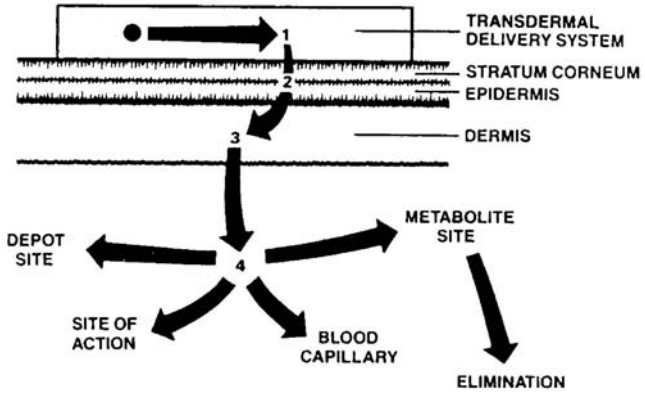


Figure 6.2 Process of transdermal permeation. (From Higuchi, T., *Curr. Prob. Dermatol.*, 7, 121, 1978. With permission of S. Karger, AG Basel, Switzerland.)

The alternate strategy incorporates materials such as penetration enhancers into the formulation. These enhancers are chemicals that enter the skin and reversibly alter it to promote the penetration of a drug. The desirable attributes of enhancers include: they should be pharmacologically inert, preferably not interacting with receptors in the skin or elsewhere in the body; the enhancer should not be toxic, irritating, or allergenic; the onset of enhancer activity and the duration of effect should be predictable and controllable; the skin should show an immediate and full recovery of its normal properties when the enhancer leaves the tissue; the accelerant should promote penetration into the skin without developing significant problems of loss of body fluids, electrolytes, or other endogenous materials; the chemical should be compatible with a wide range of drugs and pharmaceutical adjuvants; where appropriate, the substance should be a suitable solvent for the drug; for traditional formulations, the material should spread well on the skin, and it should have a suitable skin "feel;" the chemical should formulate into creams, ointments, gels, lotions, suspensions, aerosols, skin adhesives, and delivery devices; and it should be odorless, tasteless, colorless, and relatively inexpensive.[21]

V. The theory for penetration-enhancer activity

Penetration enhancers can interact with the polar head groups of lipid via hydrogen and ionic bonding. The subsequent change in hydration spheres of the lipids, and alterations in head group interactions, will affect the packing at the head region. This change can decrease the retarding action, which then can affect the diffusion of polar penetrants. A second response may be to increase the volume of the aqueous layer so that more water enters the tissue. Subsequently, the swelling that occurs provides a greater cross-sectional area for polar diffusion and a larger fractional volume that is distinct from the structured water at the lipid interface.

This modification may also happen with simple hydration. The change in interfacial structure can alter the packing of the lipid tails such that the lipid hydrophobic route becomes more disordered and more easily traversed by a lipid-like penetrant.

In addition to any effect a penetration enhancer has on the aqueous region by increasing its water content, there can be a direct action whereby temporal changes can occur in its chemical constitution. With high concentrations of solvents, such as dimethylsulfoxide, propylene glycol or ethanol, in a vehicle or device, a large quantity may penetrate into the aqueous region of the tissue, thereby becoming a better solvent for steroidal molecules, such as hydrocortisone and estradiol. The partition coefficient in this instance favors elevated drug concentration in the skin. The solvent then diffuses out into the dermis, followed by the drug diffusing down its concentration gradient.[22]

An important feature of the activity of certain penetration enhancers is the correct choice of a cosolvent for materials such as Azone (1-dodecylazacycloheptane-2-one) and cis-unsaturated oleic acid. For these enhancers to reach the polar surface of the lipid bilayer in relatively large amounts, they may need an additive, such as propylene glycol. This addition can alter the polarity of the aqueous region and therefore increase its solubilizing ability for lipid-like materials.

The polar heads of oleic acid and Azone can place themselves between the head groups of the lipid and the enhancer tails and flip over to insert between the hydrophobic groups of the membrane lipids, thus increasing the fluidity of the lipid domain. Azone is not readily soluble in water, and under extreme conditions it may move fully into the internal region of the lipid to provide maximum disordering. This relationship between the elements of cosolvent systems operates particularly with Azone/propylene glycol mixtures. Not only does propylene glycol help the penetration of Azone into the stratum corneum, but Azone also increases the flux of propylene glycol through the skin, which subsequently increases the amount of Azone in the tissue.

When the resistance of the horny layer is reduced to that of an equivalent thickness of viable tissue, even more drastic disorder in the intercellular domain may result.[5] This situation can permit drug penetration at rates that are several orders of magnitude greater than those operating in the unaffected horny layer. The final stage in this process would be the dissolution of the lipid to form a homogeneous phase with little resistance to molecular diffusion. This disruption would occur only in the presence of high concentrations of molecules with good solvent properties for lipid components. If, for a particular penetrant, the intracellular route supplies a significant permeation pathway, the enhancer could interact with whatever lipid remains within the corneocyte.

Regarding the keratin fibrils, it is important to be cognizant of typical interactions, which materials such as the aprotic solvents (e.g., dimethylsulfoxide) and surfactants undergo with proteins. These mechanisms include interactions with polar groups, relaxation of binding forces, and alterations

in helix conformations. Pore routes may form through this tissue. Most investigators now largely reject the fact that the transcellular route presents a significant pathway for molecular diffusion through the stratum corneum. Nonetheless, the corneocyte may sequester and retain certain molecules within its structure.

VI. Development of the transdermal therapeutic system

A. Transdermal penetration of drugs

In the past 50 years, many terms have been used to describe one of the objectives of a transdermal delivery system (i.e., penetration of a substance from the outside of the skin through the skin and into the bloodstream), such as percutaneous absorption. Other terms, such as persorption, permeation, and penetration, have been used also. All these processes relate to passively driven mass transfer; some terms, such as sorption, have other conflicting meanings. No matter how it is referred to, absorption through the skin involves passive diffusion through the outer and middle structures of the skin until the systemic circulation is attained.[23–25]

As described previously, the skin is stratified histologically into the stratum corneum, epidermis, dermis, and subcutaneous tissue, and as such it can be considered a laminate of barriers. This laminate consists of the stratum corneum, the viable epidermis, and a portion of the dermis. For most purposes, subcutaneous tissue is not considered to be involved in percutaneous absorption, although it may act as a potential depot. To review, permeation can occur by diffusion via transcellular penetration through the stratum corneum, intercellular penetration through the stratum corneum, and transappendageal penetration, especially including the sebaceous pathway of the pilosebaceous apparatus and the aqueous pathway of the salty sweat glands. The first two mechanisms require further diffusion through the rest of the epidermis and dermis. The third mechanism allows diffusional leakage into the epidermis and direct permeation into the dermis.[26–30]

B. Formulation

The formulation of transdermal systems is essential for providing suitable delivery rates of drugs. The components of the system impact on the rate the drug is released to the skin and on the adherence of the device to the skin, and thus on the design of the final product.

The drug must be incorporated into some type of physical structure that both serves as a reservoir and provides for diffusive "communication" of the drug with the surface of the skin. This physical structure, or laminar construction, serves as a "platform" for the drug. The platform could consist of a liquid, a semisolid, a nonflowing (three-dimensionally stable) material, or a combination of any of these. A liquid by itself is rather impractical for any extended wearing. However, if well contained, it could be made useful.

The semisolid platform, exemplified by the traditional ointment or semisolid gel material, with containment, is truly acceptable for wearing on the skin. Even without containment, such materials are ideal for spreading over irregular surfaces. A three-dimensionally stable material (such as a polymeric film or rubbery gel) has a discrete size and shape and can be easily contained. This type can be called a "solid-state" platform. The solid-state delivery system is more amenable for wearing and removing from the skin. On the other hand, it may not as easily conform to the application area, and complete system-to-skin contact is less certain.

Platforms thus consist of materials that are liquid, semisolid, or solid. Some investigators have referred to these platforms as monoliths, slabs, reservoirs, vehicles, films, polymer matrices, or just matrices. A matrix can be totally morphous and of varying viscosities, crystalline, or a combination of both. If a barrier or some material is placed in the path of the diffusing molecule so that it controls the rate of flux, it will be referred to as a membrane or film. Hwang and Kammermeyer[31] have classified membranes in terms of their nature, structure, application, or mechanism of action. The nature of a membrane can be said to be either natural (such as skin or intestinal walls) or synthetic (such as polymeric films). Defining membranes structurally, they can be either porous (such as microporous polymeric films, filters, etc.) or nonporous (such as films of polyethylene, vinyl, or other polymers commonly used in packaging).

The analysis of data on matrix or film diffusion can be presented in several formats. The most common methods are to observe either the cumulative amount of a drug that permeates or by the rate that it diffuses out of or through a matrix or membrane. Depending on the system selected, the drug will have a particular release-rate profile curve. Mathematical diffusion models have been reviewed extensively and are useful references.[32–38]

C. *Adhesion*

The modern transdermal product is a unique delivery system in that it is worn on the skin. This requires good skin contact over the total area of application and ease of applying and removing the transdermal patch. Also, if the transdermal delivery system is made of two or more laminating structures, good bonding between these layers must take place. Other parts of the system must not adhere well, such as the release liner (peel-away strip that is removed). If the drug is to be formulated into the adhesive itself, care must be taken that the drug or any adhesives do not influence the adhesiveness of the adhesive.

Along with an understanding of the effect of the formulation on drug release, one has to consider trade-offs with optimized adhesive properties. A good understanding of adhesion, adhesive properties, and adhesive materials, particularly in relation to pressure-sensitive adhesives, is helpful when dealing with these materials. Although the literature provides little specific information on pressure-sensitive adhesives, there are some reviews on the

practical and theoretical aspects of adhesives. Generally, the adhesive–cohesive properties, peel-strength, tack, and creep qualities of adhesives are basic properties used in formulating suitable pressure-sensitive adhesives. The basic construction of pressure-sensitive tapes has been reviewed in the literature. The facestock, or backing, can be a material that is occlusive (serves as a barrier, such as vinyl, polyethylene, polyester films, etc.) or nonocclusive (allows water and gases to readily flow through, such as nonwoven or porous films). The backing serves as a platform or carrier for the adhesive and is essential for application to and removal from the skin.[39,40]

The adhesive layer is pressure-sensitive and the anchor of the system. The American Society for Testing and Materials (ASTM) definition of a pressure-sensitive adhesive is a viscoelastic material which in solvent-free form remains permanently tacky.[41] Such material will adhere instantaneously to most solid surfaces with the application of slight pressure. The adhesive can then be removed from a surface, such as the skin or release liner, without leaving a residue. The pressure-sensitive adhesives (called adhesive mass) commonly used in medical applications are based on natural or synthetic rubbers, polyacrylates, or silicone. The release liner (also called release paper or peel-away strip) is a sheet that serves as a protectant or carrier for an adhesive film or mass, which is easily removed from the adhesive mass prior to use. The release liner consists of paper, polystyrene, polyethylene, polyester, or other polymeric films with a light coating of such compounds as silicones, long-chain branched polymers, chromium complexes, fluorochemicals, or various hard polymers.[42,43]

In a transdermal delivery system (TDD), the choice or design of adhesive is critical because it will have a strong effect on a patch's drug release, stability, and wear properties. The most common pressure-sensitive adhesives used for TDD systems are acrylates. Silicones tend to contain fairly limited properties, whereas acrylates can be tailored to achieve a wide range of performance in regards to various drugs, excipients, and particular product requirements. Cantor and Wirtanen[189] described novel acrylates adhesives — hydroxyethyl acrylate or pyrrolidoneethyl acrylate — as polar monomers to control drug stability and a graft macromer to control adhesive performance in 3M's latitude transdermal systems. These investigators studied solubility of drugs such as buprenophine, cyproheptadine, phenobarbital, testosterone, captopril, haloperidol, morphine, and atenolol.

D. Bioactivity

Other dosage forms intended to deliver drugs to the systemic circulation often provide highly fluctuating levels in the blood and tissues, especially after repeated dosing. The transdermal method offers an alternative whereby this problem is minimized. To determine if the transdermal route is indeed a workable alternative, one must ask what problems exist with the current dosage forms of a particular drug. In most cases, the therapeutic effect of a drug is related to drug concentration. There is an upper and lower limit of a drug that

will establish a "therapeutic window." In this range, the diseased state can be treated with minimal side effects. Some drugs may have nominal inherent side effects in this window but reach toxic proportions when higher levels are achieved. When levels go below the therapeutic threshold, the drug essentially becomes ineffective (e.g., a subtherapeutic level). Ideally, a drug delivery system should provide drug levels within the limits of the therapeutic window.[44]

In order to achieve systemic levels from a transdermal delivery system, the drug must first dissolve in the matrix and then migrate from the matrix through the skin and into the capillary plexus. Pharmacokinetic treatment of percutaneous absorption in the literature concentrates largely on drugs permeating into rather than through the skin. However, Beckett et al.[45] compared the transdermal route against the oral route of four ephedrine derivatives. They showed that metabolites were formed in smaller amounts and that the combination of unchanged drug and its metabolites was less using the percutaneous route. Riegelman[46] also showed the skin is rate-limiting and indicated that by adjusting drug loading, vehicle components, and surface area, prolonged steady-state blood levels can be sustained.

The use of pharmacokinetic parameters provides a useful tool for the development of transdermal systems. It can allow one to establish what steady-state fluxes of the drug are needed to reach a therapeutic level systemically. Pharmacokinetic parameters are also important from the biopharmaceutics point of view as part of the U.S. Food and Drug Administration review for market approval in order to support drug labeling. Furthermore, the system must show reproducibility of plasma levels and that these levels are within the therapeutic limits of a standard dosage form.

E. Polymers in transdermal delivery systems

Polymers are the backbone of transdermal delivery systems. These systems are fabricated as multilayered, polymeric laminates in which a drug reservoir or a drug–polymer matrix is sandwiched between two polymeric layers: an outer, impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive or rate-controlling membrane. The physicochemical and mechanical properties of various polymers that are currently used in commercially available transdermal drug delivery systems are summarized in the following tables. This summary is intended as a guide for the selection of polymers for developing such systems.

VII. Examples of transdermal applications

Transdermal systems, such as Nitrodur and Nitrodisc, are referred to as monolithic systems because they contain the drug as a semisolid solution or dispersion. With these systems, the drug reservoir is manufactured by dissolution of all components, including the polymer that serves as the matrix, with subsequent casting and drying. In some cases, the solvent may form

the continuous phase of the matrix, and processing may involve mixing high-viscosity fluid at an elevated temperature before forming the gelled matrix, either in sheet form or as a solid cylinder. The individual units must then be punched from the sheet or sliced cylinder.[47]

Once the drug reservoir, having the specified surface area, is obtained, it must be assembled with the system backing, peripheral adhesive, and protective liner. This process is the most labor-intensive and, consequently, the most expensive part of the manufacturing process. In the future, monolithic systems will undoubtedly be manufactured by more continuous processes, such as extrusion, injection molding, and laminating lines.[48–51]

Transderm-Nitro and Transderm-Scop are examples of membrane-controlled transdermal systems. Their methods of manufacture are somewhat different, however, in that the former is a product of technologies originating in the packaging industry, referred to as form-fill-seal, while the latter system derives purely from lamination processes. The technologies for both processes are well established, having been applied for some time in the food and cosmetics industries. Hence, these processes make it possible to produce pharmaceutical products under good manufacturing practices (GMP) regulations (see Figure 6.3).

In the case of form-fill-seal systems, the formulation of the drug reservoir can be accomplished by techniques utilized in the pharmaceutical industry. With the processes of lamination, however, dosing of the drug

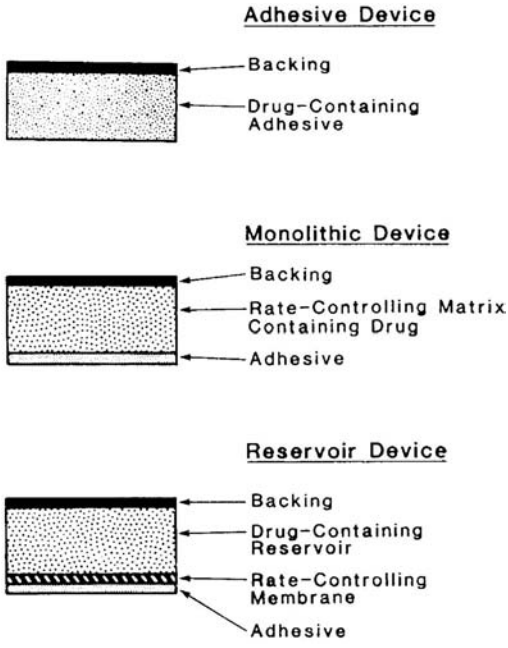


Figure 6.3 Types of transdermal delivery devices. (From *Pharm. Tech.*, The Latest Developments in Drug Delivery Systems, Conf. Proc., 1987, 27. With permission.)

reservoir and heat sealing must be refined and adapted somewhat before the overall manufacturing process becomes general and routine. Nevertheless, it seems this technology may be closer to finding a place in pharmaceutical production than those technologies needed for efficient production of monolithic systems.

The female reproductive hormones estradiol and progesterone are obvious choices for transdermal delivery. Estradiol is particularly promising because its oral administration causes a large fraction of the dose to be converted in the liver to the less-active metabolite estrone. Transdermal administration avoids most hepatic metabolism and results in therapeutic blood levels of estradiol at total doses much lower than those required by oral administration.

Diseases of the cardiovascular system lend themselves quite readily to transdermal administration of drugs because of the nature of the diseases. Drug treatment of hypertension and angina is generally a protracted process, often requiring continuous use for many years. As such, compliance with the established regimen is important and can be a problem — particularly with hypertension, because the disease is often asymptomatic, giving the patient no incentive to take his or her medication on time. Two beta blockers, timolol and propranolol, have been studied in their free-base form in skin-permeation models and have been shown to provide sufficient skin permeability to obtain significant blood levels. Both of these compounds are used in oral form to treat hypertension and angina. Neither of these is cardioselective, and several of the hepatic metabolites of propranolol are active beta-adrenergic antagonists. Timolol has been introduced in an ocular formulation for the treatment of ocular hypertension (glaucoma). It seems likely that both timolol and propranolol, administered transdermally, would have some efficacy in reducing blood pressure.[52,53]

Compounds used to control pain continue to be of general interest in the medical and pharmaceutical communities. It is important, however, to understand when a transdermal delivery system, or any controlled delivery system for that matter, is an advantage in the control of pain. Clearly, the amelioration of acute pain requires fast onset of action and probably is not an appropriate use of transdermal therapy. Still, control of chronic pain may well lend itself to transdermal therapy. At least one group has studied transdermal delivery of salicylates. It appears, however, that dosing requirements may prove too great for common nonnarcotic analgesics. At the same time, many fundamental questions regarding the development of tolerance during continuous dosing must be answered before any transdermal analgesics can become a reality.[54]

There may be a need for continuous delivery of both over-the-counter (OTC) and prescription antihistamines, particularly in the treatment of certain allergies. At least one pharmaceutical company is developing a transdermal delivery system for chlorpheniramine. The primary advantage of continuous transdermal delivery of antihistamines is the possibility of maintaining histamine-receptor antagonism while reducing the occurrence of

central nervous system (CNS) side effects, such as drowsiness. Because chlorpheniramine has a relatively long half-life, it is believed that its transdermal administration may not provide major advantages in a dosing interval, unless the system can be designed to last more than one day. Substantial benefit in minimizing side effects, however, may well overcome modest benefits in duration of effect. The primary drawback to transdermal administration of antihistamines, particularly the tertiary amines, is the possibility of skin irritation or hypersensitization.

In a paper describing skin permeability[55] of physostigmine, a cholinesterase inhibitor, the authors studied a transdermal system that delivered the drug at a sufficient rate through pig skin *in vivo* to inhibit the breakdown of acetylcholine by 30 to 40% over 4 days. This mode of treatment could have far-reaching effects for certain dementias involving a deficit in CNS acetylcholine, including Alzheimer's disease. One must, however, be cautious, because physostigmine is not specific to the CNS, and peripheral side effects must be carefully controlled. Nonetheless, this system provides a convenient means of delivering physostigmine at a controlled rate to the systemic circulation — bypassing hepatic metabolism — over a long period of time. It should prove useful in studying the treatment of these diseases and their responses to cholinesterase inhibition.

Tables 6.1 and 6.2 contain partial lists of transdermal controlled-release products and devices.

The following drugs are also under development using a transdermal therapeutic system: ketoprofen, 5-fluorouracil, metoprolol, terodiline, primaquine, ibuprofen piconol, nitrendipine, diclofenac, corticosteroids, sandimune (cyclosporine A), fluazifopbutyl, glyceryl trinitrate, azido-profen esters, methotrexate, medroxyprogesterone acetate, levonorgestrel, mepindolol, oxycodone, prostaglandins, and 9-β-D-arabinofuranosyladenine (Ara-A).

A. Iontophoresis

An alternate strategy to drive drugs through the skin that seems to be enjoying a revival of interest is iontophoresis. In this method, a battery is connected to two electrodes on the skin. If an ionized drug is placed in contact with one electrode, it will migrate under the influence of the voltage gradient through the skin and enter the systemic circulation. Substantial delivery can be obtained in this way (see Figure 6.4).

The earliest patents describing the essential features of iontophoresis date back to the 1890s, although apparently their objective was to shock their subjects rather than drug them. The first modern device appeared in 1972, and advances since then have enabled smaller and smaller devices to be built. The newest devices, from Drug Delivery Systems, have a built-in battery layer and are comparable in size to a normal transdermal patch. The patents in this area so far deal with device design and do not specify particular drugs. There is considerable potential for innovative work in this specialized area.

Table 6.1 Transdermal controlled-release products and devices

Drug	Trade name	Type of device	Indication
Scopolamine (Hyoscine)	Transderm-Scop Kimite Patch	Reservoir	Motion sickness
Nitroglycerine[a]	Transderm-Nitro	Reservoir	Angina
	Deponit	Mixed monolithic reservoir	Angina
	Nitro-Dur	Monolithic	Angina
	Nitrodisc	Monolithic	Angina
	NTS	Monolithic	Angina
Isosorbide-dinitrate	Frandol Tape	Monolithic	Angina
Clonidine	Catapress-TTS	Reservoir	Hypertension
Estradiol	Estraderm	Reservoir and ethanol enhancer	Hormone treatment
Estradiol esters	—	**	Hormone treatment
Testosterone	TheraDerm-LRS	**	Hormone treatment
Timolol	—	**	Cardiovascular
Propranolol	—	**	Cardiovascular
Fentanyl	Duragesic	—	Opioid analgesic
Glycol salicylate	—	**	Analgesic
Methyl salicylate	—	—	—
Chlorpheniramine	—	**	Antihistamine
Diphenhydramine	Zenol	—	Antihistamine
Physostigmine	—	**	Cholinergic
Insulin	—	**	Diabetes
Albuterol	—	**	Bronchodilator
Piroxicam	—	**	Arthritis
Ketorolac (Toradol)	—	**	Nonnarcotic analgesic
Flurbiprofen	Zepolas	—	Anti-inflammatory
Indomethacin	Indomethin	—	Anti-inflammatory
Bufuralol	—	**	Angina, hypertension
Bupranolol	—	**	Angina, hypertension, antiglaucoma agent
Nicotine	Habitrol, Nicoderm, Nicotrol, PROSTEP	—	Aid to smoking cessation, Tourette's syndrome

[a] Other trade names are Diafusor, Minitran, Nitriderm, Nitrol Patch, Nitrocine, Deponit, Millistrol Tape, and Herzer.

** In research and development.

Table 6.2 Transdermal products under development

Drug	Trade name	Producer/marketer
Minocycline	(Topical) Sunstar	American Cyanamid, Takeda
Eperisone	E-2000	Eisai
Estradiol+ Norethisterone	Estracombi TIS	Ciba-Geigy, Alza, Ethical Pharmaceuticals
Estradiol+Progestin	—	Cygnus Research, Elf Sanofi
Estradiol	Menorest	Noven Pharmaceuticals, Cygnus Research, Ciba-Geigy, Elf Sanofi, Pierre Fabre, Rhone-Poulenc, Johnson & Johnson, Warner-Lambert, Rotta Research Fournier, Forest Labs, Hercon, Ethical Pharm., Nikko Denko, Pharmed, Pharmetrix Recordati, Teikoku Hormone
Estrogen+ Progestogen	—	Noven Pharm., Rhone-Poulenc-Rorer, Fournier, 3M Pharm., Pharmetrix Biosearch
DHEA (Androgen)	—	Pharmedic
Eptazocine	—	TheraTech, Nichiiko
Fentanyl	—	Anaquest, CygnusResearch
Pain-Drug	—	Syntex-Roche, TheraTech
Progesterone	—	TheraTech, Solvay
Analgesic	—	Ethical Pharm., TheraTech, Syntex-Roche
Lipophilic iron Chelators	—	Yissum
Buprenorphine	—	Pierre Fabre, Cygnus Research, Whitby Pharmaceuticals
Triamcinolone acetonide	—	Whitby Pharmaceuticals
Antoproliferative compound	Topical formulation	Yissum
Anthralin	Percutaneous delivery	Vuman

The iontophoretic system currently marketed (Phoresor, Motion Control, Inc.) uses a continuous, waveless, unidirectional current of low voltage (DC). All ions are either positive or negative. For a drug to be phoresed, it must be ionizable and its polarity determined. The drug is then injected into a reservoir in the active pole (electrode). This electrode is smaller than the inactive or indifferent electrode in order to concentrate the drug's effects. When the pads are placed, they should be as directly opposite each other as possible (e.g., on either side of the elbow). When the system is activated, the drug is driven out of the active pole toward the inactive pole. The inactive pole, being the opposite polarity of the drug will, therefore, theoretically attract the drug, allowing it to be distributed to the tissues between the two electrodes.

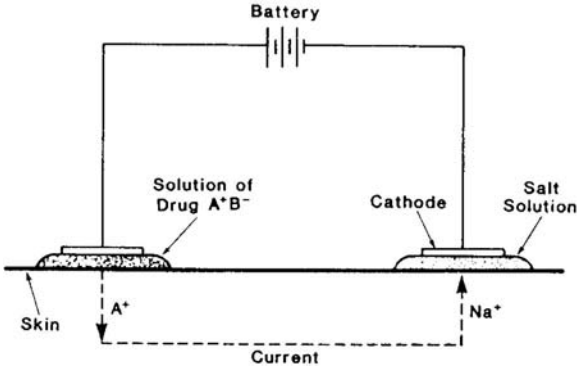


Figure 6.4 Schematic diagram illustrating the principles of iontophoresis. (From *Pharm. Tech.*, The Latest Developments in Drug Delivery Systems, Conf. Proc., 1987, 31. With permission.)

Human skin has a limited tolerance for flow of electric current, however. Therefore, the unit must be turned on and off slowly to avoid muscle stimulation. Turning the unit on or off suddenly, changing the electrode placement, or changing the polarity while the unit is running may cause the patient to receive a shock. When lower voltages are used, the patient will have less sensation of penetration, but the level of drug penetration will also be lower. The amount of drug delivered is equal to the current applied multiplied by the duration of treatment. The recommended treatment time is 20 minutes, and the recommended maximum current is 4 mA. Therefore, the amount of drug delivered would be 80 mA/min. Iontophoresis is currently used for the treatment of acute musculoskeletal and neuromuscular inflammatory problems using a mixture of lidocaine and dexamethasone or dexamethasone alone. Lidocaine alone is also used for local anesthesia. Many drugs are being studied for the feasibility of their delivery via iontophoresis. They are listed in Table 6.3.

VIII. Transdermal controlled-release products and devices

Lectec Corporation has developed a solid-state, hydrophilic reservoir system that uses body heat and humidity to hydrate the skin and allows the diffusion of drug through the skin for systemic absorption.

Health-Chem Corporation has developed a transdermal laminar system that releases a drug by using different polymers in the reservoir and protective layers. The Zetachron Company has developed its own transdermal system that can slow down skin permeation of drugs that are highly permeable. This is useful in transdermally delivering low-dose, potent drugs, such as antihypertensive and antianginal agents. Its transdermal systems are believed to be easier to manufacture than conventional transdermal patches.[56]

Table 6.3 Transdermal iontophoretic delivery

Drug	Use
Lidocaine	Local anesthesia
Dexamethasone	Arthritis
Hydrocortisone	Arthritis
Acetic acid	Calcified tendonitis
Iodine	Scar tissue removal
Penicillin	Burns
Salicylates	Arthritis, myalgias
Histamine	Peripheral vascular disease
Hyaluronidase	Edema
Lithium	Gouty arthritis
Magnesium	Arthritis
Calcium	Myospasm
Copper	Fungal infections
Zinc	Scars, adhesions
Acetate	Calcifications
Isopropamide	Anticholinergic
Piroxicam	NSAID
Sufentanil	Analgesic, anesthetic
Insulin	Diabetes
Sotalol	Antianginal, antiarrhythmic
Leuprolide	Antineoplastic
ACE inhibitors	Hypertension
Amino acid derivatives	—
Alanine tripeptides	—
Melatonin, melanin	Mediator of photic-induced antigonadotrophic activity
Verapamil	Antianginal, antiarrhythmic

The Elan Company has developed two transdermal systems: Dermaflex and Panoderm. Both of these systems are to be worn like bracelets. The active ingredients are absorbed from the bracelet by electrical impulses.

The Moleculon Biotech Company has developed a poroplastic membrane system. This system is a molecular sponge that can hold within its pores a large quantity of solid, solubilized compounds. This membrane system is quite flexible. It can alter release rate by adding various compounds to deliver drugs from a few hours to months (see Figures 6.5 and 6.6).[56]

Finally, some examples of skin applications are pressure-sensitive adhesive compositions containing chlorhexidine or PVP-1 and iodine as antimicrobial agents and for administering tretinoin for acne; topical treatments for dermatological conditions (e.g., tricyclic antidepressants, such as imipramine, amitryptyline, and doxepin, for pruritis and anthracenone derivatives for psoriasis)[57] and antiphlogistic analgesic adhesive containing indomethacin for arthritis.[58] Electrically assisted delivery by iontophoresis or electroporation was used *in vitro* to deliver the calcium-regulating hormones salmon calcitonin (sCT) and parathyroid hormone (PTH) through

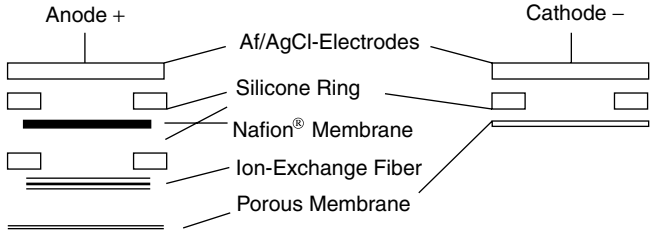
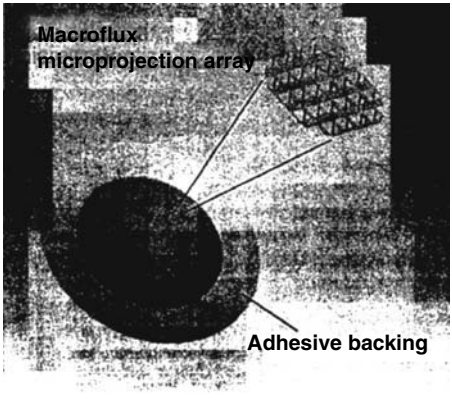
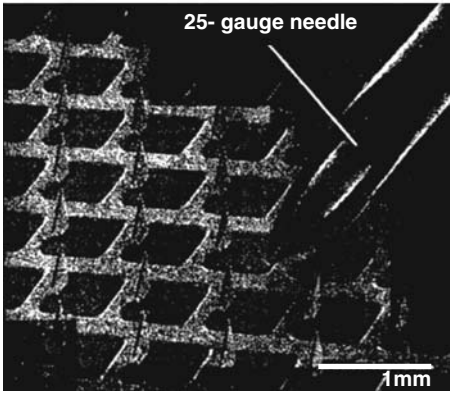


Figure 6.5 Transdermal iontophoresis of tacrine. The structure of the ion-exchange fiber device. (With permission, Kluwer Publishers, *Pharm. Res.*, 19, 5, 704, 2002.)



(A)



(B)

Figure 6.6 (A) Schematic representation of the Macroflux® microprojection array integrated with an adhesive patch. (B) Scanning electron photomicrograph of an array of microprojections (330 μm length). For scale, a 25-gauge needle is shown adjacent to the array. (With permission, Kluwer Publishers, *Pharm. Res.*, 19, 1, 64, 2002.)

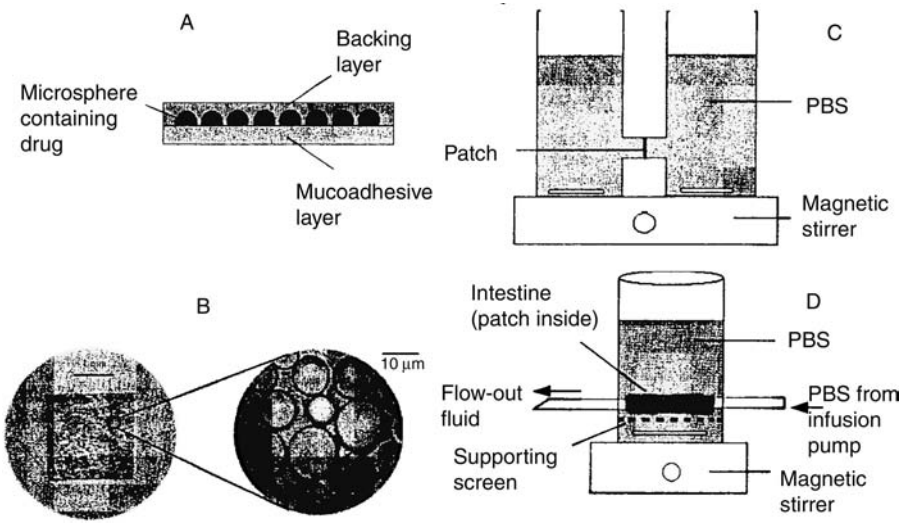


Figure 6.7 (A) Schematic representation of the patch design. The patch consists of a film of a mucoadhesive polymer. A monolayer of cross-linked bovine serum albumin (BDA) microspheres (10–30 μm) is dispersed on the mucoadhesive film. The drug to be delivered is encapsulated in the microspheres. The microsphere monolayer is covered by a film of poorly permeable polymer. (B) Intestinal patches (4 mm^2). (Right figure indicates the microstructure of the patch.) (C) Schematic representation of the diffusion cell used to measure release of model drugs from the patch. (D) Schematic representation of flow-through setup for measurement of transport across the intestinal wall. (With permission, Kluwer Publishers, *Pharm. Res.*, 19, 4, 391, 2002.)

human epidermis. Such delivery could be useful for chronic treatment of postmenopausal osteoporosis and other clinical indications as a superior alternative to parenteral delivery.[128–130] Transdermal and topical delivery of macromolecules of at least 40 kDa was also achieved by skin electroporation. Spatially constrained skin electroporation with sodium thiosulfate and urea was found to create transdermal microconduits.[131–135]

Gelatin-containing, microemulsion-based organogels (MBGs) (see Figures 6.7 and 6.8) have been formulated using pharmaceutically acceptable surfactants and oils, such as Tween 85 and isopropyl myristate. MBGs provide a convenient means of immobilizing a drug such as sodium salicylate and are rheologically similar to their hydrogel counterparts at comparable gelatin concentrations. MBGs also offer improved microbial resistance in comparison to aqueous solution or hydrogels.[141–147] Bhatia and Singh[158] investigated the effects of 5% terpenes (e.g., limonene, carvone, thymol, and cineole) and iontophoresis on the *in vitro* permeability of leutinizing hormone (LH-RH) through the porcine epidermis and biophysical changes in the stratum corneum (SC) lipids by Fourier transform infrared (FT-IR). They found that terpenes/EtOH increased permeability by enhancing the extraction of the SC lipids. Iontophoresis synergistically enhanced the permeabil-

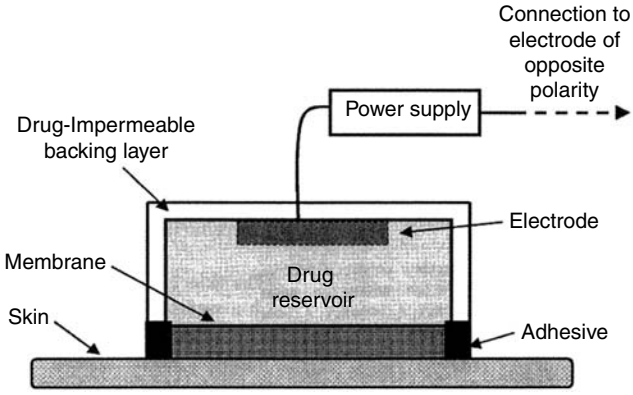


Figure 6.8 Schematic drawing of a transdermal drug delivery patch in contact with the skin. For iontophoretic delivery, an electrode of the same polarity as the charge of the drug is placed in the drug reservoir. The electrical circuit is completed by the application of a second electrode of the opposite polarity at a different skin site. (With permission, Elsevier, *J. Control Rel.*, 81, 335–345, 2002.)

ity of LHRH through terpenes/EtOH-treated epidermis. Other researchers have also investigated transdermal iontophoresis of oligonuclide drugs, the electrotransport of representative bases (uracil and adenine), and nucleosides (uridine and adenosine) and nucleotides (AMP, ATP, GTP, and imido-GTP) across mammalian skin *in vitro*. Vanbever et al.[179] found that skin electroporation could be a good way to improve the transdermal diffusion of fentanyl. Langer[38] found that application of therapeutic ultrasound (frequency 1 to 3 KHz and intensity 0 to 2W/cm^2) enhances transdermal drug transport, although typically by a factor of less than 10. They studied permeants such as estradiol, salicylic acid, corticosterone, sucrose, aldosterone, water, and butanol across human cadaver skin. They concluded that low-frequency ultrasound enhances transdermal transport of drugs more effectively than that induced by therapeutic ultrasound. Cevc[182] described transferosomes, which are supramolecular aggregates better than liposomes or niosomes. These are found to increase the agents' diffusivity or partitioning in the organ.

IX. Recent advances

Transdermal drug absorption can be enhanced to a degree by various chemical and physical methods. Chemical enhancers exert their influence on lipids in the stratum corneum as well as on lower dermal layers, and possibly capillary beds. Physical enhancers seem to promote the penetration of the stratum corneum, while diffusional permeation seems to be important in the lower layers of the skin. In addition, the effect that the chemical enhancers might have on the activity of the drug in the delivery device must always be considered. A means of enhancement that can provide reproducible trans-

dermal delivery through a variety of skins under various conditions is needed. Iontophoresis has an advantage over chemical methods because it apparently offers better control of transdermal drug delivery. However, it requires a device separate from, and in addition to, the drug delivery reservoir and therefore often is considered cumbersome to use and uncertain from a regulatory standpoint. This is an important consideration for companies attempting to commercialize such a product. Rolf[59] has described some examples of amphoteric enhancers, such as sodium lauryl sulfate, lauryl amine oxide, azone decylmethyl sulfoxide, lauryl ethoxylate, and octanol.

Using the cell or the cylinder method, Aiche et al.[60] have evaluated the rate of release and dissolution of trinitrine from a membrane-reservoir transdermic delivery system. Both methods yielded the same results in terms of the quantity of drug released per unit area per hour and thus ensure a satisfactory quality control of the system. Regardless of the method used, the drug release is zero-order at 1 hour after diffusion and thereafter. The authors conclude that the method proposed by the supplier (the cylinder method) is validated against that described by the pharmacopoeia.

Despite the great need for effective transdermal permeation enhancers, the search is still largely empirical. Very few studies have involved systematic evaluation of enhancer congeners. The enhancer congeners that have been evaluated by Chow and Hseih[61] include surfactants of alkyl sulfates, saturated fatty acids, fatty alcohols with different numbers of double bonds, unsaturated fatty acids with equal numbers of double bonds at different positions or with different configurations, and cyclic compounds with various carbon numbers and sizes.

Pressure-sensitive adhesives (PSAs) are necessary components in transdermal systems because they ensure intimate contact of the device with the skin. PSAs are used in many system designs that can be configured using an adhesive overlay face adhesive, adhesive matrix, and multilaminated PSA matrix. The science and engineering involved in the selection, formulation, and optimization of PSA properties is critical to the successful development of transdermal systems. Adverse interactions between the drug, excipients, cosolvents, and permeation enhancers in reservoir or matrix-type systems can compromise the performance of the adhesive, resulting in system failure.[62]

The skin is a vital metabolic and immunocompetent organ that serves as the body's first line of defense against environmental attack. Certain chemicals, however, are capable of producing immediate and delayed hypersensitivity reactions within the skin by interacting directly or indirectly with certain cells in the epidermis and dermis. For this reason, the delivery of drugs through the skin might produce adverse reactions by affecting responsive cells. Dunn[63] has discussed work regarding the biological response of whole skin and isolated epidermal keratinocytes to phorbol esters, potent drugs, irritants, and mitogens.

The article by Pfister[64] illustrates how silicone pressure-sensitive adhesives can be customized to accommodate specific drug, material, and coating

requirements of transdermal delivery systems. Physiochemical properties of silicone PSAs and their end-use properties, such as tack, adhesion, and cohesive strength, are characterized. The article also describes how these properties can be varied either chemically — by altering silanol functionality, resin-to-polymer ratio, or choice of solvent — or physically — by adjusting coating thickness. Finally, relationships between silicone PSAs and drug-release kinetics are addressed, and methods of developing formulations to optimize system performance are suggested.

Because of the side effects associated with the oral administration of tetra-hydrocannabinol (THC), Touitou et al.[65] tested the use of the skin as a noninvasive portal for the sustained delivery of the drug. Rat skin was found to be approximately 13 times more permeable than human skin. Autoradiographs showed that after 24 hours, the drug was concentrated in the stratum corneum, in the upper epidermis, and around the hair follicles, which suggests that THC penetrates through the lipophilic pathways.

Touitou[66] have also investigated the permeation-enhancement properties of n-decyl methyl sulfoxide (decylMSO) in the presence of water and propylene glycol *in vitro* through hairless mouse skin. 5-Fluorouracil and idoxuridine were used as test drugs because of their respective hydrophilic and hydrophobic properties. Results showed that the enhancement of permeation by decylMSO occurred only in an aqueous medium and only at concentrations greater than the critical micelle concentrations.

Ashton et al.[67] have investigated the influence of sodium lauryl sulfate (SLS) and Brij 36T on the thermodynamic activity of methyl nicotinate in aqueous gels. The permeability of skin *in vivo* was assessed by measuring the time required for nicotine esters and hexyl nicotinate in aqueous gels. The time required for SLS gels to cause erythema correlates with *in vitro* release rates. Because SLS is considered to be a powerful penetration enhancer, the results of this study indicate that these two surfactants exert their influences in different ways.

Key Pharmaceuticals has received approval to market Nitro-Dur II (nitroglycerine) transdermal infusion system for prevention of severe angina pectoris. Applied once a day to the chest or upper arm, it delivers nitroglycerine for a full 24 hours.[56]

Cygnus Research, in collaboration with Family Health International, is developing a weekly contraceptive patch. Patches would be replaced weekly for three weeks, and a drug-free patch worn on the fourth week.[56]

Forest Laboratories has formulated nitroglycerine in a transdermal polymer gel. The gel, which Forest will market, is applied in liquid form to the skin, where it quickly dries and is absorbed.[56]

A transdermal formulation of ketoprofen for orthopedic use is being developed for the treatment of osteoarthritis, tenditis, and bursitis. The formulation comprises a flexible pad and adhesive layer containing the water-based drug.[56]

MacroChem has filed a patent application for enhancing the transdermal delivery of minoxidil. This technology will be employed in the company's

Dermelec product, a transdermal device to be worn and adjusted by patients to control the rate and amount of dosage.[56]

Transdermal delivery of glibenclamide from polymeric matrices of eudragits, ethylcellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone carboxymethyl cellulose, and polyvinyl acetate with plasticizers has been studied. It was reported that the permeation rate was enhanced, depending on the type and the concentration of the enhancers. The advantage of using an enhancer combination was also observed.[68]

Occlusion of skin under a transdermal patch may facilitate the occurrence of adverse dermal reactions. In order to minimize such reactions, a novel system has been developed which is ultrathin, breathable (oxygen- and moisture-permeable), and has excellent conformability to the skin. This system is ideally suited for topical application of medications such as antibiotics, anti-inflammatory, and antifungal agents and for transdermal delivery of relatively nontoxic and nonvolatile drugs.[69]

During the course of work on the development of a transdermal levonorgestrel (LN) delivery system, a number of permeation enhancers have been investigated that can be used in conjunction with ethanol to achieve therapeutically effective fluxes of LN through the intact stratum corneum. The effectiveness of this enhancer for 5-fluorouracil, estradiol, and hydrocortisone was also studied.[70]

The article by Bodde et al.[71] focuses on two aspects of transdermal peptide delivery: transepidermal penetration and intra(epi)dermal biotransformation using the example of desenkephalin endorphin, a highly potent neuropeptide. *In vitro* studies with this peptide, using both intact human skin samples and cultured human skin cells, showed transdermal fluxes (without enhancers). From these results, it is anticipated that the transdermal delivery of small peptides, even hydrophilic ones, is a distinct possibility.

Based on long-term physical and chemical stability results, a transdermal contraceptive (TCS) formulation has been developed. Extensive effort was then devoted to the development of procedures and technology for scale-up manufacturing of TCS patches. A continuous operation-type fabrication machine (SFM) was designed. The patches fabricated were evaluated by measuring their weight variation and content uniformity, as well as the release and skin-permeation rates of levonorgestrel and estradiol against the patches prepared by the hand-operated, compression-coated (HCC) process.[72]

A transdermal delivery system for verapamil was developed and applied for a 24-hour period on the chest skin of eight healthy male volunteers. Plasma concentration was monitored during 48 hours after application. Verapamil and its active metabolite (norverapamil) were detected in plasma. Plasma concentration reached steady state within approximately 10 hours after application. Clinical data was found to be comparable to *in vitro* penetration of hairless mouse skin with the help of a computer simulation technique.[73]

A transdermal polymeric delivery system for hydromorphone has been developed. Various penetration enhancers, such as isopropylmyristate, azone, hexamethylene palmitamide, hexamethy lauramide, aliphatic acids,

alcohols, and esters, were incorporated in the polymer matrix. The rate of drug penetration across hairless mouse skin increased and lag time decreased as enhancer concentration increased. Among the enhancers investigated, hexamethyl lauramide most significantly improved penetration of hydromorphone.[74]

The transdermal route offers several advantages over other routes of administration. However, a key problem is the low permeability of skin to most drugs. Low skin permeability often requires impractically large devices if useful drug delivery rates are to be achieved. Highly potent drugs that are effective at low dosage rates, and hence do not demand large devices, are promising candidates for the transdermal delivery route. LN is one such drug and is capable of suppressing ovulation.[75]

A multilaminate-type transdermal drug delivery (mTDD) system was recently developed for controlled administration of various drugs. The skin-permeation rates of progestins and other drugs were found to be substantially enhanced, to varying degrees, by releasing different types of skin-permeation enhancers from the surface adhesive layers to modify skin permeability.[76]

BIOTEK has developed a Universal Transdermal Delivery System, which is highly versatile and adaptable to a wide variety of drugs and dosing requirements. Its unique features include a macroporous non-rate-controlling membrane, a viscous liquid base as a solvent for the drug, and suspended drug microparticles as reservoirs. After application, the system maintains a thin film of drug solution in direct contact with the skin, providing for skin occlusion. The system is compatible with enhancers and additives, and its delivery rate and duration are controllable by formulation variables. The system has been evaluated *in vitro* and *in vivo* for the simultaneous delivery of estradiol and levonorgestrel.[77]

Polydimethylsiloxane (PDMS) PSAs are used in transdermal drug delivery systems, in part because of excellent biocompatibillity and high permeability of this class of materials. BIO-PSA® 355 silicone pressure-sensitive adhesive is well-suited as a contact adhesive in reservoir-type delivery systems. Its properties are somewhat compromised, however, when co-formulated with amine-functional agents. BIO-PSA® Q7-2920 was developed to exhibit amine resistance. PSA either functions as a contact adhesive or may potentially act as a drug-loaded adhesive matrix, a conceptually simple, yet technologically complex, drug delivery system. Preliminary suitability of BIO-PSA® Q7-2920 as a drug-loaded matrix was determined by characterizing the release kinetics of nitroglycerine, indomethacin, estradiol, progesterone, propranolol, and testosterone from the PSA and testing the adhesive-tape properties (release, adhesion, and tack) of the drug-loaded matrices as a function of time.[78]

Actibase (Schering Corp., Kenilworth, NJ) is an optimized vehicle of propylene glycol, propylene glycol stearate, white wax, and white petrolatum used in the formulation of topical betamethasone dipropionate.[79] Erythromycin formulated with a hydroalcoholic solution composed of ethanol and propylene glycol seems to be effective, as does tetracycline (e.g., Topi-

cycline, Proctor & Gamble, Cincinnati, OH) formulated with the enhancer decyl methyl sulfoxide.[79]

Actiderm (Bristol Myers Squibb, Princeton, NJ), a patch that does not contain any drug, was introduced in 1988 for use as an occlusive dressing. The patch is placed over topically applied corticosteroids to enhance their efficacy by promoting hydration of the stratum corneum. This treatment leads to enhanced percutaneous absorption and prolonged activity, thus minimizing the need for high-potency steroids.[80]

Hercon has developed a laminated reservoir system for the controlled transdermal delivery of agents to the systemic circulation, achieving steady-state blood levels for extended periods while minimizing side effects. The system is thin and flexible and consists of two to four layers, including a backing membrane, the drug reservoir, a rate-controlling membrane, and an adhesive that holds the system to the skin. The system is suited to compounds that require either a one-day or seven-day frequency of delivery. Hercon has signed agreements with several pharmaceutical companies to develop or market its polymeric transdermal system for selected products, which include antiarthritics, antiemetics, antihistamines, beta-blockers, antihypertensives, antiasthmatics, antiaddictives, calcium antagonists, tranquilizers, and hormonal agents.[81]

The penetration of azidoprofen through excised hairless mouse skin has been investigated. Formulation factors influencing skin permeation, such as pH and solute and cosolvent concentrations, were studied and found related to physicochemical parameters such as pka and partition coefficient. In addition, the effect of a range of penetration enhancers on the transport of azidoprofen was also assessed. Pretreatment with azone in propylene glycol resulted in an increased flux with increasing pH, and thus appeared to facilitate penetration of the ionized species.[82]

The feasibility of achieving transdermal delivery of the opioid analgesic ketobemidone in human skin penetration studies *in vitro*, using both ketobemidone and three carbonate ester pro-drugs, has been studied. Whereas ketobemidone had only limited ability to permeate the skin from either polar or apolar vehicles, the ester pro-drugs readily penetrated the skin when present in certain solvents, such as isopropyl myristate, ethanol, and ethanol-water. This study demonstrated the feasibility of achieving transdermal delivery of ketobemidone based on enzymatic conversion and favorable skin-penetration properties of the ester pro-drugs, which, in turn, is attributed to their high solubilities in both polar and apolar solvents.[83]

Pro-drug fatty acid esters of N-(2-hydroxyethyl)-2-pyrrolidone have also been synthesized in order to test the previously mentioned approach. It was found that a twofold order of magnitude increase in permeability for hydrocortisone through mouse skin could be achieved *in vitro* with these enhancers. The ester linkage was readily cleaved by hydrolytic enzymes in plasma and skin homogenates, while having relatively good solution stability at neutral and slightly acidic pH. These agents appear to have much less irritation potential than traditional penetration enhancers.[84]

The effect of simultaneous use of 1-menthol and ethanol on skin permeation of six potent cardiovascular agents — nicardipine, atenolol, captopril, nifedipine, vinpocetine, and nilvadipine — has been investigated to evaluate the feasibility of their use in a transdermal therapeutic system. *In vitro* diffusion experiments were carried out using excised hairless rat and human skin. The application area of the transdermal system required for the minimum effect was estimated by pharmacokinetic calculation. Marked enhancement of penetration by the 1-menthol-ethanol system was found independent of drug lipophilicity, while the mode of drug action was dependent on lipophilicity.[85]

The synthesis of ε-aminocaproic acid esters has been described. Two representative members from a group of five analogues of 1-alkylazacycloheptanone derivatives were evaluated *in vitro* for their effectiveness on transport of theophylline through excised human cadaver skin in comparison with azone. The 1-octyl and 10-dodecyl-ε-aminocaproic acid esters (OCEAC and DDEAC) showed excellent penetration enhancement. OCEAC and DDEAC did not exhibit acute dermal irritation *in vivo* on rabbits at a 5% concentration in white petrolatum.[86]

Hisetal contains properties of melanotropin, an endogenous pituitary peptide hormone. The permeability coefficient of hisetal is on the same order of magnitude as that of amino acids (5.58×10^{-5} cm · hr^{-1}). Oleic acid enhanced the permeation of hisetal by a factor of 28. Dodecyl N,N-dimethylamino acetate (3%) enhanced the permeation of hisetal 1.5 times more than azone at the same concentration. The effects of the penetration enhancers were irreversible within 12 hours. For the treatment of multiple sclerosis, assuming the same permeation rate as in hairless mouse skin, this would not achieve desired delivery of hisetal.[87]

A technique to deliver drugs through the skin by means of a millisecond, high-voltage pulse has been described by scientists from the Massachusetts Institute of Technology. The method, which the investigators call electroporation, temporarily alters the permeability of the skin. Millisecond pulses of 100 volts applied to human skin preparations or to anesthetized small animals every five seconds delivered approximately 1 microgram of test compound per square centimeter of skin per hour. Test compounds were calcein, lucifer yellow, and a derivative of erythrosine, all chosen for their detectability by fluorescence.[88]

An attempt has been made to establish a predictive method for determining the steady-state permeation rate of drugs through human skin. The method is based on the assumption that the stratum corneum is the main barrier in the skin and that it can be considered a membrane with two permeation pathways: lipid and pore. The authors derived an equation for predicting the steady-state permeation rate. Results showed that the skin-permeation potential of each drug in humans was different than that occurring in the hairless rat. The permeability of lipophilic drugs was slightly higher in humans than in the hairless rat, however, that of hydrophilic drugs was lower than in the hairless rat. Factors accounting for other species differences in skin permeability were discussed.[89]

Recently, patches containing polyisobutylene, azone, liquid paraffin, and 50 mg of nitrendipine (a calcium channel blocker) have been studied. *In vitro* release rates revealed that the cumulative release of nitrendipine was 31.5% of the initial loading dose in 34 hours and 40% in 72 hours. The results showed that this form of drug delivery not only decreases blood pressure effectively, but also reduces the adverse side effects induced by high plasma concentrations of the drug. Clinical trials involving 150 hypertensive patients showed that the patches reduced both systolic and diastolic blood pressure to within normal limits in 86% of the patients. The patches, applied to different skin locations, caused no skin irritation in either rabbits or human subjects during a 3-day period.[90]

The transfer of 13 drugs from transdermal patches to intact and stripped rat skin has been carried out to correlate transfer with the physicochemical properties of the drug. The drugs tested had melting points up to 234°C, lipophilic indexes of 0.475 to 5.336, and molecular weights of 122 to 392. The percentage of drug transferred to intact skin was lower when the melting point, lipophilic index, and molecular weight were high. Using stripped skin, the authors obtained similar results, although the percentage of drug transferred was markedly higher. The impact of the stratum corneum against drug transference tended to be greatest when the melting point and lipophilic index were low.[91]

The authors investigated the effects of various additives on the crystallization of ketoprofen in polyisobutylene adhesive matrix. The addition of Tween 80, Labrasol, or PVP K 30 significantly reduced the decrease in the flux of ketoprofen within this matrix during a storage time of 3 weeks.[148,149]

Terpenes, menthol, terpineol, cineole, and menthone were found to be effective permeation enhancers for imipramine HCl. Results of this study were explained with the help of H-bond breaking potential and self-association of terpenes. In order to elucidate the effect of terpenes on stratum corneum, FT-IR was used.[154,155]

Oral administration of tripolidine and antihistamines may cause many adverse side effects, such as dry mouth, sedation, and dizziness, and transdermal drug delivery was therefore considered. The transdermal controlled-release of the tripolidine system could be developed using the poly(4-methyl-1-pentene [TPX]) polymer, including the plasticizer. Among the plasticizers used, such as alkyl citrates, phthalates, and sebacate, tetra ethyl citrate showed the best enhancing effects.[151,152]

To formulate a transdermal drug delivery system of captopril, monolithic, adhesive-matrix-type patches containing 20% captopril, different pressure-sensitive adhesives, and various permeation enhancers were prepared using a labcoater. Fatty alcohols resulted in a pronounced enhancing effect on the skin permeation of captopril, while dimethyl sulfoxide, N-methyl-2-pyrrolidone, oleic acid, transcutol, and polysorbate 20 showed no significant enhancing effect.

Transdermal enhancement effects of electroporation applied only on the stratum corneum by two electrode types, the stamp-type electrode and the

frog-type electrode, were investigated *in vitro* using excised rat skin. Carboxyfluorescein was selected as a model compound and used successfully in this work.

Ketotifen fumarate is effective in low doses in the treatment of bronchial asthma, particularly types of allergic origin. It is substantially metabolized when given orally. Isopropyl myristate and a linoleic acid combination and isopropyl myristate alone produced promising results in drug-release kinetics and skin-permeation profiles.

The influence of an erbium, Nd:YAG laser on the transdermal delivery of drugs across skin, was studied *in vitro*. Indomethacin and nalbuphine were selected for these studies. The authors found that the use of this technique for enhancing transdermal absorption of both lipophilic and hydrophilic drugs was acceptable since it allowed precise control of stratum corneum removal, and this ablation of SC can be reversible to the original normal status.[156,157]

Takahashi and Rytting[136] reported a novel approach to improve permeation of ondansetron, an antagonist of the 5-HT3 receptor used for the treatment of chemotherapy-induced emesis, across shed snakeskin as a model membrane. Oleic acid enhanced the permeation of ondansetron, probably in two ways: by a direct effect on the stratum corneum or via counter-ion formation of an ion-pair.

Venter et al.[137] reported on a comparative study of an *in situ* adapted diffusion cell and an *in vitro* Franz diffusion cell method for transdermal absorption of doxylamine. They found that excised skin might undergo sublethal injury (necrosis) during *in vitro* experiments.

Ilic et al.[138] described the microfabrication of individual 200-micron-diameter transdermal microconduits using high-voltage pulsing in salicylic acid and benzoic acid. They hypothesized that spatially localized electroporation of the multilamellar lipid bilayer membranes provides rapid delivery of salicylic acid to the keratin within corneocytes, leading to localized keratin disruption and then to a microconduit.

Recently, the FDA approved Ortho-McNeill's (J & J Co.) Ortho-EVRA as a transdermal patch containing ethinyl estradiol/norgestromin for contraception.

Lake and Pinnock[139] reported on a transdermal drug-in-adhesive estradiol patch system that is more acceptable to patients than the reservoir system for the treatment of postmenopausal estrogen deficiency. Characteristics of this patch system include ease of remembering once-weekly patch application, improved cosmetic appearance, and better adhesion.

The Cygnus transdermal fentanyl device showed great variability in the rate of fentanyl absorption, resulting in highly variable plasma fentanyl concentrations, but sometimes leading to toxicity. The currently available Duragesic transdermal fentanyl device has been contraindicated for postoperative analgesia. Vanbever et al.[179] used skin-electroporation techniques to improve the transdermal diffusion of fentanyl. According to Lehmann et al.,[173] however, the transdermal fentanyl patch, if properly used, could be effective in providing a background of analgesia in various pain states.

Ramachandran and Fleisher[140] discuss the feasibility of delivering drugs such as biphosphonates across the skin for the treatment of bone diseases. According to Zitzmann and Nieschlag,[143] transdermal systems provide the pharmacokinetic modality closest to natural diurnal variations in testosterone levels. Verma and Iyer[145] reported on controlled transdermal delivery of propranol using hydoxypropylmethylcelluslose matrices. In another study, estradiol transdermal system (OESCLIM) was developed for hormone replacement therapy (HRT), and it was shown that this system was as effective as Estraderm TTS at reducing vasomotor symptoms, even in highly symptomatic women.

Foldvari[150] investigated delivery of interferon (IFN) alpha, an antiviral agent used in the treatment of condylomata acuminata (genital warts), using lipid-based delivery systems (LBDS). They investigated the use of liposomes and fatty acylation as ways to increase IFN alpha delivery into human skin.

Chang et al.[144] used delta sleep-inducing peptide (DSIP), a peptide of nine amino acid residues, as a model drug to investigate the effects of pH, electric current, and enzyme inhibitors on the transdermal iontophoretic delivery of peptide drugs.

The polarities of four elastomers made of silicon oligomers of different viscosities were investigated by measuring the uptake of swelled solvent in different polarity solvents after 24, 48, and 72 hours of treatment. The solvent uptake provided a good characterization for the polarity of the inside of the matrix.

A proniosome-based transdermal system of LN was developed and extensively characterized, both *in vivo* and *in vitro*. The proniosomal structure was a liquid crystalline-compact niosomes hybrid, which could be converted into niosomes upon hydration. The system was evaluated *in vitro* for drug loading, rate of hydration (spontaneity), vesicle size, polydispersity, entrapment efficiency, and drug diffusion across rat skin. This study demonstrated the utility of proniosomal, transdermal-patch-bearing LN for effective contraception.[159,160]

Use of electroporation pulses as a physical penetration enhancer enabled delivery of a significant amount of cyclosporine-A (CSA) for the treatment of psoriasis. Transdermally delivered CSA was mostly bound to the skin, and only a small amount was seen to cross the full skin into the receiver compartment.[161,163]

According to Hippius et al.,[171] although topical drugs are usually applied at a convenient site, the target for the drug interaction may be systemic. Phonophoresis is the use of ultrasound to enhance the delivery of topically applied drugs. The purpose of their study was to investigate the *in vitro* penetration and the *in vivo* transport of flufenamic acid in dependence of ultrasound. Percutaneous absorption studies were performed in various *in vitro* models to determine the rate of drug absorption via the skin. These investigators designed a phonophoretic drug delivery system to study the influence of ultrasound on transmembrane transport of different drugs.

Dinslage et al.[174] reported on a new transdermal delivery system for pilocarpine in glaucoma treatment. They studied the intraocular pressure

(IOP)-lowering effects and the side effects of the new system (known as TDS). A substantial amount of pilocarpine was released from the TDS to the dermis, causing detectable plasma levels of pilocarpine at 12 and 20 hours after administration.

According to Thacharodi and Rao,[176] and Rao and Diwan,[162] membrane permeation-controlled transdermal delivery devices for the controlled delivery of nifedipine were developed using collagen and chitosan membranes as a rate-controlling membrane. To increase the stability of nifedipine in the systems, alginate gel was used as a drug reservoir. Drug release was found to depend on the type of membrane used to control the drug delivery, suggesting that drug delivery is efficiently controlled in this system by the rate-controlling membranes.

According to Pillai et al.,[153] epidermal enzymes play an important role in the process of differentiation of keratinocytes. Their preliminary study was undertaken to observe if topical enzyme treatment influenced permeation of compounds across the skin. Their study showed that phospholipase A2 significantly enhanced permeation of benzoic acid and mannitol, while it did not have any effect of the penetration of testosterone.

A homologous series of N-acetic acid esters of 2-pyrrolidone and 2-piperidinone were prepared and evaluated for their ability to enhance the skin content and flux of hydrocortisone 21-acetate in hairless mouse skin *in vitro*. Enhancement ratios (ER) were determined for flux (J), 24-hour diffusion cell receptor cell concentrations (Q24), and 24-hour full-thickness mouse skin steroid content (SC) and compared to control values. In this study, 2-oxopyrrolidine-alpha-acetic acid decyl ester showed the highest enhancement ratio of (SC).[166,167]

Transdermal systems bearing captopril were developed using a low-temperature casting method and aqueous-based polymers (e.g., Eudragit RL-100 and polyvinylpyrrolidone).[164,165]

Finally, developments continue for the transdermal delivery of old compounds, such as nitroglycerine, nicotine, isosorbide dinitrate, and insulin. Other developments have also been reported for drugs and therapeutic agents such as albuterol, chlorpheniramine maleate, nadolol, terbutaline sulfate, selegiline, ethylcellulose-polyvinyl pyrrolidone films containing diltiazem HCl and indomethacin, diclofenac diethyl ammonium in a pressure-sensitive adhesive system, Clonidine (M-5041T system), Zidovudine (AZT), pro-drug of gestodene, physostigmine (for organophosphate poisoning), propranolol (chitosan-based), tacrine for treating symptoms of Alzheimer's disease, and dideoxynucleoside-type anti-HIV drugs.[170–188]

X. Conclusion

Many factors must be considered in designing a delivery system for a drug to be applied via the skin. Certain aspects, such as drug stability, physical stability of the formulation, irritation and sensitization properties, preservation, and aesthetic acceptability, are all critical parameters. None of these

considerations can be neglected in developing a new drug for transdermal delivery. There is little doubt that the vehicle can grossly affect drug bioavailability and, thus, influence the clinical efficacy of the drug. Unfortunately, there is no blueprint that can be followed to ensure development of an optimal product. Much depends on the specific pharmacologic properties of the drug, its physicochemical properties, and its clinical function. In addition, there can be no assurance that maximizing drug penetration into the skin is, in every case, synonymous with optimizing drug delivery. Topical products can be applied to skin that has been completely stripped of its barrier properties, as well as to skin that is anatomically intact and enormously resistant to drug diffusion. These two situations only define the extremes as far as the diffusional resistance of skin is concerned. It should be recognized that the same topical product cannot be ideal, in terms of drug bioavailability, for every type of skin disease or for every patient.[92–95]

There is no doubt that the physicochemical properties of the drug determine the ease or difficulty with which it passes through the skin barrier. However, in view of recent evidence, it now seems clear that the vehicle must be regarded as something more than a solvent in which the drug is placed to ensure uniform contact with the skin surface. If one's intent is to manipulate the diffusion rate of a drug across the skin, there are two general mechanisms by which this might be accomplished. One is to change the degree of interaction between drug and vehicle (i.e., affect the drug's thermodynamic activity). The other is to produce changes in the stratum corneum that will affect its diffusional resistance. In general terms, one can describe these two approaches as involving either drug-vehicle interactions or vehicle-barrier interactions. Both effects are generally involved, and distinction of the specific mechanism may be difficult. Careful characterization of the physical properties of a delivery system and the solubility and partitioning properties of the drug in this system will aid considerably in analyzing subsequent *in vitro* and *in vivo* penetration data involving human skin.[96–106]

For the great majority of substances, it is diffusion through the stratum corneum that represents the rate-limiting step in percutaneous absorption. Almost all substances used as drugs can be expected to penetrate even intact skin to some degree. Even particles of considerable size appear to pass through skin, although the rates are infinitesimally small. Characteristically, the penetration rate of most drugs will be small, and only a fraction of the total applied to the skin will reach the systemic circulation and be excreted. Obviously, if a finite rate of absorption occurs, the drug will ultimately be completely absorbed if it remains on the skin surface. In practice, much of the drug, along with the debris of the vehicle in which it is applied, will be removed by contact with dressings, clothing, and other objects, or simply be washed off by the patient. Because the skin is a complex, biological barrier that is not yet fully understood, generalizations about its relative permeability to different types of compounds must be made with considerable caution.[56,107–117]

Transdermal therapy appears to be ready for a rapid expansion of rate-controlled administration of potent, nonallergenic agents with suitable

physicochemical properties where current methods of administration pose problems. By the mid-1990s, approximately 70% or more of all drugs potentially might have been delivered by transdermal delivery systems. However, because of the constraints imposed by drug potency, skin permeability, or topical reactions, transdermal administration may not become the preferred dosage route for a high percentage of drugs. Problems exist, such as cutaneous metabolism and the fact that a small volume of the skin has to deliver the entire load of a drug. Possibilities for future transdermal systems include making more use of pro-drugs, penetration enhancers, and specific nontoxic enzyme inhibitors. Certainly, a need exists for significant expansion in research on the fundamental understanding of skin metabolism as it affects drug transformation as well as pro-drug activation/inactivation.[118–121]

A specific challenge for future drug therapy is to efficiently deliver peptide drugs developed by the biotechnology industry. At present, it would not seem probable that simple application to the skin of a peptide would produce desirable clinical results. One possible approach may be to develop delivery devices that will synchronize the introduction of a suitable penetration enhancer into the stratum corneum together with the peptide. Another possibility would be to use iontophoresis, a technique that has been employed for a number of ionic drugs, and possibly use it in conjunction with penetration enhancers.[122–125]

Drug molecules may also be redesigned to achieve higher skin penetration. Most drugs in today's market are not only structured to elicit a particular pharmacological response, but also designed to have suitable solubilities, particularly with respect to oral and parenteral dosage forms. Perhaps more lipid-soluble molecules (pro-drugs) could be made from currently approved drugs to provide a more favorable prognosis for the transdermal approach in cases where drugs do not have the requisite physiochemical attributes.[81,126,127,168]

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