

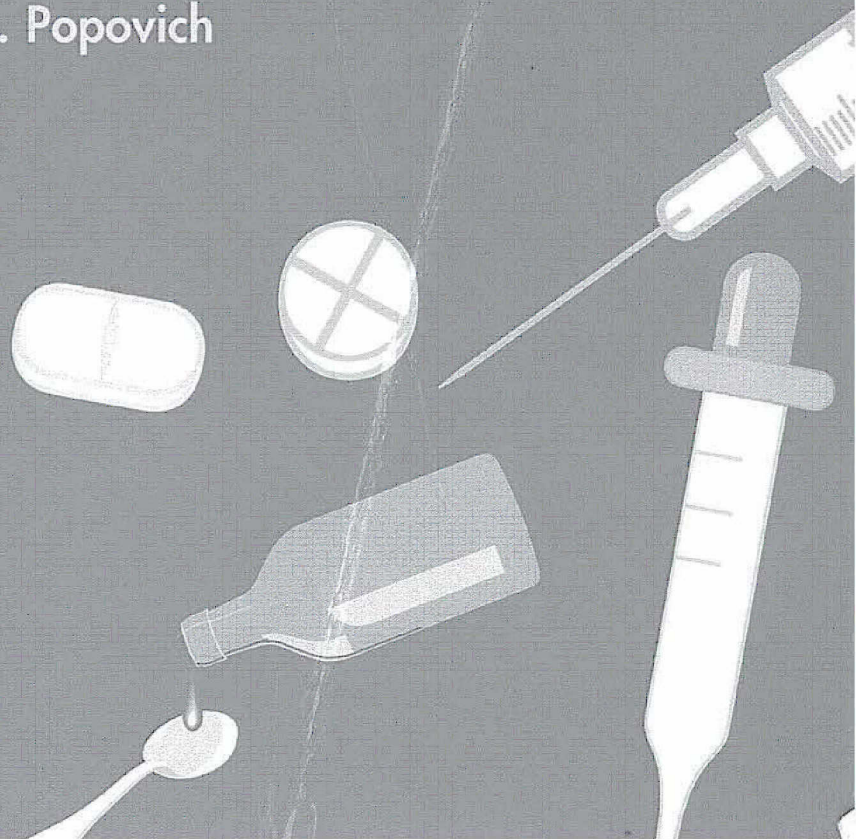
SEVENTH EDITION

PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS

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TRANSDERMAL DRUG DELIVERY SYSTEMS

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General Clinical Considerations in the Use of TDDSs

TRANSDERMAL DRUG delivery systems (TDDSs) facilitate the passage of therapeutic quantities of drug substances through the skin and into the general circulation for their systemic effects. The concept for the *percutaneous absorption* of drug substances was first conceived by Stoughton in 1965 (1). The first transdermal system, Transderm Scop [Ciba (now Novartis)] was approved by the Food and Drug Administration in 1979 for the prevention of nausea and vomiting associated with travel, particularly by sea.

Evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and/or its metabolites in the urine, and through the clinical response of the patient to the administered drug therapy. With transdermal drug delivery, the blood concentration needed to achieve therapeutic efficacy may be determined by comparative analysis of patient response to drug blood levels. For transder-

mal drug delivery, it is considered ideal if the drug penetrates through the skin to the underlying blood supply without drug buildup in the dermal layers (2). This is in direct contrast to the types of topical dosage forms discussed in the previous chapter, in which drug residence in the skin, the target organ, is desired.

As discussed in the previous chapter, the skin is comprised of the stratum corneum (the outer layer), the living epidermis, and the dermis, which together provide the skin's barrier layers to penetration by external agents (see Fig. 9.6). The film that covers the stratum corneum is comprised of sebum and sweat, but because of its varied composition and lack of continuity it is not a significant factor in drug penetration nor are the hair follicles and sweat and sebaceous gland ducts which comprise only a minor proportion of the skin's surface.

The percutaneous absorption of a drug generally results from the direct penetration of the drug

through the stratum corneum, a 10 to 15 μm thick layer of flat, partially desiccated nonliving tissue (3–4). The stratum corneum is composed of approximately 40% protein (mainly keratin) and 40% water, with the balance being lipid, principally as triglycerides, free fatty acids, cholesterol, and phospholipids. The lipid content is concentrated in the extracellular phase of the stratum corneum and forms to a large extent the membrane surrounding the cells. Because a drug's major route of penetration is through the intercellular channels, the lipid component is considered an important determinant in the first step of the absorption process (5). Once through the stratum corneum, drug molecules may then pass through the deeper epidermal tissues and into the dermis. When the drug reaches the vascularized dermal layer, it becomes available for absorption into the general circulation.

The stratum corneum, being keratinized tissue, behaves as a semipermeable artificial membrane, and drug molecules penetrate by passive diffusion. It is the major rate-limiting barrier to transdermal drug transport (6). Over most of the body, the stratum corneum has 15–25 layers of flattened corneocytes with an overall thickness of about 10 μm (6). The rate of drug movement across this skin layer depends on the drug concentration in the vehicle, its aqueous solubility, and the oil/water partition coefficient between the stratum corneum and the vehicle (7). Substances that possess both aqueous and lipid solubility characteristics are good candidates for diffusion through the stratum corneum as well as through the epidermal and dermal layers.

Factors Affecting Percutaneous Absorption

Not all drug substances are suitable for transdermal drug delivery. Among the factors playing a part in percutaneous absorption are the physical and chemical properties of the drug, including its molecular weight, solubility, partitioning coefficient and pKa, the nature of the carrier-vehicle and the condition of the skin. Although general statements applicable to all possible combinations of drug, vehicle, and skin condition are difficult to draw, the consensus of the majority of research findings may be summarized as follows (2–11).

1. Drug concentration is an important factor. Generally, the amount of drug percutaneously absorbed per unit of surface area per time interval increases as the concentration of the drug substance in the TDDS is increased.
2. More drug is absorbed through percutaneous absorption when the drug substance is applied to a larger surface area (e.g., a larger size TDDS).
3. The drug substance should have a greater physicochemical attraction to the skin than to the vehicle in which it is presented for the drug to leave the vehicle in favor of the skin. Some solubility of the drug in both lipid and water is thought to be essential for effective percutaneous absorption. In essence, the aqueous solubility of a drug determines the concentration presented to the absorption site and the partition coefficient influences the rate of transport across the absorption site. Drugs generally penetrate through the skin better in their unionized form. Polar drugs tend to cross the cell barrier through the lipid-rich regions (transcellular route) whereas the nonpolar drugs favor transport between cells (intercellular route) (6).
4. Drugs with molecular weights between 100 and 800 with adequate lipid and aqueous solubility can permeate skin. The ideal molecular weight of a drug for transdermal drug delivery is believed to be 400 or less.
5. The hydration of the skin generally favors percutaneous absorption. TDDS act as occlusive moisture barriers through which the sweat from the skin cannot pass, resulting in increased skin hydration.
6. Percutaneous absorption appears to be greater when the TDDS is applied to a skin site with a thin horny layer than with one that is thick.
7. Generally, the longer the period of time the medicated application is permitted to remain in contact with the skin, the greater will be the total drug absorption.

These general statements on percutaneous absorption apply to skin in the normal state. Skin that is abraded or cut will permit drugs to gain direct access to the subcutaneous tissues and the capillary network obviating the designed function of the TDDS.

Percutaneous Absorption Enhancers

There is great interest among pharmaceutical scientists to develop chemical permeation enhancers and physical methods that can increase the percutaneous absorption of therapeutic agents.

Chemical Enhancers

By definition, a chemical skin penetration enhancer *increases skin permeability by reversibly dam-*

aging or by altering the physicochemical nature of the stratum corneum to reduce its diffusional resistance (12). Among the alterations are increased hydration of the stratum corneum and/or a change in the structure of the lipids and lipoproteins in the intercellular channels through solvent action or denaturation (4, 13–17).

Some drugs have an inherent capacity to permeate the skin without need of chemical enhancers. However, in instances in which this is not the case, chemical permeation enhancers may be effective in rendering an otherwise impenetrable substance useful in transdermal drug delivery (17). More than 275 different chemical compounds have been cited in the literature as skin penetration enhancers including acetone, azone, dimethylacetamide, dimethylformamide, dimethylsulfoxide (DMSO), ethanol, oleic acid, polyethylene glycol, propylene glycol and sodium lauryl sulfate (13–15). The selection of a permeation enhancer in developing a TDDS should be based not only on its efficacy in enhancing skin permeation, but also on its dermal toxicity (low), and its physicochemical and biocompatibility with the system's other components (16).

Iontophoresis and Sonophoresis

In addition to chemical means, there are some physical methods being used to enhance transdermal drug delivery and penetration, namely, iontophoresis and sonophoresis (6,15,18–23). *Iontophoresis* involves the delivery of charged chemical compounds across the skin membrane using an applied electrical field. A number of drugs have been the subject of such iontophoretic studies, including lidocaine (18), dexamethasone, amino acids/peptides/insulin (19–20), verapamil (6), and propranolol (21). There is particular interest to develop alternative routes for the delivery of biologically active peptides. These agents are presently delivered by injection, because of their rapid metabolism and poor absorption after oral delivery. They are also poorly absorbed from the transdermal route, because of their large molecular size, ionic character and the general impenetrability of the skin (20). However, iontophoretic-enhanced transdermal delivery has shown some promise as a means for peptide/protein administration.

Sonophoresis, or high-frequency ultrasound, is also being studied as a means to enhance transdermal drug delivery (22–23). Among the agents examined have been hydrocortisone, lidocaine, and salicylic acid in such formulations as gels, creams, and lotions. It is thought that high-frequency ultra-

sound can influence the integrity of the stratum corneum and thus affect its penetrability.

Percutaneous Absorption Models

Skin permeability and percutaneous absorption have been the subject of numerous studies undertaken to define the underlying principles and to optimize transdermal drug delivery. Although many experimental methods and models have been used, they tend to fall into one of two categories: 1) *in vivo*, and 2) *in vitro* studies.

In Vivo Studies

In vivo skin-penetration studies may be undertaken for one or more of the following purposes (24):

1. To verify and quantify the cutaneous bioavailability of a topically applied drug;
2. To verify and quantify the systemic bioavailability of a transdermally delivered drug;
3. To establish bioequivalence of different topical formulations of the same drug substance;
4. To determine the incidence and degree of systemic toxicologic risk following the topical application of a specific drug/drug product; and
5. To relate resultant blood levels of drug in human to systemic therapeutic effects.

The most relevant studies are performed in humans; however, animal models may be used insofar as they may be effective as predictors of human response. Animal models include the weanling pig, rhesus monkey, and hairless mouse or rat (24–25). Biological samples used in drug penetration/drug absorption studies include skin sections, venous blood from the application site, blood from the systemic circulation and excreta (urine, feces and expired air) (24–28).

In Vitro Studies

Skin permeation testing may be performed *in vitro* using various skin tissues (human or animal whole skin, dermis or epidermis) in a diffusion cell (29). *In vitro* penetration studies using human skin are limited because of difficulties of procurement, storage, expense, and variability in permeation (30). Excised animal skins may also be variable in quality and permeation. Animal skins are much more permeable than human skin. One alternative that has been shown to be effective is shed snake skin (*Elaphe obsoleta*, black rat snake), which is nonliv-

ing, pure stratum corneum, hairless, and similar to human skin, but slightly less permeable (30–31). Also, the product Living Skin Equivalent (LSE) Testskin (Organogenesis, Inc.) was developed as an alternative for dermal absorption studies. The material is an organotypic coculture of human dermal fibroblasts in a collagen-containing matrix and a stratified epidermis composed of human epidermal keratinocytes. The material may be used in cell culture studies or in standard diffusion cells.

Diffusion cell systems are employed *in vitro* to quantify the release rates of drugs from topical preparations (32). In these systems, skin membranes or synthetic membranes may be employed as barriers to the flow of drug and vehicle, to simulate the biologic system. The typical diffusion cell has two chambers one on each side of the test diffusion membrane. A temperature-controlled solution of the drug to be contained in the TDDS is placed in one chamber and a receptor solution in the other chamber. When skin is used as the test membrane, it separates the two solutions. Drug diffusion through the skin may be determined by periodic sampling and assay of the drug content in the receptor solution. The skin may also be analyzed for drug content to show drug permeation rates and/or drug retention in the skin (29).

The USP describes the apparatus and procedure to determine the drug dissolution (drug release) of medication from a transdermal delivery system and provides an "Acceptance Table" against which the product must conform to meet the monograph standard for a given article (33). Commercial systems are available that utilize transdermal diffusion cells and autosampling systems to determine the release rates of drugs from transdermal systems (34).

Design Features of Transdermal Drug Delivery Systems (TDDSs)

Transdermal drug delivery systems (also often called transdermal "patches") are designed to support the passage of drug substances from the surface of the skin, through its various layers and into the systemic circulation. Examples of the configuration and composition of TDDSs are described in the text, presented in Table 10.1 and shown in Figures 10.1 through 10.4. Figures 10.5 through 10.8 depict the manufacture of TDDSs. Technically, TDDSs may be categorized into two types, monolithic and membrane-controlled systems.

Monolithic systems incorporate a drug matrix layer between backing and frontal layers (Fig. 10–3). The drug-matrix layer is composed of a polymeric

material in which the drug is dispersed. The polymer matrix controls the rate at which the drug is released for percutaneous absorption. The matrix may be of two types; with or without an excess of drug with regard to its equilibrium solubility and steady-state concentration gradient at the stratum corneum (21,35). In types having no excess, drug is available to maintain the saturation of the stratum corneum only as long as the level of drug in the device exceeds the solubility limit of the stratum corneum. As the concentration of drug in the device diminishes below the skin's saturation limit, the transport of drug from device to skin gradually declines (35). In systems that have an excess amount of drug present in the matrix, a drug reserve is present to assure continued drug saturation at the stratum corneum. In these instances, the rate of drug decline is less than in the type having no drug reserve.

In the preparation of monolithic systems, the drug and the polymer are dissolved or blended together, cast as the matrix and dried (21). The gelled matrix may be produced in sheet or cylindrical form, with individual dosage units cut and assembled between the backing and frontal layers. Most TDDSs are designed to contain an excess of drug and thus have drug-releasing capacity beyond the time frame recommended for replacement. This ensures continuous drug availability and absorption as used TDDSs are replaced on schedule with fresh ones.

Membrane-controlled transdermal systems are designed to contain a drug reservoir or "pouch", usually in liquid or gel form, a rate-controlling membrane, and backing, adhesive, and protecting layers (Fig. 10–2). Transderm-Nitro (Novartis) and Transderm-Scop (Novartis) are examples of this technology. Membrane-controlled systems have the advantage over monolithic systems in that as long as the drug solution in the reservoir remains saturated, the release rate of drug through the controlling membrane remains constant (21–22). In membrane systems, a small quantity of drug is frequently placed in the adhesive layer to initiate prompt drug absorption and pharmacotherapeutic effects on skin placement. Membrane-controlled systems may be prepared by preconstructing the delivery unit, filling the drug reservoir, and sealing, or by a process of lamination, which involves a continuous process of construction, dosing and sealing (Figs. 10.5 through 10.8).

In summary, either the drug delivery device or the skin may serve as the rate-controlling mechanism in drug transport from transdermal systems.

Table 10.1. Examples of Transdermal Drug Delivery Systems (40–44, 47–51)

Therapeutic Agent	TDDS	Design/Contents	Comments
Clonidine	Catapres-TTS (Boehringer Ingelheim)	Four-layered patch: (1) a backing layer of pigmented polyester film; (2) drug reservoir of clonidine, mineral oil, polyisobutylene, and colloidal silicon dioxide; (3) a microporous polypropylene membrane controlling the rate of drug delivery; and (4) an adhesive formulation of agents noted in (2) above.	Transdermal therapeutic systems designed to deliver a therapeutic dose of the antihypertensive drug clonidine at a constant rate for 7 days, permitting once-a-week dosing. TDDS generally applied to hairless or shaven areas of upper arm or torso.
Estradiol	Estraderm (Novartis)	Four-layered patch: (1) a transparent polyester film; (2) drug reservoir of estradiol and alcohol gelled with hydroxypropyl cellulose; (3) an ethylene-vinyl acetate copolymer membrane; and (4) an adhesive formulation of light mineral oil and polyisobutylene	Transdermal system designed to release 17 β -estradiol continuously. The transdermal patch is generally applied twice weekly over a cycle of 3 weeks with dosage frequency adjusted as required. The patch is generally applied to the trunk including the abdomen and buttocks, alternating sites with each application.
	Vivelle (Novartis)	Three-layered patch: (1) a translucent ethylene vinyl alcohol copolymer film; (2) estradiol in a matrix of a medical adhesive of polyisobutylene and ethylene vinylacetate copolymer; and (3) a polyester release liner which is removed prior to application.	Use and application is similar to the Estraderm TDDS.
	Climara (Berlex)	Three-layered system: (1) a translucent polyethylene film; (2) acrylate adhesive matrix containing estradiol; and (3) a protective liner of siliconized or fluoropolymer-coated polyester film which is removed prior to use.	Use and application similar to the Estraderm TDDS. System may be applied once weekly.
Fentanyl	Duragesic (Janssen)	Four-layered patch (1) a backing layer of polyester film; (2) drug reservoir of fentanyl and alcohol gelled with hydroxyethyl cellulose; (3) a rate-controlling ethylene-vinyl acetate copolymer membrane; and (4) a fentanyl-containing silicone adhesive.	Transdermal therapeutic system providing continuous 72-hour systemic delivery of fentanyl, a potent opioid analgesic. The drug is indicated in patients having chronic pain requiring opioid analgesia.

continued

Table 10.1. Examples of Transdermal Drug Delivery Systems (40-44, 47-51)

Therapeutic Agent	TDDS	Design/Contents	Comments
Nicotine	Habitrol (Novartis Consumer)	Multi-layered round patch: (1) an aluminized backing film; (2) a pressure-sensitive acrylate adhesive; (3) methacrylic acid copolymer solution of nicotine dispersed in a pad of nonwoven viscose and cotton; (4) an acrylate adhesive layer; and (5) a protective aluminized release liner that overlays the adhesive layer and is removed prior to use.	Transdermal therapeutic systems providing continuous release and systemic delivery of nicotine as an aid in smoking cessation programs. The patches listed vary somewhat in nicotine content and dosing schedules.
	NicoDerm CQ (SmithKline Beecham Consumer)	Multi-layered rectangular patch: (1) an occlusive backing of polyethylene/aluminum/polyester/ethylene-vinyl acetate copolymer; (2) drug reservoir of nicotine in an ethylene vinyl acetate copolymer matrix; (3) rate-controlling membrane of polyethylene; (4) polyisobutylene adhesive; and (5) protective liner removed prior to application.	
	Nicotrol (McNeil Consumer)	Multi-layered rectangular patch: (1) outer backing of laminated polyester film; (2) rate-controlling adhesive, nonwoven material, and nicotine; (3) disposable liner removed prior to use.	
	Prostep (Lederle)	Multi-layered round patch: (1) beige-colored foam tape and acrylate adhesive; (2) backing foil, gelatin and low-density polyethylene coating; (3) nicotine-gel matrix; (4) protective foil with well; and (5) release liner removed prior to use.	
Nitroglycerin	Deponit (Schwarz Pharma)	A three-layer system: (1) covering foil; (2) nitroglycerin matrix with polyisobutylene adhesive, plasticizer and release membrane; and (3) protective foil removed before use.	

continued

Table 10.1. Examples of Transdermal Drug Delivery Systems (40–44, 47–51)

<i>Therapeutic Agent</i>	<i>TDDS</i>	<i>Design/Contents</i>	<i>Comments</i>
	Nitro-Dur (Key)	Nitroglycerin in a gel-like matrix composed of glycerin, water, lactose, polyvinyl alcohol, povidone and sodium citrate sealed in a polyester-foil-polyethylene laminate.	TDDSs designed to provide the controlled release of nitroglycerin for treatment of angina. Daily application to chest, upper arm or shoulder.
	Transderm-Nitro (Novartis)	Four-layered patch: (1) backing layer of aluminized plastic; (2) drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide, and silicone medical fluid, (3) an ethylene/vinyl acetate copolymer membrane; and (4) silicone adhesive.	
Scopolamine	Transderm Scōp (Novartis Consumer)	Four-layered patch: (1) backing layer of aluminized polyester film; (2) drug reservoir of scopolamine, mineral oil, and polyisobutylene; (3) a microporous polypropylene membrane for rate delivery of scopolamine; and (4) adhesive of polyisobutylene, mineral oil, and scopolamine	TDDS for continuous release of scopolamine over a 3-day period as required for the prevention of nausea and vomiting associated with motion sickness. The patch is placed behind the ear. When repeated administration is desired, the first patch is removed and the second patch placed behind the other ear. Also FDA-approved for prevention of nausea associated with certain anesthetics and analgesics used in surgery.
Testosterone	Testoderm (Alza)	Three-layer patch: (1) backing layer of polyethylene terephthalate; (2) matrix film layer of testosterone and ethylene-vinyl acetate copolymer; and (3) adhesive strips of polyisobutylene and colloidal silicone dioxide.	The patch is placed on the scrotum in the treatment of testosterone deficiency.
	Androderm (SmithKline Beecham)	Five-layer patch: (1) backing film of ethylene vinyl acetate copolymer/polyester laminate; (2) drug reservoir gel of testosterone, alcohol, glycerin, glyceryl monooleate, methyl laurate gelled with an acrylic acid copolymer; (3) a microporous polyethylene membrane; (4) acrylic adhesive; (5) an adhesive polyester laminate.	The patch is placed on the back, abdomen, upper arms or thighs in the treatment of testosterone deficiency.

If the drug is delivered to the stratum corneum at a rate less than the absorption capacity, the *device* is the controlling factor; if the drug is delivered to the skin area to saturation, the *skin* is the controlling

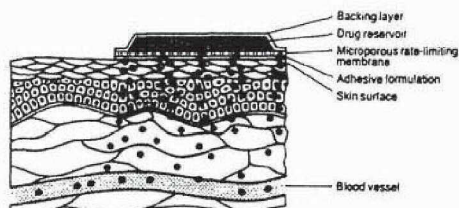


Fig. 10.1 Depiction of a four-layered therapeutic transdermal system showing the continuous and controlled amount of medication released from the system, permeating the skin and entering the systemic circulation. (Courtesy of Alza Corporation.)

factor to the rate of drug absorption. Thus, the rate of drug transport in all TDDSs, monolithic and membrane, is controlled by either artificial or natural (skin) membranes.

Transdermal drug delivery systems may be constructed of a number of layers, including 1) an occlusive backing membrane to protect the system from environmental entry and from loss of drug from the system or moisture from the skin; 2) a drug reservoir or matrix system to store and release the drug at the skin-site; 3) a release liner, which is removed before application and enables drug release; and 4) an adhesive layer to maintain contact with the skin after application. TDDSs are packaged in individual sealed packets to preserve and protect them until use.

The backing layer must be occlusive to retain skin moisture and hydrate the site of application

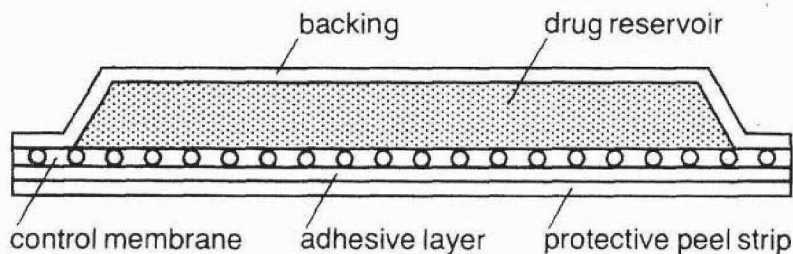


Fig. 10.2 The Transderm-Nitro Transdermal Therapeutic System (Summit). The patch delivers nitroglycerin through the skin directly into the blood stream for 24 hours. Transderm-Nitro is used to treat and prevent angina. The system consists of a water-resistant backing layer, a reservoir of nitroglycerin, followed by a semipermeable membrane to control precisely and predictably the release of medicine, and an adhesive layer to hold the system onto the skin. The adhesive layer also contains an initial priming dose of nitroglycerin to insure prompt release and absorption of the medication. (Courtesy of Summit Pharmaceuticals [Novartis]).

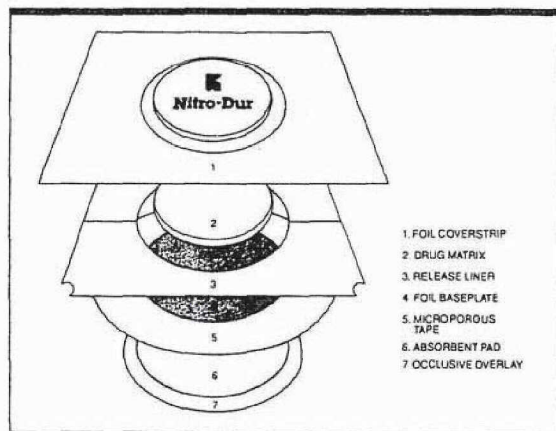


Fig. 10.3 Nitro-Dur Transdermal Infusion System, depicting the construction of the product. (Courtesy of Key Pharmaceuticals, Inc.)

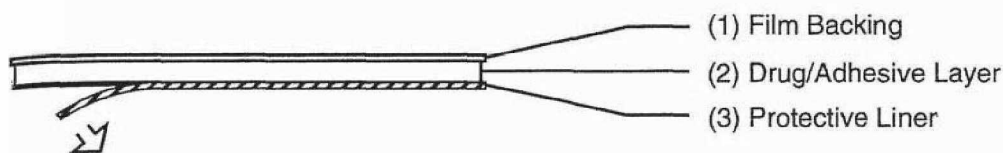


Fig. 10.4 Depiction of a two-layered transdermal drug delivery system, excluding the protective liner which is removed prior to application.

enabling increased drug penetration. Preferred backing materials are approximately 2–3 mm in thickness and have a low moisture vapor transmission rate of approximately $<20 \text{ g/m}^2/24 \text{ hr}$ (36). Films of polypropylene, polyethylene, and polyolefin which are transparent or pigmented are in use in TDDSs as backing liners.

The adhesive layer must be pressure sensitive, providing the ability to adhere to the skin with minimal pressure and remain in place for the intended period of wear. The adhesive should be non-irritating, allow easy peel-off after use, permit unimpeded drug flux to the skin and must be compatible with all other system components. The adhesive material is usually safety tested for skin compatibility including tests for skin irritation, skin sensitivity and cytotoxicity (37). In some TDDSs, the drug is contained within the adhesive layer. Polybutylacrylate is commonly used as the adhesive in TDDSs.

The drug release membranes are commonly made of polyethylene, with microporous structures of varying pore sizes to fit the desired specifications of the particular transdermal system.

Included among the design objectives of TDDSs are the following (2,8,35,38–39). A TDDS should do the following:

1. Deliver the drug at an optimal rate to the skin for percutaneous absorption at therapeutic levels;
2. Contain medicinal agents having the necessary physicochemical characteristics to release from the system and partition into the stratum corneum;
3. Occlude the skin to ensure the one-way flux of the drug into the stratum corneum;
4. Have a therapeutic advantage over other dosage forms and drug delivery systems;
5. Have components as adhesive, vehicle, and active agent which are not irritating or sensitizing to the skin; and
6. Adhere well to the patient's skin and have a patch-size, appearance, and site-placement that encourages patient acceptance.



Fig. 10.5 Pilot scale manufacture of transdermal patches. (Courtesy of Elan Corporation, plc.)

Advantages and Disadvantages of TDDSs

Among the advantages of TDDSs are the following:

1. They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal

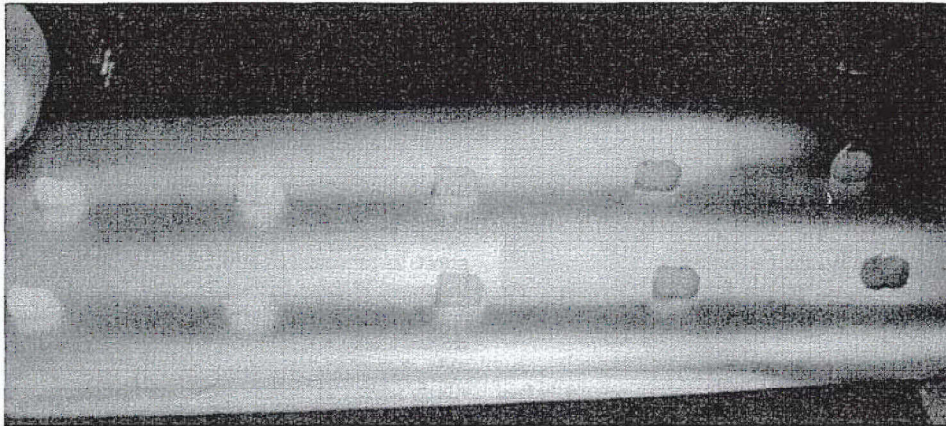


Fig. 10.6 Measured dose for reservoir, placed on web prior to sealing into the transdermal delivery system. (Courtesy of CIBA Pharmaceutical Company.)

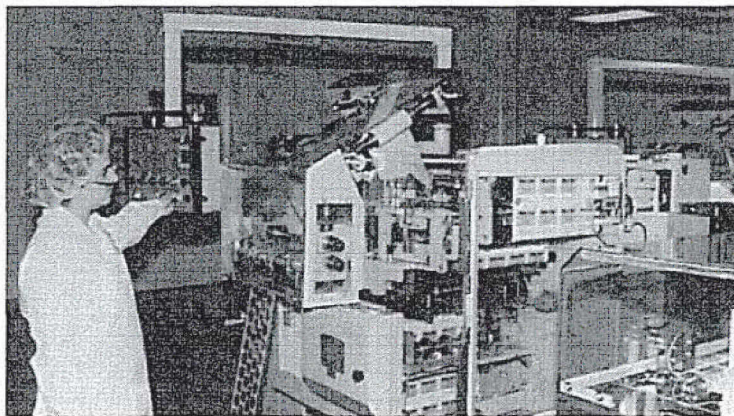


Fig. 10.7 Equipment utilized in the cutting and packaging of transdermal drug delivery patches. (Courtesy of Schering Laboratories)

pH, enzymatic activity and drug interactions with food, drink, or other orally administered drugs.

2. They can substitute for oral administration of medication when that route is unsuitable, as in instances of vomiting and/or diarrhea.
3. They avoid the *first-pass effect*, that is, the initial pass of a drug substance through the systemic and portal circulation following gastrointestinal absorption, thereby possibly avoiding the drug's deactivation by digestive and liver enzymes.
4. The systems are noninvasive, avoiding the inconvenience of parenteral therapy.
5. They provide extended therapy with a single application, thereby improving patient compliance

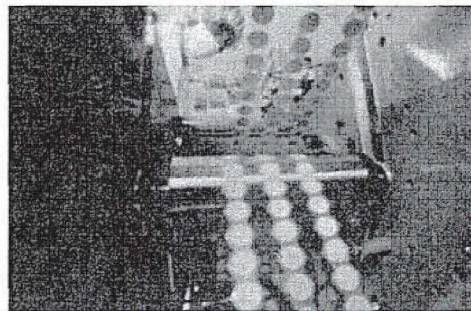


Fig. 10.8 Rotary die-cutting pressure executes the final step in manufacturing Transderm Scop systems prior to packaging. (Courtesy of Alza Corporation.)

over other dosage forms requiring more frequent dose administration.

6. The activity of drugs having short half-lives is extended through the reservoir of drug present in the therapeutic delivery system and its controlled release characteristics.
7. Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.
8. Ease of rapid identification of the medication in emergencies (e.g., nonresponsive, unconscious, or comatose patient) due to the physical presence, features and identifying-markings on the TDDS.

The disadvantages of TDDSs are:

1. Only relatively potent drugs are suitable candidates for transdermal delivery due to the natural limits of drug entry imposed by the skin's impermeability.
2. Some patients may develop contact dermatitis at the site of application due to one or more of the system components, necessitating discontinuation.

Examples of Transdermal Drug Delivery Systems

The following sections briefly describe some of the TDDS in current use. Table 10.1 describes the specific design components of representative examples of these systems.

Transdermal Scopolamine

As noted at the outset of this chapter, transdermal scopolamine was the first TDDS to receive FDA approval. Scopolamine, a belladonna alkaloid, is used to prevent travel-related motion sickness as well as the nausea and vomiting which results from the use of certain anesthetics and analgesics used in surgery.

The Transderm-Scop system is a circular flat patch 0.2 mm thick and 2.5 cm² in area (40). It is a four-layer system described in Table 10.1. The TDDS contains 1.5 mg of scopolamine and is designed to deliver approximately 1 mg of scopolamine at an approximately constant rate to the systemic circulation over the 3-day lifetime of the system. An initial priming dose of 200 mcg of scopolamine, contained in the adhesive layer of the system, saturates the skin binding sites and rapidly brings the plasma concentration to the re-

quired steady-state level. The continuous release of scopolamine through the rate-controlling microporous membrane maintains the plasma level constant. The rate of release is less than the skin's capability for absorption and thus, the membrane, not the skin, controls the delivery of the drug into the circulation.

The patch is worn in a hairless area behind the ear (Fig. 10.9). Because of the small size of the patch, the system is unobtrusive, convenient, and well-accepted by the patient. The TDDS is applied at least 4 hours before the antinausea effect is required. Only one disk should be worn at a time and may be kept in place for up to 3 days. If continued treatment is required, a fresh disk is placed behind the second ear. The most common side effects encountered are dryness of the mouth and drowsiness. Use, particularly in the geriatric population, also may result in an interference with orientation, cognition and memory. The TDDS is not intended for use in children and should be used with caution during pregnancy.



Fig. 10.9 *Transderm Scop (scopolamine) disc provides protection from the nausea and vomiting of motion sickness. (Courtesy of Alza Corporation and CIBA Consumer Pharmaceuticals).*

Transdermal Nitroglycerin

A number of nitroglycerin-containing TDDSs have been developed, including: Deponit (Schwarz), Minitran (3M Pharmaceuticals), Nitro-Dur (Key) and Transderm-Nitro (Novartis). The design of each of these systems briefly is described in Table 10.1. Each of these products maintains nitroglycerin drug delivery for 24 hours after application.

Nitroglycerin is a drug substance utilized widely in the prophylactic treatment of angina. The drug has a relatively low dose, short plasma half-life, high-peak plasma levels and inherent side-effects when taken sublingually (a popular route for its administration). It is rapidly metabolized by the liver when taken orally; this first-pass effect is obviated by the transdermal route.

The various commercially available TDDSs control the rate of drug delivery through a rate-controlling membrane and/or through controlled drug-release from the drug matrix or drug reservoir. When a TDDS is applied to the skin, nitroglycerin is absorbed continuously resulting in active drug reaching the target organs (heart, extremities) before being inactivated by the liver. Only a portion of the total nitroglycerin in the system is delivered over the usual 24 hours use-period; the remainder serves as the thermodynamic energy source to release the drug and remains in the system. For example, in the Deponit TDDS system, only 15% of the nitroglycerin content is delivered after 12 hours of use (41).

The rate of drug release is dependent upon the system. For example in the Transderm-Nitro system, 0.02 mg nitroglycerin is delivered per hour for every cm^2 of applied system size whereas in the Deponit system, each cm^2 delivers approximately 0.013 mg of nitroglycerin per hour (41–42). Systems of various surface areas and nitroglycerin content are provided to accommodate individual patient requirements. Because of different release rates, these systems cannot be used interchangeably by a patient.

The Nitro-Dur matrix is in a highly kinetic equilibrium state (43). Dissolved nitroglycerin molecules are constantly exchanging with adsorbed nitroglycerin molecules bound to the surfaces of the suspended lactose crystals. Sufficient nitroglycerin is adsorbed to the lactose in each matrix to maintain nitroglycerin in the fluid phase (aqueous glycerol) at a stable but saturated level (5 mg nitroglycerin/ cm^2 matrix). When the matrix is applied to the surface of the skin, nitroglycerin molecules migrate from solution in the matrix, by diffusion, to solution in the skin. To make up for the molecules lost to the

body, there is a shift of equilibrium in the matrix such that more molecules of nitroglycerin leave the crystals than are adsorbed from solution. When balance is restored, the solution is again at a saturated level. Thus, the crystals of lactose act as a "reservoir" of drug to maintain drug saturation in the fluid phase. The Nitro-Dur matrix, in turn, acts as a saturated "reservoir" for diffusive drug input through the skin (43).

The construction of the nitroglycerin systems are not all alike. For example, the Transderm-Nitro TDDS is a four-layer drug-pouch system, as described in Table 10.1 and depicted in Figure 10.2, whereas the Deponit TDDS is a thin two-layered matrix system resembling that shown in Figure 10.4.

Patients should be given explicit instructions regarding the use of nitroglycerin transdermal systems. Generally, these TDDSs are placed on the chest, with the back, upper arms, or shoulders (Fig. 10.10). The site selected should be free of hair, clean, and dry so that the patch adheres without difficulty. The use of the extremities below the knee or elbow is discouraged as are areas that are abraded or have lesions or cuts. The patient should understand that physical exercise and elevated ambient temperatures, e.g., sauna, may increase the absorption of nitroglycerin.

Transdermal Clonidine

In 1985, the first transdermal system for hypertension, Catapres TTS (clonidine transdermal therapeutic system, Boehringer Ingelheim), was marketed. The drug clonidine lends itself to transdermal delivery because of its lipid solubility, high volume of distribution and therapeutic effectiveness in low plasma concentrations. The TDDS provides controlled release of clonidine for 7 days. The product is a four-layered patch as described in Table 10.1.

Catapres TTS is available in several sizes with the amount of drug released proportional to the area of the patch-size. To ensure constant release over the seven-day use period, the drug content in the system is greater than the total amount of drug delivered. The energy source of drug release derives from the concentration gradient existing between a saturated solution of drug in the system and the much lower concentration prevailing in the skin. Clonidine flows in the direction of the lower concentration at a constant rate limited by a rate-controlling membrane (44).

The system is applied to a hairless area of intact skin on the upper outer arm or chest. After appli-

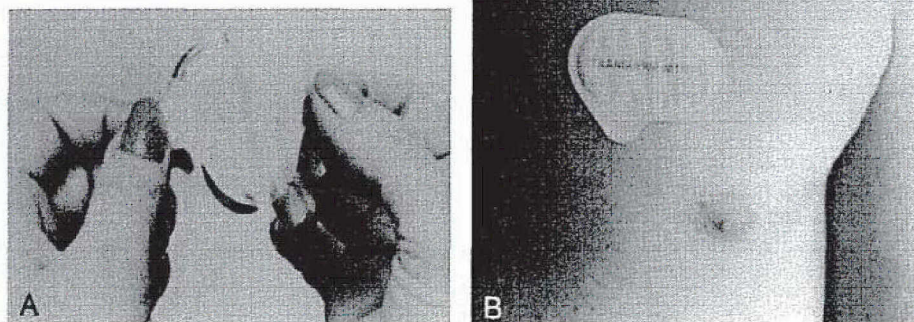


Fig. 10.10 *The Transderm-Nitro patch. Prior to applying to the skin, a plastic liner is removed exposing the adhesive side of the patch. Transderm-Nitro delivers nitroglycerin at a constant and predetermined rate through the skin directly into the bloodstream. The patch is designed to provide 24-hour protection against angina attacks. (Courtesy of Alza Corporation and CIBA Pharmaceuticals [Novartis]).*

cation, clonidine in the adhesive layer saturates the skin sites. Then, clonidine from the drug reservoir begins to flow through the rate-controlling membrane and through the skin to the systemic circulation. Therapeutic plasma clonidine levels are achieved 2 to 3 days after initial application. Application of a new system to a fresh skin site at weekly intervals maintains therapeutic plasma concentrations. If the patch is removed and not replaced with a new system, therapeutic plasma clonidine levels will persist for about 8 hours and then decline slowly over several days. Over this time period, blood pressure returns gradually to pretreatment levels. If the patient experiences localized skin irritation before completing 7 days of use, the system may be removed and replaced with a new one applied on a fresh skin site (44).

Transdermal Nicotine

Nicotine TDDSs are used as adjuncts (e.g., along with counseling) in smoking cessation programs. They have been shown to be an effective aid in quitting the smoking habit when used according to product-recommended strategies (45). In a blinded study, users of nicotine TDDSs are more than twice as likely to quit smoking than individuals wearing a placebo patch (45).

The nicotine TDDSs provide sustained blood levels of nicotine as "nicotine-replacement-therapy" to help the patient establish and sustain remission from smoking (46). Motivation to quit smoking is enhanced through the reduction of

withdrawal symptoms and by partially satisfying the nicotine craving and desired sensory feelings provided by smoking (46).

The commercially available patches contain from 7 to 22 mg of nicotine for daily application during the course of treatment ranging from about 6 to 12 weeks. Different treatment regimens are used for light versus heavy smokers. Examples of nicotine TDDSs are described in Table 10.1. A nicotine TDDS usually is applied to the arm or upper front torso, with patients advised not to smoke when wearing the system. The TDDS is replaced daily, with sites alternated. Some of the nicotine replacement programs provide a gradual reduction in nicotine dosage (patch strength) during the treatment program. Used TDDSs should be discarded properly because the retained nicotine content is poisonous to children and pets.

Transdermal Estradiol

The estrogen, estradiol, has been developed for transdermal delivery. The Estraderm (Novartis) TDDS delivers 17β -estradiol through a rate-limiting membrane continuously upon application to intact skin (47). Two systems (10 or 20 cm²) provide delivery of 0.05 or 0.1 mg estradiol per day. Estraderm is a four-layer TDDS as described in Table 10.1.

Estradiol is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause; female hypogonadism; female castration; primary ovarian failure; and atrophic conditions caused by deficient endogenous estrogen

production, such as atrophic vaginitis and kraurosis vulvae.

Orally administered estradiol is rapidly metabolized by the liver to estrone and its conjugates, giving rise to higher circulating levels of estrone than estradiol. In contrast, the skin metabolizes estradiol only to a small extent. Therefore, transdermal administration produces therapeutic serum levels of estradiol with lower circulating levels of estrone and estrone conjugates than does oral therapy and requires a smaller total dose. Research has demonstrated that postmenopausal women receiving either transdermal or oral therapy will obtain the desired therapeutic effects from both dosage forms, e.g., lower gonadotropin levels, lower percentages of vaginal parabasal cells, decreased excretion of calcium and lower calcium-to-creatinine ratio. Studies have also demonstrated that systemic side effects from oral estrogens can be reduced by using the transdermal dosage form. Because estradiol has a short half-life (~1 hour), transdermal administration of estradiol allows a rapid decline in blood levels after the transdermal system is removed, e.g., in a cycling regimen (47).

Therapy is usually administered on a cyclic schedule (e.g., 3 weeks of therapy followed by 1 week without) especially in women who have not undergone a hysterectomy. The transdermal system is applied to a clean dry area of the skin on the trunk of the body, either the abdomen or upper quadrant of the buttocks. The patch should not be applied to the waistline because tight clothing may damage or dislodge the system.

The Vivelle (Novartis) and the Climara (Berlex) estradiol TDDSs are two-layered matrix systems described in Table 10.1 and resembling that shown in Figure 10.4. The estradiol is contained in the adhesive layer (48–49). These systems are used in the same general manner as Estraderm TDDS; however, some of these systems are applied every 7 days.

Transdermal Testosterone

Testosterone transdermal systems, Testoderm (Alza) and Androderm (SmithKline Beecham), are available with various delivery rates as hormone replacement therapy in men who have an absence or deficiency of testosterone (50–51).

The Testoderm TDDS is a two-layer system as described in Table 10.1. For optimal absorption, it is applied to clean, dry scrotal skin that has been dry-shaved. Scrotal skin is reported to be at least five times more permeable to testosterone than other skin sites (50). The TDDS is placed on the scrotum

by stretching the scrotal skin with one hand and pressing the adhesive side of the TDDS against the skin with the other hand, holding it in place for about 10 seconds. The TDDS is applied daily, usually in the morning to mimic endogenous testosterone release (52). Optimum serum levels are reached within 2 to 4 hours after application. The patch is worn 22 to 24 hours daily for 6 to 8 weeks.

The Androderm TDDS is designed to be applied nightly to a clean, dry, unabrased area of the skin of the back, abdomen, upper arms or thighs. It should not be applied to the scrotum (51). The five-layer system is described in Table 10.1.

Other Transdermal Therapeutic Systems

In addition to the drugs currently incorporated into TDDSs, others are under study, including: diltiazem, isosorbide dinitrate, propranolol, nifedipine, mepindolol and verapamil, cardiovascular agents; levonorgestrel/estradiol for hormonal contraception, physostigmine and xanomeline for Alzheimer's disease therapy, naltrexone and methadone for substance addiction, buspirone for anxiety, bupropion for smoking cessation, and papaverine for male impotence.

General Clinical Considerations in the Use of TDDSs

The patient should be advised of the following general guidelines as well as product-specific instructions in the use of TDDSs (53–54).

1. Percutaneous absorption may vary according to the site of application. There is a preferred general application site stated in the literature/package insert for each product. The patient should be advised of the importance of using the recommended site and rotating locations within that site in the application of replacement patches. Rotating locations is important to allow the skin beneath a patch to regain its normal permeability characteristics after being occluded and also to prevent the possibility of skin irritation. Skin sites may be reused after a week.
2. TDDSs should be applied to clean dry skin areas that are relatively free of hair and not oily, irritated, inflamed, broken or calloused. Wet or moist skin can accelerate drug permeation beyond that which is intended. Oily skin can affect the adhesion of the patch. If hair is present at the intended site, it should be carefully cut and not

wet-shaven nor should a depilatory agent be used since the latter can remove the outermost layers of the stratum corneum and affect the designed rate and extent of drug permeation.

3. Use of skin lotions should be avoided at the application site because they affect skin hydration and also can alter the partition coefficient between the drug in the TDDS and the skin.
 4. TDDSs should not be physically altered by cutting (as in an attempt to reduce the dose) since this would destroy the integrity of the system.
 5. A TDDS should be removed from its protective package, being careful not to tear or cut into the unit. The protective backing should be removed to expose the adhesive layer while being careful not to touch the adhesive surface (which sometimes contains drug) to the fingertips. The TDDS should be pressed firmly against the skin-site with the heel of the hand for about 10 seconds to assure uniform contact and adhesion.
 6. A TDDS should be placed at a site that is not subject to being rubbed off by clothing or movement (as the belt line). TDDSs generally may be left on when showering, bathing or swimming. Should a TDDS prematurely dislodge, an attempt may be made to reapply it, or it may be replaced with a fresh system, the latter being worn for a full time period before it is replaced.
 7. A TDDS should be worn for the full period of time stated in the product's instructions. Following that period, it should be removed and replaced with a fresh system as directed.
 8. The patient or caregiver should be instructed to cleanse the hands thoroughly before and after applying a TDDS. Care should be taken not to rub the eyes or touch the mouth during handling of the system.
 9. If the patient exhibits sensitivity or intolerance to a TDDS or if undue skin irritation results, the patient should seek reevaluation.
 10. Upon removal, a used TDDS should be folded in half with the adhesive layer together so that it cannot be reused. The used patch, which contains residual drug, should be placed in the replacement patch's package pouch and discarded in a manner safe to children and pets.
2. Black CD. Transdermal drug delivery systems. *US Pharm* 1982;1:49.
 3. Shah VP, Behl CR, Flynn GL, et al. Principles and criteria in the development and optimization of topical therapeutic products. *Pharm Res* 1992;9:1107-1111.
 4. Walters KA. Percutaneous absorption and transdermal therapy. *Pharm Tech* 1986;10:30-42.
 5. Hadgraft J. Structure activity relationships and percutaneous absorption. *J Controlled Release* 1991;25:221-226.
 6. Ghosh TK, Banga AK. Methods of enhancement of transdermal drug delivery: part I, physical and biochemical approaches. *Pharm Tech* 1993;17:72-98.
 7. Surber C, et al. Optimization of topical therapy: partitioning of drugs into stratum corneum. *Pharm Res* 1990;7:1320-1324.
 8. Cleary GW. *Transdermal concepts and perspectives*. Miami, FL: Key Pharmaceuticals, 1982.
 9. Melendres JL, et al. In vivo percutaneous absorption of hydrocortisone: multiple-application dosing in man. *Pharm Res* 1992;9:1164.
 10. Barr M. Percutaneous absorption. *J Pharm Sci* 1962;51:395-409.
 11. Idson B. Percutaneous absorption. *J Pharm Sci* 1975;64:901-924.
 12. Shah VP, Peck CC, Williams RL. Skin penetration enhancement: clinical pharmacological and regulatory considerations. In: Walters KA and Hadgraft J, eds. *Pharmaceutical skin penetration enhancement*. New York: Dekker, 1993.
 13. Osborne DW, Henke JJ. Skin penetration enhancers cited in the technical literature. *Pharm Tech* 1997;21:50-66.
 14. Idson B. Percutaneous absorption enhancers. *Drug Cosmetic Ind* 1985;137:30.
 15. Rolf D. Chemical and physical methods of enhancing transdermal drug delivery. *Pharm Tech* 1988;12:130-139.
 16. Ghosh TK, Banga AK. Methods of enhancement of transdermal drug delivery: part IIA, chemical permeation enhancers. *Pharm Tech* 1993;17:62-90.
 17. Ghosh TK, Banga AK. Methods of enhancement of transdermal drug delivery: part IIB, chemical permeation enhancers. *Pharm Tech* 1993;17:68-76.
 18. Riviere JE, Monteiro-Riviere NA, Inman AO. Determination of lidocaine concentrations in skin after transdermal iontophoresis: effects of vasoactive drugs. *Pharm Res* 1992;9:211-219.
 19. Green PG, Hinz RS, Cullander C, Yamane G, Guy RH. Iontophoretic delivery of amino acids and amino acid derivatives across the skin in vitro. *Pharm Res* 1991;8:1113-1120.
 20. Choi HK, Flynn GL, Amidon GL. Transdermal delivery of bioactive peptides: the effect of n-decylmethyl sulfoxide, pH, and inhibitors on enkephalin metabolism and transport. *Pharm Res* 1990;7:1099-1106.
 21. D'Emanuele A, Staniforth JN. An electrically modulated drug delivery device III: factors affecting drug stability during electrophoresis. *Pharm Res* 1992;9:312-315.

References

1. Stoughton RD. Percutaneous absorption. *Toxicol Appl Pharmacol* 1965;7:1-8.

22. Bommannan D, Okuyama H, Stauffer P, Guy RH. Sonophoresis I: the use of high-frequency ultrasound to enhance transdermal drug delivery. *Pharm Res* 1992;9:559-564.
23. Bommannan D, Menon GK, Okuyama H, Elias PM, Guy RH. Sonophoresis II: examination of the mechanism(s) of ultrasound-enhanced transdermal drug delivery. *Pharm Res* 1992;9:1043-1047.
24. Shah VP, et al. In vivo percutaneous penetration/absorption. *Pharm Res* 1991;8:1071-1075.
25. Bronaugh RL, Stewart RF, Congdon ER. Methods for in vitro percutaneous absorption studies II. Animal models for human skin. *Toxicol Appl Pharmacol* 1982;62:481-488.
26. Nugent FJ, Wood JA. Methods for the study of percutaneous absorption. *Canadian J Pharm Sci* 1980;15: 1-7.
27. Addicks W, et al. Topical drug delivery from thin applications: theoretical predictions and experimental results. *Pharm Res* 1990;7:1048-1054.
28. Kushla GP, Zatz JL. Evaluation of a noninvasive method for monitoring percutaneous absorption of lidocaine in vivo. *Pharm Res* 1990;7:1033-1037.
29. Chaisson D. Dissolution performance testing of transdermal systems. *Dissolution Technologies* 1995; 2:8-11.
30. Itoh T, Magavi R, Casady RL, Nishihata T, Rytting JH. A method to predict the percutaneous permeability of various compounds: shed snake skin as a model membrane. *Pharm Res* 1990;7:1302-1306.
31. Itoh T, Wasinger L, Turunen TM, Rytting JH. Effects of transdermal penetration enhancers on the permeability of shed snakeskin. *Pharm Res* 1992;9: 1168-1172.
32. Rolland A, Demichelis G, Jamouille JC, Shroot B. Influence of formulation, receptor fluid, and occlusion, on in vitro drug release from topical dosage forms, using an automated flow-through diffusion cell. *Pharm Res* 1992;9:82-86.
33. United States Pharmacopeia, 23rd ed. Rockville, MD: United States Pharmacopeial Convention, Inc., 1995.
34. Microette Transdermal Diffusion Cell Autosampling System. Chattsworth CA: Hanson Research Corporation, 1992.
35. Good WR. Transdermal drug-delivery systems. *Medical Device & Diagnostic Ind* 1986;8:37-42.
36. Godbey KL. Development of a novel transdermal drug delivery backing film with a low moisture vapor transmission rate. *Pharm Tech* 1997;21:98-107.
37. 3M transdermal drug delivery components. St. Paul, MN: 3M, 1996.
38. Fara JW. Short- and long-term transdermal drug delivery systems. In: *Drug delivery systems*, Pharm Tech. Springfield, OR: Aster Publishing Corporation, 1983:33-40.
39. Shaw JE, Chadrasekaran SK. Controlled topical delivery of drugs of systemic action. *Drug Metab Rev* 1978;8:223.
40. Transderm-Scop Transdermal Therapeutic System: professional literature. Summit, NJ: Novartis Consumer Pharmaceuticals, 1998.
41. Deponit Nitroglycerin Transdermal Delivery System: professional literature. Milwaukee, WI: Schwarz Pharma, 1998.
42. Transderm-Nitro Transdermal Therapeutic System: professional literature. East Hanover, NJ: Novartis Pharmaceuticals, 1998.
43. Nitro-Dur Transdermal Infusion System: professional literature. Kenilworth, NJ: Key Pharmaceuticals, 1998.
44. Catapres-TTS: professional literature. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, 1998.
45. Fiore MC, Smith SS, Jorenby DE, Baker TB. The effectiveness of the nicotine patch for smoking cessation. *JAMA* 1994;271:1940-1947.
46. Wongwiwatthanakul S, Jack HM, Popovich NG. Smoking cessation: part 2—pharmacologic approaches. *JAPhA* 1998;38:339-353.
47. Estraderm Estradiol Transdermal System: professional literature. East Hanover, NJ: Novartis Pharmaceuticals, 1998.
48. Vivelle Estradiol Transdermal System: professional literature. East Hanover, NJ: Novartis Pharmaceuticals, 1998.
49. Climara Estradiol Transdermal System: professional literature. Wayne, NJ: Berlex Laboratories, 1998.
50. Testoderm Testosterone Transdermal System: professional literature. Palo Alto, CA: Alza Pharmaceuticals, 1998.
51. Androderm Testosterone Transdermal System: professional literature. Philadelphia, PA: SmithKline Beecham Pharmaceuticals, 1998.
52. Levien T, Baker DE. Reviews of transdermal testosterone and liposomal doxorubicin. *Hosp Pharm* 1996;31:973-988.
53. Black CD. A pharmacists guide to the use of transdermal medication. Washington DC: The American Pharmaceutical Association, 1996.
54. Berba J, Banakar U. Clinical efficacy of current transdermal drug delivery systems: a retrospective evaluation. *Am Pharm* 1990;NS30:33-41.