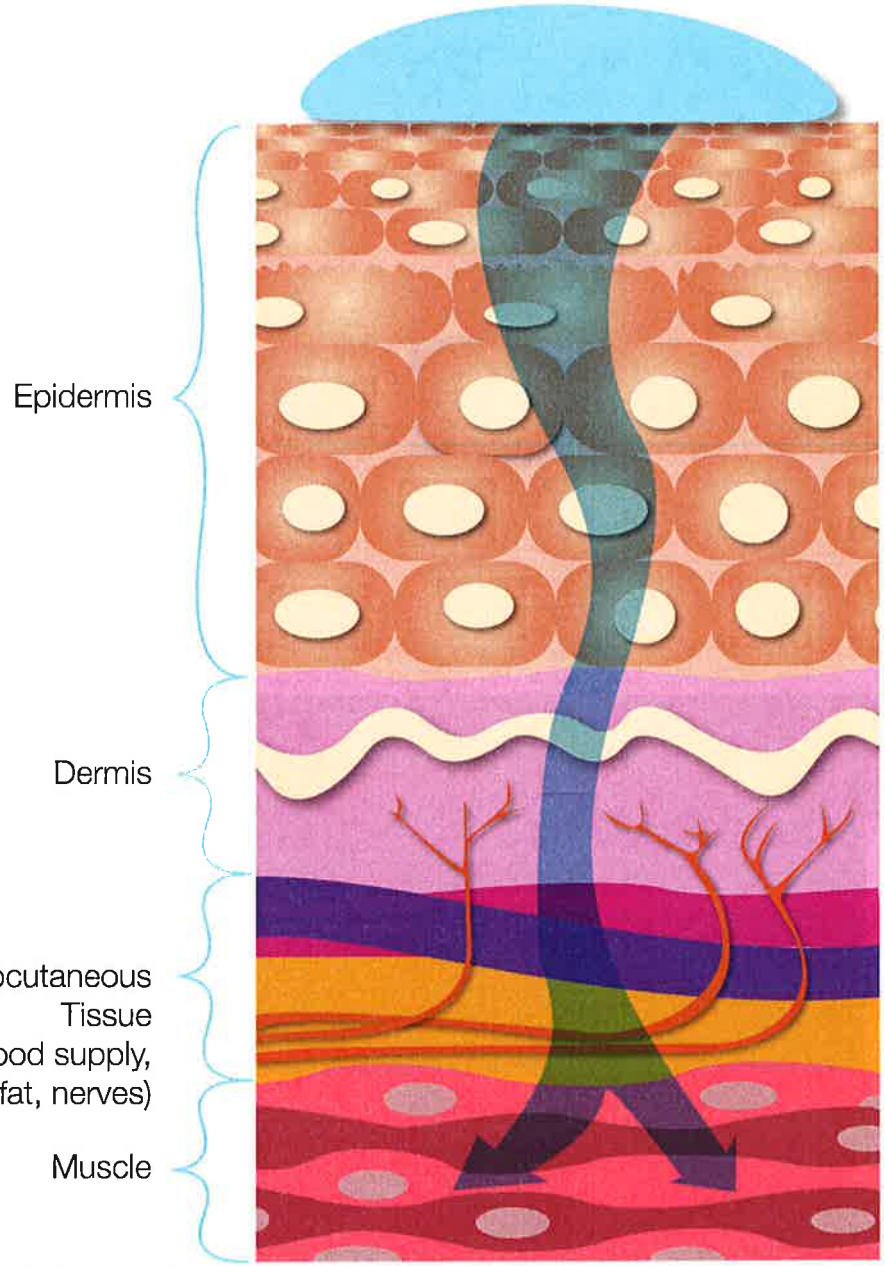
Transdermals:

The Skin as Part of a *Drug Delivery System*



Loyd V. Allen, Jr., PhD, RPh

Abstract

Transdermal delivery of drugs is effective and widely used to treat many different conditions. Transdermal drug delivery can be "individualized" for each patient by changing the drugs used, their concentrations, and the formulation. This type of drug delivery is routinely used for delivery of hormones, pain medications, nonsteroidal anti-inflammatory drugs, antinauseant medications, and many, many others. This article discusses the mechanism, the factors involved, the different penetration enhancers, how to control the rate of delivery, and provides some of the advantages and disadvantages of transdermal drug delivery.

***Dr. Loyd V. Allen, Jr.** is the editor-in-chief for the* International Journal of Pharmaceutical Compounding, *Edmond, Oklahoma.*

Transdermal (TD) drug delivery involves the passage of therapeutic quantities of drug substances through the skin and into the general circulation for systemic effects. Numerous manufactured drug products (e.g., gels, creams, patches, ointments) are on the market and are routinely compounded utilizing different technologies for enhancing the amount of drug delivered through the skin. Evidence of actual percutaneous drug absorption may be found through one or all of the following:

- Measurable blood levels of the drug
- Detectable excretion of the drug and/or its metabolites in the urine
- Clinical response of the patient to the therapy

Not all three of these evidences may necessarily occur in every situation. For transdermal drug delivery, it is considered ideal for the drug to migrate through the skin to the underlying blood supply without buildup in the dermal layers.

How Transdermals Work

MECHANISM

Percutaneous absorption of a drug generally results from direct penetration of the drug through the stratum corneum (SC), a 10- to 15-micrometer thick layer of flat, partially desiccated, nonliving tissue. The SC 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 SC 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 absorption. Once through the SC, drug molecules may 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.

(Antinauseant/Motion Sickness)

Rx SCOPOLAMINE HYDROBROMIDE 0.25-MG/0.1-ML PLURONIC LECITHIN ORGANOGEL

For 100 mL

Scopolamine hydrobromide		250 mg
Soy lecithin:isopropyl palmitate solution		25 mL
Buffer solution (pH 5)		2.5 mL
Pluronic F-127 20% gel	qs	100 mL

METHOD OF PREPARATION

1. Calculate the quantity of each ingredient required for the prescription.
2. Weigh and/or measure each ingredient accurately.
3. Dissolve the scopolamine hydrobromide in the pH 5 buffer solution.
4. Add the soy lecithin:isopropyl palmitate solution to the ingredients in step 3 and mix well.
5. Add sufficient Pluronic F-127 20% gel to make 100 mL and mix thoroughly.
6. Package and label.

Rx PROMETHAZINE 25-MG/ML PLURONIC LECITHIN ORGANOGEL

For 100 mL

Promethazine hydrochloride		2.5 g
Ethoxydiglycol		5 mL
Lecithin:isopropyl palmitate 1:1 solution		22 mL
Pluronic F-127 20% gel	qs	100 mL

METHOD OF PREPARATION

1. Calculate the quantity of each ingredient required for the prescription.
2. Weigh and/or measure each ingredient accurately.
3. Mix the promethazine hydrochloride with the ethoxydiglycol to form a smooth paste.
4. Add the soy lecithin:isopropyl palmitate solution and mix well.
5. Add sufficient Pluronic F-127 20% gel to make 100 mL and mix thoroughly using a shear mixing method.
6. Package and label.

Rx DEXAMETHASONE 1.2%, LORAZEPAM 0.1%, HALOPERIDOL 0.1%, DIPHENHYDRAMINE HYDROCHLORIDE 2.4% AND METOCLOPRAMIDE HYDROCHLORIDE 2.4% IN PLURONIC LECITHIN ORGANOGEL

For 100 mL

Dexamethasone		1.2 g
Lorazepam		100 mg
Haloperidol		100 mg
Diphenhydramine hydrochloride		2.4 g
Metoclopramide hydrochloride		2.4 g
Ethoxydiglycol		10 mL
Lecithin:isopropyl palmitate 1:1 solution		22 mL
Pluronic F-127 20% gel	qs	100 mL

METHOD OF PREPARATION

1. Calculate the quantity of each ingredient required for the prescription.
2. Weigh and/or measure each ingredient accurately.
3. Mix the powders together.
4. Incorporate the ethoxydiglycol to form a smooth paste.
5. Add the soy lecithin:isopropyl palmitate solution and mix well.
6. Add sufficient Pluronic F-127 20% gel to make 100 mL and mix thoroughly using a shear mixing method.
7. Package and label.

The SC, 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. Over most of the body, the SC has 15 to 25 layers of flattened corneocytes with an overall thickness of about 10 micrometer. The rate of drug movement across this layer generally depends on its concentration, aqueous solubility, and the oil–water partition coefficient between the SC and the vehicle. Substances with both aqueous and lipid solubility characteristics are good candidates for diffusion through the SC, epidermis, and dermis.

(Anxiolytic)

Rx BUSPIRONE HYDROCHLORIDE 2.5 MG/0.1 ML IN PLURONIC LECITHIN ORGANOGEL

For 100 mL

Buspirone hydrochloride		2.5 g
Ethoxydiglycol		10 mL
Lecithin:isopropyl palmitate 1:1 solution		22 mL
Pluronic F-127 20% gel	qs	100 mL

METHOD OF PREPARATION

1. Calculate the quantity of each ingredient required for the prescription.
2. Weigh and/or measure each ingredient accurately.
3. Mix the buspirone hydrochloride with the ethoxydiglycol to form a smooth paste.
4. Add the soy lecithin:isopropyl palmitate solution and mix well.
5. Add sufficient Pluronic F-127 20% gel to make 100 mL and mix thoroughly using a shear mixing method.
6. Package and label.

Rx LORAZEPAM 1 MG/ML IN PLURONIC LECITHIN ORGANOGEL

For 100 mL

Lorazepam		100 mg
Ethoxydiglycol		10 mL
Lecithin:isopropyl palmitate 1:1 solution		22 mL
Pluronic F-127 20% gel	qs	100 mL

METHOD OF PREPARATION

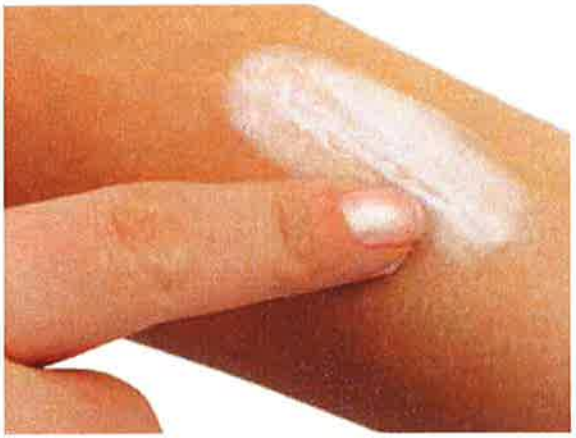
1. Calculate the quantity of each ingredient required for the prescription.
2. Weigh and/or measure each ingredient accurately.
3. Mix the lorazepam with the ethoxydiglycol to form a smooth paste.
4. Add the soy lecithin:isopropyl palmitate solution and mix well.
5. Add sufficient Pluronic F-127 20% gel to make 100 mL and mix thoroughly using a shear mixing method.
6. Package and label.

Research Summary

FACTORS INVOLVED

Not all drug substances are suitable for transdermal delivery. Among the factors playing a part in percutaneous absorption are the physical and chemical properties of the drug, including its molecular weight, solubility, partition coefficient, dissociation constant (pK_a), 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, most research findings may be summarized as follows:

1. Generally, the amount of drug absorbed per unit of surface area per time interval increases with an increase in the concentration of the drug in the dosage form.
2. The larger the area of application, the more drug is absorbed.
3. The drug should have a greater physicochemical attraction to the skin than to the formulation vehicle so that the drug will 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 the skin better in their nonionized form. Nonpolar drugs tend to cross the cell barrier through the lipid-rich regions (transcellular route), whereas the polar drugs favor transport between cells (intercellular route).
4. Drugs with molecular weights of 100 to 800 and 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. Hydration of the skin generally favors percutaneous absorption. The dosage form often acts as an occlusive



moisture barrier through which sweat cannot pass, increasing skin hydration.

6. Percutaneous absorption appears to be greater when the dosage form is applied to a site with a thin horny layer than with a thick one.
7. Generally, the longer the medicated application is permitted to remain in contact with the skin, the greater is the total drug absorption.

(Hormone Replacement Therapy)

Rx PROGESTERONE 10% TOPICAL CREAM

For 100 g

Progesterone, micronized		10 g
Glycerin		5 mL
Oil-in-water cream vehicle	qs	100 g

METHOD OF PREPARATION

1. Calculate the quantity of each ingredient required for the prescription.
2. Weigh and/or measure each ingredient accurately.
3. Add the glycerin to the micronized progesterone and form a smooth paste.
4. Incorporate the cream vehicle geometrically and mix until uniform. *Note: As an option, run through a roller ointment mill.*
5. Package and label.

Rx ESTRADIOL 0.5-MG/ML TOPICAL GEL

For 100 mL

Estradiol	50 mg
70% Isopropyl alcohol	71 mL
Carbomer 940	500 mg
Triethanolamine	670 mg
Purified water	28 mL

METHOD OF PREPARATION

1. Calculate the quantity of each ingredient required for the prescription.
2. Weigh and/or measure each ingredient accurately.
3. Dissolve the estradiol in the 70% isopropyl alcohol.
4. Add the carbomer 940 slowly to this mixture, stirring constantly. *Note: A blender or high-speed mixer can be used.*
5. Add the triethanolamine to the purified water.
6. Add the triethanolamine solution to the alcohol solution by slowly stirring. Mix thoroughly until the gel is formed. *Note: Slow stirring minimizes the introduction of air into the product.*
7. Package and label.

Rx ESTRADIOL 2-MG/ML VAGINAL GEL

For 100 g

Estradiol	200 mg
Polysorbate 80	1 g
Methylcellulose 2% gel	99 g

METHOD OF PREPARATION

1. Calculate the quantity of each ingredient required for the prescription.
2. Weigh and/or measure each ingredient accurately.
3. Levigate the estradiol with the polysorbate 80.
4. Add the methylcellulose 2% gel geometrically and mix thoroughly.
5. Package and label.

Rx TESTOSTERONE:MENTHOL EUTECTIC MIXTURE

For 100 g

Testosterone	31.6 g
Menthol	68.4 g
Methyl alcohol	qs

METHOD OF PREPARATION

1. Calculate the quantity of each ingredient required for the prescription.
2. Weigh and/or measure each ingredient accurately.
3. Use sufficient methyl alcohol to dissolve both the testosterone and menthol.
4. Allow the alcohol to evaporate while occasionally stirring the mixture. *Note: It can take a day or two to evaporate to dryness.*
5. Pulverize the mixture thoroughly after it dries and store it in a tight, light resistant container.

Rx TESTOSTERONE:MENTHOL EUTECTIC OINTMENT (2% TESTOSTERONE)

For 100 g

Testosterone:menthol eutectic mixture (formula above)	4.33 g
Hydrophilic petrolatum/ Aquabase/Aquaphor	95.67 g

METHOD OF PREPARATION

1. Calculate the quantity of each ingredient required for the prescription.
2. Weigh and/or measure each ingredient accurately.
3. Mix the testosterone:menthol eutectic mixture with a small quantity of the base.
4. Incorporate the remaining drug geometrically into the base and thoroughly mix.
5. Package and label.

(Nonsteroidal Anti-inflammatory Drug Gel)

Rx KETOPROFEN 5% IN PLURONIC LECITHIN ORGANOGEL

For 100 mL

Ketoprofen		5 g
Ethoxydiglycol		10 mL
Lecithin:isopropyl palmitate 1:1 solution		22 mL
Pluronic F-127 20% gel	qs	100 mL

METHOD OF PREPARATION

1. Calculate the quantity of each ingredient required for the prescription.
2. Weigh and/or measure each ingredient accurately.
3. Mix the ketoprofen with the ethoxydiglycol to form a smooth paste.
4. Add the soy lecithin:isopropyl palmitate solution and mix well.
5. Add sufficient Pluronic F-127 20% gel to make 100 mL and mix thoroughly using a shear mixing method.
6. Package and label.

Rx PIROXICAM 0.5% IN AN ALCOHOLIC GEL

For 100 mL

Hydroxypropylcellulose	1.75 g
70% Isopropyl alcohol	98.25 mL
Propylene glycol	4.1 mL
Polysorbate 80	1.7 mL
Piroxicam 20-mg capsules	25 capsules

Note: Piroxicam powder can be used if available.

Note: It is important to use an alcoholic water mixture, such as 70% isopropyl alcohol, or a gel may not form.

METHOD OF PREPARATION

1. Calculate the quantity of each ingredient required for the prescription.
2. Weigh and/or measure each ingredient accurately.
3. Make a hydroxypropylcellulose gel by mixing the hydroxypropylcellulose in the alcohol until a clear gel results.
4. Make a paste with the piroxicam powder (from capsules), the propylene glycol, and the polysorbate 80.
5. Add enough hydroxypropylcellulose gel to the paste using geometric dilution to make 100 g of the preparation.
6. Package and label.

PRESCRIBING TRANSDERMAL FORMULATIONS

(Note: This list contains examples only. Contact your compounding pharmacist for many other options.)

Antinauseant/Motion Sickness

- Scopolamine Hydrobromide 0.25-mg/0.1-mL Pluronic Lecithin Organogel
- Promethazine 25-mg/ mL Pluronic Lecithin Organogel
- Dexamethasone 1.2%, Lorazepam 0.1%, Haloperidol 0.1%, Diphenhydramine Hydrochloride 2.4%, and Metoclopramide Hydrochloride 2.4% in Pluronic Lecithin Organogel

Anxiolytic

- Buspirone Hydrochloride 2.5 mg/0.1 mL in Pluronic Lecithin Organogel
- Lorazepam 1 mg/mL in Pluronic Lecithin Organogel

Hormone Replacement Therapy

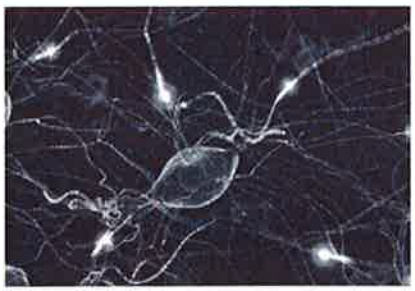
- Estradiol 0.5-mg/mL Topical Gel
- Estradiol 2-mg/mL Vaginal Gel
- Progesterone 10% Topical Cream
- Testosterone:Menthol Eutectic Ointment (2% Testosterone for Men)

Nonsteroidal Anti-inflammatory Drug Gel

- Ketoprofen 5% in Pluronic Lecithin Organogel
- Piroxicam 0.5% in an Alcoholic Gel

Pain, Neuropathic

- Amitriptyline Hydrochloride 2% and Baclofen 2% in Pluronic Lecithin Organogel
- Capsaicin 0.075%, Ketamine Hydrochloride 2%, and Ketoprofen 10% in Pluronic Lecithin Organogel



How Drugs Get Through

PENETRATION ENHANCERS

Some drugs have an inherent capacity to permeate the skin without chemical enhancers. However, when this is not the case, chemical permeation enhancers may render an otherwise impenetrable substance useful in TD drug delivery. Penetration enhancers facilitate the absorption of drugs through the skin. Some of these ingredients have a direct effect on the permeability of the skin, whereas others augment percutaneous absorption by increasing the thermodynamic activity of the penetrant, thus creating a greater concentration gradient across the skin. A chemical skin penetration enhancer increases skin permeability by reversibly altering the physicochemical nature of the SC to reduce its diffusional resistance. Among the alterations are increased hydration of the SC, a change in the structure of the lipids and lipoproteins in the intercellular channels through solvent action or denaturation, or both.

More than 275 chemical compounds have been cited in the literature as skin penetration enhancers. The selection of a permeation enhancer for pharmaceuticals should be based not only on its efficacy in enhancing skin permeation but also on its dermal toxicity (low) and its physicochemical and biologic compatibility with the system's other components. A list of examples of chemical penetration enhancers is shown below:

- Acetone
- Azone
- Dimethyl acetamide
- Dimethyl formamide
- Dimethyl sulfoxide
- Ethanol
- Laurocapram (Azone)
- Oleic acid
- Polyethylene glycol
- Polysorbates
- Propylene glycol
- Sodium lauryl sulfate

Because of its occlusive nature, water is the most prevalent absorption enhancer, even in "anhydrous" systems. (See the sidebar that accompanies this article for examples of penetration enhancers.)

How to Slow them Down

RATE CONTROLLER

Either the drug delivery device or the skin may serve as the rate-controlling mechanism. If the drug is delivered to the SC 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 factor. Thus, the rate of drug transport is controlled by either artificial (some patches) or natural (skin) membranes as well as the composition of the formulation (which can be designed for the drug to have more affinity to the formulation and escape into the skin at a slower rate).

Included among the design objectives of TD delivery are the following:

1. Deliver the drug to the skin for percutaneous absorption at therapeutic levels at an optimal rate
2. Contain medicinal agents having the necessary physicochemical characteristics to release from the system and partition into the SC
3. Occlude the skin to ensure one-way flux of the drug into the SC
4. Have a therapeutic advantage over other dosage forms and drug delivery systems
5. Not irritate or sensitize the skin

(Pain, Neuropathic)

Rx **AMITRIPTYLINE HYDROCHLORIDE 2% AND BACLOFEN 2% IN PLURONIC LECITHIN ORGANOGEL**

For 100 mL

Amitriptyline hydrochloride		2 g
Baclofen		2 g
Ethoxydiglycol		5 to 10 mL
Lecithin:isopropyl palmitate solution		22 mL
Pluronic F-127 20% gel	qs	100 mL

METHOD OF PREPARATION

1. Calculate the quantity of each ingredient required for the prescription.
2. Weigh and/or measure each ingredient accurately.
3. Combine the amitriptyline hydrochloride and baclofen powders.
4. Add sufficient ethoxydiglycol to form a smooth paste.
5. Add the lecithin:isopropyl palmitate solution and mix well.
6. Add sufficient Pluronic F-127 20% gel to volume and mix well.
7. Package and label.

Rx **CAPSAICIN 0.075% KETAMINE HYDROCHLORIDE 2% AND KETOPROFEN 10% IN PLURONIC LECITHIN ORGANOGEL**

For 100 mL

Capsaicin		75 mg
Ketamine hydrochloride		2 g
Ketoprofen		10 g
Ethoxydiglycol		10 mL
Lecithin:isopropyl palmitate		22 mL
Pluronic F-127 30% gel	qs	100 mL

METHOD OF PREPARATION

1. Calculate the quantity of each ingredient required for the prescription.
2. Weigh and/or measure each ingredient accurately.
3. Combine the capsaicin, ketamine hydrochloride, and ketoprofen powders.
4. Add sufficient ethoxydiglycol to form a smooth paste.
5. Add the lecithin:isopropyl palmitate solution and mix well.
6. Add sufficient Pluronic F-127 30% gel to volume and mix well.
7. Package and label.

Advantages of Transdermal Drug Delivery

1. Avoids gastrointestinal (GI) drug absorption difficulties caused by GI pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs
2. A substitute for oral administration of medication when that route is unsuitable, as with vomiting and diarrhea
3. Avoids the *first-pass effect.* That is, the initial pass of a drug substance through the systemic and portal circulation following GI absorption, possibly avoiding the deactivation by digestive and liver enzymes
4. Noninvasive, avoiding the inconvenience of parenteral therapy
5. Provides extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration
6. Activity of drugs having a short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release
7. Drug therapy may be terminated rapidly by removal of the application from the surface of the skin

Disadvantages of Transdermal Drug Delivery

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

What the Patient Needs to Know

1. Percutaneous absorption may vary with the site of application. The patient should be advised of the importance of using the recommended site and rotating locations within that site. Rotating locations is important to allow the skin to regain its normal permeability after being occluded and to prevent skin irritation. Skin sites may be reused after 1 week.
2. Application should be to clean, dry skin and not to oily, irritated, inflamed, broken, or callused skin.
3. Use of skin lotion should be avoided at the application site because lotions affect skin hydration and can alter the partition coefficient between the drug and the skin.
4. The drug should be placed at a site that will not subject it to being rubbed off by clothing or movement (as the belt line) or onto another person or pet.

5. The patient or caregiver should be instructed to cleanse the hands thoroughly before and after applying the drug. Care should be taken not to rub the eyes or touch the mouth during handling of the system.
6. If the patient exhibits sensitivity or intolerance to the drug or if undue skin irritation results, the patient should seek reevaluation.
7. Patients should be counseled about the proper application of a gel. They should be instructed on how to handle and store the package, as well as the need to keep it tightly closed.
8. Counseling for proper applications of ointments and creams may differ depending on the dosage form, active ingredients, and desired therapeutic outcomes.
9. Generally, only a thin film of the preparation is required. A sufficient quantity is removed from the container and applied and gently rubbed into the area, unless otherwise indicated.
10. A glove can be worn during application. Otherwise, wash hands before and after the application to remove any medication from the hands.
11. Instruct the patient not to wash the area for a few hours to allow the drug to have sufficient time to have an effect. If the area is covered, for example, by clothing, it may be advisable to use a protective pad over the area to prevent the preparation from being removed by the clothing.
12. Usually, it is best to continue using the preparation for a short while after the symptoms or injury has been resolved, depending on the specific situation.

Conclusion

Many different conditions have been effectively treated with the TD of drugs, making it a widely used option of drug delivery. This article lists only a few of the formulations that can be prepared for the use of TD. A compounding pharmacy can individualize medications to meet the pharmaceutical needs of patients.

For beyond-use-dates for the formulations included in this article, please visit our website at CompoundingToday.com

Address correspondence to Loyd V. Allen, Jr., PhD, RPh, International Journal of Pharmaceutical Compounding, 122 N. Bryant Avenue, Edmond, OK 73034. E-mail: lallen@ijpc.com