

Broadway Apothecary
1515 Oak Street
Eugene, Oregon 97401

RxTriad

VOLUME 13
NUMBER 5

RxTriad Compliments of



Broadway
Apothecary

Customized Prescriptions for Healthy Living

1515 OAK STREET
EUGENE, OREGON 97401

Pharmacists:

Kate James, R.Ph.
Sheri Cannell, R.Ph.
Heather Wilson, R.Ph.

Tel: 541-684-9352

Fax: 541-684-0858

www.broadwayapothecary.com
broadway@broadwayapothecary.com

HOURS:
9 AM - 6 PM
Monday - Friday

Transdermals: The Skin as Part of a Drug Delivery System

Lloyd V. Allen, Jr., PhD, RPh

Editor-in-Chief

International Journal of Pharmaceutical Compounding
Edmond, Oklahoma

Transdermal (TD) delivery of drugs is effective and widely used to treat many different conditions. TDs can be "individualized" for each patient by changing the drugs used, their concentrations, and the formulation. TDs are routinely used for delivery of hormones, pain medications, NSAIDs, antinauseant medications, and many, many others.

Transdermal 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 (1) measurable blood levels of the drug, (2) detectable excretion of the drug and/or its metabolites in the urine, and/or (3) clinical response of the patient to the therapy; not all three 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 Does it 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.

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.

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.

How Do 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. Chemical penetration enhancers include acetone, azone, dimethyl acetamide, dimethyl formamide, dimethyl sulfoxide, ethanol, laurocapram (Azone), oleic acid, polyethylene glycol, polysorbates, propylene glycol, sodium lauryl sulfate, and others. Because of its occlusive nature, water is the most prevalent absorption enhancer, even in "anhydrous" systems. (See the Callout Box 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

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.



Prescribing Transdermal Formulations

(Note: This list only contains examples. 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)

NSAID 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

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 a 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. Gels: Patients should be counseled about the proper application of the gel. They should be instructed on how to handle and store the package, as well as the need to keep it tightly closed.
8. Creams and Ointments: Counseling for proper applications for 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.