

Topical and Transdermal Drug Delivery: What a Pharmacist Needs to Know

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Ratna Mehta, Ph.D.

Assistant Professor
Pharmaceutical Sciences
College of Pharmacy – Glendale
Midwestern University
Glendale, Arizona

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Learning Objectives

Following a successful review of this article, the reader should be able to:

1. Explain basic concepts of skin physiology and mechanisms of percutaneous drug absorption.
2. Classify the different types of commonly used topical and transdermal delivery systems, and how these influence rate and extent of drug release.
3. Compare and contrast the advantages and disadvantages of various topical and transdermal products.
4. Counsel patients and health care professionals to select the most appropriate delivery systems for effective therapeutic applications.
5. Counsel patients on appropriate handling and storage of topical and transdermal products.

Abstract: The extent and rate of percutaneous drug absorption and transportation are influenced by various factors including skin physiology, physicochemical properties of drugs and excipients, as well as fabrication and design of the delivery systems. The goal of this article is to review some of these important features and to discuss how these relate to patient counseling on various topical and transdermal products.



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DRUG APPLICATION TO THE SKIN

Both topical and transdermal drug products are intended for external use. However, topical dermatologic products are intended for localized action on one or more layers of the skin (e.g.,

sunscreens, keratolytic agents, local anesthetics, antiseptics and anti-inflammatory agents). Although some medication from these topical products may unintentionally reach systemic circulation, it is usually in sub-therapeutic concentrations, and does not produce effects of any major concern except possibly in special situations, such as the pregnant or nursing patient. On the other hand, transdermal drug delivery systems use the percutaneous route for systemic drug delivery, but the skin is not the primary target organ.

Percutaneous Drug Absorption

The skin is made up of several layers including stratum corneum, viable epidermis and dermis, and it contains appendages that include sweat glands, sebaceous glands, and hair follicles.

The stratum corneum is the outermost desquamating 'horny' layer of skin, comprising about 15-20 rows of flat, partially desiccated, dead, keratinized epidermal cells. Depending upon the region of the body, the thickness of this layer ranges from 10-20 μm , with the thickest layer on the palms of the hands and soles of the feet. Of the various skin layers, it is the stratum corneum that is the rate-limiting barrier to percutaneous drug transport. In fact, the stratum corneum is a remarkably more formidable barrier to drug transport than the epithelial barriers of gastrointestinal, nasal, buccal, vaginal, or rectal delivery routes.

Transport of hydrophilic or charged molecules is especially difficult attributable to the lipid-rich nature of the stratum corneum and its low water content; this layer is composed of about 40% lipids, 40% protein, and only 20% water. Transport of lipophilic drug molecules is facilitated by their dissolution into intercellular lipids around the cells of the stratum corneum. Absorption of hydrophilic molecules into skin can occur through 'pores' or openings of the hair follicles and sebaceous glands, but the relative surface area of these openings is barely 1% of the total skin surface. This small surface area limits the amount of drug absorption.

Percutaneous absorption of drug molecules is of particular importance in the case of transdermal drug delivery systems because the drug has to be absorbed to an adequate extent and rate to achieve and maintain uniform, systemic, therapeutic levels throughout the duration of use. In general, once drug molecules cross the stratum corneal barrier, passage into deeper dermal layers and systemic uptake occurs relatively quickly and easily.

Generally, drug absorption into the skin occurs by passive diffusion. The rate of drug transport across the stratum corneum follows Fick's Law of Diffusion (see box below). In other words, the rate of drug transport depends not only on its aqueous solubility, but is also directly proportional to its oil/water partition coefficient, its concentration in the formulation vehicle, and the surface area of the skin to which it is exposed; it is inversely proportional to the thickness of the stratum corneum. The stratum corneum is thickest in the plantar (soles) and palmar regions and thinnest in the postauricular, axillary, and scalp regions of the body. An understanding of the transport behavior of drugs is vital for designing an effective topical or transdermal product, as well as reasonably predicting and comparing drug behavior in various formulations. The latter is of practical importance to the pharmacist who is required to suggest one or more effective drug products out of the many commercial formulations available or to counsel patients on proper use and handling of topical and transdermal products.

Fick's Law of Diffusion as applied to drug transport across stratum corneum

$$\frac{dM}{dt} = \frac{D \cdot \Delta C \cdot K}{h}$$

where dM/dt is the steady-state flux across stratum corneum

D is the diffusion coefficient or diffusivity of drug molecules

ΔC is the drug concentration gradient across the stratum corneum

K is the partition coefficient of the drug between skin and formulation medium, and

h is the thickness of the stratum corneum

Design of Topical Drug Products

Dermatologic products applied to skin are diverse in formulation and range in consistency from liquids to solid powders, but the most popular products are semisolid preparations. Some of these may be nonmedicated, in the sense that these may be devoid of any therapeutically active ingredients. The distinction of such preparations as therapeutic products may sometimes be blurred and these preparations may become categorized as cosmetics. Nevertheless, these products can provide desired outcomes, such as through their protective, moisturizing, or emollient physical effects on the skin.

Topical liquids include aqueous solutions (aluminum subacetate topical solution), hydroalcoholic solutions or tinctures (iodine tincture, Cleocin T[®] topical solution), organic solvent-based collodions (salicylic acid collodion), sprays (Benadryl[®] Itch Relief Spray), or the more viscous lotions (calamine lotion, Selsun[®] shampoo). Lotions are free flowing suspensions, emulsions, or colloidal solutions for external use, and these may be greasy or water-washable. There are only a handful of topical products of solid consistency, and these include powders (tolnaftate, Desenex[®]), pastes (zinc oxide), plasters, and soaps. Medicated and non-medicated powders are generally sprinkled over the skin for antisepsis or to absorb skin secretions. Soaps may be medicated or nonmedicated, and are used generally for cleansing healthy or infected skin. Use of pastes and plasters is restricted to more specific clinical conditions. Pastes are generally used to protect local skin tissue, and have a higher capacity to absorb skin secretions compared with ointments and creams. On the other hand, plasters are kept on the skin for a longer period and are primarily used to provide mechanical protection to internal tissues beneath the skin.

The majority of topical products comprise semisolid formulations that include ointments, creams, and gels. A semisolid preparation intended for external application to the skin or mucous membranes is officially defined as an 'ointment.' In practice, however, this term is used mainly for those products that have a translucent appearance, whereas preparations with an opaque, creamy white appearance are termed as 'creams.' Traditional ointment bases have been oleaginous in nature. These include hydrocarbons (petrolatum, beeswax, etc.) or vegetable oils that do not allow inclusion of any water or fatty alcohols (cholesterol, lanolin, wool alcohol, or stearyl alcohol, etc.) that do allow inclusion of limited amounts of water. Commercial examples of oleaginous bases include Vaseline and vegetable shortening, whereas Aquaphor and hydrophilic petrolatum are anhydrous absorption bases that are most suitable for absorbing serous discharges or for incorporating a drug in aqueous solution. These ointments are greasy in

nature and are excellent for emollient effects, but it is difficult to wash these off the skin unless soap and warm water is used. Water-washable ointments are also now available, which are translucent in appearance like the oleaginous ointments. However, these are prepared with water-soluble bases, such as polyethylene glycol (also known as macrogols), and are nongreasy in texture. More importantly, these bases differ in their occlusion properties. When applied over skin, an oleaginous ointment film can prevent or occlude moisture evaporation from the skin, whereas the water-soluble ointments are poor occlusive barriers.

Creams are emulsions of oleaginous substances and water, and spread more easily over skin than ointments. Oil-in-water (o/w)-type creams are easily water-washable, while the water-in-oil (w/o) ones are not. Cold cream, Eucerin cream and hydrous lanolin are w/o emulsions that can absorb limited amounts of water. The o/w emulsion bases, such as Dermabase, Unibase, and hydrophilic ointment can absorb some water, but the consistency begins to thin as water is incorporated into the continuous phase of the emulsion.

Gels are a relatively newer class of dosage form created by entrapment of large amounts of aqueous or hydroalcoholic liquid in a network of colloidal solid particles, which may consist of inorganic substances, such as aluminum salts or organic polymers of natural or synthetic origin. Depending upon the nature of colloidal substance and the liquid in the formulation, the gel will range in appearance from entirely clear to opaque. Most topical gels are prepared with organic polymers, such as carbomers, that impart an aesthetically pleasing, clear, sparkling appearance to the product, and are easily washed off the skin with water.

The type of base used in formulating a topical dermatologic product greatly influences its effectiveness. Bases containing large amounts of oleaginous substances provide an emollient effect to dry, irritated skin. More importantly, bases made up of non-volatile oleaginous substances (e.g., hydrocarbon bases) can form an occlusive barrier on the skin that prevents escape of moisture from the skin into the environment. As a result, moisture accumulates between the skin and the ointment layer that causes hydration of the stratum corneum. Hydration of stratum corneum allows 'opening up' of intra- and inter-cellular channels and pathways for easier passage of drug molecules. Additionally, the moisture layer provides a medium for dissolution of the drug that is otherwise dispersed as fine particles in the ointment base. Since only the dissolved drug presented to the skin as an individual molecular entity is able to enter the stratum corneum, skin occlusion generally results in enhanced percutaneous drug absorption. Systematic studies of cortisone uptake by the skin have shown that drug penetration is poor through dry skin, but is remarkably enhanced when humidifying the stratum corneum. Creams have good emollient properties, especially the w/o types, which maintain some degree of occlusion. However, the less hydrophobic films formed with o/w creams and water-soluble bases and gels do not provide an occlusive barrier to the skin and, thus, allow moisture to escape from its surface. Some well-formulated gels have been successful in facilitating greater drug permeation into the skin, when compared with ointments and creams, in which the drug may be dispersed as fine particles, but dissolution is inadequate because of their limited water content. Gels have a higher aqueous component that permits greater dissolution of drugs, and also permit easier migration of the drug through a vehicle that is essentially a liquid, compared with the ointment or cream bases. In addition, many gels contain penetration enhancers, such as alcohol, in the formulation. Topical dermatologic products that require drugs to penetrate and localize in

viable epidermal or dermal sites (such as local anesthetics or anti-inflammatory agents) may also occasionally include a vasoconstrictor, such as epinephrine, in the formulation to retard systemic uptake of the drugs and, thereby, prolong its local effect.

Counseling Issues Related to Topical Products

Topical drug products may be used for prophylaxis (e.g., sunscreens, astringents) or for treatment of skin conditions; such as bacterial, fungal, and viral infections; inflammation; pruritis; corns; warts; and other dermatologic conditions. While the list of intended applications of dermatologic products may be limited, there is a multitude of over-the-counter (OTC) and prescription products available in a variety of formulations (e.g., gentamycin is available as an ointment and cream; benzoyl peroxide is available as a lotion, cream, and gel; and hydrocortisone is available as an ointment, cream, gel, and lotion). Add to this list numerous non-medicated dermatologics that are used to provide moisturizing, emollient, or protective effects. It is challenging for the pharmacist to remain aware of these products and provide suitable suggestions to the patient. Yet, several guidelines can be helpful in providing optimal recommendations and when counseling patients regarding these products.

- Greasy products are less acceptable to patients, as these are greasy, may stain clothing, or are difficult to wash off, but are superior to water-soluble bases like polyethylene glycol in their emollient action. The latter may be attractive in term of ease of use, but are capable of irritating traumatized or broken skin.
- Creams provide an excellent emollient effect, have superior spreadability, and are less staining than oleaginous ointments. However, one needs to consider the skin condition and environmental factors when selecting a medicated or non-medicated cream or ointment. While both provide very good emollient effects, oleaginous ointments are preferred for dry, chapped skin in an environment of low humidity because of its occlusive properties. Creams are preferred for use over normal, healthy skin in more humid environments, as these permit some moisture evaporation from the skin and allow skin to ‘breathe.’
- When drug penetration into deeper skin layers is desired, oleaginous bases have proven superior to creams and water-soluble bases, which are attributable to their skin-hydrating properties. Steroids have been more effective topically when applied in a petrolatum base than when applied in a cream (o/w) vehicle.
- Gel formulations generally provide faster drug release compared with ointments and creams, and may be suggested when available. These are superior in terms of use and patient acceptability. However, gels flow only if the container is shaken well each time one uses it, and this may cause an inconvenience to the elderly or weak patients.
- The presence or absence of serous discharges from skin lesions will also dictate the best-suited formulation for a dermatologic application. For example, zinc oxide has protective properties in minor skin irritations, burns, and abrasive lesions. Zinc Oxide Paste USP, which contains 25% zinc oxide and 25% starch in a hydrocarbon vehicle, is capable of absorbing the discharges because of its starch content. On the other hand, zinc oxide ointment, which is more readily available OTC, contains 20% zinc oxide in a vehicle similar to that of the paste, but it lacks starch, and, therefore, it has a poor capacity to absorb liquid.
- Certain ointments and creams may be available in jars as well as tubes. In such cases, the pharmacist may want to evaluate the situation and discuss the pros and cons of using either packaging. While jars are economical when larger quantities are needed, a product is better

protected from the environment and contamination when packaged in a tube. Besides, it may be more convenient for the patient to carry a tube rather than a jar.

- Special precautions should be used in handling products that contain inflammable ingredients (collodions, tinctures, gels), and these should be stored in original containers with tight closures, away from heat and light. Direct skin contact with the collodion should be avoided except to the region of application, and it should be applied carefully with an applicator brush that is usually provided with the container. Disposal of unused product also requires special precautions that should be clearly explained to the patient.
- Emulsions (creams, lotions) may break down if exposed to excessive heat or sudden changes in temperature.
- Lotions should be shaken well prior to each use. While lotions are easier to apply, these do not remain on the skin as well and are generally less convenient to carry around compared with ointments, creams, or gels.
- A topical product should never be applied over open wounds or broken skin unless it is labeled as a sterile product. Besides the risk of infection, such an application is often associated with problems of significant systemic drug absorption.
- The patient should be counseled on proper handling and storage of topical products, so as to avoid contaminating the product during use.
- Care should also be used in applying any drug to inflamed skin. The integrity of inflamed skin is generally compromised, resulting in increased percutaneous migration and systemic absorption of most drugs.

Transdermal Drug Delivery Systems

From 1979, when the Food and Drug Administration approved the first transdermal drug delivery system (Transderm Scop[®] Patch), to the current transdermal delivery systems, there evolved a successful alternative to systemic drug delivery. Despite their relatively higher costs, transdermal delivery systems have proved advantageous for delivery of selected drugs, such as estrogens, testosterone, clonidine, nitroglycerin, scopolamine, fentanyl, and nicotine. Compared with oral dosage forms, these systems offer not only improved patient compliance, but also superior uniformity of drug concentrations in plasma throughout their duration of use. Most transdermal patches are designed to release the active ingredient at a zero-order rate for a period of several hours to days following application to the skin. This is especially advantageous for prophylactic treatment or maintenance therapy in chronic conditions where the patient is otherwise required to carry around oral medications and remember to take them several times a day. Development of long-acting, extended-, or sustained-release oral medications has been beneficial in such cases. However, these dosage forms need to be taken at least once a day compared with transdermal patches that can extend drug release for up to seven days (e.g., Catapres-TTS[®] or Climara[®]). Earlier, parenteral delivery was the only alternative for drugs that were inactivated by gastrointestinal enzymes or gastrointestinal pH, and could not be given orally (e.g., estrogens, testosterone, nitroglycerin). These drugs can now be delivered directly into systemic circulation by a non-invasive transdermal route through well-designed patch systems. Most importantly, unlike injectables, drug therapy can be interrupted by removal of the patch at any desired time if toxicity develops.

More recently, enhanced percutaneous delivery of charged hydrophilic drugs has become possible with the use of iontophoresis. An electric current is applied to the skin that provides the

driving force to enable penetration of ions into the skin. Similarly, phonophoresis uses ultrasound energy for enhancing drug penetration into the skin. These approaches require special machinery and training, and their use is currently restricted to medical clinics and hospitals. These will not be discussed further in this article, and are mentioned here only to identify other related percutaneous methods of drug delivery.

Design of Transdermal Delivery System and Drug Release Kinetics

The restrictive nature of percutaneous absorption through the skin limits the use of the transdermal delivery route to medications that are of low molecular weight, and are small molecules with moderate lipophilicity and high therapeutic potency. This method of administration is useful with medications that are used for relatively long-term preventive treatment or maintenance therapy of chronic conditions.

The basic components of any transdermal delivery system include the drug(s) dissolved or dispersed in an inert polymer matrix that provides support and platform for drug release; an outer backing film of paper, plastic, or foil; and a pressure-sensitive adhesive that anchors the patch to the skin. The adhesive is covered by a release liner, which needs to be peeled off before applying the patch to the skin. While the rate-limiting step in drug delivery can be either the drug release from the delivery system or its absorption into the skin, a well-designed patch system ensures that the former is the rate-limiting step, in order to provide drug uptake at a predetermined rate that is independent of inter-patient skin variability.

There are two basic designs of the patch system that dictate drug release characteristics and patch behavior: (i) matrix or monolithic and (ii) reservoir or membrane. In the matrix system, the inert polymer matrix binds with the drug and controls its release from the device (e.g., Nitro-Dur[®] Patch, Nicotrol[®] Patch [OTC], and Vivelle[®] Transdermal). In the reservoir system, the polymer matrix does not control drug release. Instead, a rate-controlling membrane present between the drug matrix and the adhesive layer provides the rate-limiting barrier for drug release from the device. Transderm-Nitro[®] Patch, Transderm Scop[®] Patch, Catapres-TTS[®] Transdermal, Estraderm[®] Transdermal, Duragesic[®] Transdermal, Nicoderm[®] CQ Patch, and Androderm[®] Transdermal System are examples of reservoir-type patch systems. Each type of patch design has its advantages and disadvantages. While reservoir systems offer true zero-order (constant) drug release rates, drug release rates from matrix systems undergo a slight decline over time because of progressive increase in length of the diffusional pathway as the drug is being depleted from the system. However, with most well-designed matrix systems, this decline is insignificant and provides a pseudo zero-order or apparently constant drug release rate during the designated period of patch use. With the reservoir system, there is a tendency for the drug molecules to diffuse into the control membrane over time and saturate it. If these patches are stored on the pharmacy shelf for a long time before use, it is possible for the patient to experience a 'burst effect' attributed to initial release of a large amount of drug from the patch and subsequent absorption into the skin. The burst effect may be advantageous for drugs that normally exhibit a considerable lag time between patch application and therapeutic effect. On the other hand, any damage to the control membrane while in storage or handling during application can cause uncontrolled release of large amounts of drug, resulting in potential toxicity.

Regardless of the design, most patches are intended to deliver drug into the skin at a constant rate over a designated period of time. Since drug diffusion occurs passively according to Fick's Law, the rate of flux remains constant (zero-order) as long as the concentration gradient across the barrier is unchanged. In other words, there needs to be a significantly large amount of drug in the device in order to maintain a uniform concentration gradient over the duration of patch use. When drug concentrations in the patch are depleted significantly, the drug release rate begins to drop, and the zero-order rate is no longer maintained. Most patches should be removed before reaching this stage. This means there is still a significant amount of drug remaining in the patch after it is 'used up' (e.g., Lidoderm Patch is recommended to be worn for 12 hours for treatment of post-herpetic neuralgia). These patches, which deliver about 150 mcg/cm² of lidocaine over 12 hours of 'wear' time, contain 700 mg of the drug in the patch before use, and 665 mg still remain in the patch when removed after 12 hours of use. Similarly, most patches contain at least 95% of the drug after use. This warrants special precautions in handling and disposal of the patch. If a pet or child accidentally ingests the patch, it can be absorbed in lethal doses and prove to be fatal. It is especially important for the pharmacist to understand this fact and offer appropriate counseling to the patient in this regard.

Patient Counseling Issues Related to Transdermal Systems

The list below includes some general topics on counseling patients using transdermal drug delivery systems. The pharmacist should be able to provide more detailed and specific guidelines regarding proper handling and storage of any particular system after studying its design and fabrication and understanding its drug-release kinetics.

- The patch should be applied to a clean, dry, non-hairy area of the skin with reasonable and uniform pressure. Oily, inflamed, broken, or calloused skin should not be used. If hair is present at the intended site, it should be carefully cut and not removed with a depilatory agent, since the latter can damage the stratum corneum and alter rate and extent of drug permeation.
- Percutaneous absorption may vary depending upon site of patch application. Each product generally states the preferred application site. The patient should be encouraged to follow the recommended application sites. Regions of the skin with thick epidermal layers, such as palms and soles, should be avoided. The post-auricular region is best suited for small-sized patches, as it is richly innervated by blood vessels. Despite higher drug permeability, the axillary and scalp regions are unsuitable for application of a transdermal patch. Most often, larger patches are applied on the forearm, inner thigh, lower back, or chest.
- The patch should be worn only for the designated period of time and not any longer, as drug release rate is not ensured beyond the designated time. In some cases (e.g., nitroglycerin patches), the patient may be required to follow a daily 'on' (12-14 hours during the day) and 'off' (10-12 hours at night) period of application to prevent nitrate tolerance.
- For repeated use of transdermal patches, application sites should be rotated. The new patch should not be placed over the site of the patch immediately preceding it. This is to minimize skin irritation and sensitization.
- Transdermal patches should be stored in original sealed pouches until the time of use. If the package is damaged or if the patch is removed prematurely from its pouch, it may lead to drug loss or altered physicochemical properties of one or more components, resulting in a

defective product, such as Transderm-Nitro[®] Patch, Nitro-Dur[®] Patch, and other similar products containing nitroglycerin, which is highly volatile.

- Handling of the patch during removal from its package and its application is especially important. Care should be taken to avoid touching or damaging the adhesive surface (which may contain drug) after removal of the release liner.
- When applying a patch to the skin, it should be firmly pressed against the skin with the heel of the hand for about 10 seconds to ensure uniform contact and adhesion.
- Cutting of the patch and applying a portion of it should be avoided as it damages the integrity of the system. This is especially so in the case of reservoir systems where cutting the patch can destroy the control membrane and alter drug release kinetics.
- Adherence to the skin is still the most common problem with patch design. Hence, the patch should be applied at a site that is not easily rubbed off by clothing or movement. If a patch dislodges or falls off prematurely, one may attempt to reapply it provided it has not been contaminated or fallen off for too long. Otherwise, a fresh patch should be applied and worn for a full time period from then onwards before further replacement. However, a well-adhered patch can be left on when showering, bathing, or swimming.
- Upon removal, a used patch should be folded into half with the adhesive layers sticking together, so that it cannot be reused. Since the used patch may contain residual drug, it should be disposed of carefully, making sure that children or pets cannot obtain it. Toxic outcomes are likely to occur if a child or pet chews upon a used patch or ingests it.
- If application of the patch to any area of the skin results in skin irritation or inflammation, the patient should contact the physician and seek medical attention as well as reevaluation of product used.

Finally, when using any dermatologic product including patches, it is very important to follow proper administration protocol. In general, patients should clean the affected skin area well with warm water and soap and pat it dry with a soft cloth before applying any product. Ointments, creams, and gels may be applied with clean fingers to form a thin layer over the affected skin area(s). In few instances, a bandage may be applied over the application to provide an occlusive dressing or protect the area from environmental contact or contaminants. Touching the eyes, mouth, or any other region of the body should be avoided when applying a topical product or handling a patch. After each application, it is very important to wash the hands thoroughly with soap and warm water. This helps to not only minimize systemic absorption of the drug from fingers, but also prevents contaminating other regions of the body with the drug product.

It is common for patients using dermatologic products to develop a hypersensitivity reaction at any stage during use, which may have an immunologic basis or occur as a result of direct irritation caused by one or more ingredients in the product. Skin may react to any active ingredient in the product or to inactive ones, including the vehicle. For example, lanolin used as a vehicle in ointments is commonly known to cause hypersensitivity reactions. The adhesive used in transdermal patches is another ingredient that can cause skin reaction in some users. The skin reaction typically manifests as a rash accompanied by redness, burning, itching, heat, and swelling. One or more of these symptoms may occur in sensitive patients. The patient should be counseled to observe for any of these symptoms, and if they persist, the product should be discontinued and corrective measures should be taken after consulting the physician or pharmacist.

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