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Transdermal Drug Delivery Systems: A Review of Skin Permeation, Formulation Approaches and Current Challenges

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Abstract

Delivering a drug through the skin and into the systemic circulation is an attractive alternative to swallowing a tablet or receiving an injection. A transdermal patch avoids first-pass metabolism, keeps plasma levels fairly steady, and can be removed if side effects appear. Even so, only a modest number of molecules have reached the market in this form, mainly because the outermost skin layer, the stratum corneum, is an excellent barrier. This review summarises the structure of the skin and the routes by which molecules cross it, the physicochemical limits on suitable drug candidates, and the main patch designs in use today. Strategies for improving permeation are discussed under three headings: chemical enhancers, physical methods (iontophoresis, sonophoresis, microneedles) and vesicular carriers. We also outline the standard evaluation tests for patches, list representative marketed products, and discuss the problems that still hold back wider use, including skin irritation, dose limits and manufacturing cost. Recent progress in microneedle technology suggests that large molecules such as peptides and vaccines may become feasible candidates in the coming years.

Keywords: Transdermal patch; stratum corneum; skin permeation; penetration enhancers; microneedles; iontophoresis

1. Introduction

The idea of placing medicine on the skin to treat the whole body is old, but the modern transdermal patch is relatively young. The first patch approved in the United States, a scopolamine system for motion sickness, appeared in 1979, and nitroglycerin, clonidine, estradiol and nicotine patches followed over the next two decades [1,2]. Since, then the field has moved through several stages: simple passive patches for small, potent and lipophilic drugs; chemically or physically enhanced systems; and, more recently, devices that make microscopic channels in the skin [1].

Oral dosing remains the usual first choice, yet it has well-known drawbacks. Many drugs are broken down in the gut or liver before reaching the blood, peaks and troughs in plasma concentration can cause side effects or

loss of effect, and patients who forget doses or cannot swallow are poorly served. Injections bypass these problems but are painful, need trained staff and generate sharps waste. Transdermal delivery sits between the two. A patch worn for one to seven days can maintain a near-constant input rate, which is useful for drugs with a narrow therapeutic window or a short half-life [3].

The skin is not an easy route, however. Barry described it as a barrier designed by evolution to keep things out, and for most molecules it does that very well [4]. This article reviews how the barrier works, what kinds of drugs and patch designs have succeeded, and which technologies are being developed to push beyond the present limits.

2. Skin Structure and Permeation Pathways

Human skin is made up of three main parts: the epidermis, the dermis and the subcutaneous tissue (Figure 1). The epidermis is itself layered. At the surface lies the stratum corneum, only 10–20 μm thick when dry, which consists of flattened, keratin-filled dead cells (corneocytes) embedded in a matrix of ceramides, cholesterol and free fatty acids. This arrangement is often compared with bricks and mortar [5]. Beneath it is the viable epidermis, which has no blood vessels, so a drug must diffuse across it before reaching the dermis. The dermis is a connective tissue several hundred micrometres to a couple of millimetres thick and contains the capillary network, lymphatics and nerve endings. Once a molecule reaches these capillaries it enters the systemic circulation.

Three routes are usually described. In the intercellular route, molecules travel through the lipid channels between corneocytes; this winding path is long, but it is considered the dominant route for most drugs [5,6]. In the transcellular route, the molecule crosses corneocytes and the lipid layers in turn, which requires repeated partitioning between hydrophilic and lipophilic environments. The appendageal route uses hair follicles and sweat ducts as shunts. Follicles occupy only around 0.1% of the skin surface, so this route contributes little to steady-state flux, but it may matter for ions, large polar molecules and nanoparticles, and during the early lag period [6].

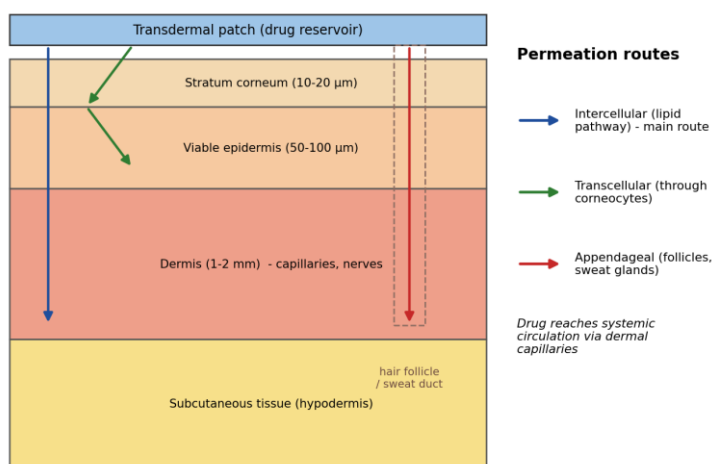


Figure 1. Layers of the skin and the three routes of drug permeation from a transdermal patch.

Passive diffusion across the skin is described by Fick's first law. The steady-state flux (J) can be written as $J = (D \times K \times \Delta C) / h$, where D is the diffusion coefficient of the drug in the stratum corneum, K is its partition

coefficient between the vehicle and the skin, ΔC is the concentration gradient and h is the diffusional path length. The equation shows why formulation matters: flux rises with a higher drug concentration in the patch, with better partitioning into the skin, and with a thinner or more permeable barrier. It also shows that no amount of formulation work can rescue a drug whose intrinsic diffusivity is very poor.

3. Factors Affecting Transdermal Permeation

The rate at which a drug crosses the skin depends on the drug, the formulation and the person wearing the patch, and all three groups of variables have to be considered during development.

Biological factors. Skin thickness and lipid content differ between body sites; the postauricular region and scrotum are far more permeable than the forearm or sole, which is why scopolamine is placed behind the ear. Hydration increases permeability, and occlusion by the backing layer is partly responsible for this effect. Age, disease states such as psoriasis or eczema, and local blood flow also change absorption. Skin temperature matters because diffusion speeds up when it rises. Finally, the skin contains esterases and other enzymes capable of metabolising some drugs, which is exploited in prodrug design [5,7].

Physicochemical factors. Solubility, partition coefficient, molecular size, ionisation and melting point all influence flux. Since the stratum corneum is acidic (pH about 4.5–5.5), the pH of the vehicle controls how much of a weak acid or base is in the un-ionised, more permeable form. Hydrogen-bonding capacity also plays a part; molecules with many donor groups usually permeate poorly [6,8].

Formulation factors. The choice of polymer, adhesive, solvent and enhancer determines the thermodynamic activity of the drug in the patch, which is the true driving force for diffusion. A drug held at saturation has maximum activity, so many matrix patches are deliberately made saturated. The thickness and area of the patch, and the compatibility of excipients with the skin, add further constraints [3,5].

4. Advantages and Limitations

The commonly cited benefits of transdermal systems are listed below, and they explain the continued commercial interest in the area [2,3].

- Avoidance of gastrointestinal degradation and hepatic first-pass metabolism.
- Controlled, prolonged input that reduces fluctuations in plasma level.
- Fewer doses per day, which tends to improve adherence, especially in elderly patients and children.
- Easy termination of therapy by removing the patch.
- Non-invasive and suitable for self-administration.

The limitations are just as real. Only potent drugs can be used, because the area of a patch cannot sensibly exceed about 50–100 cm² and the amount absorbed per day is therefore small. Contact dermatitis from the drug, enhancer or adhesive is a recurring problem. Drugs that need high blood levels quickly are unsuitable because of the lag time. Patch adhesion can also vary with sweating, movement, hair and skin site [2,7].

5. Properties of a Suitable Drug Candidate

Decades of experience with approved patches have produced a fairly consistent profile of the drug that works well. The molecular weight is generally below 500 Da, a limit often referred to as the “500 dalton rule” [8]. The log P (octanol–water) should fall roughly between 1 and 3, so that the drug can enter the lipid barrier yet still leave it for the aqueous viable epidermis. A melting point under about 200 °C is helpful because it tends to go with higher solubility. The daily dose should be low, usually a few milligrams or less, and the drug should be non-irritating and non-sensitising. Few drugs satisfy every one of these criteria, which is why enhancement techniques receive so much attention.

6. Types of Transdermal Patch

Patches differ mainly in how the drug is stored and how its release is regulated. Figure 2 shows a typical multilayer arrangement. Four designs are commonly described.

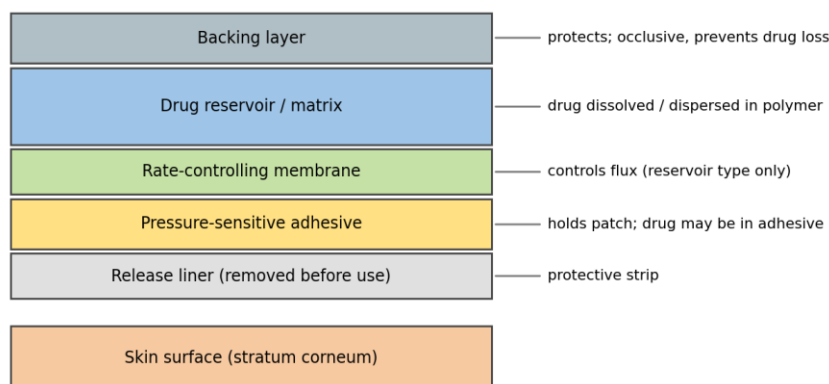


Figure 2. Cross-section of a typical multilayer transdermal patch placed on the skin.

Reservoir (membrane-controlled) systems. The drug is held as a solution or gel in a compartment bounded by a backing layer and a rate-controlling membrane. Release follows near zero-order kinetics because the membrane, not the skin, controls the rate. The disadvantage is the risk of “dose dumping” if the membrane leaks. The early scopolamine and clonidine patches used this design [2].

Matrix systems. The drug is dispersed in a polymer matrix that is in direct contact with the skin. There is no separate membrane, so the patch is thinner and more flexible, and a failure of one part is less likely to release the whole dose. Release usually falls over time, following a square-root-of-time relationship.

Drug-in-adhesive systems. Here the drug is mixed straight into the pressure-sensitive adhesive, which serves as both reservoir and attachment layer. This is the simplest and thinnest design and is now very common, for example in many nicotine and estradiol products [2,9].

Micro-reservoir systems. These combine the two previous ideas: the drug is suspended in a water-miscible solvent, which is then dispersed as tiny droplets in a lipophilic polymer. Cross-linking fixes the droplets in place and gives a stable, controlled release profile.

7. Generations of Transdermal Technology

Prausnitz and Langer suggested that the field can be viewed as passing through three generations [1]. The first generation covers the early patches mentioned above. These rely on the natural ability of a small, lipophilic molecule to cross intact skin and need no enhancement, which explains why the list of drugs from this period is short and similar in character.

The second generation sought to widen the range of candidates by temporarily increasing skin permeability while protecting deeper tissue. Chemical enhancers, iontophoresis and non-cavitation ultrasound belong here. Success has been real but limited, in part because the more strongly one disrupts the stratum corneum, the more likely it is that irritation will appear before enough drug has crossed [1,17].

The third generation targets the stratum corneum directly, with methods strong enough to create pathways for large or hydrophilic molecules while avoiding damage to deeper layers. Microneedles, thermal ablation,

microdermabrasion, electroporation and cavitation ultrasound are typical examples. Many of these are still being tested in clinical trials, but they are the group that would permit delivery of proteins, DNA and vaccines [1,15].

8. Strategies to Enhance Skin Permeation

Because the stratum corneum limits flux, a large part of the research effort goes into overcoming it. Approaches are usually grouped as chemical, physical and carrier-based, summarised in Table 1.

Table 1. Main permeation-enhancement approaches.

Approach	Examples	Proposed mechanism	Main limitation
Chemical enhancers	Ethanol, oleic acid, propylene glycol, terpenes, azone, DMSO	Disorder stratum corneum lipids; improve drug solubility or partitioning	Irritation; effect depends on drug and vehicle
Iontophoresis	Low-level electric current (0.1–0.5 mA/cm ²)	Electrorepulsion and electro-osmosis move charged or polar molecules	Needs a device; local skin reactions
Sonophoresis	Low-frequency ultrasound (about 20–60 kHz)	Cavitation disrupts lipid bilayers	Equipment cost; thermal effects
Microneedles	Solid, coated, dissolving and hollow types	Create micron-scale channels through the stratum corneum	Reproducible insertion; sterility; patient acceptance
Vesicular carriers	Liposomes, transfersomes, ethosomes, niosomes	Fusion with lipids, carrier deformability, fluidising effect of ethanol	Stability; scale-up; inconsistent human data

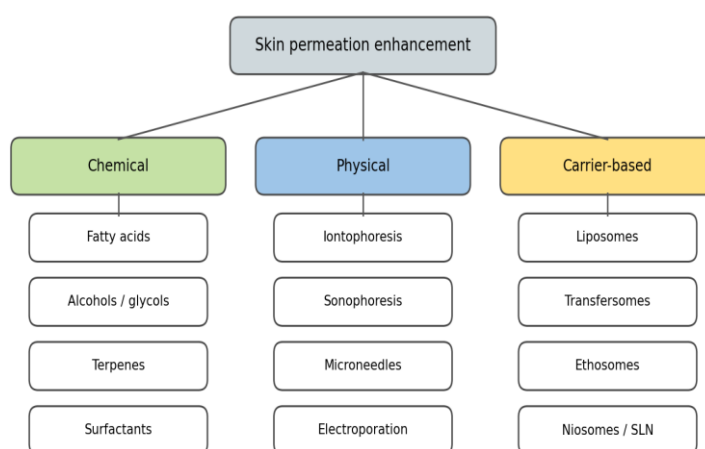


Figure 3. Classification of strategies used to enhance transdermal drug permeation.

8.1 Chemical enhancers

Chemical penetration enhancers reversibly reduce the barrier function of the stratum corneum. Williams and Barry classified their action as disruption of the intercellular lipid structure, interaction with intracellular keratin, and improved partitioning of the drug or co-solvent into the tissue [10]. Fatty acids such as oleic acid create separate lipid-rich domains, ethanol extracts some lipids and raises drug solubility, and terpenes loosen the packing of ceramides. An ideal enhancer would be pharmacologically inert, non-toxic, compatible with the drug and fully reversible, but no single compound meets all of these conditions. In practice, mixtures are often more effective than a single agent, although this also increases the possibility of irritation [10,11].

8.2 Physical methods

Iontophoresis applies a small electric current to drive ionised drugs across the skin and has been explored for lidocaine, fentanyl and several peptides [12]. The amount delivered is related to the total charge passed, so dose can in principle be programmed. Sonophoresis uses ultrasound, and at low frequency the collapse of cavitation bubbles near the skin surface produces transient defects in the lipid bilayers [13]. Electroporation, thermal ablation and radiofrequency methods also exist, but they remain mostly at the research stage for routine patches.

Microneedles are among the most promising developments. These are arrays of needles typically 50–900 μm long, long enough to cross the stratum corneum but short enough to avoid most pain receptors and blood vessels [14]. Solid needles pierce the skin before a patch is applied, coated needles carry a dry drug film, dissolving needles are made of a soluble polymer that releases the payload as it degrades, and hollow needles allow infusion of a liquid. The approach has been tested with insulin, vaccines and large biologics that would never pass through intact skin [14,15]. Questions about reproducible insertion on different skin types, drug loading capacity, and the regulatory pathway are still being addressed.

8.3 Vesicular and nanocarrier systems

Liposomes were first reported to interact with skin in the 1980s, and they were followed by deformable vesicles. Cevc and Blume proposed that highly flexible vesicles (transfersomes) can squeeze through narrow gaps in the stratum corneum driven by the water gradient across the skin [16]. Ethosomes contain a high ethanol level that fluidises both the vesicle bilayer and the skin lipids. Niosomes, which are built from non-ionic surfactants, offer greater chemical stability than phospholipid vesicles. Solid lipid nanoparticles and nanoemulsions are being studied for the same purpose. Results in animal and ex vivo skin are often encouraging, but in human studies it is not always clear whether the intact vesicle crosses the barrier or acts mainly as a penetration enhancer at the surface.

9. Evaluation of Transdermal Patches

Quality assessment covers physicochemical tests, in vitro and ex vivo permeation studies, skin safety testing and in vivo studies. Physicochemical tests include thickness, weight uniformity, folding endurance, moisture content and uptake, drug content and flatness. Adhesive performance is assessed by peel adhesion, tack, shear strength and release-liner peel tests, since a patch that lifts at the edges will under-deliver.

In vitro permeation is normally measured in Franz-type diffusion cells, where a piece of excised human or animal skin (or a synthetic membrane) separates the donor and receptor compartments, and the receptor fluid is sampled over 24–72 hours [17]. Pig ear skin is used frequently because its permeability is reasonably close to that of human skin. The cumulative amount permeated is plotted against time, and the steady-state flux and lag time are obtained from the linear portion. Irritation and sensitisation are checked with the Draize test in animals and later in human patch tests, and stability studies follow ICH guidelines. Finally, pharmacokinetic studies confirm bioavailability and the relationship between in vitro and in vivo results.

10. Marketed Transdermal Products

A selection of approved systems is shown in Table 2. Most contain small, potent molecules, and a majority are used for chronic conditions in which the steady dosing matters, such as pain, hormone replacement, Parkinson's disease and nicotine dependence [2,9].

Table 2. Examples of marketed transdermal drug delivery systems.

Drug	Indication	Patch type	Typical duration
Scopolamine	Motion sickness	Reservoir	3 days
Nitroglycerin	Angina prophylaxis	Matrix / drug-in-adhesive	12–24 hours
Nicotine	Smoking cessation	Drug-in-adhesive	16–24 hours
Fentanyl	Chronic severe pain	Reservoir / matrix	3 days
Estradiol	Menopausal symptoms	Matrix / drug-in-adhesive	3–7 days
Rivastigmine	Alzheimer's dementia	Matrix	24 hours
Rotigotine	Parkinson's disease	Drug-in-adhesive	24 hours
Lidocaine	Post-herpetic neuralgia	Matrix	12 hours on / 12 off

10.1 Selected examples

Three products illustrate how the principles above play out in practice. Nicotine is a small, lipophilic molecule with good skin permeability, and its patch was one of the first to reach very wide use. Dosing is stepped down over several weeks, and the continuous input provides a baseline level that reduces craving, although it cannot reproduce the sharp peaks that follow smoking. Sleep disturbance and local redness are the most frequent complaints, and rotating the application site limits the latter [2,3].

Fentanyl shows the benefits and the risks of the approach. It is highly potent, with a molecular weight of about 336 Da, and so only a modest amount has to cross the skin to relieve chronic pain. Because the skin acts as a depot, the drug continues to be absorbed for many hours after a patch is removed, and a fever or direct heat can accelerate delivery. For these reasons the product is restricted to opioid-tolerant patients and carries strong warnings about storage and disposal [2,7].

Estradiol patches deliver a hormone that would be largely metabolised in the liver after an oral dose. Transdermal administration yields a ratio of estradiol to estrone closer to the premenopausal pattern and avoids some of the hepatic effects of oral therapy. Both matrix and drug-in-adhesive types are available, and twice-weekly and weekly versions give patients a choice [2,9]. Together these cases show that a low dose, adequate permeability and a clear clinical reason for steady plasma levels are the features that most reliably lead to a successful patch.

10.2 Patient-related considerations

Even a well-designed patch can fail if it is used incorrectly. Patients should apply it to clean, dry, intact skin at the site recommended in the label, press it firmly for several seconds, and avoid cutting it unless the product is designed for this. The site should be changed with each application so that the same area is not used repeatedly. Used patches still contain drug and must be folded with the adhesive sides together and discarded

safely, particularly in households with children. Clear counselling by pharmacists on these points is a simple way of improving both safety and effect [2,7].

11. Challenges, Safety and Future Directions

Looking at the history of the field, Wiedersberg and Guy pointed out that despite more than thirty years of work the number of marketed active ingredients has grown slowly, and most new products are reformulations or new combinations of molecules already on the market [18]. The reasons are mostly the ones described above: the barrier, the limit on dose, and skin tolerance. Some further practical issues deserve mention. Residual drug left in used patches creates a risk of misuse or accidental exposure, particularly with opioids, and this has led to disposal warnings. Heat from fever, saunas or heating pads can raise absorption of drugs such as fentanyl and cause overdose. Generic development is also harder than for tablets because adhesion and skin-irritation studies add cost and variability.

Regulatory expectations add to the workload. A patch is regulated as a drug product, so the sponsor must show content uniformity, release or flux consistency, adhesion performance and acceptable irritation scores in addition to the usual stability data. Because the same drug can behave differently in patches with different adhesives, bioequivalence for generic patches is judged with product-specific guidance rather than simple dissolution tests. These requirements are reasonable, since a patch delivers its dose over many hours, but they extend development time compared with oral dosage forms.

Several trends may help. Microneedle patches are moving towards vaccine delivery, where they could remove the need for cold-chain storage and trained vaccinators. Combination approaches, for example a microneedle pre-treatment with a conventional matrix patch, are being studied. Wearable devices that combine drug delivery with sensors may eventually adjust dose in response to measured physiological signals. Better predictive models, including artificial membranes and computer simulation of skin transport, should reduce reliance on animal skin and shorten formulation development [1,19].

12. Conclusion

Transdermal delivery offers real benefits in steady dosing, avoidance of first-pass metabolism and patient convenience, and it has produced a steady stream of useful products since the late 1970s. The stratum corneum remains the central obstacle, which restricts the approach to small, lipophilic, potent drugs unless enhancement technology is used. Chemical enhancers and vesicular carriers have extended the range modestly, while physical methods, and microneedles in particular, hold the greatest promise for peptides, proteins and vaccines. Progress will depend on proving that these newer systems are reproducible, safe and economical on a manufacturing scale.

Declaration of Conflicting Interests

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