Published in final edited form as:
Ther Deliv. 2010 July ; 1(1): 109–131.

Challenges and opportunities in dermal/transdermal delivery

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Abstract

Transdermal drug delivery is an exciting and challenging area. There are numerous transdermal delivery systems currently available on the market. However, the transdermal market still remains limited to a narrow range of drugs. Further advances in transdermal delivery depend on the ability to overcome the challenges faced regarding the permeation and skin irritation of the drug molecules. Emergence of novel techniques for skin permeation enhancement and development of methods to lessen skin irritation would widen the transdermal market for hydrophilic compounds, macromolecules and conventional drugs for new therapeutic indications. As evident from the ongoing clinical trials of a wide variety of drugs for various clinical conditions, there is a great future for transdermal delivery of drugs.

Delivery of drugs through the skin has been an attractive as well as a challenging area for research. Advances in modern technologies are resulting in a larger number of drugs being delivered transdermally including conventional hydrophobic small molecule drugs, hydrophilic drugs and macromolecules. Transdermal systems are a desirable form of drug delivery because of the obvious advantages over other routes of delivery. Transdermal delivery provides convenient and pain-free self-administration for patients. It eliminates frequent dosing administration and plasma level peaks and valleys associated with oral dosing and injections to maintain a constant drug concentration, and a drug with a short half-life can be delivered easily. All this leads to enhanced patient compliance, especially when long-term treatment is required, as in chronic pain treatment and smoking cessation therapy. Avoidance of hepatic first-pass metabolism and the GI tract for poorly bioavailable drugs is another advantage of transdermal delivery. Elimination of this first-pass effect allows the amount of drug administered to be lower, and hence safer in hepato-compromised patients, resulting in the reduction of adverse effects. Transdermal systems are generally inexpensive when compared with other therapies on a monthly cost basis, as patches are designed to deliver drugs from 1 to 7 days. The other advantage of transdermal delivery is that multiple dosing, on-demand or variable-rate delivery of drugs, is possible with the latest programmable systems, adding more benefits to the conventional patch dosage forms. The general acceptability of transdermal products by patients is very high, which is also evident from the increasing market for transdermal products. The transdermal drug delivery market, worth $12.7 billion dollars in 2005, is expected to reach $32 billion in 2015 [1].

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Financial & competing interests disclosure

Audra L Stinchcomb is funded by NIH grants R01DA13425, R01DA18822, R43DA26266 and RC2DA28984. Courtney L Swadley is funded by NIH Grant F31DA025424. Nicole K Brogden is funded by NIH grant F31DA029374. Audra L Stinchcomb is a significant shareholder in and Chief Scientific Officer of AllTranz Inc., a transdermal company. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Transdermal delivery systems (TDS) were introduced onto the US market in the late 1970s [2], but transdermal delivery of drugs had been around for a very long time. There have been previous reports about the use of mustard plasters to alleviate chest congestion and belladonna plasters used as analgesics. The mustard plasters were homemade as well as available commercially where mustard seeds were ground and mixed with water to form a paste, which was in turn used to form a dispersion type of delivery system. Once applied to the skin, enzymes activated by body heat led to the formation of an active ingredient (allyl isothiocyanate). Transport of the active drug component took place by passive diffusion across the skin – the very basis of transdermal drug delivery [3,4,201].

Since then a long path has been traversed in the field where we have seen the development of numerous transdermal patches ranging from nicotine to methylphenidate and testosterone to lidocaine [4]. The TDSs that have been developed over the years have been classified into different generations by Prausnitz *et al.* [2]. According to the classification, the first generation dealt mostly with small, lipophilic and uncharged molecules that can be delivered in the therapeutic range by passive diffusion alone. Most of the TDS that are currently on the market belong to this generation. But with the advancement of science and engineering we have seen the use of chemical enhancers and techniques such as ultrasound and iontophoresis for the delivery of drug molecules that cannot undergo passive diffusion. These belong to the second generation of transdermal products that target reversible disruption of the skin's outer layer, the stratum corneum or use an additional driving force for drug delivery. One of the best examples is the delivery of lidocaine (a charged molecule), for which an iontophoretic delivery system was developed and marketed. A third generation of delivery systems is currently under development employing techniques such as microneedles and electroporation for delivery of macromolecules. This third generation of systems targets its effect towards the stratum corneum, rather than modification of the drug molecule itself.

A number of recently published reviews deal with various aspects of transdermal delivery, for example, classification of transdermals into generations and the transdermal market [2], and nanotechnology in transdermal delivery [5]. Patent reviews on formulation aspects of transdermal delivery and enhanced transdermal delivery techniques [6–8] have also been published. The first aim of this article is to provide an updated overview of the transdermal products currently on the US market and in clinical trials. The second aim is to focus on the challenges and solutions for overcoming skin permeation and skin irritation.

Transdermal products currently on the US market

A previously published review by Prausnitz and Langer described the various US FDA-approved transdermal patches and delivery systems [2]. This article contains an updated listing of transdermal products currently on the US market, as well as a separate section on transdermal products meant for local dermal delivery, as compared with systemic delivery. Table 1 lists all the transdermal products available in the USA. The first patch to be introduced onto the US market in 1979 was the scopolamine patch. It was a small reservoir type patch where a liquid dispersion of the drug was prepared and sealed between an impermeable backing layer and a rate-controlling membrane, which stays in contact with the skin and is responsible for the delivery of the drug. The nitroglycerin patch was introduced next in 1981 for angina and was much bigger in size. The clonidine patch (Catapres TTS®) was introduced in 1984 for high blood pressure as the first 7-day patch system. These were followed by the estradiol and fentanyl patches in 1986 and 1990, respectively. The original estradiol delivery system was eventually developed as a matrix type patch where the drug was dispersed in the adhesive matrix itself (Climara®), rather than in a separate formulation. But the TDS that revolutionized the transdermal market was the nicotine patch, which was

first introduced in 1991 as a treatment for smoking cessation. Since then there has been development of a number of different patches, including a testosterone patch for hypogonadism in males and combination patches of estradiol and norethindrone or levonorgestrel for menopausal symptoms. TDS using ultrasound and iontophoresis were marketed in 1995 for delivery of small charged molecules such as lidocaine and fentanyl HCl. Although some of these prescription drug systems have been removed from the market for various reasons, ultrasound and iontophoresis are still used to deliver drugs for pain treatment in physical therapy clinics. The field of transdermal delivery now seems to be expanding further into the chronic treatment of neurological disorders, which has been showcased by the introduction of TDS-containing drugs such as methylphenidate for attention-deficit hyperactivity disorder (introduced in 2006), rotigotine for Parkinson's disease (2007) and rivastigmine for dementia (2007) [2,9,201,202]. This expansion into neuroscience-related drugs is quite possibly due to the fact that small, potent molecules that can cross the blood–brain barrier also have good characteristics for crossing the skin, in addition to the fact that chronic disease states are ideal for multiple-day controlled-release delivery.

Most of the focus on transdermal systems has been on the patch dosage form, but a variation in the patch system of the transdermal era is a metered spray, for example Evamist®, which delivers estradiol or the gel formulations such as Androgel®, which delivers testosterone. The newer transdermal gels are technically just a return to the early approved nitroglycerin ointment technology; however, the new formulations have better cosmetic feel and consumer appeal. These systems are highly effective and cost efficient, and provide a good alternative to patch manufacturing for very potent drug molecules. One of the primary cost and safety issues associated with all patches currently on the market is that they usually contain a large amount of residual drug after use in order to maintain a saturated concentration of drug throughout the entire delivery period. For example, only 3% of the total drug content is absorbed from the lidocaine patch (Lidoderm®) [202], so it is very important to remove the patches carefully and discard according to provided directions. The residual drug in the patch can pose a danger to children who may pull the patches from the trash, and this residual drug is also a highly desired source of controlled substance for addicts. Therefore, the development of metered-dose pumps or active diffusion systems might thus be very beneficial to make transdermal products with more efficient drug use and improved safety/abuse liability profiles.

The stability of the transdermal patches is also important for delivering drugs effectively. Proper packaging of the individual patches is critical since the patches may contain a volatile solvent or hygroscopic substance. Each individual patch thus needs to be heat sealed into a multilaminate packaging consisting of foil, paper and heat sealable polyethylene portions. This requires an extra step in the manufacturing process, and adds some extra expense, as compared with most tablets and capsules that can be packaged easily in a multientry bottle.

Table 2 shows the topical gel and patch products currently available in the USA for the transdermal treatment of local tissue sites. These products are mainly indicated for the treatment of pain associated with arthritis, neuropathy, and muscle sprain and strain, apart from their use in local anesthesia. One FDA-approved lidocaine/tetracaine product for local anesthesia (Synera®) utilizes CHADD® technology. CHADD utilizes controlled heat to enhance transdermal drug permeation. CHADD units may either be incorporated directly into the drug-containing patch (as with Synera) or placed on top of a transdermal patch to temporarily increase the local temperature [203]. The FDA approved the first topical diclofenac product for osteoarthritis joint pain in 2007. Topical drugs penetrate slowly below the site of application leading to a relatively high drug concentration in the dermis,

subcutaneous tissue and/or in the joint synovium, but delivering small amounts into the systemic circulation. New drug molecules for topical treatment of pain need to be developed given that some topical products such as capsaicin and diclofenac have side effects and are not effective for all patients.

Transdermal products currently in clinical trials

There are currently a large number of ongoing FDA-approved active clinical trials related to transdermal products (Table 3). These trials range from Phase I to IV studies, and most involve previously FDA-approved transdermal systems, including such compounds as fentanyl, nicotine and hormone therapies (to name just a few). These studies target a wide variety of disease states, and many are investigating the use of currently available transdermal products for new indications or in various combinations with other drugs. This article provides a description of the presently ongoing FDA-approved clinical trials related to TDS.

Besides the trials utilizing both investigational agents and currently approved transdermal products (described in Table 3), there is also extensive work taking place in the development of microporation technologies and devices, most of which are targeted to disrupt or bypass the stratum corneum. Such microporation techniques that are currently in development (and are in various stages of the FDA approval process) include laser, radiofrequency, thermal microporation technologies and microneedle systems. In addition to the large number of technologies in development, these products are being investigated with a wide variety of drug compounds, including (but not limited to) parathyroid hormone, lidocaine, insulin, fentanyl and diclofenac sodium. Several recently published reviews provide excellent overviews of the technologies typically used to enhance transdermal delivery, as well as the technologies currently in development, and the reader is referred to these reviews for more details [9–11]. Table 4 describes all the currently ongoing FDA-approved active clinical trials involving microporation techniques for transdermal delivery.

In addition to the active trials that are ongoing with TDS, there are several products in development that have completed Phase III trials but are not yet available on the US market. These products include a buprenorphine TDS for various pain conditions (Purdue Pharma LP) and a sumatriptan iontophoretic transdermal patch (Zelrix™) for migraine disorders (NuPathe Inc., NDA filing expected in 2011) [204–206]. There are also products that have completed some Phase II trials and are expected to continue to progress through further trials, such as the Altea thermal ablation device for insulin delivery, transdermal bupivacaine patch (Eladur™, Durect and AlPharma Inc.), transdermal sufentanil (TRANSDUR™-sufentanil, Durect and AlPharma Inc.) and ViaDerm™-human parathyroid hormone (TransPharma Medical) [207,208].

Challenges & solutions for overcoming the skin permeation barrier

Owing to the selective nature of the skin barrier, only a small pool of drugs can be delivered systemically at therapeutically relevant rates. Approximately 15 drugs constitute the whole segment of the transdermal drug market (Table 1). Besides great potency, the physicochemical drug characteristics often evoked as favorable for percutaneous delivery include moderate lipophilicity and low-molecular-weight [12]. However, a large number of pharmaceutical agents do not fulfill these criteria. This is especially true for macromolecules, such as insulin, human growth hormone or cyclosporine, which are very challenging from the drug delivery point of view. Overcoming low skin permeability to xenobiotics can be achieved by a variety of approaches, and is an active field of research. Their effectiveness and applicability will vary from drug to drug depending on the physicochemical nature of the compound. Here, a brief overview of the enhancement

methods including chemical methods, physical methods and a prodrug approach will be provided with special emphasis on the recent developments.

Chemical methods

Chemical permeation enhancers facilitate drug permeation across the skin by increasing drug partitioning into the barrier domain of the stratum corneum, increasing drug diffusivity in the barrier domain of the stratum corneum or the combination of both [13]. The heterogeneous stratum corneum is composed of keratin 'bricks' and intercellular continuous lipid 'mortar' organized in multilamellar strata [14–16]. Depending on the nature of the drug either of these two environments may be the rate-limiting milieu (barrier domain) for the percutaneous transport. As a consequence it is anticipated that the magnitude of permeation improvement obtained with a given permeation enhancer will vary between lipophilic and hydrophilic drugs. Several mechanisms of action are known: increasing fluidity of stratum corneum lipid bilayers, extraction of intercellular lipids, increase of drug's thermodynamic activity, increase in stratum corneum hydration, alteration of proteinaceous corneocyte components and others. More detailed discussion of the modes of action has been reported elsewhere [17,18]. Permeation enhancers are conventionally divided into several groups based on their chemical structure rather than the mechanism of action. This is partially due to the difficulty determining a primary or mixed mode of action for many of them. Furthermore, compounds from the same group can exert their effect through different mechanisms. More than 300 substances have been shown to have skin permeabilization potential and this number is still growing. Most known enhancers fall into the following categories: alcohols (ethanol, pentanol, benzyl alcohol, lauryl alcohol, propylene glycols and glycerol), fatty acids (oleic acid, linoleic acid, valeric acid and lauric acid), amines (diethanolamine and triethanolamine), esters (isopropyl palmitate, isopropyl myristate and ethyl acetate), amides (1-dodecylazacycloheptane-2-one [Azone®], urea, dimethylacetamide, dimethylformamide and pyrrolidone derivatives), hydrocarbons (alkanes and squalene), surfactants (sodium laureate, cetyltrimethylammonium bromide, Brij®, Tween® and sodium cholate), terpenes (D-limonene, carvone and anise oil), sulfoxides (dimethyl sulfoxide) and phospholipids (lecithine). The importance of water, or hydration of the stratum corneum, is not to be underestimated. A fully hydrated stratum corneum (under occlusion) presents lesser diffusional resistance to xenobiotics than its dehydrated counterpart. However, a common drawback of permeation enhancers is that their efficacy is often closely mimicked by skin irritation. In general, the same mechanisms that are responsible for enhanced drug transport such as disrupting ordered stratum corneum lipid bilayers or corneocyte structural organization are also responsible for skin irritation [19]. One possibility to address this concern is to identify mixtures of permeation enhancers that exhibit synergistic effects [20]. Karande *et al.* successfully used a screening approach to test 5000 binary mixtures of chemicals [21,22]. The details are described in the next section of this article. Most of the products on the transdermal market use the effect of occlusion, which can be classified as an enhancement technique acting through the hydration of the stratum corneum. Additionally, drugs such as nitroglycerin (Nitro-Dur®, Nitro Disc® and Transderm-Nitro®) use fatty acid esters and lidocaine (Lidoderm®) use urea and propylene glycol as chemical enhancers. Traditionally, chemical enhancers have been used to increase the delivery of small molecules and showed only limited success in permeation enhancement of macromolecules. Overall, chemical methods, although effective, cannot compete with physical enhancement methods that provide a greater magnitude of skin permeabilization.

Physical methods

The oldest and by far the most popular way of overcoming the skin barrier physically is the use of hypodermic needles. In many cases it is the only viable method of delivery for poorly absorbable and highly unstable compounds. Typically, drug solution is forced under piston

pressure directly into the bloodstream or tissue (skin and muscle). Such drug administration results in quick delivery of large amounts of drug. If controlled drug delivery over longer periods of time is desired, indwelling catheters are used. However, both require mechanical perforation of skin with a needle, which causes pain and trauma. According to Hamilton, needle phobia is a medical condition that affects at least 10% of the population [23]. This condition is a serious problem in the healthcare system in the sense that people with needle phobia tend to avoid medical care. To address these drawbacks, several alternative physical skin enhancement methods such as jet injections, dermabrasion, thermal ablation, laser, microneedles, iontophoresis, electroporation, ultrasound and combinations of the above have been investigated. These methods aim at developing more user-friendly and flexible delivery systems, and are able to produce bolus type as well as sustained drug delivery profiles.

Jet injections involve the delivery of liquid or solid particles driven by high-pressure accelerators across the stratum corneum [24]. The concept of drug delivering jets is not new as first reports date back to the 1940s; however, first attempts of using this technology translated into limited success. Technology advances in the later decades enabled the construction of more reliable and effective devices based on compressed helium [25]. It proved its potential in the delivery of insulin to diabetic patients [26]. This method is similar to the hypodermic injection in that it enables rapid delivery of large amounts of drug, but it has resulted in improved patient compliance [27]. Shortcomings of jet injections include inability to deliver drugs over longer periods of time; however, they seem to be well suited for vaccination delivery [28].

Dermabrasion has been traditionally used to treat acne, scars and other dermatologic and cosmetic conditions [29]. Recently, the potential of this technique for transdermal drug delivery has been recognized. Mechanistically, crystal microdermabrasion uses microcrystals blown onto the skin surface to perform the exfoliating process. Several-fold improvement in flux for low-molecular-weight drugs was shown by various researchers with the use of this technique [30,31]. A recent study by Gill *et al.* investigated the effect of microdermabrasion on stratum corneum removal in rhesus macaques and human volunteers *in vivo*. The effectiveness of the skin barrier removal correlated with the number of passes of the mobile dermabrasion device and selective removal without damage to the viable epidermis was possible [32].

Thermal ablation takes advantage of the external source of thermal energy, which propagates into the stratum corneum to create microchannels. Heating of the skin surface to hundreds of degrees for a very short period of time allows the thermal damage to be limited to the stratum corneum alone without further heat propagation to live epidermal layers. An interesting publication by Park *et al.* discussed the effect of heat on skin permeability [33]. The authors pointed out skin permeability changes to a model hydrophilic compound at different temperature ranges. While an intermittent increase in the skin temperature to 100–150°C causes a moderate increase in the flux of a hydrophilic compound, 150–250°C translates into one to two orders of magnitude increase, and a temperature of over 300°C adds yet another tenfold augmentation in the transdermal flux. Different mechanisms were postulated to be responsible for such change at each temperature range. Altea Therapeutics developed a PassPort™ system that comprises a single-use disposable patch and a re-useable handheld applicator. Phase I and II clinical trials have been completed for the delivery of insulin via this enhancement system.

A laser can also be used to thermally ablate parts of the stratum corneum creating pores. These pores allow drug molecules applied to the surface of the skin to bypass the diffusional barrier and gain easy access to the vascularized deeper layers of the skin. This method has been able to extract interstitial fluid to measure glucose levels in diabetic patients as well as

being effective in augmenting transdermal flux of hydrophilic and hydrophobic molecules [34–36]. A transdermal laser system P.L.E.A.S.E.® (Pantec Biosolutions) has been developed and granted a European patent in 2009. Furthermore, laser-assisted drug delivery (Norwood Abbey) was developed and the device has been cleared for marketing by the FDA for the delivery of a topically applied local anesthetic. The pitfall of the laser approach is that it is a relatively complicated technology associated with high costs.

Microneedles became one of the major enhancement techniques in the transdermal drug delivery field after advancements in microfabrication techniques were made in recent years. Long enough to perforate the topmost layers of the epidermis but short enough not to excite nerve endings in the skin, microneedles offer painless and powerful dermal permeabilization [37]. A variety of different microneedle designs have been used in *in vitro* testing. Solid microneedles are used to pierce microchannels through the skin followed by application of a transdermal patch, and microneedles themselves can be coated with a drug or contain a drug dissolved in their matrix. Yet another option involves hollow microneedles through which a convective flux of drug is delivered into deeper skin layers. Henry *et al.* showed an increase in the transdermal flux of calcein by up to four orders of magnitude [38]. A multitude of other studies proved that microneedles effectively permeabilize skin to drugs [39–42]. A first-inhuman microneedle study showed that therapeutically relevant plasma levels of naltrexone, an opioid antagonist, were achieved after skin pretreatment with microneedles and subsequent application of transdermal patches [43]. Currently, several systems based on microneedles are being investigated, such as Microstructured Transdermal Systems (3M), Macroflux® (Zosano) or MicroCor™ (Corium), and have shown efficacy in preclinical trials.

There are several methods that use electric current as a means to permeabilize the skin. Iontophoresis relies on the continuous electric current to drive charged drug molecules across the skin via electrophoresis and electroosmosis [44]. It is commonly stated that iontophoresis mainly provides additional electrochemical driving force for drug transport across skin, rather than increasing the permeability of the skin. The first *in vivo* animal investigation showing the effectiveness of this approach was carried out at the beginning of the 20th century. Since then many drug delivery systems were tested for small molecules such as pilocarpine [45], lidocaine [46] or zolmitriptan [47] and large molecules such as calcitonin, insulin, parathyroid hormone or vasopressin [48–52]. Clinical studies, however, have been limited to small agents such as lidocaine, cortisone or fentanyl [53–55]. Although there have been reports indicating the presence of erythema under the electrode application site [56], the irritation correlates well with the current and as long as the current is low, adverse effects are not substantial. Both continuous and intermittent delivery of drugs is feasible. A couple of drug delivery systems using iontophoretic devices were approved by the FDA in the past, for example, lidocaine HCl with epinephrine (Iontocaine® and Lidosite® topical system) and fentanyl HCl (IONSYS™) [209]. IONSYS, however, was never marketed in the USA. These products have now been listed as discontinued by the FDA (Iontocaine since 2005, Lidosite topical system since 2006 and IONSYS since 2008). The discontinuation of IONSYS in the USA was affected primarily by the European Medicines Agency's [210] recall of the product and suspension of marketing because of corrosion of a component in the system, which can lead to release of fentanyl without patient activation. The limitations of this delivery method include the relatively high cost of the iontophoretic device.

Another method – electroporation – is based on the use of short (micro- to milli-second), high-voltage electrical pulses to create transient disruptions in the structure of the stratum corneum [57]. Such disruptions, or pores, facilitate the transport of small and large molecules otherwise unable to permeate at all. Drug molecules are believed to be transported through skin by electrophoretic movement and diffusion. Examples proving *in*

vitro effectiveness of electroporation include small molecules such as timolol [58], as well as larger molecules such as oligonucleotides, heparin and IgG antibodies [59].

Ultrasound skin enhancement (sonophoresis) is achieved by the use of high (MHz) or low (kHz) frequency devices, the latter showing greater percutaneous drug flux improvement. At low frequencies the ultrasound applied to the skin results in the production of cavitational bubbles, which by oscillation disrupt the stratum corneum structure. *In vitro* experiments have shown substantial increase in the skin permeability to small molecules such as estradiol, aldosterone or lidocaine [60], as well as macromolecules such as insulin, erythropoietin or γ-interferon [61–65]. In 2004, the FDA approved an ultrasound system (SonoPrep®) to accelerate the action of lidocaine for local dermal anesthesia. The same system is intended to be used for delivering vaccines, insulin and antibiotics, and blood glucose monitoring in the future. An interesting feature of the device is real-time skin impedance feedback that stops the sonication procedure when the desired level of conductance has been achieved. This method does not cause pain or irritation when used within certain limitations. A ViaDerm system (TransPharma) has been developed and preclinical trials demonstrated effectiveness of this method of skin enhancement. Moreover, clinical trials involving the ViaDerm system coupled with human parathyroid hormone (1–34) and human growth hormone are underway.

Combinations of enhancement techniques have the potential of showing synergistic effects [66]. Some combinations that have been studied include electroporation–ultrasound [67], electroporation–iontophoresis [68,69] and microneedle–iontophoresis [70,71]. The observed synergistic effects may be rationalized by different mechanisms by which enhancement methods work, for example electroporation disrupts stratum corneum barrier structure increasing its permeability to drugs, while iontophoresis provides additional driving force for diffusion of charged particles above that of just passive diffusion.

Prodrugs

The **prodrug** approach in percutaneous drug delivery includes several different areas of interest: permeation across skin, chemical and enzymatic stability, as well as skin irritation potential. While all of these things need to be considered for design of a successful prodrug, usually the main reason to use this approach is to modify the physicochemical properties of a parent drug such that the flux of the prodrug is increased over that of the parent molecule. A chemical modification of the compound of interest presents great opportunity to alter its ability to cross the stratum corneum barrier. In the most conventional case, when the diffusional barrier is represented by the lipid domain of the stratum corneum and parent drug is relatively hydrophilic, increasing its lipophilicity can result in improved percutaneous flux. A penalty, however, is paid for with the increase in the size of the permeant. By contrast, it has also been possible to improve the flux of extremely hydrophobic compounds (which undergo viable tissue controlled diffusion, in comparison to stratum corneum controlled diffusion) by creating more hydrophilic prodrugs. A good discussion of the prodrug approach in percutaneous drug delivery can be found elsewhere [72]. More recent reports include the delivery of ketorolac piperazinylalkyl prodrugs [73], a pilot clinical trial involving prodrugs of levodopa [74], effects of PEGylation on transdermal flux of acetaminophen [75], naltrex-one prodrugs [76,77] and bupropion prodrugs [78]. Currently, there are no transdermal prodrugs available on the market.

Challenges & solutions for overcoming skin irritation

A major advantage of topical and transdermal drug delivery is the reduction of systemic side effects. On the other hand, delivery of drugs by these routes adds the potential for side effects in the form of skin irritation at the delivery site. Skin irritation reactions include

irritant contact dermatitis (ICD), an inflammatory response caused by repeated or direct exposure of the skin to weak irritants, and allergic contact dermatitis (ACD), delayed, T-cell-mediated inflammatory response to a specific allergen. ICD reactions range from erythema and scaling to necrotic burns while ACD reactions include erythema, edema and occasionally vesiculation. Additionally, the onset of ACD reactions is highly variable, and is dependent on the irritant that initiated the reaction and the individual who expresses the allergic response.

Factors that contribute to skin irritation include changes in the physiological pH of the skin, disruption of the stratum corneum barrier (i.e., delipidization, hydration and disruption of stratum corneum lipid packing), immunological and physiological reactions, bacteria proliferation at the delivery site, and chemical/pharmacological features of the drug or vehicle. Many features of topical and transdermal systems contribute to skin irritation including the active pharmaceutical ingredient (API), formulation (including skin permeation enhancers and excipients), occlusion of the skin, duration of device application and the type of delivery device used. Additionally, patch adhesives and membranes, solvents, enhancers and the active drug have all been demonstrated to contribute to the development of ACD reactions. The risk of causing **cutaneous irritation** can be minimized through management of the device and formulation components during the device design process. Additional means to reduce adverse skin responses have been reported; pretreatment of the skin with a corticosteroid before application of the system, inclusion of corticosteroids in the formulation and structural alterations of chemical permeation enhancer are just a few of these. Factors identified as contributing to skin irritation as well as methods to prevent or remedy these reactions are discussed in greater detail later.

The role of drug features in skin irritation

The API included in the topical or transdermal pharmaceutical preparation has been indicated as the major cause of ACD in patients [79]. Drugs that exhibit moderate-to-severe irritation in animal studies are often ruled out for further use in topical formulations. Unfortunately, it is difficult to predict the irritation potential of a drug without first testing it in an animal or cell model. Some studies have been performed to identify characteristics of drugs that may be potential irritants. For instance, it has been reported that the dissociation constant (pKa) of an API can affect the physiological pH of the skin and by this cause cutaneous irritation. Berner *et al.* have shown that benzoic acid derivatives with pKa values of 4 or less caused irritation after 24 h of exposure to the skin in humans [80,81]. Furthermore, drugs that possess pKa values greater than 8 have been shown to irritate the skin as well. A trend of increasing irritation with increasing pKa was reported by a number of groups [82,83]. Based on these studies, it is predicted that drugs with pKa values between 4 and 8 should provide minimal skin irritation. Additionally, instead of excluding potentially irritating drugs, simply minimizing their concentration included in a topical or transdermal formulation may reduce their resulting irritation to safe and tolerable levels.

Pharmacological responses of the skin to a drug can also present irritation and should be considered. For example, capsaicin is marketed as a topical preparation indicated for relief of local pain and irritation. This drug induces its action through interaction with the epidermal nervous system. After initial application, capsaicin causes pain and a burning sensation at the site of action. To reduce these effects capsaicin is applied multiple times a day at a low dose to induce resistance in the skin to irritation while also building local therapeutic levels. Here, the dose and dosing regimen of capsaicin is controlled to bring about the therapeutic response without causing significant, long-term irritation [84]. It has also been reported that subsequent exposure to an irritant can induce resistance of the skin to the irritant, a process called accommodation. Both downregulation of the inflammatory

response and skin hardening by upregulation of ceramide 1 synthesis have been attributed to the development of resistance by the skin [85,86].

Substitution of equally or more potent derivatives of an irritating drug for the parent in a topically applied delivery system may also reduce skin irritation. For example, synthetic derivatives of capsaicin have shown decreased irritation over the parent drug. In a study where capsaicin, nonivamide and sodium nonivamide acetate were applied to the forearms of male human volunteers, sodium nonivamide was found to produce the least erythema and painful sensation. Although its transdermal flux was determined to be the least of the three drugs tested, sodium nonivamide is more potent than capsaicin in its pharmacological action. Nonivamide was also found to be less irritating than capsaicin in this study while displaying similar flux to capsaicin as well [87].

The role of vehicle & devices in skin irritation

The pH of the skin's surface has been reported to be in the range of 5.4 to 5.9 and is important in the maintenance of skin **barrier function** and defense against infection and disease [88]. The skin also has an excellent buffering capacity against large changes in pH. Albeit, external factors such as washing and applying solutions, drugs and cosmetics to the surface of the skin can raise its surface pH and can likewise increase or induce skin irritation. For example, alkaline solutions of pH 9 and above applied to the skin have been reported to cause skin irritation. In the same study, aqueous solutions of pH 5 and 7 did not cause irritation when applied to the skin [89]. In another study, Ananthapadmanabhan *et al.* showed that a solution at pH 10 when applied to the skin, compared with a pH of 4 or 6.5, increased the transition temperature of stratum corneum lipids [90]. Observed adverse effects were swelling of the stratum corneum and disruption of the skin barrier function, as indicated by an increase in **transepidermal water loss**. Therefore, to avoid skin irritation it is very important to buffer formulations applied to the skin as close to the skin's surface pH as possible. Some universal pharmaceutical solvents are irritating to the skin and therefore cannot be used in topical preparations. Prior to *in vivo* investigation, these solvents should be replaced by alternative solvents with acceptable irritation and safety profiles. Topical solvents deemed to be safe for use include isopropyl alcohol, propylene glycol, isopropyl myristate and polyethylene glycols to a certain percentage (up to 60% used in marketed products) [91].

Most topical systems and transdermal systems require prolonged complete occlusion of the skin in the form of a patch, cream, lotion or other pharmaceutical preparation. Water-impermeable occlusion of the skin has been found to increase the pH and temperature of the skin's surface, as well as trapping moisture and sweat to create a humid environment. These conditions are favorable for bacterial and yeast overgrowth on the surface of the skin. Sweat itself has been shown to cause occlusion-induced irritation [92]. ICD reactions are commonly seen after skin occlusion and its incidence has been reported to increase with the duration of occlusion [93,94]. Additionally, occlusion may increase the irritation potential of the topically administered API. For instance, Van der Valk and Maibach have shown that in ten healthy subjects the irritation response to repeated short-term exposure of sodium lauryl sulfate was enhanced with postexposure occlusion [95]. Functional damage to the skin barrier by occlusion, detected by transepidermal water loss, has also been reported [96].

Finally, the choice of a matrix type versus a reservoir-type patch for drug delivery can affect the incidence of skin irritation. Components of each system have been reported to contribute to skin reactions upon use. In the case of transdermal delivery of estradiol, skin reactions have been described in response to the adhesive, hydroxypropyl cellulose and ethanol in the original TDS [79]. In addition, reactions to methacrylate in the transdermal nicotine patch have been reported [97]. Since most reactions to patches tend to be ACD responses, it is

difficult to predict the irritation potential of the individual patch components. Furthermore, studies discerning irritation caused by the application of matrix type versus reservoir type patches are inconclusive. However, one source has reported that drug-loaded matrix patches tend to cause fewer cutaneous reactions than reservoir release patches [98]. By contrast, similar skin irritation was observed after application of either a matrix or reservoir patch containing fentanyl to the skin of healthy human subjects [99].

Impact of formulation on skin irritation

It has been shown that the formulation used to deliver a drug can influence the appearance and degree of skin irritation. Hydrogels, for instance, have been reported to reduce skin irritation by absorbing moisture from the skin's surface [94]. A study comparing the safety and efficacy of a lotion containing benzoyl peroxide entrapped in polymeric microspheres to a lotion containing free benzoyl peroxide showed that controlled release of benzoyl peroxide from the microspheres reduced skin irritation in humans, without sacrificing efficacy. Based on these results, it was concluded that controlled-release systems might be useful in reducing irritation induced by topically applied drugs [100]. Liposomes have also been shown to reduce skin irritation. The postulated mechanisms for reduction of skin irritation by liposomes include hydration of the epidermis and the sustained release of drugs, hence avoiding the buildup of toxic drug concentrations in the skin [101]. For example, tretinoin formulated in liposomes demonstrated decreased skin irritation with respect to the equipotent gel formulation when administered to patients [102]. It is possible that using a hydrogel or a cream containing liposome- or microsphere-entrapped drug may decrease the skin irritation potential of the formulation applied to the skin's surface.

Reinforcing the protective barrier of the skin by addition of an emollient to topical formulations has been shown to reduce or prevent skin irritation as well. For example, Zhai *et al.* showed that applying a cream containing paraffin wax in cetyl alcohol to the skin prior to treatment with sodium lauryl sulfate or ammonium hydroxide prevented irritation caused by these known irritants in the absence of the applied cream [103]. Additionally, in a clinical study conducted by Wigger-Albeti *et al.* [104], it was shown that the irritant effect of known irritants sodium hydroxide, toluene and lactic acid on human skin was prevented by applying petrolatum to the skin before the irritant. Petrolatum was found to be less effective against toluene-induced irritation.

Chemical permeation enhancers

The stratum corneum is a formidable barrier to exogenous agents including drugs. Therefore, it is often necessary to add permeation-enhancing chemicals to aid drugs in passing through the stratum corneum. Permeation-enhancing chemicals include fatty acids, organic solvents (i.e., acetone and ethanol), alcohols, esters and surfactants, among many others described earlier in this article. It is generally understood that for enhancers, increased potency is directly correlated with increased skin irritation. Difficulty in reducing the irritation of these agents has been expressed since the same mechanisms responsible for increasing permeation cause irritation. While potent enhancers are effective at transiently compromising the integrity of the stratum corneum barrier, their action is not entirely limited to the stratum corneum and the interaction with viable epidermis can cause cytotoxicity and irritation. However, studies have been performed with the objective of reducing the irritancy potential of known permeation enhancers without decreasing their potency with some success. Published methods for reducing the skin irritation of permeation enhancers include combining permeation enhancers (synergistic mixtures) and manipulation of their chemical structures. Ben-Shabat, Baruch and Sintov prepared propylene glycol mono- and di-ester derivatives of saturated and unsaturated fatty acids to improve their permeation enhancement ability without increasing their irritation [105]. None of the

derivatives tested showed greater permeation enhancement than the corresponding fatty acid, although the propylene glycol conjugates of oleic and linoleic acid diminished skin irritation and maintained equivalent enhancement capability when compared with the free fatty acid. Sintov and Ben-Shabat have also reported on the formation of fatty acid–drug conjugates to increase permeation without jeopardizing their safety [106]. Finally, Karande and Mitragotri have summarized numerous permeation enhancer combinations, their safety and the synergistic enhancement of these combinations in increasing drug permeability [107]. One example given was a cyclodextrin–enhancer complex that reduced side effects of the enhancer while maintaining its permeabilization ability. In summary, it appears that combinations of permeation enhancers, solvents and drugs may be able to increase potency without causing excess irritation.

Anti-irritants & corticosteroids in reducing skin irritation

Pre-application of steroids to the skin and incorporation of steroid or anti-irritants into irritant formulations have been demonstrated to reduce skin reactions. Topical pretreatment with a 0.1%-triamcinolone acetonide cream was shown to decrease the incidence and/or severity of skin reactions associated with TDS exposure in humans. This was determined based on the comparison of cumulative irritation scores obtained in patients that were pretreated with steroid versus those to whom pretreatment was not applied [108]. Lastly, incorporation of anti-irritants into irritant formulations has been shown to decrease adverse skin reactions [109]. Some anti-irritants reported to decrease side effects caused by irritants are glycerol [110,111], triamcinolone acetonide, [111], lobetasol and diphen-hydramine [112]. These systems were shown to reduce sodium lauryl sulfate-, nonanoic acid- and captopril gel-induced skin irritation, respectively.

Future perspective

Expanding the use of novel permeation enhancement techniques with macromolecules and other conventional molecules for a wider range of indications is highly desirable for the transdermal industry. Physical enhancement methods afford substantial improvement in the rate of delivery of therapeutic agents across skin. Currently, a variety of them are undergoing extensive investigation and new device-based TDS can be expected in the near future. One can also expect the first transdermal prodrug product to emerge on the market in the near future. Novel prodrugs would not only help to reach the therapeutic levels for some drugs, but may also help alleviate skin irritation.

The incidence and significance of skin irritation reactions will decrease with the increasing availability of physical permeation enhancement methods and new breakthroughs in topical drug formulations, such as liposomes, microemulsions, nanoparticles and evaporating gels. Breakthroughs in chemical permeation enhancer analogs showing significant improvements in limiting cutaneous irritation show promise for the development of safe chemical enhancers and should be further examined in the future.

Executive summary

- Approximately 20 transdermal and 10 topical/dermal products make up the current US transdermal market.
- Most transdermal products on the US market today are in the conventional patch form, but a few variations such as a programmable patch, metered spray or the gel formulations have also been approved by the US FDA. These transdermal products are indicated for a wide range of therapies.

- Although reservoir and matrix patches share an almost equal ratio among the approved patch products, matrix patches are the most desired and the ideal goal for future products. The newer patches are much smaller in size compared with the older conventional systems.
- Transdermal products for local treatment currently available on the US market come in gel and patch forms. These products are mainly indicated for local pain treatment of a variety of conditions.
- Transdermal products that are currently in FDA-approved clinical trials are investigational agents, as well as approved transdermal products for new indications or in various combinations with other drugs.
- Microporation techniques have gained momentum in the drug approval process and products may be on the market soon for a wide range of molecules.
- Increase in skin permeability is a prerequisite for successful delivery of new macromolecular drugs and improved delivery of conventional drugs.
- Although many individual chemical enhancers often fail to provide the desired enhancement level without exhibiting safety concerns, some combinations of chemical enhancers act synergistically to overcome these limitations.
- Physical enhancement methods afford substantial improvement in the rate of delivery of therapeutic agents across skin. Currently, a variety of them are undergoing extensive investigation.
- Prodrugs allow the physicochemical properties of drug molecules to be changed, which facilitates crossing of the stratum corneum barrier.
- It is difficult to predict the incidence of cutaneous irritation caused by drugs, patch components and formulation components prior to *in vivo* testing.
- Drug and permeation enhancer analogs have shown superior safety over their corresponding parent forms.
- Reported ways to prevent or reduce skin irritation of topical and transdermal systems include:
  - Maintaining the pH of the topically applied formulation near the skin pH
  - Avoiding drugs that possess a dissociation constant (pKa) of less than 4 or greater than 8
  - Formulating the active pharmaceutical ingredient in a hydrogel or liposomal system
  - Adding corticosteroids or anti-irritants to the drug formulation

Key Term

Chemical permeation enhancer	A substance that temporarily changes the nature of the skin barrier, stratum corneum, so that the passage of the drug molecules across it is facilitated
Prodrugs	A pharmacologically inactive substance that undergoes *in vivo* activation to form the active metabolite (parent molecule)

Cutaneous irritation	A complex biological reaction to exogenous stimuli applied to the skin or caused by damage to the skin barrier, identified by superficial pH, transepidermal water loss, skin hydration, skin color, blood flow and barrier resistance
Barrier function	Intactness of the stratum corneum barrier of the skin and its ability to deter chemicals, microbes and loss of water from the viable skin layers
Transepidermal water loss	Evaporation of water from the skin's surface as well as a physical tool for assessing perturbations of the skin barrier

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Table 1

List of transdermal products currently on the US market.

Active ingredients	Type of delivery system	Name	Company	Type of patch	Dose and application	Regulatory status	Uses
Clonidine	Transdermal patch extended release	Catapres TTS®	Boehringer Ingelheim	Drug in reservoir and in adhesive formulation	3.5–10.5-cm^2 patches deliver 0.1–0.3 mg/day for 7 days Applied to hairless skin on the upper outer arm or chest	Rx	Essential hypertension
		Clonidine	Par Pharm	Reservoir type	0.1–0.3 mg/24 h for 7 days		
Estradiol	Transdermal patch extended release	Alora®	Watson Laboratories	Adhesive matrix drug reservoir	9–36-cm^2 patches deliver 0.025–0.1 mg/day and continuous delivery for twice weekly dosing Applied to lower abdomen	Rx	Menopause, postmenopausal and osteoporosis, in case of lowered estrogen levels
		Climara®	Bayer Healthcare	Adhesive matrix containing drug	6.5–25-cm^2 patches deliver 0.025–0.1 mg/day for 7 days Applied to lower abdomen or upper quadrant of buttock		
		Estraderm®	Novartis	Reservoir type	0.05 or 0.1-mg/day and continuous delivery for twice weekly application		
		Estradiol	Mylan Technologies	Adhesive matrix containing drug	0.025–0.1 mg/day continuous delivery once weekly patch		
		Menostar®	Bayer Healthcare	Adhesive matrix containing drug	3.25-cm^2 delivers 14 μg/day for 7 days Applied near lower abdomen		
		Vivelle®/Vivelle-Dot	Novartis/Novogyne	Adhesive formulation contains drug	Patches having active surface area of 2.5–10 cm^2 deliver 0.025–0.1 mg/day and twice weekly application Applied to the abdomen		
	Transdermal gel	Divigel®	Upsher-Smith Laboratories	0.1% gel	0.25–1 g dose available Applied to a small area (200 cm^2) of the thigh in a thin, quick-drying layer		
		Elestrin®	Azur Pharma	0.06% gel supplied in a non-aerosol, metered-dose pump container	Applied once daily to the upper arm using a metered-dose pump that delivers 0.87 g of Elestrin® gel per actuation		
		Estrogel®	Ascend Therapeutics	0.06% estradiol in an absorptive hydroalcoholic gel	1.25 g in a single dose and applied to 750-cm^2 area Applied to arm between wrist and shoulder		
	Transdermal spray	Evamist™	KV Pharm/Ther-Rx	Topical application to the skin of a rapidly drying homogeneous solution of 1.7% drug	One, two or three sprays/day (90 μl/spray) to adjacent nonoverlapping 20-cm^2 areas	Rx	Menopause, postmenopausal and osteoporosis, in case of lowered estrogen levels

Active ingredients	Type of delivery system	Name	Company	Type of patch	Dose and application	Regulatory status	Uses
				from a metered-dose pump	on the inner surface of the arm between the elbow and the wrist and allowed to dry		
Estradiol and levonorgestrel	Transdermal patch extended release	Climara Pro™	Bayer Healthcare Pharmaceuticals	Drug in adhesive layer	22-cm^2 Climara Pro™ system contains 4.4 mg estradiol and 1.39 mg levonorgestrel and delivers 0.045 mg estradiol and 0.015 mg levonorgestrel/day for 7 days applied to lower abdomen	Rx	Menopausal symptoms
Estradiol and norethindrone acetate	Transdermal patch extended release	Combipatch®	Novartis	Adhesive layer contains both drugs	9–16-cm^2 patches deliver 0.05/0.14 or 0.05/0.25 mg estradiol/norethindrone acetate per day and applied twice weekly to lower abdomen	Rx	Menopausal symptoms
Ethinyl estradiol and norelgestromin	Transdermal patch extended release	Ortho Evra®	Ortho McNeil Janssen	Adhesive matrix containing drug	6.00 mg norelgestromin and 0.75 mg ethinyl estradiol in each 20-cm^2 patch and delivers for 7 days Applied to buttock, abdomen, upper outer arm or upper torso	Rx	Contraception
Fentanyl	Transdermal patch extended release	Fentanyl transdermal system	Actavis, Mylan Technologies, Lavipharm Labs, Noven, Watson Laboratories and Teva Pharms	Matrix type (Mylan technologies and Teva Pharms) and reservoir (Actavis and Watson laboratories)	10–40-cm^2 patches deliver 25–100 μg/h	Schedule II	Chronic pain (opioid tolerant) that cannot be managed by any other means
		Duragesic®	Ortho McNeil Janssen	Drug in reservoir and in adhesive formulation	5–40-cm^2 patches deliver 12.5–100 μg/h continuous systemic delivery for 72 h applied to flat surface such as the chest, back, flank or upper arm		
Granisetron	Transdermal patch extended release	Sancuso®	Prostraken	Adhesive matrix containing drug	52-cm^2 patch containing 34.3 mg of granisetron. The patch releases 3.1 mg of granisetron per 24 h for up to 7 days Applied to upper outer arm	Rx	Chemotherapy-induced nausea and vomiting
Methylphenidate	Transdermal patch extended release	Daytrana®	Shire	Adhesive-based matrix type patch	12.5–37.5-cm^2 patches deliver 10–30 mg/9 h per patch applied to the hip area 2 h before an effect is needed and should be removed 9 h after application	Schedule II	Attention-deficit hyperactivity disorder
Nicotine	Transdermal patch extended release	Nicoderm® CQ	Aventis	Matrix type patch	7–21 mg over 24 h at different stages of the treatment	OTC	Smoking cessation
		Nicotine transdermal system	Novartis Consumer, Watson Laboratories, Cardinal Health and Aveva	Matrix type patch	7–21 mg/24 h at different stages of treatment		
		Habitrol®	Novartis and Novartis Consumer	Reservoir type	17.5–52.5 mg that delivers 7–21 mg/day for the duration of treatment		
Nitroglycerin	Transdermal patch extended release	Nitro Dur®	Key Pharmaceuticals	Drug in adhesive	5–40-cm^2 patch delivers 0.1–0.8 mg/h for 12–14 h	Rx	Angina prophylaxis

Active ingredients	Type of delivery system	Name	Company	Type of patch	Dose and application	Regulatory status	Uses
		Nitroglycerin	Noven, Hercon Laboratories, Kremers Urban and Mylan Technologies	Drug in adhesive	Delivers nitroglycerin at 0.2 mg/h		
		Minitran Transdermal System™	Graceway Pharmaceuticals	Drug in adhesive	Delivers 0.1–0.6 mg/h		
	Transdermal ointment	Nitroglycerin	Fougera	2%	7.5–30 mg applied in the morning and again 6 h later to a 36-inch^2 area of truncal skin		
Oxybutynin	Transdermal patch extended release	Oxytrol®	Watson Laboratories	Adhesive matrix containing drug	39 cm^2 system containing 36 mg and has a nominal *in vivo* delivery rate of 3.9 mg oxybutynin per day consistently for 3–4 days Applied to abdomen, hip or buttock	Rx	Bladder muscle dysfunction
Oxybutynin chloride	Transdermal gel	Gelnique®	Watson Labs	10% gel	100 mg applied once daily to dry, intact skin on the abdomen, upper arms/ shoulders or thighs (area of application rotated)	Rx	Bladder muscle dysfunction
Rivastigmine	Transdermal patch extended release	Exelon®	Novartis	Matrix reservoir containing drug	4.6–9.5 mg/24 h from 5–10-cm^2 patches Preferable application to upper or lower back	Rx	Dementia associated with Alzheimer's disease and Parkinson's disease
Scopolamine	Transdermal patch extended release	Transderm Scop®	Novartis	Matrix reservoir containing drug	2.5-cm^2 patch delivers 1.0 mg for 3 days Applied to the hairless area behind one ear	Rx	Motion sickness, Postoperative nausea and vomiting (prophylaxis).
Selegiline	Transdermal patch extended release	Emsam®	Somerset	Drug in adhesive	6–12 mg/24 h from 20–40-cm^2 patch Applied to the upper torso, upper thigh or the outer surface of the upper arm	Rx	Major depressive disorder
Testosterone	Transdermal patch extended release	Androderm®	Watson Laboratories and Watson Pharma	Reservoir type	2.5 or 5 mg/day from 37–44-cm^2 patch	Schedule III Rx	Hypogonadism (testosterone deficiency)
	Transdermal gel	Androgel®	Unimed Pharma and Solvay/Abbott	1% gel	5–10 g contains 50–100 mg, 10% of the applied testosterone dose is absorbed across skin of average permeability during a 24-h period Applied 5 g once daily to shoulders and upper arms and/or abdomen		

OTC: Over-the-counter drug; Rx: Prescription drug.

Data retrieved from [201,202,211,212].

Table 2

List of transdermal products for local tissue treatment currently on the US market.

Active ingredients	Type of delivery system	Name	Company	Concentration	Dose and application	Regulatory status	Uses
Capsaicin	Topical patch (drug in adhesive)	Qutenza®	NeurogesX, Inc.	8%	Four patches (maximum) can be applied every 3 months for a 60-min application Applied by healthcare professional and local topical anesthetic may be required	Rx	Neuropathic pain associated with postherpetic neuralgia
Diclofenac epolamine	Topical patch (drug in adhesive)	Flector®	Inst Biochem	1.3%	Each 10 × 14-cm patch contains 180 mg Applied twice daily	Rx	Pain relief
Diclofenac sodium	Topical gel/jelly	Voltaren® gel	Novartis Consumer Health	1%	2–4 g applied maximum of four-times daily	Rx	Osteoarthritis
		Solaraze®	Nycomed US	3%	0.5 g gel used on each 5 cm^2 lesion site		Topical treatment of actinic keratoses
	Topical solution	Pennsaid®	Nuvo Research Inc.	1.5%	Each 1 ml solution contains 16.05 mg of drug Applied ten drops at a time, four times for each application	Rx	Osteoarthritis of the knee
Lidocaine	Topical patch (drug in adhesive)	Lidoderm®	Teikoku Pharm	5%	10 × 14-cm patch, 70 mg/patch, three patches can be applied at one time for 12 h in a 24-h period	Rx	Postherpetic neuralgia
Lidocaine	Topical cream utilizes SonoPrep® or laser-assisted drug delivery technology		Echo Therapeutics and Norwood Abbey	4%	Treatment with the device prior to application of 4% topical cream	Rx	Local dermal anesthesia
Lidocaine and prilocaine	Topical cream	Emla®	App Pharms	2.5% of each drug	1–10 g/10 cm^2 of skin surface area is applied for varying lengths of time as required	Rx	Local anesthetic
Lidocaine and tetracaine	Topical patch utilizes CHADD® technology	Synera®	Zars Pharma	70 mg of each drug/patch	Typically applied 20–30 min before the procedure	Rx	Local anesthetic for superficial dermatological procedures/venous access

Active ingredients	Type of delivery system	Name	Company	Concentration	Dose and application	Regulatory status	Uses
Menthol and capsaicin	Topical liquid	Absorbine Jr® arthritis strength	WF Young	4% menthol, 0.025% capsaicin	Thin film three- to four-times daily	OTC	Arthritis pain, musculoskeletal pain and neuropathic pain
Menthol and methyl salicylate	Topical patch	Salonpas® arthritis pain	Hisamitsu America	31.5 mg menthol, 105 mg methyl salicylate	Patch can be used up to four-times daily	OTC	Arthritis pain
Salicylic acid	Topical patch	Trans-Ver-Sal®	Doak	15%	6–20-mm patch	OTC	Acne vulgaris, hyperkeratotic psoriasis and removal of wart
Trolamine salicylate	Topical cream	Joint and muscle pain relief	Flex-Power	10% cream	Massaged three- to four-times daily	OTC	Muscle and joint pain

OTC: Over-the-counter drug; Rx: Prescription drug.

Data retrieved from [201,202,211,212].

Table 3

Ongoing FDA-approved active clinical trials involving transdermal delivery systems.

Drug	Sponsor (collaborators)	Transdermal product/intervention	Phase	Disease state/other comments
Buprenorphine	Mundipharma Research Limited	Buprenorphine transdermal patch extended release	I and II	Chemotherapy-induced mucositis and mouth pain in children
Fentanyl	Cristália Produtos Químicos Farmacêuticos Ltda.	Transdermal fentanyl	III	Pain and palliative care
	Janssen Korea, Ltd., Korea	Transdermal fentanyl	IV	Pain
Hormone therapy	Washington University School of Medicine (American College of Obstetricians and Gynecologists)	Transdermal estradiol versus oral naproxen or placebo	-	Contraception bleeding
	Massachusetts General Hospital	Transdermal 17β-estradiol versus oral estrogen versus placebo	III	Amenorrhea and female athlete triad syndrome
	Bayer	Ethinylestradiol/gestodene (BAY86–5016)	II	Contraception and ovulation inhibition
	Bayer	Ethinylestradiol/gestogene (BAY86–5016)	II	Contraception
	Bayer	Ethinylestradiol/gestodene (BAY86–5016)	III	Contraception
	Stanford University	Transdermal estrogen versus oral estrogen	-	Ovarian failure, premature
	University of Chicago (Novo Nordisk, University of Michigan, Johns Hopkins University, Massachusetts General Hospital, University of Oklahoma, University of South Florida and Thomas Jefferson University)	Transdermal estradiol plus growth hormone	-	Turner's syndrome
	National Institute on Aging	Gonadotropin-releasing hormone plus transdermal estradiol	III	Obesity
	Imperial College London (National Cancer Institute)	Transdermal estrogen versus luteinizing hormone-releasing hormone analog	II	Anemia, cardiovascular complications, hot flashes, osteoporosis and prostate cancer
	University of Pittsburgh	Transdermal estrogen patch versus oral sertraline or placebo	IV	Postpartum depression
	Robert H Lurie Cancer Center (National Cancer Institute)	Transdermal 4-hydroxytamoxifen or placebo plus oral tamoxifen citrate or placebo	II	Breast cancer
	Weill Medical College of Cornell University	Oral contraceptive pills/microdose lupron versus transdermal estradiol patch/gonadotropin-releasing hormone antagonist	IV	Infertility
	Population Council	Transdermal NES/E2 gel	II	Ovulation
	Procter and Gamble	Transdermal testosterone versus placebo	II	Heart failure
	Steven Lamm (Solvay Pharmaceuticals)	AndroGel® (transdermal testosterone gel)	I	Hypogonadism
	M et P Pharma	Transdermal testosterone versus intranasal testosterone	I	Hypogonadism

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Drug	Sponsor (collaborators)	Transdermal product/intervention	Phase	Disease state/other comments
	Karolinska Institutet (Karolinska University Hospital, UroHealth Skövde, Universitätsklinikum MünsterInstitut für Reproduktionsmedizin, Krankenanstalt der Stadt Wien Rudolfstiftung, Medical University of Graz, Krankenhaus der Stadt Wien Lainz, Medizinische Universität Wien, Endokrinologikum and Charite University)	Transdermal testosterone versus placebo	III	Metabolic syndrome
	National Institute on Aging	Ganirelix acetate plus transdermal estradiol or placebo	-	Arterial stiffening, aging and menopause
	The Alfred (Stanley Medical Research Institute)	Transdermal estradiol versus placebo	-	Schizophrenia, schizoaffective disorder and schizophreniform disorder (not in manic phase)
	Massachusetts General Hospital	Transdermal estrogen plus gonadotropin-releasing hormone plus gonadotropin-releasing hormone antagonist	II and III	Healthy postmenopausal women
	University Hospital	Transdermal versus oral estradiol	IV	Postmenopausal
	Center for Epidemiology and Health Research (Procter and Gamble)	Transdermal testosterone patch plus estrogen	IV	Ovariectomy, hysterectomy and hypoactive sexual desire disorder
	Boston University (Eunice Kennedy Shriver National Institute of Child Health and Human Development)	Transdermal testosterone (active or placebo) plus open-label sildenafil citrate	IV	Erectile dysfunction, testosterone deficiency and diabetes
	BioSante Pharmaceuticals	Transdermal testosterone versus placebo	III	Hypoactive sexual desire disorder
	Eunice Kennedy Shriver National Institute of Child Health and Human Development (Population Council)	Transdermal testosterone plus active or placebo Nestorone® gel	I	Contraception
Methylphenidate	Cox Health Systems	Methylphenidate transdermal system (Daytrana®)	-	Attention-deficit hyperactivity disorder and insomnia
	University of Virginia	Methylphenidate transdermal system (Daytrana) versus placebo	-	Attention-deficit hyperactivity disorder
	University of Utah (Shire Pharmaceutical Development)	Methylphenidate transdermal system versus placebo	III	Attention-deficit hyperactivity disorder
Nicotine	Assistance Publique – Hôpitaux de Paris	Transdermal nicotine versus usual treatment of Parkinson's disease	II	Idiopathic Parkinson's disease
	Ohio State University (American Thoracic Society)	Transdermal nicotine versus no intervention	IV	Pulmonary sarcoidosis
	National Institute on Alcohol Abuse and Alcoholism	Smoking cessation (with transdermal nicotine) plus behavioral counseling	II	Tobacco use cessation and alcohol-related disorders
	National Institute on Drug Abuse (NIDA) (National Institutes of Health Clinical Center)	Transdermal nicotine or placebo	-	Nicotine dependence and schizophrenia
	University of Pennsylvania	Transdermal nicotine ± placebo	II	Nicotine dependence

Drug	Sponsor (collaborators)	Transdermal product/intervention	Phase	Disease state/other comments
	Massachusetts General Hospital (Stanley Medical Research Institute, North Suffolk Mental Health Association)	Transdermal nicotine versus placebo patch	IV	Schizophrenia
	University of Ottawa Heart Institute (Heart and Stroke Foundation of Ontario)	Transdermal nicotine versus oral varenicline	IV	Coronary heart disease
	Ochsner Health System	Transdermal nicotine versus placebo	-	Postoperative nausea and vomiting
	National Institute on Drug Abuse (NIDA)	Transdermal nicotine	IV	Nicotine dependence
	Yale University	Transdermal nicotine versus intranasal nicotine versus placebo	II	Alcohol drinking
	Centre for Addiction and Mental Health	Transdermal nicotine plus transcranial magnetic stimulation	-	Cigarette smoking and schizophrenia
	Duke University (Shire Pharmaceutical Development)	Transdermal nicotine patch plus lisdexamphetamine or placebo	-	Attention-deficit hyperactivity disorder and nicotine dependence
	Medical University of South Carolina	Transdermal nicotine patch versus varenicline	IV	Nicotine dependence
	Butler Hospital (National Institute on Drug Abuse [NIDA])	Transdermal nicotine plus counseling	-	Nicotine dependence
	University of Texas at Austin	Transdermal nicotine versus no intervention	I	Smoking cessation
	Stony Brook University	Transdermal nicotine versus placebo	-	Postoperative pain
	University of Pennsylvania (NIH)	Transdermal nicotine	-	Nicotine dependence
	University of California, San Francisco (National Cancer Institute)	Transdermal nicotine	-	Breast cancer, chemotherapeutic agent toxicity and Palmar–Plantar erythrodysesthesia
	Medical University of South Carolina	Transdermal nicotine	-	Nicotine dependence
	Butler Hospital (National Institute on Drug Abuse)	Behavioral modification plus transdermal nicotine	II	Nicotine dependence
	Yu-Li Hospital (National Health Research Institutes, Taiwan Department of Health, Taiwan)	Transdermal nicotine plus bupropion	IV	Tobacco dependence and schizophrenia
	Centre for Addiction and Mental Health (Pfizer, Ontario Ministry of Health and Long Term Care)	Transdermal nicotine plus behavioral interventions	-	Smoking
	Department of Veterans Affairs	Transdermal nicotine plus behavioral therapy plus bupropion SR	0	Stress disorders and post-traumatic tobacco use disorder
	National Institute of Cancerología	Transdermal nitroglycerin	II	Locally advanced non-small-cell lung cancer
	University Hospital, Basel, Switzerland	Experimental treatment combination that includes transdermal nitrates	-	Acute heart failure
	University Hospital, Basel, Switzerland	Targeted therapy with nitrates, including transdermal nitroglycerin	-	Acute heart failure
Rivastigmine	Novartis Pharmaceuticals	Transdermal rivastigmine	IV	Alzheimer’s disease

Drug	Sponsor (collaborators)	Transdermal product/intervention	Phase	Disease state/other comments
	University Hospital, Lille	Transdermal rivastigmine versus placebo	III	Parkinson's disease and apathy
	Novartis Pharmaceuticals	Transdermal rivastigmine versus placebo	IV	Multiple sclerosis and cognitive impairment
Rotigotine	UCB, Inc.	Transdermal rotigotine versus placebo	III	Parkinson's disease
	UCB, Inc.	Transdermal rotigotine	I	Healthy volunteers
	University College, London (Medical Research Council)	Transdermal rotigotine	II	Right hemisphere stroke, hemispatial neglect and motor deficits
Scopolamine	Drexel University College of Medicine (Merck)	Transdermal scopolamine plus oral aprepitant or placebo	-	Nausea and vomiting
	Drexel University College of Medicine (Merck)	Transdermal scopolamine or placebo plus oral aprepitant	-	Nausea and vomiting
Miscellaneous or investigational agents	Banner Health (Phoenix Children's Hospital)	Transdermal DMPS (metal chelator approved for use in Europe)	I	Intoxication
	Somerset Pharmaceuticals	Transdermal selegiline versus placebo	IV	Mental health and major depressive disorder
	Eli Lilly and Company (TransPharma Medical)	Transdermal versus subcutaneous teriparatide	II	Osteoporosis
	Labtec GmbH	Transdermal sufentanil versus oral morphine sulfate	II	Chronic pain
	University of Nottingham	Transdermal glyceryl trinitrate patch	II and III	Stroke
	Lytix Biopharma AS (Oslo University Hospital, Karolinska University Hospital)	LTX-315 (Oncopore™), dose escalation study	I	Cancer with transdermal accessible tumor
	Otsuka Pharmaceutical Co., Ltd	SPM 962 versus placebo	II and III	Early Parkinson's disease
	Butler Hospital	Oral fluoxetine or placebo plus transdermal nicotine	III	Major depressive disorder and nicotine dependence depression
	McMaster University (The Physicians' Services Incorporated Foundation and Canadian Network and Centre for Trials Internationally)	Transdermal clonidine or placebo; active (oral) aspirin or placebo	IV	Cardiovascular disease
	Fundación Cardiovascular de Colombia (Fundación Santandereana de Diabetes y Obesidad (FUSANDE), The University of Akron, University of Santander and Instituto de Salud de Bucaramanga (ISABU))	Controlled nitric oxide releasing patch versus placebo	III	Diabetic foot
	MedtronicNeuro	Standard therapy (including transdermal oxybutynin) versus InterStim® therapy	IV	Urinary incontinence and urge overactive bladder
	Axxonis Pharma AG	Transdermal lisuride versus oral ropinorole or placebo	III	Restless legs syndrome
	NuPathe Inc.	NP101 (sumatriptan iontophoretic transdermal patch)	III	Migraine disorders

Data taken from [206].

Table 4

Ongoing clinical trials involving microporation techniques for transdermal delivery.

Microporation technique	Sponsor (Collaborator)	Intervention	Disease state/other comments
Electroporation	Karolinska University Hospital (Karolinska Institutet, Swedish Institute for Infectious Disease and Control Cyto Pulse Sciences, Inc.)	DNA vaccine delivered by intradermal electroporation (device: Derma Vax™)	Colorectal cancer
	Uppsala University (Karolinska Institutet and Cyto Pulse Sciences, Inc.)	DNA vaccine delivered by intradermal electroporation (device: Derma Vax)	Prostate cancer
Microneedles	Emory University	Microneedles versus subcutaneous catheter for insulin delivery	Type 1 diabetes
	The University of Hong Kong (Hospital Authority, Hong Kong)	MicronJet versus intramuscular injection of H1N1 vaccine	Vaccination and influenza
	NanoPass Technologies Ltd	Conventional subcutaneous injection versus MicronJet for insulin delivery	Intradermal injections and healthy volunteers
	Hadassah Medical Organization	Intradermal unadjuvanted Pandemrix® via a microneedle device, compared with intramuscular adjuvanted Pandemrix	Healthy subjects
	NanoPass Technologies Ltd	Delivery of influenza vaccine with microneedles versus intramuscular injection	Influenza vaccine
	Becton, Dickinson and Company	Extended microneedle delivery of insulin	Types 1 and 2 diabetes mellitus
Radiofrequency ablation	Eli Lilly and Company (TransPharma Medical)	Transdermal versus subcutaneous teriparatide (device: ViaDerm™ drug delivery system)	Osteoporosis

Data taken from [206].