CURRENT STATUS AND FUTURE POTENTIAL OF TRANSDERMAL DRUG DELIVERY

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The past twenty five years have seen an explosion in the creation and discovery of new medicinal agents. Related innovations in drug delivery systems have not only enabled the successful implementation of many of these novel pharmaceuticals, but have also permitted the development of new medical treatments with existing drugs. The creation of transdermal delivery systems has been one of the most important of these innovations, offering a number of advantages over the oral route. In this article, we discuss the already significant impact this field has made on the administration of various pharmaceuticals; explore limitations of the current technology; and discuss methods under exploration for overcoming these limitations and the challenges ahead.

TRANSDERMAL DELIVERY
The movement of compounds across the stratum corneum and into systemic circulation.

STRATUM CORNEUM
The outer layer of epidermis, consisting of several layers of corneocytes in a lipid-rich matrix.

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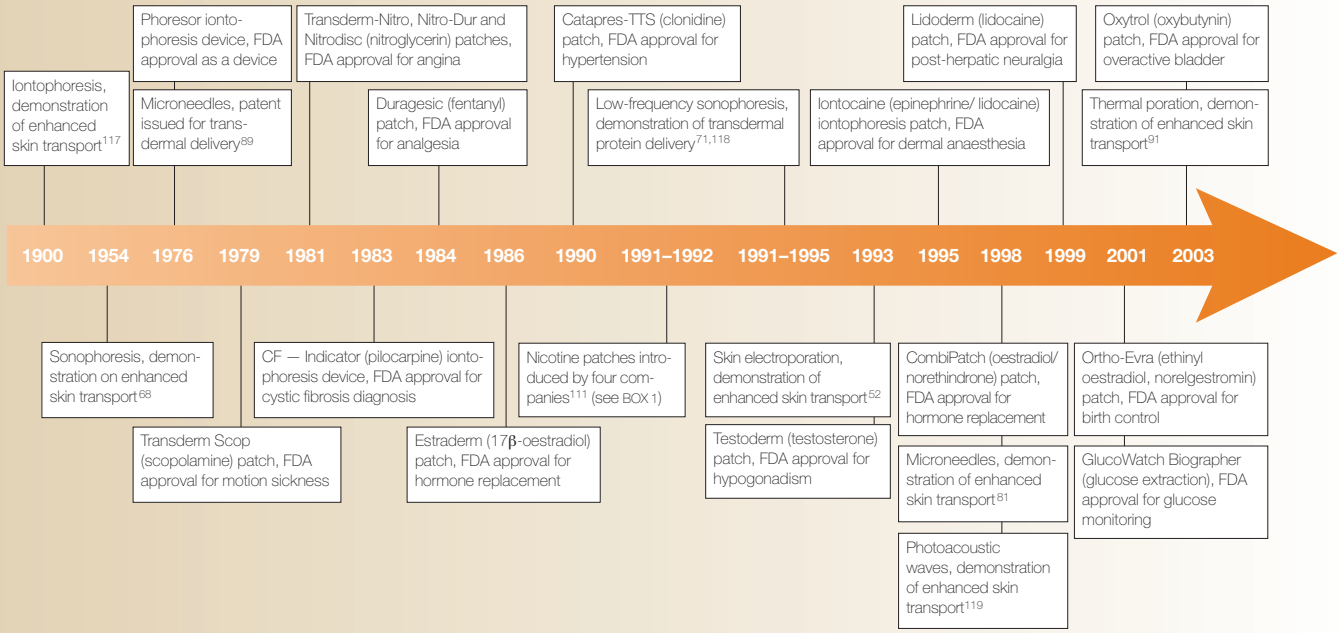
The first studies involving TRANSDERMAL DELIVERY sought to determine what caused skin to have barrier properties that prevent molecular permeation (TIMELINE). In 1924, Rein proposed that a layer of cells joining the STRATUM CORNEUM — the thin, outermost layer of the skin — to the EPIDERMIS posed the major resistance to transdermal transport[1]. Blank modified this hypothesis after removing sequential layers of stratum corneum from the surface of skin and showing that the rate of water loss from skin increased dramatically once the stratum corneum was removed[2]. Finally, Scheuplein and colleagues showed that transdermal permeation was limited by the stratum corneum by a passive process[3,4]. Despite the significant barrier properties of skin, Michaels and co-workers measured apparent diffusion coefficients of model drugs in the stratum corneum and showed that some drugs had significant permeability[5]. This led to the active development of transdermal patches in the 1970s, which yielded the first patch approved by the US FDA in 1979; it was a three-day patch that delivered scopolamine to treat motion sickness. In 1981, patches for nitroglycerin were approved.

Today there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, oestradiol, oxybutinin, scopolamine and testosterone[6]. There are also combination patches for contraception, as well as hormone replacement. Depending on the drug, the patches generally last from one to seven days. The annual US market for transdermal patches is more than US $3 billion. TABLE 1 gives a summary of patches available at present.

Transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first-pass drug-degradation effects. Patches can also reduce side effects; for example, oestradiol patches are used by more than a million patients annually and, in contrast to oral formulations, do not cause liver damage[7]. Similarly, transdermal clonidine, nitroglycerin and fentanyl patches exhibit fewer adverse effects than conventional oral dosage forms. As another example, nicotine patches have helped people quit smoking and thereby increase lifespan. One study showed that two years after transdermal nicotine-patch therapy, patients were four times more likely to have stopped smoking compared with patients who received placebos[8]. Using this success rate as an estimate, more than a million US smokers have given up smoking with the help of nicotine patches (BOX 1).

Timeline | **Important events in transdermal drug delivery***



*Events and dates have been documented based on publication of peer-reviewed papers or approval by the FDA.

Presently available transdermal patches can be classified into two categories on the basis of their design: reservoir-type and matrix-type patches. A reservoir-type patch holds the drug in a solution or gel, from which drug delivery can be governed by a rate-controlling membrane positioned between the drug reservoir and skin. Reservoir-type patches offer an advantage over matrix-type patches in terms of formulation flexibility and tighter control over delivery rates, although they can have an initial burst of drug release. Reservoir-type patches usually involve greater design complexity. By contrast, matrix-type patches, which were introduced after reservoir-type patches, combine the drug, adhesive and mechanical backbone of the patch into a simpler design that does not involve a rate-controlling membrane; skin permeability usually governs the rate of drug delivery. Although these patches are easier to fabricate, they have limited flexibility in their design compared with reservoir-type patches.

Despite these successes, the number of drugs that can be administered using conventional patches is very limited. As evidence of this, all of the drugs presently administered across skin share three constraining characteristics: low molecular mass (<500 Da), high lipophilicity (oil soluble) and small required dose (up to milligrams). The smallest drug presently formulated in a patch is nicotine (162 Da) and the largest is oxybutinin (359 Da). Opening the transdermal route to large hydrophilic drugs is one of the major challenges in the field of transdermal drug delivery.

Routes and barriers to transdermal transport

The limitations of transdermal drug delivery are governed largely by skin anatomy (FIG. 1). As the largest organ of the human body, skin provides a painless and compliant interface for systemic drug administration[9]. However, skin has evolved to impede the flux of toxins into the body and minimize water loss, which means that it naturally has a very low permeability to the penetration of foreign molecules[10]. A unique hierarchical structure of lipid-rich matrix with embedded CORNEOCYTES in the upper strata (15 μm) of skin — the stratum corneum — is responsible for this barrier.

The corneocytes, which comprise crosslinked keratin fibres, are about 0.2–0.4 μm thick and about 40 μm wide[11]. The corneocytes are held together by corneodesmosomes, which confer structural stability to the stratum corneum. The stratum corneum lipids are composed primarily of ceramides, cholesterol and fatty acids that are assembled into multi-lamellar bilayers. This unusual extracellular matrix of lipid bilayers serves the primary barrier function of the stratum corneum. The layer of lipids immediately adjacent to each corneocyte is covalently bound to the corneocyte and is important in maintaining barrier function. The stratum corneum is continuously DESQUAMATED, with a renewal period of two to four weeks. It is actively repaired by cellular secretion of lamellar bodies following the disruption of its barrier properties or other environmental insults[12].

Transdermal transport of solutes is largely controlled by stratum corneum lipid bilayers. Solute transport in stratum corneum lipid bilayers, like in other

EPIDERMIS
The outer, epithelial portion of the skin.

CORNEOCYTE
The non-living, keratin-filled squamous cell of the stratum corneum.

DESQUAMATED
Shed from the surface of the skin.

Table 1 | **Characteristics of transdermal patches***

Active ingredient	Product name	Dose and size of patch	Dose delivered	Clinical indication
Clonidine	Catapres-TTS	2.5–7.5 mg in 3.5–10.5 cm^2	0.7–2.1 mg in 7 d	Hypertension
Ethinyl oestradiol (EO), norelgestromin (N)	Ortho-Evra	0.75 mg EO and 6 mg N in 20 cm^2	0.14 mg EO and 1.05 mg N in 7 d	Birth control
Fentanyl	Duragesic	2.5–10 mg in cm^2	1.8–7.2 mg in 3 d	Analgesia
Lidocaine	Lidoderm	700 mg in 140 cm^2	10–32 mg in 12 h	Post-herpatic neuralgia
Lidocaine (L), epinephrine (E)	Iontocaine	20–50 mg L and 10–25 μg E in 5.7–11.1 cm^2	40 mAmin iontophoresis	Dermal anaesthesia
Nicotine	Habitrol Nicoderm-CQ Nicotrol Prostep	8.3–114 mg in 3.5–30 cm^2	5–22 mg in 16–24 h	Smoking cessation
Nitroglycerin	Nitro-Dur Transderm-Nitro	12.5–160 mg in 5–40 cm^2	1.2–11.2 mg in 12–14 h	Angina
17β-oestradiol	Alora, Climara Esclim, Estraderm FemPatch, Vivelle, Vivelle-DOT	0.39–20 mg in 2.5–44 cm^2	0.075–0.7 mg in 3–7 d	Hormone replacement
Oestradiol (O), norethindrone (N)	CombiPatch	0.51–0.62 mg O and 2.7–4.8 mg N in 9–16 cm^2	0.15–0.20 mg O and 0.42–1.0 mg N in 3–4 d	Hormone replacement
Oxybutynin	Oxytrol	36 mg in 39cm^2	11.7–15.6 mg in 3–4 d	Overactive bladder
Scopolamine	Transderm Scop	1.5 mg in 2.5 cm^2	1.0 mg in 3 d	Motion sickness
Testosterone	Androderm Testoderm TTS Testoderm	10–328 mg in 37–60 cm^2	2.5–6 mg in 1 d	Hypogonadism

*This list contains FDA-approved transdermal patches (not including generics) listed on the FDA website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/).

lipid bilayer systems, is highly anisotropic and size-dependent. Specifically, lipid bilayers exhibit strong structural heterogeneity that results in spatial variations in solute partition and diffusion coefficients[13]. As a result, molecules are believed to diffuse across skin following a tortuous pathway within either the tail-group (for hydrophobic molecules) or head-group (for hydrophilic molecules) regions, in which transport between bilayers can occur at bilayer–bilayer interfaces or other sites of structural disorganization.

Transdermal transport of hydrophilic solutes has received less attention than hydrophobic solutes, because hydrophilic solutes generally exhibit low permeabilities that are difficult to measure. However, with the aid of penetration enhancers the delivery of hydrophilic solutes is being investigated. Accordingly, mathematical models to describe transdermal transport of hydrophilic drugs are becoming increasingly important and are often based on transport through porous pathways across the skin. Such models have been used to describe passive transdermal transport of hydrophilic solutes[14,15]. Transdermal transport of hydrophilic solutes can also occur through hair follicles and sweat ducts (that is, shunt pathways), which could allow diffusion of solutes not only across the stratum corneum, but also across the epidermis.

The development of mathematical models to describe and predict skin permeability has been an area of active research, especially for predicting permeability of the stratum corneum to hydrophobic drugs[16–18]. These models can be categorized into quantitative structure–permeability relationships (QSPRs), expressions based on diffusion mechanisms, or a combination of both[19]. One equation, developed by Potts and Guy[18], correlates skin permeability (P) to a drug in aqueous solution with solute molecular mass (M) and octanol–water partition coefficient ($K_{o/w}$) by equation 1:

$$\log P \cong -2.7 + 0.71 \cdot \log K_{o/w} - 0.0061 \cdot \mathrm{M} \qquad (1)$$

Similar equations have been proposed by other investigators[20,21]; parameters such as hydrogen bonding[22,23] and melting point[24] have also been added to better fit the data.

Other methods for estimating skin permeability include group contribution approaches[25], as well as newer techniques including combinations of molecular orbital calculations with neural networks[26] and random-walk calculations[27]. Additional models have been proposed to explain the size-dependence of skin permeation[28]. Most models attempt to use a single equation to describe skin permeability for all molecules, which implicitly assumes that the permeation pathways are the same for all solutes.

Box 1 | **The race to market the first nicotine patch**

In the mid-1980s, the pharmaceutical industry recognized the opportunity to develop a nicotine patch to help smokers quit. Although many factors influence whether attempts at smoking cessation are successful, addressing a smoker's physical addiction to nicotine increases the odds of additionally overcoming the psychological and emotional barriers[109]. With approximately 50 million smokers in the United States at that time, of whom about one third attempted to quit smoking each year[110], the potential market size for an effective smoking cessation aid was huge. So, the race to develop a nicotine patch was on.

Four development teams — Ciba-Geigy, Lederle/Elan, Marion Merrell Dow/Alza and Warner-Lambert/Cygnus — each vied to reach the market first. Although Ciba-Geigy had sufficient transdermal expertise in house, the other pharmaceutical companies approached three of the leading drug delivery companies to develop their nicotine patches in partnership. All of the patches — Habitrol, Prostep, Nicoderm and Nicotrol — contained a contact adhesive, a drug reservoir and an impermeable backing. The Nicoderm design included a membrane that controlled the release rate from the patch, whereas the others relied on the variable barrier properties of the skin to control release rate. Nicotrol was designed as a 16-hour patch, which avoided night-time sleep disturbances, in contrast to the 24-hour patches developed by the other three, which were more effective in preventing early-morning cigarette cravings[111].

Despite different patch designs, a range of project start times and a lawsuit between two of the companies, the US FDA approved all four nicotine patches within a few months at the end of 1991 and beginning of 1992. Total sales during the first year of marketing approached US $1 billion. Transdermal delivery surged into clinical practice and 'the patch' became a household word.

Chemical enhancers

Because the skin provides such a formidable barrier to the delivery of most drugs, a broad range of different chemical additives have been tested to enhance transdermal penetration. In contrast to physically enhanced delivery methods discussed below, chemical penetration enhancers provide certain advantages, including design flexibility with formulation chemistry and an easier possibility of patch application over a large area (>10 cm^2). Extensive research during the past two decades has led to the formulation of several different classes of penetration enhancers, including SURFACTANTS (for example, Tween)[29], fatty acids/esters (for example, OLEIC ACID)[30], terpenes (for example, limonene), and solvents (for example, dimethyl sulphoxide and ethanol). However, only a small number of chemical enhancers have been shown to induce significant (therapeutic) enhancement of drug transport. Enhanced delivery of high-molecular-mass drugs is even more limited.

As an additional limitation, potent chemical enhancers are usually potent irritants to the skin at concentrations necessary for achieving useful levels of penetration enhancement and are therefore physiologically incompatible[31]. With limited success, attempts have been made to synthesize novel chemical penetration enhancers — for example, lauracapram (Azone) — that safely achieve therapeutic transport enhancement[32,33]. Some of the newer 'specialty' penetration enhancers, such as 2-n-nonyl-1,3-dioxolane (SEPA), also attempt to enhance skin permeation without irritation and are being evaluated for clinical applications[34].

Chemical penetration enhancers can increase skin permeability by various mechanisms, including enhancing solubility, increasing partitioning into the stratum cornuem, fluidizing the crystalline structure of stratum cornuem and causing dissolution of stratum cornuem lipids[35,36]. Enhanced solubility of drugs is of special interest for hydrophobic drugs, such as oestradiol. Ethanol and propylene glycol are often used as solubilizers. Oleic acid is one of the leading penetration enhancers used for transdermal applications. Detailed mechanistic studies have revealed that oleic acid pools in the stratum cornuem and increases bilayer fluidity[37]. Surfactants, though commonly used in topical cosmetic products, have not been used extensively in transdermal delivery applications. Surfactants are potent transport enhancers by virtue of their ability to solubilize/extract lipids and denature keratin. Colloidal carriers using emulsions, micelles, liposomes and deformable vesicles have been used extensively in the TOPICAL DELIVERY of cosmetic and dermatological agents, but their applications in transdermal drug delivery are still under development[38].

Although individual chemical enhancers have had limited success, combinations of chemical enhancers offer new opportunities in transdermal formulations. However, the rational design of enhancer combinations is limited by the lack of mechanistic information on the interactions between individual chemical enhancers and the stratum corneum. High-throughput methods for screening transdermal formulations directly address this bottleneck and might lead to the discovery of previously unknown enhancer mixtures (BOX 2)[39].

Iontophoresis

Rates of transdermal transport can also be increased through IONTOPHORESIS, which uses an electric field to move both charged and uncharged species across the skin. Transdermal iontophoresis has been most extensively applied to the delivery of anti-inflammatory agents and other compounds for local effects in the context of physical therapy[40]. Other FDA-approved uses include pilocarpine delivery to induce sweating as part of a cystic fibrosis diagnostic test[41], tap-water delivery to treat HYPERHIDROSIS[42], lidocaine delivery for local anaesthesia, especially before venipuncture[43], and extraction of interstitial fluid for monitoring glucose levels in diabetics[44]. Typically, a few milliamperes of current are applied to a few square centimetres of skin, which generally causes no pain or irritation beyond mild erythema[45]. In addition to the few existing FDA-approved products based on iontophoresis a number of companies are actively developing new systems for the delivery of pain medications and other drugs.

The long-term promise of iontophoresis is the prospect of delivering hydrophilic drugs and even macromolecules across the skin with a user-friendly, possibly disposable, system designed for home use. Extensive studies *in vitro* and in animals, coupled with a number of studies in humans, have established the feasibility of iontophoresis for a broad range of drugs, including dexamethasone, ketorolac, luteinizing hormone-releasing hormone and calcitonin[46]. Rates of transdermal transport can be increased by orders of magnitude relative to passive diffusion-based methods, and can be readily modulated by adjusting electrical

SURFACTANT
A molecule typically containing separate hydrophilic and hydrophobic domains that reduces surface tension of water.

OLEIC ACID
A carboxylic acid with a linear chain of 18 carbon atoms and one double bond ($C_{18}H_{34}O_2$).

TOPICAL DELIVERY
The movement of compounds across the stratum corneum and locally into the skin.

IONTOPHORESIS
The movement of molecules across the skin or other tissue under the influence of an electric field.

HYPERHIDROSIS
Excessive sweating, especially of the hands and feet.

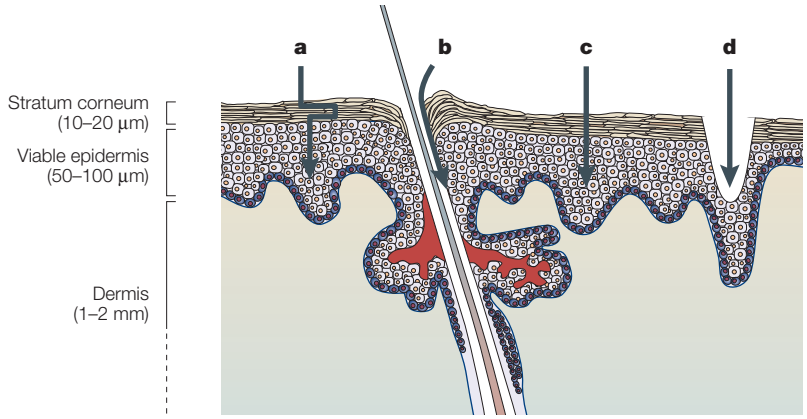


Figure 1 | **Schematic representation of a cross section through human skin.** Stratum corneum, located on the outer surface of the skin, is a non-living layer of keratin-filled cells surrounded by a lipid-rich extracellular matrix that provides the primary barrier to drug delivery into skin. The epidermis below is a viable tissue devoid of blood vessels. Just below the dermal-epidermal junction, the dermis contains capillary loops that can take up transdermally administered drugs for systemic distribution. **a** | Transdermal diffusion, possibly in the presence of a chemical enhancer, takes place by a tortuous route across the stratum corneum, winding around cells and occurring along the interfaces of extracellular lipid bilayers. **b** | Low-voltage electrical enhancement by iontophoresis can make transport pathways through hair follicles and sweat ducts more accessible. **c** | High-voltage enhancement by electroporation has been shown to occur via transcellular pathways made accessible by disrupting lipid bilayers. The application of ultrasound seems to make pathways **a** and **c** more permeable by disorganizing lipid bilayer structure. **d** | Microneedles and thermal poration create micron-scale holes in skin to provide pathways for drug transport.

parameters. The delivery of bioactive levels of peptides, such as insulin, and other small macromolecules has been demonstrated in animals, although the delivery of sufficient quantities to humans has been difficult[47].

Iontophoresis can enhance transport across skin by a number of possible mechanisms, including an ELECTROPHORETIC driving force, an ELECTRO-OSMOTIC driving force, and transiently increased skin permeability. The electrophoretic mechanism can drive charged compounds across the skin by a direct interaction with the electric field. Species with greater charge and smaller molecular mass are generally delivered more rapidly. Enhancement by electro-osmosis involves the delivery of molecules that are dragged by electrically induced solvent flow[48]. This directional movement of solvent is induced by a net flux of cations from the anode to the cathode, which is caused by the poor mobility of negatively charged proteins embedded in the skin relative to their highly mobile cationic counter ions, such as Na^+. Finally, exposure of skin to an electric field with a transdermal voltage greater than approximately 1 V can increase skin permeability[49,50] by a mechanism that is poorly understood, but which might involve permeabilization of follicular pathways[51]. At much larger voltages, disruption of the lipid structure of the stratum corneum is believed to occur by ELECTROPORATION, as discussed below.

Electroporation

Another approach to increase transdermal transport using electric fields involves the application of short, high-voltage pulses to the skin to transiently increase skin permeability by a mechanism related to electroporation[52–55]. Transdermal transport has been shown to increase by orders of magnitude using electroporation, with partial reversibility within seconds and full reversibility, in some cases, within minutes to hours[53,56]. The largest fluxes have been observed for synthetic molecules and small macromolecules (<10 kDa), including a clinical study of lidocaine delivery in humans[57]. Larger macromolecules have also been delivered, including heparin[58], insulin[59], vaccines[60], oligonucleotides[61], DNA[62] and microparticles[63], in which electroporation combined with chemical-enhancement methods have been most effective (see below). In addition, transdermal transport lag times can be reduced to seconds, which presents opportunities for rapid-response drug delivery systems[64]. Skin electroporation continues to be an active area for academic research, which is complemented by limited commercial development by industry.

Electroporation pulses of tens to hundreds of volts, applied for microseconds to milliseconds, are likely to be safe, as shown by animal experiments that directly assessed skin electroporation[56]; human studies involving high-voltage pulses applied to the skin to electroporate tumours[65]; and long-standing experience with clinical procedures that apply electrical pulses similar to those used for skin electroporation (for example, electromyography and somatosensory-evoked potential testing)[50]. In addition to being safe, these pulses can be administered painlessly using closely spaced electrodes to constrain the electric field within the nerve-free stratum corneum.

Electrical measurements show that skin resistance during an electroporation pulse can drop by three orders of magnitude within microseconds, show partial recovery within milliseconds, and exhibit additional recovery within seconds to minutes, which indicates an extremely rapid onset that is reversible over a much longer timescale[55,66]. Experimental measurements of charged molecules show increased transport, especially during each pulse, which is consistent with an electrophoretic driving force such that transport remains elevated to a lesser extent between pulses, probably driven by diffusion through permeabilized skin. Microscopy has shown that sites of transdermal transport during electroporation are heterogeneously dispersed, where molecules cross skin at specific regions of high permeability, each of which is on the order of 100 μm in size[66,67].

Acoustical methods

Ultrasonic waves, as well as short-duration shock waves, have been used to facilitate transdermal drug delivery. ULTRASOUND at various frequencies in the range of 20 kHz–16 MHz has been used to enhance skin permeability by a method called SONOPHORESIS. Traditionally, ultrasound at high frequencies (f >1 MHz, therapeutic ultrasound) was a popular choice for sonophoresis. Since Fellinger and Schmidt[68] reported the treatment of polyarthritis of the digital joints of the hand using hydrocortisone ointment with therapeutic ultrasound in the 1950s, sonophoresis has been used to facilitate topical drug delivery, especially in the context of physical therapy[69]. However, transdermal transport enhancement induced by low-frequency

ELECTROPHORESIS
The migration of molecules with a net charge under the influence of an electric field.

ELECTRO-OSMOSIS
The movement in an electric field of liquid within a porous medium having a fixed net charge.

ELECTROPORATION
The formation of aqueous pathways across a lipid bilayer by a pulsed electric field.

ULTRASOUND
A sound (that is, pressure) wave at a frequency greater than 20 kHz.

SONOPHORESIS
The movement of molecules across the skin or other tissue under the influence of an acoustic field.

Box 2 | **High-throughput screening of chemical enhancer formulations**

To assess large numbers of different chemical enhancer formulations, high experimental throughput is necessary. The throughput of standard diffusion cells is slow due to limited availability of human skin, utilization of large skin areas, prolonged contact times, and manual sampling and analysis. Although semi-automated versions of diffusion cells have been developed to make experiments more user-friendly[112,113], low throughput remains the bottleneck in transdermal formulation discovery.

The urgent need to increase rates of formulation development has led to the design of high-throughput screening methods[39,115]. Although still in the early stages, these methods have already shown promise in discovering novel formulations for transdermal drug delivery. Increased throughput has been achieved by reducing the amount of skin needed per experiment, using array formats, automation and the use of surrogate markers of skin permeability, such as skin conductivity. Compared with conventional Franz cells that typically require 1 cm^2 of skin, high-throughput methods have utilized skin areas as much as 100 times smaller[39,114]. Small skin area also facilitates the use of array formats and parallelization of experiments, which follows the paradigm now commonly implemented in the high-throughput drug discovery process[116]. With current capabilities, a throughput of up to 1,000 experiments per day has been reported for screening of formulations on the basis of potency[39]. Screening for additional properties, including safety and stability, also constitutes an important segment of formulation screening.

High-throughput screening is an emerging concept in the field of transdermal drug delivery. A number of opportunities exist to develop new methods and discover novel formulations that would be essentially undiscoverable by traditional methods. Utilization of these methods will also create a new knowledge base that can be used to rationally select the candidate pool, thereby further increasing the efficiency of formulation screening.

ultrasound (f <100 kHz) is significantly greater than that induced by therapeutic ultrasound. Accordingly, low-frequency sonophoresis has received particular attention during the past decade[70]. In addition to existing high-frequency ultrasound devices that are used for topical drug delivery, low-frequency ultrasound systems are under active commercial development for transdermal delivery.

Low-frequency sonophoresis has been shown to enhance *in vitro* transdermal transport of a variety of high-molecular mass drugs, including insulin, erythropoeitin, interferon and low-molecular weight heparin[71–73]. The efficacy of low-frequency sonophoresis to deliver macromolecules has also been demonstrated *in vivo* for insulin, for low-molecular weight heparin in animals and recently in human volunteers for topical delivery of local anaesthetics. In one of its modes, low-frequency ultrasound has been shown to quickly permeabilize human skin and maintain it in a state of high permeabilization for a number of hours, thereby opening a window for drug delivery using a simple patch[74]. Enhanced skin permeability during low-frequency sonophoresis has also been used to extract glucose and other constituents of interstitial fluid across permeabilized skin[75].

Several possible mechanisms of sonophoresis have been investigated. First, thermal effects due to absorption of ultrasound by the skin; second, acoustic streaming caused by development of time-independent fluid velocities in the skin due to ultrasound; and last, CAVITATIONAL effects due to the formation, oscillation and possible collapse of bubbles in or next to the skin[76,77]. Among these, cavitation was found to be primarily responsible for sonophoresis. Specifically, inertial collapse of cavitation bubbles, which causes a shock wave or an acoustic microjet to be emitted, has been proposed to impact the stratum cornuem and disrupt stratum corneum lipid bilayers. The greater efficiency of low-frequency sonophoresis compared with therapeutic sonophoresis orignates from the increased incidence of cavitation events and large bubble size (leading to high collapse pressures) found at low frequencies.

Non-ultrasonic shock waves (pressure amplitudes of ~300–1,000 bar and duration of 0.1–10 μs) have also been utilized to enhance transdermal drug delivery, possibly by increasing skin permeability by expanding the lacunar regions in stratum corneum lipid bilayers[78]. A single shock wave has been shown to be sufficient to permeabilize the stratum corneum and deliver macromolecules into the epidermis and dermis. This method was also shown to induce permeabilization of epidermal cells, thereby allowing local delivery at the site of application. Therapeutic doses of insulin have been delivered in diabetic rats using this approach[79].

Microneedles

Recently, arrays of microscopic needles have been used for transdermal drug delivery[80]. Needles of micron dimensions can pierce into the skin surface to create holes large enough for molecules to enter, but small enough to avoid pain or significant damage. *In vitro* experiments have shown that inserting MICRONEEDLES into skin can increase permeability by orders of magnitude for small drugs, large macromolecules and nanoparticles[81,82]. Animal experiments have similarly shown large increases in transdermal delivery of compounds, including oligonucleotides, insulin, desmopressin and human growth hormone[82–85]. Microneedle-based delivery of vaccines, including proteins[86] and DNA[87], is of special interest, in part to target LANGERHANS' CELLS in the skin's epidermis. Human studies have shown that microneedles are reported as painless when inserted into the skin of human subjects[88]. A number of Fortune 500 corporations, as well as start-up companies, are actively developing microneedles for transdermal drug delivery.

Most experiments have involved the use of solid microneedles that pierce or scrape holes in the skin. This can be carried out as a pretreatment to increase skin permeability before the subsequent application of a drug-loaded patch. Alternatively, microneedles can be coated with drug that is released from the needles while they are embedded in the skin. Hollow microneedles have also been fabricated and used to flow drug solutions into the skin[82].

Although microneedles were first proposed in the 1970s[89], the technology needed to make needles of micron dimensions did not become widely available until a decade ago. Using the low-cost, mass-production tools of the microelectronics industry (BOX 3), needles have been fabricated out of silicon, metals and other materials, with feature sizes ranging from sub-micron to millimetre dimensions[80,82].

CAVITATION
The formation of gaseous bubbles within a liquid by ultrasound or other mechanical forces.

MICRONEEDLE
A needle of micrometre dimensions usually fabricated using techniques derived from the microelectronics industry.

LANGERHANS' CELL
Dendritic clear cells in the epidermis believed to be antigen fixing and processing cells of monocytic origin.

Box 3 | **Impact of microelectronics on transdermal drug delivery**

The microelectronics revolution has changed people's lives and, more recently, is changing transdermal drug delivery. Classical methods to increase transdermal transport involve chemical enhancement methods; however, advances in microelectronics, as well as battery technology, have made electrically powered devices a practical and cost-effective possibility.

Although iontophoresis and sonophoresis have been known to increase delivery across skin for decades, the first devices designed for these applications were too bulky and expensive for portable use. Using microelectronics technology, reusable handheld iontophoresis devices are now FDA approved and fully disposable devices are under FDA review. Similarly, portable devices are under development for transdermal delivery using ultrasound, electroporation, and thermal poration. Wearable microinfusion pumps, coupled with small hypodermic needles, have also been developed.

Technology from the microelectronics industry has additionally been used to make microstructures other than transistors for integrated circuits. This approach, called microfabrication, has made it possible to fabricate arrays of micron-scale needles and other structures that are now under development to enhance transdermal drug delivery. The extensive infrastructure developed by the microelectronics industry makes the manufacturing of microfabricated devices likely to be inexpensive and readily scaled up for mass production.

Despite significant progress, the marriage of microelectronics and transdermal drug delivery has encountered significant hurdles, because it requires new devices coupled with new drugs (or at least a new route of administration). This poses challenges for academic and industry labs that typically have either medical device or transdermal delivery expertise, but rarely have both. Moreover, securing FDA approval involves scrutiny of both microelectronics device performance as well as drug safety and efficacy. Despite these challenges, microelectronics promise to have great impact on transdermal delivery, in the future.

Other approaches

A number of other methods for delivering drugs across skin have also been studied. Similar to microneedles that pierce holes into the surface of the skin, thermal methods have also been used to locally heat and ablate holes in stratum corneum, thereby increasing skin permeability. This THERMAL PORATION approach has been used to deliver conventional drugs[90] and DNA vaccines[91] to animals, and to extract interstitial fluid glucose from human subjects[92]. These applications are being actively pursued by a number of companies.

THERMAL PORATION
The formation of aqueous pathways across stratum corneum by the application of pulsed heat.

JET INJECTION
The high-velocity penetration into or across the skin of liquid droplets (or solid particles) often containing a drug.

Table 2 | **Comparison of methods to enhance transdermal delivery***

Delivery method	Increased transport	Sustained delivery	No pain/ irritation	Low cost/ complexity
Hypodermic needle	XXX	XX	X	XXX
Chemical enhancers	X	XXX	XX	XXX
Iontophoresis	XX	XXX	XXX	X
Electroporation	XX	XXX	XX	X
Ultrasound	XX	XXX	XXX	X
Microneedles	XX	XXX	XXX	X
Jet injection	XXX	X	X	X
Thermal poration	XX	XXX	XXX	X

*Delivery methods are qualitatively compared on the basis of limited (X), moderate (XX) or good (XXX) efficacy in each category. These classifications are used to illustrate rough trends and are not intended to provide absolute rankings.

After a rise and fall in popularity in the mid-twentieth century, high-velocity JET INJECTORS are receiving increased attention[93]. The focus now is on improved device designs for controlled, needle-free injection of drug solutions across the skin and into deeper tissue; insulin is delivered clinically by jet injection[94] and jet injectors for other drugs are under development. A variation on this approach propels solid drug particles into or across the skin, which is of special interest for vaccines[95]. Jet injectors are presently on the market and a number of companies are developing new devices.

Small conventional needles have also been incorporated into transdermal delivery devices. A single needle is inserted a few millimetres into the skin and drug solution is flowed through the needle into the skin at controlled rates using a micro-infusion pump that is contained within a large 'patch' affixed to the skin. Morphine has been delivered to human subjects using this approach[96]. A few companies are commercializing this technology.

Synergistic effect of enhancers

Although the various penetration-enhancement methods discussed above have individually been shown to enhance transdermal drug transport, their combinations are often still more effective. During the past ten years, several studies have supported this hypothesis[97], specifically addressing combinations of chemicals and iontophoresis; chemicals and electroporation; chemicals and ultrasound; iontophoresis and ultrasound; electroporation and iontophoresis; and electroporation and ultrasound. In addition to increasing transdermal transport in a possibly synergistic manner, a combination of enhancers can also reduce the required 'dose' of each enhancer. In this way, combinations of enhancers could increase safety and efficacy. Although combinations offer opportunities, most commercial efforts have emphasized single enhancers, probably due to the complexity of combining multiple technologies.

Combining iontophoresis with chemical enhancers, such as ethanol[98], oleic acid[99], DMSO[100], Azone[101] and limonene[102], has been shown to induce synergistic transport enhancement, which is largely attributed to iontophoresis-induced enhancer delivery into the skin. The synergy between ultrasound and chemicals has been demonstrated using a variety of chemicals, including polyethylene glycol, isopropyl myristate, linoleic acid and surfactants such as sodium lauryl sulphate[103,104]. This synergy is attributed to increased penetration and dispersion of the enhancer in the stratum corneum due to ultrasound. A synergistic effect of ultrasound and iontophores has also been reported for transdermal transport of heparin, believed to result from enhanced electrophoresis across ultrasound-induced structural changes in the skin[105]. Several literature reports showed synergistic effects between electroporation and chemicals[106,107]. These chemicals include polysaccharides (heparin and dextran), urea and sodium thiosulphate and are proposed to either enlarge or stabilize pores[107]. A synergistic

Figure 2 | **Images of selected transdermal products (marketed or under development). a** | A jet injection device marketed by Bioject. **b** | A transdermal patch marketed by Novogyne Pharmaceuticals for hormone replacement therapy. **c** | A sonophoresis device under development at Sontra Medical. **d** | A microneedle device under development at Alza. **e** | An iontophoresis devcie under development at Vyteris **f** | A transdermal patch marketed by Novartis for smoking cessation.

effect of iontophoresis and electroporation has also been reported for transdermal delivery[108]. The increased effectiveness of this combination was attributed to increased electrophoresis of molecules through skin permeabilized by electroporation.

Future directions

The development of transdermal delivery systems involves balancing increased transdermal transport with patient safety/comfort and cost. Because intact skin is not sufficiently permeable to the large majority of drugs, enhancement methods are needed. Despite extensive research during the past few decades, chemical enhancers have achieved only limited success in increasing transdermal transport of small molecules and have only a relatively poor ability to increase macromolecular transport under conditions likely to be clinically acceptable. Methods involving ultrasound and electric fields, including iontophoresis and electroporation, have more extensively increased transdermal delivery for small drugs and macromolecules. The ability of these technologies to deliver drugs effectively is partially counterbalanced by their reliance on electronically controlled devices that require an energy source, which constrains applications and cost. Methods that pierce micron-scale holes in skin, such as microneedles, thermal poration and jet injection, can dramatically increase transdermal delivery of small drugs, macromolecules and even particles, but more work is needed to establish safety/skin damage and cost effectiveness. Each of these technologies is likely to suit the needs of different applications and, in some cases, combinations of enhancers might be the most effective strategy (TABLE 2).

Given the progress being made on novel enhancement methods, it seems that transdermal drug delivery has only scratched the surface of possible clinical impact (FIG. 2). The defining feature of transdermal delivery that motivates the development of enhancement methods is that the drug reservoir remains outside the body, which provides a number of opportunities. For example, a patient or healthcare provider has easy access to a transdermal device that can be adjusted to modulate delivery through an appropriate interface. By contrast, it is difficult to alter drug-release kinetics after administration by other routes, such as the gastrointestinal tract, the lungs or inside the body. An external transdermal device also has fewer cost and materials limitations compared with some other approaches. Degradation and excretion of device materials are not relevant, and costly electronics or other features can be designed into a re-usable transdermal system. For these reasons, transdermal delivery arguably offers the greatest facility for controlled release of drugs. Overcoming the roadblock of low skin permeability using the approaches described in this review will be the crucial advance that lets transdermal delivery realize its great promise.

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Competing interests statement

The authors declare competing financial interests: see Web version for details.

Online links

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