nature biotechnology

REVIEW

Transdermal drug delivery

Mark R Prausnitz[1] & Robert Langer[2]

Transdermal drug delivery has made an important contribution to medical practice, but has yet to fully achieve its potential as an alternative to oral delivery and hypodermic injections. First-generation transdermal delivery systems have continued their steady increase in clinical use for delivery of small, lipophilic, low-dose drugs. Second-generation delivery systems using chemical enhancers, noncavitational ultrasound and iontophoresis have also resulted in clinical products; the ability of iontophoresis to control delivery rates in real time provides added functionality. Third-generation delivery systems target their effects to skin's barrier layer of stratum corneum using microneedles, thermal ablation, microdermabrasion, electroporation and cavitational ultrasound. Microneedles and thermal ablation are currently progressing through clinical trials for delivery of macromolecules and vaccines, such as insulin, parathyroid hormone and influenza vaccine. Using these novel second- and third-generation enhancement strategies, transdermal delivery is poised to significantly increase its impact on medicine.

Transdermal delivery represents an attractive alternative to oral delivery of drugs and is poised to provide an alternative to hypodermic injection, too[1–4]. For thousands of years, people have placed substances on the skin for therapeutic effects and, in the modern era, a variety of topical formulations have been developed to treat local medical conditions. The first transdermal system for systemic delivery—a three-day patch that delivers scopolamine to treat motion sickness—was approved for use in the United States in 1979. A decade later, nicotine patches became the first transdermal blockbuster, raising the profile of transdermal delivery in medicine and for the public in general. Today, there are 19 transdermal delivery systems for such drugs as estradiol, fentanyl, lidocaine and testosterone; combination patches containing more than one drug for contraception and hormone replacement; and iontophoretic and ultrasonic delivery systems for analgesia (**Table 1** and **Fig. 1**). Between 1979 and 2002, a new patch was approved on average every 2.2 years. Over the past 5 years (2003–2007), that rate has more than tripled to a new transdermal delivery system every 7.5 months. It is estimated that more than one billion transdermal patches are currently manufactured each year.

Transdermal delivery has a variety of advantages compared with the oral route. In particular, it is used when there is a significant first-pass effect of the liver that can prematurely metabolize drugs. Transdermal delivery also has advantages over hypodermic injections, which are painful, generate dangerous medical waste and pose the risk of disease transmission by needle re-use, especially in developing countries[5]. In addition, transdermal systems are noninvasive and can be self-administered. They can provide release for long periods of time (up to one week). They also improve patient compliance and the systems are generally inexpensive.

[1]School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, 311 Ferst Dr., Atlanta, Georgia 30332-0100, USA. [2]Department of Chemical Engineering, Massachusetts Institute of Technology, 77 Massachusetts Ave., Room E25-342, Cambridge, Massachusetts 02139-4307, USA. e-mail: prausnitz@gatech.edu

Published online 7 November 2008; doi:10.1038/nbt.1504

Perhaps the greatest challenge for transdermal delivery is that only a limited number of drugs are amenable to administration by this route. With current delivery methods, successful transdermal drugs have molecular masses that are only up to a few hundred Daltons, exhibit octanol-water partition coefficients that heavily favor lipids and require doses of milligrams per day or less[1–4]. It has been difficult to exploit the transdermal route to deliver hydrophilic drugs; the transdermal delivery of peptides and macromolecules, including new genetic treatment employing DNA or small-interfering RNA[6], has posed particular challenges.

Another area of great interest is the delivery of vaccines[7]. In addition to avoiding hypodermic needles, transdermal vaccine delivery could improve immune responses by targeting delivery to immunogenic Langerhans cells in the skin (**Box 1**). Given the external placement and patient control over patches, it might also be possible to develop modulated or pulsatile delivery, which could involve feedback control. Indeed, an analgesic patch was recently approved in the United States that uses patient-regulated delivery of fentanyl modulated by electricity to control pain (iontophoresis)[8], which has also been launched in Europe.

Finally, there is the possibility of not only delivering drugs, but also extracting molecules (analytes) through the skin[9]. This has already been achieved for glucose monitoring by extracting interstitial fluid using electrical means and is in clinical trials using other approaches, such as ultrasound.

From a global perspective, we propose that advances in transdermal delivery systems can be categorized as undergoing three generations of development from the first generation of systems that produced many of today's patches by judicious selection of drugs that can cross the skin at therapeutic rates with little or no enhancement; through the second generation that has yielded additional advances for small-molecule delivery by increasing skin permeability and driving forces for transdermal transport; to the third generation that will enable transdermal delivery of small-molecule drugs, macromolecules (including proteins and DNA) and virus-based and other vaccines through targeted permeabilization of the skin's stratum corneum.

In this review, we describe the transdermal delivery methods in each generation. We then comment on their current and future potential in medicine.

First-generation transdermal delivery systems

The first generation of transdermal delivery systems is responsible for most of the transdermal patches that have thus far been in clinical use. Significant advances in patch technology, and public acceptance, have enabled the recent surge in first-generation transdermal patches reaching the market (**Box 2**). However, this surge will taper off as drugs with suitable properties for such systems are depleted. First-generation delivery candidates must be low-molecular weight, lipophilic and efficacious at low doses. Usually, their transdermal delivery should be more attractive than oral delivery due to low oral bioavailability, the need or desire for less frequent dosing or steady delivery profiles, or other factors.

The first-generation approach to transdermal delivery is limited primarily by the barrier posed by skin's outermost layer called the stratum corneum, which is 10 to 20 μm thick (**Fig. 2**). Underneath this layer is the viable epidermis, which measures 50 to 100 μm and is avascular. Deeper still is the dermis, which is 1–2 mm thick and contains a rich capillary bed for systemic drug absorption just below the dermal–epidermal junction. Closer examination of the stratum corneum barrier reveals a brick and mortar structure, where the bricks represent nonliving corneocyte cells composed primarily of cross-linked keratin and the intercellular mortar is a mixture of lipids organized largely in bilayers.

Drug transport across the stratum corneum typically involves diffusion through the intercellular lipids via a path that winds tortuously around corneocytes, where hydrophilic molecules travel through the lipid head group regions and lipophilic molecules travel through the lipid tails. This transport pathway is highly constrained by the structural and solubility requirements for solution and diffusion within stratum corneum lipid bilayers.

A variation on the traditional transdermal patch of first-generation delivery systems involves no patch at all, but applies a metered liquid spray, gel or other topical formulation to the skin that, upon evaporation or absorption, can drive small lipophilic drugs into the stratum corneum, which in turn serves as the drug reservoir for extended release into the viable epidermis over hours[10]. For example, testosterone gels have been in use for several years and a transdermal spray has been recently approved for estradiol delivery.

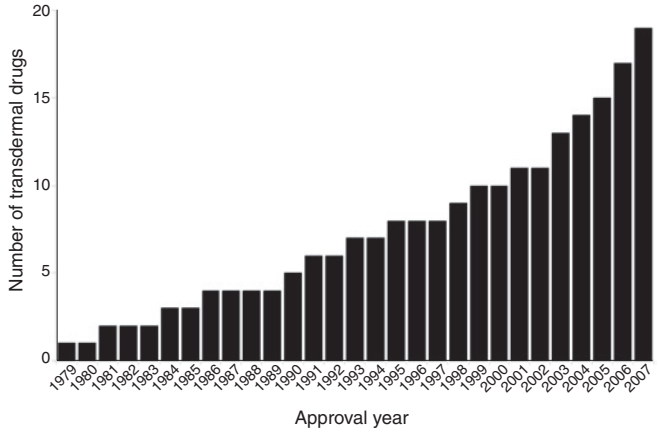

Figure 1 Cumulative number of transdermal drugs approved by the FDA since the first approval in 1979. There are currently 19 drugs and drug combinations administered by various delivery methods that are approved in the United States (see **Table 1**). Data were obtained from the FDA Orange Book[60].

Second-generation transdermal delivery systems

The second generation of transdermal delivery systems recognizes that skin permeability enhancement is needed to expand the scope of transdermal drugs. The ideal enhancer should (i) increase skin permeability by reversibly disrupting stratum corneum structure, (ii) provide an added driving force for transport into the skin and (iii) avoid injury to deeper, living tissues. However, enhancement methods developed in this generation, such as conventional chemical enhancers, iontophoresis and noncavitational ultrasound, have struggled with the balance between achieving increased delivery across stratum corneum, while protecting deeper tissues from damage. As a result, this second generation of delivery systems has advanced clinical practice primarily by improving small-molecule delivery for localized, dermatological, cosmetic and some systemic applications, but has made little clinically important effect on the delivery of macromolecules[1–4].

Conventional chemical enhancers. Recognizing the need to increase skin permeability, developers of second-generation delivery strategies have turned largely to the development of chemical enhancers[11,12]. This approach is a logical extension of the traditional pharmaceutical toolbox because it primarily involves designing new formulations with chemical excipients. Many effective chemical enhancers disrupt the highly ordered bilayer structures of the intracellular lipids found in stratum corneum by inserting amphiphilic molecules into these bilayers to disorganize molecular packing or by extracting lipids using solvents and surfactants to create lipid-packing defects of nanometer dimensions. Hundreds of different chemical enhancers have been studied, including off-the-shelf compounds and others specifically designed and synthesized for this purpose, such as Azone (1-dodecylazacycloheptan-2-one) and SEPA (2-n-nonyl-1,3dioxolane) (**Table 2**).

One challenge of this approach is that increased permeation enhancement, even of small molecules, typically correlates with increased skin irritation. A small subset of these enhancers that increase skin permeability without irritation have been used successfully to deliver small molecules, but have had limited impact on the problem of delivering hydrophilic compounds or macromolecules. Overall, chemical enhancers can increase skin permeability and provide an added driving force for transport by increasing drug partitioning into the skin (thereby increasing the concentration gradient driving diffusion), but the difficulty of localizing their effects to the stratum corneum to avoid irritation or toxicity to living cells in the deeper skin has severely constrained their application.

Mitragotri and colleagues[13] have suggested guidelines to design chemical enhancers that may increase skin permeability without causing irritation. Using Fourier transform infrared (FTIR) spectroscopy as a screening tool, they proposed that effective and nonirritating enhancers should alter stratum corneum lipid CH_2 symmetric stretching (which correlates with increased skin permeability) and avoid changes in stratum corneum protein amide I band absorption (which correlates with skin irritation). These design principles predicted that optimal chemical structures for enhancing drug delivery would be amphiphiles with long, saturated carbon tails or compounds with multiple aromatic rings; the authors went on to validate their predictions experimentally.

Liposomes, dendrimers and microemulsions have also been used as chemical enhancers with supramolecular structure that can increase not only skin permeability, but also drug solubilization in the formulation and drug partitioning into the skin[14,15]. Their supramolecular size generally precludes penetration into the skin and thereby helps localize effects to the stratum corneum. These approaches have found success for enhanced delivery of some small molecules, especially for topical dermatological and cosmetic applications. A highly deformable liposome formulation is currently in clinical trials for insulin delivery (**Table 2**).

Table 1 Transdermal drugs approved by the US FDA[a]

Approval year	Drug/Product name	Indication	Marketing company
1979	Scopolamine/Transderm-Scop	Motion sickness	Novartis Consumer Health (Parsippany, NJ, USA)
1981	Nitroglycerin/Transderm-Nitro	Angina pectoris	Novartis (East Hannover, NJ, USA)
1984	Clonidine/Catapres-TTS	Hypertension	Boehringer Ingelheim (Ridgefield, CT, USA)
1986	Estradiol/Estraderm	Menopausal symptoms	Novartis
1990	Fentanyl/Duragesic	Chronic pain	Janssen Pharmaceutica (Titusville, NJ, USA)
1991	Nicotine/Nicoderm, Habitrol, ProStep	Smoking cessation	GlaxoSmithKline (Philadelphia), Novartis Consumer Health, Elan (Gainesville, GA, USA)
1993	Testosterone/Testoderm	Testosterone deficiency	Alza (Mountain View, CA, USA)
1995	Lidocaine with epinephrine (iontophoresis)/Iontocaine	Local dermal analgesia	Iomed (Salt Lake City, UT, USA)
1998	Estradiol with norethidrone/Combipatch	Menopausal symptoms	Novartis
1999	Lidocaine/Lidoderm	Post-herpetic neuralgia pain	Endo Pharmaceuticals (Chadds Ford, PA, USA)
2001	Ethinyl estradiol with norelgestromin/Ortho Evra	Contraception	Ortho-McNeil Pharmaceutical (Raritan, NJ, USA)
2003	Estradiol with levonorgestrel/Climara Pro	Menopausal symptoms	Bayer Healthcare Pharmaceuticals (Wayne, NJ, USA)
2003	Oxybutynin/Oxytrol	Overactive bladder	Watson Pharma (Corona, CA, USA)
2004	Lidocaine (ultrasound)/SonoPrep	Local dermal anesthesia	Echo Therapeutics (Franklin, MA, USA)
2005	Lidocaine with tetracaine/Synera	Local dermal analgesia	Endo Pharmaceuticals
2006	Fentanyl HCl (iontophoresis)/Ionsys	Acute postoperative pain	Alza
2006	Methylphenidate/Daytrana	Attention deficit hyperactivity disorder	Shire (Wayne, PA, USA)
2006	Selegiline/Emsam	Major depressive disorder	Bristol-Myers Squibb (Princeton, NJ, USA)
2007	Rotigotine/Neupro	Parkinson's disease	Schwarz Pharma (Mequon, WI, USA)
2007	Rivastigmine/Exelon	Dementia	Novartis

[a]This list includes transdermal patches and delivery systems approved by the US Food and Drug Administration. Only the first approved product for a given drug or drug combination administered by a given delivery method is shown. Topical creams, ointments, gels and sprays are not included.

Another transdermal delivery approach that has been applied is the use of prodrugs. Through the addition of a cleavable chemical group that typically increases drug lipophilicity[16], such prodrugs can facilitate the transfer of a drug across the skin. This is accomplished by adding, for example, alkyl side chains with enzymatically cleavable linkers, such as esters or carbonates. One prodrug approach relies on the linkage of either two of the same or two different small-molecule drugs to each other by a labile bond, which reduces their hydrophilicity, albeit at the expense of increasing molecular weight[17].

Because the prodrug approach is based on altering drug structure, as opposed to skin structure, prodrugs usually do not cause skin irritation. Even so, advancement of this field has been limited by the complexity of prodrug design, the applicability of the approach only to small-molecule drugs and the need to gain US Food and Drug Administration (FDA) approval of the prodrug as a new chemical entity (rather than approval only of the transdermal delivery route for an already approved drug).

Iontophoresis. Iontophoresis has been studied to increase transdermal delivery for more than a century by typically applying a continuous low-voltage current[18,19]. Although there can be increased skin permeability, iontophoresis mainly provides an electrical driving force for transport across stratum corneum. Charged drugs are moved via electrophoresis, whereas weakly charged and uncharged compounds can be moved by electroosmotic flow of water generated by the preferential movement of mobile cations (e.g., Na^+) instead of fixed anions (e.g., keratin) in the stratum corneum[20]. Because iontophoresis does not primarily change the skin barrier itself, it is mostly applicable to small molecules that carry a charge and some macromolecules up to a few thousand Daltons.

The strongest asset of iontophoresis is that the rate of drug delivery scales with the electrical current, which can be readily controlled by a microprocessor or, in some cases, the patient[21]. In this way, drug delivery can be turned on and off and even modulated over time to enable complex delivery profiles. One of us found that, however, the maximum current—and therefore the maximum delivery rate—is limited by skin irritation and pain caused by the general inability of iontophoresis to localize its effects to the stratum corneum[22].

Guided by these strengths and weaknesses, current applications emphasize the ability of iontophoresis to provide control over drug dosing, because it scales with the amount of charge (that is, the product of current and time) delivered to the skin[18,19]. Iontophoresis is currently used clinically to rapidly deliver lidocaine for local anesthesia[23], pilocarpine to induce sweating as part of a cystic fibrosis diagnostic test[24] and tap water to treat hyperhydrosis (that is, excessive sweating)[25], as well as to extract glucose from the skin for glucose monitoring[26]. A recently approved iontophoretic patch enables patients to periodically activate the patch to administer a bolus of fentanyl based on their need for pain relief[8] (**Table 1**). In contrast to this costly, microprocessor-controlled system, another recently approved iontophoretic patch involves simply connecting the drug reservoir to a constant-voltage, printed battery that can also have some simple control circuitry; the patch delivers drug until the battery runs out[27]. Although the drug delivery rate is not as well controlled using this low-cost alternative, the total amount of drug administered is controlled, because the total amount of charge transferred across the skin is limited by the battery capacity. An additional alternative that seeks to achieve a balance between low cost and microprocessor control of delivery involves a single-use iontophoretic system in clinical trials for delivery of acyclovir to treat herpes labialis[28] (**Table 2**).

Noncavitational ultrasound. Ultrasound was first widely recognized as a skin permeation enhancer when physical therapists discovered that massaging anti-inflammatory agents into the skin using ultrasonic heating probes increased efficacy[29,30]. Ultrasound is an oscillating pressure wave at a frequency too high for humans to hear. Although some have hypothesized that the pressure gradients and oscillation associated with

ultrasound act as a driving force to move drugs into the skin, it appears that the dominant effect is to disrupt stratum corneum lipid structure and thereby increase permeability. The effects of noncavitational ultrasound on skin permeability have generally been limited to enhancing small, lipophilic compounds. Using more aggressive noncavitational ultrasound conditions has been limited by associated tissue heating that is not targeted to the stratum corneum and can damage deeper tissue. Under different conditions, ultrasound can also be used to generate cavitational bubble activity, which has different effects and is discussed below.

Third-generation transdermal delivery systems

The third generation of transdermal delivery systems is poised to have a large impact on drug delivery because it targets its effects to the stratum corneum. This targeting enables stronger disruption of the stratum corneum barrier, and thereby more effective transdermal delivery, while still protecting deeper tissues. We have found that in this way, novel chemical enhancers, electroporation, cavitational ultrasound and more recently microneedles, thermal ablation and microdermabrasion[31] have been shown to deliver macromolecules, including therapeutic proteins and vaccines, across the skin in human clinical trials. These advances were made possible in part by the emergence of technologies to localize effects to the stratum corneum combined with recognition that the safety afforded by localization should make these more aggressive approaches medically acceptable.

Combinations of chemical enhancers. Recent studies have suggested that suitably designed combinations of chemical enhancers can balance trade-offs between enhancement and irritation based on the hypothesis that certain enhancer combinations are especially potent when present at specific, narrow compositions. This approach enables a strategy to target effects that enhance skin permeability in the stratum corneum, but avoids irritation in deeper tissues where the formulation composition becomes diluted or otherwise altered.

Finding such rare combinations is experimentally intensive and therefore benefits from high-throughput screening. Such a study was carried out, examining close to 500 different pairs of chemical enhancers formulated to have more than 5,000 compositions[32]. Dramatically increased enhancement with low skin irritation potential was found, for example, for a combination of sodium laureth sulfate (an anionic surfactant) and phenyl piperazine (a compound with aromatic nitrogen) at concentrations of 0.35% and 0.15% by weight, respectively, in a 1:1 mixture of ethanol and phosphate-buffered saline. *In vitro* screening results were validated with *in vivo* delivery of a peptide (leuprolide acetate) to hairless rats. These results suggest that combinations of chemical enhancers may succeed for delivery of macromolecules where individual enhancers have generally failed. Work on this approach continues in industry.

Biochemical enhancers. Recently, peptides have been examined as enhancers of skin permeability. In one approach, phage display was used to screen a library of peptides, which yielded an 11-amino acid synthetic peptide that increased transdermal delivery of insulin in diabetic rats[33]. Additional analysis suggested that a pathway via hair follicles was targeted. Work in one of our laboratories[34] has shown that a natural pore-forming peptide, magainin, can be used to increase skin permeability by a mechanism proposed to target bilayer disruption in stratum corneum lipids and not in deeper tissue[34]. The magainin was only effective when used in synergistic combination with a surfactant chemical enhancer, which served the dual purpose of increasing skin permeability to the drug as well as increasing penetration of magainin into the stratum corneum. Using a prodrug approach, cyclosporine was covalently attached to a polyarginine-heptamer cell-penetrating peptide, which led to increased topical absorption that inhibited cutaneous inflammation[35]. In these examples, the highly specific bioactivity enabled by peptide chemistry can enable delivery via targeted routes through the skin.

Electroporation. The use of short, high-voltage pulses is well known as a method to reversibly disrupt cell membranes for gene transfection and other applications. Electroporation has also been shown to disrupt lipid bilayer structures in the skin[36,37]. Although the electric field applied for milliseconds during electroporation provides an electrophoretic driving force, diffusion through long-lived electropores can persist for up to hours, such that transdermal transport can be increased by orders of magnitude for small molecule drugs, peptides, vaccines and DNA. Recently, electroporation was shown to deliver a model peptide

Box 1 Rising interest in transdermal vaccines

Transdermal delivery offers compelling opportunities to improve vaccine administration. Although vaccines are typically macromolecules, viral particles or other large supramolecular constructs, their small (microgram) doses facilitate the possibility of transdermal delivery. Vaccine delivery via the skin is even more attractive because it targets the potent epidermal Langerhans and dermal dendritic cells that may generate a strong immune response at much lower doses than deeper injection[7]. The most successful vaccine of all time—the smallpox vaccine, which eradicated the disease worldwide—was administered via the skin with the aid of a small needle device to breach the stratum corneum barrier. Although effective, this approach does not provide good control over delivery, which has motivated development of new delivery methods.

The desire to eliminate hypodermic needles further motivates transdermal vaccine development[62]. In a world where needle reuse causes the deaths of at least 1.3 million people per year from hepatitis B and AIDS[5], needle-free, patch-based vaccination could have a large impact. In addition, the possibility of administering vaccine patches by minimally trained personnel or patients themselves could not only facilitate compliance with routine, seasonal and pandemic vaccination needs, but also expedite vaccination campaigns in developing countries where medical personnel are in short supply. Effective vaccination via the skin may be achieved by increasing skin permeability to the vaccine using the methods discussed in this review. Some of the physical enhancement methods have been shown to have additional adjuvant effects that increase immune response further[38,40]. The immune response can also be heightened by adding chemical adjuvants[7].

Excitement about this approach is exemplified by completion of phase 3 clinical trails and submission for registration in Europe by Sanofi Pasteur (Paris) and Becton Dickinson (Franklin Lakes, NJ, USA) for their microneedle-based influenza vaccine (**Table 2**); major investments in Iomai (Gaithersburg, MD, USA) for their transdermal vaccine patch portfolio; and a growing number of academic and industry laboratories engaging in this field of research.

vaccine into the skin of mice to generate a strong cytotoxic T-lymphocyte response[38].

Because the stratum corneum electrical resistance is orders of magnitude greater than that of deeper tissues, the electric field applied during electroporation is initially concentrated in the stratum corneum. However, upon electroporation of stratum corneum lipid bilayers, stratum corneum resistance rapidly and dramatically drops, and the electric field correspondingly distributes to a greater extent into the deeper tissues, which contain sensory and motor neurons. The associated pain and muscle stimulation can be avoided by using closely spaced microelectrodes that constrain the electric field within the stratum corneum[39]. Although electroporation has been studied extensively in animals, this approach to transdermal delivery has received limited attention to use in humans thus far owing largely to the complexity of device design.

Cavitational ultrasound. In addition to heating, ultrasound is also known to generate cavitation, which is the formation, oscillation and, in some cases, collapse of bubbles in an ultrasonic pressure field. Cavitation is generated only under specific conditions (e.g., low-frequency ultrasound) that differ from those of ultrasonic heating or imaging devices. The opportunity for transdermal drug delivery is that cavitation bubbles concentrate the energy of ultrasound and thereby enable targeted effects at the site of bubble activity[30,40]. Because bubbles are more difficult to grow and oscillate within densely packed tissue, cavitation preferentially occurs within the coupling medium (e.g., a hydrogel) between the ultrasound transducer and skin. The expected mechanism of cavitational ultrasound is that bubbles oscillate and collapse at the skin surface, which generates localized shock waves and liquid microjets directed at the stratum corneum[41]. This disrupts stratum corneum lipid structure and thereby increases skin permeability for up to many hours without damaging deeper tissues. Cavitational ultrasound is not believed to contribute a significant driving force for transport.

Already, cavitational ultrasound has been approved for enhanced delivery of lidocaine through the skin[42] and has been studied extensively in animals for delivery of insulin, as well as heparin, tetanus toxoid vaccine and other compounds[40]. Ultrasound can be applied using handheld devices, as well as low-profile, cymbal transducers that could be integrated into a patch[43]. Ultrasound has also been used to extract interstitial fluid glucose for diabetes monitoring[44] and to increase skin permeability to small molecules, as well as macromolecules up to tens of kilodaltons. Lasers have similarly been used to increase skin permeability by a related shock-wave mechanism[45].

Microneedles. A conceptually straightforward way to selectively permeabilize the stratum corneum is to pierce it with very short needles. Over the past decade, microneedles have been developed as a means to deliver drugs into the skin in a minimally invasive manner[46,47]. Solid microneedles have been shown to painlessly pierce the skin to increase skin permeability to a variety of small molecules, proteins and nanoparticles from an extended-release patch. Alternatively, drug formulations have been coated on or encapsulated within microneedles for rapid or controlled release of peptides and vaccines in the skin. Hollow microneedles have been used to deliver insulin and vaccines by infusion.

In general, microneedles (i) increase skin permeability by creating micron-scale pathways into the skin, (ii) can actively drive drugs into the skin either as coated or encapsulated cargo introduced during microneedle insertion or via convective flow through hollow microneedles and (iii) target their effects to the stratum corneum, although microneedles typically pierce across the epidermis and into the superficial dermis too (reviewed in ref. 47).

Box 2 Transdermal patch design

Almost all transdermal patch designs, the drug is stored in a reservoir that is enclosed on one side with an impermeable backing and has an adhesive that contacts the skin on the other side[63]. Some designs employ drug dissolved in a liquid or gel-based reservoir, which can simplify formulations and permit the use of liquid chemical enhancers, such as ethanol. These designs characteristically are composed of four layers: an impermeable backing membrane, a drug reservoir, a semi-permeable membrane that may serve as a rate-limiting barrier and an adhesive layer. Other designs incorporate the drug into a solid polymer matrix, which simplifies manufacturing. Matrix systems can have three layers, by eliminating the semi-permeable membrane, or just two layers, by incorporating the drug directly into the adhesive.

Several recent advances in microneedle design and formulation are worthy of note. Original fabrication methods involving clean room-based sculpting of silicon-based structures have moved to low-cost manufacturing methods to make microneedles out of metals and polymers commonly found in FDA-approved devices and parenteral formulations. We have dip-coated microneedles with a variety of compounds, including small molecules, proteins, DNA and virus particles[48]. We have also made microneedles of water-soluble polymers that encapsulate various compounds within the needle matrix[49]. These microneedles dissolve in the skin over a timescale of minutes and thereby leave no sharp medical waste after use.

Advances have also been made in delivery to humans using microneedles. In a recent study, we administered naltrexone to healthy volunteers whose skin was pretreated with microneedles[50]. After applying a naltrexone patch, blood levels of naltrexone reached the therapeutic range. Transdermal delivery without microneedle pretreatment yielded naltrexone levels below detection. Microneedle treatment was reported to be painless by the volunteers and was generally well tolerated. Other unpublished human studies have demonstrated delivery of parathyroid hormone from coated microneedles, which have advanced from animal studies through clinical trials (**Table 2**).

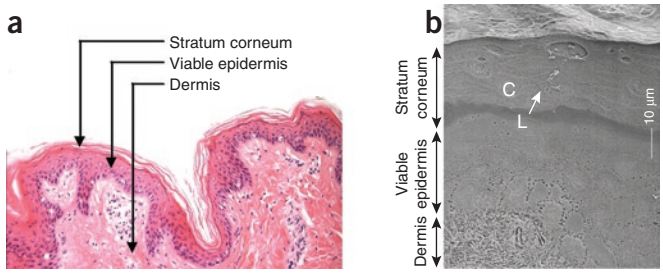

Figure 2 Histological structure of mammalian skin. (**a**) Skin structure. The skin's outermost layer is the stratum corneum, which is a nonviable tissue that provides most of skin's barrier properties. The viable epidermis is an epithelial layer that serves to continuously renew the stratum corneum, among other functions. The dermis is a largely fibrous layer that provides skin's mechanical support, as well as the skin's vasculature and anchoring of sweat gland and hair follicle appendages. (Image of H&E stained porcine skin provided courtesy of Samantha Andrews, Georgia Institute of Technology.) (**b**) Stratum corneum structure. Drug penetration across the stratum corneum is limited primarily by the lipids organized in bilayer structures (L) that fill the intercellular spaces between corneocytes (C). (Cryo-scanning electron micrograph provided courtesy of Joke Bouwstra, Leiden University and reproduced with permission from ref. 61.)

Table 2 Representative transdermal drugs in clinical development

Drug	Indication	Delivery technology	Clinical phase	Company
AB-1001	Nausea and vomiting	Passive	Phase 3	Abeille Pharmaceuticals (Princeton, NJ, USA)
Acyclovir	Herpes labialis	Iontophoresis	Phase 2	Transport Pharmaceuticals (Framingham, MA, USA)
Buprenorphine	Pain	Passive	Phase 3[a]	Purdue Pharma (Stamford, CT, USA)
Fertility hormone	Female infertility	Iontophoresis	Phase 1	Vyteris/Ferring (Fair Lawn, NJ, USA/Parsippany, NJ, USA)
Granisetron	Nausea and vomiting	Passive	Pre-registration	Prostrakan (Galashiels, UK)
Heat-labile enterotoxin of *E. coli*	Travelers' diarrhea	Skin abrasion	Phase 2	Iomai
Human growth hormone	Growth hormone deficiency	Thermal ablation	Phase 1	TransPharma Medical/ Teva Pharmaceuticals (Lod, Israel/ Petach Tikva, Israel)
Influenza vaccine	Influenza prophylaxis	Microneedles	Pre-registration	Becton Dickinson/Sanofi-Pasteur (Franklin Lakes, NJ, USA/Lyon, France)
Insulin	Diabetes mellitus	Thermal ablation	Phase 1	Altea Therapeutics (Atlanta, GA, USA)
Insulin	Diabetes mellitus	Vesicular carrier	Phase 2	Phosphagenics (Melbourne)
Ketoprofen	Osteoarthritis	Heat enhancement	Phase 3	ZARS (Salt Lake City, UT, USA)
Parathyroid hormone (1-34)	Osteoporosis	Microneedles	Phase 2	Zosano (Fremont, CA, USA)
Sufentanil	Chronic pain	Passive	Phase 2	Durect/Endo (Cupertino, CA, USA)
Testosterone	Female sexual dysfunction	Metered dose transdermal spray	Phase 2	Acrux/VIVUS (West Melbourne, Australia/Mountain View, CA, USA)
Testosterone	Male hypogonadism	Chemical enhancer (SEPA)	Phase 2	MacroChem (New York)
Testosterone	Hypoactive sexual desire disorder	Passive	Pre-registration[a]	Procter & Gamble/Watson (Cincinnati/Corona, CA, USA)
Triamcinolone acetonide	Dermatoses	Chemical enhancer (AzoneTS)	Pre-registration	Echo Therapeutics

[a]Already marketed outside of the United States.

Vaccine delivery using microneedles has also been a focus for research. In animal studies we have demonstrated delivery of live attenuated virus, inactivated virus, protein sub-unit, and DNA vaccines against influenza, hepatitis B, Japanese encephalitis and anthrax using solid and hollow microneedles[51]. Human studies have demonstrated the reliability of hollow microneedles to achieve intradermal injection without special training[52]. Administration of influenza vaccine using these microneedles has recently progressed through completion of clinical trials and filing for registration in Europe (**Table 2**).

Thermal ablation. Thermal ablation selectively heats the skin surface to generate micron-scale perforations in the stratum corneum. Transiently heating the skin's surface to hundreds of degrees for microseconds to milliseconds localizes heat transfer to the skin surface without allowing heat to propagate to the viable tissues below[53,54]. This spares these tissues from damage or pain. Mechanistically, thermal ablation may involve rapidly vaporizing water in the stratum corneum, such that the resulting volumetric expansion ablates micron-scale craters in the skin's surface. In more recent studies we find that temperatures well above the boiling point of water are needed and that other processes, such as tissue combustion, may be at play[55].

Animal studies have demonstrated the ability of thermal ablation to deliver a number of different compounds, such as human growth hormone and interferon α-2b (refs. 54,56). Skin heating has been achieved using ohmic microheaters and radio-frequency ablation. The microscopic length scales of localized skin disruption caused by thermal ablation have resulted in the procedure being well tolerated. Unpublished studies report clinical trials for delivery of a number of drugs, including human growth hormone and insulin (**Table 2**).

Microdermabrasion. A final way to remove the stratum corneum barrier employs abrasion by microdermabrasion or simply using sandpaper. Microdermabrasion is a widely used method to alter and remove skin tissue for cosmetic purposes. This abrasive mechanism, which is related to sand blasting on the microscopic scale, has been shown to increase skin permeability to drugs, including lidocaine and 5-fluorouracil, which suggests possible applications in transdermal drug delivery[57]. Vaccine delivery across the skin has also been facilitated by skin abrasion using sandpaper[58]. Initial studies in animals generated strong immune responses to several vaccines when administered topically in combination with a potent adjuvant (that is, heat-labile enterotoxin of *Escherichia coli*). More recently, human trials have addressed vaccination against traveler's diarrhea and influenza (**Table 2**).

Comparison of transdermal delivery systems

In addition to more than 100 drugs formulated as creams and ointments, there are now 19 drugs or drug combinations administered using FDA-approved transdermal delivery systems (**Fig. 1**). Most of these first-generation delivery systems rely primarily on appropriate drug properties that permit absorption into the skin without significant enhancement of skin permeation. However, advances in the field through second- and third-generation transdermal delivery systems are opening the door to transdermal administration of hydrophilic molecules, macromolecules and vaccines (**Table 2**).

Most enhancement approaches increase skin permeability without providing an added driving force for transdermal transport. Chemical enhancers are an exception, because they can disrupt stratum corneum structure as well as increase drug solubility and thereby increase the drug concentration-gradient driving force. Microneedles are another exception, because they not only pierce the skin, but also carry drug into the skin via coating and encapsulation using solid microneedles or infusion through hollow needles. Although electrical methods of delivery can affect skin permeability as well as provide an electrical driving force, iontophoresis acts primarily to drive drugs into the skin and

electroporation acts largely to disrupt stratum corneum structure. Because iontophoresis provides a transport driving force, it may be especially useful when coupled with another method that increases skin permeability. Such combined enhancement strategies have received previous attention in the literature[59].

Successful transdermal delivery is based on achieving a suitable balance between effective delivery and safety to the skin. Some of the third-generation systems rely on the hypothesis that relatively large, micron-scale defects in the stratum corneum should be well tolerated by patients as long as significant damage is not done to living cells in the viable epidermis and dermis. Reports to date suggest that this hypothesis is reasonable, based on data from a growing collection of clinical trials that have advanced through phase 1 safety trials and into phase 2 and 3 studies of efficacy, especially using microneedles and thermal ablation (**Table 2**). This may not be surprising, given that the skin reliably repairs itself without scarring or infection after being routinely subjected to microscopic defects caused by scrapes, scratches, shaving, hypodermic injection and other minor mechanical trauma.

Clinical impact relies not only on a transdermal delivery system that administers drugs in a safe and effective manner, but one that is also low cost and easy to use, given that most transdermal delivery systems are designed for self-administration at home. The various chemical enhancers can be integrated into small, inexpensive patches that patients find convenient. The various physical enhancers may be more effective to deliver macromolecules and vaccines, but are generally driven by handheld devices that require electrical power. As a result, most physical enhancers rely on relatively costly, reusable devices that interface with a disposable drug reservoir component. Microneedles are an exception, because they can deliver macromolecules and vaccines, should be inexpensive to manufacture as single-use patches and do not require a power supply. However, microneedles are also unique in that they are physically invasive, which raises additional safety and sterility considerations.

Future outlook and conclusions

Looking to the future, it is likely that first-generation patch technology will continue to be used for delivery of small-molecule drugs with the right set of properties, especially those drugs that are currently administered orally and by injection that are coming off patent. Second-generation chemical enhancers should find continued use as formulation excipients in topical dermatological creams and ointments and some systemic patches for small-molecule drugs. They will probably have little impact on delivery of hydrophilic drugs and macromolecules, because the most effective chemical enhancers generally diffuse out of the stratum corneum and irritate deeper tissue. Targeted, third-generation combinations of chemical enhancers and biochemical approaches offer strategies for more targeted enhancement, but are still in the early stages of development.

Second-generation physical enhancement using iontophoresis has already lead to changes in the clinic, especially for rapid, localized delivery to the skin. Its electronic control over delivery rates gives iontophoresis a special property that can be exploited for patient-controlled dosing and other complex delivery profiles. However, because iontophoresis does not substantially change the skin barrier, it appears unlikely to affect macromolecule or vaccine delivery, unless used in combination with other methods that increase skin permeability. Likewise, noncavitational ultrasound has found use in transdermal delivery of anti-inflammatories in physical therapy, but does not appear suitable for delivery of large compounds.

Third-generation physical enhancement using cavitational ultrasound and electroporation enhance transdermal delivery by disrupting stratum corneum on the nanometer scale. Cavitational ultrasound has already been approved for transdermal delivery of lidocaine and may be approved in the future for peptides and other small macromolecules. Although effective, applications of cavitational ultrasound may be limited by the need for a sophisticated device that only increases skin permeability at the nanometer scale and thereby may not be broadly applicable to macromolecules and vaccines.

Skin can be disrupted on the micron scale by third-generation physical enhancement using microneedles, thermal ablation and microdermabrasion. These methods have special promise, because they appear broadly capable of delivering not only small molecules, but macromolecules and vaccines as well. Unpublished clinical trails appear to yield promising results, and published data suggest that these methods can be safe and effective. A microneedle product for vaccine delivery has been submitted in Europe for regulatory approval and other microneedle and thermal ablation products are proceeding through advanced clinical trials.

A limitation of diffusing large compounds through micron-scale disruptions is that diffusivity is a strong inverse function of molecular size. Thus, even though, for example, an inactivated virus particle vaccine can easily fit though a micron-sized hole, it may take a long time to diffuse through. When rapid delivery is desirable, it may be preferable to use microneedles that actively drive macromolecules and drugs into the skin or to combine micron-scale disruption with an added driving force, such as iontophoresis.

Overall, transdermal drug delivery offers compelling opportunities to address the low bioavailability of many oral drugs, the pain and inconvenience of injections, and the limited controlled-release options of both. Building off the successes of first-generation transdermal patches, second-generation chemical enhancers and iontophoresis are expanding delivery capabilities for small molecules, whereas third-generation physical enhancers (including ultrasound, thermal ablation and microneedles) could enable transdermal delivery of macromolecules and vaccines. These scientific and technological advances that enable targeted disruption of stratum corneum while protecting deeper tissues have brought the field to a new level of capabilities that position transdermal drug delivery for an increasingly widespread impact on medicine.

ACKNOWLEDGMENTS

We thank Daniel Bucks, Gary Cleary, Robert Gale, Samir Mitragotri and Audra Stinchcomb for helpful discussions. M.R.P. is the Emerson-Lewis Faculty Fellow and works at the Center for Drug Design, Development and Delivery and the Institute for Bioengineering and Bioscience at Georgia Tech. This work was supported in part by the National Institutes of Health.

COMPETING INTERESTS STATEMENT

The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturebiotechnology/.

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