Is transdermal drug delivery research still important today?

Transdermal delivery provides opportunities for innovative, challenging, interesting and worthwhile research with patient benefit

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When measured by the number of medicines consumed or prescriptions written, the topical and transdermal routes of drug delivery pale into insignificance compared with oral therapy. Industrial colleagues, therefore, occasionally adopt a somewhat utilitarian stance and question the value of academic research into skin treatment and drug permeation, with the rather parochial argument that it is of limited use to the UK pharmaceutical industry. To consider the validity of this somewhat dismissive approach, which in its extreme form essentially regards universities as servants of industry, we can consider the worldwide position with respect to commercial activity in dermatologicals and patches. We can then look at the intellectual challenges that make transdermal research so demanding (a prime role of universities is to seek out and tackle the difficult problems and, particularly, to pose such challenges to their PhD students). In skin research, it is essential that investigators apply fundamental physicochemical principles to an extremely variable and complex biological tissue. The work discussed here provides avenues for further research.

The relative position of transdermal delivery as an innovative area of pharmaceutical science is often underestimated. In the USA alone, recent data show that 51 transdermal- or dermal-systems products that are under clinical evaluation are listed, out of 129 drug-delivery candidates; 30% of 77 candidate products in preclinical development represent such drug delivery.

Drug targets in skin

The alleviation of the psychological and physical suffering and the cure, or at least amelioration, of disfiguring diseases such as eczema, psoriasis, icthyosis and the skin cancers are noble aims. For example, in the UK alone there are 44,000 skin carcinoma cases per year, of which 2000 are fatal. However, we are often as ignorant to the nature of the molecular receptors involved in these conditions as to how to target the diseased site. Fundamental research on receptors should go hand-in-hand with pharmacology and drug-delivery science. We need to optimize the pharmacokinetics of treatments such as psoralen photochemotherapy (PUVA) for psoriasis and photodynamic therapy for skin cancers, relative to both photon delivery and drug administration. Can we develop vaccines that produce immunization via simple topical administration, as is now claimed?

The main reason for many problems with transdermal drug delivery is that the impermeability of human skin limits daily drug dosage delivered, for example, from an acceptable sized patch at ~10 mg. How to increase this low limit for topical systems in general provides a major challenge to scientists and many university laboratories worldwide, these include; [Utah, California, Connecticut, MIT, Michigan, Florida, South Carolina (USA), Brisbane (Australia), Leiden, Munich, Heidelberg (Germany), Cardiff, Aston, Greenwich, De Montford, London and Bradford, (UK)]. Human skin effectively inhibits drug permeation, mainly because of the stratum corneum. Thus, to maximize drug flux, formulators reduce the hindrance of this barrier, although sometimes drug transport via the hair follicle might also be involved. The remainder of this article considers the challenges of circumventing a resistant barrier with significant and troublesome patient variability.

Can we simply compute drug fluxes?

The experimental measurement of transdermal drug permeation is fraught with difficulties, including problems with obtaining human skin samples. Therefore, several groups have developed computational methods for predicting fluxes. These include several models based on multiple regression methods[1]. Further work is required to produce a solution based on simple physicochemical properties alone (values preferably obtainable from the literature), which predicts the flux of all molecules, especially hydrophilic, high molecular weight drugs. However, for the foreseeable future, drug regulators will always demand confirmation of computer predictions from experiments with human skin.

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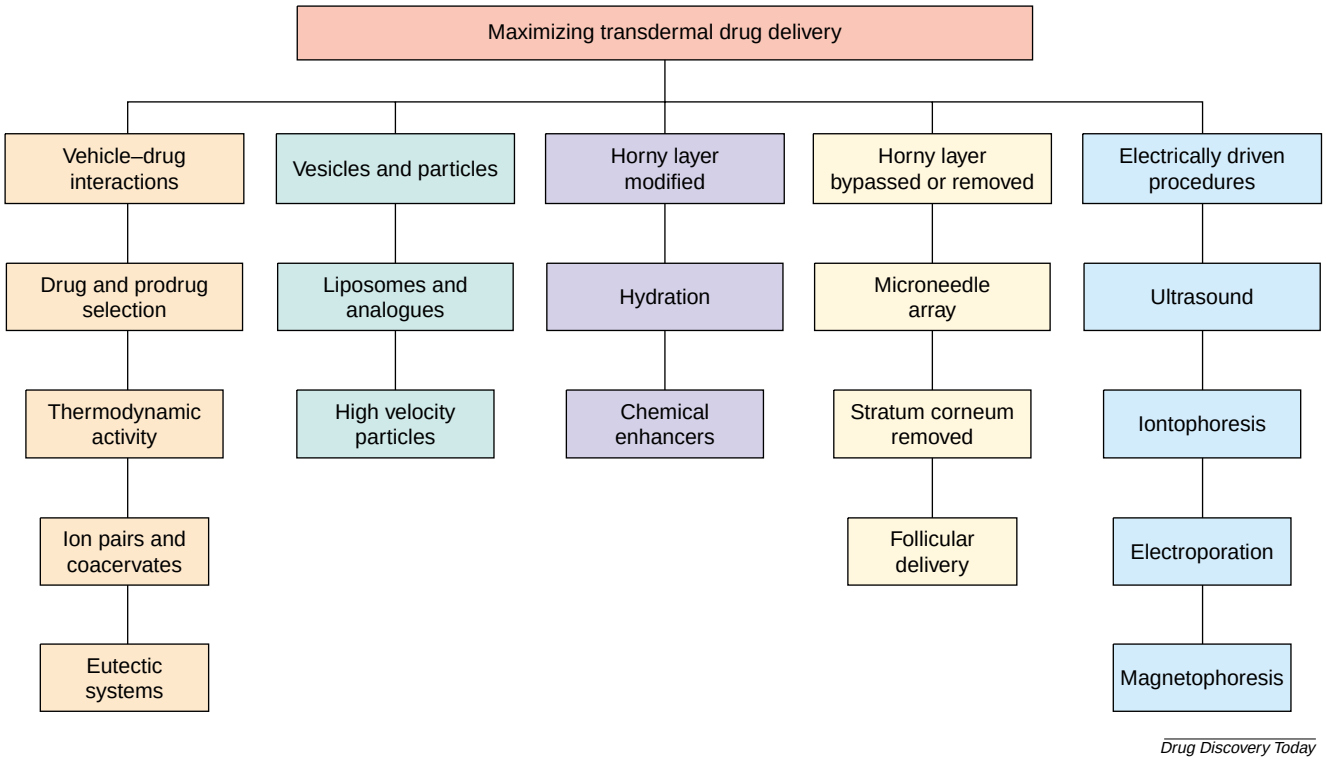

Figure 1. Some methods for maximizing transdermal drug therapy (modified from Reference 2).

Maximizing transdermal drug delivery

Figure 1 summarizes some selective ways for circumventing the stratum corneum barrier, all of which provide areas for further research[2], examples of which are now discussed.

Vehicle and drug interactions

The simplest approach to transdermal drug delivery selects a drug from a congeneric series or pharmacological class with the correct physicochemical properties to translocate across the barrier at an acceptable rate. The ideal properties of a molecule that effectively penetrates the stratum corneum (horny layer) are:

- Low molecular weight (<600 Da), when its diffusion coefficient tends to be high.
- Adequate solubility in oil and water – so that the membrane concentration-gradient (the driving force for diffusion) can be high. Saturated solutions (or suspensions having the same maximum thermodynamic activity) promote maximum flux.
- A high, but balanced (optimal), partition coefficient (too large a value of *K* could inhibit clearance by viable tissues).
- Low melting point, correlating with good ideal solubility.

(Nicotine transdermal patches illustrate these requirements well.)

The partition coefficient is crucially important in establishing a high initial-penetrant concentration in the first stratum corneum layer. If a drug does not possess the correct physicochemical properties (usually the *K* value is too low), a suitable prodrug could have an optimal partition coefficient for skin entry. Following permeation to viable tissues, enzymes then activate the prodrug.

For maximum penetration rate, the drug should be at its highest thermodynamic activity (i.e. saturated). Thus, all vehicles containing drug as a finely ground suspension should produce the same penetration rate, providing that the systems behave ideally. This ideal behaviour is difficult to achieve because most topical vehicles interact to some extent with the horny layer of the skin.

Supersaturated solutions could arise, either by design or via a cosolvent evaporating on the skin. The theoretical maximum flux could then greatly increase. Polymers can be incorporated to inhibit crystallization in unstable supersaturated preparations. The metastability period is usually short, but can be prolonged in transdermal patches because of their mode of preparation: drug dissolution in hot solvents, evaporation to supersaturation and crystal inhibition by polymers of the high-viscosity matrix or adhesive. It would be useful to develop supersaturated systems that are stable throughout product shelf-life.

The role of vesicles and particles in bioavailability

Liposomes are colloidal particles formed from concentric bimolecular layers that can entrap drugs and deliver them to the skin. Most reports cite a localizing effect, whereby vesicles accumulate drugs in the stratum corneum or other upper skin layers. Generally, liposomes are not expected to penetrate into viable skin. The efficacy of these vesicles at transporting drugs through the skin is debatable and represents an important area for further study.

Transferosomes™ The introduction of Transfersomes™, which incorporate surfactant 'edge activators', increased this controversy. The inventors claimed that such vesicles, being ultra-deformable, could squeeze through pores in the stratum corneum of less than one-tenth of the liposome's diameter, *in vivo* and were driven by a hydration gradient[2]. Traditional liposomes are thought to confine themselves to the surface or upper layers of the stratum corneum, where they dehydrate and fuse with skin lipids. Remarkable results are claimed for Transfersomes™. Data indicate that as much as 50% of a topical dose of a protein or peptide (such as insulin) penetrates the skin *in vivo* in 30 minutes[2].

Other workers have measured drug delivery from ultra-deformable liposomes and traditional vesicles *in vitro*. Both vesicle types improved maximum flux and skin deposition compared with saturated aqueous drug solution (under maximum thermodynamic control). However, positive results did not reach the values obtained by Cevc and coworkers[2], as only 1–3% of drug was delivered.

Ethosomes Liposomes that are high in ethanol content are known as ethosomes. They can penetrate the skin and enhance compound delivery both to deep skin strata and systemically. This is thought to be because the ethanol fluidizes both ethosomal lipids and bilayers of the stratum corneum intercellular lipid. The soft, malleable vesicles then penetrate the disorganized lipid bilayers.

Niosomes Vesicles formed from nonionic surfactants are known as niosomes. They have been actively promoted by the cosmetic industry, sometimes as almost magical targeting systems.

PowderJect™ The PowderJect™ system (Powderject Vaccines, Madison, WI, USA) is a fascinating development that fires solid particles through the stratum corneum into the lower skin layers using a supersonic shock wave. The therapy claims major advantages but problems arise with bruising and particles bouncing off skin surfaces. The European Medicines Evaluation Agency and Food and Drug Administration will need convincing that particles smashing through the stratum corneum do not damage this complex structure, thus exposing it to environmental contamination or transporting surface denizens, such as bacteria, into living tissues.

Intraject™ This device (Intraject, Weston Medical Group, Peterborough, UK), which was developed from the vaccine gun, inserts liquids through the skin without using needles. Following the extensive use of similar devices for vaccination – such as by the US military – it is surprising that it was not developed earlier for drug delivery.

The market for needle-free injector systems is expected to rise to a billion dollars per year by 2005.

How can we modify the horny layer for drug access?

Hydration of the horny layer promotes the flux of nearly all drugs, opening up the compact structure of the cornified tissue. Moisturizing factors, occlusive films, hydrophobic ointments and transdermal patches all enhance drug bioavailability into the skin but, outside the cosmetic and food industries, it is difficult to make significant profit out of water.

Chemical-penetration enhancers can optimize drug flux. An important theme in enhancer research is how to classify the accelerant action and explain the mechanisms that are responsible for increased drug permeation. The structural diversity of enhancer molecules makes the development of an all-encompassing theory a challenge.

One simple classification is via the lipid–protein–partitioning (LPP) concept, which suggests that enhancers have three main actions.

- Lipid disruption: the enhancer disrupts stratum corneum lipid organization, making it permeable to drugs. Many enhancers operate mainly in this way [e.g. Azone, terpenes, fatty acids, dimethylsulfoxide (DMSO) and alcohols].
- Protein modification: ionic surfactants, decylmethylsulfoxide and DMSO interact well with keratin in corneocytes, opening up the dense protein structure and making it more permeable.
- Partitioning promotion: many solvents change the solution properties of the horny layer and thus increase the partitioning of a drug, coenhancer or cosolvent. For example, ethanol increases the penetration of nitroglycerin and estradiol.

Many accelerants combine these three LPP mechanisms. Thus, high concentrations of DMSO (>60%) disturb intercellular organization, extract lipids, interact with keratin and facilitate lipid–drug partitioning.

Because of the availability of an extensive data bank, SARs can be probed, for example, those based on factors such as chain length, polarity, unsaturation and the presence of special groups. Another scheme develops a conceptual diagram of three areas based on the organic and inorganic characters of enhancers. One area comprises accelerant solvents, another designates promoters for hydrophilic drugs and the third area represents enhancers for lipophilic compounds.

Many potent enhancers can irritate because they also interfere with viable cell membranes. Therefore, pharmaceutical companies often limit their investigations for a suitable enhancer to benign materials, such as GRAS (generally recognised as safe) substances.

Can we bypass the horny layer?

The horny layer can be circumvented by injection, and one interesting development is the microneedle array, which consists of 400 tiny needles that insert the drug just below this barrier. Solid silicon needles (coated with drug) or hollow metal needles (filled with solution) penetrate the stratum corneum without stimulating pain fibres. Massive increases in drug delivery, using this technology, are claimed[2]. The microneedle array can be driven by iontophoresis (the electrical driving of charged molecules into tissue) and a future possibility could be the addition of a microchip to control drug release via the needles.

In addition to representing a drug-delivery target for conditions such as acne, the pilosebaceous unit (hair follicle, hair shaft and sebaceous gland) also provides a route that bypasses the intact stratum corneum. Even a large molecule such as naked DNA can be used to immunize by topical application, and the possible use of the hair follicle as a gene-therapy target is exciting. It has been proposed that normal follicles have efficient mechanisms for inducing immune responses to proteins. A formulation containing antibodies from transgenic plants, when rubbed into the scalp of patients undergoing chemotherapy, prevented hair loss[2]. Colloidal particles, such as liposomes and their analogues and small crystals can target the hair follicle. In general, particles >10 µm remain on the skin surface, at ~3–10 µm they concentrate in the follicle and at <3 µm they penetrate follicles and the stratum corneum alike.

Will electrically driven procedures reach the outpatient?

Ultrasound can be used to massage a topically applied drug preparation. Cavitation disturbs lipid-packing in the stratum corneum and the increased free volume enhances drug penetration. Low frequency (~20 kHz), rather than therapeutic, ultrasound (>1 MHz) increases this enhancement one thousand-fold. A major goal is the transdermal delivery of large polar molecules, and thus ultrasonic work using insulin, erythropoietin and interferon is especially significant. However, ultrasound requires validation for patient efficacy and safety and, as yet, it is not readily suitable for home use.

Iontophoresis passes a small direct current through a drug-containing electrode placed in contact with the skin, with a grounding electrode to complete the circuit. Three important mechanisms enhance drug transport: (1) the driving electrode repels oppositely charged species; (2) the electric current increases skin permeability; and (3) electro-osmosis moves uncharged molecules and large polar peptides. The transdermal delivery of therapeutic peptides, proteins, oligonucleotides and many other drugs shows considerable promise, although hopes for early marketing have been dashed. However, clinical trials of this technology have proceeded for lidocaine and fentanyl – a lidocaine–adrenaline device for local anaesthesia is now available – and work to develop iontophoretic patch systems is under way.

Polar neutral molecules can be delivered by the current-induced convective flow of water, termed electro-osmosis. This could even be the main force driving peptides and proteins through the skin.

Reverse iontophoresis is an interesting development in which systemic molecules (such as glucose) can be extracted at the skin surface using electro-osmosis. Thus, the blood glucose concentrations in diabetics can be monitored using this procedure (GlucoWatch® Biographer, Cyngus, Redwood City, CA, USA).

Although the apparent current-density per unit area in iontophoresis is low, a problem is that most of the current penetrates via the low-resistance route of the appendages, particularly hair follicles. Thus the actual current-density in the follicle might be high enough to damage viable hair cells. Other possible irreversible changes to the skin give cause for concern. As with ultrasound, outpatient use is problematic, although work has been done on miniaturizing systems (e.g. paper batteries and wristwatch-like devices are under investigation).

Skin electroporation creates transient aqueous pores in skin lipid-bilayers by applying brief, high-voltage electrical pulses. These pores provide pathways for drug penetration that travel straight through the stratum corneum. During the pulse, drugs move via iontophoresis and/or electro-osmosis. Significant penetration also occurs between pulses by simple diffusion because relatively persistent changes in the corneum lower its resistance. Drug fluxes can increase up to 10,000-fold for neutral and highly charged molecules of up to 40 kDa. This technique can also deliver vaccines, liposomes, nanoparticles and microspheres. An interesting development is electroporation used to deliver physostigmine as a pretreatment for anticipated organophosphate poisoning. Macromolecules and small molecules might enhance electroporation delivery by sterically stabilizing pores created in the skin. Therefore, we could possibly microengineer aqueous pathways both for transdermal drug delivery and for sampling skin fluids. Electroporation coupled with iontophoresis can enhance the penetration of peptides, such as neurotensin, calcitonin, vasopressin and LHRH. Electroporation has also been combined with ultrasound. However, instrumentation for the home use of this

potent technique is problematical and concern relating to possible skin damage requires further study.

Limited research has probed the ability of magnetic fields to move diamagnetic materials through the skin. An interesting idea is to employ intelligent systems based on magnetism or microchip technology to deliver drugs in a controlled, pulsatile mode, which is the way normal physiological processes work.

Will transdermal patches continue to be successful?

The worldwide transdermal patch market approaches £2 billion, although it is based on only 10 drugs. There are probably nearly 50 traditional transdermal patches in development, with considerable ongoing efforts to formulate iontophoretic patches. If such electrical devices (including those based on electroporation) can be introduced successfully, not only would it enable the delivery of problem molecules, such as peptides, proteins and antisense compounds, but also the major disadvantage of an extended lag-time could be overcome. The US military is developing 'smart' patches, loaded with vitamins, minerals and essential nutrients[2]. The concept is that these could be triggered either by satellite signals directly or by a watch-sized monitor that checks the physiological condition of each soldier. If this was applied to patients, we might reach the Holy Grail of individualized, controlled treatment that is responsive to biofeedback. Transdermal drug delivery will still provide opportunities for innovative, challenging, interesting and worthwhile research for the benefit of patients worldwide.

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