

Transdermal drug delivery may be a common technique in the future

In this second article in our series looking at developments in new drug technologies, **Jenny Bryan** describes the techniques that companies throughout the world are developing to push drugs through the skin

Research companies are investigating ways of getting drugs into the bloodstream quickly and efficiently through the skin

At first glance, using a small electric current to push medicines through their skin may not appeal to many patients. But specialist transdermal drug delivery companies in the US, Israel and Australia are confident that, within five to 10 years, electricity, ultrasound, radiofrequencies and micro-needles will be widely used to get many commonly used products into the bloodstream quickly and efficiently, through the skin.

Iontophoresis

This autumn, New Jersey-based Vyteris Inc will launch Lidosite, an iontophoretic formulation of lidocaine and noradrenaline, in the US. Recently licensed by the Food and Drug Administration for local analgesia prior to superficial dermatological procedures, Lidosite is likely to be targeted at the paediatric market. It will numb a child's skin in just a few minutes instead of the one to two hours it takes for an anaesthetic cream to work.

Lidosite is a patch with two reservoirs. One contains lidocaine and noradrenaline, the other saline. The patch is wired to a device containing a battery and a pre-programmed microcomputer which controls the electric charge that is administered.

Although no licence application has been submitted yet in the European Union for Lidosite, Jonathan Hadgraft, professor of biophysical chemistry in the department of pharmaceuticals at the School of Pharmacy, University of London, believes that the Food and Drug Administration decision will encourage manufacturers to press on with their research.

"Previously, there were concerns about how the licensing authorities would deal with products that use these novel delivery devices, but this decision opens the window for active transdermal preparations," he says.

Companies have been putting drugs into patches since the late 1970s. But the lipid-rich matrix of the stratum corneum means that only small, lipophilic molecules that are required in low doses are suitable for the passive diffusion-based transdermal products marketed to date.

Adding chemical penetration enhancers, including surfactants, fatty acids/esters, terpenes or solvents, can increase skin permeability by enhancing solubility or by dissolving the crystalline or lipid areas of the stratum corneum. But success has been limited and the more powerful chemical enhancers can irritate the skin, hence the current interest in active physical methods of enhancing transdermal drug delivery.

Iontophoresis can enhance delivery by driving charged compounds across the skin by a direct interaction with the electric field. Those with the greatest charge, and smaller molecules, get across quickest. Alternatively, molecules can be dragged across by electronically induced solvent flow. Next on Vyteris's list for transdermal development are tryptans for migraine treatment and dopamine agonists for Parkinson's disease.

Richard Guy, newly appointed professor of pharmaceutical sciences in the department of pharmacy and pharmacology at the University of Bath, explains that iontophoresis has been around for years, but it is only in the past few years that researchers have been matching the right drugs to the technique.

"In the 1980s, people tried to use iontophoresis with insulin, but the molecule is too large and it is hard to get it across the negatively charged skin because it, too, is negatively charged," he says.

Professor Guy points out that the real attraction of iontophoresis is that it does not rely on a concentration gradient and it is not affected by individual differences in skin permeability. When the electric current is switched on, an electric circuit is established. Positively charged ions and drug molecules move from the positively charged electrode chamber (anode) through the stratum

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corneum and are then attracted back out to the negatively charged cathode. (Similarly, negatively charged molecules move from the cation into the skin and are attracted back to the anode.) At the same time, electrons travel externally between the electrodes, and the number of electrons flowing in this “exterior” part of the circuit determines the number of ions moving through the skin. This means that the same amount of drug will always be delivered for the same amount of charge.

The technique also has the potential to deliver pulses of drugs, for example, hormonal treatments, such as luteinising hormone releasing hormone, simply by switching the current on and off.

Electrical patch

Hot on Vyeris’s heels is the Alza Corporation, part of Johnson & Johnson, with its credit card-sized, electrical patch delivery system, called E-TRANS, for delivering fentanyl. Having submitted a licence application in the US last September, the company is currently addressing issues raised by the FDA.

In addition to its iontophoretic patches, Alza is also developing a microprojection system for transdermal drug delivery. Called Macroflux, it consists of a thin titanium screen with 200µm projections attached to the underside. When this is applied to the skin, it creates superficial pathways through the stratum corneum.

Drug can be coated onto the microprojections for bolus delivery, or it can be attached to a drug reservoir for continuous or iontophoretic application. Alza considers that the system could be particularly useful for deliv-

ering vaccines, small molecules and biopharmaceuticals.

In preclinical studies, peak plasma levels of bolus doses of peptides were achieved within one hour of administration. Macroflux has also been successfully combined with E-TRANS for pulse and continuous delivery of recombinant human growth hormone.

Professor Hadgraft predicts that microprojection systems (and the related hollow microneedle approach) will be slower to market than iontophoretic products.

“They appear to be painless but, by making holes in the skin, they do open up the potential for other compounds to go through that are not wanted. Research is therefore looking at how quickly the holes are regenerated,” he explains.

Using low frequency ultrasound to improve penetration may have fewer safety issues than microneedles. *In vitro* studies have shown that it can be used successfully to enhance transport of high molecular mass drugs, including insulin, erythropoietin and interferon, and low molecule weight heparin.

The most likely mechanism appears to be cavitation — development of bubbles in the skin that expand and contract to disorganise the lipid bilayer of the stratum corneum. This leads to formation of reversible microchannels in the skin through which drugs can be delivered.

Ultrasound

SonoPrep is an ultrasound device which has been developed by Sontra, a Massachusetts-based company set up in 1996 initially to develop the ultrasound system from research carried out at the Massachusetts Institute of Technology. The company claims that its

SonoPrep topical anaesthesia can significantly reduce the time to achieve analgesia compared with conventional devices.

Professor Guy believes that the technology may be more useful for biochemical monitoring than for drug delivery.

“You can render the skin permeable with a fairly short burst of ultrasound, but the channels stay open for about 12 hours, making it useful for glucose monitoring,” he explains.

Radiofrequencies

In Israel, TransPharma has used radiofrequencies as the energy source to create highly localised microchannels in the skin. In healthy volunteer studies, patches containing the anti-emetic agent, granisetron, were applied to treated areas of skin, and consistent plasma levels achieved for at least 24 hours before the patches were removed.

Like Professor Hadgraft, Professor Guy questions the feasibility of long-term transdermal drug treatments that rely on making holes, however small, in the skin.

He sees significant potential in the field of immunisation but, realistically, he considers it unlikely that someone with diabetes, for example, will apply ultrasound to his or her skin three times a day for life.

“The field is littered with cute ideas for controlling drug delivery, but the bottom line for [the pharmaceutical industry] is to create billion dollar drugs and there are not too many cases where the method of delivery has converted a drug into a blockbuster,” Professor Guy points out. “For the time being, I think that [the industry] will be happy to watch and wait, and maybe invest in what the small companies are doing later on.”