

TRANSDERMAL**Transpharma: drug delivery using radio**

There are several companies now developing methods of enhancing transdermal absorption by applying energy to the skin in various forms, including heat, light, ultrasound or electricity. In each case, the effect is to disrupt the integrity of the stratum corneum and the upper epidermis, to allow active molecules to pass through to the subcutaneous capillary bed more quickly.

The Israeli company, **TransPharma Medical**, is developing *ViaDerm*, which uses alternating electrical current at radio frequency (RF) to create channels, 100 μm in diameter, through the skin. The channels are wide enough for the largest drug molecules to pass through.

Dr Daphna Heffetz, TransPharma's founder and chief executive officer, said that *ViaDerm* drug delivery was generally equivalent to subcutaneous injection but without any pain. She added that it was inexpensive and could be used by the patient at home. Compared with conventional transdermal delivery, *ViaDerm* could deliver larger doses of larger molecules more rapidly and achieve greater bioavailability, she said.

The company has conducted several preclinical animal studies to demonstrate its technology's effect on transdermal absorption. Using a porcine ear skin model, hydrophobic and hydrophilic compounds with molecular weights of 300-1,200 were absorbed significantly faster and to a greater degree following *ViaDerm* treatment compared with skin that had not been treated with *ViaDerm*.

In anaesthetised diabetic pigs, application of insulin (a 50-amino acid hydrophilic peptide of molecular weight 6,000) in solution to skin sites that had been treated with *ViaDerm* resulted in a similar decrease in blood glucose levels over six hours to that from insulin injection. This compared with an increase in blood glucose in pigs receiving insulin solution applied to the skin without *ViaDerm* pretreatment.

Another preclinical experiment demonstrated enhanced transdermal delivery of recombinant human growth hormone (rhGH), a 22kDa protein. In hypophysectomised rats, rhGH applied to the skin produced peak plasma levels of rhGH within four hours. This was followed by an increase in levels of IGF-1, indicating that the rhGH remained active after delivery. The AUC for both rhGH and IGF-1 following *ViaDerm* transdermal delivery were similar to those from subcutaneous injection.

clinical data...

TransPharma has also conducted clinical trials. In 18 healthy volunteers, *ViaDerm* administration of granisetron, a water-soluble compound of molecular weight 348.9, was compared with passive transdermal and oral administration. *ViaDerm*-delivered granisetron resulted in a steady increase in average plasma levels to around 6 ng/ml within 12 hours, which had decreased to 5 ng/ml at 24 hours.

This compared with a double peak in average plasma levels – of 6 ng/ml at two hours and 7 ng/ml at 16 hours – from oral administration. Passive transdermal administration produced plasma levels close to zero.

Side-effects of *ViaDerm* included slight irritation (erythema and oedema) at the application site. Transdermal water loss at the treatment site was 3-4 times greater than that from adjacent untreated skin.

Dr Heffetz said that the company was planning to conduct clinical safety trials necessary for European registration in the near future.

technology overview...

The technology comprises a re-usable hand-held electronic unit and a disposable micro-electrode array consisting of hundreds of closely spaced electrodes, which is packaged separately and snapped onto the handset. Once attached to the handset, the array is pressed lightly against the treatment site, activating the handset to begin microchannel formation.

Alternating RF current is applied to the electrodes for several milliseconds. The number of active electrodes determines the rate at which the drug crosses the skin. When the microchannels have been formed, the current halts automatically and visual and audible signals on the handset alert the user.

This is controlled by a closed-loop electronic feedback mechanism, which monitors the current being applied, can detect when the microchannels have reached the required depth, and modifies the current accordingly. The system ensures that no matter what inpatient or outpatient variations there might be in skin type, microchannels of the correct depth are formed. The feedback system also detects misapplications and device faults.

TransPharma noted that the microchannels penetrate only as far as the upper epidermis, where there are no nerves or blood vessels, and the frequencies used are too high to stimulate nerves or muscles. The procedure is therefore pain free and skin trauma is minimised.

The third component of the technology is a patch containing the active compound formulated for delivery through RF-induced microchannels. After microchannel formation, the microarray is lifted away from the skin and the patch is applied. As well as applications where rapid transdermal delivery was favoured, Judith Kornfeld, TransPharma's vice-president of business development noted that the technology was suitable for use with sustained-release patches where constant blood levels of active compound were desired, since the microchannels remained intact for up to 24 hours.

commercialisation strategy...

Development so far has been conducted using a fully functional *ViaDerm* prototype. Dr Kornfeld said that a commercial version, which was essentially the same as the prototype but "incorporated new design features at the device/human interface", would be completed later this year. It is to be manufactured in Israel.

TransPharma is forming partnerships for the development of specific compounds for delivery using *ViaDerm*. The resulting product would be submitted for approval as a drug-device combination. Dr Kornfeld said that four undisclosed collaborations had been signed so far, three of which were with global pharmaceutical companies for the development of blockbuster proteins.

☛ Potential partners should contact Judith Kornfeld at TransPharma. Tel: +972 3 632 6067. Fax: 972 3 632 3065. Email: judithk@transpharma.co.il.