



## RF-Microchannel-Based Transdermal Delivery

By Galit Levin  
and Judith Kornfeld at  
TransPharma Medical

A novel system for active transdermal drug delivery has been developed consisting of a device to form radio-frequency (RF) MicroChannels in the skin and a patch containing the active drug – thereby offering a transdermal solution for the delivery of polypeptides, other large molecules and water-soluble small molecules.

Transdermal drug delivery has many advantages. It enables the drug of choice to circumvent degradation in the GI tract, or the consequent processing in the liver (first pass effect); it is also advantageous for a more controlled, uniform rate of delivery, leading to reduced systemic side effects compared with oral delivery or hypodermic injections. The convenience and non-invasive nature of transdermal drug delivery leads to increased patient compliance and quality of life.

There are two major modes of transdermal drug delivery – passive and active. Passive delivery – while having been used for almost 30 years – suffers from various limitations, primarily due to lack of permeability of many drugs. Chief among its many functions, the skin is the natural protective barrier of our body – a function well reflected in its anatomy. Structurally, the skin consists of two main parts: the thin, external layer called the epidermis, and a thicker inner layer called the dermis. The outermost layer of the epidermis, termed the stratum corneum (SC), is mainly responsible for the barrier function of the skin. The SC consists of flattened dead cells (corneocytes), which are filled with keratin. The regions between cells are filled with lipids, which are responsible for the skin's natural barrier. Hence, the skin is quite permeable to small molecules (generally under 500Da) with relatively low aqueous solubility, but on the whole impermeable to large molecules, such as peptides or proteins, and highly water-soluble molecules.

Due to these limitations, different methods of active transdermal drug delivery are being developed, using various means to mechanically disrupt the continuity of the SC and enable efficient penetration of drugs to the

blood stream. These include iontophoresis, electroporation, microneedles and more. However, most of these methods are still more suitable for small molecules, or else are not practical enough to offer viable solutions for pharmaceutical needs. This is due to various limitations such as an insufficient delivered dose or duration of delivery.

In this article, we describe a novel system for active transdermal drug delivery, based on creating microchannels in the skin using radio-frequency (RF) electrical current. This novel and unique approach provides various advantages, primarily a predicted and precisely controlled drug delivery rate, efficient delivery of a wide range of molecular sizes including proteins and other macromolecules, and a convenient, pain-free system suitable for self application at home.

### FORMATION OF RF-MICROCHANNELS

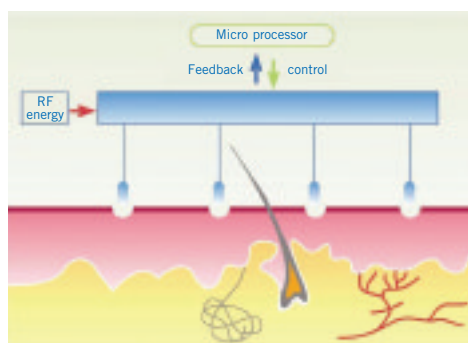
RF ablation is a well-known medical technology used to eliminate living cells. It is widely used for various medical procedures such as performing incisions in minimally invasive operations or destroying small tumours.

RF ablation is performed by conducting an alternating electrical current at a frequency higher than 100 KHz (radio frequency) through a particular tissue. The alternating current induces ionic vibrations in the vicinity of the electrode, resulting in heat. This, in turn, leads to water evaporation and cell ablation.

RF MicroChannels are created by placing against the skin an array of closely spaced, tiny electrodes of very precise dimensions (see Figure 1). The alternating electrical current passing through the microelectrodes ablates the cells underneath each electrode, forming microscopic passages in the epidermis and outer dermis. These RF MicroChannels span only the outer layers of the skin, where there are no blood vessels or nerve endings, thus minimising skin trauma and unpleasant sensations. The whole process is completed within seconds. Immediately after formation, the microchannels fill with interstitial fluid, which is responsible for their hydrophilic nature. As a result, RF MicroChannels serve as aquatic channels into the inner layers of the skin that are embedded in the hydrophobic surroundings of the SC. The microchannels may last up to 24 hours, enabling prolonged drug delivery. After 36 hours, the drug delivery rate drops back to values characteristic of intact skin.

The unique microelectrode-array is also designed to overcome differences in skin texture and elasticity between different people and different areas of the body.

**Figure 1:** Formation of radio-frequency (RF) microchannels





The microelectrode array design adapts to differences in skin type within and between treatment sites. This design is essential for forming RF MicroChannels with consistent, well-controlled depths, enabling the drug to reach the capillary bed without unnecessary trauma to the inner layers of the skin.

### THE VIADERM DELIVERY SYSTEM

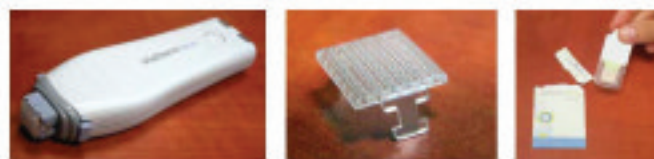
At TransPharma Medical, we have developed a system (ViaDerm™) consisting of a device used to pretreat the skin and form the RF MicroChannels in the outer layers, and a patch containing the drug, which is placed on top of the pretreated skin (see Figure 2).

The device consists of a handheld electronic control unit and a microelectrode array. The control unit (see Figure 2a) is battery-operated, rechargeable and reusable for at least 1,000 applications. This particular device is available in three sizes (treatment area of 1, 2.5 or 5cm<sup>2</sup>), depending on the desired dose of drug to be delivered.

The microelectrode array (see Figure 2b) contains hundreds of microelectrodes, is disposable and low-cost. The array is based on a proprietary design and made of biocompatible materials that are well established in medical devices. Within a few seconds, the control unit and the array create a matrix of RF MicroChannels, thereby preparing the treatment site for the patch containing the drug. After application of the patch (see Figure 2c) on the pretreated area, the drug passively diffuses from the patch through the RF MicroChannels into the inner layers of the skin and into the systemic circulation.

### PATCH TECHNOLOGY FOR PROTEIN DELIVERY

Currently, commercially available patch technologies are not suitable for the incorporation of proteins. The ViaDerm printed-patch technology for transdermal delivery of proteins complements RF cell ablation. The manufacturing method involves dispensing very small droplets of a concentrated protein solution on a transdermal liner in a predetermined pattern. The liquid is dried, leaving a thin layer of formulated protein on top of the liner. After pretreatment with the ViaDerm device, the patch is placed on the selected skin area, and the highly water-soluble proteins are dissolved by the interstitial fluid that is secreted through the RF MicroChannels, thus forming a highly concentrated protein solution *in situ*. The diffusion of the dissolved molecules occurs through the RF MicroChannels into the viable tissues of the skin across a steep concentration gradient. This process results in a high delivery rate of the drug and a peak-shaped blood profile resembling that of subcutaneous injections. This method fully retains the stability and biological activity of the protein drug. Printed patches were used in studies in which human growth hormone, insulin and teriparatide



(a) The device

(b) The microelectrode array

(c) The patch

(hPTH<sub>1-34</sub>) were successfully delivered in animals (guinea pigs and pigs) and humans.

### DELIVERY OF WATER-SOLUBLE DRUG MOLECULES

The skin's low permeability limits the types of drugs that can be delivered transdermally. Many drugs with a hydrophilic nature permeate the intact skin too slowly to be of therapeutic benefit. The RF MicroChannels significantly enhance the permeability of water-soluble compounds, such as Granisetron HCl (350 Da), which was delivered at a rate of greater than 8mg/cm<sup>2</sup>/24hr using full-thickness porcine skin that had been pretreated with the device. Even drugs that are mildly soluble in water can still benefit from the technology, by increasing solubility using various formulations, such as drug-cyclodextrin complexes or by dissolving the drug in a water-alcohol mixture. For example, testosterone encapsulated by beta-hydroxypropyl cyclodextrin (molecular weight of ~2.5kDa) was delivered at a rate of 0.5mg/cm<sup>2</sup>/24hr after dissolving in an aqueous solution. The delivery rate increased linearly with the concentration of the applied compound.

### EFFECT OF MOLECULAR SIZE ON DELIVERY RATE

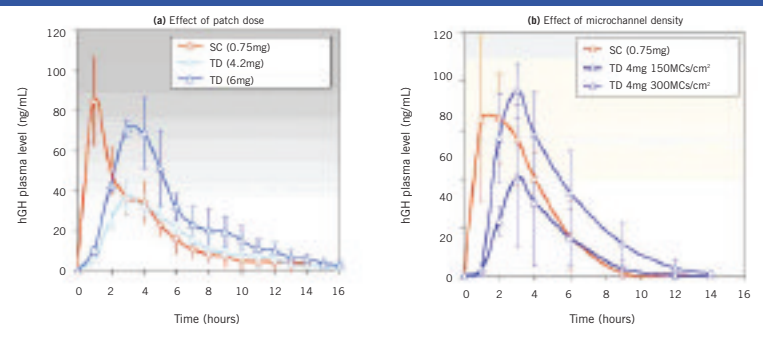
The effect of molecular size on the delivery rate of macromolecules through the treated skin was shown in a study using fluorescein isothiocyanate-labeled dextran molecules of various sizes: 10, 40 or 70kDa. This *in vitro* experiment tested the delivery of these macromolecules through a full-thickness porcine skin that had been pretreated with the device. Delivery rate was, naturally, inversely proportionate to molecular size, but it is important to note that even the largest 70kDa molecule was successfully delivered transdermally through the RF MicroChannels.

### EFFECT OF PATCH TECHNOLOGY ON PHARMACOKINETIC PROFILES

The ViaDerm system can induce two types of blood concentration profiles of a drug, based on the patch technology used. When a patch based on a dry formulation is used (that is, a protein-printed patch), a peak-drug profile is observed in the blood, which resembles the profile of a subcutaneous injection. Figure 3 (see page 68) shows the blood profile of human growth hormone delivery in pigs. The peak concentration, C<sub>max</sub>, increases with the patch dose

**Figure 2:** ViaDerm – a microelectronic system based on radio-frequency cell ablation

**Figure 3:** The pharmacokinetic profile of human growth hormone (hGH) delivery in pigs



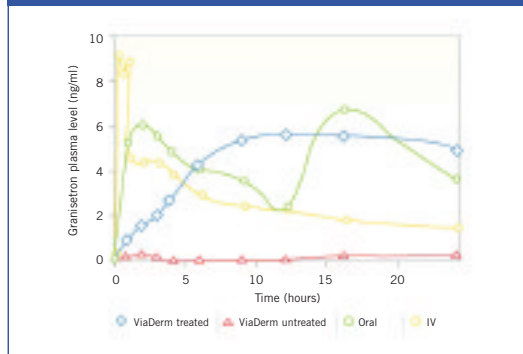
SC - subcutaneous delivery  
TD - transdermal delivery  
MC - microchannel

or microchannel density. Delivery rate doubled when the drug load on the patch increased from 4.2mg to 6mg (see Figure 3a), or when microchannel density increased from 150 to 300 microchannels/cm<sup>2</sup> (see Figure 3b). This technique also significantly increased the relative bioavailability of the drug.

Alternatively, it is possible to achieve a sustained drug flux for up to 24 hours by incorporating the active material into a moist matrix such as a hydrogel that serves as an infinite reservoir. The matrix contains the drug in a soluble form, which makes it available for delivery through the aqueous microchannels. The matrix releases the drug slowly at a rate suitable for delivery, enabling the drug concentration in the blood to be maintained for as long as 24 hours.

We assessed the effect of a hydrogel patch in a human study of granisetron-HCl delivery. Granisetron-HCl, a charged, water-soluble molecule, was administered using a small (5.6cm<sup>2</sup>) hydrogel patch and the ViaDerm system. This delivery mode was compared with other routes, including passive transdermal delivery, oral delivery (one tablet every 12 hours), and intravenous (IV) delivery. The

**Figure 4:** Plasma levels of granisetron in humans using various delivery modes



study was conducted on six healthy adult volunteers in each test group. The results (see Figure 4) revealed differences in the plasma-drug profiles between the treatments. The IV and oral deliveries displayed a peak or peak-and-valley profile corresponding to the administration regimen. In contrast, the transdermal delivery through RF MicroChannels resulted in a concentration increase up to nine hours and a constant level up to 24 hours, indicating that the channels enabled drug delivery for at least 24 hours. The control group (labelled 'ViaDerm untreated' in Figure 4) showed very low plasma levels across the entire time period, emphasising that the skin pretreatment used to form microchannels enabled the transdermal delivery of this water-soluble molecule. Together, Figures 3 and 4 demonstrate that RF MicroChannels could be used to achieve various drug concentration profiles, depending on the type of patch used.

### LACK OF RESERVOIR IN THE SKIN

One of the most disturbing issues regarding passive delivery is the accumulation of drug in the SC, due to the affinity between hydrophobic drugs and this lipid-rich tissue. A drug in the reservoir continues to be released into circulation long after the treatment stops, thereby decreasing the effectiveness of the treatment. The microelectronic system based on RF cell ablation used in this study delivered water-soluble drugs that cannot be accumulated in the lipid-rich SC, thereby eliminating the risk of forming a skin reservoir.

### CONCLUSION

A microelectronic system based on radio-frequency cell ablation may be used in various therapeutic applications. Such a system offers a transdermal delivery solution for polypeptides, other large molecules and water-soluble small molecules. This system also allows enhanced immunizations by providing a painless, safe and effective alternative to current intramuscular or subcutaneous vaccination methods. RF MicroChannels also improve penetration of the drug substance and dosage control.



**Dr Galit Levin** is Vice President of R&D, Pharmaceutical, at TransPharma Medical located in Israel. Prior to joining the company, she held senior positions in the R&D Division of Teva Pharmaceuticals, responsible for guiding formulations through all stages of development, culminating in Phase III clinical trials. Galit received her DSc in 1994 from the Faculty of Food Engineering and Biotechnology at the Technion-Israel Institute of Technology. Email: galitl@transpharma.co.il



**Judith Kornfeld** is Vice President of Business Development at TransPharma, and is currently based in the US. Prior to joining the company, she held the position VP of Business Development at leading biotechnology concerns, responsible for creating collaborations with major medical device companies and academic organisations. Judith specialises in bringing innovative medical technologies to prosperity in the medical industry. She holds a BSc in Biology and an MBA, and also has an academic background in electrical engineering. She is the member of the Beta Gamma Sigma society. Email: judithk@transpharma.co.il