Liquid Transdermal Drug Delivery: The State of the TDS® Art

Kenneth Kirby

President, Transdermal Technologies, Inc., 1368 N. Killian Drive, Lake Park, FL 33403, US

Ken Kirby is President and Founder of TransDermal Technologies, a Florida company focused on innovative transdermal delivery of drugs, nutritional substances and cosmetics. Ken is co-inventor of the TDS® technology. He is active in the life sciences community in the United States and United Kingdom, and serves on a number of industry, academy and governmental advisory boards.

Introduction

To date, transdermal delivery has been effective in delivering only a very few drugs due to difficulties in moving larger, and chemically non-compatible, molecules across the skin's biologically-active barrier. Drugs with higher melting points, drugs of molecular weight greater than 500 Daltons and drugs requiring pharmacological doses of more than 40 mg in 24 hours can not employ patch- or gel-based transdermal delivery as a safe and effective modality. More recently, alternative approaches have been attempted to expand possibilities, employing various devices and modalities, such as micro-needle arrays in patches, or phonophoresis or iontophoresis to breach what is designed to keep the outside out and the inside in.

While the avoidance of toxicity and side-effects is a major motivator in the quest for a liver first-bypass delivery modality, until now a truly flexible, convenient enabler of transdermal dosing has been lacking. This article discusses developments in this mode of delivery made by **TransDermal Technologies, Inc.** (TTI) with its patented TDS® liquid spray-on delivery technology.

Early Days

In 1995 a small team at TTI began to work on the challenge of transdermal delivery. TTI began operations as a pharmaceutical company producing over-the-counter products. Its active ingredient was an ammonium compound that was assumed too large to trans-migrate the skin, but which, nevertheless, seemed to work quite well for arthritis and trauma-related symptoms, as testified to by clinicians and patients. The inventor of the patent underlying this product, Daniel Stout, only focused on delivering what he referred to as a cloud of cationic charges, which he believed had a beneficial effect in assisting the body to restore its own pain-free dynamic equilibrium.

Upon considering the broad range of analgesic and anti-traumatic effects the compound possessed, the TTI team focused on how it could be applied topically. Some of these effects were known to be present in simple ammonia solutions and compounds containing urea. Some transmigration was considered a possibility. Stout noted in his patent (Stout, 1982) that amphoteric and zwitterionic

quaternary ammoniums could induce pain relief although they did not produce only cations, the central operant in his mode of action. Furthermore, there was no other science supporting this beneficial cation theory. It could not adequately explain the analgesic and anti-inflammatory effects and, therefore, it was rejected.

Proven Technology

Upon further analysis of existing commercialised transdermal delivery, the team sought to understand why patches and gels were dogged with limitations. Ground-breaking work by Alejandro Zaffaroni of **ALZA** and Alec Keith of **Watson Drugs**, plus subsequent developments with hydro-alcohol gels by **Laborotoire Besins**, revealed that the composition and small volume of the patch-delivery solutions prevented much engineered enhancement (Pfister and Hsieh, 1990).

These formulations of alcohol and propylene glycol enable the solution of small doses. However, although the emulsion chemistry of gels enables a larger volume of solvent into which the active can be dissolved (thereby increasing delivery application over a larger surface area), they do not allow for the inclusion of enhancers to increase flux of the payload. Such inclusions make these systems unstable. Strengthening the patch's solvent system to enable the solution of larger molecules and doses, or enhancing penetration and perfusion in the skin tended to disassemble the plastic polymers that comprise standard reservoir patches or monolithic drug-in-adhesive configurations. This increased irritation and even caused sensitising reactions to the drug.

Another Approach

The brilliant team at **Noven Pharmaceuticals** with their innovative dual-drug-in-adhesive dot-matrix system has greatly increased the horizon for patch delivery. They side-stepped the 'solvent volume versus enhancer challenge' by developing a system that isolates the drug and solvent from the plastics in the patch barrier material. Their recent success with Methylphenidate HCL is a testimony to this approach and their Vivelle® products are acknowledged leaders in the female hormone replacement market segments. Nevertheless, some challenges remain even for this innovative approach associated with the first order kinetics of patch delivery. The challenge of the relatively slow flux from patches and gels has led many experts, such as **Ghosh** and **Pfister**, to hypothesise that certain drugs may never be delivered transdermally, even if they could be delivered by patch; their physical chemistry would be identified rapidly after introduction by the skin's defences which would blockade it and render it impractical.

TTI observed that, regardless of the volume of solvent used, all of the successfully commercialised approaches to transdermal drug delivery grew from a common paradigm. Drugs were fitted to a delivery device or a formula designed only to overcome the physical barrier of the Stratum Corneum; they then released a unit dose of drug to migrate by osmosis as conditions allowed. If a physiological defence mechanism did not oppose it, a drug could transmigrate to a receptor as long as its therapeutic dose was relatively small. The TTI team began to feel the need for a paradigm shift that would approach the challenges from a new perspective; namely a new hypothesis that assumed that delivery of large complex drug- and carrier-systems was possible. Therefore, investigation began proceeded into what compounds, and what sorts of compounds could transmigrate the skin readily and rapidly.

Analysis of Demonstrated Success

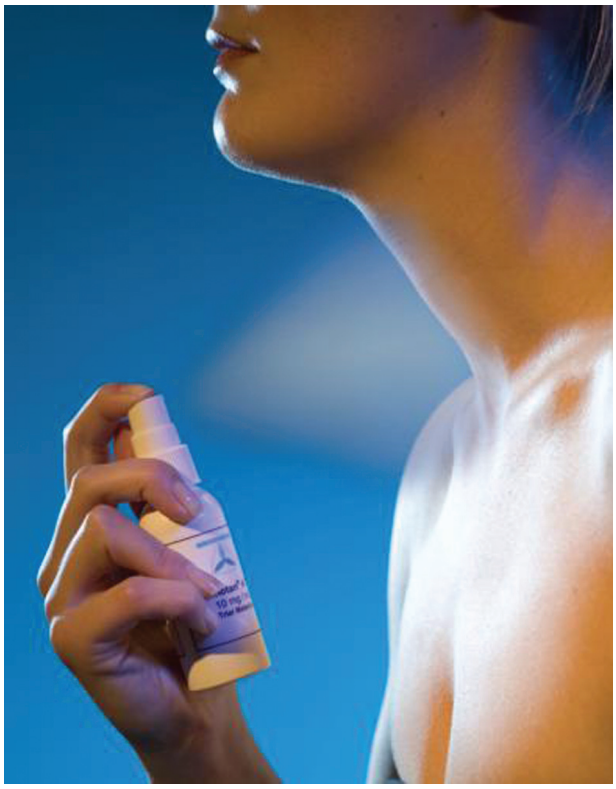
TTI noted various organic compounds that possessed the ability to rapidly transmigrate, such as Dimethyl Sulfoxide (DMSO), Dimethyl Sulfone (Rahman *et al.*, 1992), some petro-chemicals and physiological substances as Hyaluronic Acid (Falk and Asculai, 1994). It was further noted that some of these compounds, either inadvertently or intentionally, had been employed as carriers for other compounds. Therefore it was established that large complex molecules could transmigrate intact skin and, perhaps physical size was not the real issue after all.

The team suspected that the physical chemistry of the compounds was operant in exposing most drugs to the skin's defence mechanisms. Therefore, TTI looked for ways to use elements of physiology as camouflage for transdermal delivery. Extensive work in this area, done at the Department of Experimental Pathology at St. Bartholomew's and The Royal London School of Medicine by Chandan Alam, Derek Willoughby, Michael Seed and Adrian Moore, had successfully demonstrated the use of Hyaluronic Acid to deliver certain NonSteroidal Anti Inflammatory Drugs. Their premise was that if the body recognised the vehicle as 'self', it would permit more efficient transdermal delivery. This technique worked to a degree but the Hyaluronic Acid that bound the drug so effectively meant that once the drug was in the body it was not completely bio-available. It was also noted from their work that regular chronic doses of these compounds tended to break the skin down.

TTI concluded that in order to offset the irritation potential of the delivery system, and/or the drug, they must avoid the use of substances in the delivery system which would react and bond covalently, thereby insuring that the delivery system releases a bio-active and bio-available form of the drug.

The Way Forward

TTI noted that certain dermatological drugs were migrating at least as far as the viable skin, provoking both an acute and a chronic set of responses by the skin. Drugs which could be tolerated by the skin for short courses often become irritating over time while drugs required for chronic use had to be delivered in very low doses to avoid reactions (Gordon, 1992). This further reinforced the growing conviction that the latency of the drug in the skin played a major role in mediating the potential for immune response. It seemed reasonable that if the drug were made to move rapidly through the various strata of the skin's defences, allowing little or no time for the immune system to target the drug, there would be little possibility for sensitised reaction.



Putting the Pieces Together

The team concluded that in order to succeed at transdermal delivery, a system must:

- be able to expand the area of application dramatically;
- rapidly move the drug through the skin, and at the same time;
- consider the living biological nature of the barrier and employ compounds in the delivery system that are at some level compatible;
- be able to work reversible changes to the physical-chemical state of the drug.

So How to Proceed?

The ability of various solvents to disrupt safely and reversibly the elastin-collagen mortar between the dead cells of the Stratum Corneum is well established, so this was used as a starting place. However, the team also knew that getting the drug under the Stratum Corneum was not sufficient to survive the skin's defences. TTI reasoned that if drug could be rendered less recognisable as something to blockade, at the same time reducing the drug and solvent's potential for irritation, one might be able to deliver a reasonable dose of a drug down to the capillary plexus, rapidly and more importantly, in a bio-available form.

TTI also considered that they could design a solution of acceptable solvents and excipients that had the ability to transmigrate rapidly. These solution modifiers could serve either to enable the solution of relatively large amounts of drug, or to render the payload more compatible with other excipients. This would minimise irritation and/or enable solution in the solvent itself.

The Physical Chemistry Solution

Using some cutting-edge concepts in solution chemistry, the team sought to engage the ingredients into a complex by manipulating short forces (the molecules' quasi-gravitational attractions and repulsions) instead of covalent bonding, which might have the effect of modifying the drug and rendering it, at best, non bio-available and, at worst, toxic. The team was able to design such a system and successfully place a diverse list of drugs and combinations of drugs into solution, in doses sufficient to accomplish therapeutic blood levels. The inclusion of compounds, which stimulate *in situ* production of cAMP, proved to have the desired preventative effect on premature uptake and metabolism of the drug in the dermis. A thorough review of the patent literature failed to discover any similar approaches and two patents for the technology, dubbed and trademarked as TDS®, have now been issued, with at least one more divisional application pending, plus some new art and at least one use patent pending (Kirby and Pettersson, 2002 and 2004).

System Toxicity

The typical TDS® ingredient list is composed, with one exception, of substances which are otherwise Generally Regarded As Safe (GRAS) for inclusion into food or nutritional products. The single non-GRAS excipient, a nutritional supplement in the US, has been evaluated in the MatTek EpiDerm® model using the Neutral Red Uptake assay as non-toxic and this ingredient has an estimated LD50 at 91.3 mg/Kg and occurs in most TDS® formulae at less than a tenth of a milligram (Raabe and Moyer, 2005).

A blank TDS® vehicle was evaluated and found to be non-toxic and non-irritating (Raabe, 1998), and a TDS® drug product has been evaluated for dermal toxicity side-by-side with a gel product for delivery of the same active ingredient. The TDS® product proved markedly less toxic (Raabe and Moyer, 2005).

What do the experts think?

Dr Alam's team of scientists at The William Harvey Institute at St. Bartholomew's in London already had experience with pre-clinical and phase I studies of transdermal drug delivery, therefore, the team was a logical partner for TTI's establishing proof of concept. After four years the collaboration has produced fifteen trials of twelve different molecules including several clinical trials, the reports of which have been accepted for peer-reviewed publications. The TDS® technology has successfully demonstrated delivery of a broad spectrum of drugs, including the highly lipophillic Morphine Sulphate, with onset of activity in five minutes, routinely showing therapeutic doses in the blood stream within thirty minutes. Over 400 clinical exposures have resulted in no skin irritations, reddening or reactions. The system has proven that it delivers its drug payload and releases it in a bio-available and active form reliably and efficiently. It has been calculated that in excess of 90% of the dose (compounded into 1 ml or less of liquid) delivered through the skin is bio-available (*Table 1*).

Drug	Category	Status
Cystamine	Anti-neovascular	Pre-clinical PK/POC
Hydroxyzine	Antihistamine	Pre-clinical PK/POC
Acyclovir	Anti-viral	Pre-clinical PK/POC
Morphine Sulphate	Opiate	Pre-clinical PK/Metabolite
Ibuprofen	NSAID	Pre-clinical PK/Dose Response
Ibuprofen	NSAID	Pre-clinical Therapeutic outcome
Acetaminophen	NSAID	Pre-clinical PK/POC
Acetaminophen	NSAID	Pre-clinical Therapeutic outcome
Quaternary Ammonium	NSAID	Phase II Therapeutic outcome
Lidocaine	Narcotic	Pre-clinical PK/POC
Lidocaine/Tetracaine	Narcotic	Phase I/IIa
Testosterone	Hormone	Pre-clinical PK/POC
Testosterone	Hormone	Phase I Dose range
Testosterone	Hormone	Phase II Dose Response
αMSH	Peptide Hormone	Pre-clinical Dose range

Table 1 – The results of investigative trials by the TTI into a variety of molecules.

The team at the William Harvey Institute at St. Bartholomew's is awaiting permission to begin recruiting patients for a dose-ranging trial of the delivery, by TDS®, of the peptide drug known as Melanotan (analogue Alpha Melanocyte-stimulating Hormone). The TDS® system successfully delivered this peptide in a pivotal trial in a proprietary Guinea pig model and is the first transdermal delivery system documented to do so through intact skin.

Conclusion

TransDermal Technologies believes that the next evolutionary step for transdermal delivery technology could be to build a unique liquid delivery system that would spray the drug product directly onto intact skin. With a strong and growing IP position, proof of concept with a diverse list of pharmaceutical actives, including a small peptide and bolstered by a growing list of pre-clinical and peer-reviewed published clinical successes and encouraged by a growing list of industry partners who are expressing strong interest, the Team at TransDermal Technologies is excited about the future of its new addition to the options for non-invasive dosing of drugs and peptides, TDS®.

References

Falk RE, Asculai SS, 1994. Treatment of Disease Employing Hyluronic Acid to Facilitate Transport of Non-steroidal Anti-inflammatory Drugs, CA Patent 2,089,621 & 2,089,635.

Gordon V, 1992. In: *Cosmetics and Toiletries Manufacture*, CFTA, US, 178-182.

Kirby KB, Pettersson BIR, 2002. US Patent 6,444,234.

Kirby KB, Pettersson BIR, 2004. US Patent 6,787,152.

Pfister WR, Hsieh DST, 1990. *Phar Technol* **14**(10):54-60.

Raabe HA, 1998. *Anti-inflammatory Assay using Epiderm® Skin Model with MTT and Ccytokine Endpoints*, Institute for In Vitro Sciences, Gaithersburg, MD.

Raabe HA, Moyer GO, 2005. *Neutral Red Uptake Bioassay in Normal Human Keratinocytes*, Institute for In Vitro Sciences, Gaithersburg, MD.

Rahman MS, Gallo MA, Umbreit TH, Zatz JL, 1992. *J Soc Cosmet Chem*, **43**:251-258.

Stout Daniel W, 1982. *A Therapeutic Method*, US Patent 4,330,551.

If you have found this article of interest and would like copies for promotional purposes, please contact:
Paul Sanders
Tel: +44 (0) 1865 784 171
Fax: +44 (0) 1865 784 178
E-mail: paul.sanders@pharmaventures.com