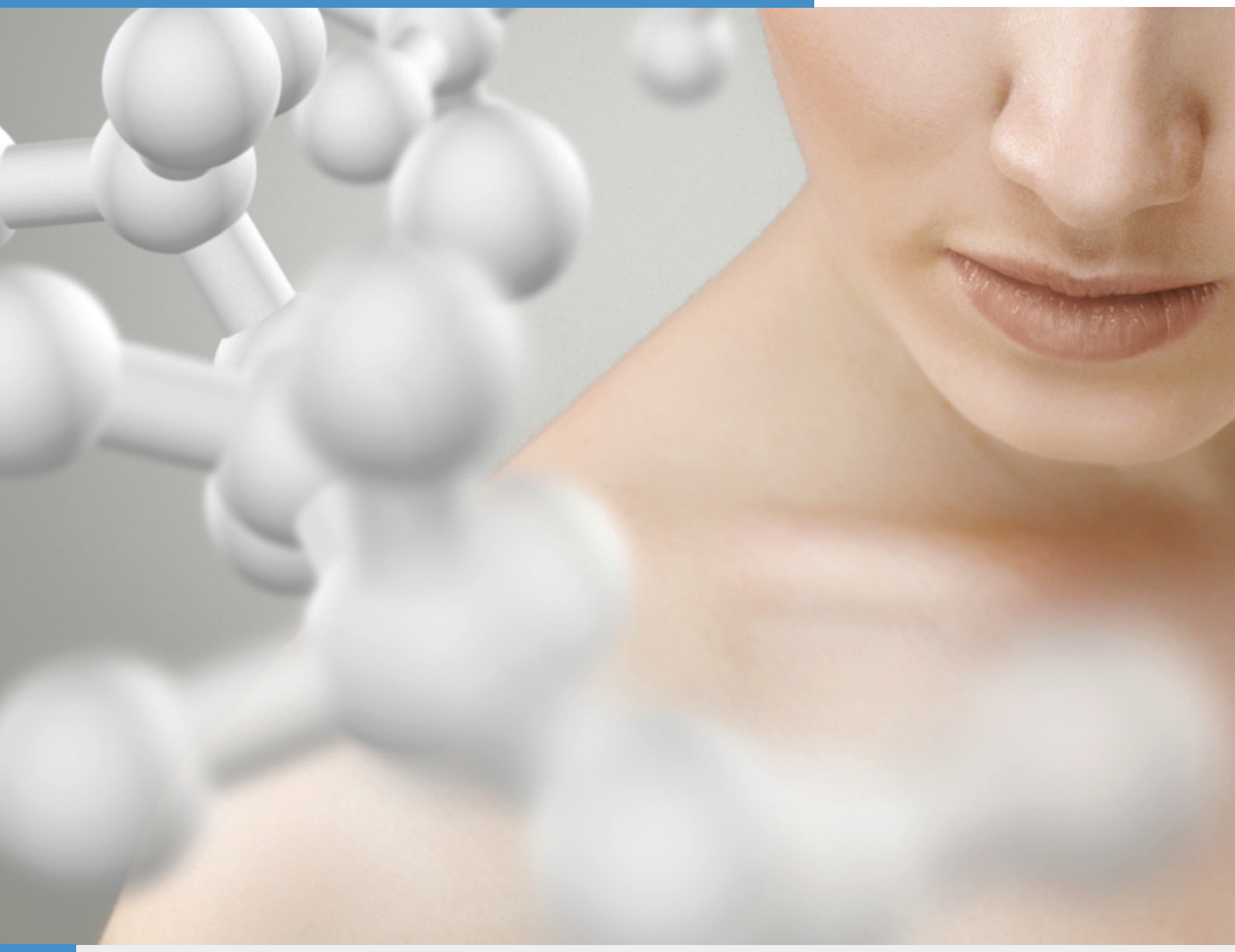
TRANSDERMAL DELIVERY, MICRONEEDLES & NEEDLE-FREE INJECTION

ON drugDELIVERY



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TRANSDERMAL SPECIALTIES

ONdrugDelivery Issue N° 49, May 16th, 2014

Transdermal Delivery, Microneedles & Needle-Free Injection

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

EDITORIAL CALENDAR 2014/15

May: Pulmonary & Nasal Drug Delivery
May/June: Injectable Drug Delivery: Devices Focus
June: Injectable Drug Delivery: Pharmaceutics Focus
July: Novel Oral Delivery Systems
Sep: Drug Formulation & Delivery Solutions & Services
Oct: Prefilled Syringes
Nov: Pulmonary & Nasal Drug Delivery
Dec: Delivering Biotherapeutics
Jan: Ophthalmic Drug Delivery
Feb: Prefilled Syringes

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INTRODUCTION
SKIN IN THE GAME: TRANSDERMAL DELIVERY AS A NEW SOURCE FOR BIOPHARMA INNOVATION

By Kevin Pang, PhD, MBA

Transdermal delivery technologies, despite great promise, have thus far failed to live up to their potential as powerful delivery devices for the sustained and controllable delivery of active pharmaceutical ingredients (APIs). Although an almost-30-year-old platform technology, today only about 16 drugs are actively on market for delivery via transdermal patches. Hurdles to adoption range from cultural and consumer preferences, to drug abuse problems, to limited API application due to solubility and penetration issues.

However, we believe that this is about to change in a big way. The convergence of advanced formulation technologies, combined with printed electronics, will transform the adhesive transdermal patch platform into a new fifth generation of devices and a new source of delivery innovation for biopharma companies and patients (Figure 1).

Current or fourth-generation platform technologies use active or electronic delivery, e.g. Nupathe's (now Teva) iontophoretic sumatriptan patch. The combination of active delivery with advanced formulation for enhanced skin penetration constitutes our definition of a fifth-generation platform.

> "If we assume that only 20% are US FDA- and/or EU EMA-approved over the next 2-3 years, then we can expect to see at least 16 new transdermal patch products come to market"

The unique strength of transdermal patch delivery is the ability to deliver constant regulated levels of API for the treatment of chronic conditions. Treatment of neurological diseases and conditions like Parkinson's disease, depression and pain are extremely well suited to this unique strength, avoiding the typical peak and trough phenomena experienced with oral solids (Figure 2) as well as first-pass clearance for greater sustained bioavailability. An example of this is Nupathe's 2013 US FDA-approved iontophoretic sumatriptan delivery patch for migraine, prompting Teva Pharmaceuticals to quickly purchase the company for its battery powered transdermal patch franchise and technology platform.

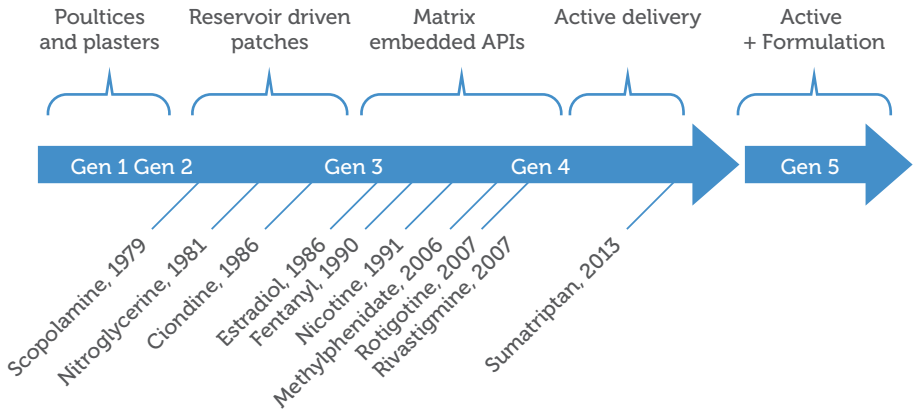

Figure 1: A brief and compressed history of transdermal delivery.

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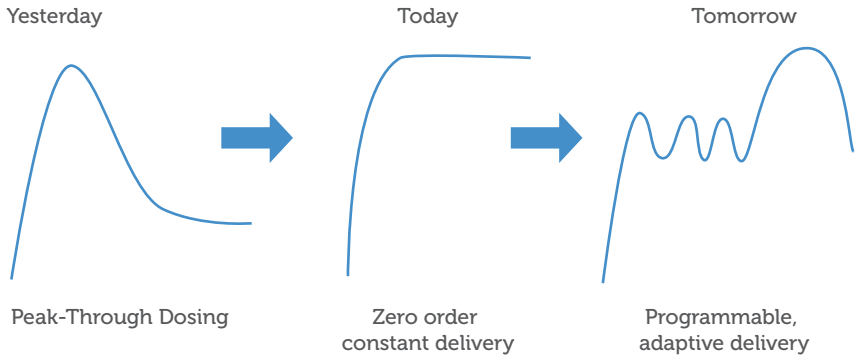

Figure 2: Transitioning into increasingly sophisticated delivery paradigms.

Electronics enables much more constant and dose effective delivery today. Increasing sophistication and application of software, algorithms, sensor incorporation, web and analytics, along with increasingly effective at-will skin penetration and delivery, will drive personalised and adaptive drug delivery.

The promise of thin, flexible, printed circuits and batteries layered on top of the transdermal platform is the increasing potential capability to titrate and customise drug delivery, in effect, personalising drug delivery tied to an individual's metabolism and disease state. Further convergence and application of advanced microfluidics, sensors, and web-based analytics will enable the eventual build of powerful biofeedback loops for even more exquisite near real-time modulation. At the same time, innovators in the sector will push the miniaturisation frontier, resulting in increasing ergonomics and comfort, and lower the development and production cost curves.

As a result, we believe transdermal drug delivery is in the midst of experiencing a renaissance in development and application as part of the armamentarium of intelligently and co-ordinately dealing with multiple medication management. Advances in micro- and nano-needle technology (e.g. Micropoint); the use of ultrasound (e.g., Transdermal Specialties), iontophoresis (e.g. Nupathe), electroporation (e.g., Ichor Medical Systems), and even heat generation (e.g., MedPharm), more effectively to drive drug delivery; the use of printed electronics and algorithms to create feedback loop driven mini-pumps; and advances in physiological knowledge with integration into circadian rhythms, will enable transdermal patches to be much more powerful and functional to the patient.

The number of transdermal patch-delivered drugs in clinical trials provides a rich landscape by which technology providers can partner with drug companies to enhance functionally and create multiple product line extensions in the future. An estimated 81 clinical trials are ongoing currently, more than half for nervous disorders, pain management, and behaviour modification such as drug and smoking cessation (see Figure 3).

One of the major barriers to skin-based delivery is the low permeability of skin that makes it difficult to deliver molecules greater than 500 Da in size. Figure 4 details a few examples of companies that are working on advanced formulation to enhance delivery, not just of small molecules, but even biologics of 106 Da or greater in size, as either biological drugs or vaccines. Many are working on enhanced large molecule delivery, including biomolecules such as hyaluronic acid, vaccines, enzymes, and potentially therapeutic antibodies.

We predict that combining active electronic delivery with advanced formulation will provide unprecedented innovation by expanding the size range of deliverable APIs, and efficacy of delivery of APIs, greater bioavailability, and controlled release that is not just chemical and thermodynamically derived, but electronically enhanced and programmed per individual. Fifth-generation transdermal delivery should not only open up more effective and efficacious ways to deliver drugs to patients, but also provide new forms of intellectual property extension for biopharma companies.

To provide an example of how big and dynamic we expect the transdermal patch drug delivery market to grow, we

"We predict that combining active electronic delivery with advanced formulation will provide unprecedented innovation by expanding the size range of deliverable APIs, and efficacy of delivery of APIs, greater bioavailability, and controlled release that is not just chemical and thermodynamically derived, but electronically enhanced and programmed per individual"

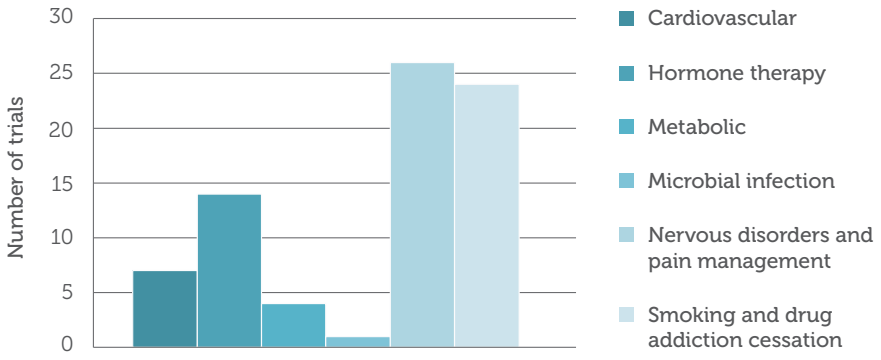

Figure 3: A robust clinical trial pipeline.

Company	Technology
Halozyme	Hyaluronidase skin penetration enhancer for biologics
Apricus Biosciences	Small molecule amphiphilic amino acid-fatty acid moiety skin penetration enhancer
Nanocyte	Sea anemone injectors to form channels in skin
JRX Biotechnology	Oils/alcohol/PEG formulation for large molecule delivery
Salvona Technologies	Micro- and nano-encapsulation platform
Transdermal Technologies	Polar solvent matchup to API for ionic liquid formation
Convoy Therapeutics	11-mer peptide skin penetrant directly conjugated to API or embedded in liposome
NewGen BioPharma	Multiphase oil:water emulsion (licensed from Novavax)
Nuvo Research	Membrane penetration enhancers + heat generation

Figure 4: Example companies developing skin penetration enhancement technologies.

constructed potential demand curves for Nupathe's (now Teva) sumatriptan iontophoretic delivery patch for chronic migraine (see Figure 5). Conservative estimates of prevalence growth and market penetration still indicate the potential for a blockbuster drug for Teva by 2021, despite the API, sumatriptan (Imitrex™) being generic, and available for injection via prefilled syringe. Patch convenience, which obviates the need for patient self-injection; and the ability to program desired kinetics, we believe are powerful drivers in favour of this revitalising delivery platform.

Given the 81 ongoing clinical trials, it seems likely that some will be approved. If we assume that only 20% are US FDA- and/or EU EMA-approved over the next 2-3 years, then we can expect to see at least 16 new transdermal patch products come to market. While each market is different, in general our model assumes 9-10 years from launch to peak year sales, that many of the targeted disease indications will yield opportunities in the US$500 million to $1 billion peak year sales levels, we therefore expect to see up to an additional $10 billion in annual sales via transdermal patch delivery by 2025.

Even a few successes with the current pipeline would be highly stimulatory for further innovation in this field. The predicted three ball collision between pharma, electronics, and formulation and delivery companies will give rise to fifth-generation devices. We see several non-traditional players poised to participate in the transdermal patch drug delivery evolution. Examples include: Blue Spark Technologies, which is already targeting thin-film printed batteries for patches; PragmatIC Printing, which prints logic circuits for potential sensor hookups; and ThinFilm's recent acquisition, Kovio Technologies, which combines its printed memory and sensor platform with near field communications for wider range communication (e.g. remote analytics and services). Conversely, firms like MC10, which prints flexible adhesive integrated circuits for remote biosensing, might themselves evolve to become drug delivery platform companies.

The potential for personalised delivery of vaccines, nutrients, and both small- and large-molecule drugs via intelligent transdermal patches is here. Furthermore, the true potential of personalised delivery lies in the integration of physiologic feedback loops, i.e. sensors and analytics to create low cost, accurate, highly convenient patches, perhaps linked to services, making the transdermal patch a truly powerful platform.

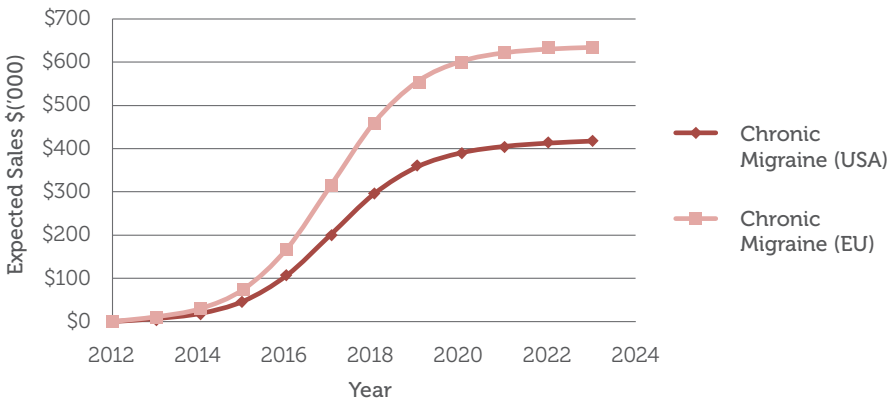

Figure 5: Estimated demand curve for Zecuity based on chronic migraine prevalence and incidence rates in the US and EU. (Application is assumed for chronic migraine only and forecasted out 10 years from 2013. Total sales expected to hit $1B by 2021. Nupathe estimates that key patents covering their platform extend through 2027, covering our forecasted range.)

Kevin Pang, PhD, MBA, was the lead analyst on the Lux Research report, "Skin in the Game: The Coming Rise of Transdermals", which was published in January 2014, and is available to clients of Lux Research. Find out more at: https://portal.luxresearchinc.com/research/report_excerpt/15923.

Download the 2014 Media Pack for more information!

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ONdrugDelivery 2014/15 EDITORIAL CALENDAR

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June	Injectable Drug Delivery: Pharmaceutics Focus	May 12th
July	Novel Oral Delivery Systems	June 9th
September	Prefilled Syringes	August 4th
October	Drug Formulation & Delivery, Services & Solutions	September 15th
November	Pulmonary & Nasal Drug Delivery (OINDP)	October 13th
December	Delivering Biotherapeutics	November 10th
January 2015	Ophthalmic Drug Delivery	December 15th
February 2015	Prefilled Syringes	January 12th
March 2015	Transdermal Patches, Microneedles & Needle-Free Injection	February 6th
April 2015	Pulmonary & Nasal Drug Delivery	March 2nd
May 2015	Injectable Drug Delivery: Devices Focus	April 13th

OVERVIEW: TRANSDERMAL DELIVERY DEVICE DESIGN

By Bruce K Redding Jnr

The product development process for a transdermal drug delivery (TDD) system is multidisciplinary in nature. Much of the scientific literature in the field of transdermal delivery pertains to skin permeation and methods of skin penetration enhancement because these are the fundamental issues that must be addressed for any transdermal drug candidate. However, in addition to the basic questions of skin permeability and dose delivered, the development process must also address other basic questions, such as the following:

- What is the appropriate patch design?
- What are the appropriate materials to use in the patch construction?
- Will the target drug be compromised by either the design or the materials used in the patch construction?
- Choice of the skin pathway, either sweat pore, hair follicle, micro-fissure penetration or poration of the skin.

CONVENTIONAL PATCH DESIGNS

The two main traditional/conventional types of patch design – reservoir patches and matrix patches – are shown in figures 1 and 2, respectively.

Reservoir Type Patch

Characterised by the inclusion of a liquid reservoir compartment containing a drug solution or suspension, which is separated from a release liner by a semipermeable membrane and an adhesive.

Commercial examples include:

- Duragesic® (fentanyl, Janssen)
- Estraderm® (estradiol, Novartis (discontinued))
- Transderm-Nitro® (nitroglycerin, Novartis)

Matrix Type Patch

Similar to the reservoir type patch design but has two distinguishing characteristics:

- The drug reservoir is provided within a semisolid formulation
- There is no membrane layer

Commercial examples include:

- Habitol® (nicotine)
- Nitrodisc® (nitroglycerine)
- ProStep® (nicotine)

Drug-In-Adhesive Type Patch

The drug in adhesive (DIA) patch is a type of matrix match, characterised by the inclusion of the drug directly within the skin-contacting adhesive (Wick, 1988). In this design the adhesive fulfills the adhesion-to-skin function and serves as the formulation foundation, containing the drug and all the excipients (Wilking, 1994). This category also has two sub-sections: monolithic and multilaminate.

Commercial examples include:

- Monolithic DIA: Climara® (estradiol)
- Multilaminate DIA: Nicoderm® (nicotine)

The DIA patch design has several advantages in reducing the size of the overall patch and provides a more concentric seal upon the skin. DIA patches tend to be more comfortable to wear and very thin. A typical DIA patch is 165-200 µm thick.

Major disadvantages include a longer drug delivery profile. The release of the drug from a DIA patch follows first-order kinetics, that is, it is proportional to the concentration of drug within the adhesive. As the drug is delivered from the DIA patch the drug concentration will eventually begin to fall. The delivery rate therefore falls off over time and this fact needs to be considered in the clinical evaluation phase of development.

> "Each of these approaches to delivering drugs through the skin brings with it unique advantages but at the same time challenges, be they technical, clinical, regulatory or commercial"

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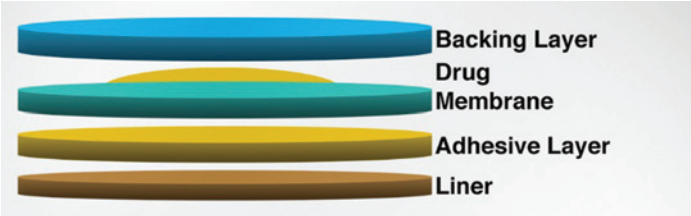

Figure 1: Reservoir transdermal patch construction.

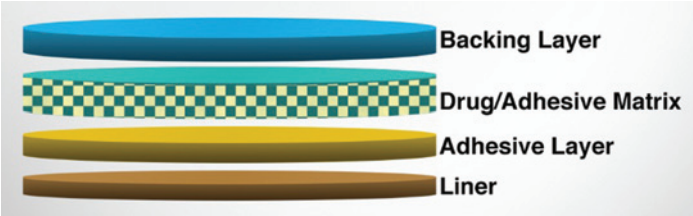

Figure 2: Drug-in-adhesive matrix patch construction.

A significant problem with most of the main forms of transdermal patch is the intermingling of the drug with adhesive compositions. These result in new profiles and in many instances the drug is degraded through the interaction with the adhesive composition. The chemistry of the adhesive can alter the stability, performance and function of certain drugs. In the case of insulin, for example, the intermingling of the adhesive with the drug can denature the insulin and any deposited insulin would now be a mixture of insulin + adhesive, which may not be a safe blend for dosing purposes.

Additionally there are limits to the molecule size of drugs, which can be delivered via a passive system. Typically drug candidates are below 500 Da for DIA patches and below 1,000 Da for matrix and reservoir patches, even through the use of skin enhancers.

GETTING THROUGH THE SKIN

The skin is a natural barrier, as shown in Figure 3. To deliver a compound transdermally your options are:

1) Microporate the skin such as through a catheter or needle. Essentially puncture the skin. Mirconeedle systems and reduced length injectables are designed to reduce the pain associated with skin puncturing.
2) Passive absorption through the *stratum corneum*. Drugs less than 500 Da in size can more easily be absorbed. Drugs between 500 and 1,000 Da require skin enhancers such as alcohol or surfactants to increase skin absorption.
3) Dilation of the skin pore. The normal pore diameter is 50 µm (on the body). Dilating the pore to expand its diameter can allow larger molecule drugs to be absorbed.
4) Dilation of the pore surrounding the hair follicle. The normal hair follicle pore diameter is 50 µm (on the body). Dilating the pore, to expand its diameter, can allow larger molecules to wick down the hair to the root and from there into the epidermis.
5) Fracturing of the skin micro-fissures. By using an energy medium the skin micro-fissures can be dilated and this will allow certain large molecule drugs to be absorbed into the *stratum corneum*.
6) Accelerating the drug to high speeds so it has enough kinetic energy to pass straight through the *stratum corneum* and other skin layers, coming to rest at the required depth, as with liquid and powder needle-free injection systems.

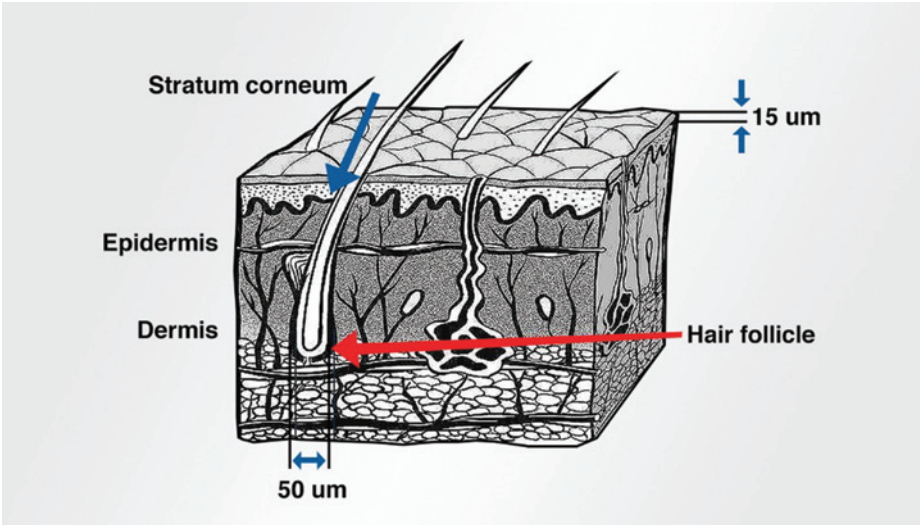

Figure 3: The basic structure of human skin.

Each of these approaches to delivering drugs through the skin brings with it unique advantages but at the same time challenges, be they technical, clinical, regulatory or commercial. On the following pages in this issue of *ONdrugDelivery Magazine*, the abovementioned techniques will be described in more detail.

DEBIOTECH S.A. Switzerland
Innovative Medical Systems

YOUR SOLUTION FOR SUCCESSFUL INTRADERMAL DELIVERY

In this article, Paul Vescovo, PhD, Project Manager, and Laurent-Dominique Piveteau, PhD, MBA INSEAD, Chief Operating Officer, both of Debiotech, discuss the design of the Debioject™ microneedle device and inserter, and its applications, particularly in intradermal delivery of vaccines. Clinical development is underway and encouraging preliminary results are reported.

For many years, the transdermal route has been considered an interesting alternative to the oral or standard parenteral routes for the injection of drugs. Compared with the former, it prevents the active ingredient undergoing degradation in the gastrointestinal tract as well as the first-pass hepatic metabolism. Compared with the latter, it prevents patient pain induced by the shot as well as safety risks associated with contaminated needles. Despite this, there are very few drugs that are delivered today using this method.

> "The peak time of insulin can be halved compared with subcutaneous injections. For vaccines, when compared with intramuscular injections, doses required to reach sufficient immune response can be reduced by a factor of up to ten or, at constant dose, immune response can be enhanced significantly."

The top layer of skin, the so-called *stratum corneum*, which has a thickness of 10-15 µm, acts as a tight barrier that prevents most chemical compounds penetrating into the body. Only small molecules, with adapted lypophilicity and sufficiently solubility may potentially be delivered in this way. Unfortunately, the vast majority of APIs do not match these criteria.

In addition to the advantages relating to the injection mode, the skin presents particularly interesting characteristics. Several studies have shown that the pharmacokinetics of certain compounds can be dramatically modified when infused within the skin. The peak time of insulin, the molecule forming the basis of diabetes treatment, can be halved compared with subcutaneous injections. For vaccines, when compared with intramuscular injections, doses required to reach sufficient immune response can be reduced by a factor of up to ten (as this is the case for rabies) or, at constant dose, immune response can be enhanced significantly (such as for flu in elderly patients).

All these factors have encouraged the development of a variety of tools to facilitate the crossing of the upper layer of the skin by a wider range of molecules. Two major approaches have been followed. The first one, using chemical methods, has focused on the modification of the molecules or on their combination with other molecules to facilitate their passage through the *stratum corneum*. The second one has been focusing on physical methods to create passages through which molecules can penetrate into the skin. Electrical currents (electrophoresis) or ultrasound (sonophoresis) for example are used to make the *stratum corneum* porous for a certain period of time. By placing a simple drug container on the treated surface, the drug could then

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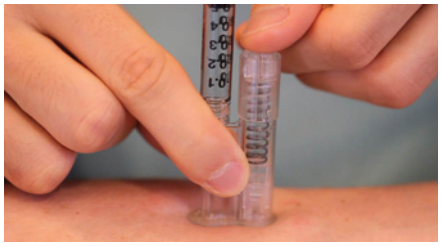


Figure 1: DebioJect™ is very easy to use.

slowly diffuse into the tissue. Microneedle technologies are part of these physical approaches. By their form, microneedles dig passages through the protective layer of the skin that will be used by the drug to diffuse into the tissue.

They are four different ways usually described to perform intradermal injections using microneedles:

POKE AND PATCH

The so-called "Poke and Patch" method is similar to what we described earlier with the electro- and sonophoresis approaches. Microneedles are used to create pathways in the skin mechanically, which are then covered by a patch containing the drug to be delivered. As long as these pathways stay open, the drug diffuses into the skin.

COAT AND POKE

In the "Coat and Poke" approach, needles are coated with a formulation comprising the active agent combined with a polymer that will dissolve after insertion of the needles into the skin. Minutes after placement, the needles are removed, the coating has disappeared and the active agent has been delivered.

POKE AND RELEASE

In the "Poke and Release" approach, needles are made of a soluble material containing the medicament. Once in the tissue, the needles will dissolve and release the active principle.

POKE AND FLOW

Finally, in the so-called "Poke and Flow" approach, hollow microneedles play the same role as conventional needles by creating a mechanical channel through the skin which will be used by a liquid formulation to penetrate the tissue. DebioJect™ microneedles, recently named as MDEA Awards 2014 finalists, are part of this latter category.

Figure 2: Single microneedle mounted on a connector.

Figure 3: Multiple microneedles mounted on a connector.

MEDICAL DESIGN EXCELLENCE AWARDS® 2014 FINALIST

THE DEBIOJECT™ SYSTEM

The DebioJect™ System is intended for injecting any liquid substance or drug fluid into the dermis. This CE marked device is very easy to handle and doesn't require any special skills (Figure 1). The depth of injection and the amount of substance delivered are both reached precisely and in a controlled way. DebioJect™ can inject a bolus of up to 500 µL within less than five seconds.

The system comprises two main elements:

- a single or an array of hollow microneedles (Figures 2 and 3) in fluidic connections with a reservoir containing the medical substance to be delivered into the dermis
- an inserter (Figure 4) to place the microneedles into the dermis at the targeted depth and maintain them in place during the whole injection.

Although the innovative hollow microneedles are the heart of the system, the inserter plays an essential role.

MICRONEEDLES

Due to the thin nature of the dermis layer, the needles must be very short – less than 1 mm – in order to ensure delivery of the medical substance into the targeted region (Figure 5). They are made of high-purity monocrystalline silicon covered with a native thin layer of silicon dioxide. Silicon offers very interesting mechanical properties. It is a non-ductile material with an incredibly high tensile strength and hardness. With such mechanical properties, and as it was demonstrated experimentally, there is nearly no risk of microneedle breakage in the skin. Furthermore, silicon and silicon oxide have excellent biocompatibility.

Microneedles are monolithic and made without any assembly. They consist of a flat substrate sustaining the microneedle part. A fluidic micro-channel goes through the whole needle, from under the substrate to the delivery hole which is placed, not

"Silicon offers very interesting mechanical properties. It is a non-ductile material with an incredibly high tensile strength and hardness. With such mechanical properties, and as it was demonstrated experimentally, there is nearly no risk of microneedle breakage in the skin."

Figure 4: Two kinds of inserters.

on the tip of the microneedle, but on its side (Figure 6).

The length of the microneedle and the position of the delivery hole can be changed by design in order to deliver the fluid at any required depth between 150 µm and 900 µm. A microneedle can have one or several delivery holes placed circumferentially (Figure 7). The outer shape of the microneedle is designed with a very sharp tip to puncture the skin easily. The microchannel drives the injected fluid from the injection line through the delivery hole into the patient's skin.

DebioJect™ microneedles are produced using well established industrial Micro Electro Mechanical System (MEMS) technologies (Figure 8). MEMS are manufactured using modified semiconductor device fabrication technologies, commonly used to manufacture IC circuits. It allows the manufacturing of very small devices with a sub-micron precision, far better than standard micromechanical technologies. DebioJect™ microneedles are currently manufactured by Leti (Grenoble, France), which is part of CEA, one of the world's largest organisations for applied research in micro-electronics and nanotechnology. It offers extensive facilities for micro and nanotechnology research, including fabrication lines, 11,000m² of cleanroom space, and first-class laboratories and equipment.

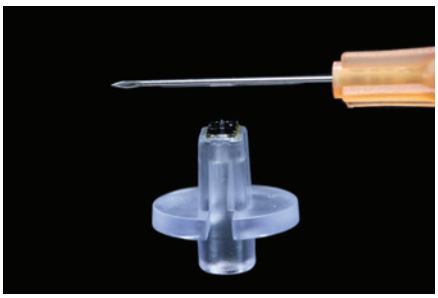


Figure 5: Comparison between a microneedle and a 25G needle.

The manufacturing process developed with Leti/CEA is completely compatible with the major industrial MEMS foundries.

The needles are processed on 200 mm (8 inch) diameter silicon wafers. About 1,500 microneedle chips can be produced on a single wafer. The entire process is conducted in an ISO Class 3 cleanroom environment. MEMS technologies enable the manufacturing of high volumes of devices at a very low cost.

INSERTER

The inserter must provide the microneedle with the right dynamic parameters (force, velocity, energy) to ensure its full

Figure 6: SEM image of a 700µm long microneedle with single hole.

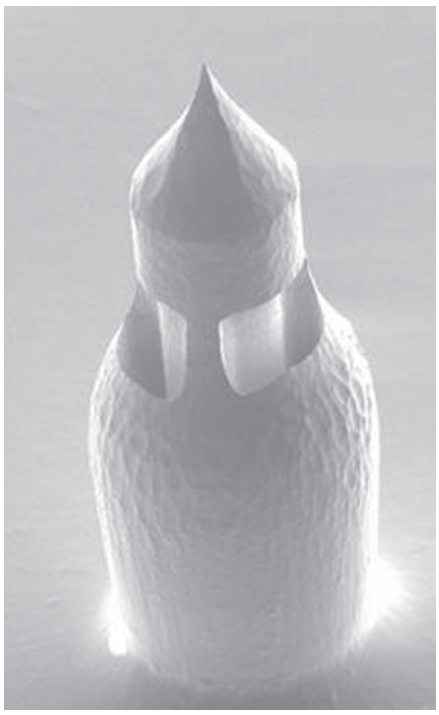


Figure 7: SEM image of a 700µm long microneedle with mutiple holes.

penetration into the skin without any rebound. Once the needles are in place, it has to maintain its position throughout the whole injection procedure. The issue is very challenging, as the inserter must ensure precise positioning on a soft substrate, even though both the patient and the practitioner will undoubtedly make normal uncontrolled tiny movements. Regarding the length of the microneedle, even very small motions below 1 mm are critical. This issue has been extensively studied *in vivo* in humans with a micro camera mounted on an inserter (Figure 9).

"The fluidic jet is oriented horizontally at the exit of the needle and the delivered drug will have a natural tendency to pursue its course in the same direction"

A properly designed inserter should guarantee injections without any leakage which is one of the major issues of intradermal injection with microneedles. It's particularly critical as even a tiny leak may be significant relative to the small injected volume, and could lead to a medical treatment failure.

The design of the microneedles and the inserter must be adapted to satisfy each application and targeted population.

DEBIOJECT™ KEY ADVANTAGES / ID INJECTION CHALLENGES

As described above, the *stratum corneum* forms a strong barrier to protect the underlying tissues yet in order to reach the dermis the microneedle has to go through this layer. It must therefore have a sharp tip to easily pierce the tissue and be made of a strong and hard material, especially since the microneedle will contact the skin at a relatively high speed, to penetrate it. The microneedle contact area with the skin must be minimal to facilitate the penetration and limit tissue damage. For the patient this means no pain, a fast healing and no leakage at the base of the microneedle.

Even though the microneedle diameter must be as small as possible, the inner microchannel has to be large enough to limit the fluidic resistance and allow a good passage for the drug. Thanks to that, even highly viscous solutions have been successfully injected with the device.

The structural components of the dermis are collagen, elastic fibers and extra-fibrillar matrix. It forms a dense and incompressible structure. For this reason the hydrostatic pressure will tend to increase during injection, especially if the delivery hole is positioned at the tip of the microneedle. The tip of the needle is compressing the tissue and as a consequence it increases the fluidic resistance in this area. It's therefore very beneficial to place the delivery hole on the side of the microneedle as the fluid will be delivered into a region which is less compressed and presents a lower fluidic resistance. Another advantage is that it tends to push the injected liquid in the dermis, and not in the subcutaneous tissues (Figure 10). The fluidic jet is oriented horizontally at the exit of the needle (contrary to "classical" needles) and the delivered drug will have a natural tendency to pursue its course in the same direction. Another major advantage of a delivery hole which is not placed at the microneedle tip is of the absence of coring and as a consequence of clogging of the micro-channel which may lead to high fluidic resistance or even complete occlusion when using conventional straight-hole needles.

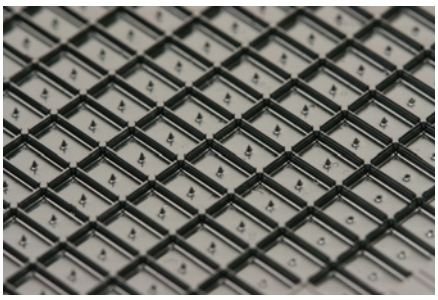


Figure 8: Microneedles on a wafer.

PRECLINICAL & CLINICAL STUDIES

DebioJect™ microneedles have undergone several preclinical and clinical studies. Preclinical studies conducted on various animal models such as mice, rats or pigs, are covering areas ranging from basic research to preliminary tests for clinical trials of new drugs. In the more fundamental trials, the objective is to understand the distribution of an injected fluid into the dermis precisely. Here the control in depth that can be achieved thanks to the design of the needle is of particular interest.

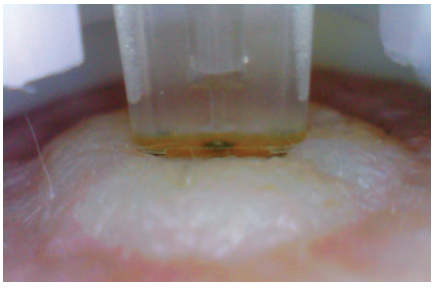


Figure 9: Microscopic view of an injection on human skin in vivo.

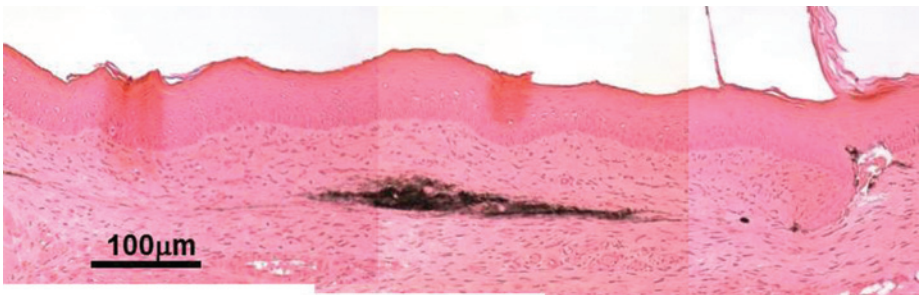


Figure 10: Transverse histological section of mouse skin after injection with DebioJect™.

Clinically, both the DebioJect™ microneedles and the effectiveness of the intradermal route are being tested. For the former, the perception by the patient and the possible side effects of the DebioJect™ are evaluated, while for the latter the response to different molecules injected intradermally (sometimes at lower doses) is compared with that obtained when using conventional subcutaneous or intramuscular injections.

A study currently underway and conducted in collaboration with the Vaccine and Immunotherapy Centre of the Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne, Switzerland, compares the injection of rabies vaccine (Vaccin rabique Pasteur®, Sanofi Pasteur, Lyon, France) intramuscularly, with the Mantoux method and using DebioJect™ microneedles. The sixty-six volunteers involved in this study are divided into three groups. Each group receives injections with all three methods, but only one of the injection devices is filled with antigen, the other two containing placebo.

In this double blinded study, each patient after an inclusion visit receives three series of injections: one at T_0 (where the antibody level baseline is also measured), a second one at T_0 + 7 days and a third one at T_0 + 28 days. For each injection, the pain perceived during the insertion of the needle as well as the pain perceived during the injection of the active ingredient are measured. This is described by each volunteer on a scale of zero to 10 (zero for no pain and 10 for maximal pain). This distinction allows for segregating the impact of the microneedle of the effect of the infused drug product itself. The order in which injections are done is changed at each visit in order to limit the comparison effect. Side and adverse events such as redness, pruritus and irritation are also recorded. Finally, during each session as well as three weeks after completion of the last injection, a blood sample is taken and analyzed by RFFIT to determine anti-rabies IgG levels.

A first series of intermediate results has already revealed some highly interesting information. Upon insertion of the needle, the perceived pain is slightly higher for the intramuscular injection than the Mantoux method. The use of a DebioJect™ microneedle is significantly less painful. Upon injection of the active agent, the perceived pain of the intramuscular shot and of the DebioJect™ is similar, but statistically lower than that perceived when using the Mantoux method (Figure 11). The absence of leaks (or partial leaks) during the injection is also a noticeable point. These results are very favourable to the approach using DebioJect™. As the study has not yet been unblinded, it is impossible to attribute the different IgG levels measured to the different immunisation routes. It is however interesting to note that all patients are fully immunised, regardless of the method used. These results tend to show non-inferiority of the DebioJect™ approach.

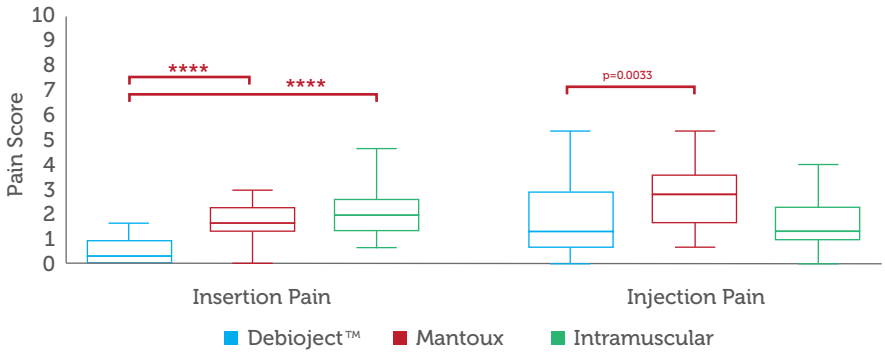


Figure 11: Pain perception comparison.

CONCLUSION

When speaking about intradermal injection, the first application that comes to mind is undoubtedly the vaccination. Since the visionary work of Charles Mantoux and Louis Tuft at the beginning of last Century, many studies have focused on this path often with encouraging results. More recently these have included the treatment of skin cancer, desensitisation, but also various applications in the field of cosmetics that have been developed. With the emerging availability of technologies enabling successful intradermal injections without special education or in-depth training, there are undoubtedly many other application areas that will generate interest for this delivery route.

DebioJect™ microneedles have been conceived to replace conventional needles, but their very particular design allows considering for the future having them filled with solid formulations that will dissolve over time inducing a controlled release over long duration.

ABOUT DEBIOTECH

Debiotech SA is a Swiss Company with more than 20 years' experience in developing innovative medical devices, based on micro- and nanotechnology, microelectronics, and innovative materials. The company concentrates on implantable and non-implantable systems, in particular for drug delivery and diagnostics, with a demonstrated competence lying in the identification of breakthrough technologies and their integration into novel medical devices.

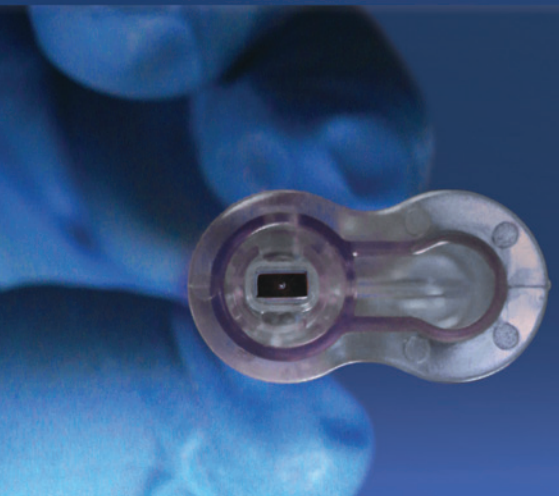
Devices developed by Debiotech are ultimately licensed to major international pharmaceutical and medical device companies, and Debiotech has a track-record of over 40 license agreements worldwide. Examples of products, in addition to the DebioJect™ microneedles for intradermal injections, include: the I-Vantage™ IV pump for hospital and home-care; the CT Expres™ Contrast Media injector for CT-Diagnostic Imaging (recently acquired by Bracco Imaging); the JewelPUMP for diabetes care; the DialEase™ home-care miniaturised dialysis equipment; and others under development.

DebioJect™

Microneedle Intra-Dermal Injection

Simple and Reliable ID System

- easy to use and reproducible
- painless injection
- automatic insertion
- precise depth control
- up to 500 µl in 3 seconds



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Innovative Medical Systems

DERMAL DELIVERY OF BIOLOGICS

Here, Faz Chowdhury, PhD, Chief Executive Officer, and Richard Toon, PhD, Technical & Business Development Manager, both of Nemaura Pharma, describe one of the company's key technologies for the delivery of biologics, the Micropatch™.

Nemaura Pharma provides solutions for drug delivery through the skin using its proprietary platform technologies. The Micropatch™ skin insertion platform offers a versatile topical or transdermal delivery platform for a large range of molecules, including biologics.

An increasing number of drug companies are turning to transdermal drug delivery platforms both for existing molecules as well as for the delivery of new chemical entities and biologics, as an effective means of painlessly delivering the drug. Nemaura Pharma has a portfolio of proprietary technologies including conventional matrix patches, and intuitive microneedle-based technologies for the rapid and efficient delivery of a range of molecules. These technologies have been developed to be cost-effective alternatives to conventional modes of drug delivery, yet provide accurate, robust and reproducible-dosing with minimal patient intervention.

THE POTENTIAL & CHALLENGES OF MICRONEEDLES

Microneedles are needles whose length is in the hundreds-of-microns range, which can be produced from a wide variety of materials including polymers, metals, and the drug formulation itself. Microneedle systems are in widespread development and have been successfully clinically tested for a number of different molecules. However, there are a number of significant challenges that must be addressed before they can be commercialised:

- Dose loading is very low, and doses delivered are usually in the microgram to low milligram range.
- Larger doses require larger patch sizes but larger patches are associated with uncontrolled non-reproducible skin application thus poor reproducibility of dosing.
- Formulations must be able to adhere on to the needle surface, or in the case where the needles are produced from the drug itself the drug must have the requisite physico-chemical properties to maintain tip sharpness for adequate skin penetration. Many drugs will not have the requisite properties therefore and thus be rendered unsuitable for microneedle delivery, or require protracted pharmaceutical development programmes.
- It is very difficult to verify that a dose has actually been delivered other than where the needles are required to dissolve into the skin and where upon removal of the patch from the skin there is visual evidence of the needles having dissolved and no longer being present on the patch. In the case of drug adhesive patches an

Figure 1: Images of hollow drug loaded pellets used in the Micropatch™ Drug Delivery system.

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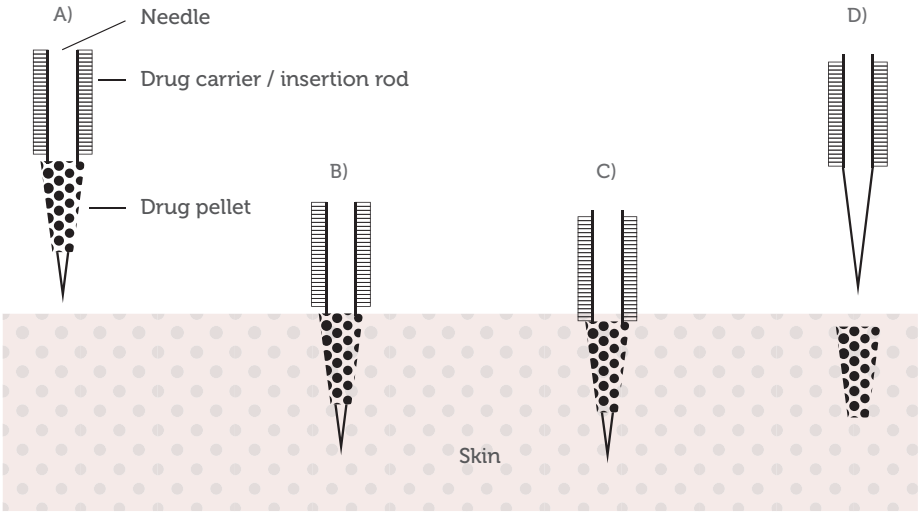

Figure 2: Sequence of microneedle delivery via the Micropatch™.
A) Microneedle or needle containing a hollow drug loaded pellet
B) The needle is inserted into the skin, engineered to insert to the desired depth.
C) Drug carrier slides down the side of the needle inserting the drug into the skin and then
E) The needle is retracted from the skin with the drug 'package' remaining inside the skin.

analogous scenario is delamination of the patch from the edges of the skin leading to inaccurate dosing, however in this case the needles would need to remain inserted into the skin over the entire surface area for the duration of dosing.

- The depth of penetration of the microneedles will vary from person to person based on skin thickness and toughness and reproducibility of application.
- The residence time of the needles inside the skin cannot be adequately controlled or determined and movements of the body will lead to motions that have potential to dislodge the needles out of the skin given their very shallow depth of penetration. Long residence time can also be a source of skin irritation that may lead to rubbing of the patch thus dislodging the needles from the skin.

Collectively, the above pose some significant obstacles that must be overcome before the mass utilisation of microneedle technologies for drug delivery applications becomes a reality.

BENEFITS OF NEMAURA'S MICROPATCH MICRONEEDLE SYSTEM

Nemaura's Micropatch was designed and engineered with a view to addressing these challenges. The device can be compared with the "poke-and-patch" method that is defined in microneedle terminology as a process whereby the skin is first prepared by applying the needles followed by the application of a drug loaded patch or gel for example. However, in this case the procedure is precise whereby the drug is inserted directly into the holes created using the needle(s) after removal of the needles from the skin, or the drug is placed into the skin along the side of the needle using a 'carrier' whilst the needle is still inside the skin, followed by removal of the needle and carrier from the skin.

These features impart the following advantages to the Micropatch:

- Drug loading may be µg to mg without any restrictions to drug insertion being imposed by the drug physico-chemical properties, thus reducing the complexity of the pharmaceutical development stage.
- A finite dose is delivered according to needs, ranging from µg to 10's of mg or more (using multiple doses on a single device).
- The delivery time, and thus residence time of the needles inside the skin, is in the order of a few seconds, i.e. near instant delivery.
- Dose delivery can be verified as the dosage is clearly visible within the carrier section of the device.
- Depth of delivery can be modulated as required from hundreds of µm to a few mm, depending on the dose and desired penetration depth.
- The device is a single mass producible disposable unit, though a non-disposable applicator and a disposable drug portion can also be accommodated.

This device provides a means for the delivery of both small molecules as well as biologics, with the possibility of modulating drug release based on formulation excipients and processing method. Importantly this provides a means for self-administration of drugs through the skin that may otherwise have to be administered by a healthcare professional.

Figure 1 shows images of hollow drug pellets used in the Micropatch delivery system, Figure 2 shows a schematic of the mechanism by which the Micropatch operates and Figure 3 shows images of the skin following insertion of the micro-pellets, which indicate that the skin completely seals up after administration, and any superficial signs of skin trauma disappear within an hour of insertion.

The Micropatch can be used for the delivery of a single drug or multiple drugs simultaneously using multiple needles on a single device. Needle length can be varied from hundreds of microns leading to minimum sensation, or several millimeters in length for deeper depot delivery of drug 'packages'. The drug packages may be formulated according to a range of geometries in the diameter range of tens to hundreds of microns, making it easy to administer precise doses, effortlessly with minimal pain sensation.

Nemaura Pharma already has global license agreements with pharmaceutical companies for some of its technology platforms. Nemaura is actively seeking to broaden the list of partnerships and collaborations for the delivery of small molecules and biologics which may otherwise suffer from drug delivery challenges.

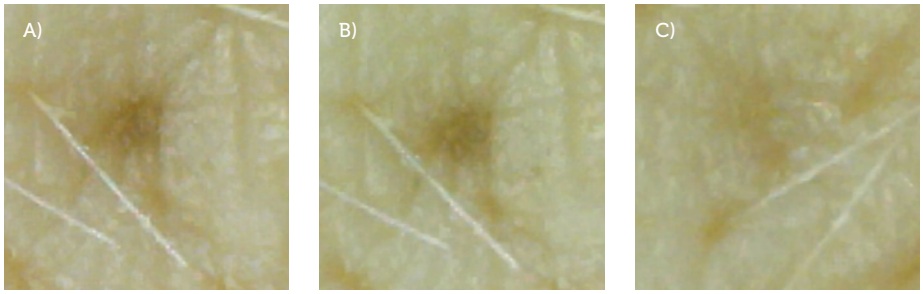

Figure 3: Insertion of 500 µm BSA particle in porcine skin. A shows the initial insertion of BSA. B after 30 minutes, C after 70 minutes, taken using a USB microscope.

INTERVIEW: PATRICK ALEXANDRE, CROSSJECT

Crossject is developing a pipeline of high-value supergenerics and new therapeutic entities using its needle-free injection system, Zeneo®. The first Zeneo product is expected to reach the market in 2015.

Crossject's needle-free, prefilled, single-use & fixed-dose Zeneo injection systems are unique in that they can be tailored to deliver drugs intradermally, subcutaneously and intramuscularly. This means that Zeneo can allow a wide range of drugs and vaccines for a broad range on indications to be developed and approved in a very short period of time.

In addition to building its own portfolio, Crossject anticipates partnering Zeneo with other pharma/biotech companies looking to improve the lifecycle management of their key drugs or biologics.

Shortly after Crossject's successful IPO on the French NYSE Euronext Paris Exchange (Paris Bourse), company Co-Founder and Chief Executive Officer Patrick Alexandre spoke about Crossject, its technology and strategy for the future as a publically traded company.

Q: Why did you decide to do an IPO?
A: We decided to do an IPO because we had progressed Zeneo to the point where we were close to commercialising this unique needle-free injection system and we needed additional funding to support and complete this process. We felt that executing an IPO would not only help in terms of funding but also in raising the profile of the Crossject business globally.

Q: Why was the IPO so successful?
A: I think we had a compelling proposition for public investors. Zeneo (see Figure 1) is great needle-free injection system which has been developed in conjunction with world-class partners both in France and internationally, it is expected to generate its first revenues in 2015 and has the potential to be used to deliver a broad range of small-molecule drugs, and biologics. Another key factor is that the development risk associated with the system is close to zero. Taken together these arguments were persuasive enough to generate significant interest from both institutional investors and retail investors in France.

> "Our IPO raised €17 million and was 4.4 times oversubscribed, which was very satisfying"

Figure 1: Crossject's prefilled, single-use, Zeneo® needle-free injector.

Our IPO raised €17 million and was 4.4 times oversubscribed, which was very satisfying.

Q: What will you do with the proceeds?
A: The proceeds from the IPO will be used mainly to build the commercial production line for Zeneo. We anticipate that our partners will introduce the first products using the Zeneo system in Europe in 2015. We are fortunate to be working with first-class partners, including Hirtenberger and Recipharm, to produce the final product that will be commercialised. In addition, we intend to use some of the funds from the IPO to complete the regulatory work in Europe around our two lead supergenerics products.

Q: How long has Zeneo taken to develop?
A: It has taken about 12 years and an investment of close to €60 million to develop Zeneo to this stage. During this process I have been very fortunate to work with some great partners who have applied their world-leading expertise to help us create the Zeneo system we have today. Amongst our partners have been Groupe SNPE (France) and Hirtenberger (Austria), both of which are specialists in propulsion technologies as well as Schott (high pressure glass, Germany), Rexam (specialists in nozzle technology, UK) and Recipharm (aseptic pharmaceutical filling, Sweden).

Q: What are the key advantages of Zeneo?
A: Zeneo is an excellent needle-free injection system that provides benefits for patients, our pharmaceutical partners and for payers. In the case of patients it provides better safety and efficacy and overcomes the problem of needle phobia. For our partners it provides clear differentiation and is an excellent tool for efficient lifecycle management. It is also able to deliver drugs intramuscularly, subcutaneously and intradermally, which is unique.

In the case of payers they benefit from better patient compliance and the ability to control costs due to more patients being able to self-administer the drugs that they need.

Q: What is your strategy to build your business based on Zeneo?

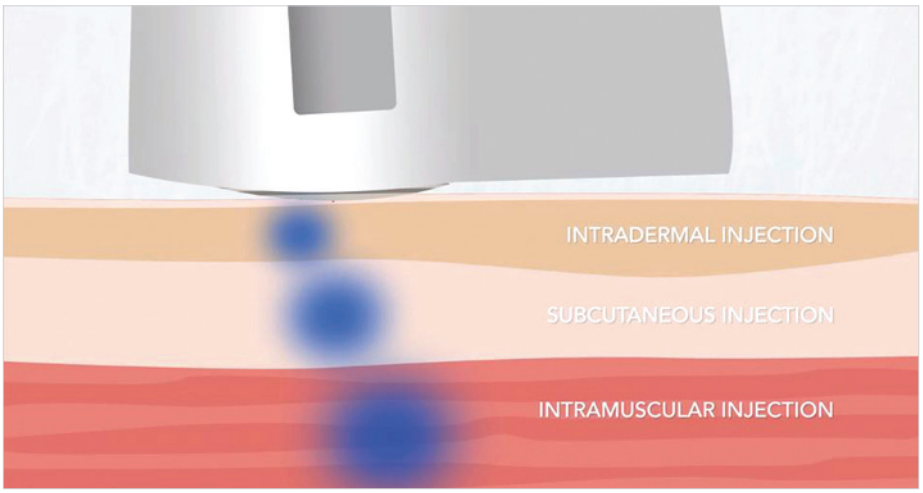

Figure 2: Zeneo can be tailored to deliver drugs intradermally, subcutaneously and intramuscularly.

A: We have a very clear strategy to generate sales and value from Zeneo. The first element of our strategy is to develop our own pipeline of supergeneric products that we can develop and commercialise through partners in various parts of the globe. At present we have three supergenerics in our pipeline; Zeneo methotrexate for the treatment of rheumatoid arthritis, Zeneo adrenaline for anaphylactic shock and Zeneo sumatriptan for the treatment of migraine.

The first of these two products have partners and are expected to be launched in Europe in 2015. We are continuing to look for partners for this pipeline to provide us with access to a broader range of markets and to ensure that they are a commercial success on a global basis.

We believe that we can further develop this pipeline of supergenerics through evaluating other injectable drugs that would benefit from delivery via a needle-free injection system.

> "In recent years more and more biologics have been provided as prefilled syringes and we see the adoption of Zeneo for many of these products as a natural next step"

In parallel with our own pipeline, we intend to sign selective partnering deals that would give pharma or biotech companies access to Zeneo for their products. We strongly believe that access to Zeneo would be extremely helpful for them in providing clear differentiation and in developing very strong arguments for reimbursement/market access with regard to the economic benefits of using this patient-friendly, needle-free injection system.

Q: What is the potential for Zeneo to deliver biosimilars and biologics?

A: We see this as an important market for Zeneo given the multiple benefits that it can deliver. In recent years more and more biologics have been provided as prefilled syringes and we see the adoption of Zeneo for many of these products as a natural next step.

There are several barriers that prevent injectable products from allowing perfect self-administration and good compliance, of which three of the main ones are: needle-phobia, the risk of needle-stick injury, and the more complex process of administration using a needle requires.

We are particularly keen to start working with biotech companies with their biologic drugs during the actual development process so that when these products come to market they provide a clear and significant advance in terms of therapy, patient convenience and economics.

As you sense we have great confidence in our Zeneo system and what it can deliver for patients, partners and payers.

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Patrick Alexandre is Crossject's CEO and a co-founder of the company. Patrick has been the driving force in the development of Crossject's technology since its inception 1997 when it was a research effort at Fournier Laboratoires. He has more than 15 years' experience in the pharmaceutical industry. Patrick also has ten years industrial R&D experience in the steel industry. Patrick graduated as an engineer from Supélec, France.

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TECHNOLOGY PROFILE: ZENEO®

CROSSJECT
Medical Technology

ZENEO®: THE NEXT REVOLUTION IN INJECTABLE MEDICINE

ZENEO® is a unique, automatic needle-free jet injector for SC, IM and ID routes, developed by Crossject. With ZENEO®, injection is fast, easy and secured:

- 10% of the population has a needle phobia
- The prefilled system ensures the accuracy of administration, even in emergency situations
- The injection can neither fail, nor harm, the patient : improved comfort, autonomy and compliance in treatments for a better healthcare outcome
- Ergonomic, automatic and very simple to use, ZENEO® is perfectly designed for self-injection (Figure 1).
- ZENEO® reduces hospital admissions & spending on healthcare due to a self & secured automatic injection.

"With ZENEO®, our ambition is to revolutionise treatments requiring injections in emergency situations, such as with chronic conditions. Thanks to its flexibility, our ZENEO® device can address more than 200 injectable drugs currently on the market. ZENEO® will allow patients to take their treatments more easily and health care organisations to reduce their costs. Last but not least, pharma companies will maximise the lifecycle of their products thanks to a quick route to commercialisation: two to three years between feasibility, bioequivalence study & obtaining marketing authorisation," said Crossject's Chief Business Officer, Tim Muller.

Figure 1: ZENEO® is perfectly designed for self-injection.

The ZENEO® prefilled, automatic, disposable, needle-free jet injector (left) and a cut-away image with the outer case removed, showing the device's internal mechanism (right).

> "Pharma companies will maximise the lifecycle of their products ... two to three years between feasibility, bioequivalence study & marketing authorisation"

The ZENEO® prefilled, automatic, disposable, needle-free jet injector (Figure 2):

- Allows three routes of administration: SC, IM, ID
- Delivers an automatic injection in one tenth of a second
- Has more than 400 patents granted
- Has benefitted from €60 million and 12 years dedicated to R&D
- There have been more than 10.000 tests completed
- Seven preclinical & seven clinical studies have been performed
- Will have three products on the market from 2015
- Its developer, Crossject, is headquartered in France, a spin-off from Fournier in 2001, recently listed on Euronext Exchange.

READY FOR MANUFACTURING

Crossject's partners are Hirtenberger and Recipharm. The industrial production lines will be built for the end of 2015, in order to be ready for marketing and sales. Thus Crossject should market ZENEO® from the moment it obtains marketing authorisations for its first products, epinephrine and methotrexate, which are expected in 2015.

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DESIGNING AN ULTRASOUND-ENABLED PATCH FOR INSULIN

In this piece, Bruce K Redding Jr, President & CEO, Transdermal Specialties, Inc, tells the story of the design and development of the U-Strip™ Insulin Transdermal Delivery System, which involved the development of an electronic delivery controller attached to an insulin transdermal delivery device. Various electronic delivery signals were considered but it was determined that ultrasound had the most promise.

ELECTRONICALLY ASSISTED TRANSDERMAL DEVICES

There are several approaches used to assist transdermal delivery electronically, including iontophoresis, laser and sonophoresis ultrasound. These systems are designed either to increase the flow of drugs across the *stratum corneum* or to microporate the skin, to allow the delivery of macromolecules across the *stratum corneum* into the dermis or underlying tissue.

Such electronically assisted transdermal delivery devices (TDDs) often use an outside electronic system, which is not connected to a drug-containing patch, or the patch has electrodes within it to assist in ionic transfer. Direct connection to a disposable transdermal patch is often impractical because the electrodes, or ultrasonic transducer system, are not disposable.

Any electronic signal sent through the TDD to liberate insulin from the patch must be reviewed for damage to the drug itself. Iontophoresis was found to induce electrical charges to the insulin which was found to be deleterious to its protein structure. Laser and infra-red transmissions through the TDD photo-damaged the insulin.

Sonophoresis, the application of sinusoidal ultrasound through the skin, can induce cavitation, which can usefully microporate and develop micro pathways through the skin, but the explosive energy of cavitation can heat and damage the insulin, and cause severe damage and discoloration to the skin. Therefore a two-step approach was tried – initial microporation of the skin, after which a patch containing insulin was placed over the skin site. Problems with this approach included insufficient intra-application dose control as the absorption of the porated skin section can have an irregular penetration diameter through the skin; and that the skin tends to seal such capillary punctures on its own.

So we faced the following challenges for transdermal insulin delivery:

- Insulin is too large a molecule to pass passively through the skin.
- Skin enhancing chemicals could interact with insulin and denature the drug.
- Ionotphoresis could denature the drug.
- Laser or IR transmissions sent through the skin would photo-damage the insulin.
- Sonophoresis, sinusoidal ultrasound, through cavitation can cause severe damage to the skin and discoloration and lead to a breakdown of the drug.

We decided to go for ultrasound. Of all the electronic systems, ultrasound offers the most promising capability for transdermal insulin delivery. It has an ability "push" the drug from the TDD through the skin because of vibrational energy. We were aware that sinusoidal ultrasound-induced cavitation could damage both the drug and the skin. Therefore, in order to use ultrasound, the problem of cavitation had to be defeated.

At this point in our design attempt to bring an insulin TDD into fruition, the first obstacle was to find a method to deliver a 6,000 Da compound through the skin. That was accomplished by the use of the sawtooth ultrasonic transmission, and through the skin pathway choice of targeting the skin pores for dilation. Our next problem was cavitation via traditional ultrasound. This

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was solved by interrupting one waveform with a switch to another wave form. In this case sawtooth to square wave (see Figure 1).

ALTERNATING ULTRASONIC WAVEFORM DYNAMIC

A unique alternating ultrasonic transmission was developed whereby ultrasound wave forms are altered just before cavitation could develop. An unusual function of sawtooth waves is the ability, when contacting a surface, to transverse that surface laterally instead of vertically. So a sawtooth wave transmission can flex the pores of the skin, dilating the skin pathway into a larger diameter. The sawtooth wave has been shown to dilate and enlarge human skin pores from the normal diameter of approximately 50 µm up to 110 µm within 10 seconds (Figure 2). The pores remain dilated as long as the ultrasound is active but return to original size three hours after ultrasound cessation.

The square waveform is the "ramming force" which pushes the drug into the enlarged pores. As the waveform switches from one to the other the potential for cavitation is minimised. By increasing the time on the square wave transmission we were able to obtain deeper drug penetration of the insulin within the skin.

A 30-second sawtooth-only waveform transmission at the start of the signal generation, known as skin priming, has the effect of dilating the pores. Therafter the alternating signal engages, sequencing between sawtooth and squarewave transmissions, with no degradation of the insulin and no skin damage.

TRANSDUCER DESIGN

We found that conventional piezoelectric transducers could not develop the alternating waveform effect. No matter what electrical signal was given, they generated a sinusoidal wave, which is to be avoided in ultrasonic drug delivery.

A new approach with changes in the design and the material selection for the U-Strip transducers produced the Generation-5 transducer, which could convert the electrical waveform into a sonic waveform at the same wave shape, period, frequency and intensity.

The transducer's mechanical force output will mirror exactly the electronic signal given to it from the ultrasonic driver circuit within the control device. An alternating waveform can be generated, consisting of any combination of primary and secondary waveform. For insulin delivery to the dermis, the sawtooth + square alternating waveforms work best.

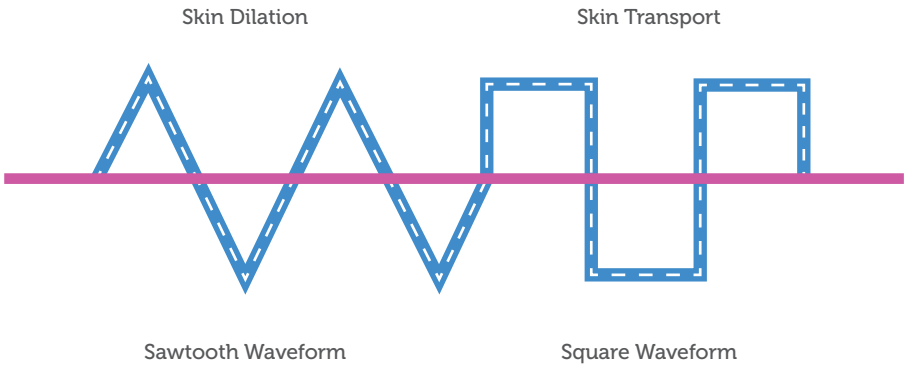

Figure 1: Alternating the waveform of the ultrasonic transmission eliminated or reduced the effect of cavitation.

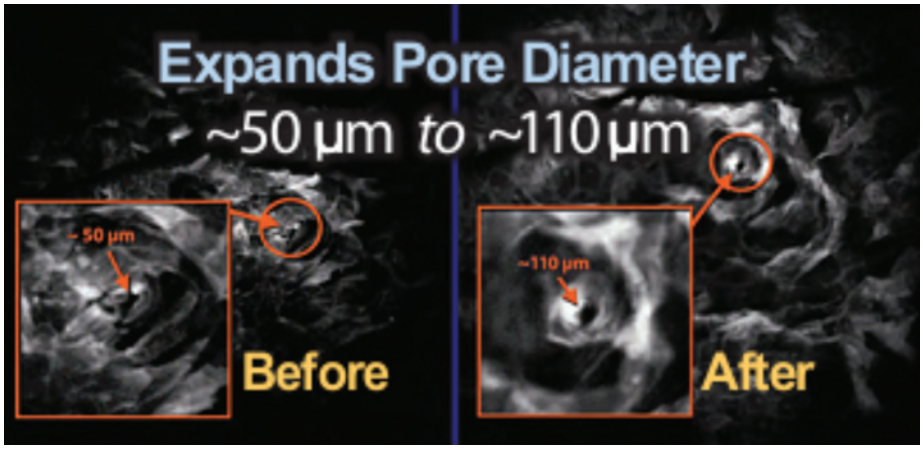

Figure 2: Pore dilation due to ultrasonic excitation.

TRANSDERMAL PATCH DESIGN

To solve the problems of electronically assisted transdermal delivery systems, to enable them to become more portable or wearable by the patient, and in consideration of conventional patch designs wherein drug contamination or denaturing may be caused through interaction with an adhesive or polymer component within the patch design, a new-patented two-part transdermal patch, Patch-Cap™ was developed. It is designed specifically for ultrasonic and other electronic drug delivery applications where a conventional patch is unsuitable due to its reliance of a drug/adhesive mixture.

In the Patch-Cap (see Figure 3) an absorbent pad is used to store the drug until ultrasound, delivered from a snap-on transducer coupler, liberates the drug from the cap and onto the patient's skin surface.

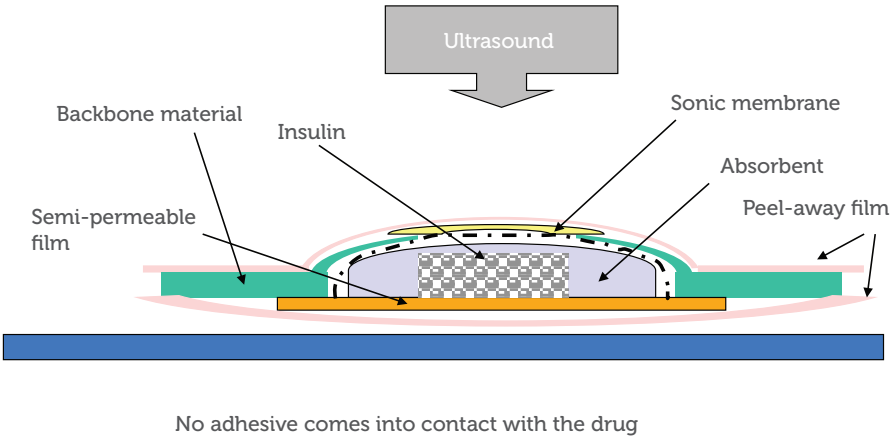

Figure 3: Use of an adhesive pad to store and release insulin. Elimination of adhesive.

Figure 4: Low-profile Patch Cap with butterfly shaped backbone (7.5 cm across).

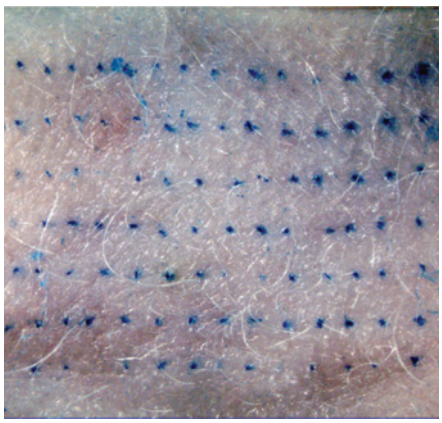

Figure 5: A filter at the bottom of the patch gives a dot pattern distribution of insulin on the skin, improving delivery.

The Transducer Coupler contains up to four miniature ultrasonic transducer elements and is powered by the re-usable U-Strip Ultrasonic Drug Delivery System. The Patch-Cap contains the drug, and is disposable. The current design holds up to 150 units of insulin, enough for a two-day supply for most diabetics using the U-Strip delivery system. The Patch-Cap is designed to be replaced every 24 hours.

Absorbent Pads to Contain the Drug

In reservoir, matrix and drug-in-adhesive versions of transdermal patches only a low drug concentration is possible. The delivery rate is often dependent upon the surface area of the patch. In the Patch-Cap the thickness of the absorbent pad can be varied to marry with the absorbency factor, so that more of the active drug can be contained within the fabric of the absorbent pad. For example a 1 cm^2 of cellulosic pad can hold up to 12 times its weight in moisture at 1 mm thickness. The same pad thickness, but using a nylon pad holds only three times its weight. By varying the material used and altering the thickness the absorbent pad can be adjusted to meet a desired release rate and longevity, far exceeding that of conventional patches.

No Drug-Adhesive Contact

The use of adhesives that directly contact the drug is eliminated in this design. Adhesives may be used in the border of the Patch-Cap, but the drug-in-adhesive, matrix or reservoir designs are discarded in favour of an absorbent pad which is held in place in the cap by the use of an inner snap ring.

Ultrasonic Signal Emmitter-Skin Coupling

In conventional ultrasound systems a hydrogel is used to provide a coupling agent. The use of a gel-coupling agent could possibly interfere with and even contaminate an active drug substance liberated from the patch onto the skin surface. The Patch-Cap avoids the requirement for a coupling gel by using the liberated drug itself as the coupling agent to transmit the sonic signal from the transducer to the patient's skin.

Low-Profile Patch

Initial Patch-Cap designs was somewhat bulky so continued development lead to a much smaller, more compact TDD, called the Low-Profile Trans-Insulin Patch, which was more easily worn by the patient. The backbone of the patch is butterfly shaped with wings containing an adhesive border to enable it to stick to the skin (Figure 4). The centre section of the patch holds the insulin, but the patch is designed so that no adhesive comes into direct contact with the insulin.

Dose Limiting Safety Feature

The U-Strip insulin TDD has a special on/off feature. Insulin is liberated from the patch by ultrasonic transmission and passes through a semi-permeable film which acts to retard the flow rate of the insulin and also acts as an on/off valve. It limits the maximum rate at which insulin can be released from the patch to no more than two units per minute, irrespective of ultrasound intensity, or the length of time the ultrasound is present. This top limit of dose control prevents over-dosing.

In addition the semi-permeable film will not permit insulin release from the patch until the ultrasound is active. No ultrasound, no delivery. This on/off valve function is therefore also a safety mechanism to prevent any extra insulin delivery after the controller switches the ultrasound off.

Delivery Pattern upon the Skin

To improve the speed of drug absorption upon liberation from the patch, the delivery pattern of the insulin is directed to enter the skin at the site of the skin pores. A filter at the bottom of the Trans-Insulin patch reduces the drug to miniature droplets which approximate the spacing for the skin's pore structure. As a result the insulin is absorbed more completely into the skin and at a faster pace. See Figure 5, where the insulin is marked with a blue dye, and is more readily absorbed at the pore distribution sites.

The insulin droplet pattern approach reduced the quantity of insulin needed to be stored within the TDD and increased the speed of absorption into the skin. In clinical testing of the original design of the Patch-Cap it took five hours of constant ultrasound to reduce the glucose by just 40 points, compared with just 30 minutes for 87% of the volunteers tested using the device with the dot pattern.

DELIVERY RATES, DURATIONS AND SCHEDULES

The U-Strip® Desktop Unit is designed to provide fast glucose reduction for both excessively high starting glucose and for emergency situations. The portable device, which can be worn on a belt (Figure 9) or on the arm, is designed to deliver insulin at a rate of no more than 7 units/hr.

Patch Designation	Load Capacity	Liberation rate	Duration Max Constant Ultrasound	Duration Max Using Standard +15/-45 Delivery Schedule
U-100	100 u	15.1 u/hr.	6.62 hrs.	26.43 hours
U-150	150 u	16.6 u/hr	9.03 hrs	36.01 hours

Figure 6: Table comparing delivery longevity from U-Strip devices with two different load capacities (desktop control unit).

Patch Designation	Load Capacity	Insulin	Liberation rate at full U/S
U-150	150 u	Lispro R	A = 1.9 to 7.65 /hr.... capability for 1-4 hours
U-150	150 u	Lispro R	B= 1.2 to 5.125/hr. capability for 4-6 hours
U-150	150 u	Lispro R	C= 1.9 to 7.65 /hr.... capability for 6-8 hours

Figure 7: Three possible delivery schedules from U-Strip (mini control unit).

The recommended delivery rate for a 90 kg (200 lb) male for Lispro insulin is 15.2-30 units per eight hours, or 1.9-3.75 units/hr. The delivery rate of the U-Strip Desktop Unit can be as high as 16.6 units/hour.

The U-Strip, holding 100 units or up to 150 units can provide 6.6 or 9.0 hours, respectively, under constant ultrasound. An intermittent activation schedule has been developed whereupon the device is activated for 15 minutes out of every hour and remains deactivated for the balance of 45 minutes of each hour for standard basal operations. Under this schedule, at the maximum liberation rate the patches would supply insulin for up to 36 hours. Since most Type-2 diabetics would not need more than 1.9 units/hr these patches could last more than three days (see Figure 6).

One of the most prevalent problems with diabetes is high morning glucose. This is due to a slacking off of the insulin potency over the night from a standard injection therapy, and in the morning the liver can produce more glucose, in anticipation of the day's events. A unique delivery schedule has therefore been developed using U-Strip whereupon insulin is pulsed from the patch for the first four hours. As shown in Figure 7, under the "A" schedule the patch is set to deliver from 1.9 to a high of 7.65 units/hour for the first four hours, assuming an eight-hour sleep. For the two hours between hour four and hour six, the delivery rate ramps downward to ensure glucose does not drop too low during the night. Just before waking the U-Strip increases the insulin delivery to enable the patient to wake with the glucose level of a healthy non-diabetic. Glucose stability exceeded the glucose control variants of metformin, the most widely prescribed oral medicine for Type-2 diabetics.

SAMPLE CLINICAL DATA

In one clinical trial, named HPT-6A, in volunteers given a meal immediately before treatment, the U-Strip system defeated the glucose spike that would normally occur post-meal. The post-meal application of Lispro insulin from U-Strip brought each volunteer to the range of healthy / normal in as little as 35 minutes. The plasma glucose in all volunteers dropped by 8-10 points in just the first five minutes of treatment. Additional trials are underway, including a 500 patient trial, before applying for regulatory approval.

In over 200 Type-2 patients studied there have been no adverse events, with complete reduction and stabilisation of glucose levels at healthy normal range (85-110 mg/dl) from starting levels as high as 300 mg/dl.

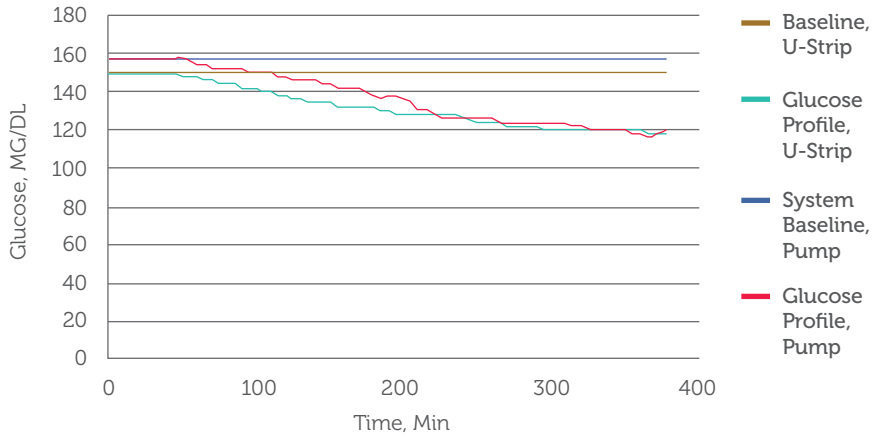

Figure 8: Glucose reduction over 5hr – U-Strip compared with an insulin pump.

Compared with an insulin pump (Figure 8) the U-Strip was just as effective in obtaining glucose control, except the U-Strip was totally non-invasive and can achieve the same results with far less delivered insulin. In these trials the efficiency of ultrasonically administered insulin was found to be 400% greater than pump delivered insulin in obtaining compatible glucose control. The bioavailability and pK values of ultrasonically delivered insulin are greater than that provided by insulin pumps.

SUMMARY

U-Strip is a transdermal delivery system capable of delivering large-molecule drugs through the skin, non-invasively. The company is presently developing an insulin patch aimed at Type-1 and insulin-dependent Type-2 diabetics (market potential 4 million patients in the US alone). The patient can wear the insulin patch product, in the form of a two-part transdermal drug delivery device, the Patch-Cap, powered by an ultrasonic delivery controller, during their daily routine (Figure 9). The device regulates the dosing of insulin in both basal and bolus delivery needs.

Figure 9: The U-Strip System, comprising arm-mounted mini controller and patch.

The use of a two-Part TDD solved many critical concerns limiting the use of transdermal patches in drug delivery applications, especially considering electronically assisted delivery systems.

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NOVEL TRANSDERMAL DELIVERY SYSTEMS FOR TREATMENT OF DIABETES

In the context of a diabetes epidemic, which he characterises in terms of incidence, prevalence and healthcare costs, Alan Smith, PhD, Vice-President, Clinical, Regulatory & Operations, 4P Therapeutics, outlines the stages of Type 2 diabetes treatment, progressing to extenatide and insulin injections, and makes the case, using clinical data, for the transdermal route as a viable alternative to injections.

DIABETES EPIDEMIC

According to the International Diabetes Federation, as of 2013, 382 million people worldwide suffered from diabetes of which 46% are undiagnosed. In the US, there are 24 million people with diabetes and 27% are undiagnosed. The number living with diabetes worldwide is expected to grow to 592 million by the year 2035 (a 55% increase).

> "A safe and effective non-injectable method to treat diabetes has been pursued since insulin therapy was first developed more than 90 years ago"

The burden of diabetes is significant causing more than five million deaths every year (one death every six seconds) and treatment of diabetes and its complications costs a significant amount of all healthcare expenditures. In 2013, US$548 billion was spent on diabetes worldwide which is 11% of the total worldwide spending on healthcare. This is projected to exceed $627 billion by 2035.

Diabetes is a chronic disease that occurs when the body cannot produce enough insulin or cannot use insulin effectively. Insulin is a hormone produced in the pancreas that allows glucose from food to enter the body's cells where it is converted into energy needed by muscles and tissues to function. A person with diabetes does not absorb glucose properly, and glucose remains circulating in the blood in excess (hyperglycemia) damaging body tissues over time. This damage can lead to disabling and life-threatening health complications. Type 1 diabetes occurs due to insulin deficiency caused by destruction of the pancreatic beta cells and requires daily insulin administration. Type 2 diabetes occurs due to insulin resistance and deficiency. Worldwide, approximately 10% of people with diabetes have Type 1 diabetes and 90% have Type 2 diabetes.

As the majority of people with diabetes are Type 2, it is critical to get the disease under control early in its progression and prevent further deterioration in health. As patients move through treatments needed to achieve glycemic control, they typically start with diet and exercise and one oral antidiabetic (metformin), proceed to multiple oral therapeutics (including insulin sensitisers and dipeptidyl peptidase-4 (DPP-IV) inhibitors), and then eventually to injections after the orals fail to maintain control.

Injections include either basal insulin (insulin glargine, insulin detemir, insulin degludec), or glucagon-like peptide-1 (GLP-1) agonists (exenatide, liraglutide, lixisenatide), or combinations thereof. It is generally accepted that the majority of people with Type 2 diabetes will eventually need insulin [1] and that early initiation of injected therapy will slow down and potentially prevent further deterioration of pancreatic beta cell function (see Figure 1).

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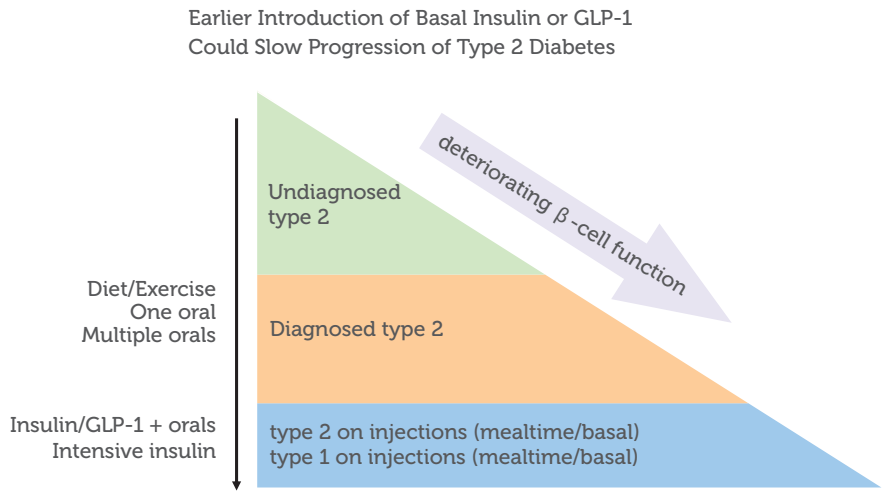

Figure 1: Conventional Type 2 diabetes treatment sequence and relationship with pancreatic beta cell function: need for early initiation of injected therapy.

UNMET CLINICAL NEED

There is reluctance by patients and healthcare professionals to initiate insulin therapy for several reasons including the patients' fear of disease progression and needle anxiety; mutual concerns about hypoglycaemia and weight gain; and health professionals' use of insulin as a threat to encourage compliance with earlier therapies.[2] Despite advances in less painful insulin injections and pens, insulin injections are seen as a last resort by patients and providers. Finally, there is the real concern of insulin injections causing hypoglycaemia. Physicians, particularly general practitioners (GPs), may lack the support services required to train patients on how to determine the correct dosage and to perform injections properly.

Once patients start on injections, they struggle with compliance. Most patients will only inject at home and one-third will skip injections once per week. Noncompliance affects glycaemic control and treatment outcomes. Clearly, injections are a barrier to initiating therapy and maintaining compliance, but what alternative delivery options are there? A safe and effective non-injectable method to treat diabetes has been pursued since insulin therapy was first developed more than 90 years ago. In spite of this long history, however, no satisfactory non-injectable insulin delivery system has emerged.

Certainly, inhaled insulin has made significant progress towards providing a non-invasive alternative to mealtime insulin injections and possibly even once-daily basal injections. The Pfizer/Inhale (now Nektar Therapeutics) inhaled insulin product, Exubera®, was taken off the market in 2007 as a result of low sales and poor market uptake mainly due to issues of device size, ease of use and high cost. Mannkind Corporation is awaiting a decision on approval in the summer 2014 for its Technosphere® inhaled insulin, Afrezza®, which offers a more rapid absorption profile than subcutaneous injection, and Dance Biopharm/Aerogen are making headway with their aerosol insulin product, OnQ™, towards Phase III trials planned for 2015. However, there is a risk that there will always be the safety concern of delivering a growth factor such as insulin to the lungs which will potentially limit uptake of the product in the marketplace.

Other options in development include oral pills or sprays and varying degrees of success have been achieved by several groups including Generex (Oralyn™ mouth spray), and the recent initiative undertaken to develop an oral insulin tablet by Novo Nordisk.

TRANSDERMAL INSULIN DELIVERY

Insulin is a 5,808 Da peptide that that is produced and stored in the pancreas as a hexamer (35 kDa) but active as a monomer. It is typically administered as a subcutaneous injection either as a bolus before meals or as a once or twice daily long-acting injection to achieve a basal profile.

Transdermal delivery of insulin offers several potential benefits. Delivery through the skin bypasses metabolism in the gastrointestinal tract which typically contributes to the very low bioavailability of oral formulations of proteins and peptides. In addition, transdermal delivery is well suited for steady infusion throughout the day as a way to meet the basal insulin needs of patients. Basal insulin typically accounts for 50% of the daily insulin needs of patients with diabetes. Transdermal patches are conventionally used to achieve steady serum levels of drug and avoid the "peak-valley" effect; however they are limited for use with small-molecule lipophilic drugs. This is mainly due to the barrier function of the *stratum corneum*, which is rate-limiting for transdermal transport.

There is a plethora of methods used to deliver insulin through the skin, including iontophoresis, permeation enhancers, solid and hollow microneedles, microporation by thermal ablation, radiofrequency ablation, erbium:YAG laser used directly on the skin, ultrasound, electroporation, pressure waves, nanoparticulate and microparticulate systems and use of carrier molecules. However, each of these methods has limitations in terms of success, typically limited to academic settings in preclinical models. Two approaches though – microneedles and microporation – have been utilised to deliver insulin in human subjects at therapeutic levels.

Microneedles can be used to deliver peptides and proteins through the skin but the dose per needle may be limited when using microneedles with a shallow depth of penetration and maintaining a reasonable patch sizes. In addition microneedle systems are more suited for bolus pharmacokinetic pro-

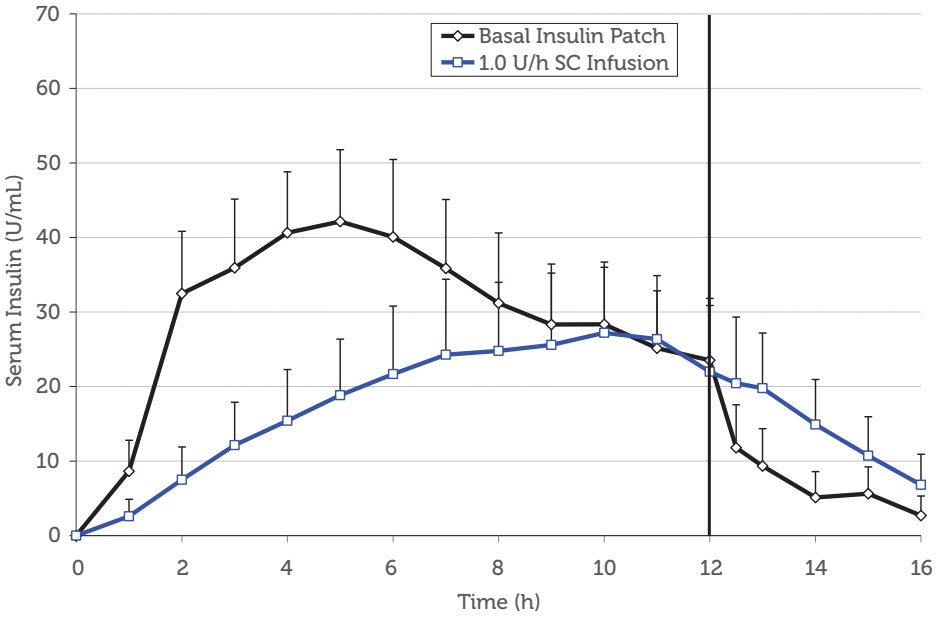

Figure 2: Basal insulin microporation patch versus continuous subcutaneous infusion pump (CSII) set at 1.0 U/hr. At 12 hr, patch removed and insulin pump turned off/infusion set removed. (Mean +SE, N=7).

files. However, relatively long microneedles have been used to achieve a therapeutically relevant intradermal injection of insulin as an alternative to SC injection.[3] The microporation approach (thermal ablation) is well suited for relatively large doses and for a sustained basal delivery pharmacokinetic profile, although it depends on the specific technology being utilised.

Microporation technologies have been developed that overcome the *stratum corneum* barrier by creating micropores by thermal ablation that extend into the viable epidermis. Micropores are created by the rapid localised application of thermal energy to the skin surface that results in the vaporisation of the *stratum corneum* cells in a microscopic area. One microporation approach that has had some success utilises an array of resistive filaments applied to the skin surface which are briefly heated by applying a short pulse of electric current to create micropores approximately 100 µm wide and 50 µm deep, which extend through the *stratum corneum* into the viable epidermis. This technique has been investigated in clinical studies for the rapid extraction of skin interstitial fluid for glucose monitoring[4] and for the delivery of insulin[5-8] for the development of a basal insulin microporation patch intended for daily administration in patients with Type 1 or Type 2 diabetes.

An open-label randomised crossover pharmacokinetic / pharmacodynamic (glucose clamp) and safety study in C-peptide negative patients with Type 1 diabetes evaluated transdermal insulin *versus* continuous subcutaneous insulin infusion (CSII insulin pump).[8] The study was conducted to demonstrate unambiguous therapeutic insulin levels in comparison with CSII as all subjects were required to be C-peptide negative (no endogenous insulin secretion). Subjects stopped use of long-acting insulin injection (48 hours prior) or discontinued insulin pump use prior to dosing (eight hours prior). Subjects were randomly assigned to one of two treatment arms: insulin patch applied for 12 hours followed by CSII treatment at 1.0 U/hr for 12 hours or CSII treatment at 1.0 U/hr followed by an insulin patch. In clinical use, insulin infusion basal rates are typically 0.5 U/hr to 2.0 U/hr.

The basal insulin microporation patch had an active area of 12 cm^2 with 80 micropores/cm^2 and contained a dry-polymer film formulation of 15 mg recombinant human insulin. The CSII treatment consisted of a Medtronic Paradigm 722 insulin pump with Humulin® R 100 U/mL (Eli Lilly). Glucose levels were clamped at 100 mg/dL which was initially reached by IV infusion of insulin lispro and maintained after insulin treatment by IV glucose infusion (D-20). Serum samples were analysed for insulin using an insulin-specific ELISA (no cross-reactivity to lispro).

The basal insulin patch mean serum insulin concentration curve reached a C_{max} of 42 µU/mL at five hours. The insulin pump (1.0 U/hr CSII) reached a steady state level of 27 µU/mL at seven hours until the pump was discontinued at 12 hours (see Figure 2).

Although the patch did not achieve a pharmacokinetic profile suitable to maintain a steady state level after repeated daily dosing, transdermal insulin therapeutic levels were achieved within two hours and the pharmacokinetic profile indicated a faster transdermal infusion rate in the first six hours than the second six hours. This may be desirable from a pharmacodynamic perspective (tailored profile to match morning or evening needs as a daytime or nighttime patch). The relative bioavailability of the patch compared with the CSII was approximately 4% using a non-optimised system. The transdermal insulin patch was well tolerated and the skin response was limited to mild transient erythema at the application site.

The study demonstrated that the basal insulin microporation patch achieved a therapeutic basal infusion rate comparable with that achieved by a continuous subcutaneous insulin infusion pump in patients with Type 1 diabetes.

TRANSDERMAL EXENATIDE DELIVERY

Exenatide (exendin-4) is a GLP-1 receptor agonist with a molecular weight of 4,186.6 Da (39 amino acid peptide amide). It is a synthetic version of a salivary protein found in the Gila monster lizard. It exhibits similar glucoregulatory effects to the naturally occurring incretin hormone glucagon-like peptide-1 (GLP-1) but has a longer half-life.

GLP-1 is a naturally-occurring peptide that is released within minutes of eating a meal. It is known to suppress glucagon secretion from pancreatic alpha cells and stimulate insulin secretion by pancreatic beta cells. The half-life of GLP-1 is approximately two minutes due to dipeptidyl peptidase-4 (DPP-IV) inactivation. Exenatide is 53% identical to native human GLP-1. It binds to known human GLP-1 receptors on pancreatic beta cells *in vitro* and is resistant to dipeptidyl peptidase-4 (DPP-IV) inactivation. As a result, the half-life of exenatide is 2.4 hours which is 10 times longer than GLP-1.

Exenatide was developed by Amylin and

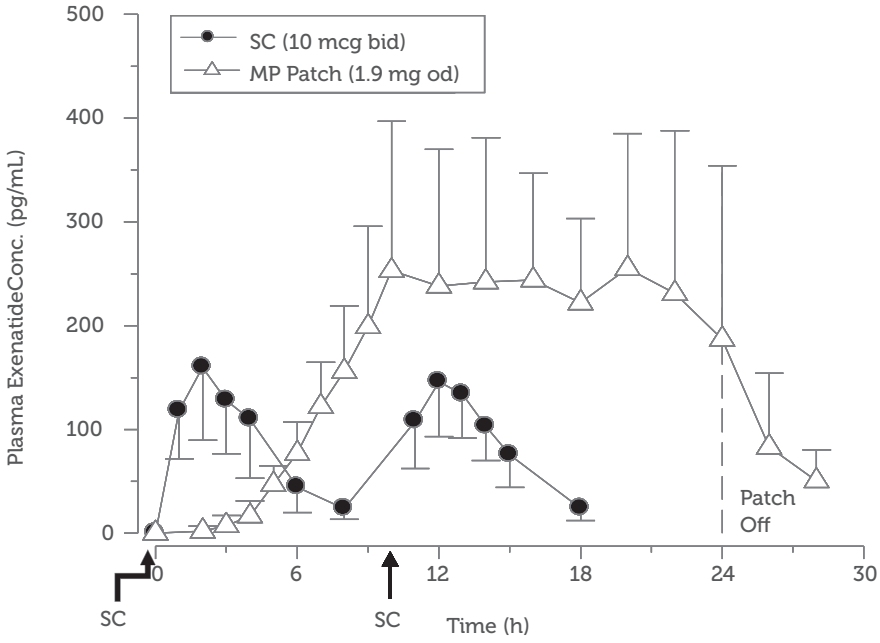

Figure 3: Plasma exenatide concentration comparing SC injection to transdermal microporation patch (TDP) (patch mean+SD, SC mean-SD; N=8).

Lilly and is currently marketed by Bristol-Myers Squibb and AstraZeneca (co-marketing arrangement). It is administered as a twice-daily subcutaneous injection given one hour before the breakfast and dinner meals (Byetta® 5 µg or 10 µg) or as a once-weekly subcutaneous injection (Bydureon® 2 mg exenatide extended-release microsphere suspension).

A Phase I clinical study was conducted using a transdermal exenatide microporation patch.[9] The study design was a double-blind, placebo controlled, three-period, three-treatment study evaluating the pharmacokinetics/ pharmacodynamics (PK-PD) and safety of the exenatide transdermal patch (TDP) in nine Type 2 diabetics. On separate days, subjects received a single dose of exenatide TDP (1.9 mg exenatide, 3 cm^2, 120 microchannels/cm^2) or exenatide SC (10 µg bid Byetta®). The investigator and subject were blinded to exenatide/placebo patch content for assessment of skin responses. Standardised breakfast, lunch and dinner meals were provided. The skin response to the patch was evaluated by visual scoring (modified Draize scale) and transepidermal water loss (TEWL) measurements. Exenatide concentrations were determined by ELISA.

After a single exenatide patch application, plasma exenatide concentrations increased gradually for 10 hours reaching a C_{max} of 301 pg/mL. On average, plasma concentrations were sustained after 10 hours at approximately 250 pg/mL until the patch was removed at 24 hours (see Figure 3). Plasma exenatide concentrations were maintained above 50 pg/mL for 21 hours (median) with a range of 14-25 hours. The minimum effective plasma exenatide concentration required for a glucose lowering effect is 50 pg/mL.[10] The relative bioavailability of the exenatide patch compared with the 10 mcg SC injection treatment was approximately 3% using a patch formulation that was not optimised for bioavailability. There were no skin reactions and the exenatide patch was well tolerated in terms of skin response. As the exenatide microporation patch is a drug delivery system, with several key variables that can be optimised, the film formulation can be adjusted to decrease the delay and increase bioavailability while maintaining sustained plasma exenatide concentrations for 24 hours.

The studies reported here showed that insulin and exenatide can be administered by the transdermal route resulting in sustained therapeutic blood concentrations suitable for treatment of diabetes.

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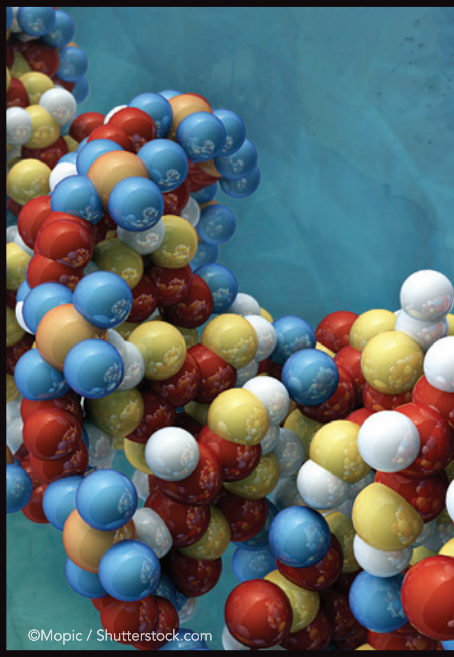

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