TRANSDERMAL PATCHES, MICRONEEDLES & NEEDLE-FREE INJECTION: MANUFACTURING LINES ROLL AS CONCEPTS BECOME PRODUCTS

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ONdrugDelivery Issue Nº 40, March/April 2013

"Transdermal Patches, Microneedles & Needle-Free Injection: Manufacturing Lines Roll as Concepts Become Products"

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.

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Apr:	Pulmonary & Nasal Drug Delivery
May:	Injectable Drug Delivery: Formulations Focus
Jun:	Injectable Drug Delivery: Devices Focus
Jul:	Oral Drug Delivery
Sep:	CROs & CMOs Offering Drug Delivery Solutions
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Front cover image "An LTS Lohnmann Manufacturing Line in Action", supplied by LTS Lohmann Therapie System AG. Reproduced with kind permission.

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AN INTERVIEW WITH DR CHARLES POTTER FOUNDER & CHIEF BUSINESS OFFICER GLIDE PHARMA

In this interview, following the award of a significant pharmaceutical product development grant, the completion of a major funding round and the appointment of a new chief executive officer, Charles Potter, PhD, Founder & Chief Business Officer of Glide Pharma, speaks exclusively with *ONdrugDelivery Magazine* about the next chapter in the development of a truly novel dosage form and delivery device.

Q1. Firstly, please could you tell us what is the Glide SDI® (Solid Dose Injector)? Why is it different?

When you think of an injection, typically you think of a needle and syringe and therefore the drug is in a liquid form. Glide Pharma has developed a very different technology where we are formulating and injecting the drug in a solid dosage form. So the technology is very different from any other system that is out there.

The only company that has ever developed anything for automatically injecting a solid before was PowderJect, whose technology injected powders. There are some products that have been on the market for a while that are delivered in a depot/implant form. The best known of these is Zoladex (AstraZeneca's anticancer drug goserelin acetate) which is delivered through a needle and pushed out with a trocar under the skin. However, this is a clinical procedure that can only be carried out by trained healthcare professionals.

Glide, in contrast, has a very simple technology for delivering a solid dosage form, which can be used for self-administration of injectable drugs by patients in the home environment.

Q2. So how does the Glide SDI achieve solid dose delivery? How does it work?

The formulated drug is effectively the needle. We have a tiny dosage form, much smaller than even a grain of rice, and it has a point at one end (see Figure 1). The drug is formulated with excipients to ensure that the formulation is solid enough to penetrate the skin, and when the dosage has been pushed into the skin it dissolves and releases the drug or vaccine. The technology is applicable to drugs and vaccines of any molecular weight, although there is a limitation on the maximum dose that can be incorporated in a formulation. The excipients are chosen to give the drug stability as well as the physical strength to penetrate the skin.

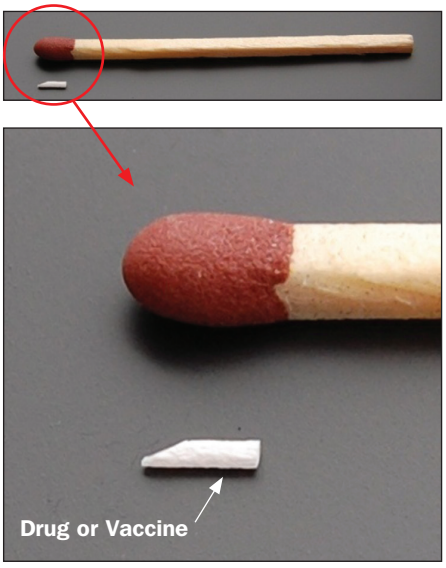

Figure 1: The tiny Glide SDI dosage form shown next to a match-head for scale.

"THE SOLID DOSAGE FORM IS ONLY PART OF THE STORY BECAUSE OF COURSE WE NEED TO DELIVER IT. FOR THIS WE HAVE A REALLY SIMPLE HAND-HELD, SPRING-POWERED DELIVERY DEVICE COMPRISING TWO MAIN COMPONENTS. ONE COMPONENT IS THE CASSETTE AND THE OTHER IS THE ACTUATOR"

The solid dosage form is only part of the story because of course we need to deliver it. For this we have a really simple hand-held, spring-powered delivery device comprising two main components. One component is the cassette and the other is the actuator (Figure 2).

The cassette is a single-use, disposable component, prefilled with the drug in a sterile dosage form. The cassette is removed from its packaging and placed into the end of the actua-

tor, and the whole device is pushed against the skin. At a preset spring force, an audible click is heard signifying that the drug has been delivered. The cassette is removed from the actuator and thrown away and the actuator automatically resets ready for reuse.

Q3. Thinking about storage, this cassette is significantly smaller than, for example, a vial or prefilled syringe isn't it?

Yes, this system would be smaller in terms of shelf space. The other crucial advantage in terms of storage is that because it is a solid dosage form it is potentially more stable than a liquid, and may not require cold storage. This means that storage in the home is significantly simpler of course, but there are also savings all the way down the supply chain from warehouses to transport and storage in the pharmacy. There are not only cost savings; a stable solid dosage form avoids a lot of issues too. There is evidence in the literature that up to 50% of vaccines end up getting thrown away because of breakages in the cold chain. If you don't even have to have that cold chain, the advantages are clear.

Q4. In terms of its applications, how is the Glide SDI differentiated from other injection approaches such as traditional needle-based systems and NFIs such as liquid jet injectors?

Importantly, we push the drug into the skin. We do not fire the drug. Liquid jet injectors fire the drug at the skin and, depending on the velocity with which they fire it and depending on whether the skin is that of a male or female, older or younger, and depending on where it is administered – on the arm, or the leg, for example – it will go to different depths. Everybody's skin is different.

The Glide SDI *pushes* the drug. It pushes it hard enough to get through the tougher skin of a 'hairy male adult' and then when it stops pushing the dosage stops moving. It is not moving fast, it is not a bullet. Therefore, we believe we are implanting to the same depth in the skin with every injection, independent of skin type, and anticipate a more accurate, reliable and repeatable delivery than perhaps even with a needle and syringe where the injection depth varies depending on injection technique.

We are also in control of the release profile. This is dependent on the formulation and we can formulate with sugar-based formulations

Figure 2: The simple hand-held, spring-powered delivery device comprising the cassette and the actuator.

which dissolve very quickly (within seconds) in the tissue and can release the drug with the same profile as with a needle and syringe. We can achieve bioequivalence with subcutaneous injection meaning our first products can be brought to market relatively quickly as differentiated generics. Or we can put polymers into the formulation causing the drug to be released over days, weeks or even months, depending on the polymers used. We can tailor the release profile and that is one of the key benefits of the technology. Additionally, in vaccine delivery, in a number of preclinical studies, we've demonstrated increased efficacy compared with needle and syringe. We have several sets of data already and are building on this. Vaccines are likely to become a big part of our business.

The device is a simple mechanical system. It is a needle-free device and although this advantage is not foremost in our ranking of our product's various advantages, it is still a very significant benefit. We have data showing that, in volunteers, the Glide SDI technology is preferred to a standard injection with a needle and syringe.

"IMPORTANTLY, WE PUSH THE DRUG INTO THE SKIN. WE DO NOT FIRE THE DRUG. LIQUID JET INJECTORS FIRE THE DRUG AT THE SKIN AND ... IT WILL GO TO DIFFERENT DEPTHS. EVERYBODY'S SKIN IS DIFFERENT"

Q5. How does the SDI benefit the patient, compared with other delivery systems? What sets Glide SDI apart?

We believe the Glide SDI will benefit people in three broad categories: patients, healthcare professionals and pharmaceutical companies. We offer significant benefits across all three of these key categories. The really major benefit for the patient is actually a benefit that feeds back to healthcare providers and pharmaceutical companies also. That benefit is compliance.

For any pharmaceutical treatment, patients not taking their medication is a major problem, and this is especially true of injections. A really simple technology is needed, which provides medication that patients are happy to take, and that is convenient for them to take in order to ensure that they will take it. When patients do take the medication, their disease is treated more effectively, healthcare costs are reduced, doctors are happy, and pharma companies are happy because their products are being used rather than wasted, and so there is a benefit across the whole system. Getting a product out there that patients are happy to use is really key for Glide Pharma. Indeed it's crucial for the whole of drug delivery and it's crucial for all of the pharma industry too.

Q7. A novel dosage form is transformative for the industry, but doesn't the prospect of scaling-up the manufacturing of such a novel dosage form for market bring with it particular difficulties?

As well as being the most exciting thing about the Glide SDI, the fact that we have an entirely novel dosage form is at the same time the biggest challenge for us. We can't just go and buy a tableting machine or ampoule filler off the shelf. We have to develop our equipment ourselves. Now whilst this is the biggest hurdle for us, it will also in time become one of our major strengths because once we have that in place, and we have the IP protecting it, we will have a novel dosage form, in the same way that inhalers and patches were once novel, and we will have the patented process for manufacturing it. If we can emulate even just a fraction of the success that inhalers and patches have had, but we maintain the intellectual property for it, then we're in a very strong position.

"FOR ME THE MOST EXCITING THING ABOUT THIS TECHNOLOGY IS THE FACT THAT WE HAVE A TRULY NOVEL DOSAGE FORM. I AM NOT AWARE OF ANY RECENTLY DEVELOPED NOVEL DOSAGE FORMS THAT CAN DELIVER A BROAD RANGE OF DRUGS AND VACCINES"

Q6. What is the most exciting thing about the Glide SDI?

For me the most exciting thing about this technology is the fact that we have a novel dosage form. If you go back to inhalers, patches, fast-melt tablets, those are all 20-25 years old. When they came out they were novel dosage forms and if you look at the impact that they have had on drug delivery, it is tremendous, accounting for hundreds of new drugs being taken by millions of patients around the world. Since then there have been very, very few novel dosage forms. I am not aware of any recently commercialised novel dosage forms that can deliver a broad range of drugs and vaccines and so, for me, developing a novel dosage form is hugely exciting.

The process involves mixing our drug with the selected excipients in a standard mixing process. We then put the mixture into a standard twin-screw extruder and it is extruded at room temperature (we do not need to heat). The extrudate is then cut into individual dosages using a modern laser to give a sharp point on one end and a flat surface at the other end. The final dosage form is then filled into a cassette. Whilst it is a novel process, which we are currently refining and scaling-up, it is not rocket science.

This is our focus for the current year – getting the manufacturing process in place. There are going to be challenges along the way I am sure but we know what we require from the process and we know how we are going to go about achieving it.

Q8. You invented the SDI technology back in 2001, creating the very first sharp, strong solid dosage forms at home in your kitchen. Glide now has a clinical-stage technology, which has attracted significant funding, and a growing team. What has been the biggest challenge along the way?

I guess the challenges are two-fold. Funding is always a challenge and we've had a slightly unusual funding history in that all of our funding up until recently has come from business angels and small venture capital trusts in the UK. Most companies of our sort would have gone out and got the venture capital groups on board early on. We hadn't, so we were taking on relatively small amounts of funding every year or two. That was great, it meant that we had some very supportive shareholders, and we could raise money fairly quickly, but we could only do a limited amount of work with each funding round. That has allowed us to demonstrate that the technology works, that we can do controlled release, that we can achieve good stability and that we can get very good vaccine responses. In particular, we have shown that the technology works in humans and that they like it.

The key thing we are now doing but hadn't done up to now is process development scale-up. But you need sufficient funds to put a pilot manufacturing scale process in place. This is why we've recently raised a larger amount in investment. It will enable us to put that pilot scale manufacturing line in place.

Q9. There have been three very significant developments at Glide Pharma recently: the awarding of a large grant from the UK Biomedical Catalyst at the end of 2012 for the

development of a new parathyroid hormone (PTH) product; the completion of a £14 million funding round at the end of February; and the appointment of a new Chief Executive Officer at the beginning of March. These are exciting times for the company. Can you tell me how these recent successes have positioned Glide for the next chapter in its story?

Yes, a couple of months ago we were awarded a £2.3 million pound grant from the Biomedical Catalyst, which is run by the UK Medical Research Council and the Technology Strategy Board, for the development of a PTH product. This is very important not only because this is a product development project that we have been eager to do, but also because when it came to the more recent investment round, we were able to say to investors that part of the funding would be matching the existing grant. The key purposes of the recent large investment funding are to demonstrate the manufacturing capability and also then to take our first products through into clinical trials.

Mark Carnegie-Brown coming on board as our new Chief Executive is an important part of this process. He will build the management team that will help him take the company through these next stages. He has extensive operational experience in the pharmaceutical industry and is well positioned to move the company forward from where we are now to bring the first products to market.

Up until now we have kept the number of employees to a minimum. At the point of the recent funding we were just twelve people. We have three new staff members starting in March and two more in April. We're entering a period of scale up in order to manage both the PTH project and the other internal technology development programmes.

Q10. Can you tell us about the company's business model and strategy, including key milestones and the planned timeframe for reaching them?

The technology is heavily patent protected. We have granted patents in most of the territories around the world and more patent applications coming through. This makes the technology applicable for the lifecycle management of drugs that are coming off-patent or which simply require a better delivery system, in addition to being suitable for new drugs coming onto the market, or for creating differentiated generic drug products.

We want to take our own pipeline forwards, firstly because it gets our first products to market more quickly and initiates a revenue stream and, secondly, this also demonstrates the commercial viability of the technology and that then mitigates the risk from the point of view of prospective pharmaceutical partners. When pharma companies can see products moving through the clinic and through the regulatory process then we are better positioned for larger licensing agreements with big pharmaceutical companies.

Because we can achieve bioequivalence with a subcutaneous injection with a needle and syringe, it means that we can select drugs that are coming off patent or that are off patent, reformulate them into a solid dosage form with all of the benefits we've talked about, and take them through the preclinical and clinical process. We will license them out at a later stage to partners as we are not going to do the sales and marketing, but we can add value to these products. To demonstrate the manufacturing process we have to put a real drug through it. We believe it should be one that is commercially viable and that we are adding value to. The PTH project is a great example.

Q11. How will the Glide SDI change the pharmaceutical industry?

We believe the Glide SDI has the potential to change the pharmaceutical industry by bringing out products that patients are happy to have administered or administer themselves, which will change their lives and change the way they take injectable drugs. Obviously it holds true that if a drug can be taken as a tablet then it will be. But for drugs that need to be injected we believe that this will be the patient-preferred way of doing things.

If we look beyond the developed world, into the developing world, we can potentially make a big impact. If you can get away from cold-chain storage, and you can get away from needles, and you can do it at low cost (we have a low cost disposable component), then you can really start addressing vaccination in the developing world. In this context our technology could have a phenomenal impact on the landscape for the pharmaceutical industry.

For now we have got to focus on the simple, immediate-release formulations. We now have the funding in place and we are focused on getting first products to market and into patients' hands.

"IF YOU CAN GET AWAY FROM COLD-CHAIN STORAGE, AND YOU CAN GET AWAY FROM NEEDLES, AND YOU CAN DO IT AT LOW COST (WE HAVE A LOW COST DISPOSABLE COMPONENT), THEN YOU CAN REALLY START ADDRESSING VACCINATION IN THE DEVELOPING WORLD. IN THIS CONTEXT OUR TECHNOLOGY COULD HAVE A PHENOMENAL IMPACT ON THE LANDSCAPE FOR THE PHARMACEUTICAL INDUSTRY"

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Dr Charles Potter is the inventor of the Glide technology and founder of Glide Pharma. He holds an engineering degree and PhD from Cambridge University. He spent six years undertaking research within the Transplant Unit at Papworth Hospital, a specialist cardiothoracic centre, where he gained extensive medical experience. Charles has worked in four other successful start-up companies including nearly six years at PowderJect Pharmaceuticals where he saw the company grow from just five employees to over 1,000.

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MICRONEEDLES AS A TRANSFORMATIVE TECHNOLOGY IN DRUG DELIVERY

Here, Kris Hansen, PhD, MTS Technology & Product Development Manager, 3M Drug Delivery Systems Division, makes the case for microneedles as a potentially transformative drug delivery system, with applications across a variety of therapeutic areas and in multiple types of drug molecule. Dr Hansen highlights particular potential applications in: enhancing the efficacy of vaccines, increasing the efficiency of biotherapeutics and, as a more acceptable alternative to needle-based delivery systems, improving patient adherence and outcomes.

The potential for intradermal delivery to improve the efficacy of certain drugs was recognised in the early 1930s when Tuft *et al* documented results of a series of experiments demonstrating that a partial dose of typhoid vaccine, administered intradermally, elicited an antibody response equal to or better than that achieved following a full dose of vaccine administered subcutaneously or intramuscularly.[1] Since that time, much effort has been devoted to understanding both why drugs deposited in the skin can provide more efficacious therapy and how routinely to deliver drugs accurately and easily into this compartment of the body.[2] Although, historically, development of intradermal delivery methods has focused primarily on vaccines,[3] more recent efforts have considered the broader potential of intradermal delivery to optimise the delivery of drugs targeting local or systemic delivery.[4-8] These studies demonstrate that intradermal delivery may offer faster absorption,[6-8] higher peak blood levels [5] and higher bioavailability of certain therapies [9] *versus* what can be achieved via conventional delivery routes.

"MICRONEEDLE-BASED DRUG DELIVERY SYSTEMS CAN BE APPLIED TO THE DELIVERY OF MICROGRAM LEVELS OF SMALL MOLECULES OR PEPTIDE THROUGH TO DELIVERY OF HUNDREDS OF MILLIGRAMS OF HIGH VALUE FORMULATIONS OF PROTEINS"

MICRONEEDLE-BASED DRUG DELIVERY SYSTEMS

In an effort to leverage the benefits of intradermal delivery, many different delivery methods have been considered.[3] Perhaps the most active area of development is in the use of microneedles to deposit drugs or vaccines into the dermis and/or epidermis. Many variations of microneedles have been developed, including solid, drug-coated microneedles, drug-impregnated dissolvable microneedles and hollow microneedles for delivery of liquid drug formulations.[10] Microneedles are made from many different materials including silicon, metal, glass and plastic (see Figure 1).

Microneedle-based drug delivery systems can be applied to the delivery of microgram levels of highly potent small molecules or peptides [8,11-13] through to delivery of hundreds of milligrams of high value formulations of proteins.[5,9,14]

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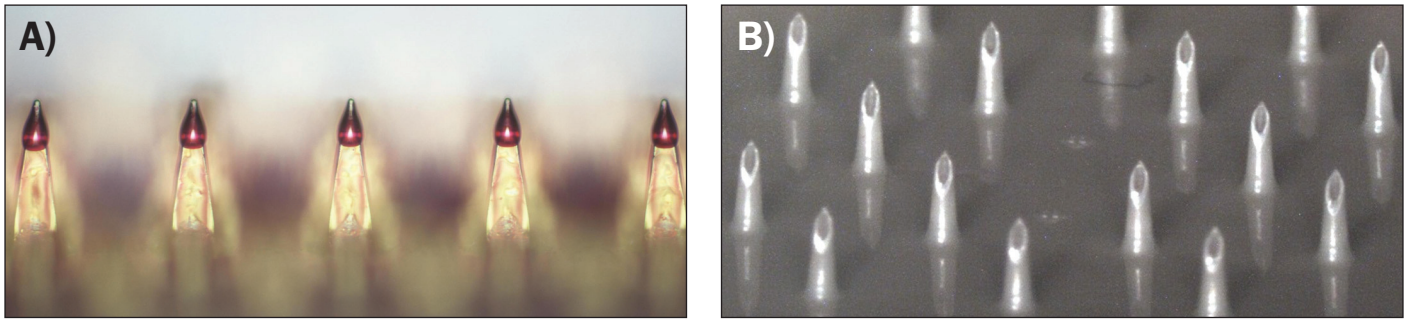

Figure 1: A) Solid, drug-coated microneedles and B) hollow microneedle array. Solid microneedles are 250μm in length; hollow microneedles are 900μm tall. Both solid and hollow microneedles are moulded from medical-grade plastic.

AN ALTERNATIVE TO INJECTABLE THERAPIES

In a study published in 2012, researchers discussed results of a series of Phase I studies wherein the safety, tolerability and wear characteristics of a synthetic peptide developed for the treatment of osteoporosis coated on solid microneedles were evaluated. Microneedle-based delivery of the peptide was evaluated *versus* an injectable form of the drug. Data collected in over 300 post-menopausal women aged 50-80 years demonstrated that microneedle-based delivery was fast—nearly complete delivery was achieved in just one minute—and achieved desirable PK characteristics, including rapid absorption of the drug into the systemic circulation.

A subsection of subjects received seven repeat daily doses of the drug coated on microneedles. In this group, a rapid rise in blood levels of a biomarker for bone formation was observed, consistent with data collected previously for this drug when administered by injection.[13] These data were consistent with preclinical studies conducted in rats and monkeys [12] and demonstrate the utility of microneedles to provide an alternative delivery option for injectable therapies.

The mechanism credited with the rapid and efficient uptake of biologics delivered to the dermis is the lymphatic system. The dermis is particularly rich with lymphatic capillaries and the rate of fluid exchange in the dermis exceeds any other compartment in the body.[15] Large molecules delivered to subcutaneous or intramuscular tissues may not be absorbed by the lymphatic capillaries as fast as they would be in the dermis; as a result, intradermal delivery is characterised by PK profiles that often show rapid absorption (early T_{max}), higher peak blood levels (higher C_{max}) and more complete uptake (higher AUC).[4,9] These changes in PK may be ideal for administration of drugs, such as insulin, where rapid absorption is desired or for delivery of high-value drugs where more complete absorption may allow for a reduction in dose.

The skin may be an optimal compartment for vaccine delivery for different reasons. Langerhans and dermal dendritic cells, in the epidermis and dermis respectively, are an important component of the immune system unique to the skin. These cells are sentinels, quickly processing microbial antigens, such that the body can rally defences sooner and more effectively than if the antigen is presented to the intramuscular tissue, as it is with traditional vaccination methods.[16] These unique characteristics of the skin have been leveraged commercially with the introduction of Fluzone®, a vaccine for influenza that is administered into the dermis by a clinician.[17]

An understanding of the unique physiological opportunities the dermis offers provides exciting speculation for utilisation of this delivery route to enhance therapeutic profiles for a variety of existing medicines, including oncology drugs, cancer vaccines, rescue medicines, nanoparticle-based therapies, and delivery of new chemical entities that have volumes or viscosities that make them incompatible with traditional syringe/autoinjector administration.

BENEFITS FOR INCREASED PATIENT COMPLIANCE

In addition to the potential to improve the efficacy of therapies, microneedles are a compelling delivery route due to their level of overall acceptability by patients and by healthcare providers.[18-21]

Microneedles offer a patient-accepted alternative for the administration of injectable therapies where patient noncompliance, especially in chronic conditions such as rheumatoid arthritis and diabetes, is around 10%;[22-24] needle phobia plays a significant role in this noncompliance. Studies suggest that 10% of all Americans are needle phobic and an even greater percentage cite their dislike of needles as the reason for foregoing medical treatment.[25] Even healthcare professionals avoid routine vaccination because they "dislike shots".[26] These studies speak to the potential benefit of developing non syringe-based delivery systems for the routine administration of chronic therapies and vaccines.

As our understanding of how to manufacture and where best to apply microneedle-based delivery systems grows, there is the potential for much wider utility of these systems as a means of efficiently delivering drugs and overcoming global compliance challenges.

According to a 2003 WHO report, adherence to long-term therapies is around 50% in developed countries and much lower in countries with emerging economies.[27] A study of compliance in patients diagnosed with osteoporosis found that approximately 75% of women who initiated drug treatment were non-adherent within 12 months and nearly 50% had completely discontinued therapy during this period.[28] This non-adherence has both humanitarian and economic consequences: experts suggest that up to 50% of women and 25% of men older than the age of 50 will break a bone due to osteoporosis.[29] There is a substantial increase in mortality associated with hip and vertebrae fracture in this population.[30] Yearly healthcare costs associated with osteoporosis are expected to top US$25 billion (£16.5 billion) by 2025.[29]

CONCLUSION

Microneedle-based drug delivery has the potential to be a transformative technology for the delivery of biologics and vaccines. Microneedle delivery may provide enhanced therapeutic profiles for therapeutics and vaccines, allowing for administration of lower levels of drugs to achieve the same therapeutic endpoints. Additionally, microneedles provide an alternative to traditional needles and thus a means of overcoming one of the biggest barriers to patient compliance for the treatment of chronic diseases and routine vaccination.

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"MICRONEEDLES OFFER A PATIENT-ACCEPTED ALTERNATIVE FOR THE ADMINISTRATION OF INJECTABLE THERAPIES, ESPECIALLY IN CHRONIC CONDITIONS, WHERE PATIENT NONCOMPLIANCE IS AROUND 10%"

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LTS Lohmann Therapie-Systeme

LTS TRANSDERMAL TECHNOLOGY: PROVEN PRINCIPLE IN DEVELOPMENT & COMMERCIALISATION

In this article, Klaudia Haczkiewicz, Head of Business Development, LTS Lohmann Therapie-Systeme AG, describes the benefits of transdermal drug delivery systems and the particular advantages LTS, with capabilities throughout the research and development process, and a proven track-record taking transdermal products to market, offers its partners.

TTS – TRANSDERMAL TECHNOLOGY IN OVERVIEW

Transdermal patches, or transdermal therapeutic systems (TTS), are pharmaceutical dosage forms for various active ingredients that are applied to the human skin. By using such a system, drugs can be absorbed through the skin directly into the blood stream and distributed within the body. The permeation is not based on pores but on absorption into the cells or the intercellular spaces. Therefore, the active ingredients must show lipophilic as well as hydrophilic properties. Unlike oral dosage forms the drugs do not need to pass by the gastrointestinal system.

The main advantage of TTS is the continuous release of active ingredients over an extended period. Typical posology of TTS ranges from 24 hours up to seven days. Conventional dosages forms can usually only supply the drug for a limited time (several hours up to one day). In addition every orally administered drug absorbed must past the metabolic system of the liver which will eliminate a substantial fraction before distribution to the systemic circulation (the first-pass effect). Consequently, plasma levels are constantly changing, from super-dosing right after application to sub-therapeutic levels at the end of the application period. These peak-trough levels are often associated with unwanted side effects. A TTS, on the other hand, provides constant delivery maintaining drug plasma level well within the therapeutic range (see Figure 1). As a TTS delivers the drug right into the systemic circulation by-passing liver metabolism, less drug is needed to achieve the desired therapeutic effect.

Although there are many different TTS designs the basic principles are quite similar. Covered by a protective layer, usually a plastic film, the drug-containing layer acts as a kind of reservoir from which the active ingredient is constantly released to the skin. The drug-containing layer may consist of several different layers with different concentrations of the active ingredient. Membranes may be used to control the release profile. The drug-containing layer is covered with a release liner which will be removed prior to application.

LTS uses innovative technologies to develop pharmaceutical products to maximise the potential of the active ingredient, for example, improved bioavailability, reduced exposure risks, lifecycle management or improved patient compliance. It is our commitment to maximise the potential of the active ingredient with the optimum drug delivery technique. For this reason we consistently explore new drug delivery techniques to identify extensions to our existing technology portfolio, such as the built-in abuse deterrent feature in transdermal patch delivery ("self-destructive" transdermal patch) and, for oral delivery, the explorative development of newly designed gastro-retentive systems.

R&D: MAKE THE MEANINGFUL POSSIBLE

Since the founding of LTS pharmaceutical research and development, this work has played an exceptional and vital role at LTS. Apart from

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our core expertise in first-line development of NCEs, LTS helps when existing galenical concepts are not fully utilised, cannot act optimally, or are simply inconvenient to patients. LTS is committed to provide innovative technical solutions to address medical needs in current therapies and to realise the full therapeutic potential of the active ingredient.

Together with our co-operation partners, we develop innovative transdermal and oral-mucosal drug delivery systems seeking approval by the regulatory agencies across the globe. We are committed to extend the range of our formulation portfolio and process technology to be ready for future challenges.

LTS consistently evaluates discoveries in new technologies and drug delivery which provide best solutions to technical challenges. Global active patent applications and granted patents enable LTS to secure know-how and intellectual property to benefit any development efforts for LTS's corporate partners.

One of our key advantages is the efficient communication and team work between pharmaceutical scientists, engineering and production departments. This collaborative philosophy ensures that as soon as a drug product design becomes defined, our engineering and production staff can engage in preparatory activities for commercial launch. The early integration of new product and process development activities enables a reduction in timeline and successful scale up and commercialisation activities.

LTS

LTS stands for innovative drug dosage forms for pharmaceutically active ingredients providing superior therapy and high comfort level to patients. We successfully compete on the market as a leading company in global drug delivery business. LTS has a proven track record of turning active ingredients into successful innovative transdermal or oral-mucosal active ingredient films.

LTS is in a leading market position in the transdermal field and offers commercial production of transdermal delivery systems (TDS) as well as oral-mucosal films (Oral Thin Films – OTF).

LTS offers and provides what innovators and drug manufacturers expect from an experienced and reliable partner in product development and manufacture:

- innovative and reliable drug product development
- readily available technology platforms
- broad range of technical solution to specific challenges
- competency in clinical research
- state-of-the-art production facilities from laboratory scale to full scale industrialisation
- reliable production and supply chain
- second source of supply within the LTS group
- meeting the quality and handling standards of the US FDA and DEA, the EU EMA, Japanese PMDA and Brazilian ANVISA, among others
- customised solutions.

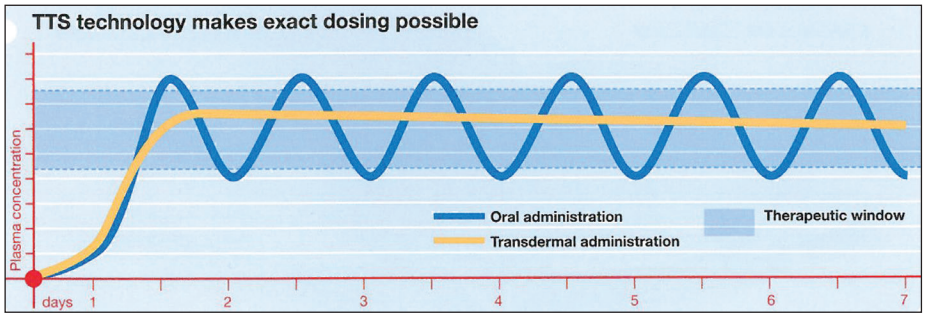

Figure 1: TTS technology provides constant delivery of active ingredients.

LTS - FROM DEVELOPMENT TO COMMERCIALISATION

LTS provides all relevant steps in drug product development: ranging from research via technical and clinical development of new drug delivery formulations to full-scale commercialisation (technology transfer, scale-up, production, and quality testing and release). Our production sites in Europe and in USA provide the highest degree of supply chain reliability and can be used interchangeably.

Our state-of-the-art, in-house resources for clinical testing ensure optimum communication from the development staff and clinical staff, providing shortest timelines for project transition into clinical Phase I and Phase II testing during drug product development. Part of the LTS group is Clinical Research Services (CRS) Andernach, one of the largest CROs in Europe, based on bed capacities.

CRS has been conducting Phase I clinical trials for over 35 years. The institute is well-equipped to successfully process almost any clinical pharmacology task within the shortest period of time. This is due to the presence of highly qualified employees, generously furnished medical departments, a well-sorted toolbox with non-invasive measurement methodology and four Phase I/II Clinical Pharmacological Units with more than 230 research clinic beds.

LTS provides high-quality manufacturing equipment and facilities, with capacities to launch and commercialise new products on a regional or global basis, with a proven track record of several billions of transdermal and oral-mucosal films that have already been produced in the LTS plants in Europe and the US. The know-how of experienced pharmaceutical scientists and engineers allows us to tailor manufacturing equipment and facilities to the desired product design and moreover to adapt rapidly to the changing requirements of the pharmaceutical world market.

OUR PRODUCTION: ONE OF THE SPECIAL STRENGTHS OF LTS

Whether we're talking about small laboratory batches or a production campaign to address the demands of the global market, we provide what we promise. If the product design cannot be established by existing or conventional equipment LTS will develop and establish new manufacturing technology for commercial production.

LTS provides the entire range of production services from small to large commercial scale. Small production projects executed at laboratory scale can be developed in the pilot facility of our research and development department. For global market quantities, high-performance

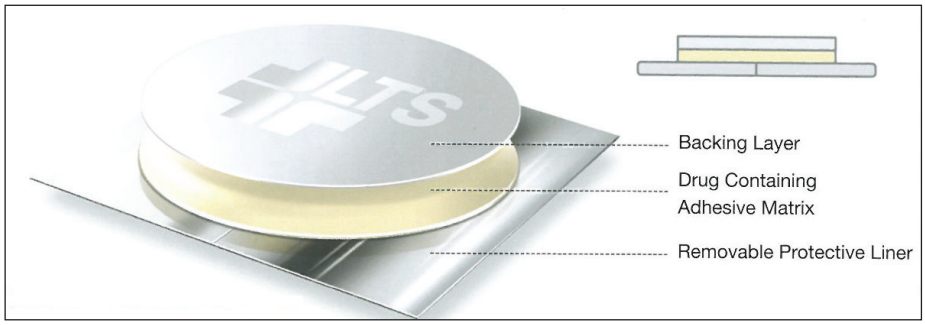

Figure 2: Basic TTS design: monolithic transdermal matrix system.

Figure 3: The nearly identical processing capabilities of the LTS production plants in Germany and in the US ensure excellent production and supply chain security.

facilities with large production capacity are ready to be used. The nearly identical processing capabilities of our production plants in Andernach, Germany, and in West Caldwell, NJ, US, ensure excellent production and supply chain security (Figure 3).

LTS AS BUSINESS PARTNER

LTS offers its valued worldwide co-operation advantage with respect to other development companies: systems developed in conjunction with LTS can also be produced by LTS. The intimate knowledge of our production processes facilitates the development efforts leading to more cost-effective solutions. As LTS is not in the business of marketing pharmaceutical products, resources are created, dedicated entirely to benefit research, development, and production. One-stop-shop solutions (including CRO services) ensure seamless transition through all phases of product development and manufacture.

With this broad expertise, and depending on the customer's wishes, the collaboration with LTS can be structured in various ways. This approach is reflected in specific co-operation offering such as:

- Theoretical assessment with LTS's benchmarking Assessment Tool
- Practical feasibility study including screenings of NCEs
- Full development program
- Establishment of commercial manufacture process
- Scale up and commercial production in scope of contract manufacture
- Licensing of internally developed projects.

However a co-operation is structured, LTS always tailors research and development, technological know-how, and production capacity to partner's demands and expectations.

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COMPANY PROFILE – ALLTRANZ INC

AllTranz is a leader in the formulation and development of unique dermal drug products to treat a variety of disorders. AllTranz was founded in 2004 by Dr Audra Stinchcomb, an expert in the field of transdermal drug delivery, working with several pharmaceutical firms, the US National Institutes of Health (NIH), and the US FDA.

The AllTranz intellectual property estate is the result of two decades of research conducted by Dr Stinchcomb. Since inception, AllTranz has established its reputation as a leader in the field of drug formulation, prodrug development, and dermal delivery products.

AllTranz is currently developing four products utilising proprietary dermal delivery technology that exploits the company's expertise in formulation, prodrug development, abuse deterrent systems, and microneedle formulations. AllTranz seeks to leverage its expertise by developing pathways to treat pain, osteoarthritis, cancer chemotherapy nausea and vomiting, alcoholism, and decreased appetite in AIDS and cancer patients, as well as an abuse-deterrent treatment for opiate addiction and pain to bring underserved patient populations new treatment options expeditiously.

NEW SOLUTIONS TO ASSIST TRANSDERMAL DRUG DELIVERY

Microneedles are micron-scale needles, usually in an array, that are used for transdermal drug delivery and controlled release. Microneedles mechanically open the outer layers of skin creating drug delivery channels. However, current technical limitations only permit relatively short-term release of drug into the body. AllTranz has developed a proprietary microneedle technology that *allows for up to 7-days of sustained systemic release* of small molecules or biologics that are otherwise unable to cross the dermal barrier.

Prodrug development involves the modification of existing chemical entities with strong clinical outcomes to produce important new chemical entities that are pharmacologically improved and necessitate new patent coverage. Scientists at AllTranz have discovered and designed prodrug delivery technology that facilitates transdermal delivery of drugs with up to 20-times greater penetration rates across the skin. These new drug compounds delivered transdermally demonstrate improved drug efficacy, patient compliance and reduced side effects.

"SCIENTISTS AT ALLTRANZ HAVE DISCOVERED AND DESIGNED PRODRUG DELIVERY TECHNOLOGY THAT FACILITATES TRANSDERMAL DELIVERY OF DRUGS WITH UP TO 20-TIMES GREATER PENETRATION RATES ACROSS THE SKIN. THESE NEW DRUG COMPOUNDS DELIVERED TRANSDERMALLY DEMONSTRATE IMPROVED DRUG EFFICACY, PATIENT COMPLIANCE AND REDUCED SIDE EFFECTS"

In conjunction with prodrug development, AllTranz has developed a patented abuse-deterrent patch delivery system for addictive and abuse prone drugs. This novel technology combines an agonist that permeates the skin with a drug antagonist that is retained within the patch, preventing opioid abuse via injectable and buccal routes. The company is directing development efforts for its abuse deterrent patch toward a buprenorphine prodrug product for the treatment of moderate to severe pain, in addition to treating opiate and alcohol addiction.

PATENT & TECHNOLOGY PIPELINE

The AllTranz patent portfolio includes filings across all aspects of the transdermal delivery pipeline of gels, patches and microneedle systems, including new chemical entities, an abuse-deterrent patch system, and extended porosity following microneedle treatment, allowing for delivery of drugs over a seven day period.

AllTranz is utilising unique dermal drug delivery technology to develop its own products for broad market appeal, as well as partnering with other pharmaceutical companies seeking to leverage the AllTranz technology platform to improve delivery of existing drugs to form new chemical entities thereby extending patent franchises.

Currently, the company has nine issued patents and multiple pending applications including PCT, US, Japanese and Canadian patents (see Table).

RELATED PUBLICATIONS:

- *Brogden N, Ghosh P, Hardi L, Crofford L, Stinchcomb AL, "Development of in vivo impedance spectroscopy techniques for measurement of micropore formation following microneedle insertion". J Pharm Sci. In press (2013).*
- *Brogden NK, Banks SL, Crofford LJ, Stinchcomb AL, "Diclofenac enables unprecedented week-long microneedle-enhanced delivery of a skin impermeable medication in humans". Pharm Res. In press (2013).*
- *Ghosh P, Pinninti RR, Hammell DC, Paudel KS, Stinchcomb AL, "Development of a codrug approach for sustained drug delivery across microneedle-treated skin". J Pharm Sci 2013. Article first published online: Feb 15, 2013 (DOI: 10. 1002/jps. 23469).*
- *Milewski M, Pinninti RR, Stinchcomb AL, "Naltrexone salt selection for enhanced transdermal permeation through microneedle-treated skin". J Pharm Sci, 2012, Vol 101(8), pp 2777-2786.*
- *Milewski M, Stinchcomb AL, "Estimation of maximum transdermal flux of non-ionized xenobiotics from basic physicochemical determinants". Molecular Pharmaceutics, 2012, Vol 9(7), pp 2111-2120.*
- *Banks SL, Paudel KS, Brogden NK, Loftin CD, Stinchcomb AL, "Diclofenac enables prolonged delivery of naltrexone through microneedle treated skin". Pharm Res, 2011, Vol 28(5), p 1211-1219.*
- *Milewski M, Stinchcomb, AL, "Vehicle*

Table: Summary of AllTranz Issued Patents	
EP 2222274	Methods and compositions for enhancing the viability of microneedle pores
EP 1895960	Transdermal delivery of cannabinoids
US 8,293,786	Prodrugs of cannabidiol, compositions comprising prodrugs of cannabidiol and methods of using the same
US 8,227,627	Prodrugs of tetrahydrocannabinol, compositions comprising prodrugs of tetrahydrocannabinol and methods of using the same
US 8,309,568	Transdermally deliverable opioid prodrugs, abuse-resistant compositions and methods of using opioid prodrugs
US 7,511,054	Transdermally deliverable opioid prodrugs, abuse-resistant compositions and methods of using opioid prodrugs
US 12/511,226 (number pending)	Transdermal delivery of cannabidiol
US 11/157,034 (number pending)	Transdermal delivery of cannabidiol
US 13/079,758 (number pending)	Abuse-deterrent opioid formulations of opiate agonists and agonist-antagonists

composition influence on the microneedle-enhanced transdermal flux of naltrexone hydrochloride". Pharm Res, 2011, Vol 28(1), pp 124-34. PMID: 20577787.

- *Banks SL, Stinchcomb AL, Paudel KS, (Edited by Rundfeldt C), "Microneedle-Assisted Transdermal Delivery of Opioid Antagonists for the Treatment of Alcoholism, Drug Development - A Case Study-Based Insight into Modern Strategies". ISBN: 978-953-307-257-9, InTech, Available from: http://www.intechopen.com/articles/show/title/microneedle-assisted-transdermal-delivery-of-opioid-antagonists-for-the-treatment-of-alcoholism.*
- *Stinchcomb AL, "The role of entrepreneurial activities in academic pharmaceutical science research". J Pharm Sci, 2010, Vol 99(6), pp 2532-2537.*
- *Milewski M, Brogden N, Stinchcomb AL, "Current aspects of formulation efforts and pore lifetime related to microneedle treatment of skin". Expert Opinion on Drug Delivery, 2010, Vol 7(5), pp 617-629.*
- *Banks SL, Pinninti RR, Gill HS, Paudel KS, Crooks PA, Brogden NK, Prausnitz MR, Stinchcomb AL, "Transdermal delivery of naltrexol and skin permeability lifetime after microneedle treatment in hairless guinea pigs in vivo". J Pharm Sci, 2010, Vol 99(7), pp 3072-3080.*
- *Paudel KS, Hammell DC, Agu R, Valiveti S, Stinchcomb AL, "Cannabidiol bioavailability after nasal and transdermal application: Effect of permeation enhancers". Drug Development and Industrial Pharmacy, 2010, Vol 36(9), pp 1088-1097.*
- *Paudel KS, Milewski M, Swadley C, Brogden N, Ghosh P, Stinchcomb AL, "Challenges and opportunities in dermal/transdermal delivery". Therapeutic Delivery, 2010, Vol 1(1), pp 109-131.*
- *Yerramreddy T, Milewski M, Penthala N, Stinchcomb A, Crooks P, "Novel 3-O-pegylated carboxylate and 3-O-pegylated carbamate prodrugs of naltrexone for microneedle-enhanced transdermal delivery". Bio-organic and Medicinal Chemistry Letters, 2010, Vol 20(11), pp 3280-3283.*
- *Milewski M, Yerramreddy TR, Ghosh P, Crooks P, Stinchcomb AL, "In vitro permeation of a pegylated naltrexone prodrug across microneedle-treated skin". J Controlled Release, 2010, Vol 146(1), pp 37-44.*
- *Paudel KS, Banks SL, Kiptoo PK, Hammell DC, Pinninti RR, Strasinger CL, Stinchcomb AL. "Development of opioid transdermal delivery systems". Opiate Receptors and Antagonists: From Bench to Clinic, 2009 (1st Edition), p 525. Edited by Dean R, Bilsky E, and Negus S, Humana Press.*
- *Kiptoo PK, Paudel KS, Hammell DC, Pinninti RR, Chen J, Crooks PA, Stinchcomb AL, "Transdermal delivery of bupropion and its active metabolite, hydroxybupropion: a prodrug strategy as an alternative approach". J Pharm Sci, 2009, Vol 98(2), pp 583-594.*
- *Stinchcomb AL, "The importance of angel and seed funding to life science start-ups: the 'first-company' scientific founder perspective". Medical News, May 2009, p 6.*
- *Wermeling D, Banks SL, Hudson D, Gill H, Gupta J, Prausnitz M, Stinchcomb AL, "Microneedles permit transdermal delivery of a skin-impermeable medication to humans". PNAS, 2008, Vol 105(6), pp 2058-2063.*
- *Strasinger CL, Scheff NN, Stinchcomb AL, "Prodrugs and codrugs as strategies for improving percutaneous absorption". Expert Review of Dermatology, 2008, Vol 3(2), pp 221-233.*
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- *Banks SL, Pinninti RR, Gill HS, Crooks PA, Prausnitz MR, Stinchcomb AL, "Flux across microneedle-treated skin is increased by increasing charge of naltrexone and naltrexol in vitro". Pharm Res, 2008, Vol 25(7), pp 1677-1685.*

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CONFERENCE REVIEW: 2ND INTERNATIONAL CONFERENCE ON MICRONEEDLES (MICRONEEDLES 2012)

Following the very successful inaugural meeting at Georgia Institute of Technology, Atlanta, GA, US, in May 2010, it was clear that demand existed for a sustained conference series dedicated solely to microneedle technologies, and so the 2nd International Conference on Microneedles (Microneedles 2012) was held in Cork, Ireland, May 13-15, 2012. The event was chaired by Dr Conor O'Mahony of the Tyndall National Institute at University College Cork.

A short course on Microneedle Technology on Sunday afternoon was organised and run by Dr James Birchall (Cardiff University, Cardiff, Wales) and Prof Mark Prausnitz (Georgia Institute of Technology). The course, which included aspects of microneedle fabrication, characterisation and commercial development, was intended to provide an introduction to those new to the microneedle field, and was attended by more than 80 delegates.

The conference proper was increased to two full days to cater for increased demand, and was run in single-session format including poster and exhibitor space. In total, 186 delegates from 26 countries were represented at the event, of whom 53 registered under the Student/Postdoc category. Reflecting the significant industrial importance of microneedle technology, 79 delegates from 60 companies were also present, and this diverse mix of new and established scientists from both industry and academia led to some very stimulating discussions.

Almost 80 technical contributions were presented in a variety of oral and poster formats, including 11 invited and keynote presentations, supported by an extended poster session and exhibition.

The conference kicked off on Monday morning with a welcome from Mr Sean Sherlock, TD, Irish Minister of State. Following the formalities, the technical programme opened with a session entitled "Design and technology I – solid and hollow microneedles", which included a keynote presentation by Prof Prausnitz on the evaluation of microneedles on human subjects. The second session of the day was entitled "Design and technology II – polymer and biodegradable microneedles". Invited speakers for this session were Dr Kris Hansen from 3M Drug Delivery Systems in the US, who outlined progress on 3M's polymer-based microneedle technologies, and Prof Jung-Hwan Park from Gachon University (Seongnam, South Korea), who described hydrogel swelling-mediated separation of biodegradable polymer microneedles separation in skin.

Delegates at Microneedles 2012, Cork, Ireland, May 13-15th 2012.

The third session discussed updates on coatings and formulations. Highlights were a keynote presentation on the use of the Nanopatch vaccination concept by Prof Mark Kendall of the University of Queensland (St Lucia, Queensland, Australia), and an invited talk from Dr Ron Pettis of BD Technologies (Franklin Lakes, NJ, US) on lymphatic targeting using microneedles. Session Four was based around the rapid-fire 'flash' style, during which ten poster contributors were each given the opportunity to present a key highlight of their work in a strictly limited five-minute presentation. This was followed by a lively poster session, at which 45 posters were presented on all aspects of microneedle technologies.

During the conference dinner, best paper award winners were:

- Thakur Singh *et al*, (Queen's University Belfast, UK), "Characterization of pore forming hydrogels: application in transdermal delivery systems"
- Rosalind Chong *et al*, (Welsh School of Pharmacy at Cardiff University, Wales, UK), "Microneedle delivery of siRNA to skin: in vitro and in vivo proof of concept"
- Mee-Ree Han *et al*, (Gachon University, Republic of Korea), "Dissolving microneedles containing minoxidil for treatment of alopecia".

Vaccine delivery proved to be a topic of great interest to many, and merited two full sessions. The first began on Tuesday morning with a keynote presentation from Prof Joke Bouwstra (Leiden University, Leiden, the Netherlands) on transcutaneous vaccination using polymeric nanoparticles, and also included an invited presentation of the Nanopass technology from Dr Yotam Levin. The second session featured an invited talk from Dr Kate Broderick, who discussed Inovio Pharmaceuticals (Blue Bell, PA, US), and its use of electroporation device to enhance DNA vaccine delivery to skin.

Dr John O'Dea from Crospon presented details of the spin-out Janysis (Dangan, Galway, Ireland) and its active microneedle technology during his invited talk. The final session focused on the very relevant topic of microneedle clinical translation. It included a keynote presentation from Dr Peter Daddona who described progress made by Zosano Pharma (Fremont, CA, US) towards commercialisation of its ZP-PTH osteoporosis patch, and an invited talk on the practicalities of microneedle usage by Dr Birchall.

Following the conclusion of a very successful gathering, the organisers would like to thank our Platinum Partner, Science Foundation Ireland, our Gold Partner, Zosano Pharma, and all of our sponsors, without whom an event of this quality would not have been possible. Our warm and sincere thanks go also to the members of the International Steering Committee, invited speakers and exhibitors.

We now look forward to meeting old and new acquaintances at Microneedles 2014, which will take place in Baltimore, MD, US, on May 20-22, 2014. The conference will be chaired by Dr Audra Stinchcomb of the University of Maryland School of Pharmacy (Baltimore, MS, US), and will again feature sessions on all aspects of microneedle technology and applications.

The gathering promises a lively mix of academic, industrial, and regulatory delegates, and will include networking opportunities during extended poster and exhibition sessions and social activities. Later in 2013, details of sponsorship opportunities, a call for papers and delegate registration details can be found at: www.international-microneedles.org. We look forward to seeing you in Maryland for Microneedles 2014!

The 3rd International Conference on Microneedles will take place in Baltimore, MD, US, from May 20-22, 2014.

Save the Date: May 20 - 22, 2014

Microneedles 2014 BALTIMORE

Mark your calendar for the 3rd International Microneedles Conference, May 20 - 22, 2014, at the University of Maryland School of Pharmacy in Baltimore, Maryland.

Hosted by Audra Stinchcomb, PhD, a professor of pharmaceutical sciences at the University of Maryland School of Pharmacy and chair of Microneedles 2014.

The conference promises to be a lively mix of academic, industrial, and regulatory delegates, and will include networking opportunities during poster and exhibition sessions, as well as social activities. For details on sponsorship opportunities, calls for papers, and delegate registration, visit www.international-microneedles.org.

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THE ART OF INJECTING RE-INVENTED: THE FUTURE OF DRUG DELIVERY IS HERE NOW

In this article, Karim Menassa, Founder, President & CEO, Medical International Technologies (MIT Canada) Inc, describes how the company has developed a portfolio of globally marketed needle-free jet injector products, beginning with gas-powered devices for animal health, then moving in to human medical applications in vaccinations and other fields. He also introduces MIT Canada's most recent innovations, a range of hand-held jet injectors for personal use.

MIT Canada was founded in 2000 with a vision to develop a needle-free drug delivery system with a state-of-the-art technology for the veterinary and human medicine communities and make the world needle-free. Today, MIT Canada's patented needle-free injectors are the most advanced devices on the market; our technology combines speed, accurate dosage and volume adjustability to produce a highly efficient method of drug delivery. MIT Canada utilises a low-pressure system, which is virtually pain free. The needle-free injectors are safer, simpler and more cost effective than the standard needle and syringe.

"MIT CANADA HAS THE ONLY NEEDLE-FREE, GAS- OR AIR-POWERED INJECTOR FAMILY OF PRODUCTS IN THE WORLD THAT IS CAPABLE OF MASS INOCULATION IN BOTH HUMANS AND ANIMALS WITH VOLUMES VARYING FROM 0.02-5ML, AND ALLOWING FOR MORE THAN 800 INOCULATIONS PER HOUR"

MIT Canada's marketing strategy was to introduce an animal product first, and in 2001 and 2004 a number of trials were conducted in collaboration with animal health divisions of large pharma companies and universities.[1-6] The studies mostly focused on evaluating the efficacy of different vaccines using MIT Canada Agro-Jet® needle-free injectors in comparison with traditional syringe and needle administration.

For example, in a 2003 research report from the University of Saskatchewan, (Saskatoon, Canada), Willson compared immune responses and protection from Actinobacillus pleuropneumoniae Serotype 1 (AP-37) challenge in pigs vaccinated at six and nine weeks of age with Pleurostar-APP® delivered by Agro-Jet® with those vaccinated by conventional IM delivery. The report stated that there were no post-vaccination reactions in the pigs given the commercial vaccine by either technique that were attributable to the vaccination process. All immunised pigs seroconverted to both antigens tested and developed a significant antibody titre after the second immunisation. There was a tendency for pigs immunised by the Agro-Jet® to have higher IgG2 titers to both antigens; however the difference was not significant. There was a tendency for pigs vaccinated using the Agro-Jet® to have better survival, lower mortality and fewer sick days; however these differencs were not significant.

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The Agro-Jet® treatment group had significantly ($p<0.05$) lower clinical score after challenge. Postmortem examination showed that pigs immunised using the Agro-Jet® tended to have less pneumonia and a lower rate of infection; however these differences were not significant. Hence, pigs immunised using the Agro-Jet® developed protective immunity that was as good as, or better than, that which was developed by pigs immunised using a conventional needle and syringe.[1]

In the delivery of iron dextran, in a research report from the Department of Farm Animal Health & Resource Management, College of Veterinary Medicine, North Carolina State University (Raleigh, NC, US), Almond showed, in neonatal pigs, that the Agro-Jet MIT-II injector effectively delivered sufficient iron dextran, there were no differences in growth and performance between pigs injected with the MIT-II injector and pigs injected with hypodermic needles. WBC counts showed no inflammatory reaction following MIT-II administration, nor infection at the site of injection. "It is apparent that the MIT-II injector is a viable alternative to traditional hypodermic needles for the administration of iron dextran to piglets," the report concluded.[2]

In summary, in all the trials and resulting publications, MIT Canada's Agro-Jet® low-pressure, needle-free jet injection family of products were shown to be equivalent to, or better than, syringe and needle. In some of the trials we also evaluated pain, abscesses that are caused by needles, the speed of injections, the number of broken needles, and cross-contamination due by the use of repeated needle injections from one animal to the next in all the industries including pork, cattle, poultry and others.

HUMAN MEDICAL PRODUCT DEVELOPMENT

Based on all the positive clinical as well as marketing and sales results from the animal market, we decided to develop our technology for the human market product. The decision was to start by introducing our human product line, Med-Jet® (Figure 1), into the aesthetic market and, for medical applications, to the dermatology market. We initiated a series of preclinical and clinical trials, conducted by Antranik Benohanian, MD, a leading dermatologist at Saint-Luc Hospital, Montreal University Hospital Center (Montreal, Canada).[7-14]

In April 2002, Lamontagne and Brossard reported that in a controlled study investigating the risk of transmission of hepatitis virus in a murine model using Med-Jet, according

Figure 1: The Med-Jet MIT-MBX Gas-Powered Needle-Free Injector for Human Use.

to the clinical observations and virus detection assaya, no transmission of infectious MHV3 virus was demonstrated. No clinical signs, no macroscopic lesions of hepatitis and no infectious viruses in the liver were detected in normal mice injected with PBS immediately after the injection of MHV3-infected mice. In addition, no infectious viruses were detected on the injector. These results are in accordance with the fact that no bleeding and no skin abrasion or lesion were observed in both MHV3-infected mice and normal injected mice.[7]

A subsequent review article entitled: *Needle-Free Jet Injection Revisited*, and co-authored by Dr Benohanian with Danielle Brassard, MD, stated: "Infection is no longer a threat with the availability of disposable anticontaminant devices, spacers, splash guards together with advanced sterilisation techniques. The key issue for a successful procedure is the thorough understanding of the skin properties in order to select the opti-

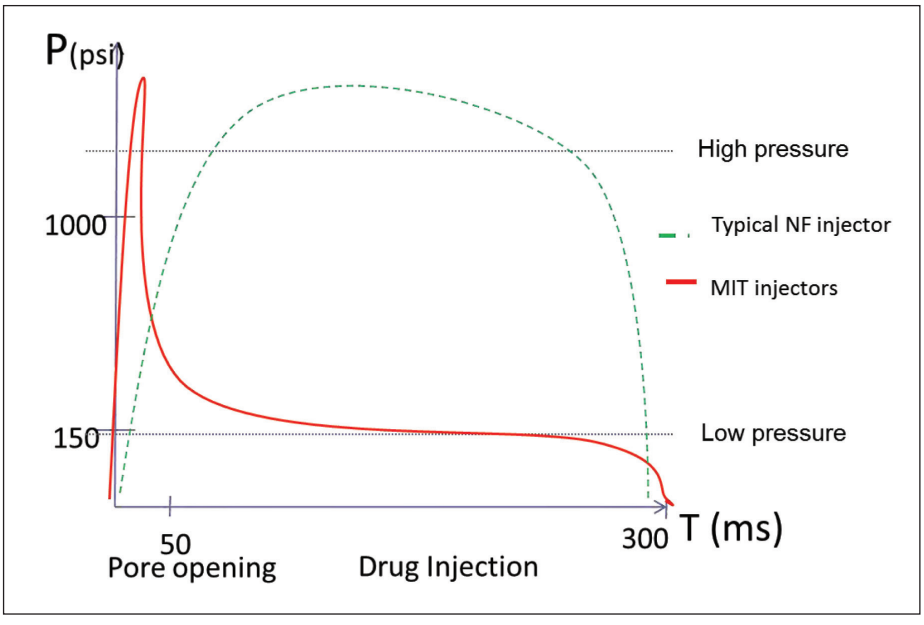

Figure 2: Graph Comparing Injection Pressure Profiles of Needle-Free Injections (1 mL Water, 0.15 mm Nozzle).

Figure 3: The MIT Hand-Held Device Featuring an Auto-Disabling Disposable Cartridge Making it Easy to Draw up the Precise Amount of Biologic Product.

mal parameters, particularly in relation to: driving pressure, volume per spurt, small orifice and optimal distance from the tip of the nozzle to the skin surface. Like any other medical instrument, improper use of the injector can cause significant pain and injury, therefore, proper training and thorough commitment from the clinician are crucial to develop skill with the device.

"Jet injection looks promising in experienced hands to alleviate phobia and pain at injection. It also allows painless treatment of large areas of skin lesions. In certain anatomical areas such as the palms, deeper penetration of the injected fluid may increase the risk of pain and injury. Future research should elaborate more on measurable parameters of jet injection to insure a safe and effective outcome. MIT Canada has revolutionised the field of needle-free parenteral administration by developing injectors that avoid most of the shortcomings of the earlier devices. This new technology relies on a variable pressure profile (see Figure 2), featuring an initial jolt of pressure set high enough (>1000 psi / >6000 kPa) to create dermal pore opening while the actual injection of the substance is done at low pressure (130-160 psi / 900-1100 kPa). As a result, the injectable is delivered accurately and precisely into the targeted area at the desired depth of tissue and virtually pain free."[8]

In a recent paper, just published in February in the Aesthetic Surgery Journal, Nantel-Battista *et al* reported the selection of safe parameters for injection of botulinum toxin in palmar hyperhidrosis using a CO_2-powered jet injector. Initially, they administred needle-free anaesthesia prior to botulinum toxin (BoNT-ONA) injection with a needle, a procedure that had been performed at their office since 2004, successfully on more than 500 patients. However, they said that more recently "we have also had success with injecting BoNT-ONA directly into the palmar skin. The procedure was almost painless and lasted close to one minute.[14] A video of the procedure is available at http://hyperhidrose.ca/media/direct_btx_injection_for_palmar_hh/index.html.

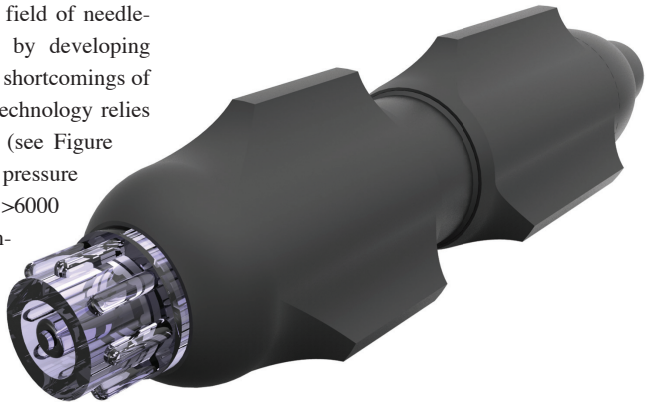

Figure 4: The Dart Device for Intradermal Applications such as Vaccination & Allergy Testing.

Based on the feedback from these various clinical trials we were able to refine and improve our design, develop new models for more applications and therefore increase our clientele in more than 30 countries.

MIT Canada has the only needle-free, gas- or air-powered injector family of products in the world that is capable of mass inoculation in both humans and animals with volumes varying from 0.02-5ml, and allowing for more than 800 inoculations per hour.

HAND-HELD DEVICE DEVELOPMENT

Now that we have proven our gas-powered jet injector technology in the marketplace in many countries, both for animal and human application, we are developing a hand-held needle-free jet injector family of products using our low pressure technology that can be used with all marketed biologic injectable products. It features a unique auto-disabling disposable cartridge (see Figure 3), making it easy to draw up the precise amount of biologic product needed for an intradermal, subcutaneous or intramuscular injection.

Patients are provided with a safe and hygienic operation with unique pressure and volume adjustability for maximum comfort to suit any patient's skin type. The injected medication disperses in a mist or spray as it enters the subcutaneous tissue. The minute fluid particles of medication are then in close contact with the absorbent tissue, the rate of absorption increases as the surface area to which the medication is exposed increases. The small penetration area (approximately a quarter of the size of a 33G needle) results in reduced trauma to the site due to the limited tissue contact. Needle and syringe injection absorption is slower compared with jet injection systems, which also of course avoid the stress associated with traditional needle-based delivery. Risk of infection from contaminated needles is also eliminated.

Within the same family of hand-held products we will be introducing our latest product, Dart, which is shown in Figures 4 and 5. Dart has been developed specifically for intradermal applications such as vaccination and allergy testing, using the same base technology by incorporating the low pressure and pressure adjustment features.

Our main objectives in our R&D department are to further our understanding through collaborations with our distributors/users across many countries. These include veterinarians, farmers, doctors, nurses and patients. Areas of investigation and study include:

- the ergonomic use of the product
- the environment where the product will be used
- the size and weight of the product acceptable for different users
- simple designs to increase cost effectiveness
- aesthetic designs that attract users

INTERNATIONAL CERTIFICATION

The Med-Jet® is fully certified under the ISO, the Canadian Medical Device Conformity Assessment Systems, China's SFDA, the Korean KFDA, a Russian Certification, and COFEPRIS Mexico, and has a European CE Mark.

US FDA CERTIFICATION

MIT Canada is in the process of filing its application with the US FDA and is expecting approval of the Med-Jet® system during the third quarter of 2013. MIT Canada has been working closely with a US consultant and the FDA. Once MIT Canada receives FDA approval, it will be able to sell the Med-Jet® in the US making it a truly worldwide system.

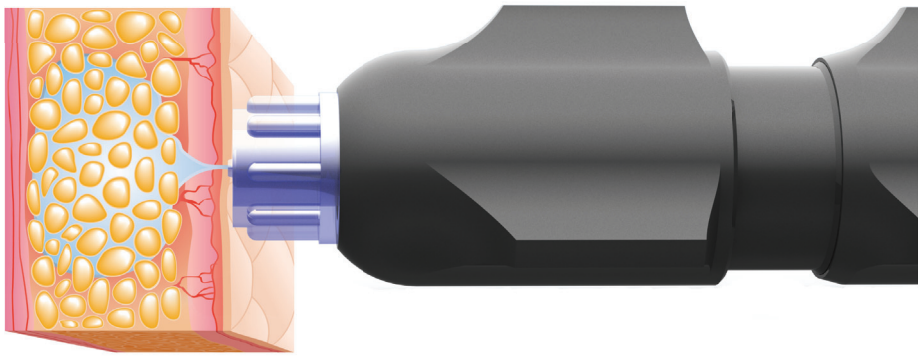

Figure 5: Illustration of the Dart Device Injecting into the Skin.

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THE SECOND INTERNATIONAL:

SKIN VACCINATION SUMMIT 2013

4-6 September 2013, Bell Harbor Conference Center, Seattle, Washington, USA

Following the success of the inaugural SKIN VACCINATION SUMMIT in October 2011, the follow-up meeting SVS 2013 will again provide the skin vaccination community an opportunity to meet and discuss current developments and technologies in the field.

Recognition of the skin by vaccinologists as an ideal anatomical target has gathered momentum in the past decade. The premise that the dense population of APCs can be targeted, stimulated and loaded with antigens to induce robust immune responses and result in more efficacious vaccines has stimulated many efforts to understand skin physiology, the skin immune system antigen presenting cells, effector responses and modes of immune stimulation and delivery formats. The field is ripe to have broad interchange on relevant related disciplines to focus both research and development efforts on more effective and informative directions. With several products in late stage development and a newly licensed delivery device, a timely multi disciplinary interchange is greatly needed to help set the stage for progress that can lead to capitalizing on the immunopotency of the skin to bring about better human health.

The second SKIN VACCINATION SUMMIT – SVS 2013 will again offer an international forum for researchers, both academic and industrial, plus regulators and skin delivery technologists to meet and discuss the current developments and future direction and technology trends in the dynamic field of skin mediated vaccination.

The SVS 2013 meeting will comprise keynote presentations and special sessions and in addition the SVS 2013 organisers invite oral and poster abstract submissions to be considered for inclusion in the meeting schedule.

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To receive further information and SVS 2013 programme details please contact:
John Herriot at Meetings Management (jherriot@meetingsmgmt.u-net.com)

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MVAF 2013 – MODERN VACCINES/ADJUVANTS FORMULATION
15-17 May 2013, Lausanne, Switzerland

PBVA 2013 – PLANT-BASED VACCINES & ANTIBODIES
5-7 June 2013, Verona, Italy

SVS 2013 – SKIN VACCINATION SUMMIT
4-6 September 2013, Seattle, Washington, USA

MUCOVAD 2013 – MUCOSAL VACCINES, ADJUVANTS & DELIVERY
25-27 September 2013, Copenhagen, Denmark

RSVVW 2013 – RSV VACCINES FOR THE WORLD
14-16 October 2013, Porto, Portugal

VED 2013 – VACCINES FOR ENTERIC DISEASES
13-15 November 2013, Bangkok, Thailand

To receive further information concerning future events please contact:
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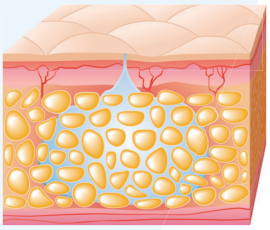
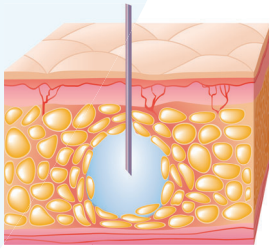


Jet Injection



Needle Injection

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SKIN DELIVERY OF BIOLOGICS

In this article, Richard Toon, PhD, Technical and Business Development Manager, Nemaura Pharma Limited, describes one of the company's key technologies – the Micropatch™, focusing on its applications in the delivery of biologics.

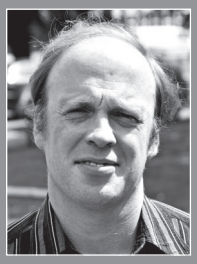
Nemaura Pharma provides end-to-end, turn-key solutions for drug delivery through the skin using its proprietary platform technologies. The Micropatch™ skin insertion platform offers a versatile topical or transdermal delivery platform for a large range of molecules, including biologics.

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.

MICRONEEDLES: THE POTENTIAL & THE CHALLENGES

Microneedles are needles whose length is in the hundreds-of-microns range, which are 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.

Figure 1: The Micropatch™ single use particle insertion device. The recess in the centre is where the patient applies pressure using the thumb to activate the device.



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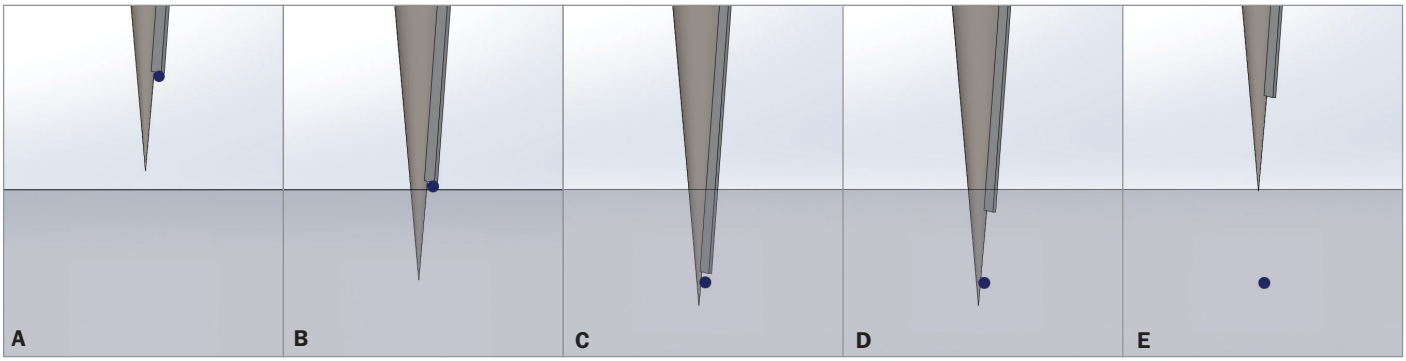

Figure 2: Sequence of microneedle delivery via the Micropatch™.

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 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 would be rendered unsuitable for microneedle delivery, or require protracted pharmaceutical development programs.
- 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 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.
- 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 challenges that must be overcome for the mass utilisation of microneedle technologies for drug delivery applications.

BENEFITS OF NEMURA'S MICROPATCH™ SYSTEM

Nemaura's Micropatch (see Figure 1) was designed and engineered with a view to addressing these challenges. The device, which was previously featured in an article entitled: "*Skin Drug Delivery: Improving Quality of Life*" (ONdrugDelivery Magazine, Issue No 32, June 2012, pp 12-15), 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.

"NEMAURA'S MICROPATCH WAS DESIGNED AND ENGINEERED WITH A VIEW TO ADDRESSING THESE CHALLENGES"

In this case however 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.

Figure 2 shows a schematic of the mechanism by which the Micropatch™ operates:

A) Microneedle or needle with adjacent drug loaded carrier.
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
D) The carrier is retracted.

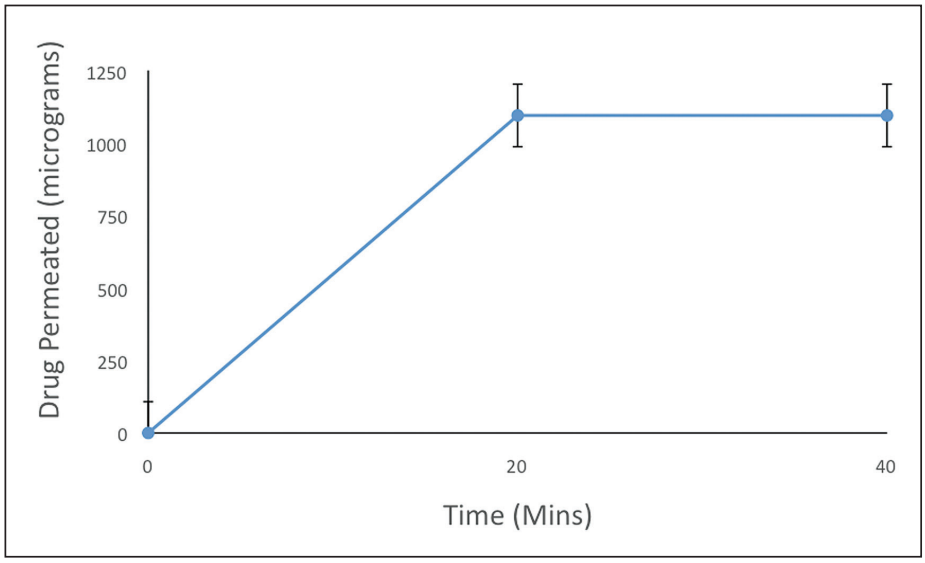

Figure 3: Franz Diffusion Cell study of Bovine Serum Albumin absorption after Micropatch™ delivery.

E) The needle is retracted from the skin with the drug 'package' remaining inside the skin.

As a result, the Micropatch has the following benefits:

- Drug loading may be in the μg-to-mg range without any restrictions being imposed by the active molecule's physico-chemical properties, thus also allowing a rapid and efficient pharmaceutical development stage.
- A finite dose is delivered according to needs, ranging from µg to 10s of mg.
- The delivery time, and thus residence time, of the needles inside the skin is in the order of one or two seconds.
- Dose delivery can be verified as the dosage will be 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.

"THE DRUG IS INSERTED DIRECTLY INTO THE HOLES CREATED USING THE NEEDLES 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'."

Figure 3 summarises the results from a Franz Cell skin permeation study using the Micropatch™ whereby three microneedles were used (tip radius 10 µm, diameter 450 µm) to deliver 500 µm diameter pellets of Bovine Serum Albumin (1mg dose, neat), using full thickness porcine epidermis obtained from the ear of the pig. The results clearly show that the full dose of 100% has permeated through the skin after application into the skin, within the first 20 minutes.

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 the 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 4 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, that would be pain free, or several millimetres in length for deeper depot delivery of drug packages. Such 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 and mostly painlessly.

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.

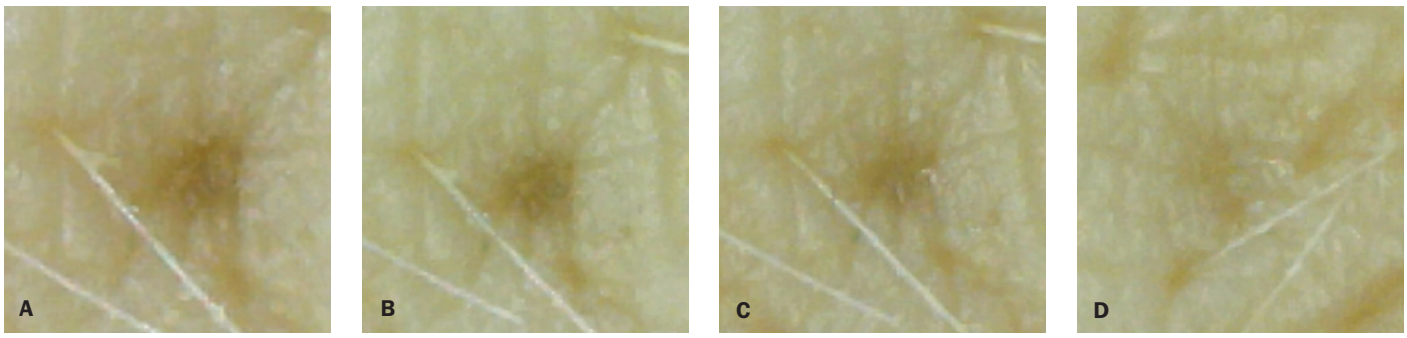

Figure 4: USB microscope images of porcine skin at and post-insertion of a 500 μm BSA particle A) at initial insertion, B) after 30 minutes, C) after 1 hour, and D) after 1 hour 10 minutes.

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MICRONEEDLE ARRAY PENETRATION TESTS: UNDERSTANDING THE "BED OF NAILS" PHENOMENON

In this paper, Marion Sausse Lhernould, Post-Doctoral Researcher, Christophe Gobillon, Engineering Student, and Pierre Lambert, Assistant Professor, all of the Bio-, Electro-, and Mechanical Systems (BEAMS) Department of the Université Libre de Bruxelles, report their findings having investigated the "bed of nails" effect in microneedle arrays.

INTRODUCTION

With the advent of micro-electro mechanical systems (MEMS), the field of transdermal drug delivery has seen the emergence of new technologies to bypass the skin's protective barriers. Researches are currently developing microstructures that can pierce the stratum corneum, and allow drugs to be administrated through the skin. These are designed in order to reduce pain upon injection, and reduce infection risks and skin irritations at the injection site.

Microneedles can be classified into hollow or solid types. Hollow needles allow the injection of a fluid into the skin. Solid needles are used, either as a pretreatment to make the skin permeable to drugs, or in combination with a coating.[1] Dissolvable needles have also been developed recently.[2] For all those microneedle types, insuring correct insertion into the skin with a reasonable force is very important, not only for proper administration, but also regarding pain.

The phenomenon referred to as "bed of nails" was born from the observation that, when

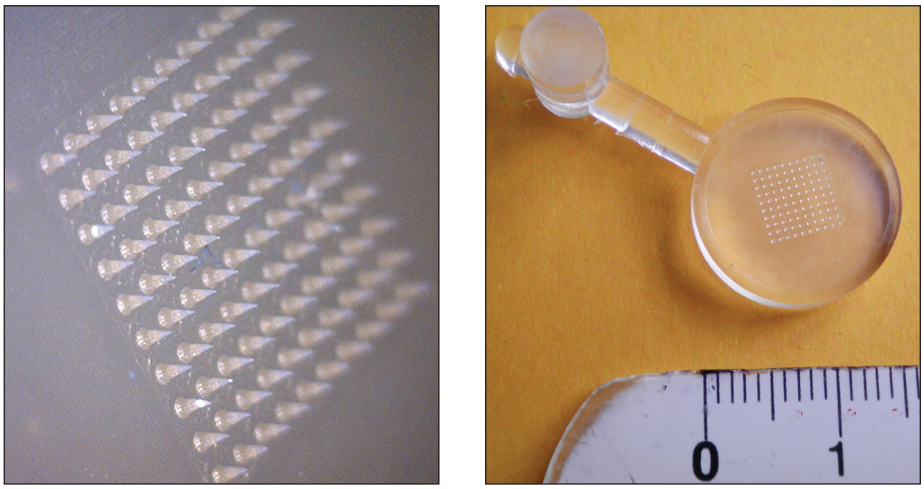

Figure 1: Prototypes of 100 micro-moulded microneedles made by Sirris Microfabrication Application Lab (Seraing, Belgium).

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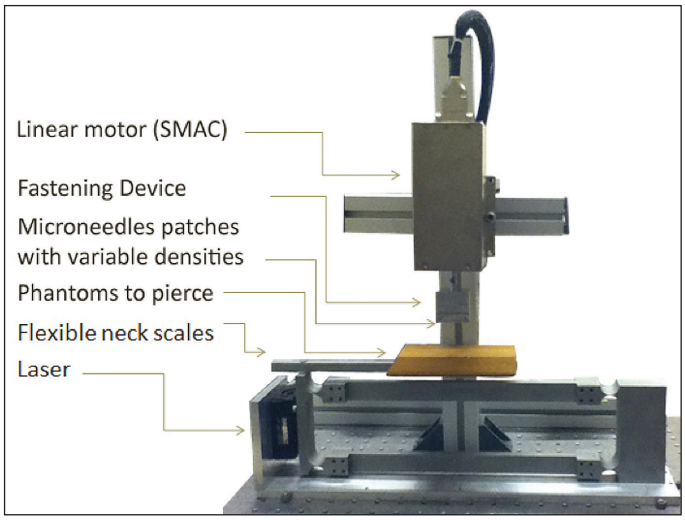

Figure 2: The test bench.

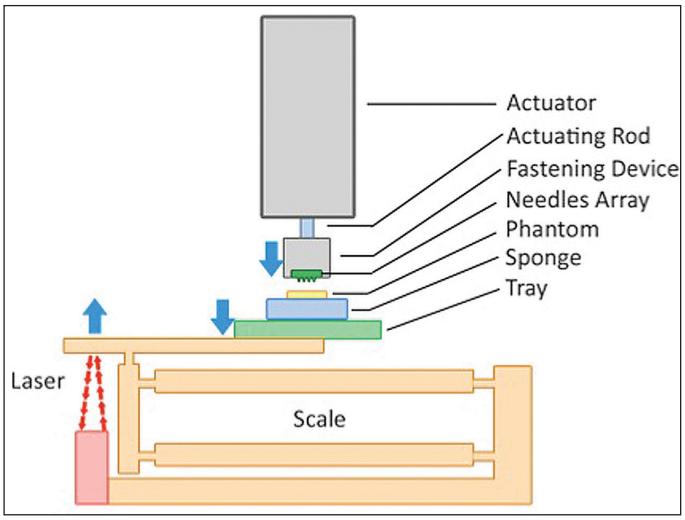

Figure 3: Principle of the test bench.

needles are placed too close to each other, they fail to pierce the skin. While the phenomenon has not been extensively documented in the context of microneedle insertion, some papers mention it.[3,4,5] The force necessary to pierce the skin mainly depends on needle tip, the sharper needle requiring the smallest force, [6] but it may not always be easy and cost efficient to manufacture very sharp needles. This explains why some microneedle patch developers also integrate an impaction system (applicator system), in order to overcome the problem.[7]

Figure 1 shows our prototype 10x10 polycarbonate micro-moulded needle array.[8] The needles are 500 µm tall, have a diameter of 270 µm, a 30° wall angle, and are separated by 600 µm from centre to centre. While manufacturing the polymer microneedle array using micromoulding was successful, attempts to penetrate porcine skin with the prototype have failed. The explanation can be found in the "bed of nails" effect which, because of the high number of needles and their close spacing, prevents correct penetration.

TEST BENCH USED FOR MEASURING INSERTION FORCES

The experiments require the evaluation of the influence of several parameters: the density of microneedles, the material properties, the application speed, and the insertion force. A test bench has been set-up, composed of a linear motor with adjustable velocity, a device to fix the microneedles arrays on the motorized part of the engine, a set of matrices with variable densities of microneedles, a substrate used for simulating the skin as described before, a force measurement system constituted of a scale using flexible hinges and a laser. It is important to note that the experiments and the test bench do not pretend to reproduce and simulate the real

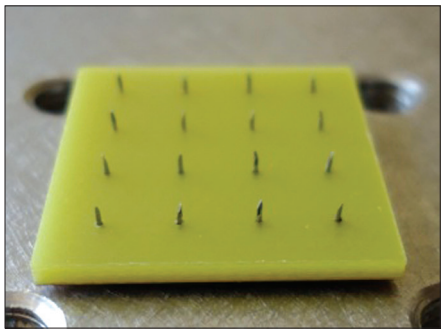

Figure 4: Picture of the microneedle array used in experiments.

behavior of the insertion of microneedles arrays into human skin. Rather, the test bench (Figures 2 and 3) was designed to give evidence of the phenomena called bed of nails effect.

Several materials were evaluated in order to be substituted to the skin: silicones, Agar gel and silicone rubbers. Silicon rubbers have Young's moduli of about 1- 2.8MPa. It is in the same order of magnitude as homogenised skin. In order to simulate the influence of soft tissues under the skin, a sponge-like material is placed under the substrate during the experiments. It is responsible for bending the sample when the force array is pressed against it, a behavior also observed with human skin.

The microneedle arrays under development in our facilities comprise micro-moulded polymeric materials. Manufacturing moulds being very expensive, we cannot test a wide range of needle densities using this fabrication method. A cheaper alternative was found consisting of the assembly of needles commonly used for insulin injection (30G). These needles have an external diameter of 300 µm and a length of 13 mm. Microneedles patches of 16 needles (see Figure 4) have been made using squared elements of printed circuit board (20x20x1.2 mm), drilled to allow the insertion of the needles with a determined spacing, needles emerging on the other side with a uniform height of 1 mm. To evaluate the impact of density, 10 patches were manufactured with different spacing.

EXPERIMENTAL PROTOCOL

An experimental protocol was established to establish evidence parameters influencing the ease of insertion. To evaluate the effects of needles density, needles contact the sample at a controlled speed of 10 mm/s. The insertion force of 1-10 N is applied over two seconds. The actuator then returns to its initial position at 10mm/s. Speed is a parameter which could also influence material elasticity.[9] If needle motion is high, the material has no time to move under the needle. The relaxation time is a characteristic of the sample and depends on Young's modulus,

"WHEN THE DENSITY IS HIGH, NEEDLES INFLUENCE EACH OTHER, AND THE FORCE APPLIED BY THE INNER NEEDLES OF THE ARRAY IS EXERTED ON AN ALREADY STRETCHED MATERIAL. "

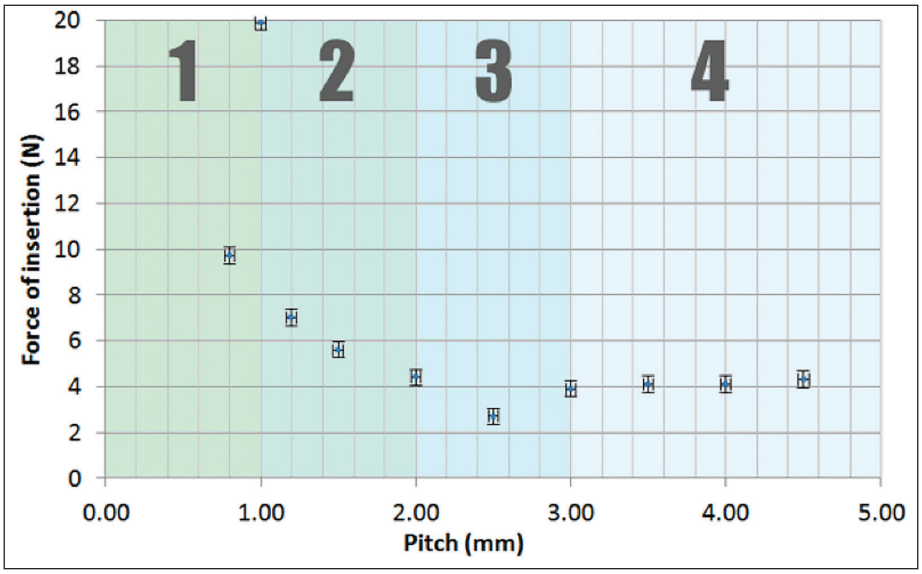

Figure 5: Influence of needle density on insertion forces.

and sample inertia. If the insertion time is lower than the relaxation time, the elastic phenomenon disappears. Experiments only modifying the speed in a reasonable range from 10 to 100mm/s have also been conducted. It is also possible to modify the elastic properties of the material locally by simply applying a thin layer of adhesive tape.

RESULTS

The results of our investigation are summarized in Figure 5. It can be separated into four regions. In the first region (1), the insertion force exceeds the range of admissible values (achievable by medical staff or patient). The spacing between needles is very narrow and disparities are observed between the stresses under the internal needles and those external. This phenomenon is the "bed of nails effect". The "bed of nails" is based on optimising the spacing between nails, in order to reduce the pressure exerted on each nail, resulting in a less painful and hazardous bed when the spacing is narrow.

However, it is important not to confuse the impact of needle density and that of needle number. If the needle number is kept constant, and the spacing is changed, the density varies. At high density (small spacing), the sample under the internal needles is subject to fewer stresses than under those external. Indeed, the tension exerted on the external needles is more important than the one exerted on the center needles. The material tends to counteract the bending due to the needles. In the external zone of the applied force, the material reaction force, due to its stiffness, is applied only on these external needles.

In the internal zone, the reaction force is shared between the local needles and the nearest needles. The internal needles push against the material, which is already stretched by the neighboring needles. At the extremities of the needle arrays, local needles are the only cause of stretching. In this region, the insertion force is high. If the spacing is lowered, the insertion force becomes higher. Nevertheless, it can be supposed that, with a decreasing spacing, the reduction in insertion force will, beyond a certain limit, level out.

In Figure 5, the first value (for p=0.8mm) is kept as an interesting observation. The measured value is indeed due to a phenomenon of pinching of the sample between the needles but not to an effective piercing. A careful examination of the sample confirmed this.

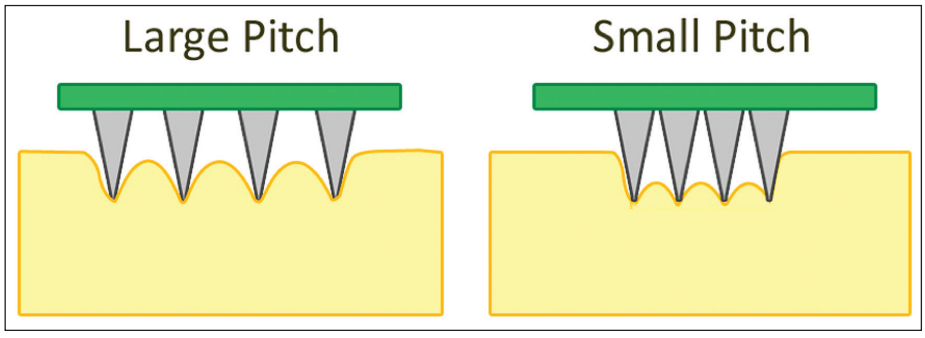

Figure 6: The influence of spacing on needles' ability to pierce a membrane.

The second region provides evidence for the importance in the decrease of the insertion force with the increase of needles spacing. By moving the needles apart, their interaction and their mutual influence are reduced. The stretching phenomenon increases and the insertion is facilitated, because the stress under each needle has increased. The figure presents a minimum insertion force at around about p=2.5 mm. The presence of a minimum shows that needle density is a parameter which cannot be chosen without dimensioning. The insertion force at this point is about 2.5 N.

The last region shows a slight increase of the insertion force with spacing increasing. This phenomenon is due to the influence of the system holding the microneedles array. Bending of the sample was clearly observed. By increasing the spacing, needles are more spread over the surface of the patch, and placed closer to the wedges of the holding system. Those wedges take a part from the applied force and stretch the material. If the spacing is too high, needles are too close from the wedges, and the external needles are subject to a decreasing force. The external needles press the material, which is already stretched between the wedges and the middle needles. The force, which appears on the external needles, is thus reduced. This effect complicates the insertion of the needle arrays in the material. The design of the connection device between a micro needle array and its applicator is thus very important in terms of needles insertion.

The experiments did not show any significant variation of the insertion force with speed. An increase of speed beyond realistic range (achievable without an applicator device) could highlight a decrease of the force required to insert the needles at a given depth.

Elasticity is a parameter that significantly influences insertion force. If the stiffness is too high, the arrow due to bending is reduced and the insertion is easier. The influence of each needle on the others is also reduced, and the spacing can be smaller.

DISCUSSION & CONCLUSION

Our experiments evidence the "bed of nails" effect and the fact that the phenomenon appears at given needle densities for specific needle sizes (here 30G). When the density is high, needles influence each other, and the force applied by the inner needles of the array is exerted on an already stretched material.

Thus, stress under these needles is reduced, and the insertion force required to pierce the sample increases, even to the extent that it becomes impossible to pierce the sample with a reasonable force. It was also observed that the

device that holds the microneedle array and is used to press it against the sample is of significant importance.

Material stiffness also plays an important role with regards to the insertion force. By pasting a stiffer material to the sample, the overall properties of the material are locally modified and the insertion is eased. The insertion speed did not show any influence on the insertion force at speeds reasonable considering use by patients or medical staff. However, the speed could lead to a momentary decrease of the elasticity effects, which can be exploited when an application device is used (using a spring for example).

There are thus several approaches that can be foreseen to overcome the "bed of nails" phenomenon with microneedle patches. These include:

- working on needle length inhomogeneity
- working on needle design, and particularly on tip sharpness
- working on needle density
- working on the applicator by incorporating an insertion device
- locally changing the elastic properties of the skin
- a combination of several solutions.

ACKNOWLEDGEMENTS

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THE DERMOELECTROPORATION® SYSTEM FOR TRANSDERMAL DELIVERY OF DRUGS

In this article, Gian Franco Bernabei, PhD, Chief Executive Officer, Mattioli Engineering, introduces the company's transdermal drug delivery system for the delivery of large molecules using electroporation.

In 2004, Mattioli Engineering introduced a new concept in dermatology for the transdermal delivery of high-molecular-weight therapeutics up to 1,000 kDa. The patented, proprietary technology, known as Dermoelectroporation® (DEP) is shown in Figure 1 and 2. The DEP system delivers controlled current pulses between two adjacent electrodes to increase the permeability of the skin. The effect of the electrical pulses is the opening of water-based microchannels through *stratum corneum* and epidermis.

Thus a high-molecular-weight drug filled into two adjacent gauze-pad electrodes is then delivered into the dermis. Sonic technology is also employed to enhance delivery.

The device is covered by a broad US patent estate, which includes US patent numbers: 6518538; 6535761; 6587730; 6687537; 6743215; 6748266; 6980854; 7010343; 7083580; 7376460; 7471979; 7496401; 7520875; 7532926; and 7945321.

The device is EU CE marked and US FDA-cleared for the transdermal delivery of lidocaine. Many other drugs are successfully deliverable, although not yet FDA-approved. These include: Botulinum toxin, phosphatidylcholine, aminophylline, L-carnitine, amino acids, heparin, collagen, various vitamins, various steroids, diclofenac and others.

Figure 1: The Dermoelectroporation® (DEP) System.

To date, the technology has been used mainly in cosmetic dermatology for delivering sub-

"INSTEAD OF USING THE STANDARD ELECTROPORATION HIGH-VOLTAGE CONTROLLED PULSES, THAT COULD DAMAGE THE SKIN DUE TO THE UNPREDICTABLE CURRENT DENSITY, DEP APPLIES CONTROLLED CURRENT PULSES TO THE SKIN"

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Figure 2: The Dermoelectroportation® (DEP) System and Mobile Stand.

Figure 3: On the DEP handpiece is mounted an optional computerised liquid dispenser that delivers the drug to the disposable cap by pushing a disposable drug-loaded syringe.

stances like non-crosslinked hyaluronic acid, in conjunction with a microdermabrasion treatment. The microdermabrasion treatment is a standard in cosmetic dermatology and it is needed in order to have the assurance that the *stratum corneum* has a maximum permeability so that that the drug is really transdermally delivered.

The DEP technology developed by Mattioli is an improvement on the standard electroporation pulse systems that have been in use for more than a decade and are known to be able to deliver macromolecules through *stratum corneum* and epidermis.

Instead of using the standard electroporation high-voltage controlled pulses, that could damage the skin due to the unpredictable current density, DEP applies controlled current pulses to the skin. This technology works perfectly if the permeability of the *stratum corneum* is enough to enable transdermal transport.

In dermatology it is normal practice to use microdermabrasion in order to pretreat the skin for further treatment and thus has not been a problem to introduce this limitation also because Mattioli is one of the major manufacturers of microdermabrasion equipment. The reason pretreatment is included is that we limit to 100V the maximum voltage that the device applies to the skin, in order to avoid adverse effects.

Recently, in order to broaden the use of the technology, a means to verify sufficient *stratum corneum* permeability has been added to the equipment. This is done by measuring the electrical impedance of the skin during the current pulse. This makes it possible to check if pretreatment is needed and, further, to judge whether full microdermabrasion pretreatment is required or whether simpler pretreatment using scrubs or even gently abrasive paper would suffice.

The DEP comprises a machine body and a handpiece. On the handpiece is mounted an optional computerised liquid dispenser that delivers the drug to the disposable cap by pushing a disposable drug-loaded syringe (see Figure 3). Two sizes of syringes (10 cm^3 and 20 cm^3) and two handpiece sizes (small and large) are available. The typical injection speed over a skin surface of 30 cm^2 is between 0.5-1 cm^3/min, depending on drug and handpiece size.

The device has been validated in a number of clinical studies conducted by the Department of Anatomy at the University of Florence, Italy. Amongst the many studies that have used the device, some of the most significant include:

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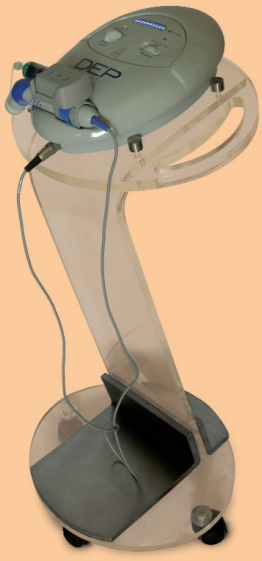

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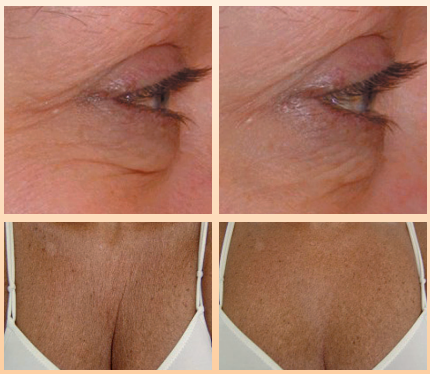

** Transdermal delivery of Clostridium botulinum toxin type A by pulsed current iontophoresis

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