SKIN DRUG DELIVERY: TRANSDERMAL & MICRONEEDLES

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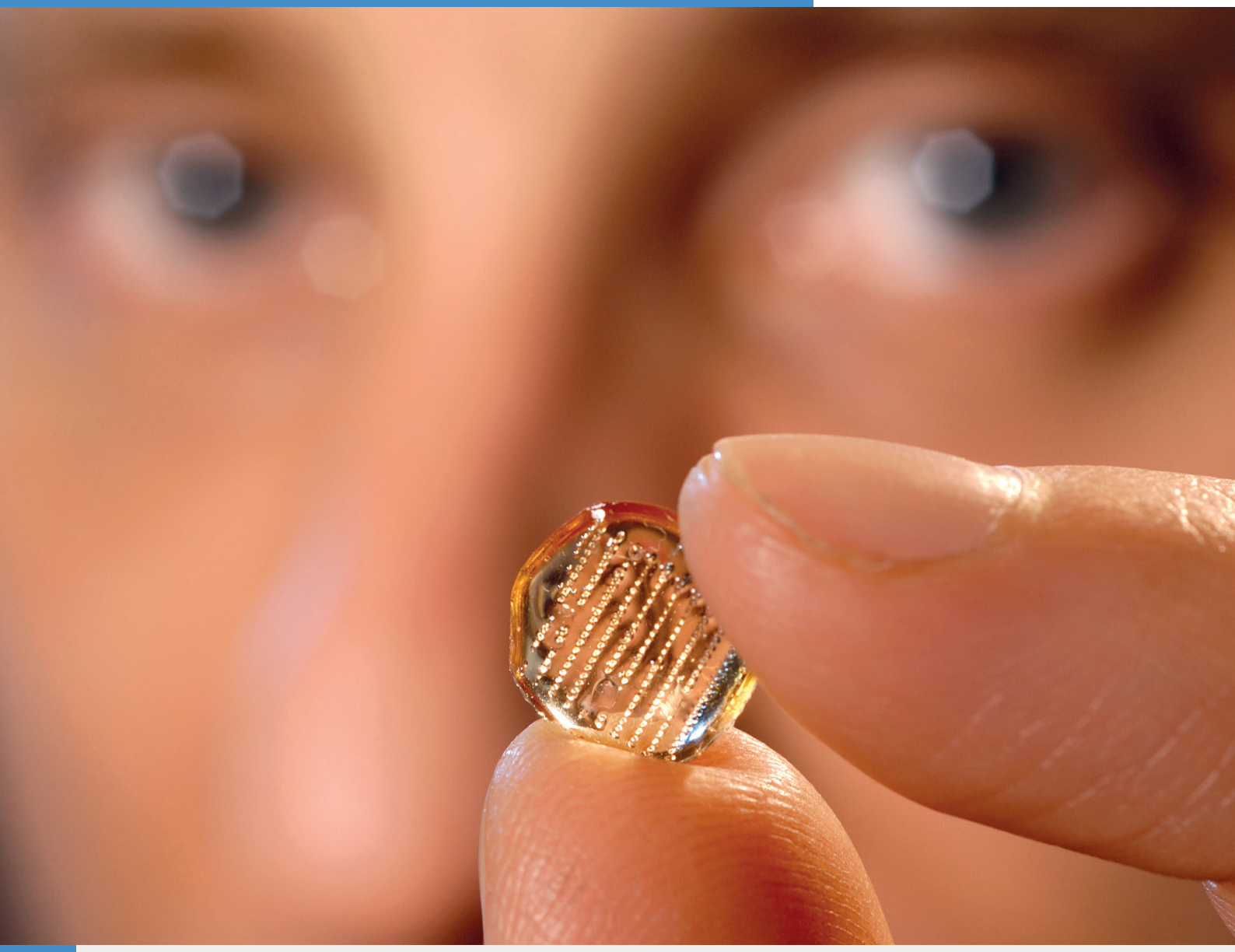

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SKIN DRUG DELIVERY: TRANSDERMAL & MICRONEEDLES

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Front cover image, "Patch containing 100 polymer microneedles" supplied by Professor Mark R Prausniz, Georgia Institute of Technology. Photo Credit: Gary Meek. Reproduced with kind permission.

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COST-EFFECTIVE APPROACHES FOR SUCCESSFUL GENERIC DERMAL DRUG PRODUCT AUTHORISATIONS

In this article, Prof Marc Brown, PhD, Chief Scientific Officer, Jon Lenn, PhD, Senior Vice-President US Operations, and Jeremy Drummond, PhD, Senior Vice-President Business Development, all of MedPharm, discuss various methods and advantages of *in vitro* bioequivalence studies for topical skin application, and how MedPharm's unique technologies and experience can be invaluable in the effective development of generics in this field.

Dermal products for topical application are an attractive option for pharmaceutical companies seeking to address unmet needs and generics developers hoping to broaden their market coverage. The topical dermal market for pharmaceutical products is currently estimated to be over US$18 billion (£13 billion),[1] a small but significant niche in the overall pharmaceutical market.

The pharmaceutical industry is highly regulated and significant investment is required to demonstrate the quality, efficacy and safety of any new product before the authorities will grant market authorisation. Once valid patents have expired it is imperative that new generic entrants can demonstrate exactly the same, or in some cases improved, standards to ensure that there is no compromise for patients. Traditionally this is done by showing that the generic product delivers the same efficacy and safety profile in clinical trials.

In the case of topical products for the treatment of skin disease it has been typically necessary to demonstrate therapeutic bioequivalence. For other routes of delivery, including transdermal patches, where the delivery is systemic, only a demonstration of pharmacokinetic bioequivalence is required by the authorities.

Clinical trials remain time consuming, expensive and risky, and can be a significant barrier to generic introduction for products within all but the largest markets. The variability in skin adds inherent risks to any clinical trial on top of the expense. As the skin also responds to most excipients there is no true placebo, just vehicle components that are accepted to have some effect. This makes primary endpoints more difficult to meet, further increasing the risk of failure. In turn this creates a challenge for governments wanting to promote the introduction of topically applied generics as a way of reducing their healthcare bills, whilst at the same time being clearly obligated to register generic products without any additional risk to patients.

> "MedPharm's experience is that regulatory authorities on both sides of the Atlantic are becoming more open to non-clinical or *in vitro* approaches."

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A recent analysis by the US Government Accountability Office of drug pricing between 2010 and 2015 showed that topical generic drug prices had increased by an average of 276%, whereas all other routes of delivery (oral, intravenous and ophthalmic) had seen no significant change.[2] This was directly related to lack of generic competition and the height of barriers to entry for new topical generic products.

THE CHANGING GUIDANCE FROM REGULATORY AUTHORITIES

MedPharm's experience is that regulatory authorities on both sides of the Atlantic are becoming more open to non-clinical or *in vitro* approaches. These approaches allow the bioequivalence of a generic topical drug product with the established reference listed drug (RLD) to be demonstrated with a high degree of confidence without the need for any clinical data.

At recent workshops, the US FDA has openly expressed a desire to have dialogue with those companies submitting topical generic applications. They have now introduced pre-ANDA meetings akin to pre-IND meetings to allow generics companies to hear opinions on their approach to bioequivalence before they complete and submit the full generic application.

In October 2017, the FDA introduced new draft guidance for four topical semi-solid products in addition to acyclovir cream, in order to stimulate generic entrants.[3] The guidance stipulates the testing data the agency expects to see in order for it to approve products without supporting therapeutic bioequivalence data. Additionally, the agency has produced guidance notes for five solution-based foam aerosols.[4] More can be expected to follow as the FDA establishes the standards needed to show equivalence using *in vitro*/*ex vivo* performance testing models.

The FDA is following its traditional approach of providing published guidance on a product by product basis. Recent communications with the UK MHRA suggest that European authorities will be focusing on a universal guidance for topical generic product submissions. All indications suggest that the MHRA and EMA will be open to submissions for topical generics using *in vitro* models to demonstrate bioequivalence, provided that they are based on sufficient scientific rigour and validation. The procedure of using scientific advice meetings is well established at the EMA, as well as at specific European countries agencies (e.g. MHRA, BPharm) to provide opinions on generic submission strategies.

In MedPharm's experience, it is important to discuss any development strategy for a generic topical product in which *in vitro* bioequivalence is being used early on with the appropriate regulatory authorities. As an example, MedPharm would typically create a proof-of-concept dataset to present to the relevant agency to support the approach being taken. MedPharm supports clients at agency meetings and in all cases regulatory authorities have demonstrated an openness to the approach, as long as the proposed studies can be demonstrated to be conducted with sufficient scientific rigour and there are no safety concerns.

> "With MedFlux-HT®, the skin is carefully and continually perfused and sample collection is automated using a high-throughput design to minimise artefacts, ensure sink conditions, reduce sampling errors and allow for continuous and rigorous sample collection."

A COST EFFECTIVE APPROACH TO DEMONSTRATING BIOEQUIVALENCE

To date, MedPharm has helped several clients convince regulatory authorities that the scientific data obtained from *in vitro* studies, demonstrating equivalence at all levels between the originator topical product and the generic product, is sufficient to demonstrate bioequivalence between the two and therefore make the need for costly clinical trials unnecessary.

MedPharm's approach to establishing a submission package acceptable to regulatory authorities revolves around two key areas:

1) Reverse-engineering of the originator product to establish concentrations and grades of the excipients listed in the patient information leaflet (PIL).
2) Rigorous performance testing to demonstrate that the generic product behaves in the same way as the originator product or RLD.

The excipients in the originator product are listed in the PIL. Concentration ranges can be established by appropriate and validated analytical methods and should be within ±5%. It is often difficult to analyse the grade of any excipient and this can have a significant bearing on product performance. As a result, MedPharm relies on its extensive formulation experience to select the most appropriate excipient grade and source. Furthermore, MedPharm will help establish the most appropriate manufacturing process based on its experience and subsequently this can be refined and validated using rigorous process development methodology (e.g. Quality by Design, Design of Experiments).

Core to the activity of developing a formulation that is fundamentally as close to the originator product/RLD as possible is ensuring that the products are qualitatively, quantitatively and structurally the same. FDA guidance[2] classifies this as:

- Q1: Qualitative Similarity
  - same components.
- Q2: Quantitative Similarity
  - same amounts of the same components.
- Q3: Structural Similarity
  - same amounts of the same components arranged in the same way.

The class of excipients (Q1) used in the RLD is stated in the PIL and is therefore in the public domain. Reverse engineering is used to establish the relative amounts of the excipients (Q2) to ±5% and where possible the grade and origin of the excipient. Q3 relates to the micro-structure of the formulation. This requires demonstration that the drug product has, for example, the API in the same polymorphic form if it is in suspension, a cream's emulsion has the same particle size range or the semi-solid drug product has the same rheological characteristics.

It is the performance testing that then demonstrates the equivalence of product performance. First, *in vitro* release testing (IVRT) is developed and validated to show the drug in the generic product has the same release characteristics as the RLD. Regulatory authorities are now requiring this as a quality control tool and mandate its incorporation into the release and stability

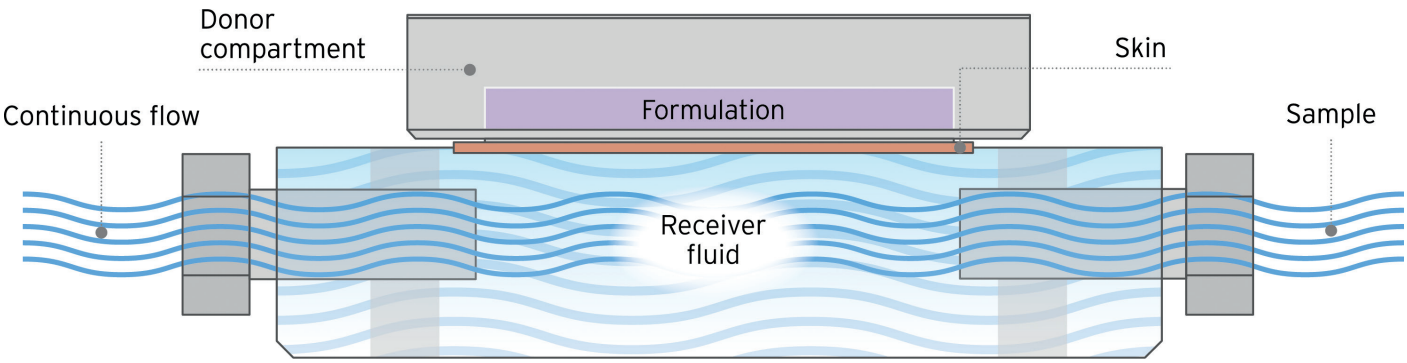

Figure 1: Schematic representation of a MedFlux-HT® cell.

specifications. Importantly the IVRT must be validated to demonstrate that the method is sufficiently sensitive for discrimination and robust enough to justify that the API release from the two formulations is the same. Recently MedPharm has developed a 24-cell, automated IVRT system, MedStat-HT™, to improve the efficiency and robustness of the method and is engaged in discussions about its use in future submissions.

IVRT is used to investigate a drug's release from the topical formulation. It does not provide any indication of how the formulation impacts the drug's absorption across the skin. This is another key component to a product's performance or equivalence so, to determine it, the appropriate methodology, *in vitro* penetration/permeation testing (IVPT), including a diffusion cell, must be utilised. MedPharm has two options here:

1. Traditional vertical diffusion cells or static Franz cells.
2. MedPharm's unique flow-through cells, MedFlux-HT® (Figures 1 & 2).

"The benefits of this approach are clear: clients can enter generic markets with a significantly lower investment cost and in a shorter timeframe. It is also clear that regulatory authorities are increasingly open to accepting bioequivalence using *in vitro* performance models for dermal products."

With MedFlux-HT, the skin is carefully and continually perfused and sample collection is automated using a high-throughput design to minimise artefacts, ensure sink conditions, reduce sampling errors and allow for continuous and rigorous sample collection. Both models allow for the permeation of the drug from the generic and originator product to be compared. The key advantage of the MedFlux-HT model is that, by having continuous clearance, it is a closer model to the clinical setting and, through automation, offers the ability to demonstrate equivalence within potentially tighter confidence limits. In both cases the layers of the skin can subsequently be analysed for drug content to show equivalence in drug penetration (skin layers) as well as permeation (receiver fluid).

These models typically require highly sensitive bio-analysis in order to detect the ultra-low drug levels inherent to all topical applications. MedPharm has experienced drug metabolism and pharmacokinetics (DMPK) bio-analysts with a specialised knowledge in the challenges of detecting low levels of drug in skin and other matrices using liquid chromatography mass spectrometry (LC-MS)/mass spectrometry (MS).

As with IVRT, it is important to validate the IVPT method chosen in order to demonstrate accurately that the generic and originator products are penetrating at the same rate and permeating in equivalent levels to the different layers of the skin.

Fundamentally, neither IVRT nor IVPT can demonstrate whether the drug is biologically active, even if it is detected in the skin layers. To address these limitations, MedPharm has developed a series of *in vitro* disease or pharmacodynamic (PD) activity models to demonstrate the equivalence of products for the treatment of skin infections (e.g. athlete's foot, onychomycosis, acne and herpes), inflammatory skin diseases (e.g. psoriasis, atopic dermatitis) or bacterial infections. Custom models can also be developed because these *ex vivo* human skin models can be kept in a functional state for up to ten days using proprietary methods. In addition, these models have the added of advantage of allowing the drug to be quantified in the skin over time via

Figure 2: MedPharm's unique flow-through cells in MedFlux-HT® are automated to allow for reduced sampling errors and continuous and rigorous sample collection.

pharmacokinetics (PK). This means that, in the same tissue, the PK and PD activity can be assessed simultaneously to create a PK/PD analysis in a mimetic disease model.

Yet again it is crucial to demonstrate to regulatory authorities that these disease activity models have an appropriate level of validation. By combining all of these approaches and tools a generic product's sameness with an RLD can be assessed and compared with an originator qualitatively, quantitatively, structurally and in terms of drug release, absorption and biological activity.

THE BENEFITS OF THE *IN VITRO* BIOEQUIVALENCE APPROACH

The benefits of this approach are clear: clients can enter generic markets with a significantly lower investment cost and in a shorter timeframe. It is also clear that regulatory authorities are increasingly open to accepting bioequivalence using *in vitro* performance models for dermal products. Such an approach lowers the barriers to market entry and hence allows governments to lower healthcare bills more swiftly than they otherwise could. Furthermore, it allows generic producers to enter markets that they would otherwise be precluded from because of the prohibitive expense of conducting suitable clinical therapeutic bioequivalence trials.

These approaches are strictly aimed at demonstrating the exact equivalence of the generic product with the originator/RLD. In this approach, equivalence must be demonstrated even when the originator's performance is known to be sub-optimal. There are opportunities through formulation for generic companies to register products which have improved performance over the originator, which may allow for faster and greater market penetration and some price premium. Currently this must be demonstrated though a therapeutic clinical trial. In such a scenario, the use of the performance models described here is also key in de-risking the decision to invest in this clinical trial. Unless a meaningful difference can be demonstrated using IVPT and/or disease activity models, it is very unlikely that endpoints showing clinical improvement will be met in any subsequent clinical trial.

ABOUT THE COMPANY

MedPharm is a leading contract provider of topical and transdermal product design and formulation development services. MedPharm has expertise in reducing risk and accelerating development times for generic and proprietary pharmaceutical customers through their unique, cost effective and industry-leading performance testing models. Well established as a global leader in dermatology, nail, mucosal membrane and transdermal product development, MedPharm can also offer innovative solutions for ophthalmic and airway preparations recognised for their scientific rigour by regulators and investors. MedPharm has fully established R&D centres in the US and UK and has its global headquarters in Guildford, UK.

ABOUT THE AUTHORS

Marc Brown co-founded MedPharm in August 1999 and has been the guiding force behind all the company's scientific developments and intellectual property. He has been Professor of Pharmaceutics at the School of Pharmacy, University of Hertfordshire (UK), since 2006 and has honorary professorships at the University of Reading (UK) and King's College London. Prof Brown has over 200 publications and 26 patents describing his work. His research interests lie mainly in drug delivery to the skin, nail and airways. To date, he has been involved in the pharmaceutical development of more than 38 products that are now on the market in Europe, America and Japan.

Jon Lenn has direct responsibility for MedPharm's operations in the US based in Durham, NC. Since joining in 2015, he has led MedPharm's development of cutting-edge performance models for assessing penetration and activity of clients' products targeted towards key biochemical pathways. He has over 15 years' experience in developing dermatological projects and has been directly involved with the development and approval of eight products. Dr Lenn received his PhD on the topical delivery of macromolecules from the University of Reading (UK).

Jeremy Drummond joined MedPharm in February 2017. He has spent over 20 years leading the commercial supply of product and services to pharmaceutical companies across the globe. He is responsible for leading revenue growth, key client relationships and marketing MedPharm to its global customer base. He started his career as a technical formulator and has a PhD in organic chemistry from the University of Cambridge (UK).

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QUALITY BY DESIGN IN TDS DEVELOPMENT: BENEFIT OR BUREAUCRATIC BURDEN?

In this article, Petra Botzem, Senior Technician in R&D, and Thomas Hille, PhD, Director of R&D, both of LTS, discuss the Quality-by-Design approach to the development of transdermal drug delivery systems as laid out in ICH guideline Q8. The authors describe the key aspects of identity, purity and strength before applying this knowledge to outline how such a development cycle would work in practice.

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INTRODUCTION

The aim of pharmaceutical development is to design a quality product and its manufacturing process. With reference to ICH guideline Q6A, the quality of a product is characterised by identity, strength, purity and its reproducible manufacturing process. These same quality requirements were already established in the historical monographs of both the German pharmacopeia (DAB) and the United States pharmacopeia (USP) using different words that hold similar meanings: Identification, Assay and Impurities.

Furthermore, other statements taken from the guideline are commonly cited when seeking to understand a product's quality, for example the statements that "Quality cannot be tested into products" and "Quality should be built in by design".

This understanding can be gained through prior knowledge or formal experimental design, which seems, at first, in opposition to the famous statement made by W Edwards Deming:

"In God we trust, all others bring data!"[1]

However, the US definition of "prior knowledge" is different from that given by the European Union. The US FDA states that prior knowledge may only be gained from experimentation and never by education alone. According to the European understanding, the Noyes und Whitney equation can be regarded as prior knowledge, however, some health authorities will request supportive experimental data.

> "Taking into account the costs of development, it is remarkable that the level of knowledge gained, rather than the volume of data, provides the basis for science-based submissions."

Taking into account the costs of development, it is remarkable that the level of knowledge gained, rather than the volume of data, provides the basis for science-based submissions.

It is also worth noting at this stage that the pharmaceutical industry itself has neither the capability nor the authority to enforce legally binding requirements upon its constituent companies. Therefore, the guidelines referenced are merely that, non-binding descriptions of how to go about the business of pharmaceutical development. That being said, they do provide the basis for the present unified development standards, and thus non-compliant companies will experience difficulties operating within the industry.

Finally, this article will not describe the design space for a manufacturing process itself (due to the similarities with process qualification, US, or process validation,

> "At present, there are no guidelines defining criteria to test identity when following a quality-by-design approach."

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non-US), but rather will deal exclusively with the establishment of the design space, including relevant documentation, with a focus on transdermal delivery systems (TDS).

IDENTITY AND PURITY

At present, there are no guidelines defining criteria to test identity when following a quality-by-design (QBD) approach. However, such an approach might be of interest to justify changes at manufacturing sites. For example, this is especially true for excipients used in TDS, such as pressure sensitive adhesives or liners.

Furthermore, it is obvious how purity within the specification, and also throughout the lifecycle, of a product can be achieved (e.g. by utilising pure drug substances and excipients in relevant specifications). The relevance of using pure excipients will be demonstrated with the aforementioned important TDS ingredient: the pressure sensitive adhesives.

Pressure sensitive adhesives contain monomers and initiators, which are critical impurities in polymers ("critical" in the sense of quality-affecting impact on the final product). Residuals of initiators, or radical starters, in a polymer are a critical factor when considering the purity of the drug product TDS. They can initiate a radical degradation of the drug substance during the manufacturing or storage of the TDS.

Furthermore, non-hazardous excipients (e.g. water) can have a critical impact due to the risk of microbiological contamination or hydrolysis of the drug substance when applied transdermally. For these reasons, the use of polymers dissolved in organic solvents, rather than aqueous polymer dispersions, is preferred for the manufacture of TDS to minimise potential risk (the growth of germs is unlikely in organic solvents).

The use of oxygen- or light-sensitive substances (e.g. nicotine, buprenorphine and nifedipine) or excipients used as tackifiers (e.g. oleic acid or abietic acid derivatives) may prove critical to the stability of TDS, but require the following adequate countermeasures to be applied:

- Inert gas flushing in the production.
- Relevant specifications of excipients (e.g. peroxide value in resins, oleic acid and PVP or residuals of initiators, or radical starters, in a polymer as mentioned prior).
- Use of antioxidants in optimal concentration, which can be found by experimentation in the design space.[2]
- Sealing TDS products in airtight sachets.
- Avoidance of light exposure during the manufacturing or storage of intermediates.

> "It is strongly recommended that two requirements of ICH Q8 concerning the selected dosage form are considered: 1) that the type of dosage form selected is suitable for the intended use, and 2) that it is suitable for patients' needs."

STRENGTH

A parameter and its optimisation are quite different in TDS in comparison to all other dosage forms. As an example, a high proportion of the drug substance in the TDS is not absorbed, but is instead retained in the TDS during and after application, which yields assay and delivery rates that are not identical, hence the unusual nature of the TDS's strength parameter, and the optimisation thereof. In general, it is justified to state that the excess drug substance acts like an enhancer, because a certain part of it is necessary to enable transdermal absorption, even though it is not absorbed. Nevertheless, the demand from health authorities to specify assay within 95-105% of the label claim is difficult to justify.

Optimisation of the utilisation of the drug substance is a major goal for QBD as applied to TDS. This means the TDS drug content should be as low as possible whilst still achieving efficacy. This approach is not only important for economic reasons, but in regards to aspects of safety, sustainability and inhibiting narcotic abuse. In general, drug substances in TDS are very potent, meaning they are toxic, expensive and, in some cases, controlled substances (e.g. buprenorphine, methylphenidate, fentanyl and testosterone).

As well as the quality parameters, it is strongly recommended that two requirements of ICH Q8 concerning the selected dosage form are considered: 1) that the type of dosage form selected is suitable for the intended use, and 2) that it is suitable for patients' needs. Please note that here the term "selected dosage form" does not refer to the selection of a TDS in a general sense, but rather the specific type of TDS, such as a liquid-filled reservoir system, matrix system (with or without a rate-controlling membrane) or micro reservoir system. Furthermore, the drug substance can be dissolved or dispersed within the polymer, where dispersion can mean either in form of a supersaturated solution (e.g. suspension) or crystals.

Besides optimisation of the assay, the clear definition of the type of dosage form helps to recognise the relevance of the physicochemical properties of the drug substance. In the case of liquid-filled reservoir systems or matrix systems, the drug is dissolved during manufacture and particle size is only important for the rate of dissolution during production, affecting only the rate of dissolution, not the solubility.

ADHESIVE

In addition to the quality parameters (mentioned in the guideline Q8, PART II as patients' needs and the intended product performance), the requirement TDS must fulfill are different from those of other dosage forms. The simplicity of the way the main features of a TDS are defined might sometimes be surprising, as the requirements are so simple that developers oftentimes just forget them. Therefore, it is strongly recommended to point out that a TDS must to adhere to the skin and to deliver the drug substance transdermally over an application period of one or more days. Afterwards the TDS has to able to be removed without any adhesive residuals and, even more importantly removal must be painless for the user.

For completeness, reversible adhesion is defined as the tendency of two dissimilar surfaces to stick to one another by wetting both surfaces with a liquid or a polymer in its rubbery state. In the field of transdermal application one surface is human skin, the other the backing layer of the TDS.

Both requirements for the TDS are fulfilled by the one essential excipient, the pressure sensitive adhesive polymer building the matrix of the TDS. One of the physical properties that defines a polymer most uniquely is its glass transition temperature

(Tg), which directly correlates with its mechanical properties. When the Tg of a polymer is lower than room temperature RT (Tg < RT), it acquires rubber-like characteristics, its surface can be wet and the polymer acts as an adhesive. Polymers exposed to temperatures below their specific Tg become hard and brittle and are no longer adhesive. Due to the decreased motion of the polymer chains the diffusion of the drug substance in relevant amounts is not sufficient and thus transdermal absorption of it is impossible.

SUPERSATURATION

Armed with this knowledge, it is now possible to work out the main items of the approach, how to optimise the assay of the drug substance with systematic and targeted experiments by taking input factors into account. If it is accepted that only a certain amount of the drug substance in TDS can be utilised via transdermal absorption, then it becomes obvious that optimisation of the drug substance assay means an optimisation of the transdermal absorption. This is because the higher the relative amount of drug substance that is is absorbed transdermally, the lower the absolute drug substance assay in the TDS. When planning experiments within the design space, prior knowledge can be applied, but should not be taken schematically.

According to Hadgraft and Davis,[3] "vehicles" containing the drug substances in the form of supersaturated solutions have a clear advantage for transdermal drug application compared with drug solutions at or below its concentration of saturation c_s. They emphasise the relevance of drug substances' "thermodynamic activities" over their concentrations, and justify this hypothesis starting with Higuchi's modification of Fick's diffusion law:

$$F = D \times c_{skin} / L$$

Where:

- F = flux/area
- D = diffusion co-efficient of the drug substance in the stratum corneum
- L = effective thickness of the stratum corneum
- c_{skin} = concentration of the drug substance in the outer layer of the stratum corneum.

Furthermore, they define:

$$c_{skin} = c_{vehicle} \times Pc$$

> "What does it matter if, by obtaining the highest possible thermodynamic activity, the TDS does not stick? Bridging the gap between an optimised flux and skin adhesion of TDS is precisely the challenge, whilst in parallel ensuring that drug substance crystallisation in the polymer should is avoided."

Where:

- $C_{vehicle}$ = concentration of the drug substance in the vehicle (which means in the TDS)
- Pc = partition co-efficient of the drug vehicle/stratum corneum.

Under stable equilibrium conditions flux will be at a maximum when the outer layer of the skin is saturated. By definition, this will occur when the TDS matrix is also saturated with the drug substance.

In that stage the calculation can be written as the equation:

$$c_{s\ vehicle} \times P_c = \text{constant}$$

That means that the higher the partition co-efficient of the drug substance vehicle/stratum corneum, the lower the drug substance c_s in the vehicle (i.e. the TDS). Consequently, the amount of drug substance absorbed transdermally depends on its concentration at saturation, but neither on its actual concentration nor, even more remarkably, on its absolute content.

Therefore, Hadgraft and Davis support the utility of supersaturated systems for the development of TDS, meaning that TDS containing the drug substance above its c_s, which can be described with the inequality:

$$c_{vehicle} > c_s$$

Without reflection, this explanation permits the conclusion that it only needs the determination of the lowest c_s of a drug substance in different polymers, followed by the manufacture of a TDS in the respective polymer and a high drug loading. As a consequence, this approach results in a TDS with a maximum of thermodynamic activity and the utmost utilisation of the drug substance. However, so far, the product's lifecycle and patients' needs have not been considered, as supersaturated systems have the tendency to crystallise during the product's shelf life, and adherence to the skin after 24 hours or longer must be assured. What does it matter if, by obtaining the highest possible thermodynamic activity, the TDS does not stick? Bridging the gap between an optimised flux and skin adhesion of TDS is precisely the challenge, whilst in parallel ensuring that drug substance crystallisation in the polymer should is avoided.

TDS DEVELOPMENT

Based on this information, a systematic development of a TDS, essentially consisting of an acrylate copolymer matrix and a drug substance, will be outlined, conforming to ICH guideline Q8. Acrylate co-polymers have been chosen because they are still the most relevant pressure-sensitive adhesives today. In general, the following explanations are also relevant for polyisobutylenes and polysiloxanes.

First of all, the drug concentration at saturation has to be determined. This parameter depends upon the chemical structures of the monomers, the dissolution is allocated in the oscillating polymer side chains, rather than the molecular weight distribution influencing the viscosity and, as consequence of this, rate of diffusion, the glass transition temperature and lastly the adhesion properties of the pressure-sensitive polymer.

After the determination of the c_s value, the so-called "systematic targeted experiments" (design space), in the form of binary blends consisting of drug substance and polymer, will be performed. Starting with the defined c_s, the test series will be continued by increasing the drug substance content (input parameter) gradually (c_s + x% drug substance in the polymer matrix) with main focus on the flux and adhesion properties (output parameter). The drug substance can have either a positive (by reducing the glass transition temperature) or a negative (by reducing the wetting properties of the surface) impact on the adhesion strength.

In parallel, monitoring the *in vitro* dissolution is recommended, because

crystallisation can be the root cause for decreasing of the dissolution. The binary mixtures have to be stored under accelerated conditions (e.g. 40°C), as increasing the temperature of the storage conditions will expedite crystallisation, as higher temperatures increase the velocity of diffusion and decreases the viscosity of the polymers.

After identifying the optimal polymer type, experiments with polymers of different relative viscosity have to be performed. In linear polymers (e.g. in polyacrylates or polyisobutylenes) dynamic and complex viscosities correlate, because both depend on the molecular weight distribution (as long as the polymers will not be further cross-linked after polymerisation). The relative viscosity will be tested in polymer solutions of defined solid content (e.g. 2%) because the content of solids and the molecular weight distribution also have an impact on the viscosity. Therefore, the viscosity allows an indirect determination of the molecular weight distribution.

The aim of these experiments is to provide knowledge as to whether the viscosity of 2% (w/w) polymer solution impacts the adhesion properties of the binary mixtures and whether the viscosity is sufficient to stabilise the supersaturated solution. A stable supersaturated solution will avoid any drug substance crystallisation or, in case of individual crystals, indicate whether an impact towards the *in vitro* dissolution can be observed.

Finally, due to the similarity of process qualification/validation and the QBD approach, it might be reasonable to adopt the process qualification approach towards documentation in the QBD approach. This means that a protocol approved prior to any experimental activities should be followed, i.e. expectations fixed prior to any experiments followed by a comparison between said expectations and experimental results. Such an approach demonstrates that the developers understand what they are doing, even if no specifications can be set in the very early phases of research and development.

CONCLUSION

In the title of the article, the provoking question had been raised as to whether the QBD approach is just a further bureaucratic burden in scientific research. In fact, the very opposite is true; ICH guideline Q8 is of great benefit, describing well-established development strategies and providing a well-structured content a platform for controlled and organised development, not only for TDS but across the full spectrum of pharmaceutical development.

ABOUT THE COMPANY

LTS Lohmann Therapie-Systeme (LTS) is a pharmaceutical technology company that develops and manufactures innovative drug delivery systems such as transdermal therapeutic patches (TTS) and oral thin films (OTF) for the pharmaceutical industry. LTS's innovation model consists of both partner-funded and self-funded initiatives, currently encompassing more than 20 marketed products and a deep and diverse pipeline targeting multiple disease indications. LTS maintains its leading position through the continuous refinement of its core TTS and OTF technologies and by advancing emerging drug delivery technologies, including Micro Array Patches for the transdermal delivery of large molecule, biological actives. Founded in 1984, LTS operates today from two sites in Andernach (Germany) and West Caldwell (NJ, US), with a representation in Shanghai (China).

ABOUT THE AUTHORS

Petra Botzem is a Senior Technician in the LTS R&D department, possessing a wealth of experience in the development and scale-up of TDS and oral thin films. She handles manufacturing site changes concerning inactive ingredient, as well as the tech transfers processes for final dosage forms. Ms Botzem's experience has been gained working at the manufacturing sites of LTS in both Europe and the US. Furthermore, Petra is the co-inventor on several patents.

Thomas Hille is a pharmacist and achieved his PhD in Natural Science at the University of Bonn. He is a Director of the LTS R&D department and has developed TDS from lab formulation all the way through to final product, resulting in international registrations and product launches across five continents. Dr Hille holds several international patents for TDS formulations and manufacturing processes, especially for TDS containing narcotics.

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SILICA NANO-SOLUTIONS FOR SKIN DELIVERY

Here, Aparajita Khatri, PhD, Chief Scientist, and Christophe A Barbé, PhD, Chief Executive Officer, both of Ceramisphere Health (a recent spin-off from Ceramisphere PTY Ltd), outline the growth of the dermal delivery market, as well as the challenges it faces. The authors go on to detail a nanocomposite lidocaine patch, developed in collaboration with Nanopharma (Pardubice, Czech Republic), and how its achievements could be a boon to the skin delivery space as a whole.

CURRENT CHALLENGES IN SKIN DELIVERY

The development of dermal delivery systems has made pain-free self-administration a real option for patients. As such, patient acceptance of, and demand for, skin delivery products has increased, which have proven to be one of the main drivers for the skin delivery market. This market accounts for more than 12% of the overall global drug delivery market today.

Transdermal patches, ointments, gels and implants are currently the popular methods for transdermal drug delivery, with patches fast becoming the preferred option, especially for the elderly and children. Currently, 40 transdermal patches are available on the market, with over 70 more in clinical trials,[1] pain relief and hormone therapy products being the most prevalent.

> "While there has been considerable progress in the development of occluded and controlled-release pain relief systems, there remain some outstanding limitations, most notable of which is the undesirably high drug content during and after application."

While there has been considerable progress in the development of occluded and controlled-release pain relief systems,[2] there remain some outstanding limitations, most notable of which is the undesirably high drug content during and after application. In most cases, systems require a very high loading to obtain constant release of drug. Such high doses can trigger adverse skin reaction, thus limiting how long the system can be applied. This is highly inefficient as most of the drug remains in the patch after use (40-97%).

In addition to being uneconomical, inappropriate use and disposal of the patches also pose a serious public health risk, especially for controlled drug applications. In the case of fentanyl patches for example, although the clinically preferred treatment for several types of chronic pain, typically up to 60% of the drug is left in the patch when discarded. Inappropriate disposal, drug abuse and unintentional exposure are limiting the patches' use in clinical medicine; lowered prescriptions have led to a drop of up to approximately 20% in annual sales of fentanyl patches. Furthermore, issues such as leakage of the drugs from the patch and/or crystallisation of the drug during

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> "Through a combination of sol-gel technology and emulsion chemistry, Ceramisphere can encapsulate a wide range of water soluble and insoluble actives inside an amorphous silica matrix."

application can lead to uncontrollable and unpredictable dose administration.

Another fast-growing facet of skin delivery based applications is bioactive wound management (BWM). It is forecast that the market for BWM will grow to US$4.9 billion (£3.5 billion) by 2020,[3] a major driver for this being the use of growth factors. Growth factors help with wound regeneration and have the potential to reduce scarring.[4] However, for these to be effective, sustained release is required during healing. This has been difficult to achieve thus far, due to these biomolecules being susceptible to rapid degradation by enzymes in the wound. The challenge of multiple high-dose administrations, frequent and painful dressing changes, and the high cost of treatment continue to impede the much needed commercialisation of these very promising bioactives.

SILICA PARTICLES FOR DRUG DELIVERY

Through a combination of sol-gel technology and emulsion chemistry,[5] Ceramisphere can encapsulate a wide range of water soluble and insoluble actives inside an amorphous silica matrix. Biodegradable spherical matrix particles are produced under ambient conditions with a tailored size (from 50nm-100µm), providing controlled release of the active (from hours to days).[6-8] The payload is released by diffusion through the 3D porous network of the silica "sponge". The release rate is controlled by the internal structure of the sphere, which is customised during synthesis. Using the same base technology, the production processes have been scaled up to 100 kg/batch (for non-pharma products[9]) and are GMP compatible.

Ceramisphere has also developed specific processes to encapsulate a wide range of biological actives, e.g. small drug molecules (hydrophilic and lipophilic), polynucleotides (RNA/DNA) and therapeutic peptides and proteins.[9] Efficient encapsulation is achieved (typically >80%) with no loss of structural integrity and function. The distinctive feature of this process is that the biomolecules are physically entrapped inside the silica matrix; this engenders excellent protection against degradative enzymes, acidic pH or temperature fluctuations. This encapsulation inside porous silica matrices is also known to prevent the crystallisation of poorly soluble drugs and enhance their bioavailability.[10]

In contrast to crystalline silica, amorphous silica has very low toxicity and is US FDA approved for non-injectable routes. *In vitro* dissolution studies using USP IV methodology have confirmed the biodegradability of Ceramisphere silica particles with dissolution ranging from hours (*in vitro*) to several days[8] or weeks *in vivo*, depending on the route of administration and final target organ. The silica nanoparticles revealed an extremely low toxicity profile in mice, even at particle doses up to 200 mg/kg IV.[9]

In contrast to polymeric drug delivery technology, Ceramisphere silica particles are compatible with a wide range of post processing techniques. They are mechanically resistant and durable and are therefore able to survive grinding, milling, extrusion and electrospinning.

NANOCOMPOSITE SILICA-POLYMER PATCHES

Nanocomposite Patch Concept

Building on the key strengths of our silica delivery platform, such as protection and sustained release of the payload, and compatibility with spinning processes, Ceramisphere has developed the concept of a biodegradable nanocomposite patch in collaboration with Nanopharma AS. The nanocomposite patch is composed of biodegradable polymeric nanofibres containing silica nanoparticles with encapsulated bioactive(s). Produced by electrospinning, the production can be scaled up to meet industrial demand. The silica matrix provides both protection to the drug molecule during electrospinning and enables sustained release during application to the skin.

It is important to stress that silica encapsulation significantly enhances the functionality of these patches, offering the potential to introduce drugs which are incompatible with the polymeric chemistry or the spinning process into the nanofibrous system. These patches have a high safety profile, given that all components (polymer, silica matrix) are biodegradable, and FDA approved for skin applications.

Nanocomposite Lidocaine Patch

To demonstrate the potential of the nanocomposite patch and in particular its clinical potential, Ceramisphere and Nanopharma have developed a lidocaine nanocomposite patch. The choice of lidocaine was motivated by its excellent

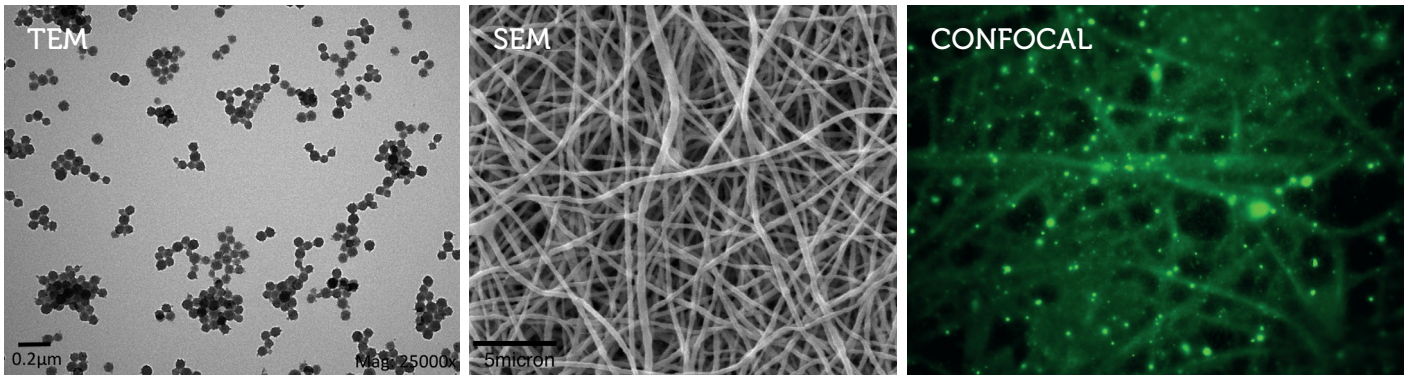

Figure 1: Lidocaine silica particles (TEM) and the nanocomposite patch (SEM and Confocal). Confocal image shows fluorescent lidocane silica particles in nanofibres.

safety profile for the treatment of post-herpetic neuralgia (PHN) (Lidoderm®, Versatis®). In addition to potentially expediting the patch development to the clinical stage, this will also provide a clean baseline to showcase the potential of this delivery system.

Representing roughly a market of $1 billion (IMS Health, 2015), the lidocaine market continues to grow, driven mainly by an ageing population. With the European patent expiry in 2017, companies are actively looking for a differentiator technology that would give them an edge over generic competitors. The current lidocaine patch uses a very high drug load, with 97% remaining in the patch after use. It can only be applied for 12 hours with a subsequent 12 hour break, due to the high levels of lidocaine in the patch causing an adverse reaction in the skin.

Ceramisphere and Nanopharma have produced a biocompatible nanocomposite lidocaine patch with the potential for a greater than 24 hour application and at least 30 times lower dose at the time of administration. The lidocaine is encapsulated inside the spherical particles (50-60 nm) of uniform morphology. The particles are then incorporated into the polymeric nanofibres using an electrospinning device to produce a non-woven nanocomposite mat (Figure 1).

The features of the nanocomposite lidocaine patch are:

- **Constant release:** The encapsulation in silica matrix does not alter the release profile of lidocaine from the nanocomposite patch *in vitro*. When tested using a Franz diffusion cell (n=4), this release was found to be linear through the human skin and comparable to the commercial patch (Figure 2A).
- **Faster pain relief:** The Franz cell studies also showed a much shorter induction time of two hours between application and initial release, compared with over four hours for the commercial patch, suggesting faster pain relief. This was confirmed in animal studies, where the release of lidocaine in the blood plasma was evident as early as one hour after application of the nanocomposite patch versus over four hours for the commercial patch. Fast pain relief is ideal for paediatric analgesia, where transdermal patches are fast becoming the route of choice.
- **Superior efficiency:** Defined here as the percentage of lidocaine released in comparison to the administered dose, this is one of the most attractive features of nanocomposite patches. In Franz cell studies, despite a between 60- and 100-fold lower lidocaine dose in the nanocomposite patch, approximately 80% of the administered lidocaine had passed through the skin after 24 hours (Figure 2B), which when combined with 17% present in the skin tissue (epidermis and dermis) (Figure 2C) suggested a total drug release of approximately 97% (i.e. less than 5% remaining in the patch after use). In

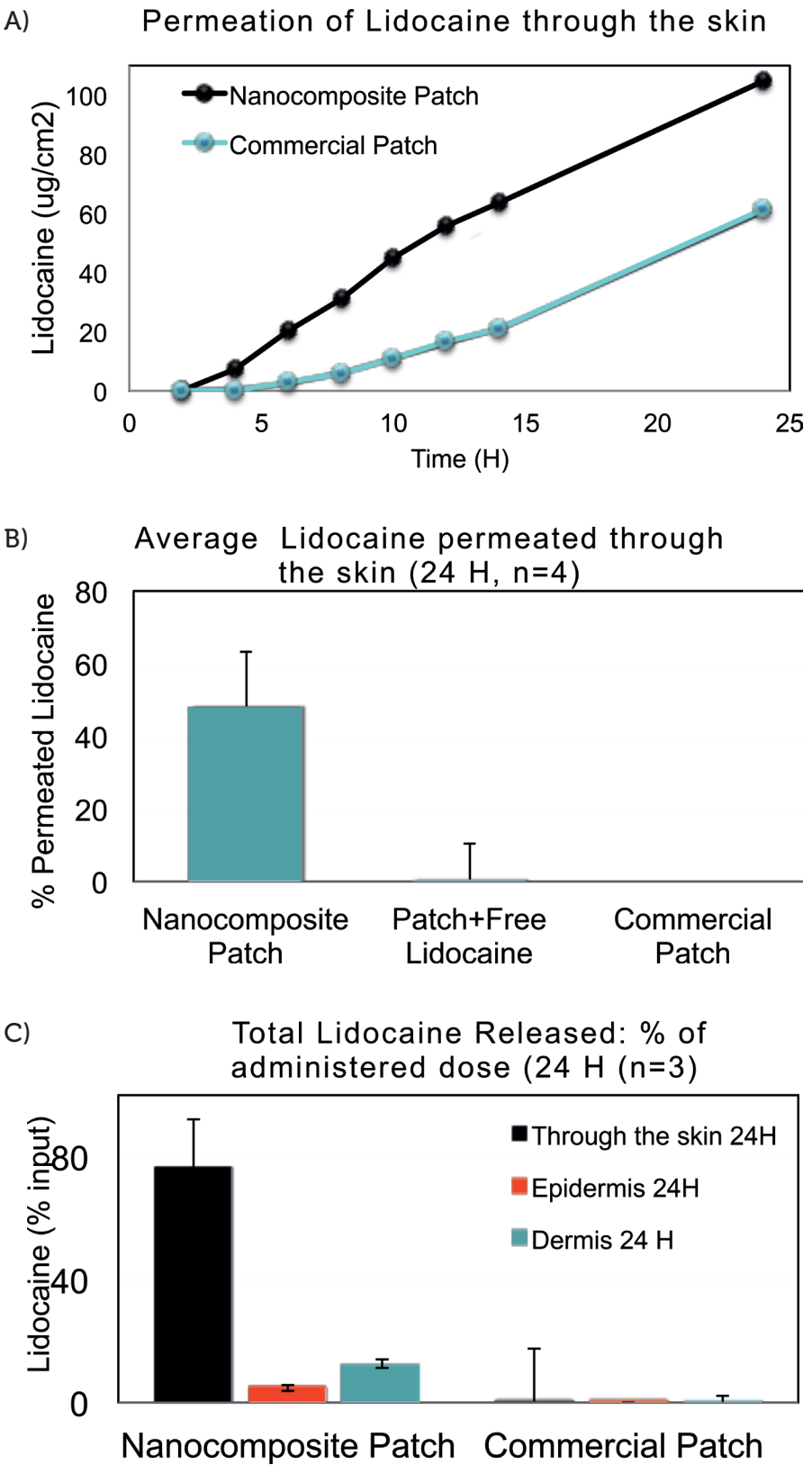

Figure 2: Comparison of patch performance in Franz cell studies using human skin.

comparison, a total of approximately 1% of lidocaine from the commercial patch was released. This was confirmed in large animal studies where, despite a 30-fold smaller dose in the nanocomposite patch, the delivery of lidocaine into blood plasma and the skin was comparable to the commercial patch (Figure 3).

- **Low potential for skin toxicity:** The nanocomposite patch is unlikely to lead to any specific nanoparticle based toxicity, as no evidence of skin penetration by fluorescent nanoparticles was found *in vitro*. This was further confirmed in animal trials, where no signs of any irritation/inflammation (redness) or swelling (Draize scoring) on the skin was recorded even after 72 hour application of the patches.

These nanocomposite patches are now ready for testing in humans and it is anticipated that clinical trials will prove these new patches to be safe and efficacious, providing a segue for new lidocaine products and posology.

Extension of the Technology to other Pain Relief Applications

Once proven in the clinic, the application of the lidocaine patches could be extended to provide analgesic relief in other neuropathies, e.g. diabetic foot ulcers or to provide surgical pain relief,[11] and in veterinary pain relief during surgical procedures for companion animals.[12]

In addition, this technology offers a clear solution to the issues dogging the delivery of opioid-based transdermal pain relief or other pain relief drugs. For example, a patch using silica with encapsulated fentanyl could be effectively administered using a much lower dose, with negligible quantities of drug remaining at the time of disposal. The danger of unintentional fentanyl release due to a temperature increase (e.g. fever) could potentially be minimised as silica-encased fentanyl will be protected against temperature fluctuations during application and storage of the patch.

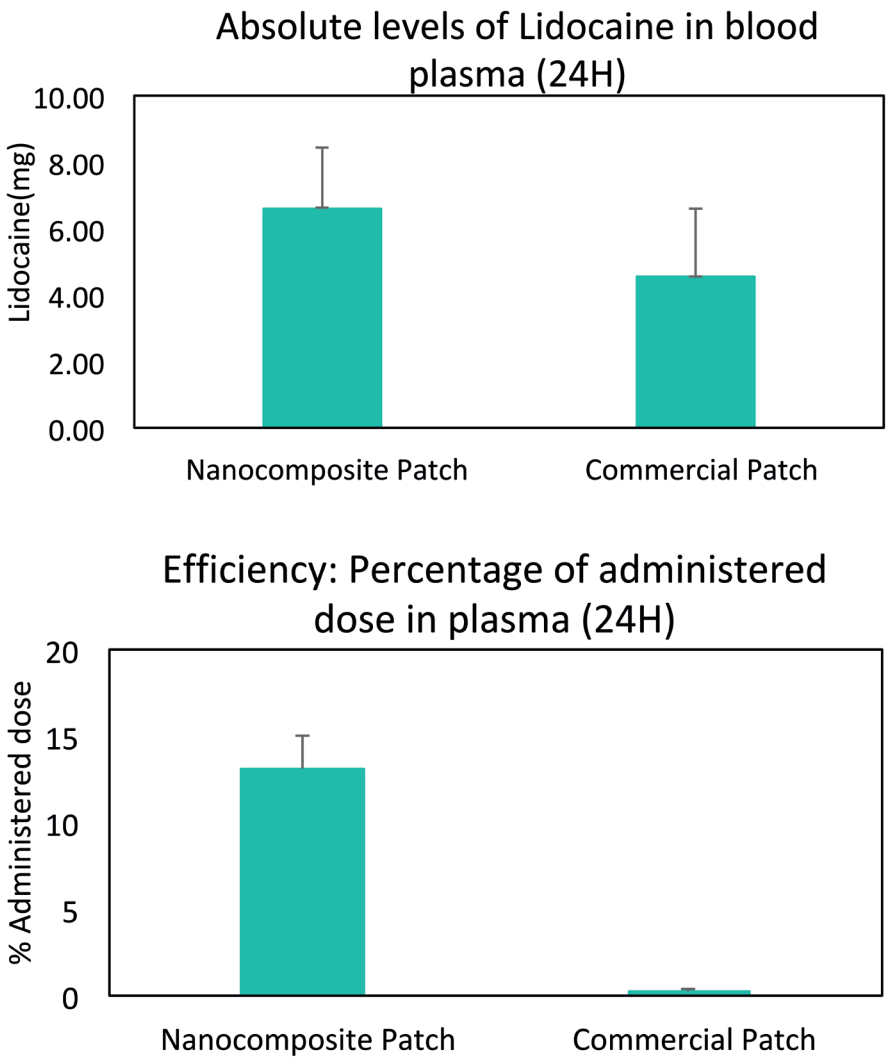

Figure 3: Comparison of patch performance in piglets.

SILICA NANO-SOLUTIONS FOR WOUND MANAGEMENT

There is an opportunity to encapsulate growth factors, such as epidermal growth factor (EGF), in the silica matrix to protect them against wound mediated degradation (e.g. proteases) and control their release over time.

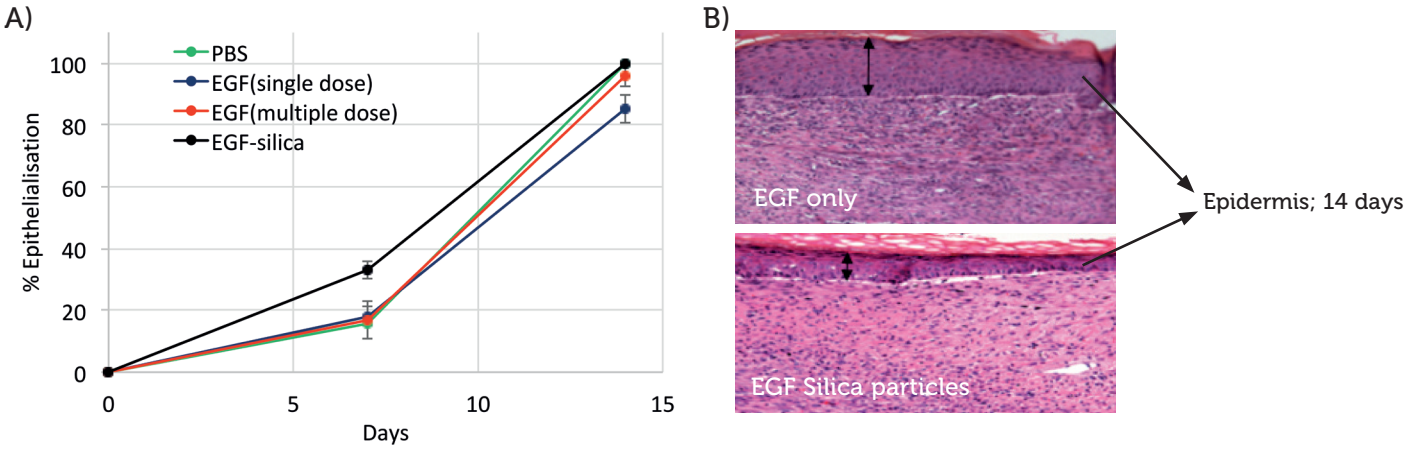

Figure 4: EGF silica particles for burn wound healing.

Ceramisphere has demonstrated that silica encapsulated EGF is functional, well protected in the wound environment and shows controlled release over a 14 day period (Figure 4A). In comparison to multiple doses of EGF, there is a clear advantage of the encapsulated EGF for re-epithelialisation of deep burn wounds at a faster rate, with potential for significant reduction in scarring (Figure 4B). This data underpins the current development of a silica particle-EGF nanocomposite patch and the development of silica particle-based smart wound dressings.

CONCLUSION

Silica particle-based delivery systems offer an overarching solution that tackles several of the challenges currently facing dermal delivery. Ceramisphere's technology allows encapsulation and protection of a large range of bioactives and co-formulation of incompatible actives. This protection inside the silica matrix not only stabilises the drug, but also enhances its compatibility with other technologies, e.g. incorporation of other polymer fibres to produce a patch.

Capitalising on these features, Ceramisphere has developed a user-friendly and commercially viable skin delivery system with high functionality and high efficiency.

The nanocomposite patch technology can:

1) **Extend the time of application:** Potentially over 24 hours for lidocaine patches, the skin irritation being minimised via drug encapsulation in the protective and biocompatible silica matrix.
2) **Increase the efficiency of the patch:** More than 95% drug release demonstrated in the nanocomposite lidocaine patch, which could easily be extended to controlled drugs (e.g. fentanyl). The main features include significantly lowered dose loading and close to nil residual remaining in the used patch. This can also provide an economically viable and effective solution for expensive drugs (e.g. growth factors).
3) **Enable multidrug treatments in one device:** Smart dressings with high functionalities can potentially be developed, allowing for multifaceted wound care, i.e. faster and better healing, low scarring and improved pain management. These systems are expected to have immediate application in skin grafts and for children, where there is a crucial need for pain-free wound healing solutions (e.g. for scalding and abrasions).

ABOUT THE COMPANY

Ceramisphere Health Pty Limited is a recent spin-off of Ceramisphere Pty Ltd. The company is based in Sydney, Australia, where it undertakes product development, scale-up, production and testing of its novel encapsulated materials. The company's aim is to develop innovative drug delivery solutions through structured commercial relationships with world leading healthcare and animal health companies. Ceramipshere Health is currently focusing its activities on the development of pioneering skin delivery-based smart solutions for small and large therapeutic molecules for human and veterinary health.

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ABOUT THE AUTHORS

Dr Aparajita Khatri leads the R&D programme at Ceramisphere Health Pty Ltd. She has a strong interest in multidisciplinary, consumer driven solutions and this is reflected in her work towards developing smart solutions through synergy between different disciplines of science. With a strong background in molecular biology and nanomedicine, Dr Khatri currently drives the development of Ceramisphere's technology for skin delivery of proteins/peptides, small molecule drugs and oligo-/poly-nucleotides for diverse indications in the field of animal and human healthcare.

Dr Christophe A Barbé is the Chief Executive Officer of Ceramisphere Health Pty Ltd. He has over 20 years of experience, spanning three continents, in developing and commercialising new materials and technologies for a wide range of applications. Dr Barbé had been leading innovation at Ceramisphere for the last eight years, prior to setting up Ceramisphere Health. His current focus is to commercialise Ceramisphere's proprietary encapsulation and controlled release technology for skin delivery.

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July 2018	Novel Oral Delivery Systems	Jun 7th 2018
August 2018	Industrialising Drug Delivery Systems	Jul 5th 2018
September 2018	Wearable Injectors	Aug 2nd 2018
October 2018	Prefilled Syringes & Injection Devices	Sep 6th 2018
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SIMPLIFIED DRUG AND VACCINE **DELIVERY** USING MICRON'S MICRONEEDLE PATCH

In this Early Insight article, Devin V McAllister, PhD, Vice-President, R&D; Sebastien Henry, MS, MBA, Vice-President, Program Management; and Mark Prausnitz, PhD, Chief Scientific Officer, all of Micron Biomedical, introduce the company's dissolving microneedle patch technology which has global potential, including in the developing world, across a range of vaccine and therapeutic applications.

Vaccines and biotechnology-derived drugs are generally delivered via injection because of their sensitivty to enzymatic degradation in the gut, and first-pass inactivation by the liver that can prematurely metabolise them. They can induce gastro-intestinal irritation, and they are not readily absorbed through the skin or mucosal layers, thus making oral, transdermal, and transmucosal delivery challenging.

Current injection technologies include hypodermic needles and syringes, pens, and mechanical autoinjectors. Although these can deliver therapeutics and vaccines reliably across the skin, their use presents a number of challenges. For example, injections require the intervention of a medical professional or patient training for proper use, and they rely on hardware and supplies that can be bulky. Injections can also result in poor patient compliance due to pain or discomfort, side effects, complex operation and/or interference with daily activities.

Additional challenges and drawbacks of conventional injection technologies include the fact that they typically bypass the skin, which has been shown to elicit enhanced immune responses for certain vaccines and to improve the pharmacokinetic and pharmacodynamic effects of some therapeutics compared with intramuscular and subcutaneous injections. The need for administration by injection constrains market sizes for drugs and vaccines, as a significant percentage of patients do not adhere to treatment, or avoid it altogether. Finally, injectable drugs require complex logistics including the need for refrigeration of the active and handling and disposal of sharps that can lead to needle-stick injury by medical professionals and caregivers.

> "Upon application of the patch to skin, the microneedles painlessly penetrate the skin and dissolve rapidly or, with proper formulation, over days or weeks."

Micron Biomedical has developed microneedle patch technology designed to overcome these challenges. Microneedles are micron-sized structures that encapsulate a drug or vaccine and are designed to create pathways into the skin to deliver actives into the epidermis and/or dermis by employing a simple-to-use patch applied to the skin.

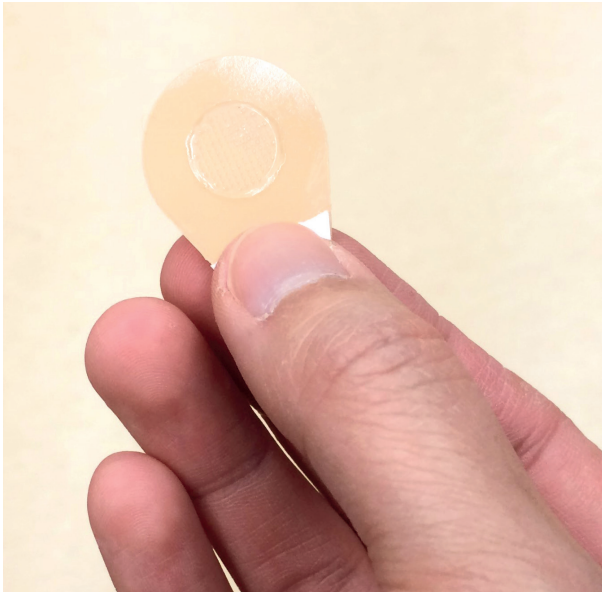

Figure 1: Micron's microneedle patch.

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Figure 2: Schematic of Micron's patch showing microneedles dissolving and releasing their active in skin.

OVERCOMING CURRENT INJECTION TECHNOLOGY DRAWBACKS

Micron's proprietary dissolving microneedle patch (Figure 1) offers a solution to the challenges of current injection technologies. Micron's patch consists of microscopic needles containing the active to be delivered along with water-soluble excipients, which can be formulated to allow for rapid or prolonged dissolution of the microneedles or sections of the microneedles. Upon application of the patch to skin, the microneedles painlessly penetrate the skin and dissolve rapidly or, with proper formulation, over days or weeks, based on the needs of the indication (Figure 2). The key features and benefits of Micron's technology are:

- **Ease of use:** Micron's patch has been designed so it is as easy to apply as a skin bandage. It is administered using the thumb and does not require an applicator. An indicator built into the patch provides the user with audible and tactile feedback indicating when enough force has been applied to enable microneedle insertion. This simple design allows both administration by minimally-trained medical personnel and self-administration by patients.
- **Painless:** The microneedles are of micron dimensions, thus they do not trigger pain, as shown in many studies.[1,2]
- **Enhanced immunogenicity or therapeutic effects via skin targeting:** The microneedles are designed to deliver their payload in the skin. As a result, dermal and epidermal dendritic cells present in the skin are recruited when a vaccine is delivered by microneedle patch, which has been shown, for certain vaccines, to result in dose sparing and enhanced immunogenicity. Moreover, the capillary bed at the epidermis/dermis interface can be targeted to take up drugs delivered by microneedle patch, which can lead to faster onset for small-molecule drugs and macromolecules compared with subcutaneous injections.[3]
- **Simplified logistics:** Micron's patch technology exhibits excellent thermal stability for many biotherapeutics and has the potential to reduce or eliminate the need for the cold chain altogether. This is because actives are incorporated into the microneedles in dry form and the microneedles are formulated with stability-enhancing excipients. Because of its small footprint, the patch is less bulky than existing injection technologies, thus making storage and transportation easier. Also, because the microneedles dissolve in skin, there is no sharps waste once the patch is removed from the skin, which simplifies disposal and essentially eliminates the risk of needlestick injury.[3]

These benefits can translate into strategic advantages for pharmaceutical companies seeking to deliver their active. Using Micron's patch, drug products may generate increased revenue, as more patients may stay on their treatment longer due to increased patient compliance, increase product margins via premium pricing, and leverage Micron's technology for product lifecycle management for actives that approach patent expiration.

Figure 3: A paperboard box containing 50 patches with 10 patches per foil pouch.

MICRON'S PATCH TECHNOLOGY IS BROADLY APPLICABLE

The Micron patch technology is flexible and can deliver a wide range of actives for diverse applications, including vaccination, systemic drug delivery or targeted local drug delivery to treat dermatological conditions. The patch is produced using scalable methods (i.e. moulding and adhesive converting processes) and the packaging leverages standard pharmaceutical packaging materials/processes (Figure 3). It is also compatible with many types of vaccine (live-attenuated, inactivated, subunit, DNA and virus-like particle vaccines) and drugs (relatively potent small molecules, peptides, proteins, and nucleic acids).

This broad compatibility stems from the flexibility of the core platform, including the types of excipients that can be incorporated into the microneedles, manufacturing conditions/processes, and patch design.

During patch design, formulation screening and optimisation are performed for each active ingredient. Excipients included in formulation development activities may include salts, sugars, water-soluble polymers and biodegradable polymers, as well as other types of molecules depending on the specific needs of active and/or product attributes. The formulation is optimised to achieve 1-2 years of shelf life, preferably at room temperature, the desired release profile (e.g. rapid release, subcutaneous injection PK profile matching, or sustained release) and mechanically robust and functional microneedles. Because many actives are sensitive to harsh processing conditions, the

manufacturing process is based on simple casting/moulding techniques that can be performed near or below room temperature with aqueous or other gentle solvent(s). This enables the incorporation of sensitive actives into the microneedles.

The microneedle design, including shape and height, and microneedle array design (i.e. the number of microneedles, microneedle-to-microneedle spacing, and array shape/layout) can all be customised by creating new moulds. These design changes can be used to achieve the desired active ingredient loading, treatment area, and/or delivery depth. For example, by increasing the number of microneedles, the amount of active contained with the patch can be increased, or by changing the microneedle height, a certain delivery depth can be targeted that may be important to treat a local dermatological condition.

INFLUENZA VACCINE PATCH CLINICAL TRIAL

The patch technology under development at Micron was studied in a Phase I clinical trial conducted by Emory University (Atlanta, GA, US) in collaboration with researchers from the Georgia Institute of Technology (Atlanta, GA, US).[1] The first-in-human trial found that influenza vaccination using microneedle patches was safe and well-tolerated by study participants, was at least as effective in generating immunity against influenza, and was strongly preferred by study participants over vaccination with a hypodermic needle and syringe. The microneedle patch was designed to enable simple self-administration, transportation and storage without refrigeration, and easy disposal after use without sharps waste.

The trial of the flu vaccine patches enrolled 100 participants aged 18-49 who were healthy and who had not received the influenza vaccine during the prior flu season. Participants were randomised into four groups: (1) vaccination with microneedle patch given by a healthcare provider; (2) vaccination with microneedle patch self-administered by study participants; (3) vaccination with intramuscular injection given by a healthcare provider; and (4) placebo microneedle patch given by a healthcare provider.

Study results showed that vaccination with the microneedle patches was safe, with no serious adverse events reported. Local skin reactions to the patches were mostly faint redness and mild itching that lasted 2-3 days. No new chronic medical illnesses or influenza-like illnesses were reported with either the patch or the injection groups. Antibody responses generated by the vaccine, as measured through haemagglutination inhibition assay of blood samples, were similar in the groups vaccinated using patches and those receiving intramuscular injection, and these immune responses were still present after six months. More than 70% of patch recipients reported they would prefer patch vaccination over injection or intranasal vaccination for future vaccinations.

No significant difference was seen between the doses of vaccine delivered by the healthcare workers and the volunteers who self-administered the patches, showing that participants were able to self-administer the patch correctly. After vaccination, imaging of the used patches found that the microneedles had dissolved in the skin, suggesting that the used patches could be safely discarded as non-sharps waste. The vaccines remained potent in the patches without refrigeration for at least two years.

GLOBAL HEALTH IMPACT OF MICRON'S PATCH GLOBAL HEALTH IMPACT OF MICRON'S PATCH

Micron is carrying out several projects to address major issues in global health. With support from the Bill and Melinda Gates Foundation (Seattle, WA, US) and in collaboration with the US Centers for Disease Control and Prevention (CDC), Micron is developing microneedle patches for both inactivated polio vaccination and measles and rubella vaccination.

While polio eradication is in sight, the eradication of wild type and vaccine-derived poliovirus requires discontinuation of live-attenuated polio vaccine (which has a small risk of genetic mutation into a virulent form) and the exclusive use of vaccination by inactivated polio vaccine that requires intramuscular injection. In the event of an outbreak, or even for routine vaccination, polio vaccination is hampered by the need for hypodermic injection requiring expert healthcare personnel who are in limited supply in developing countries. Micron is developing a microneedle patch for inactivated polio vaccination to overcome the limitations of hypodermic needles and thereby enable minimally trained personnel to administer polio vaccine, possibly in house-to-house mass campaigns, thereby vaccinating more people faster. A clinical trial of Micron's polio vaccine patch is expected in 2019.

ABOUT THE AUTHORS

Devin V McAllister, PhD, has served as Micron's Vice-President, R&D, since its inception and is a co-founder of the company. Dr McAllister has almost 20 years of experience developing medical devices and pharmaceutical dosage forms, including microneedle patch technologies. He received a BS from Rensselaer Polytechnic Institute and a PhD from the Georgia Institute of Technology, both in chemical engineering. Dr McAllister currently leads Micron's R&D activities, overseeing the development of Micron's microneedle patch technology and serving as the principal investigator on several grants and contracts.

Sebastien Henry has served as Micron's Vice-President, Program Management since its inception and is a co-founder of the company. Mr Henry has over 15 years of research, product development and project management experience in the microneedle and medical device fields. He received a BS from the University of Technology of Compiègne (France) and an MS from the Georgia Institute of Technology, both in bioengineering, as well as an MBA from the Georgia Institute of Technology. Mr Henry has eight US patents issued or pending and has worked on microneedles projects at Georgia Tech and Micron for over ten years.

Mark R Prausnitz, PhD, has served as Micron's Chief Scientific Officer since its inception and is a co-founder of the company. Dr Prausnitz is Regents' Professor of Chemical and Biomedical Engineering at the Georgia Institute of Technology. He has carried out research on drug delivery systems for more than 25 years and has co-founded five companies. Dr Prausnitz received a BS degree from Stanford University and a PhD from MIT, both in chemical engineering. He has published more than 250 research articles, almost half of which are on microneedles, and has more than 30 US patents issued or pending.

Measles still kills more than 100,000 children each year, and rubella causes more than 20,000 cases of congenital rubella syndrome, despite the existence of excellent vaccines. The Measles & Rubella Initiative seeks to eliminate measles and rubella, with a possible future goal of global eradication. Like polio vaccination, measles and rubella vaccination coverage is severely limited by the need for expert healthcare personnel to administer the vaccines by needle and syringe. Micron is therefore developing a microneedle patch for measles and rubella vaccination to increase the reach of vaccination campaigns. A clinical trial of Micron's measles and rubella vaccine patch is expected in 2019.

With support from the CDC, Micron is also developing a microneedle patch to administer inactivated rotavirus vaccine. Current rotavirus vaccines are live vaccines administered orally. However, they do not work well in many developing countries due to differences in gastro-intestinal microbiome and other factors. An inactivated vaccine given by injection can overcome the limitations of oral delivery but introduces the difficulties of needles and syringes. Therefore, Micron is developing a microneedle patch for inactivated rotavirus vaccination.

FUTURE OUTLOOK

Micron's patch technology has been designed to overcome the pain, inconvenience and inaccessibility of current injection technologies while offering a platform capable of delivering a wide range of compounds for both developed and developing countries.

The patch technology has been successfully studied in a Phase I clinical trial in influenza vaccination and is schedule to be studied in at least two more clinical trials in the near future. In addition to major support from leading public health organisations, Micron's patch development is further supported by a number of confidential partnerships with pharmaceutical companies to customise microneedle patch designs to achieve targeted outcomes.

Microneedle patches have a promising role in the future of drug delivery, and Micron is developing microneedle technology to realise that promise.

ABOUT THE COMPANY

Micron Biomedical is a clinical-stage biopharmaceutical company located in Atlanta, GA, US, that is on a rapid path to commercialise its proprietary applicator-free dissolving microneedle patch technology, designed to achieve better health outcomes through enhanced therapeutic effects, simplified logistics and improved patient compliance.

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RAPHAS

DISSOLVABLE MICRONEEDLES: APPLICATIONS AND OPPORTUNITIES

Here, Jung Dong Kim, PhD, Chief Technology Officer, and Do Hyeon Jeong, PhD, Chief Executive Officer, both of Raphas, discuss dissolvable microneedle technology and its myriad uses. The authors go on to explain the potential dissolvable microneedles offer in the medical and pharma sectors, including opportunities to serve unmet needs.

INTRODUCTION

The microneedle was originally developed as a way to deliver active ingredients painlessly into the skin. At present, many companies are trying to develop drug-loaded dissolvable polymer microneedle products for the treatment or prevention of various diseases.[1-5]

Dissolvable polymer microneedles are made by mixing active ingredients with dissolvable polymers to create a micron-sized needle shape that naturally dissolves away after skin insertion. These offer various advantages:

- First, the microneedle is a less painful way of delivering active ingredients compared with the syringe. This can potentially improve the quality of life for those who would otherwise need frequent injections.
- Second, the dissolvable microneedle is an environmentally friendly solution, leaving no dangerous or wasteful products behind, such as needles or glass, because microneedles dissolve into the skin after insertion.
- Third, cold-chain supply costs are reduced, because the solid state of the dissolvable microneedle enables greater stability during the distribution of various biopharmaceuticals without the need for refrigeration.[6-11]

Many researchers are developing techniques used in the production of dissolvable microneedles, such as micromoulding, drawing lithography, droplet-born air blowing (DAB) and centrifugal lithography.[6,12-14] Micromoulding and DAB techniques are already applied in the manufacture of commercial products, such as the skincare patch. However, pharmaceutical dissolvable microneedle products have not yet been commercialised despite more than fifteen years of research and development.[15-18]

RAPHAS' DAB TECHNOLOGY

The DAB process was developed in 2013 to reduce the time required for microneedle fabrication and to allow for gentle fabrication conditions, without the use of UV irradiation or heat. The DAB microneedle array fabrication process occurs by dispensing viscous polymer solution by symmetric air blowing. This property of DAB makes it possible to fabricate microneedles in a few minutes, without loss of activity in ingredients which are sensitive to heat or UV light.

The main advantage of this technique is its simplicity, but there are many hidden

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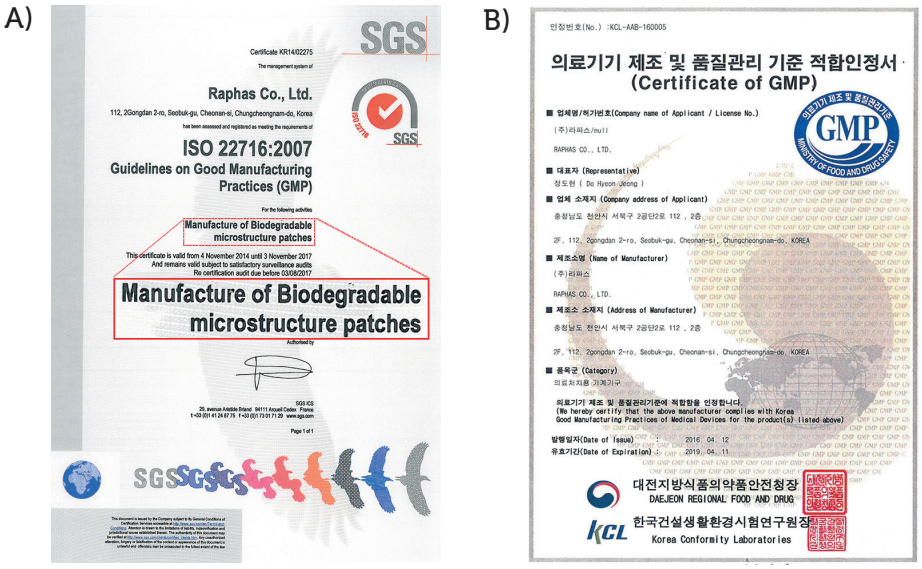

Figure 1: (A) ISO 22716 certification for GMP relating to cosmetic biodegradable microneedle patches and (B) GMP certification for Raphas' medical device.

mechanical and rheological technologies that are utilised in the successful mass production of dissolvable microneedles.[13] Additionally, DAB technology does not need to change any equipment to manufacture diverse patch patterns. Raphas has developed various microneedle patch designs using this advantage of DAB technology.

Raphas has registered a total of 24 DAB technology-related patents around the world, including in the US, Japan, China, and the EU. Raphas's DAB process has also received cosmetic GMP certifications from the ISO and medical device GMP from the Korean Ministry of Food and Drug Safety (MFDS) on microneedle patch products (Figure 1). Moreover, various Raphas products have been certified by the agencies of the EU, China, Brazil, the US and more.

SKINCARE APPLICATIONS

Raphas manufactures skincare microneedle patch products using hyaluronic acid as a matrix material. These skincare products contain various active ingredients with proven effectiveness. Raphas produces them to order from various brands in an "original development manufacturing" system. Most of these sales are for the overseas market, especially to the US and Japan. Sales of Raphas' dissolvable microneedle products totalled more than 12 million pouches (two patches per pouch) from 2013 to 2017.

Raphas continues to work closely with and support companies selling their own products with the selection of active ingredients, product design, testing and other new product development. In order to better serve as a manufacturer, Raphas launched its own brand, Acropass, to prove the efficacy and improve the quality of new products.

In addition, these products are very safe for the skin because they do not contain any preservatives. There were no significant side-effects after using Raphas' skincare products; this was tested by 25 clinical studies performed according to the good clinical practice guidelines of the Korean MFDS. Also, there were no significant side-effects reported from consumers after using Raphas products.

Wrinkle Treatment

Facial wrinkles are representative of skin ageing caused by reduction of skin elasticity and degradation of the extracellular matrix (ECM). Raphas has commercialised various wrinkle treatment microneedle patch products with a plethora of cosmetic companies. The matrix material of this microneedle is hyaluronic acid, which has been used as moisturising and filling agent for many cosmetic products. This hyaluronic acid based microneedle has wrinkle treatment efficacy by itself. Additionally, this product could be combined with a cream or essence type product for better wrinkle treatment efficacy.[19,20]

Epidermal growth factor (EGF) loaded microneedles showed significant wrinkle treatment efficacy after applying every day for 10 days (Figure 2a). This product

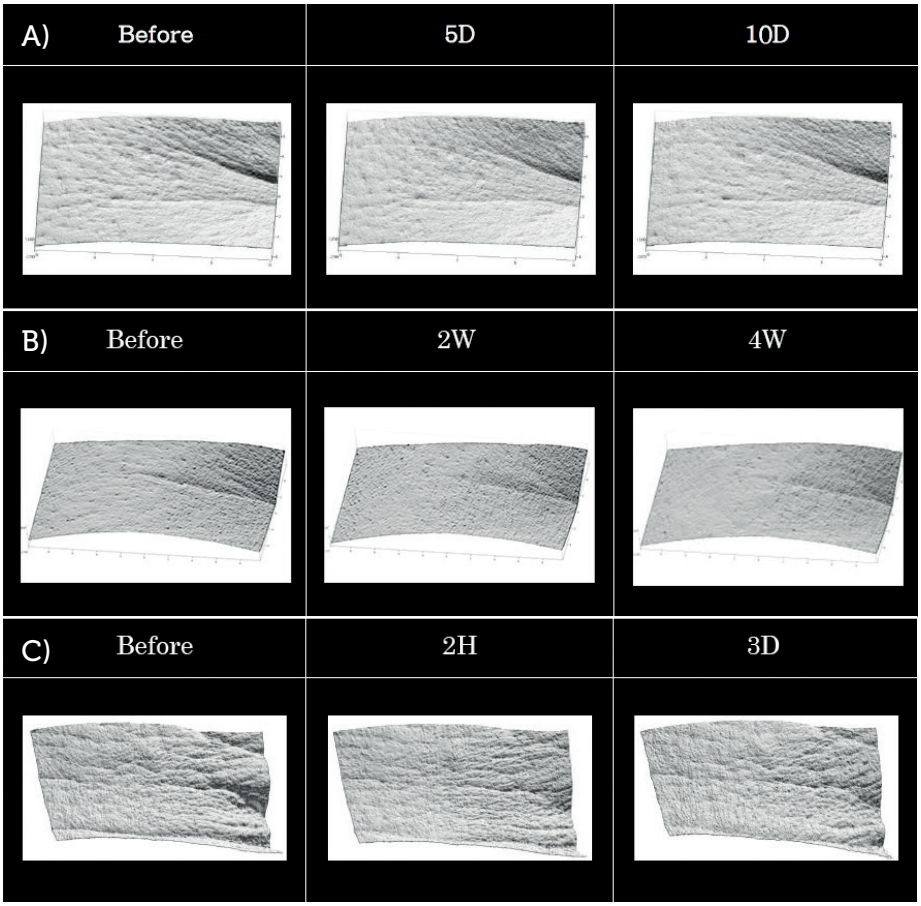

Figure 2: Clinical trial results for wrinkle care efficacy of EGF loaded microneedle patch, with (A) once daily application for 10 days and (B) twice weekly application for 4 weeks. (C) Clinical efficacy of new wrinkle care product after 2 hours of application.

also showed significant wrinkle treatment efficacy after applying twice a week for four weeks (Figure 2c).[21]

Recently, a new wrinkle care product has been prepared and finished clinical trials. This new product is composed of three major active ingredients. One of the major ingredients is acetyl octapeptide-3 which targets the inhibition of wrinkle formation and is very similar to botulinum toxin in terms of immediate efficacy. The other two ingredients, providing the long-term efficacy, are ascorbyl glucoside and sodium cyclic lysophosphatidic acid, which encourages the skin's natural rejuvenation process.

Figure 2c shows a clinical result which indicates wrinkle improvement efficacy after two hours of application; the peak of observed eye wrinkle was significantly decreased after 2 hours of using the product. These results indicate that this new product has fast-onset efficacy for wrinkle treatment.

Trouble Cure

Trouble Cure is a product for restoring acne affected skin quickly without leaving scars (Figure 3a). This product can help people manage acne efficiently and hygienically. The microneedle contains antimicrobial and anti-inflammatory ingredients within the hyaluronic acid backbone structure. The length of the microstructure is around 500 µm so that the active ingredient can be directly transferred to the hair follicle region where the bacterium causes the acne.

After application, an anti-inflammatory ingredient is delivered into the skin to suppress the inflammation of the acne, and an added antimicrobial ingredient helps to inhibit the activity of inflammation-causing bacteria. The antimicrobial ingredient is a peptide that is effective against antibiotic-resistant strains.

In general, the antimicrobial peptide is inactive at physiological salt concentrations and is rapidly degraded by proteolytic enzymes present in serum and the digestive tract.[22,23] Therefore, it is difficult to show efficacy at target area when used as ointment or cream formulation. However, Trouble Cure can deliver the antimicrobial peptide directly into the target region via the microneedle patch without loss of activity.

Clinical trial results showed that more than 90% of subjects had improved skin condition after four days from the first application of the product, which proved to be safe, without adverse skin reactions during the test (Figure 3b). In addition, this product is designed to be used hygienically with alcohol swabs and individual packaging to prevent secondary contamination occurring whilst managing the acne.

Figure 3: (A) Trouble Cure product. (B) Clinical efficacy of Trouble Cure for acne treatment. Red circle shows the Trouble Cure-treated area.

Spot Eraser

Skin whitening and brightening products are used for various hyperpigmentory disorders. Skin whitening ingredients usually act as tyrosinase inhibition to block the synthesis of melanin from melanocyte.[24,25]

Raphas has developed a novel concept for a topical whitening product by the name of Spot Eraser (Figure 4a). This product can treat topical hyperpigmented spots by inhibiting the multi-pathway of hyperpigmentation using tranexamic acid, niacinamide, ascorbic acid and arbutin. Tranexamic acid can inhibit melanogenesis

Figure 4: (A) Spot Eraser product. (B) Clinical efficacy of Spot Eraser on the post-inflammatory hyperpigmentation two weeks on from the end of four weeks of application once every other day. Blue circle shows the Spot Eraser-treated area.

> "The efficacy of topical steroids could be enhanced via a microneedle patch by physically penetrating the thickened skin."

through the activation of autophagy in a melanoma cell line. Niacinamide reduces cutaneous pigmentation by inhibiting melanosome transfer. Ascorbic acid is a strong antioxidant that can inhibit melanin oxidation to keep the melanin in a relatively brighter colour form. Arbutin is a glycosylated hydroquinone which can inhibit tyrosinase activity.

Clinical results for Spot Eraser showed significant efficacy in terms of post-inflammatory hyperpigmentation after a single application every two days for four weeks, and observing for an additional two weeks without further applications (Figure 4b). Clinical results also showed a significant decrease in melasma area and severity index (MASI). These results indicate the Spot Eraser could be a good solution for the topical treatment of hyperpigmentation.

MEDICAL DEVICE APPLICATIONS

Drug Absorption Enhancer

Therapass is a dissolvable microneedle product composed of hyaluronic acid (Figure 5a). This product does not contain any active ingredients. It enhances skin absorption of ointment, such as topical steroids, when applied to the skin after ointment application (Figure 5b).

Although topical steroids have been used as a general treatment for a variety of skin diseases, some patients, such as *prurigo nodularis* patients, do not sufficiently respond to the strong steroids, possibly due to the thickened skin leading to a low drug penetration rate. However, the efficacy of topical steroids could be enhanced via a microneedle patch by physically penetrating the thickened skin. Dermatologists have performed clinical trials using this product for two kinds of skin diseases, psoriasis and *prurigo nodularis*.

Prurigo nodularis is a skin disease characterised by itchy nodules which are distributed in symmetric and bilateral manner.[26] Patients often scratch these nodules and it causes permanent changes to the skin, including hyperkeratosis, hyperpigmentation and skin thickening. A topical steroid, with moderate to high potency, is the standard therapeutic agent, and it is the most widely practiced treatment method. However, the efficacy of topical steroids can be dependent upon the thickness of the lesion. Microneedle based therapy can help to overcome this problem. In the clinical study, microneedle-assisted delivery showed significantly enhanced efficacy of the topical steroid, decreasing the area and height of nodules ($p < 0.05$) compared with topical steroid alone.

Figure 5: (A) Therapass: Dissolvable microneedle based medical device. (B) Mechanism of Therapass as an enhancer of ointment absorption.

> "Dissolvable microneedle based pharmaceutical products are yet to be commercialised. However, many dissolvable microneedle companies, including Raphas, are developing various pharmaceutical products for various diseases."

Psoriasis is a chronic, inflammatory skin disease, which decreases quality of life, and affects roughly 2-4% of the population.[27] There is no cure for psoriasis, however, treatments such as topical steroids can help control the symptoms. In a clinical study in psoriasis patients, the median decrease of modified Psoriasis Area Severity Index (mPASI; range 0 to 12), which is a sum of scores for plaque thickness, scaliness and redness, was 60% after one week's application of the microneedle patch.[28] This result shows that use of the microneedle patch significantly enhances the therapeutic effects of topical steroids and shows fast onset for the topical psoriasis treatment compared with conventional application of topical steroids on the region ($p < 0.001$).

Diagnosis

The microneedle can be used in diagnostics as a minimally invasive patient monitoring tool. Previous studies have focused on hollow microneedle based blood or interstitial fluid extraction for glucose sensing or disease marker diagnosis.[29-32] However, hydrogel microneedle-based *in vivo* diagnosis showed the possibility for a user friendly and comfortable disposable microneedle patch sensor.[33,34] Although research has shown the potential for a microneedle-based diagnostic application, no such product has yet been commercialised.

Raphas has begun researching disposable microneedle patch sensors using DAB technology with other partners, looking to overcome the obstacles to commercialisation, including manufacturing cost and sensitivity.

PHARMACEUTICAL APPLICATIONS

Dissolvable microneedle based pharmaceutical products are yet to be commercialised. However, many dissolvable microneedle companies, including Raphas, are developing various pharmaceutical products for various diseases. Raphas is currently developing products for Alzheimer's disease, osteoporosis, immunotherapy and others.

Alzheimer's Disease

Alzheimer's disease is a chronic neurodegenerative disease which causes difficulty in remembering recent events. Donepezil tablets are a widely used oral administration for Alzheimer's disease, and clinical studies have shown modest benefits in cognition and/or behaviour.[35]

However, there is an unmet need for a new administration route of donepezil because of adverse effects in the gastrointestinal (GI) tract and patients with dysphagia.[36] Raphas and its partners have been co-developing a donepezil-loaded microneedle patch to overcome the problems inherent to the current dosage form. An IND application will be submitted to the Korean MFDS for the clinical study of this product during the first half of this year.

Osteoporosis

Many elderly people suffer from osteoporosis, a disease which causes chronic bone weakness. Parathyroid hormone injection is the only US FDA approved bone building medication for the treatment of advanced osteoporosis, requiring a once daily injection, which can adversely affect quality of life. Therefore, various companies such as Zosano Pharma, Corium and 3M are developing parathyroid hormone-loaded microneedles. Raphas has been developing this formulation with the support of the Korean government for the past two years, and an IND application will be submitted this June.

Immunotherapy

Allergen-specific immunotherapy (SIT) is an effective treatment for allergy-related symptoms, such as atopic dermatitis (AD). However, frequent clinical visits over a three-year period, as well as looming adverse events, tend to discourage patient compliance.

Raphas has been developing a house dust mite (HDM) allergen-loaded microneedle patch for HDM-SIT of AD, and this microneedle patch showed a similar efficacy to a ten times higher dosage delivered via subcutaneous injection.[37]

RAPHAS' FUTURE PLANS

Raphas plans to expand its business area beyond the cosmetic market to include medical devices and pharmaceuticals. Recently, Raphas started research into vaccine-loaded microneedle patch development with a multinational vaccine company and constructed a new building to setup GMP facilities for clinical studies. Additionally, Raphas is continuing to develop various medical products, such as a dementia treatment patch, hormonal therapy patch, and immunotherapy patch, using DAB technology.

The foundation of Raphas is closely connected with the aspirations of professional researchers into drug delivery systems. Raphas believes that this remarkable method for enjoying "a healthier life, without pain" is the future of drug delivery systems. Raphas will open up the road to this treatment for everyone in the world.

ABOUT THE COMPANY

Raphas started as a microneedle business from 2009 and its DAB technology has since drawn worldwide attention. The corporate name, Raphas is a compound of two words: Rapha, which means "heal", and Path. This represents the objective of Raphas to become a path towards healing for all of humankind. Raphas is continuously conducting innovative research towards the evolution of various technologies and products.

ABOUT THE AUTHORS

Dr Jung Dong Kim holds BS and PhD degrees in biotechnology from Yonsei University (Seoul, South Korea). Dr Kim joined Raphas in 2010 for the industrialisation of microneedles using droplet-born air blowing technology. He was a co-operative researcher with the Institute of Industrial Science, University of Tokyo, from 2014 to 2017. He was also on the steering committee of the 2016 International Conference on Microneedles. He received the IR52 Jang Young Sil Award twice from the Minister of Science, ICT and Future Planning in 2016 and Minister of Science and ICT in 2017. His research is focused on the commercialisation of dissolvable microneedle technology in the cosmetic and medical markets.

Dr Do Hyeon Jeong received a Master of Engineering degree from Yonsei University in 1993. In 2004, Dr Jeong received his PhD in Biotechnology from Yonsei University. Since 2009 he has worked as CEO and Co-Founder of Raphas. He also worked as a professor at Osan University in South Korea. He has been a member of the steering committee of the International Conference on Microneedles from 2017. He received a prize from the President of South Korea at the end of 2017 for his achievements in the commercialisation of dissolvable microneedles.

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nemaura pharma

TERIPARATIDE MICRO-PATCH™: A SOLID MICRONEEDLE PRODUCT NEARING CLINICAL TRIALS

In this article, Faz Chowdhury, PhD, Chief Executive Officer, Nemaura Pharma, details a Micro-Patch™ solid formulation of the parathyroid hormone analogue, teriparatide, for the treatment of osteoporosis. Teriparatide Micro-Patch™ is the company's first microneedle product selected to advance to clinical development, due to begin this year.

With estimates of the cost of developing and launching a new drug ranging up to US$2.6 billion (£1.9 billion), and the process taking ten years in many instances, there are clear clinical and commercial advantages in successfully developing a truly superior formulation of an existing drug, where the costs are far lower and the time to market can be four years or less.

Delivery via the skin is increasingly viewed both by patients and physicians as an attractive method of choice and, as such, the skin drug delivery market is growing rapidly, being expected to reach $40 billion this year.

Microneedle patches represent a particularly attractive class of skin drug delivery system. They can reduce or even eliminate many of the challenges and disadvantages of self-administration by needle and syringe, the route by which most biologics currently have to be administered. Such challenges – including that self-injection can be difficult, often requires training and is perceived as unpleasant and painful – reduce compliance. Microneedles represent a safer, easier-to-use, non-invasive and more convenient format.

However, many existing microneedle patches have their own drawbacks, including: slow delivery requiring the patient to wear the patch for up to 30 minutes; incomplete and variable dose delivery; and local skin irritation. These can all be problematic when it comes to market approval.

In contrast, Nemaura's microneedle patch, Micro-Patch™ (Figure 1), overcomes these barriers, delivering the complete dose two seconds after application, painlessly and with a single needle. Additionally, liquid formulations of biotherapeutic products for injection often have stability issues at room temperature, meaning that they need to be refrigerated during shipping and storage. Micro-Patch™ comprises a solid dose which is stable at room temperature and does not require refrigeration.

A UK-funded proof-of-concept for the technology (Reference: 710437) has been successfully completed with a solid dose vaccine, demonstrating efficacy compared with a liquid vaccine. Now Nemaura is taking its first product, a hormone analogue for the treatment of osteoporosis, forward.

> "Having selected teriparatide Micro-Patch™ for further development and secured £5 million in private investment in 2017, Nemaura is advancing the product, with clinical trials planned for this year."

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Figure 1: Micro-Patch™ delivers a complete solid dose of teriparatide two seconds after application, painlessly.

TERIPARATIDE: ADVANCING THE FIRST PRODUCT CANDIDATE

Nemaura Pharma has developed a Micro-Patch™ solid-dose teriparatide microneedle product, to prevent fractures in vulnerable elderly osteoporosis patients. Having selected teriparatide Micro-Patch™ for further development and secured £5 million in private investment in 2017, Nemaura is advancing the product, with clinical trials planned for this year.

Osteoporosis is a disabling and painful condition where bone strength is lost. It affects men and women over 50 and there are approximately 75 million people suffering from the condition in Europe (>3 million sufferers in the UK alone), US and Japan. It affects over 200 million women worldwide.

First-line treatments for osteoporosis are bisphosphonates such as Merck & Co's Fosamax® (alendronate sodium). These first-line treatments do not reverse bone loss, only prevent it and thus do not pose direct competition to teriparatide products. They are also associated with significant adverse effects including gastro-intestinal side-effects.

Exogenous teriparatide, a parathyroid hormone analogue, is the only anabolic (stimulating bone formation) available for the prevention of fracture or further fractures in postmenopausal women and men at high risk of fractures. Eli-Lilly's Forteo®, for example, is a liquid formulation presented in a syringe pen. The patient must self-inject each day, dispose of the needle and keep the medication at 2-8 °C to avoid loss of potency.

The logistical issues of this route and injection-site pain lead many to discontinue medication, and consequently suffer further fractures, resulting in hospitalisation, significant secondary health issues, and loss of mobility and independence. A US report indicated that at 12 months 67% of patients discontinued treatment. The consequences of another fracture can be devastating.

Despite its drawbacks, subcutaneously injected teriparatide is a clinically established treatment and Forteo® is expected to generate revenues of $5.2 billion in major markets by 2021, according to Roots Analysis. Thus, a substantial market opportunity and unmet clinical need exists for a simpler, more accessible teriparatide product. There is considerable interest in avoiding the problems associated with the subcutaneous route by seeking an alternative delivery mechanism.

The delivery of teriparatide using microneedle patches is being pursued by several biotech companies. None are yet marketed and, with the exception of teriparatide Micro-Patch™, all those in development are multi-needle (>50) arrays, which face the significant hurdles mentioned previously (longer delivery times, dose variability, incomplete dosing and local skin irritation).

MICRO-PATCH™ ADVANTAGES

Micro-Patch™ does not suffer from these disadvantages. Its patient-centric design, with simple "press on, peel off and dispose" user steps, delivers the complete dose, quickly and painlessly (Figure 2). Teriparatide Micro-Patch™ comprises solid hormone coated onto a single microneedle, and is designed to be stable at ambient temperature. Thus, it negates the need for needle-based self-injections. Patient benefits include greater safety and independence, and a reduction in fractures through improved compliance.

It also avoids the costs, inconvenience and risks posed by keeping an unstable liquid formulation of teriparatide refrigerated for a month. According to data analysed by Pharmaceutical Commerce for its annual Sourcebook, cold-chain logistics spending in 2017 was expected to be more than $13 billion worldwide, in an $80 billion overall pharma logistics market. By 2021, cold-chain biopharma logistics spending will expand to more than $16 billion. Conventional liquid formulations of biologics such as teriparatide, and vaccines, carry stability

"The delivery of teriparatide using microneedle patches is being pursued by several biotech companies. None are yet marketed and, with the exception of teriparatide Micro-Patch™, all those in development are multi-needle (>50) arrays, which face significant hurdles."

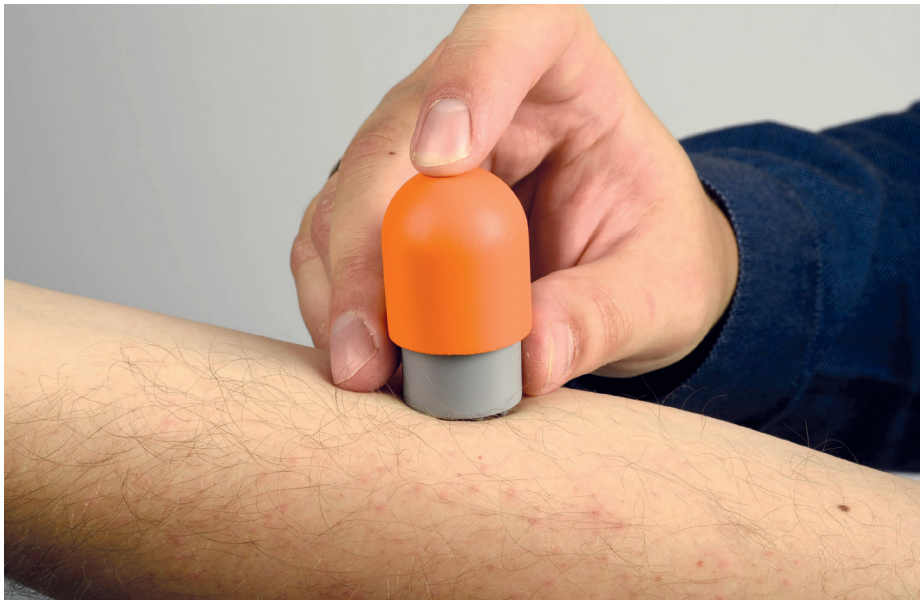

Figure 2: The patient-centric Micro-Patch™ enables self-administration via three simple user steps: "press on, peel off and dispose".

risks, especially if they aren't stored at the correct temperature. In addition to being costly, this is potentially dangerous. In solid-form, the drug can remain stable for several months without loss of potency.

The innovation in Nemaura's product lies in the development of an aseptic process for formulating the solid dose – teriparatide 20 µg – and mounting it on a single needle patch to form a shaped dose which remains in the skin when the patch is pressed on and removed. This is the Micro-Patch™ platform and, in addition to teriparatide, it is suitable for the delivery of other solid formulated biomolecules, vaccines, and low-molecular-weight drugs.

Micro-Patch™ is designed to transform the way vaccines and biologics are administered through the skin in a single-use, disposable, user-friendly device format costing just £0.10-£0.20 per unit. A releasable drug coating/sleeve of solid drug dose is applied around 1-5 stainless steel microneedles, which deposit the entire dose through the skin immediately, as shown in Figure 3.

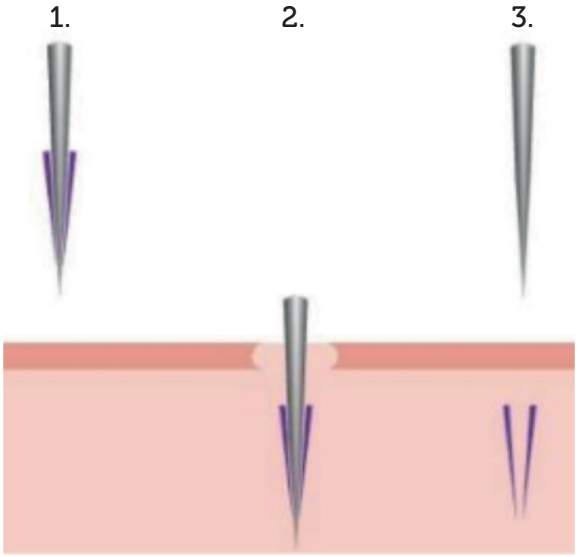

Figure 3: A releasable drug coating/sleeve of solid drug dose is applied around 1-5 stainless steel microneedles, which deposit the entire dose through the skin after which the device retracts the needle.

"The dose volume administered is a fraction of the equivalent liquid dose, reducing the cost, enhancing stability in the solid form, improving control over drug release and absorption, and reducing pain whilst enabling safe self-administration."

"The innovation in Nemaura's product lies in the development of an aseptic process for formulating the solid dose – teriparatide 20 µg – and mounting it on a single needle patch to form a shaped dose which remains in the skin when the patch is pressed on and removed."

The dose volume administered is a fraction of the equivalent liquid dose, reducing the cost, enhancing stability in the solid form, improving control over drug release and absorption, and reducing pain whilst enabling safe self-administration. The device fully and immediately retracts the microneedles so needle-stick injury is impossible, and the device is disposed of. Disposal costs are low.

Micro-Patch™ is protected through multiple global granted and pending patents (e.g. EP3052087) meaning Nemaura can confidently claim freedom to operate in the area.

SUMMARY

Nemaura Pharma is developing a microneedle teriparatide product for the treatment of osteoporosis, using its Micro-Patch™ platform, comprising a solid dose, less than 1 mm in size. Both stability at room temperature, and mechanical properties that allow the drug to be inserted into the skin as a solid dose, have been demonstrated.

Teriparatide Micro-Patch™ is clearly differentiated, in terms of patient convenience, cost and other factors, from both the existing teriparatide product on the market, which is injected subcutaneously, and also overcomes the challenges faced by other microneedle versions of the drug in development.

The global market for this product is very large and the commercial opportunity substantial. Teriparatide Micro-Patch™ is expected to enter clinical trials later this year and dossiers will be submitted next year.

ABOUT THE COMPANY

Nemaura Pharma has spent several years working with private investors to transform the way drugs are delivered through the skin. The company has made significant progress in the reformulation of traditionally injected liquid biotherapeutics using its solid dose delivery system, Micro-Patch™, for delivery through the skin. The device works by depositing the drug under the outer layer of the skin using a metal needle which then retracts completely, minimising the risk of needle-stick injuries.

Nemaura's specialism is drug delivery through the skin and the company has completed or is completing programmes involving a large number of product formats including:

- Topical gels: developed ibuprofen and diclofenac sustained-release gels
- Transdermal patches: developed patches for Alzheimer's and Parkinson's diseases
- Simple injectable drugs for subcutaneous, intradermal and intramuscular delivery using liquid micro-injectors: successfully developed insulin aspartate and insulin Glargine formulations
- Complex injectables: successfully developed risperidone and octreotide formulations

Nemaura now has patents secured or pending across multiple patent families, is ISO9001 and ISO13485 accredited, and has an in-house cleanroom for cGMP manufacture of investigational medicinal products, under aseptic conditions. It has a controlled drugs licence from the UK Home Office, and also holds an IMP licence for the manufacture of sterile solid injectable doses, sterile liquid injectables, transdermal patches and topical gels.

It has partnered with commercial manufacturers with state-of-the-art facilities for transdermal patch manufacture. Nemaura additionally has an in-house design and prototyping facility for medical devices, using medical grade materials.

nemaura
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Enhanced delivery of almost any drug, old or new, through the skin

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AN INTRADERMAL PLATFORM BUILT FOR INDUSTRY AND PATIENTS

In this article, Moe Wehbe, PhD, Drug Delivery Strategist, Iman Mansoor, PhD, Co-Founder and Vice-President of Engineering, and Sahan Ranamukha, PhD, Co-Founder and Vice-President of R&D, all of Microdermics, discuss the potential of intradermal injection for modern medicines and its advantages over the subcutaneous route. The authors go on to discuss the design considerations for a novel intradermal device and introduce Microdermics' intradermal platform.

WHY INTRADERMAL? WHY NOW?

Intradermal (ID) injections have long been known to possess efficacy and drug bioavailability advantages over their subcutaneous (SC) and intramuscular (IM) counterparts. ID injections are less invasive and enable access to the dermal skin layer, which is rich in antigen-presenting cells that are ideal for vaccination.[1] Yet, to date, there are few vaccines or drug products approved for ID use. In fact, the skin is rarely used as a drug delivery route, typically only used for topical administration for local treatment. This begs the question – why aren't ID injections being used to deliver drugs?

"As medicine advances and products shift from small molecules to large biologics, the ability to administer drugs easily and reliably must improve."

The current approved method for ID injection is known as the Mantoux technique, developed by Charles Mantoux in the early 20th century. The Mantoux technique entails a needle being inserted into the skin at a 10-15° angle, approximately 1 mm deep.[2] If performed correctly, a bleb is formed, showing the distribution of the liquid beneath the skin, which disappears minutes after. Whilst this technique has been vital in the understanding and evaluation of intradermal therapeutics, it is difficult to master and limits the use to healthcare professionals.[3] The difficulty of the Mantoux method limits ID delivery to the hospital setting, deterring its adoption as a common method of drug administration.

"There are four distinct types of microneedle designs that have been created – solid, coated, dissolvable and hollow – of which hollow microneedles have highest applicability for a wide range of drugs, since liquid drug formulations can pass through them."

As medicine advances and products shift from small molecules to large biologics, the ability to administer drugs easily and reliably must improve. Many biologics are given to patients to self-administer at home, typically by SC injection. While this method has been successful, a high burden on patients' lifestyles and needle-phobia (the extreme fear of injections) has led to challenges with patient compliance, resulting in discontinuation of therapy and increased costs. These costs and hurdles are compounded by the poor bioavailability of biologics when administered orally or by SC injection.[4] Low bioavailability requires higher doses in order to reach therapeutic plasma concentrations and, due to the high cost of these biologics, this leads to increased costs for patients and healthcare systems. Thus, the ideal medical device would allow for simple, reproducible injections or infusions of the drug into the skin with minimal or no burden on a patient's lifestyle.

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MICRONEEDLES ARE IDEAL FOR REPRODUCIBLE INTRADERMAL INJECTIONS

The concept and development of microneedles has been discussed in scientific literature for more than 25 years. There are four distinct types of microneedle design – solid, coated, dissolvable and hollow – of which hollow microneedles have highest applicability for a wide range of drugs, since liquid drug formulations can pass through them.[5] Solid microneedles are typically used to pierce the skin, allowing for improved penetration of topical drug formulations. Meanwhile, coated and dissolvable microneedles cater to an implantable design, where the drug coating gradually and passively dissolves into the skin. Hollow microneedles are the most comparable to traditional hypodermic needles as they can directly replace traditional needles in delivering a liquid formulation into the skin.

Microdermics' intradermal platform consists of a novel hollow metallic microneedle technology that has addressed many of the challenges previously limiting intradermal product design. The developed microneedle projections can easily and precisely access the dermis and inject drugs reproducibly, eliminating the large variability seen with other intradermal injection approaches.

Herein lies an opportunity to improve the safety, effectiveness, patient care and compliance around injectable formulations. While SC injections have facilitated the use of many new therapeutics, especially in home-use settings, they entail a number of drawbacks:

- Bruising at the site of injection is a common problem, especially for treatments that require repeat injections, such as *in vitro* fertility treatment.[6]
- Needle-phobia can hinder compliance, especially when the product is intended for home use.
- Extensive training is needed before patients are comfortable in administering their own drugs at home with needle-based injection systems.
- Needlestick injuries are a commonly reported incident in the hospital setting, with associated healthcare costs.[7]

As a result, extensive efforts have been made by drug delivery device designers to make devices more approachable and acceptable to patients. Various tactics have been employed, such as hiding the needle, improving usability, minimising the time required of users and installing needlestick prevention features.

> "The ability to produce drugs and medical devices at relevant quantities for patient use is a fundamental, and sometimes overlooked, requirement in the pharmaceutical industry."

Hollow microneedles can solve many of these challenges through minimally invasive dermal injections. The microneedles themselves are small projections that do not look like traditional needles. These projections only need to pierce the dermis and are often painless, making them an ideal alternative to all methods of injection using needles, catheters, infusion sets and other types of invasive injector.

With the many advantages of ID injections using hollow microneedles, the question remains – why have they not been adopted clinically? Although there is a plethora of preclinical data suggesting the advantages of hollow microneedles, the remaining barriers are largely engineering challenges rather than pharmaceutical ones. An approved medical device must be simple, manufacturable and reproducible. While many designs exist, few meet all the requirements necessary for adoption. A major hurdle is being able to fabricate large quantities of microneedles via a scaleable process able to provide for widespread adoption.

Microdermics' Adoptable Microneedle Platform

The ability to produce drugs and medical devices at relevant quantities for patient use is a fundamental, and sometimes overlooked, requirement in the pharmaceutical industry. Patients and healthcare providers expect that their treatment will not be hindered by a scarcity of life-saving medicines.

> "All Microdermics' systems are simple to use, with no requirement for complicated or intensive training, unlike the Mantoux technique or any needle-based system."

In its early stages, Microdermics focused on the development of a simple medical device that could be scaled, eventually patenting a manufacturing process that allows for a novel, scalable microneedle systems. Microdermics has developed a back-end technology to compliment the hollow metallic microneedles during ID delivery based on the company's extensive expertise on skin mechanics. As such, the company's ID systems accommodate the expansion of the skin during fluid injection, ensuring the entire dose is successfully delivered to the dermis with minimal waste, equivalent to or less than a subcutaneous hypodermic needle injection.

Microdermics has developed a number of microneedle systems capable of reproducible injections. All Microdermics' systems are simple to use, with no requirement for complicated or intensive training, unlike the Mantoux technique or any needle-based system. They are capable of delivering volumes ranging from 20 µL to greater than 5 mL, and viscosities ranging from 1-100 cP. A standard 0.1 mL dose of a low viscosity fluid (approx 1 cP), as is typical for vaccines and insulin, can be delivered into the dermis in one second, while a 1 mL dose (approx 1 cP) can be delivered in 4-10 seconds. Volumes greater than 1 mL can be delivered with virtually no pain to the patient at rates as low as 1-5 µL per second.

One of the early products is an easy-to-use adapter system that can be attached to any commonly-used syringe system and discarded after a single use (Figure 1A). The second product uses a pen design with prefilled cartridges containing the drug of interest for repeat use (Figure 1B). Both approaches have unique niches in the translation of therapeutics from other forms of injectables to ID injections for different patient populations. In fact, these systems have been used in preclinical and clinical studies and met with success. Other systems developed by Microdermics focus on wearable devices capable of drug delivery over extended periods, targeting patients where a lowered burden of self-administration is particularly important for users.

PRECLINICAL & CLINICAL STUDIES

ID drug delivery has been shown to improve the efficacy of vaccines and the bioavailability of many biologic and small molecule therapeutics. Microdermics recently completed preclinical studies assessing how its novel microneedle adapter systems compare with SC injection of epinephrine and Fiasp® insulin aspart (Novo Nordisk) in terms of pharmacokinetic profile and therapeutic efficacy. While others have examined the application of insulin via ID injection with success, Microdermics is the first to test Fiasp® – the world's fastest acting insulin formulation. These studies show clear improvements in Fiasp® absorption (fast on, fast off) when it is injected intradermally via microneedles, compared with traditional SC injection. Although these studies tested the effects only upon a single injection, the animals showed no post-injection signs of bruising or other dermal trauma. While the molecules described are small-molecular-weight drugs, Microdermics has assessed the absorption rate of large-molecular-weight antibodies upon dermal and SC injection. Preliminary results show improvements in drug absorption upon ID injection via microneedles. Identifying an improved, safer means of injection is important due to the increasing availability of antibody and large protein therapeutics; these compounds are expensive, thus greater bioavailability could save in healthcare costs.

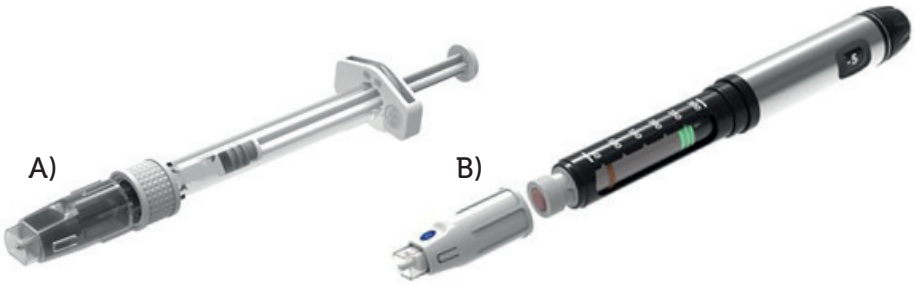

Figure 1: Microdermics intradermal drug delivery platform has been integrated as (A) syringe adapter and (B) microneedle pen designs.

Microdermics has recently completed its first-in-human clinical study assessing the safety and efficacy of microneedle injections using a syringe adapter system. The results suggest that this adapter system can be easily integrated with modern healthcare practices. While the aim remains to create a medical device suitable for at-home use, the success of the study suggests the engineering of the medical device is user-friendly for healthcare professionals as well. To date, only saline has been injected into humans using this device and further work is being performed on a variety of pharmaceutical formulations and commonly-used excipients to examine possible adverse effects at the preclinical level. It is expected that ID injections via hollow microneedles will allow for an improved patient experience, with less bruising and tenderness compared with SC injections.

CONCLUSION & FUTURE WORK

This article has outlined current successes of the Microdermics platform for ID injections via hollow microneedles. As medicine evolves, the devices used to deliver that medicine must also evolve. Whilst SC injection has allowed for the administration of many novel therapeutics, ID injection

ABOUT THE AUTHORS

Dr Moe Wehbe is a Drug Delivery Strategist at Microdermics. He specialises in preclinical drug development and has been involved in the evaluation of microneedles for vaccine, anti-cancer and anti-inflammatory indications. He earned his PhD in Pharmaceutical Sciences at the University of British Columbia under Dr Marcel Bally and Dr Helen Burt. Dr Wehbe's research interests are in nanotechnology, pharmacokinetics and medical device development.

Dr Iman Mansoor is a Co-Founder and Vice-President of Engineering for Microdermics. He has been involved in research and development of microneedles for more than ten years. He received his PhD in Electrical Engineering in 2014 from the University of British Columbia. Dr Mansoor's research interest is the application of Micro-Electromechanical Systems (MEMS) to life sciences. He currently holds several patents on various MEMS-based drug delivery systems.

Dr Sahan Ranamukha is a Co-Founder and Vice-President of Research and Development for Microdermics. He has been involved in development and testing microneedle-based drug delivery technologies for more than five years. He earned his PhD in Biomedical Engineering at UBC under Dr Stoeber, and was a recipient of the Vanier Canada Graduate Scholarship. Dr Ranamukha's research interests are in drug delivery, medical device development, and therapeutic drug monitoring.

can address many of its disadvantages and unlock benefits that may not have been thought to be possible. Microdermics is planning on assessing the capability of the hollow microneedles to improve immunisation upon vaccination and delivery of anti-cancer compounds. Additionally, microneedles are being tested in the delivery of nanoparticle formulations for local controlled-release delivery of therapeutics.

These innovative research projects will provide a rationale for considering microneedles in the development of investigational new drugs, potentially aiding in their success through improved safety, efficacy and drug bioavailability. Microdermics' goal is to develop a simple medical device to move ID injections into a clinically relevant route of administration for both small molecules and biologics, so as to truly unlock the potential of the skin in drug delivery.

ABOUT THE COMPANY

Microdermics Inc is a Vancouver (Canada)-based medical device company, built on research at the University of British Columbia, that works with pharmaceutical companies to unlock the biomedical potential of the skin. Through an innovative manufacturing process, its intradermal platform provides easy and precise access to skin for breakthrough applications in drug delivery. Broad formulation capabilities, together with a customisable injection system, enables product lifecycle extensions, innovative applications or the accommodation of specific patient needs, including safe and simple self-administration.

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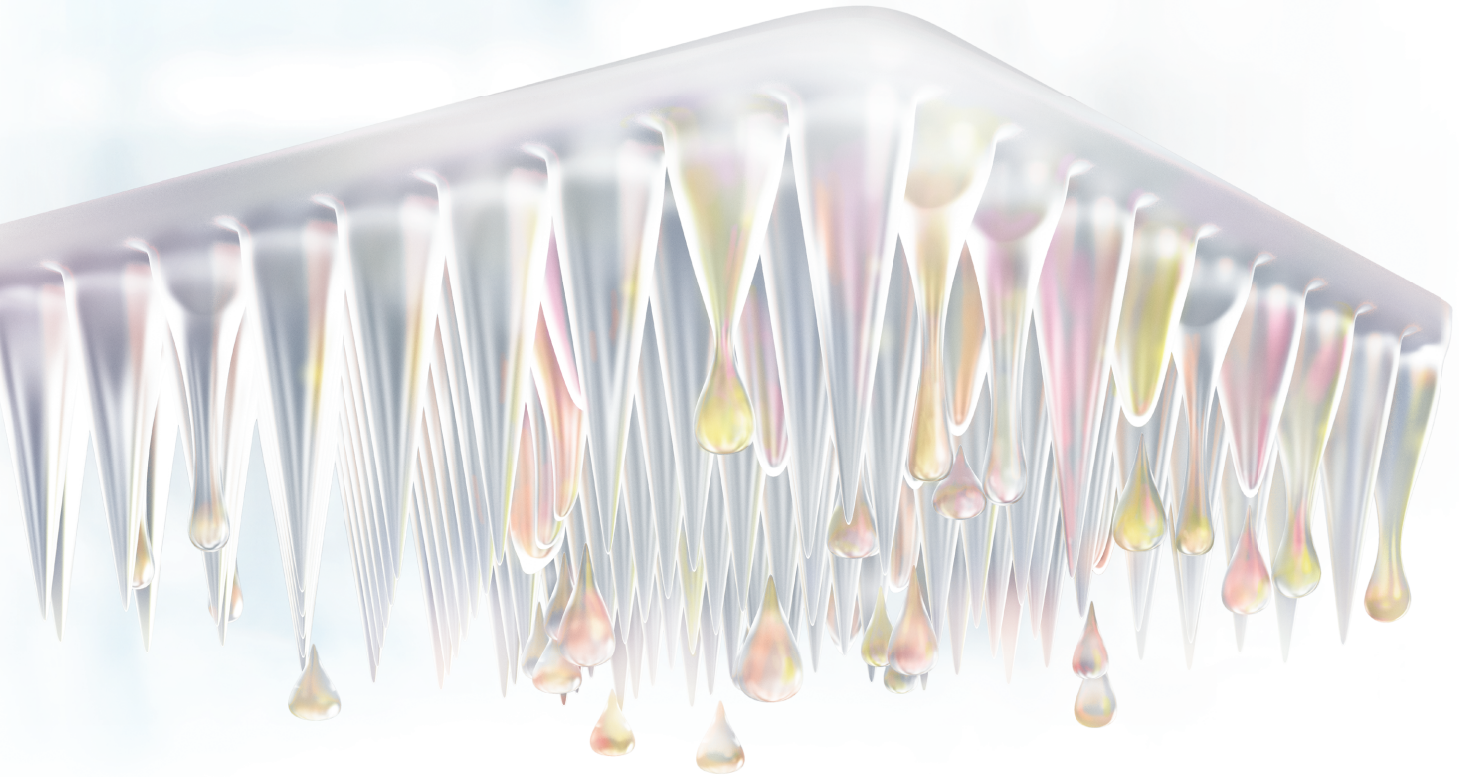

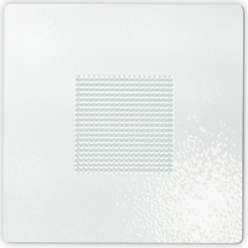

Micro Array Patches penetrate the skin with drug containing microscopic structures, which then dissolve and release their APIs.

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