TRANSDERMAL DELIVERY & MICRONEEDLES

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Transdermal Delivery & Microneedles

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2015 Apr Pulmonary & Nasal Drug Delivery
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Jun Novel Oral Delivery Systems
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Front cover image: "3M Holllow Microstructured Transdermal System, pPolymer microneedle array with 12 hollow microneedles, each approximately 1500 µm", supplied by 3M Drug Delivery Systems. Reproduced with kind permission.

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We put no limits on curiosity

Imagination and curiosity are the starting points for 3M innovation – the kind of curiosity that leads to innovative solutions for real world problems – such as creating the first metered dose inhaler, enabling patient-centric transdermal technology and converting microreplication technology to microneedle delivery systems. From development, to scale up and commercialization, let the curious minds at 3M Drug Delivery Systems provide innovative solutions to your drug delivery challenges.

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3M DRUG DELIVERY SYSTEMS

3M

INNOVATIVE DRUG DELIVERY **TECHNOLOGY** TO MEET EVOLVING NEED OF BIOLOGICS & SMALL MOLECULES

In this article, Lisa A Dick, PhD, MTS Lab Manager, 3M Drug Delivery Systems Division, provides a run-down of the concept, design and development of the company's microneedle drug delivery platform, both hollow and solid needle arrays, including recent clinical trials of the hollow-needle device.

As population demographics shift and new medicines become available, patient preference and new technologies remain top of mind for 3M. In recent years, 3M has been working on a patient-friendly and easy to use microneedle delivery platform that expands the range of drug molecules and formulations open to dermal delivery.

> "With 3M Hollow Microstructured Transdermal System, it is possible to deliver more viscous solutions, up to 25 centipoise (cp), with options for delivery of up to 80 cp"

This microneedle drug delivery technology provides solid and hollow microneedle options for enabling administration of both small and large molecules, including difficult-to-deliver biologics. These devices are well suited for dermal skin targets or systemic distribution for drugs that enter the lymphatic system.

Solid microneedles, are coated with drug and focused on relatively potent molecules and peptides that are amenable to being deposited (up to 300 µg) and dried on the tips of a microneedle array as shown in Figure 1.

For liquid formulations, **hollow microneedles** allow delivery of drug solution into the highly vascularised dermal layer of

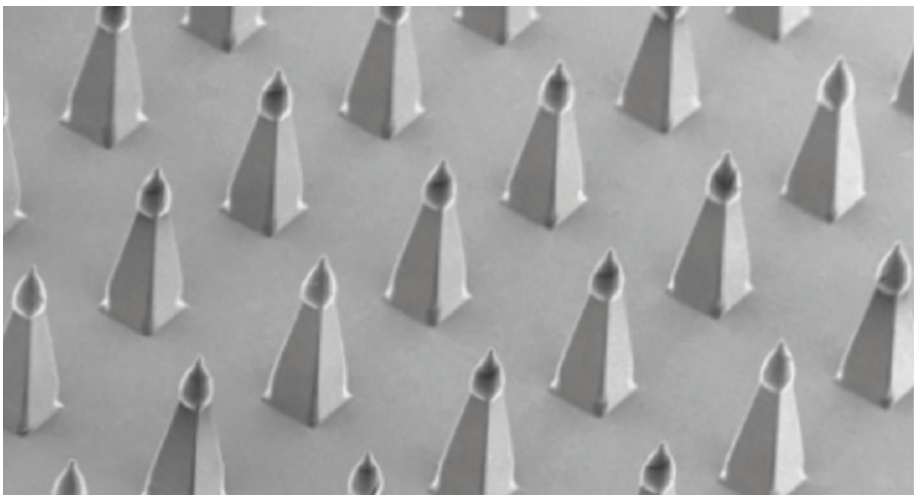

Figure 1: 3M Solid Microstructured Transdermal Array at 25x magnification (sMTS).

Dr Lisa A Dick
MTS Lab Manager
T: 1 800 643 8086
E: dds@mmm.com

3M Drug Delivery Systems
3M Center, Building 275-03-E-10
St Paul
MN 55144-1000
United States

www.3m.com/MTS

Figure 2: Left – pen injector with single needle, Right – 3M™ Hollow Microstructured Transdermal System with hollow microneedles.

the skin. 3M™ Hollow Microstructured Transdermal System accommodates a wide range of drug amounts (up to 2 mL) and molecule types, as long as stability in liquid form is maintained. This system combines patient-friendly, passive transdermal delivery with the versatility of parenteral syringe injections. For comparison, Figure 2 shows both a pen injector and 3M Hollow Microstructured Transdermal System.

3M Hollow Microstructured Transdermal System is designed for intradermal delivery of liquid formulations, including biologics, such as proteins and peptides, in addition to small molecules. Hollow microneedles have the flexibility to deliver up to 2 mL of high value biologic formulations.[1,2,3] This system also provides relatively fast delivery of a high volume of a liquid drug formulation. 3M Hollow Microstructured Transdermal System array is a 1 cm² polymeric disk composed of hollow microneedles with a sterile flow path connected to a conventional glass cartridge. During application, the microneedles are inserted into the skin penetrating the *stratum corneum* and epidermis, and creating direct access to the dermis. This hollow microneedle array, as demonstrated in Figure 3, is made from medical grade polymer with 12 microneedles 1500 µm tall. Delivery of the formulation through hollow

Figure 3: 3M Holllow Microstructured Transdermal System, pPolymer microneedle array with 12 hollow microneedles, each approximately 1500 µm.

Drug/Type	Viscosity	Volume (mL)	Injection Time
Cimzia®*	~80 cp	0.5-0.9 mL	1-2 minutes
Monoclonal AB	~20 cp	1 mL	3-5 minutes
Protein	~20 cp	2 mL	2-4 minutes

Figure 4: Injection times in preclinical models for various viscosities tested with 3M Hollow Microstructure Transdermal System. (* Cimzia is a trademark of UCB Pharma.)

microneedles is powered by a mechanical spring. A combination of drug and 3M Hollow Microstructured Transdermal System provides a fully integrated delivery device designed for reproducible intradermal delivery of liquid formulations.

DRUG PRODUCT & FORMULATION CONSIDERATIONS

The target delivery volume of 3M Hollow Microstructured Transdermal System is 0.5-2 mL, making it a viable delivery option for many biopharmaceutical therapeutics. In a recently conducted human tolerability study (3M, 2015), 3M Hollow Microstructured Transdermal System performed well, delivering 2 mL of 5% dextrose in 98% of 56 self-administered injections.

Non-viscous formulations flow readily through narrow flow paths in microneedle-based devices. Viscous formulations are more prone to plugging in the narrow channels of traditional single-channel devices or require a long delivery time. With 3M Hollow Microstructured Transdermal System, it is possible to deliver more viscous solutions, up to 25 centipoise (cp), with options for delivery of up to 80 cp.

The drug product formulation must also be chemically compatible with the device. This is essential, especially upon stability storage. In addition, drug molecules must be physically able to withstand shear forces when flowing through the device. Such physical compatibility considerations are especially important for biological drugs, which denature or become inactive.

To achieve successful formulation distribution in the intradermal layer, the number and arrangement of microneedles is key. It is desirable to have flow distributed across an array of microneedles. In order to achieve unrestricted flow, microneedles must be far enough removed from a nearest neighbour to act independently. This distance, however, is balanced by the need to have a small array, such that each needle is uniformly inserted on flat skin. Ultimately, the arrangement of microneedles must be in a geometry that is favorable to the desirable drug delivery target.

MANUFACTURABILITY OF INDIVIDUAL MICRONEEDLES

Following successful preclinical and clinical studies, a need for high-volume reproducible manufacturing of microneedle arrays will become critical. This is especially challenging for small companies and universities conducting research on a limited budget and small scale. Based on extensive expertise in drug delivery systems manufacturing and access to broader corporate resources, 3M has chosen to use its proprietary microreplication technology as a method of reproducibly manufacturing microneedle arrays in large volumes.

"The target delivery volume of 3M Hollow Microstructured Transdermal System is 0.5-2 mL, making it a viable delivery option for many biopharmaceutical therapeutics"

DESIGN INPUT AND HUMAN FACTORS

To summarise, both hollow and solid microneedle systems offer an alternative delivery method to meet the evolving needs of pharmaceutical companies, providers, and patients. With chronic conditions, noncompliance remains at around 10 percent.[4,5,6] In some cases, patients may prefer a system designed for self-administration if they can avoid traveling to their physician's office for an injection or avoid outpatient IV administration. Microneedle systems developed in conjunction with a drug may provide convenience to the patients along with overall pharmaco-economic benefits.

While considering patients' comfort and pharmaco-economic benefits associated with self-administration, it's critical to fol-

Figure 5: The 3M Hollow Microstructure Transdermal System device.

low regulatory requirements for patient-centric design and self-administration considerations.

For instance, development of the 3M Hollow Microstructured Transdermal System has been focused on human factors inputs that were gathered during usability trials. Patient acceptance and product concept research resulted in the identification of additional features that were designed to increase convenience during self-administration, especially in dexterity-challenged patient populations.

Human factors research demonstrates that it is desirable for a device to be sized for easy handling and include a textured grip for convenience of patients or their caregivers. Mechanical actuation with an audible click or visual indication, which provides sensory feedback for the patient, is also important. A device with a status indicator, such as a window with a progress bar, provides information about dosing so the patient can see when medication delivery is completed. The combination of these features in 3M Hollow Microstructure Transdermal System, as shown in Figure 5, may allow patients to feel confident in self-administering their medications.

HUMAN CLINICAL TRIAL WITH 3M HOLLOW MICROSTRUCTURED TRANSDERMAL SYSTEM

With the design features identified in human factors testing and built into the device, 3M Hollow Microstructured Transdermal System underwent a number of studies and design verification tests. Then, to reach a stage of clinical readiness, 3M followed a rigorous process, including finalizing the device design, manufacturing critical components from medical grade materials, establishing GMP for array manufacturing and device assembly, as well as filing documentation with the US FDA.

In an internal 3M clinical study designed to measure delivery time, device performance with respect to leakage, safety and skin tolerability, thirty healthy volunteer subjects were asked to self-administer four 2 mL 5% dextrose injections to the anterior thigh. As a result, the final device configuration of 3M Hollow Microstructured Transdermal System has been selected for further assessment in potential partners' clinical trials.

For the selected final clinical device design, the following results were obtained:

- 2 mL 5% dextrose self-administered by 29 people (56 deliveries, 98% success rate)
- Average delivery time <2 minutes
- Average pain score of 2.9 on a scale of zero to ten
- Average tolerability scores for erythema and oedema were <2 on a scale of zero to four.

These results provided foundational data for assessing the reliability and safety of 3M Hollow Microstructured Transdermal System.

SUMMARY

In conclusion, microneedle-based drug delivery has the potential to be a transformative technology for the delivery of a range of biologics and small molecules. 3M has taken a platform approach and developed both solid and hollow microneedle systems for use in preclinical and clinical studies. 3M Hollow Microstructured Transdermal System was also studied in a recent human clinical trial for sensation and performance. For companies interested in intradermal delivery, 3M Hollow Microstructured Transdermal System can provide reproducible intradermal delivery of difficult-to-deliver viscous biologic solutions of up to 2 mL. This evidence illustrates the device's readiness for further use with pharmaceutical partners in their preclinical and clinical studies, thus providing new options for delivering biologics and small molecules

"Microneedle-based drug delivery has the potential to be a transformative technology for the delivery of a range of biologics and small molecules"

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May 2015	Injectable Drug Delivery: Devices Focus	April 13th
June 2015	Novel Oral Delivery Systems	May 4th
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February 2016	Prefilled Syringes	January 11th
March 2016	Transdermal Delivery & Microneedles	February 8th
April 2015	Pulmonary & Nasal Drug Delivery	March 7th

AQUARMED™: TRANSDERMAL DELIVERY USING NOVEL COMPONENTS DERIVED FROM NATURAL MOISTURISING FACTOR (NMF)

In the following article, Professor Marc Brown, Chief Scientific Officer; Professor Adrian Williams, Member of Scientific Advisory Board; and James Gibbons, Commercial Manager, all of MedPharm, explain how the company has developed AquaRMed, a series of rationally designed hydrotopes that increase hydration of the skin, show anti pro-inflammatory properties and are proven penetration enhancers for topically and transdermally delivered APIs, and describe the potential benefits AquaRMed could offer patients and companies alike.

INTRODUCTION

The transdermal and topical drug delivery market is expected to reach a size of US$31.5 billion (£21.4 billion) this year.[1] This is largely the result of companies increasingly looking to take advantage of the benefits of delivering therapeutics via these routes. Such advantages range from avoidance of first-pass metabolism, to enhanced patient compliance, to product lifecycle management and brand line extension.

MedPharm, the leading topical and transdermal formulation development, testing and clinical supplies manufacturing company, helps its clients develop products for this market. As part of its continuing push for innovation MedPharm has developed an exciting, novel skin hydration technology called AquaRMed™. The technology shows promise as a new topical and transdermal drug delivery technology.

AquaRMed is a series of rationally designed hydrotopes that increase hydration of the skin, show anti pro-inflammatory properties, and are proven penetration enhancers for topically and transdermally delivered active pharmaceutical ingredients (APIs). MedPharm has patented these hydrotopes and is continuing to evaluate the technology with a view to commercialisation through collaborations with its licensees.

BACKGROUND

MedPharm has extensive expertise in developing topical and transdermal medications and has contributed to the development of more than 20 marketed products in its 16-year history. With this expertise, MedPharm has continuously strived to find the newest and best innovations to help its clients develop successful, safe and efficacious products; these include proprietary efficacy testing models and drug delivery technologies.

MedPharm's latest innovation, AquaRMed consists of a series of hydrotopes adapted from Natural Moisturising Factor (NMF), which comprises a number of compounds including urea, peptides, amino acids, sugars, lactates, inorganic acids and a variety of salts that aid water retention within the *stratum corneum* in normal physiology.[2]

NMF itself is a hydrolysis product of filaggrin, and dry, inflammatory skin conditions such as atopic dermatitis are linked to a decrease in NMF. Patients often have fewer filaggrin repeat units in the FLG gene and patients with ichthyosis vulgaris have loss of function mutations in filaggrin genes. These changes lead to a decrease in filaggrin produced and consequently a decrease in NMF levels.[3] In addition, atopic dermatitis patients with filaggrin gene mutations resulting in decreased NMF inversely show an increase in the *stratum corneum* concentration of pro-

Professor Marc Brown
Chief Scientific Officer

Mr James Gibbons
Commercial Manager

Professor Adrian Williams
Member of Scientific Advisory Board

Contact:

MedPharm Business Development Team:
T:+44 1483 457 556
E: busdev@medpharm.co.uk

MedPharm Ltd
R&D Centre
Unit 3 / Chancellor Court
50 Occam Road
Surrey Research Park
Guildford
GU2 7AB
United Kingdom

www.medpharm.co.uk

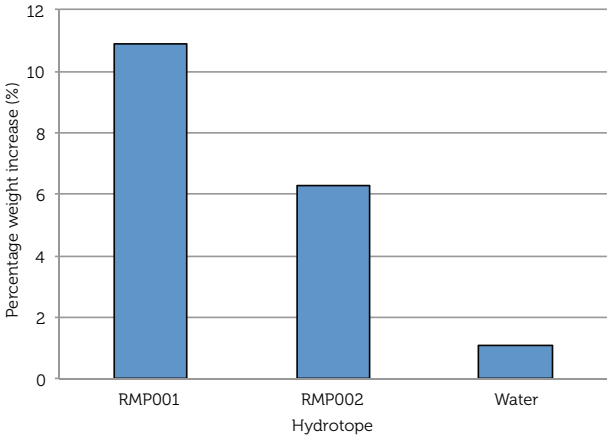

Figure 1: Weight gain of snake skin treated with AquaRMed (RMP001 and RMP002) and stored at 40% room humidity as an indication of hydration.

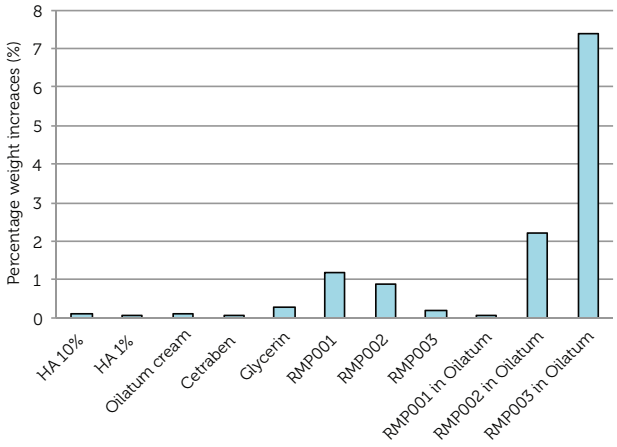

Figure 2: Weight gain as an indication of hydration following application of AquaRMed molecules (RMPXXX) and marketed moisturisers, in combination and separately (Snake skin).

inflammatory cytokine IL-1.[4] Therefore, topically applied NMF replacement has potential therapeutic benefit. With this rationale, Professors Brown and Williams aimed to develop a series of compounds that they hoped could be used to treat xerotic and inflammatory skin conditions.

AQUARMED DEVELOPMENT & EVALUATION

MedPharm developed methods to synthesise a series of compounds derived from NMF which, when left at normal room humidity, deliquesce by absorption of atmospheric water. MedPharm has now conducted a number of studies showing increased skin hydration in an *in vitro* and *ex vivo* setting. *Ex vivo* snake skin was initially used to show hydration was improved by AquaRMed molecules. Chosen because snake skin intrinsically lacks NMF, hydration was quantified by measuring weight gain (Figure 1). A significant increase in skin hydration is seen in the skin treated with AquaRMed, compared with water.

With further evaluation warranted, MedPharm next performed studies to establish hydration performance of AquaRMed compared with marketed products and other known emollients in snake skin (Figure 2), and human epidermis (Figure 3). Two of three AquaRMed hydrotopes (RMP001 and 002) performed better than all marketed moisturisers tested in these assays.

Interesting trends are apparent in Figure 3: when AquaRMed was physically combined with marketed moisturiser, oilatium (GSK), in an un-optimised formulation, there was a marked increase in hydration when compared with the moisturiser and AquaRMed molecules in isolation. However, it is important to consider that these early experiments utilise un-optimised AquaRMed solutions; thus fully optimised formulations of AquaRMed should perform even better in such hydration experiments than the results reported here show.

It is a widely accepted fact that hydration of the *stratum corneum* enhances API delivery into and across the skin, with significant enhancement possible.[5] For this reason, many topical and transdermal formulations are made to be occlusive as they reduce water loss from the skin, consequently increasing skin hydration and, therefore, API delivery. AquaRMed molecules actively hydrate the skin. With this in mind, MedPharm undertook a number of permeation and penetration studies (human epidermal sheet mounted in Franz-cells) to assess the delivery enhancement properties of AquaRMed using three model drugs (Figure 4).

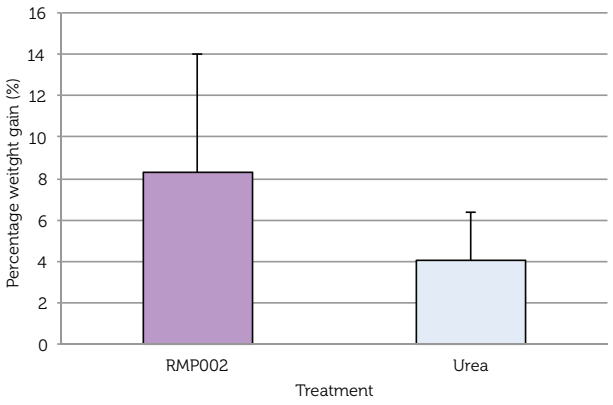

Figure 3: Weight gain of human epidermis as an indication of hydration following application of AquaRMed molecule (RMP002) compared with urea.

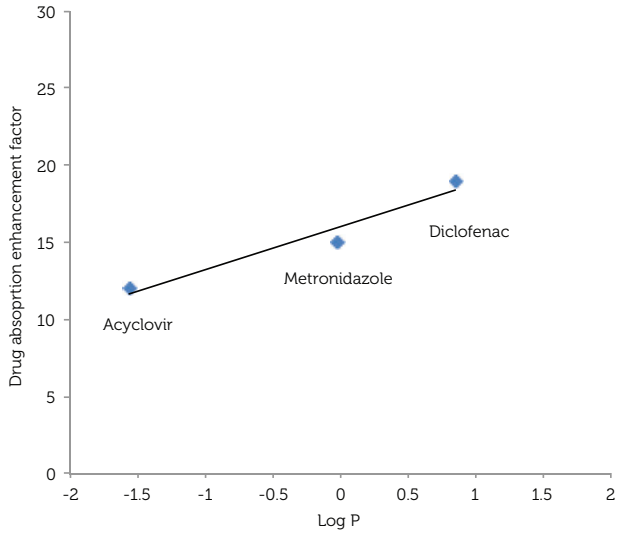

Figure 4: AquaRMed enhancement of API permeation across human epidermal sheet. Tissue pre-treated with AquaRMed or water (control) prior to model drug application; indication of LogP trend.

A significant enhancement of permeation has been observed in these studies, when AquaRMed is applied to the skin prior to the model drug. Up to a 20-fold increase in delivery was observed when diclofenac was administered following pretreatment with AquaRMed compared to diclofenac application without AquaRMed pre-treatment.

Similar enhancements were seen with metronidazole (circa 14-fold increase in delivery) and acyclovir (circa 11-fold increase in transdermal delivery). It is currently hypothesised by MedPharm that permeation enhancement magnitude correlates with the Log P of the API; i.e. the more lipophilic the drug, the greater the possible delivery enhancement (Figure 4). Further studies are ongoing to assess this theory.

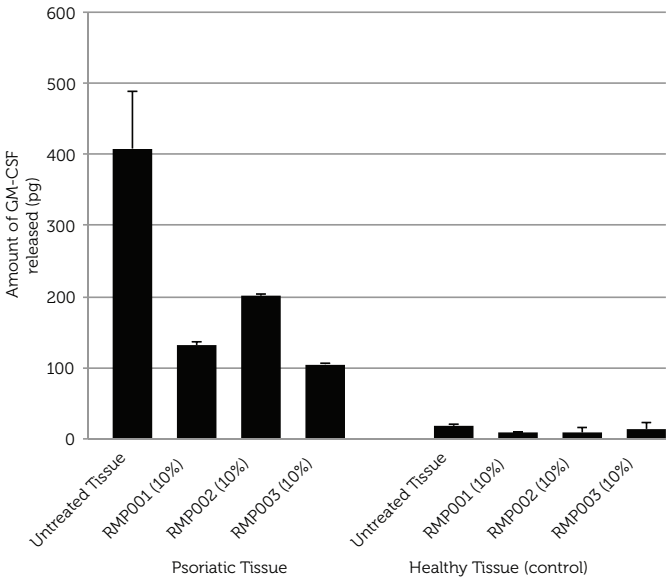

Figure 5: AquaRMed attenuation of GM-CSF release in psoriatic skin model and healthy tissue (RHE) controls.

With AquaRMed's potential as a high performing drug delivery technology validated, it was next important for MedPharm to study the safety of using AquaRMed on human skin. Irritation and toxicity profiles for AquaRMed molecules were expected to reflect their nature as endogenous substance derivatives. Theoretical toxicity reviews conducted by an independent party concluded that there were unlikely to be toxicity issues with the technology.

These theoretical predictions were supported by some *in vitro* tests conducted at MedPharm. Acute skin irritation was assessed using the SkinEthic Skin Irritation Test where AquaRMed molecules were applied to reconstructed human epidermis (RHE) tissues. The RHE tissues were incubated for 24 hours, and then assessed by MTT assay and measurement of cytokine release. ET-50 values (the time at which 50% of cultured cells are no longer viable) were also calculated using MatTek's MTT ET-50 assays. The results of these tests showed that two of the three molecules were non-irritant, with the third comparative to baby shampoo as a very mild irritant.

The advantages of treating xerotic skin conditions with AquaRMed are clear from a hydration point of view. With the hope of extending this therapeutic benefit to inflammatory skin conditions, MedPharm has also assessed the anti-pro-inflammatory properties of AquaRMed. Kezic and co-workers have previously documented NMF's role in the immune response system, showing that IL-1 levels increase in the *stratum corneum* with a decrease in NMF.[4]

MedPharm used a human cell culture based psoriatic tissue model consisting of psoriatic lesion-derived fibroblasts and normal keratinocytes to test AquaRMed's anti pro-inflammatory properties. This *in vitro* model exhibits hyperproliferation of basal epithelial cells and increased expression of pro-inflammatory cytokines and other inflammatory markers associated with psoriasis (e.g. GM-CSF) when compared to normal RHE cultures. GM-CSF is a key activator of the innate immune system involved in chronic inflammatory and autoimmune diseases such as psoriasis,[6] where macrophages, granulocytes, neutrophils, eosinophils and dendritic cells contribute to tissue damage and disease progression.[7] Numerous *in vivo* studies over the past few years have shown that blockade of GM-CSF via neutralising antibodies can prevent or even cure pro-inflammatory diseases in various models of inflammation including psoriasis.[8] In addition, patients with chronic psoriasis receiving GM-CSF therapy have been shown to have exacerbated psoriatic lesions.[9]

Due to the importance of GM-CSF in psoriasis it was selected for quantification in experiments with AquaRMed (Figure 5). A reduction in GM-CSF release was observed when the psoriatic tissue model was treated with three different AquaRMed molecules, suggesting an additional application for the technology in the treatment of inflammatory skin diseases. Indeed, GM-CSF release was halved over the course of six days following AquaRMed application to the cell cultures.

> "A significant enhancement of permeation has been observed in these studies, when AquaRMed is applied to the skin prior to the model drug. Up to a 20-fold increase in delivery was observed when diclofenac was administered following pretreatment with AquaRMed"

FUTURE PLANS

MedPharm is continuing to work on these non-toxic moisturising compounds to evaluate their penetration enhancing capabilities further using both a number of its licensees' APIs and additional model drugs, with promising results to date.

A PCT patent was filed in November 2013. MedPharm is evaluating a number of commercialisation strategies, including development of AquaRMed molecules as novel excipients that would offer a safe and elegant way to enhance topical and transdermal drug delivery.

The benefits of using AquaRMed molecules as a delivery technology are numerous; they could offer patent protection to formulations containing AquaRMed as one advantage. AquaRMed also offers notable enhancement in topical and transdermal delivery without the need for use of expensive, and often complex, drug delivery technologies such as microneedles, and active delivery systems such as phonophoresis and electrophoresis.

As part of the commercialisation process MedPharm also is evaluating the possibility of developing a portfolio of products that would include dry and inflamed skin condition treatments. These products would include AquaRMed in combination with APIs. MedPharm is currently conducting several feasibility studies with its licensees'

APIs, and is actively pursuing the possibility of licensing the technology to its clients.

CONCLUSIONS

MedPharm has developed a novel technology that, even at an early stage, offers significantly increased skin hydration when compared with the hydration ability of currently marketed emollients and humectants. In addition, human skin permeation studies have shown the potential for AquaRMed to enhance API delivery to and across the skin significantly.

AquaRMed appears to be non-irritant and may have additional anti pro-inflammatory properties.

Thus, the technology has potential application for the treatment of inflammatory and xerotic skin conditions, providing notable improvements to therapies in a market often dominated by steroid based medicines. There is also significant potential for the use of AquaRMed as a topical and transdermal delivery technology with numerous advantages over other technologies available.

MedPharm welcomes enquiries regarding assessment of AquaRMed's drug delivery potential with a view to finding new licensing partners.

ACKNOWLEDGEMENTS

MedPharm wishes to thank Natasha Ball for her work on the development of AquaRMed to date.

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Innovative Injection

HIGHLY CUSTOMISABLE HOLLOW POLYMER MICRONEEDLE SOLUTIONS

In this paper, Marion Sausse Lhernould, PhD, Novinject Project Leader; Serge Tailler, PhD, and Michel Deleers, PhD, both of Novinject; and Alain Delchambre, PhD, Professor at BEAMS, Université Libre de Bruxelles, present a hollow microneedle delivery device manufactured using a novel proprietary process in order to overcome the mechanical and functional challenges microneedles face, leading to a low-cost, fully customisable and scaleable design.

Twelve billion injections are performed each year around the world whilst 10% of the population suffers from trypanophobia (fear of needles).[1] Microneedles suppress the fear of injection, while insuring efficient injections. Because microneedles do not reach the innerved parts of the skin, injection of a pharmaceutical solution can now be performed in a non-invasive way using microneedle systems. Intradermal administration using microneedles presents all the advantages of traditional hypodermic injections (rapid onset of action and the possibility of large molecule administration, for example) without enduring any of the disadvantages such as pain and irritation.

Novinject provides hollow polymer microneedle injection systems to be used in the delivery of drugs through the skin, with a high patient compliance. The concept is based on an innovative, breakthrough development of the Université Libre de Bruxelles in the domain of micro-technologies applied to transdermal drug delivery (TDD).

Novinject is a soon to be created spin-off, which engineers customisable and affordable hollow polymer microneedle solutions for high patient comfort. Microneedles can also extend pharmaceutical product lifecycles, and open the possibility towards delivery of new therapeutic agents and self-injections. Indeed, they allow the injection of a wider range of molecules, and are easy to use. Several applications are envisioned for the technology, particularly for molecules, whose size did not allow their administration through the skin (DNA vaccination, for example), but also more traditional fields such as painkiller injection, insulin injection, vaccination, dermatological injections, CNS (central nervous system) therapeutics.[2] Novinject develops custom products that meet company needs in the domain of innovative transdermal drug delivery.

OVERVIEW: STATE-OF-THE-ART & CONTEXT OF DEVELOPMENT

Regarding manufacturing, the first microneedles were made out of silicon and metal. These choices are justified by the mechanical properties of these materials and their biocompatibility potential, besides their microelectronic origins. However inconveniences like high production costs and fragility necessitated the discovery of other options, and polymer solutions were proposed.[3] Polymer materials present several advantages fitting well with microneedle production: proven biocompatibility; biodegradable option; and adequate mechanical properties for microneedle use.

The challenge designing microneedle systems often resides in the fact that, because they should be usable in a wide range of applications, they must be optimised in terms of mechanics and fluid dynamics, as well as being cost-competitive with traditional hypodermic injections.

The main problems encountered in designing microneedle solutions concern: volume of injection; injection time; needle resistance; and, most of all, production costs. In this context, Novinject presents a technical development opening up the possibility of manufacturing microneedle arrays that meet all of the requirements in terms of mechanics, fluidics and costs.

Dr Serge Tailler
Novinject

Dr Michel Deleers
Novinject

Professor Alain Delchambre
BEAMS, Université Libre de Bruxelles

Dr Marion Sausse Lhernould
Novinject Project Leader
T: +32 2650 28 14
F: +32 2 650 24 82
E: msl@novinject.com

Novinject
Université Libre de Bruxelles
Bio-, Electro-, and Mechanical Systems Department (BEAMS)
CP165/56, Av. F.D. Roosevelt 50
B-1050 Brussels
Belgium

www.novinject.com

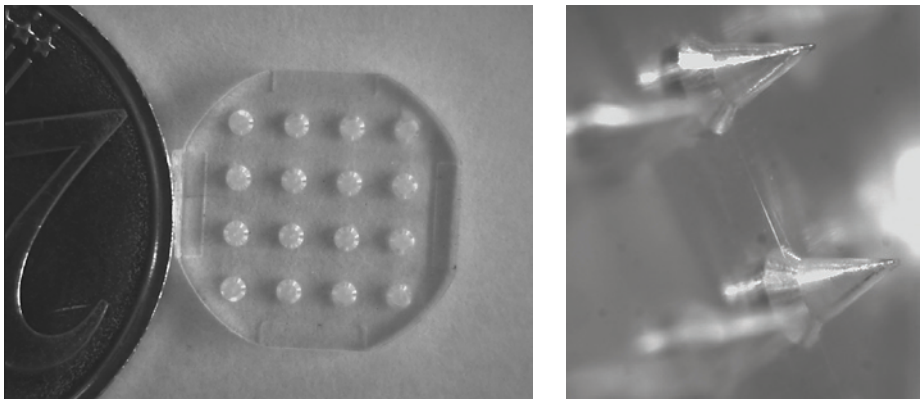


Figure 1: A 16 hollow microneedle array moulded in highly biocompatible polymeric material.

PROPOSED MICRONEEDLE SOLUTION

Novinject proposes to industrials hollow polymer microneedle solutions, adapted to their specifications, in order to meet their needs corresponding to their applications. The developments are focused on polymer microneedles because they can be manufactured using injection moulding, which is the preferable production method in view of industrialisation.

The presented microneedle arrays are realised using a breakthrough fabrication method (patent pending).[4] Their conical shape ensures good mechanical resistance, also due to the excellent mechanical characteristics of polymeric materials. The side opening prevents potential outlet clogging and ensures efficient liquid flow.

As illustrated in Figure 1, a proof-of-concept microneedle array has been designed and optimised taking into account mechanical resistance and fluid flow.[5] In this example microneedles are 900 µm tall structures, with a 600 µm base diameter, and a 100 µm diameter side-opening. The array comprises 16 microneedles with a pitch-to-pitch separation distance of 2 mm, making the array a 10x10 mm device. This density of microneedles avoids the phenomenon called the "bed of nails" effect which, due to the elastic response of skin, may prevent correct microneedles insertion. Three principal parameters may indeed affect correct insertion: size of microneedle tip; number of microneedles; and their density.

Our expertise is nevertheless at your service to meet specific demands.[6] Our vision is to work in close collaboration with industry on the co-development of the microneedle device specifically customised for specific applications.

TECHNICAL CHARACTERISTICS

The innovative manufacturing method using a double mould technology allows us to create a cavity inside the needles (Figure 2). The exit hole is simply post-processed in a second manufacturing step using excimer (exciplex) laser technology. This gives a lot of flexibility to the design and provides excellent fluid dynamic properties to the needles. The exit hole can be drilled perpendicular to the needle walls but also parallel to the axis of symmetry. Laser technology allows simultaneous drilling of all exit holes in a few seconds.

The needle outlets, resulting from the manufacturing method, are very short in length and cylindrical in shape. The charge losses are thus reduced to a minimum, meaning the device's fluid dynamics characteristics while injecting fluids are similar to those of hypodermic needles (Figure 3). This implies the possibility of injecting at relatively high flow rate with reduced injection pressures, and possibility to manage even viscous fluids.

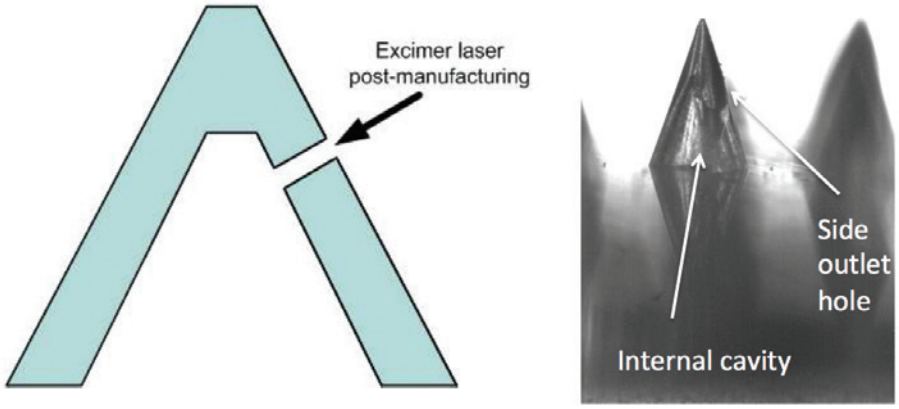


Figure 2: Original design of Novinject microneedle solutions.

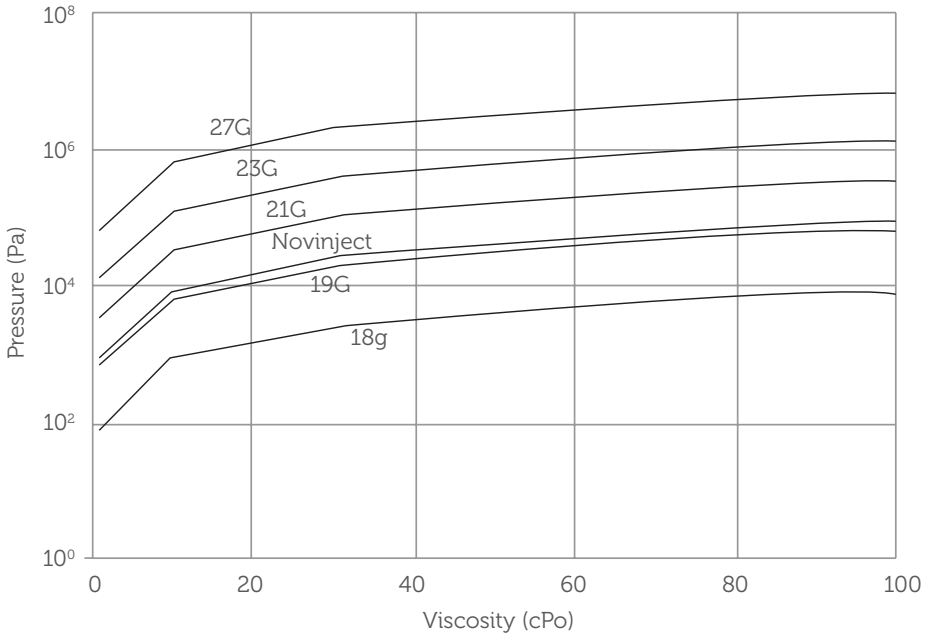


Figure 3: Theoretical pressure for different needle gauges and Novinject microneedles to inject 1 mL/min of solution.

Figure 4: Possible Luer configuration for the microneedle array.

The theoretical pressure p (Pa), necessary to push the fluid at a given rate Q (m^3/s) is given by the equation [7] :

$$p = QxR$$

where R is the hydraulic resistance, and is defined in the case of cylindrical channels such as hypodermic needles by:

$$R_{needle} = \frac{128\mu L}{nd^4}$$

where μ is the fluid viscosity (Pa.s), d is the channel diameter and L the channel length.

In the case of microneedles, the cylindrical channels are parallel outlets and the corresponding charge loss factor is:

$$\frac{1}{R_{MN\ patch}} = \frac{1}{R_{MN1}} + \dots + \frac{1}{R_{MNn}}$$

with our example of 16 identical microneedles, and since charge losses with the design principally occur at needles outlets and are negligible in the cavity,[5] this becomes:

$$R_{16MN} = \frac{8\mu L}{\pi d^4}$$

The very short length of the microneedles outlet leads to low charge losses compared with microneedle designs where there is no cavity inside the microneedles, i.e. when the micro-fluidic channel goes through the whole needle, from under the substrate. Our design even allows delivery of viscous fluids.

The Novinject microneedle array is intended to inject a liquid substance into the hypodermis and dermis. The amount of substance delivered can reach 1 mL. A full system is also proposed, which includes a fluidic connection with a reservoir containing the solution and an assisting insertion and delivery device.

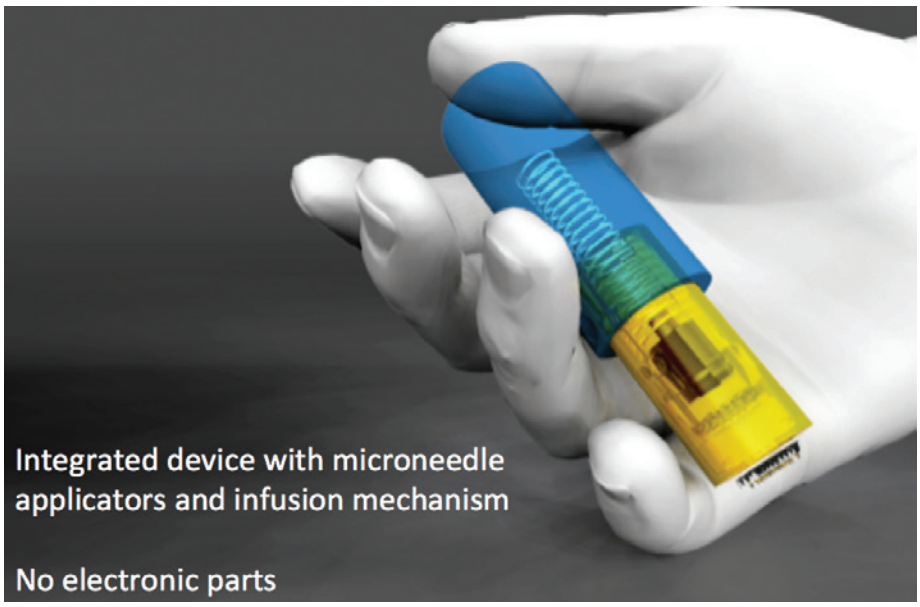


Figure 5: Representation of an impact applicator solution.

PRACTICAL USAGE OF THE SYSTEM

Several solutions are proposed to connect the microneedle array to a reservoir of fluid to be delivered. In view of proposing a standard solution the microneedle array can be fitted on a Luer connection aimed at being connected to a standard pharmaceutical container (Figure 4).

With the current proof of concept, layers 600 μm deep into the skin can be reached. An impact insertion system is envisioned in order to insert the microneedles into the skin efficiently and repeatably. As is the case for the design of the microneedle array itself, the Novinject team believes that the design of the insertion-assisting device should be adapted to targeted pharmaceutical applications. This is why, whilst Novinject already proposes some solutions, the finalised design should be optimised depending on the fluidic properties of fluid to inject, quantity to deliver, and targeted delivery site. The assisting injection device uses spring mechanisms, which can be calibrated to reach desired insertion forces (i.e. insertion depth) and injection rates.

> "The main problems encountered in designing microneedle solutions concern: volume of injection; injection time; needle resistance; and, most of all, production costs"

Polymer microneedles are very resistant with practically no risk of needle breakage into the skin. In case of accidental misuse, needles do not break but tend to bend or crush instead, leaving no residue in the skin. The material used is a highly biocompatible polymer, already widely used for biomedical applications.

DISCUSSION AND CONCLUSION

Novinject has brought together university expertise and industrial needs in order to develop a technology allowing low-cost, high-rate, microneedle production. We are able to design customised microneedle devices, which reach the underlying skin layers in order to deliver pharmaceutical or dermatological substances, in a safer and more compliant way for patients.

It is the team's belief that microneedle technology should be considered early in the development process where pharmaceutical needs can be taken into account. This is why the soon to be created Novinject spin-off offers co-development and customisation services. Looking at the microneedle array proposed and presented as a proof of concept, the principal features that can be adapted are (but not restricted to): the length of the microneedles, and size and position of the delivery hole.

Multiple outlet holes can also be designed in order to reach even faster delivery rates. Moreover, number, density and repartition of microneedles can also fit particular demands. Novinject microneedles are produced using microinjection moulding technology, enabling increased production rates with affordable costs.

NOVINJECT

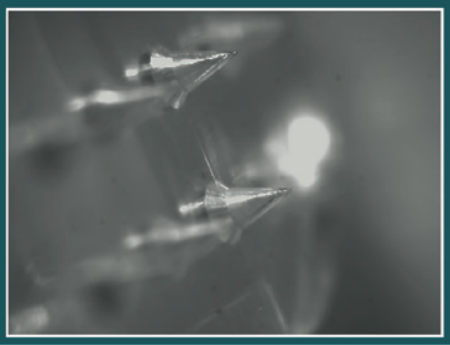
Innovative Injection

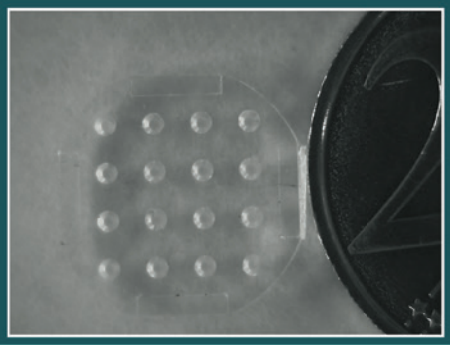
WE DESIGN MICRONEEDLE SOLUTIONS FOR TRANSDERMAL INJECTIONS

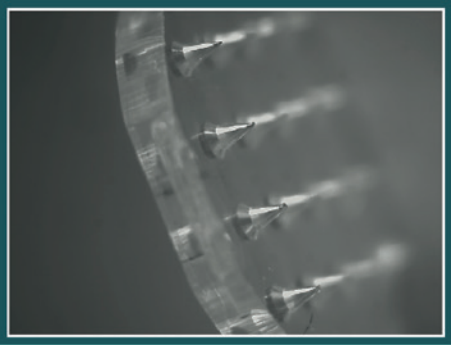
The concept is based on an innovative, breakthrough development of the Université Libre de Bruxelles in the domain of micro-technologies applied to transdermal drug delivery (TDD).

Currently, our proof of concept is a 16 microneedles patch with 900µm high microneedles, molded in a polymeric material with excellent biocompatibility properties

Microneedle array developed by Novinject







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Novinject – Université Libre de Bruxelles
Av. Roosevelt 50, CP165/56 1050 Brussels Belgium

ULB beams ECOLE POLYTECHNIQUE DE BRUXELLES Wallonie

Our expertise is at your service to support and engineer microneedles solutions for you.

LOOKING FOR PARTNERING OPPORTUNITES

Novinject is a spin out of the Université Libre de Bruxelles Bio Electro And Mechanical Systems (BEAMS) department. Four main predilection areas of research emerge from this department: microtechnologies, biomedical group, embedded systems and electrical engineering. The biomedical group focuses on the design, modelling and development of biomechanical devices for mini-invasive surgery: implantable pumps for drug delivery, laparoscopic tools for hepatic surgery, surgical station for endoscopic interventions, modelling of human organs, biomechanics, experimental and numerical analysis of the human joints and patient specific modelling; and brings thus a large added value to Novinject developments.

Today Novinject is looking for partnering opportunities with industry in order to develop the breakthrough injection device of the future.

"Novinject presents a technical development opening up the possibility of manufacturing microneedle arrays that meet all of the requirements in terms of mechanics, fluidics and costs"

ACKNOWLEDGEMENT

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Q&A: SUCCESSFUL MASS PRODUCTION OF AN INNOVATIVE DRUG DELIVERY TECHNOLOGY

In this piece, Jung Dong Kim, PhD, Chief Technology Officer at Raphas Co, answers questions about the company, its capabilities, and the mass production of an innovative dissolving microstructure drug delivery technology.

Q: What is Raphas?

A: Raphas is a combination of the words "Rapha" (heal) and "Path". Technology originally developed in Yonsei University was transferred to this company, after which four years of research and investment led to the successful development of dissolving microstructure products. As the meaning behind the name Raphas suggests, the company is devoted to providing paths to healing in the medical services sector. A key mission of the company is to pioneer an affordable delivery system for vaccines and other drugs for efficient use in developing countries.

Q: What are dissolving microstructures?

A: Although the concept of microstructures was proposed in 1970, it was not until 1990 that it was first developed.[1] There are various application principles for microstructure-mediated transdermal drug delivery:

i) less painful than the typical shot from a needle, solid microstructures are effective in creating small punctures in the skin that are ideal for allowing the skin to absorb active ingredients
ii) later on, solid microstructures were coated in medicine or creams before insertion into the skin, thereby directly delivering the active ingredients into the skin. These coated microstructures are applied for a specified duration, allowing the skin to absorb the active ingredients, before being removed
iii) the next phase was the development of hollow microstructures that delivered medicine in a tiny needle and syringe combination form. However, the previously stated microstructures tips could be broken and left under the skin, which had the potential to cause undesirable side effects, so innovative solutions were found
iv) dissolving polymer substances were mixed with medicines and active ingredients to create microstructures that naturally dissolved away after delivering their active ingredients into the skin (see Figure 1).

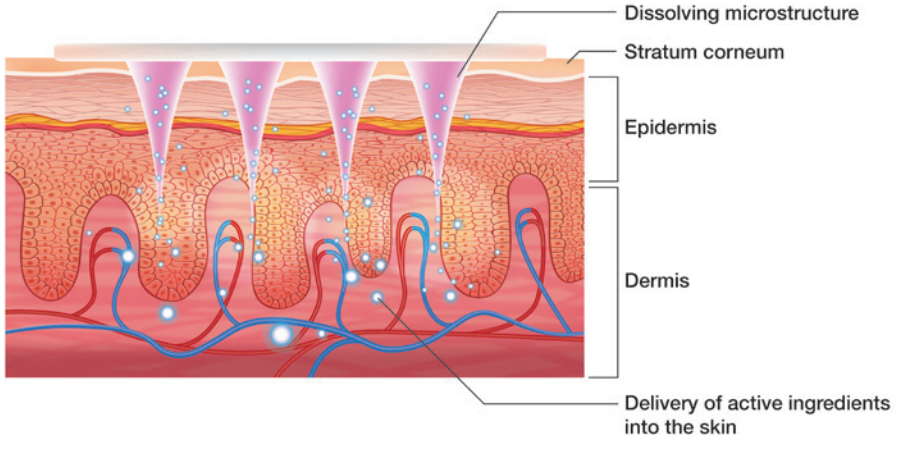
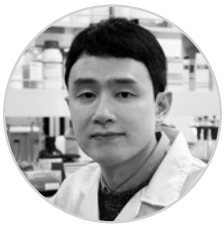


Figure 1: Diagram showing mechanism of action for dissolving microstructure delivery.



Dr Jung Dong Kim
Chief Technology Officer
T: +82 70 4483 9740
F: +82 2 2227 8052
E: info@raphas.co.kr

Raphas Co, Ltd
319-Ho
330 Seongam-Ro
Mapo-gu
Seoul
Korea 121-912

www.raphas.co.kr

The many phases of this research process led to the development of several different types of microstructures, all with their own characteristics and utilities. Although it is now well known that dissolving microstructures (Figure 2) are extremely safe, they are still not being used for the application of medicine or drugs. However, cosmetic products including sodium hyaluronate have recently been developed and marketed.

Q: What advantages are there in using dissolving microstructures?

A: The biggest advantage of dissolving microstructures is that they are much less painful than the standard needle and syringe. When applied in the form of a patch, they are easy to use for any consumer, and provide much more comfort and convenience. As opposed to liquid substances needed for application by injection needles, microstructures make it possible to distribute medicine in a safer solid state. Lastly, the use of dissolving microstructures is an environmentally friendly solution that leaves no dangerous and wasteful medical products behind, such as sharp needles or glass.

Patch microstructure products overcome the disadvantages of existing transdermal drug delivery systems, while combining the effective aspects of needle and syringe delivery methods. For these reasons, dissolving microstructures are a promising technology that is both very safe and convenient to use.

One of the many advantages of dissolving microstructures, especially in their solid state, is their ability to maintain a high level of safety in the distribution of biomedical products. This will significantly help reduce costs in the cold chain needed in the distribution of such projects, and could bring on a major turning point in the treatment of illness and disease for all of mankind.

The cold chain is in reference to the constant refrigeration process and infrastructure needed in the distribution of certain foods such as meat and seafood or medical products such as vaccines, proteins, and other biomedical items. Aside from these, there are many other products that rely on a cold chain for distribution. Studies have shown that in the biopharmaceuticals industry alone, costs for cold chain distribution of products are almost US$1 billion (£0.68 billion) a year. Current cold-chain distribution methods make it so that most products are shipped by air, greatly increasing the cost of transport. Up to 66% of biomedical products are being distributed by air, while only 33% is being shipped by sea – which is half the cost of transporting by plane.[2]

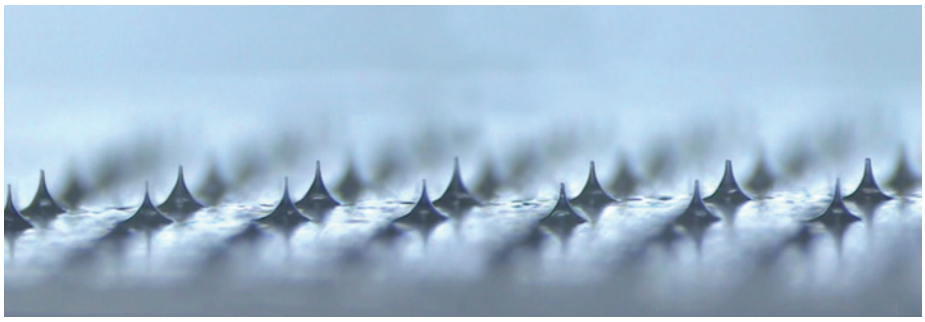


Figure 2: Microscope image showing the protrusions of a dissolving microstructure array.

Currently biopharmaceuticals for arthritis treatments, insulin shots for diabetes and other medical treatments have been developed into products. Thanks to advances in biotechnology, the mass production of biopharmaceuticals has been made easier, and this in itself has also contributed to increased research and development of the biopharmaceuticals industry. Therefore, the industry is also encroaching on the market share of synthesised drugs, which all leads to increased costs in refrigeration and storage of biopharmaceuticals. For example, vaccines are made up of various proteins that are often sensitive to heat and light, and therefore require refrigeration. The US$200-300 million annual cost of refrigerating vaccines may not be too much of a burden to bear for countries with an advanced medical industry, but less developed areas in Africa and Southeast Asia, and even countries like North Korea may not be able to afford these distribution costs. For these reasons, a large number of people around the world are not able to receive the vaccinations they need, and many are still dying from preventable diseases.[3]

In developing countries, **80% of the cost of vaccinations goes to the cold chain of distribution**, and therefore many efforts are being made throughout the world to reduce these costs.[4]

In order to solve these problems, international organisations such as the WHO and the International Society for Pharmaceutical Engineering (ISPE) have been putting out guidelines regarding cold chain management in order to help develop and propose methods to reduce costs as much as possible. However, viable cold chain methods differ between countries, so in order to reduce costs across the board, a truly ground-breaking method would have to be developed.

Microstructures are being researched by many institutions as an alternative solution to the high cost of cold-chain management, because if biopharmaceuticals can be delivered as a solid state in microstructures, its stability and effectiveness can be sustained for a long period of time. Furthermore, in the academic community there are many publications and presentations regarding stabilising agents for maximising desired effects in vaccines. In the near future, it should be possible to create microstructure vaccine patches that will greatly reduce the cost of storing and distributing vaccines.

"Patch microstructure products overcome the disadvantages of existing transdermal drug delivery systems, while combining the effective aspects of needle and syringe delivery methods. For these reasons, dissolving microstructures are a promising technology that is both highly safe and convenient to use"

Q: What unique technology has Raphas developed for the production of microstructures?

A: There are many techniques used in the production of dissolving microstructures being developed around the world, such as micro-moulding, drawing lithography, and droplet-born air blowing. There are advantages and disadvantages to each, and they are constantly being improved to maximise their efficacy. Some are undergoing clinical trials and preclinical testing,

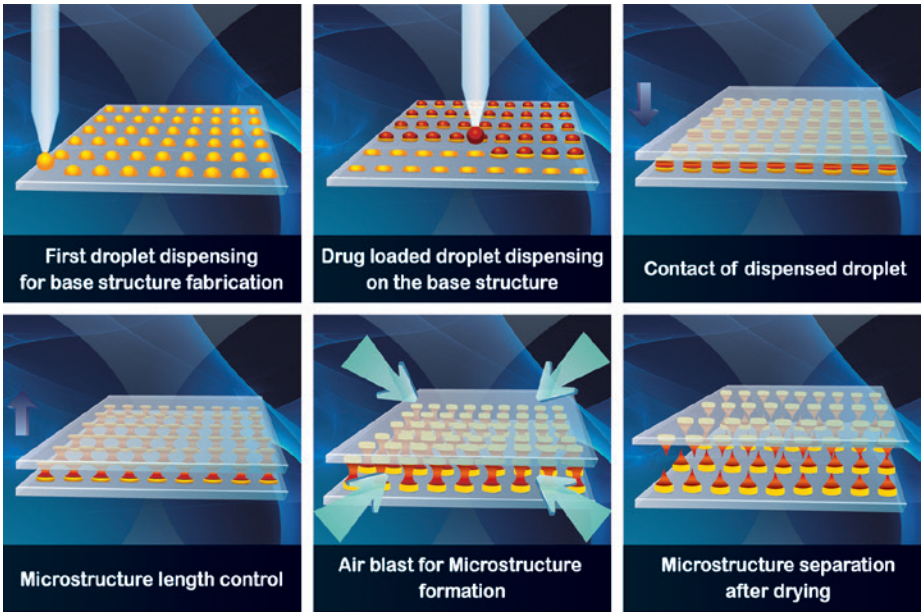


Figure 3: Steps in the Droplet-born Air Blowing (DAB) microstructure manufacturing technique employed by Raphas.

while others are in use for products currently on the market.[5]

The first dissolving microstructures were created using photolithography, which was commonly used for a semiconductor fabrication process. To create dissolving microstructures using photolithography, first various etching methods are used to create master moulds. Then, polydimethylsiloxane (PDMS) is poured to make PDMS moulds from which dissolving microstructure replicates are formed. A dissolving solution is poured into the PDMS mould, and is set using heat or UV light. Once the needles are taken out of the cast, they are just about complete.

This step, called micro-moulding, is a process used at most microstructure manufacturers. It is the process used to make the very first dissolving microstructures, and its big advantage is that access to the mould and the related equipment makes it possible to mass-produce dissolving microstructures.

Figure 5: Raphas' beauty patch product, Acropass.

However, micromoulding requires strong negative pressure using centrifuge and vacuum pumps to fill in the microscale mould with dissolving polymer solution. Furthermore, the dissolving polymers applied in this manner can be dried by carefully applying heat or UV light which has the potential to cause denaturation of sensitive proteins.

In 2010, Professor Jung Hyeong-il's research team at Yonsei University (Seoul, Korea), developed a technique called drawing lithography. In this technique, dissolving substances are coated onto a surface and heat is applied to make them stick. At the same time, microstructures are formed by pulling the surface vertically. The convenience of this technique, and its flexibility in adjusting the length and breadth of the needles made it very popular, and was featured on the inner cover of Advanced Materials and as a research highlight in Nature Phototonics. However, this process still needs the application of heat, and the coating process caused the loss of active ingredients, so the technique is not yet widely adopted for use.[6]

The technique currently being used at Raphas is called Droplet-born Air Blowing (DAB) (see Figure 3). This process was developed to reduce the microstructure fabrication time allowing for gentle fabrication conditions without the use of UV irradiation or heat. The main advantage of this technique is the ability to apply the desired amount of polymer drop in the desired location to form a single droplet into a single microstructure using a controlled air blowing. This makes it possible to fabricate microstructure in a few minutes without loss of active ingredients which are sensitive to heat or UV light.[7]

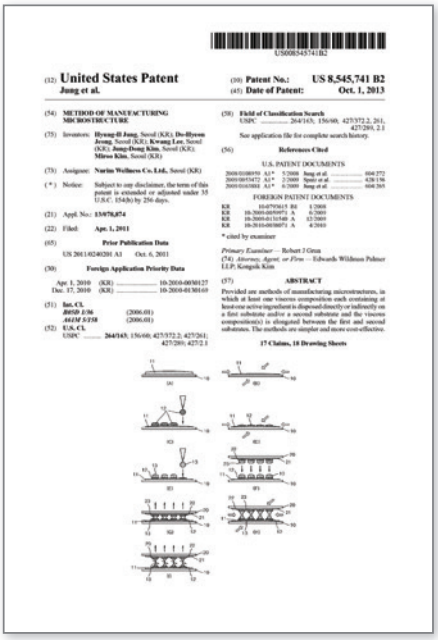


Figure 4: The key US Patent Application covering the DAB manufacturing process.

"In the biopharmaceuticals industry alone, costs for cold chain distribution of products are almost US$1 billion a year"

Figure 6: Raphas extended two production lines in 2014 to enhance its manufacturing capabilities.

Q: What types of intellectual property rights or certifications does Raphas have in relation to their techniques?

A: Raphas, using technology and rights transferred from Yonsei University, continuously works to strengthen its patent portfolio and other intellectual property. The company has registered a total of 12 patents, with its key patent DAB technique also registered in the US (Figure 5). Raphas is currently in the process of registering its patents in other countries around the world in order to strengthen its IP position further.

In addition to registration as IP, Raphas' DAB technology has received many certifications and awards in Korea and abroad. One of Raphas' many accreditations was for its microstructure skin care patch manufacturing technology, which was selected as a New Excellent Technology by the Korean Ministry of Trade, Industry and Energy in 2012. This served as a successful opportunity for Raphas' innovative industry technology to be recognised by the market and eventually led to mass distribution of its product.

In 2014, Raphas' beauty patch product Acropass (Figure 5) was approved by the Chinese CFDA, and was once again lauded for its safety and high quality. Also, Raphas' production facilities has a Class 10,000 clean room for the manufacturing of microstructure beauty patches, and has received ISO 22716 certification, ensuring consistent quality management of its products and facilities.

Q. What is the current status and future sales strategy for Raphas products?

A: Raphas product sales are primarily business to business (B2B). The company manufactures microstructure products containing a variety of raw materials with proven effectiveness, and sells them as ordered from various brands in an Original Development Manufacturing system. Most of its sales are for the overseas market, and products exported to the US and Japan make up the biggest shares of our sales. Raphas continuously works closely with companies selling their products for the selection of active ingredients, product design, testing, and other product development.

In order to serve in its role as a manufacturer better, Raphas extended two production lines in 2014 (Figure 6). Continual improvement of its processes and development of new products has pushed the company to expand to the manufacturing capacity of one million patches per month. During 2015, Raphas plans to expand its manufacturing ability by three times.

> "There are many techniques used in the production of dissolving microstructures being developed around the world, such as micro-moulding, drawing lithography, and droplet-born air blowing."

Raphas is also looking into ways it can operate as a Contract Manufacturing Organisation in the pharmaceuticals sector by co-operating on research with raw material medicine corporations and developing new products for these companies to sell. In this system, Raphas will use its technology to create drug delivery platforms for a wide variety of medicines, which will help further the company's scope of business.

As the focus of Raphas has been on development and manufacturing, close mutual co-operation with key companies has been essential to its business. Instead of simply partnering with anyone willing to sell its products, Raphas carefully seeks out partners that understand its products the best. This in itself was a process that was full of much trial and error. But through experience, Raphas found that no matter how much a large corporation was willing to mass distribute their product, a long-sustained relationship can only be possible if the seller had a deep understanding of Raphas's products and technology.

Q. What are some difficulties that Raphas has faced?

A: Raphas is the first to be using the technology that it employs, and has had to put together all of the necessary research and manufacturing equipment on its own, which came together which present challenges, naturally. In the beginning, there was much to be fixed and a lot of instability in the manufacturing. Thanks to years of hard work, Raphas now proudly maintains a consistently high-quality manufacturing system.

Also, the initial reaction of the market to Raphas's technology and products was difficult to influence. The dissolving microstructure patches that were developed took the industry time to get used to – even for those familiar with solid microstructure products. In order to overcome this, Raphas representatives travelled to every corner of the world where their products were being sold, to meet people directly and give detailed explanations of the advantages behind the technology and products. Sometimes new business was secured, and at other times Raphas was unsuccessful. However, overall there is now much more knowledge and interest in Raphas's microstructure patch products.

Q: What are the future plans for the company?

A: Up until now, the focus has been on the commercialisation of this new technology

and developing the manufacture of its related products. Now that Raphas has a solid foundation in this, we are able to produce a wide variety of beauty products. Raphas will continue to add new lines of products using microstructure technology, which will have a wide variety of features and effects. Raphas is also looking into developing new products that can be created in combination with existing cosmetic products.

In addition to this, Raphas hopes to put new efforts into the development of medical products. The current microtechnology being used can be effectively applied for use with a wide variety of drugs, especially as a platform for delivery of biopharmaceuticals.

Just as Raphas did in the beauty and skincare industry, the company plans on creating close partnerships with pharmaceutical and other companies to move quickly into this new market. By doing this, not only will Raphas contribute to the growth of Korea's pharmaceuticals industry, it will also move closer to becoming the "Path to Healing" that its name means.

"Just as Raphas did in the beauty and skincare industry, the company plans on creating close partnerships with pharmaceutical and other companies to move quickly into this new market.

ABOUT THE AUTHOR

Dr Jung Dong Kim became Director of the Raphas R&D Center in March 2014, and is now the company's Chief Technology Officer. He has also been a Co-operative Researcher at the University of Tokyo since May 2014. From September 2006 until February 2014, he completed a PhD in Biotechnology at Yonsei University, Seoul, Korea.

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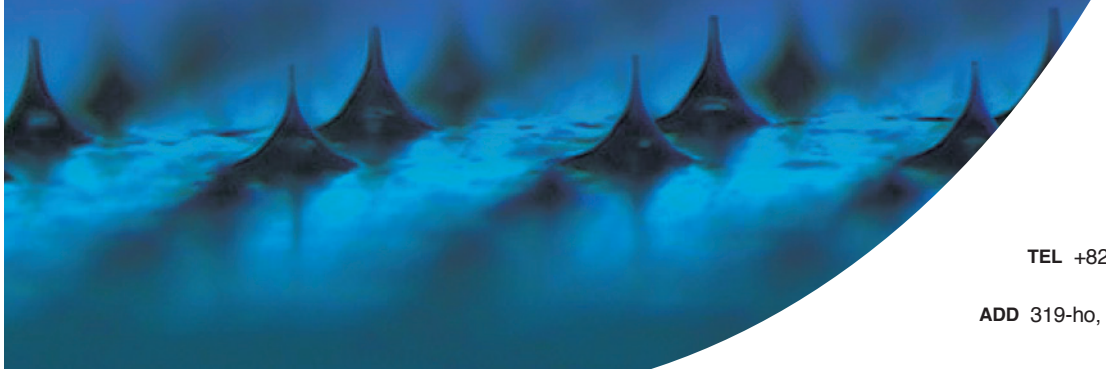
Become Beautiful Anytime

Raphas has discovered the most effective form of transdermal drug delivery. Specific quantities of medicine can be administered by carefully placing and shaping active ingredients into microstructures using Raphas's Droplet-born Air Blowing (DAB) technique. The innovative dissolving microstructures developed by Raphas minimizes loss of active ingredients, and is the most effective method for their delivery. This technology has already been developed for the beauty industry in the form of microstructure patch products, and has been commended for its surprisingly strong results. Raphas's technology can also be successfully applied to biopharmaceuticals and other industries, and in a wide variety of ways. Discover the fascinating new opportunities in transdermal drug delivery with Raphas.

Dissolving Microstructures: A New Manufacturing Solution

Ushering in a New Period of Transdermal Drug Delivery



Raphas

TEL +82-2-392-3011 **FAX** +82-2-392-3012
E-mail info@raphas.co.kr
ADD 319-ho, 330 Seongam-ro, Mapo-gu, Seoul, Korea
www.raphas.co.kr