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.

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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.

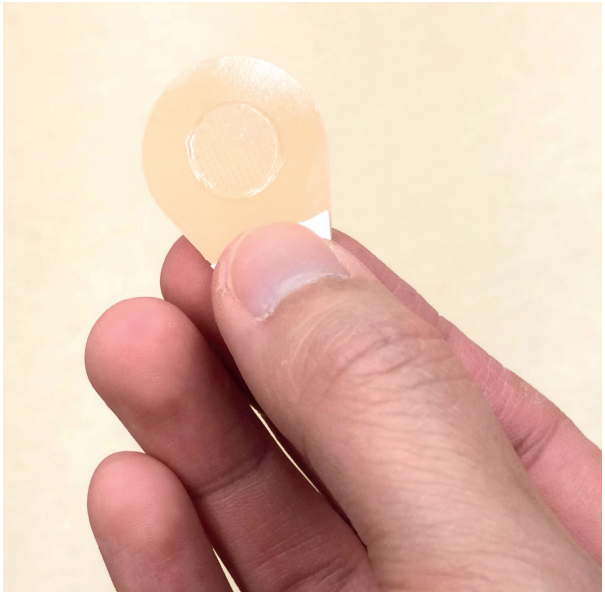

Figure 1: Micron's microneedle patch.

Dr Devin V. McAllister
Vice-President, R&D
E: dmcallister
@micronbiomedical.com

Mr Sebastien Henry
Vice-President, Program Management
T: 770-722-0306
E: shenry@micronbiomedical.com

Dr Mark Prausnitz
Chief Scientific Officer
E: mprausnitz
@micronbiomedical.com

Micron Biomedical, Inc
311 Ferst Drive NW
Suite L1309
Atlanta
GA 30332
United States

www.micronbiomedical.com

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.

REFERENCES

1. *Arya J, Henry S, Kalluri H, McAllister DV, Pewin WP, Prausnitz MR, "Tolerability, usability and acceptability of dissolving microneedle patch administration in human subjects", Biomaterials, 201, Vol 128, pp 1-7.*
2. *Rouphael NG et al, "The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): a randomised, partly blinded, placebo-controlled, phase 1 trial", The Lancet, 2017, Vol 390, pp 649-658.*
3. *Prausnitz MR, "Engineering microneedle patches for vaccination and drug delivery to skin", Ann Rev Chem Biomol Eng, 2017, Vol 8, pp 177-200.*