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.

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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.

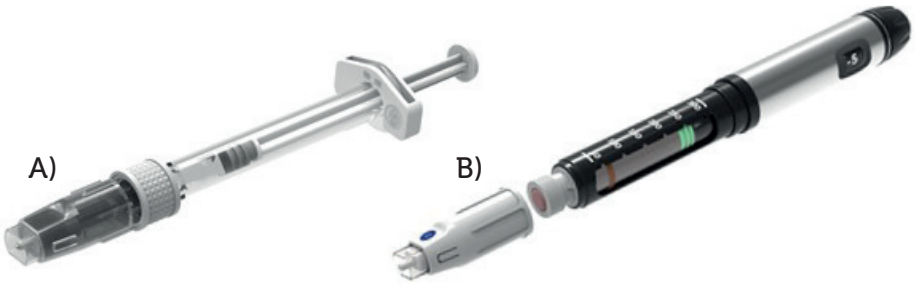

Figure 1: Microdermics intradermal drug delivery platform has been integrated as (A) syringe adapter and (B) microneedle pen designs.

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.

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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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