DEBIOTECH S.A. Switzerland
Innovative Medical Systems

YOUR SOLUTION FOR SUCCESSFUL INTRADERMAL DELIVERY

In this article, Paul Vescovo, PhD, Project Manager, and Laurent-Dominique Piveteau, PhD, MBA INSEAD, Chief Operating Officer, both of Debiotech, discuss the design of the Debioject™ microneedle device and inserter, and its applications, particularly in intradermal delivery of vaccines. Clinical development is underway and encouraging preliminary results are reported.

For many years, the transdermal route has been considered an interesting alternative to the oral or standard parenteral routes for the injection of drugs. Compared with the former, it prevents the active ingredient undergoing degradation in the gastrointestinal tract as well as the first-pass hepatic metabolism. Compared with the latter, it prevents patient pain induced by the shot as well as safety risks associated with contaminated needles. Despite this, there are very few drugs that are delivered today using this method.

The top layer of skin, the so-called *stratum corneum*, which has a thickness of 10-15 µm, acts as a tight barrier that prevents most chemical compounds penetrating into the body. Only small molecules, with adapted lypophilicity and sufficiently solubility may potentially be delivered in this way. Unfortunately, the vast majority of APIs do not match these criteria.

In addition to the advantages relating to the injection mode, the skin presents particularly interesting characteristics. Several studies have shown that the pharmacokinetics of certain compounds can be dramatically modified when infused within the skin. The peak time of insulin, the molecule forming the basis of diabetes treatment, can be halved compared with subcutaneous injections. For vaccines, when compared with intramuscular injections, doses required to reach sufficient immune response can be reduced by a factor of up to ten (as this is the case for rabies) or, at constant dose, immune response can be enhanced significantly (such as for flu in elderly patients).

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All these factors have encouraged the development of a variety of tools to facilitate the crossing of the upper layer of the skin by a wider range of molecules. Two major approaches have been followed. The first one, using chemical methods, has focused on the modification of the molecules or on their combination with other molecules to facilitate their passage through the *stratum corneum*. The second one has been focusing on physical methods to create passages through which molecules can penetrate into the skin. Electrical currents (electrophoresis) or ultrasound (sonophoresis) for example are used to make the *stratum corneum* porous for a certain period of time. By placing a simple drug container on the treated surface, the drug could then

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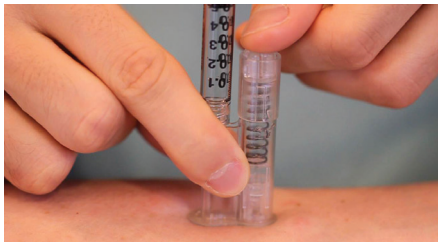

Figure 1: DebioJect™ is very easy to use.

slowly diffuse into the tissue. Microneedle technologies are part of these physical approaches. By their form, microneedles dig passages through the protective layer of the skin that will be used by the drug to diffuse into the tissue.

They are four different ways usually described to perform intradermal injections using microneedles:

POKE AND PATCH

The so-called "Poke and Patch" method is similar to what we described earlier with the electro- and sonophoresis approaches. Microneedles are used to create pathways in the skin mechanically, which are then covered by a patch containing the drug to be delivered. As long as these pathways stay open, the drug diffuses into the skin.

COAT AND POKE

In the "Coat and Poke" approach, needles are coated with a formulation comprising the active agent combined with a polymer that will dissolve after insertion of the needles into the skin. Minutes after placement, the needles are removed, the coating has disappeared and the active agent has been delivered.

POKE AND RELEASE

In the "Poke and Release" approach, needles are made of a soluble material containing the medicament. Once in the tissue, the needles will dissolve and release the active principle.

POKE AND FLOW

Finally, in the so-called "Poke and Flow" approach, hollow microneedles play the same role as conventional needles by creating a mechanical channel through the skin which will be used by a liquid formulation to penetrate the tissue. DebioJect™ microneedles, recently named as MDEA Awards 2014 finalists, are part of this latter category.

Figure 2: Single microneedle mounted on a connector.

Figure 3: Multiple microneedles mounted on a connector.

MEDICAL DESIGN EXCELLENCE AWARDS® 2014 FINALIST

THE DEBIOJECT™ SYSTEM

The DebioJect™ System is intended for injecting any liquid substance or drug fluid into the dermis. This CE marked device is very easy to handle and doesn't require any special skills (Figure 1). The depth of injection and the amount of substance delivered are both reached precisely and in a controlled way. DebioJect™ can inject a bolus of up to 500 µL within less than five seconds.

The system comprises two main elements:

- a single or an array of hollow microneedles (Figures 2 and 3) in fluidic connections with a reservoir containing the medical substance to be delivered into the dermis
- an inserter (Figure 4) to place the microneedles into the dermis at the targeted depth and maintain them in place during the whole injection.

Although the innovative hollow microneedles are the heart of the system, the inserter plays an essential role.

MICRONEEDLES

Due to the thin nature of the dermis layer, the needles must be very short – less than 1 mm – in order to ensure delivery of the medical substance into the targeted region (Figure 5). They are made of high-purity monocrystalline silicon covered with a native thin layer of silicon dioxide. Silicon offers very interesting mechanical properties. It is a non-ductile material with an incredibly high tensile strength and hardness. With such mechanical properties, and as it was demonstrated experimentally, there is nearly no risk of microneedle breakage in the skin. Furthermore, silicon and silicon oxide have excellent biocompatibility.

Microneedles are monolithic and made without any assembly. They consist of a flat substrate sustaining the microneedle part. A fluidic micro-channel goes through the whole needle, from under the substrate to the delivery hole which is placed, not

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Figure 4: Two kinds of inserters.

on the tip of the microneedle, but on its side (Figure 6).

The length of the microneedle and the position of the delivery hole can be changed by design in order to deliver the fluid at any required depth between 150 µm and 900 µm. A microneedle can have one or several delivery holes placed circumferentially (Figure 7). The outer shape of the microneedle is designed with a very sharp tip to puncture the skin easily. The microchannel drives the injected fluid from the injection line through the delivery hole into the patient's skin.

DebioJect™ microneedles are produced using well established industrial Micro Electro Mechanical System (MEMS) technologies (Figure 8). MEMS are manufactured using modified semiconductor device fabrication technologies, commonly used to manufacture IC circuits. It allows the manufacturing of very small devices with a sub-micron precision, far better than standard micromechanical technologies. DebioJect™ microneedles are currently manufactured by Leti (Grenoble, France), which is part of CEA, one of the world's largest organisations for applied research in micro-electronics and nanotechnology. It offers extensive facilities for micro and nanotechnology research, including fabrication lines, 11,000m² of cleanroom space, and first-class laboratories and equipment.

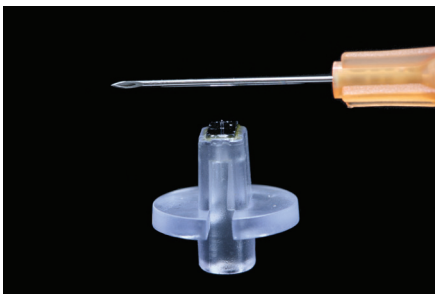


Figure 5: Comparison between a microneedle and a 25G needle.

The manufacturing process developed with Leti/CEA is completely compatible with the major industrial MEMS foundries.

The needles are processed on 200 mm (8 inch) diameter silicon wafers. About 1,500 microneedle chips can be produced on a single wafer. The entire process is conducted in an ISO Class 3 cleanroom environment. MEMS technologies enable the manufacturing of high volumes of devices at a very low cost.

INSERTER

The inserter must provide the microneedle with the right dynamic parameters (force, velocity, energy) to ensure its full

Figure 6: SEM image of a 700µm long microneedle with single hole.

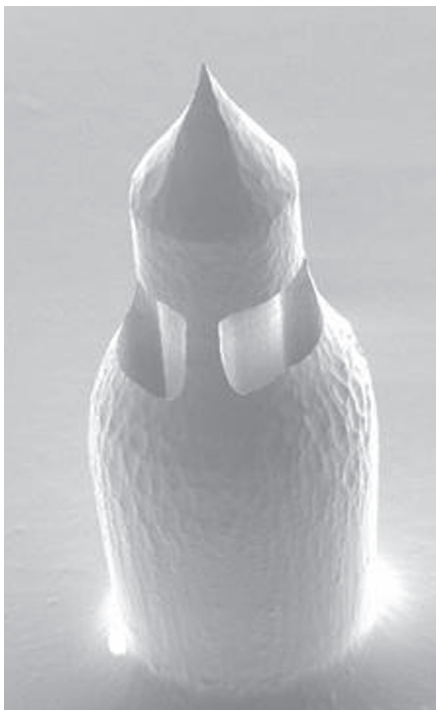


Figure 7: SEM image of a 700µm long microneedle with mutiple holes.

penetration into the skin without any rebound. Once the needles are in place, it has to maintain its position throughout the whole injection procedure. The issue is very challenging, as the inserter must ensure precise positioning on a soft substrate, even though both the patient and the practitioner will undoubtedly make normal uncontrolled tiny movements. Regarding the length of the microneedle, even very small motions below 1 mm are critical. This issue has been extensively studied *in vivo* in humans with a micro camera mounted on an inserter (Figure 9).

"The fluidic jet is oriented horizontally at the exit of the needle and the delivered drug will have a natural tendency to pursue its course in the same direction"

A properly designed inserter should guarantee injections without any leakage which is one of the major issues of intradermal injection with microneedles. It's particularly critical as even a tiny leak may be significant relative to the small injected volume, and could lead to a medical treatment failure.

The design of the microneedles and the inserter must be adapted to satisfy each application and targeted population.

DEBIOJECT™ KEY ADVANTAGES / ID INJECTION CHALLENGES

As described above, the *stratum corneum* forms a strong barrier to protect the underlying tissues yet in order to reach the dermis the microneedle has to go through this layer. It must therefore have a sharp tip to easily pierce the tissue and be made of a strong and hard material, especially since the microneedle will contact the skin at a relatively high speed, to penetrate it. The microneedle contact area with the skin must be minimal to facilitate the penetration and limit tissue damage. For the patient this means no pain, a fast healing and no leakage at the base of the microneedle.

Even though the microneedle diameter must be as small as possible, the inner microchannel has to be large enough to limit the fluidic resistance and allow a good passage for the drug. Thanks to that, even highly viscous solutions have been successfully injected with the device.

The structural components of the dermis are collagen, elastic fibers and extra-fibrillar matrix. It forms a dense and incompressible structure. For this reason the hydrostatic pressure will tend to increase during injection, especially if the delivery hole is positioned at the tip of the microneedle. The tip of the needle is compressing the tissue and as a consequence it increases the fluidic resistance in this area. It's therefore very beneficial to place the delivery hole on the side of the microneedle as the fluid will be delivered into a region which is less compressed and presents a lower fluidic resistance. Another advantage is that it tends to push the injected liquid in the dermis, and not in the subcutaneous tissues (Figure 10). The fluidic jet is oriented horizontally at the exit of the needle (contrary to "classical" needles) and the delivered drug will have a natural tendency to pursue its course in the same direction. Another major advantage of a delivery hole which is not placed at the microneedle tip is of the absence of coring and as a consequence of clogging of the micro-channel which may lead to high fluidic resistance or even complete occlusion when using conventional straight-hole needles.

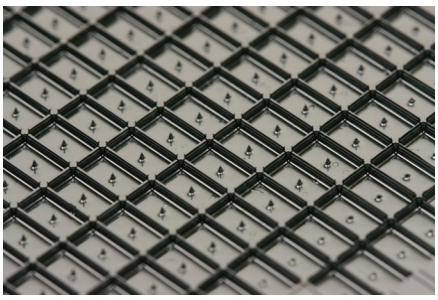


Figure 8: Microneedles on a wafer.

PRECLINICAL & CLINICAL STUDIES

DebioJect™ microneedles have undergone several preclinical and clinical studies. Preclinical studies conducted on various animal models such as mice, rats or pigs, are covering areas ranging from basic research to preliminary tests for clinical trials of new drugs. In the more fundamental trials, the objective is to understand the distribution of an injected fluid into the dermis precisely. Here the control in depth that can be achieved thanks to the design of the needle is of particular interest.

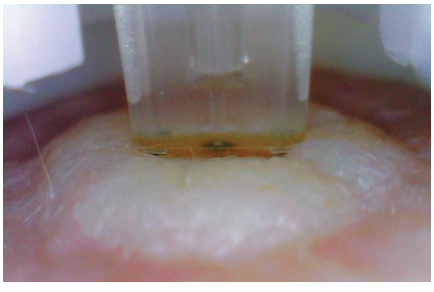


Figure 9: Microscopic view of an injection on human skin in vivo.

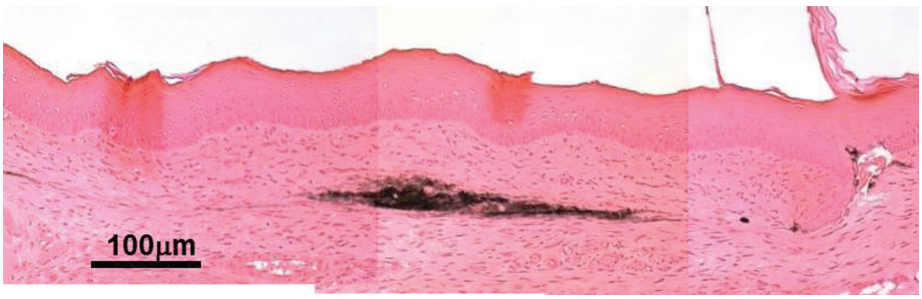


Figure 10: Transverse histological section of mouse skin after injection with DebioJect™.

Clinically, both the DebioJect™ microneedles and the effectiveness of the intradermal route are being tested. For the former, the perception by the patient and the possible side effects of the DebioJect™ are evaluated, while for the latter the response to different molecules injected intradermally (sometimes at lower doses) is compared with that obtained when using conventional subcutaneous or intramuscular injections.

A study currently underway and conducted in collaboration with the Vaccine and Immunotherapy Centre of the Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne, Switzerland, compares the injection of rabies vaccine (Vaccin rabique Pasteur®, Sanofi Pasteur, Lyon, France) intramuscularly, with the Mantoux method and using DebioJect™ microneedles. The sixty-six volunteers involved in this study are divided into three groups. Each group receives injections with all three methods, but only one of the injection devices is filled with antigen, the other two containing placebo.

In this double blinded study, each patient after an inclusion visit receives three series of injections: one at T_0 (where the antibody level baseline is also measured), a second one at T_0 + 7 days and a third one at T_0 + 28 days. For each injection, the pain perceived during the insertion of the needle as well as the pain perceived during the injection of the active ingredient are measured. This is described by each volunteer on a scale of zero to 10 (zero for no pain and 10 for maximal pain). This distinction allows for segregating the impact of the microneedle of the effect of the infused drug product itself. The order in which injections are done is changed at each visit in order to limit the comparison effect. Side and adverse events such as redness, pruritus and irritation are also recorded. Finally, during each session as well as three weeks after completion of the last injection, a blood sample is taken and analyzed by RFFIT to determine anti-rabies IgG levels.

A first series of intermediate results has already revealed some highly interesting information. Upon insertion of the needle, the perceived pain is slightly higher for the intramuscular injection than the Mantoux method. The use of a DebioJect™ microneedle is significantly less painful. Upon injection of the active agent, the perceived pain of the intramuscular shot and of the DebioJect™ is similar, but statistically lower than that perceived when using the Mantoux method (Figure 11). The absence of leaks (or partial leaks) during the injection is also a noticeable point. These results are very favourable to the approach using DebioJect™. As the study has not yet been unblinded, it is impossible to attribute the different IgG levels measured to the different immunisation routes. It is however interesting to note that all patients are fully immunised, regardless of the method used. These results tend to show non-inferiority of the DebioJect™ approach.

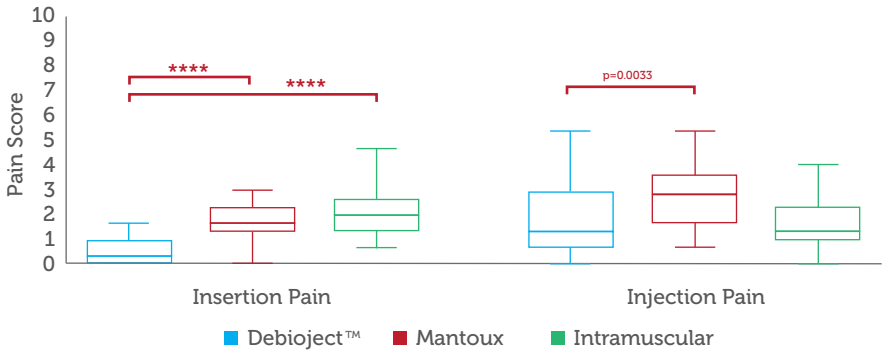


Figure 11: Pain perception comparison.

CONCLUSION

When speaking about intradermal injection, the first application that comes to mind is undoubtedly the vaccination. Since the visionary work of Charles Mantoux and Louis Tuft at the beginning of last Century, many studies have focused on this path often with encouraging results. More recently these have included the treatment of skin cancer, desensitisation, but also various applications in the field of cosmetics that have been developed. With the emerging availability of technologies enabling successful intradermal injections without special education or in-depth training, there are undoubtedly many other application areas that will generate interest for this delivery route.

DebioJect™ microneedles have been conceived to replace conventional needles, but their very particular design allows considering for the future having them filled with solid formulations that will dissolve over time inducing a controlled release over long duration.

ABOUT DEBIOTECH

Debiotech SA is a Swiss Company with more than 20 years' experience in developing innovative medical devices, based on micro- and nanotechnology, microelectronics, and innovative materials. The company concentrates on implantable and non-implantable systems, in particular for drug delivery and diagnostics, with a demonstrated competence lying in the identification of breakthrough technologies and their integration into novel medical devices.

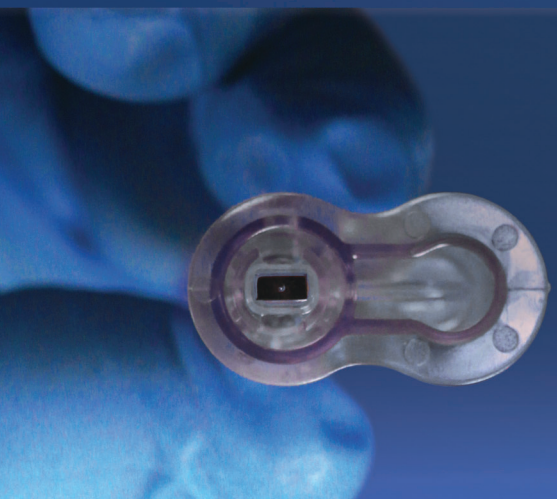
Devices developed by Debiotech are ultimately licensed to major international pharmaceutical and medical device companies, and Debiotech has a track-record of over 40 license agreements worldwide. Examples of products, in addition to the DebioJect™ microneedles for intradermal injections, include: the I-Vantage™ IV pump for hospital and home-care; the CT Expres™ Contrast Media injector for CT-Diagnostic Imaging (recently acquired by Bracco Imaging); the JewelPUMP for diabetes care; the DialEase™ home-care miniaturised dialysis equipment; and others under development.

DebioJect™

Microneedle Intra-Dermal Injection

Simple and Reliable ID System

- easy to use and reproducible
- painless injection
- automatic insertion
- precise depth control
- up to 500 µl in 3 seconds



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