DERMAL DELIVERY OF BIOLOGICS

Here, Faz Chowdhury, PhD, Chief Executive Officer, and Richard Toon, PhD, Technical & Business Development Manager, both of Nemaura Pharma, describe one of the company's key technologies for the delivery of biologics, the Micropatch™.

Nemaura Pharma provides solutions for drug delivery through the skin using its proprietary platform technologies. The Micropatch™ skin insertion platform offers a versatile topical or transdermal delivery platform for a large range of molecules, including biologics.

An increasing number of drug companies are turning to transdermal drug delivery platforms both for existing molecules as well as for the delivery of new chemical entities and biologics, as an effective means of painlessly delivering the drug. Nemaura Pharma has a portfolio of proprietary technologies including conventional matrix patches, and intuitive microneedle-based technologies for the rapid and efficient delivery of a range of molecules. These technologies have been developed to be cost-effective alternatives to conventional modes of drug delivery, yet provide accurate, robust and reproducible-dosing with minimal patient intervention.

THE POTENTIAL & CHALLENGES OF MICRONEEDLES

Microneedles are needles whose length is in the hundreds-of-microns range, which can be produced from a wide variety of materials including polymers, metals, and the drug formulation itself. Microneedle systems are in widespread development and have been successfully clinically tested for a number of different molecules. However, there are a number of significant challenges that must be addressed before they can be commercialised:

- Dose loading is very low, and doses delivered are usually in the microgram to low milligram range.
- Larger doses require larger patch sizes but larger patches are associated with uncontrolled non-reproducible skin application thus poor reproducibility of dosing.
- Formulations must be able to adhere on to the needle surface, or in the case where the needles are produced from the drug itself the drug must have the requisite physico-chemical properties to maintain tip sharpness for adequate skin penetration. Many drugs will not have the requisite properties therefore and thus be rendered unsuitable for microneedle delivery, or require protracted pharmaceutical development programmes.
- It is very difficult to verify that a dose has actually been delivered other than where the needles are required to dissolve into the skin and where upon removal of the patch from the skin there is visual evidence of the needles having dissolved and no longer being present on the patch. In the case of drug adhesive patches an

Figure 1: Images of hollow drug loaded pellets used in the Micropatch™ Drug Delivery system.

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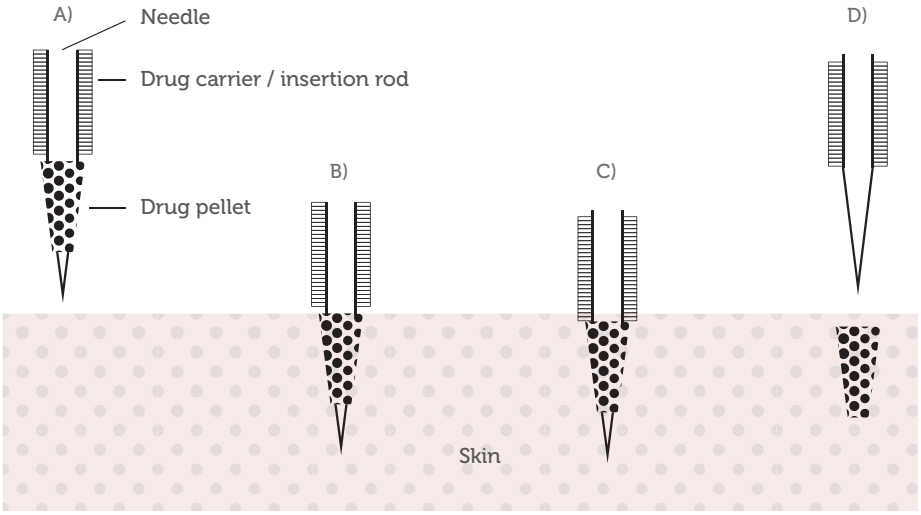

Figure 2: Sequence of microneedle delivery via the Micropatch™.
A) Microneedle or needle containing a hollow drug loaded pellet
B) The needle is inserted into the skin, engineered to insert to the desired depth.
C) Drug carrier slides down the side of the needle inserting the drug into the skin and then
E) The needle is retracted from the skin with the drug 'package' remaining inside the skin.

analogous scenario is delamination of the patch from the edges of the skin leading to inaccurate dosing, however in this case the needles would need to remain inserted into the skin over the entire surface area for the duration of dosing.

- The depth of penetration of the microneedles will vary from person to person based on skin thickness and toughness and reproducibility of application.
- The residence time of the needles inside the skin cannot be adequately controlled or determined and movements of the body will lead to motions that have potential to dislodge the needles out of the skin given their very shallow depth of penetration. Long residence time can also be a source of skin irritation that may lead to rubbing of the patch thus dislodging the needles from the skin.

Collectively, the above pose some significant obstacles that must be overcome before the mass utilisation of microneedle technologies for drug delivery applications becomes a reality.

BENEFITS OF NEMAURA'S MICROPATCH MICRONEEDLE SYSTEM

Nemaura's Micropatch was designed and engineered with a view to addressing these challenges. The device can be compared with the "poke-and-patch" method that is defined in microneedle terminology as a process whereby the skin is first prepared by applying the needles followed by the application of a drug loaded patch or gel for example. However, in this case the procedure is precise whereby the drug is inserted directly into the holes created using the needle(s) after removal of the needles from the skin, or the drug is placed into the skin along the side of the needle using a 'carrier' whilst the needle is still inside the skin, followed by removal of the needle and carrier from the skin.

These features impart the following advantages to the Micropatch:

- Drug loading may be µg to mg without any restrictions to drug insertion being imposed by the drug physico-chemical properties, thus reducing the complexity of the pharmaceutical development stage.
- A finite dose is delivered according to needs, ranging from µg to 10's of mg or more (using multiple doses on a single device).
- The delivery time, and thus residence time of the needles inside the skin, is in the order of a few seconds, i.e. near instant delivery.
- Dose delivery can be verified as the dosage is clearly visible within the carrier section of the device.
- Depth of delivery can be modulated as required from hundreds of µm to a few mm, depending on the dose and desired penetration depth.
- The device is a single mass producible disposable unit, though a non-disposable applicator and a disposable drug portion can also be accommodated.

This device provides a means for the delivery of both small molecules as well as biologics, with the possibility of modulating drug release based on formulation excipients and processing method. Importantly this provides a means for self-administration of drugs through the skin that may otherwise have to be administered by a healthcare professional.

Figure 1 shows images of hollow drug pellets used in the Micropatch delivery system, Figure 2 shows a schematic of the mechanism by which the Micropatch operates and Figure 3 shows images of the skin following insertion of the micro-pellets, which indicate that the skin completely seals up after administration, and any superficial signs of skin trauma disappear within an hour of insertion.

The Micropatch can be used for the delivery of a single drug or multiple drugs simultaneously using multiple needles on a single device. Needle length can be varied from hundreds of microns leading to minimum sensation, or several millimeters in length for deeper depot delivery of drug 'packages'. The drug packages may be formulated according to a range of geometries in the diameter range of tens to hundreds of microns, making it easy to administer precise doses, effortlessly with minimal pain sensation.

Nemaura Pharma already has global license agreements with pharmaceutical companies for some of its technology platforms. Nemaura is actively seeking to broaden the list of partnerships and collaborations for the delivery of small molecules and biologics which may otherwise suffer from drug delivery challenges.

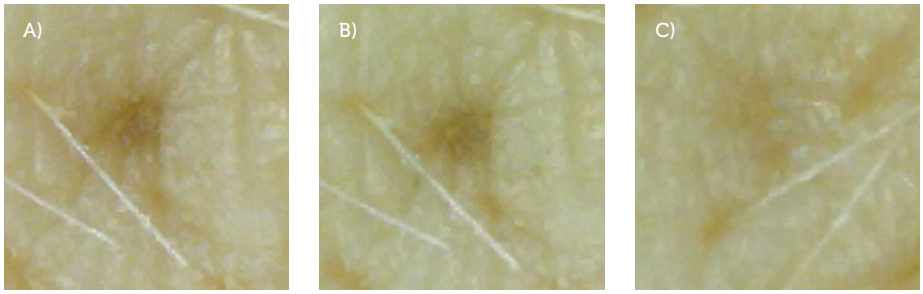

Figure 3: Insertion of 500 µm BSA particle in porcine skin. A shows the initial insertion of BSA. B after 30 minutes, C after 70 minutes, taken using a USB microscope.