NOVINJECT
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.

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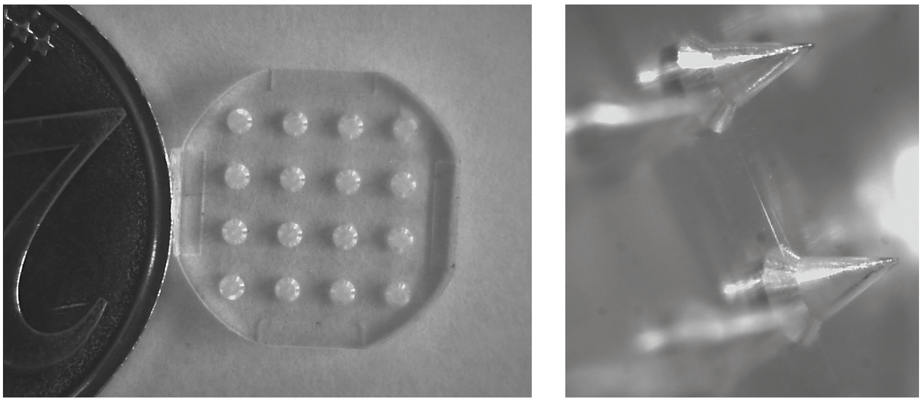

Figure 1: A 16 hollow microneedle array moulded in highly biocompatible polymeric material.

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.

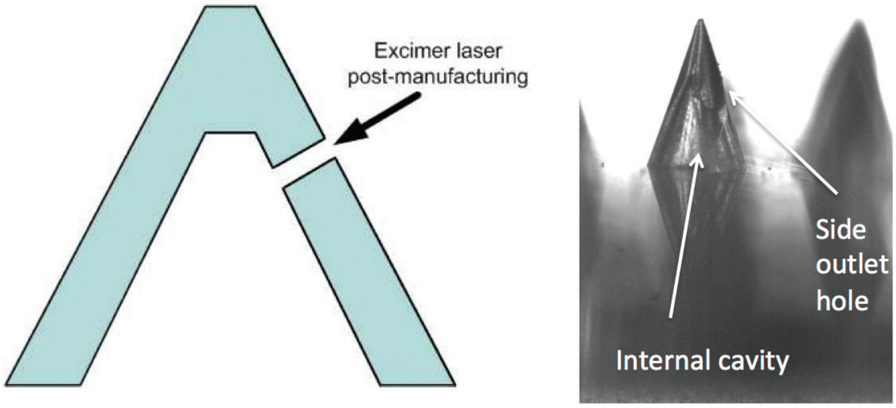

Figure 2: Original design of Novinject microneedle solutions.

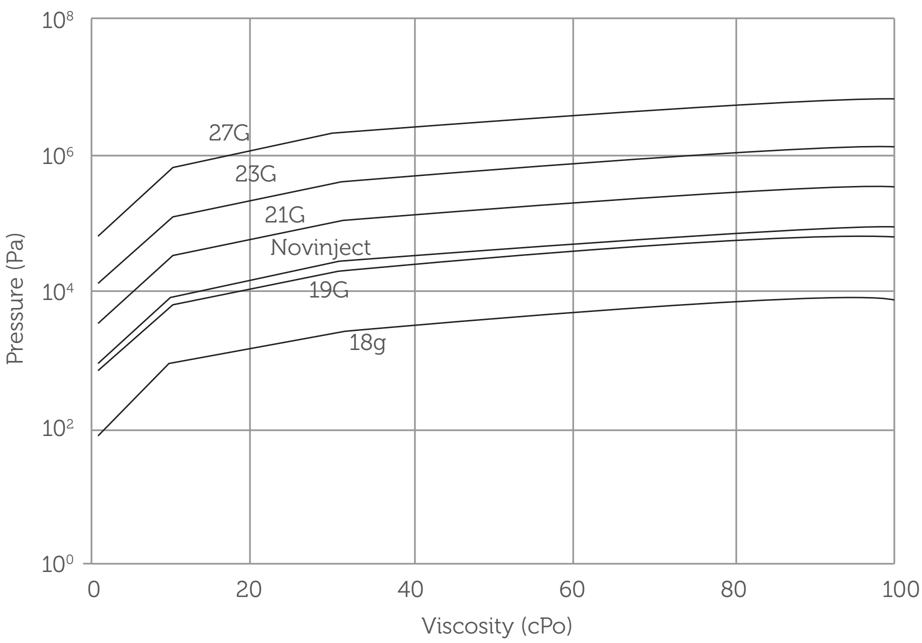

Figure 3: Theoretical pressure for different needle gauges and Novinject microneedles to inject 1 mL/min of solution.

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:

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

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:

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

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.

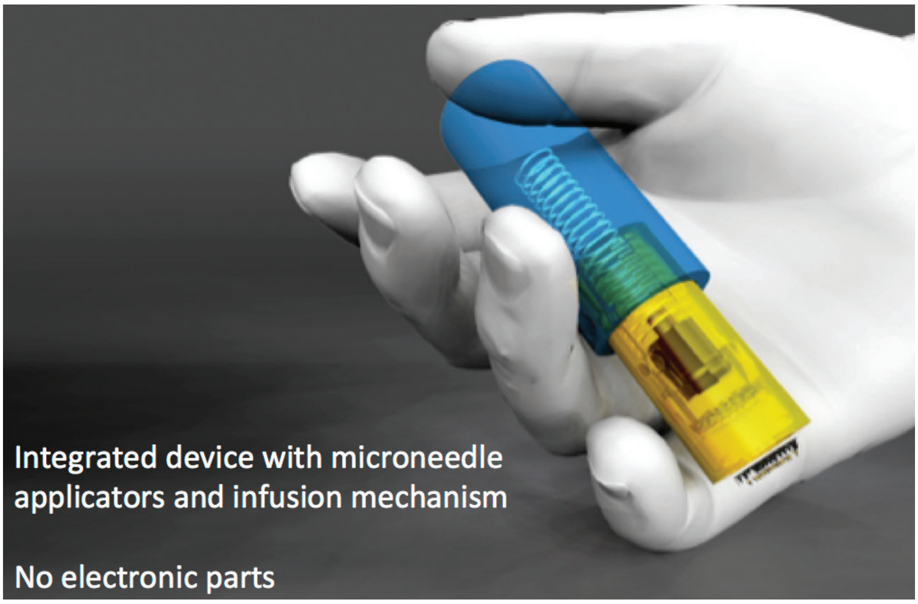

Figure 5: Representation of an impact applicator solution.

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.

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.

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ACKNOWLEDGEMENT

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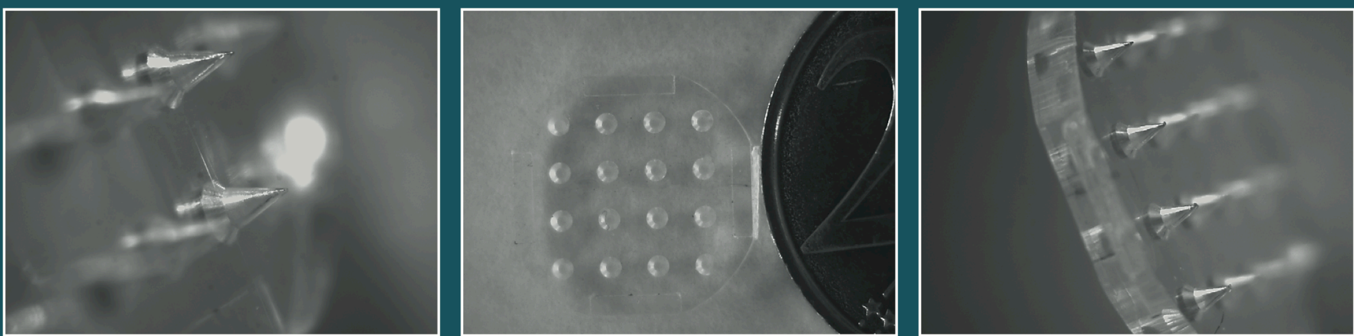
WE DESIGN MICRONEEDLE SOLUTIONS FOR TRANSDERMAL INJECTIONS

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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