MEDICSEN: NEEDLE-FREE SMARTPATCH FOR PAINLESS DRUG DELIVERY

In this article, Eduardo W Jørgensen, MD, Chief Executive Officer, Juan César de Mercado, Chief Operations Officer, and José Carlos Montesinos, Chief Technology Officer, all of Medicsen, describe the Smartpatch, a novel technology for subcutaneous delivery of drugs via a comfortable, pain-free patch using sonophoresis, based on Medicsen's patented miniaturised ultrasound technology.

DRUG DELIVERY IS A PROBLEM

There is a clear market trend in drug delivery pointing towards products that deliver greater comfort, control and standardisation. However, the traditional market remains focused on painful and uncomfortable needles and pumps, with new innovations having major drawbacks, such as iontophoresis devices that only work with small, charged molecules or the formulation hurdle of needing to modify the drug for different, less painful methods of administration like inhalation.

There are over 16 billion injections per year, each creating biowaste and over 2,000 needlestick injuries per day in the US, generating over US$3 billion (£3.2 billion) in associated costs every year. The World Health Organization has called for a global effort on smart injectors to reduce the problems associated with traditional needle-based injections, and the transdermal pathway has a promising future as first choice for the delivery of most molecules. However, there have been major challenges in the drive to develop wearable, connected and painless transdermal devices that could be used with virtually any drug.

Figure 1: Medicsen's Smartpatch..

> "Medicsen's research suggests that the only efficient approach towards a universal needle-free device is through sonophoresis, but this technique has traditionally required large devices with significant power demands."

Microneedles offer limited benefits and are hardly controllable, jet-injectors are painful and bulky, and implants can be unsafe for certain drugs. Medicsen's research suggests that the only efficient approach towards a universal needle-free device is through sonophoresis, but this technique has traditionally required large devices with significant power demands. To improve the viability of sonophoresis, Medicsen has centred its R&D efforts on optimising ultrasonic skin stimulation for drug delivery and enclosing the technology in an intuitive and comfortable device.

MEDICSEN´S SMARTPATCH

The Smartpatch is a wearable, needle-free drug delivery device based on Medicsen's patented skin permeabilisation technology (Figure 1). Medicsen's specific combination of ultrasonic waves creates a transitory disorganisation of the stratum corneum of the skin. This allows macromolecules of up to 2,000 kDa (e.g. heparin, insulin, interferon, antibodies, vaccines) to cross the skin barrier without the patient experiencing pain or other abnormal feelings. Permeability is only present while the device is activated, with skin returning to normal shortly after stopping stimulation.

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The specific ultrasound setting is slightly adapted to each patient by the Smartpatch to optimise performance in different skin types. Changes to the ultrasound settings also allow the device to modify the absorption rate and depth reached by the drug. Medicsen's tests have shown absorption rates of 0.05–0.2 mL/minute on a 1 cm^2 pig skin area. Drug penetrates through the skin, reaching the hypodermis, and then diffuses to the capillary vessels and circulatory system following the same pharmacokinetics and pharmacodynamics of the drug with its original delivery method (subcutaneous or intradermal).

In short, the Smartpatch uses sonophoresis, an alternative delivery methodology, for the proven subcutaneous administration route. It could be described as a syringe with no needle or a pump with no catheter. It provides painless, wearable and controllable drug delivery (Figure 2).

Figure 2: Smartpatch and accompanying phone app.

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The device involves two major components:

- A durable, reusable part that contains the electronics and ultrasound generators. Medicsen and its research partners, such as CSIC (Spanish National Research Council, Madrid, Spain), made possible this state-of-the-art technology by reducing the size and power consumption of the ultrasound actuators, which was a necessary step towards a truly wearable device.
- A disposable piece with biocompatible reservoirs for containing the drug and hypoallergenic adhesive that can be replaced in less than two minutes. Reservoirs can be loaded by the patient using traditional drug presentations, such as vials and syringes.

The Smartpatch is designed to last for up to 24 hours in full operation; the drug reservoir can hold 2 mL of drug per cm^2 of skin to be stimulated. This capacity means that Smartpatch is capable of delivering most subcutaneously administered chronic daily treatments, such as insulin or interferon. The device can be operated from a Smartphone app, via a Bluetooth connection, but is also operable using the physical buttons on the device itself.

How It Works

The Smartpatch is operated using four simple steps (Figure 3):

1. **Load:** Users inject their drug into the reservoir using a traditional syringe
2. **Insert:** The disposable piece is inserted in the durable part of the Smartpatch device
3. **Place & Activate:** The device is attached to the body via its adhesive or elastic band. The dose can be selected on the device or on the app
4. **Detach:** The reservoir is ejected by pressing a button and then disposed of for recycling.

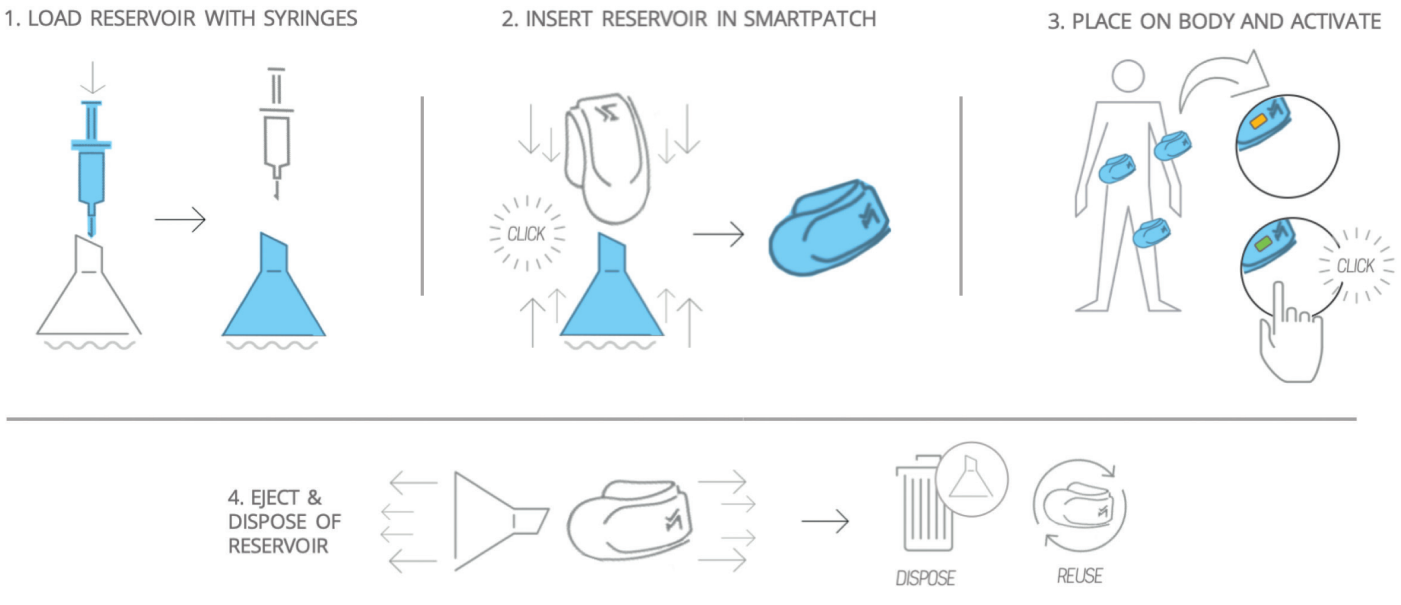

Figure 3: How the Smartpatch works.

CURRENT STATE AND TRIALS

Medicsen's Smartpatch is currently an *in vivo* working prototype undergoing miniaturisation to reach its final version. Getting to this stage has required over three years of trials, moving from the basic science to development of the full prototype.

Medicsen has chosen to focus on insulin as the first molecule to validate with the Smartpatch, since improving treatment for diabetes is core to Medicsen's identity and, given the prevalence of diabetes in society, a successful, pain- and needle-free insulin delivery method will have a huge impact. Medicsen conducted hundreds of *in vitro* trials with insulin and ultrasound on pig skin with the aim of demonstrating:

- **Permeability:** Density of energy, flow rate, conductance, timings, etc
- **Skin Safety:** Absence of damage to the pig skin, tested by electronic microscopy and enzyme-linked immunosorbent assay (ELISA) of tumor necrosis factor alpha (TNF-α) and interleukin-2 (IL-2)
- **Insulin Safety:** High-performance liquid chromatography (HPLC) and circular dichroism studies show conserved bioactivity and structure
- **Replicability:** The ability to replicate the studies with alternative molecules, such as interferon.

Following positive results in the final *in vitro* trials, Medicsen prepared and completed *in vivo* animal trials in 2020 during the global pandemic. The pig trials have projected the optimal parameters for

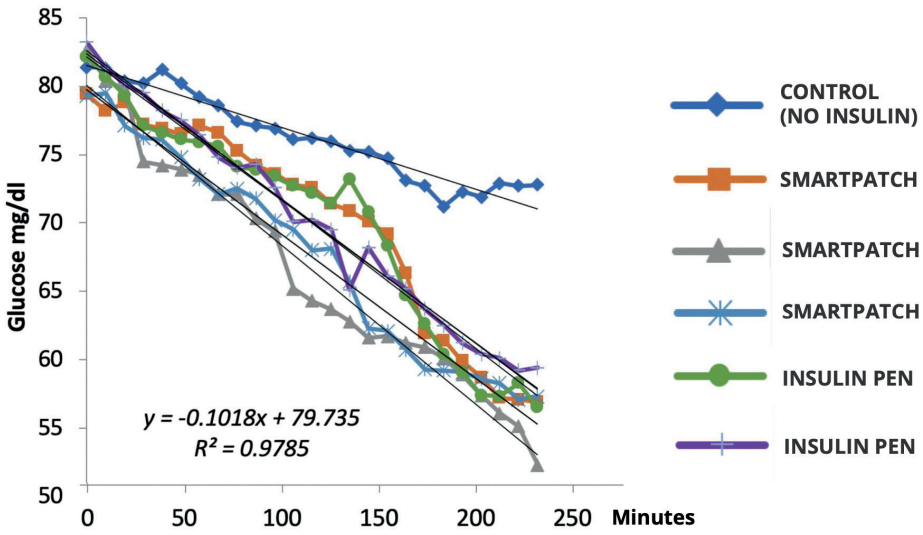

Figure 4: Glucose reduction in pig trials.

device configuration and confirmed the safety, absorption efficacy and correct functionality of the Smartpatch, allowing Medicsen to decrease the risk in upcoming *in vivo* human trials.

Medicsen performed individual pig trials with sus scroffa (landrace) pigs, which had their blood glucose measured before and after administering a controlled dose of insulin (25 units) with both the Smartpatch and a traditional insulin Novorapid® pen (Novo Nordisk, Bagsværd, Denmark). The test results showed an average slope of the glucose reduction curve of -0.09 with the Novorapid® pen and -0.10 with the SmartPatch (Figure 4), which proves that Smartpatch is as effective as an insulin pen when delivering insulin. Safety concerns have also been waived since there was no evidence of conduct alteration on the pigs, no signs of tissue damage upon dermatoscopic examination and no toxic by-products on the analysis of the post-administration skin's exudate.

POTENTIAL APPLICATIONS

As the market moves towards standardisation, Medicsen focused on building a device that could work with as many drugs as possible and as both an injector and an infuser, creating the possibility of reaching agreements with pharmaceutical stakeholders in different verticals. Medicsen envisions the use of the Smartpatch for chronic diseases that require daily or weekly subcutaneous delivery of macromolecules, such as multiple sclerosis, but also for punctual on-site injections, such as vaccine delivery, or even to optimise delivery of cosmetics to the optimal layer of action (Figure 5).

Figure 5: Different Smartpatches for different molecules.

With positive results in animal trials, Medicsen is on the way to succeed in human trials in 2021 and disrupt the drug delivery landscape shortly after. This makes now the perfect time to get in touch and secure a partnership with the Smartpatch.

ABOUT THE COMPANY

Medicsensors SL is a technology start-up, located in Madrid (Spain), founded in 2015. The story of Medicsensors started when a 10-year-old girl with diabetes rejected an insulin pump in a hospital in front of Dr Jørgensen due to the insulin delivery method.

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Since then, Medicsensors has been committed to shaping the future of drug delivery and chronic disease management, initially oriented towards improving the control of diabetes and patients' quality of life and then moving towards standardising treatment methodology for chronic disease management with a multi-award-winning and patented technology.

ABOUT THE AUTHORS

Eduardo Jørgensen, MD, has led various projects since he studied medicine at university, creating and guiding teams to solve complex tasks through lean start-up-based R&D. Instead of clinical practice, he focused on leadership and technological healthcare innovation with the goal of improving quality of life for millions of patients. He is a passionate and creative problem solver who has persevered through the initial phases of creating businesses and validating technological assets until market entry.

Juan César de Mercado is a telecommunications engineer with experience in databases and signal analysis. Mr Mercado has a desire to make things easier and safer through technology and strives to reach the latest technological methodologies and their practical application. As well as experience as a data analyst and database technician, he has also held management positions that have given him operational experience.

José Carlos Montesinos holds a degree in Telecommunications Engineering from Universidad Politécnica de Madrid (Spain) and a Master's degree in Biomedical Engineering from the same university. Mr Montesinos has experimented with ultrasound on several occasions throughout his career, combines management skills with deep technological understanding, brings five-plus years of experience in the development of combined hardware and software, and has been co-founder of previous award-winning IT companies.