DEBIOTECH S.A. Switzerland
Innovative Medical Systems

LOW-COST DISPOSABLE WEARABLE INJECTOR PLATFORM FOR LARGE VOLUMES OF VISCOUS DRUGS

In this article, Eric Chappel, PhD, R&D Project Manager, Dimitry Dumont-Fillon, R&D Engineer, and Laurent-Dominique Piveteau, PhD, Chief Executive Officer, all of Debiotech, discuss Debiotech's novel wearable injector technology, which utilises a propellant vapour system to drive the injection, making the device both space- and cost-efficient.

There is a wide variety of device types available for injectable drugs. Pen injectors, jet injectors and others, including piston syringes or mechanically operated injectors, are designed to inject single or multiple doses of drug, contained in a cartridge or reservoir, via an automatically or manually inserted needle, or through a high-velocity jet. Depending on the application (acute intervention, prevention or long-term treatment) the intended user can be a healthcare professional, a caregiver or the patient themselves. Injectors can be generic or dedicated to a single class or family of drugs. The injection routes targeted include subcutaneous (SC), intradermal, intramuscular and intravenous.

Today, there is a growing interest in providing a wearable injector platform dedicated to the delivery of viscous formulations. Thousands of injectable drugs are currently in development.[1] Many of them are large-molecule biologics and the viscosity of the formulation is relatively high after concentration. The concept of syringeability (or injectability) is commonly used to characterise a drug formulation.[2,3] While pen injectors are generally preferred for injecting aqueous solutions up to 3 mL, wearable injectors become the more desirable option in the case of viscous solutions and/or a large volume. Particle characteristics are also an important factor to consider for syringeability. Specific SC formulations, such as for trastuzumab, comprise recombinant human hyaluronidase as an excipient to lower the resistance of the tissues during injection, via localised hydrolysis of the extracellular matrix.[4]

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The development of a wearable injector could also be driven by product lifecycle management considerations, a trend initiated by Amgen (Thousand Oaks, CA, US) and its product Neulasta® (pegfilgrastim). This drug stimulates the bone marrow to produce more white blood cells (neutrophils) in order to decrease the incidence of infection after chemotherapy. Since 2015, Neulasta has been combined with the Onpro® kit, a wearable injector which is an interesting solution not only to improve patient convenience, but also to stave off biosimilar competition.

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Many bolus injectors, such as Amgen's Pushtronex® and Onpro®, comprise a complex engine that moves a plunger inside a cylindrical barrel containing the drug, with the reservoir being either prefilled or filled by the user. In addition to the cost associated with the motor and its assembly, such technology limits the size ratio between the drug reservoir volume and the device volume, the maximum plunger displacement being limited to about half of the device length.

A fully disposable wearable injector platform should ideally utilise a low-cost, reliable engine to be compatible with reimbursement policies. It should be able to deliver a large range of viscous fluids in volumes from 1 to 10 mL. Finally, it should be reliable and exhibit a low dead volume as many biologics are expensive.

DEBIOTECH'S WEARABLE INJECTOR TECHNOLOGY

Debiotech has developed a new wearable injector with the following considerations:

- The device structure should be cost efficient by design.
- The reservoir should be semi-flexible and made with the same materials as previously developed JewelPUMP™ micropump patch insulin delivery system due to their well-proven drug stability.[5]
- The device shall be compatible with the state-of-the-art cannula available on the market.
- The standard version of the device shall contain no battery, no electronics and no software to speed up time-to-market and to alleviate both regulatory requirements and patient hazards.
- The dead volume of the device shall be equal to or lower than existing wearable injectors.

Figure 1: Wearable injector and its needle protection.

The device is a fully disposable wearable bolus injector made of two different parts:

- The drug reservoir and its fully mechanical engine and indicator
- The cannula patch and its automatic inserter.

Sequence of High-Level Steps to Start the Therapy

The device and the cannula are provided in the same package. The cannula patch is first affixed to the patient skin using the automatic inserter that retracts the inserter needle to prevent user injury after positioning. The user can then fill the drug reservoir with a syringe and verify that filling is complete by checking a visual indicator. The protective cap on the device's needle (Figure 1) is then removed and the user can slide the device onto the cannula patch, where it is permanently affixed, making the device ready to use. The infusion is started by pressing the activation button and can be monitored using a mechanical infusion status indicator, where the presence of an element visible through a window indicates that the full dose has been administered. Once the infusion is complete, the user can remove and discard the patch and device.

Filling Gauge

The device contains a semi-flexible drug reservoir that is initially collapsed against the rigid part, and user-filled with a syringe. This action inflates the reservoir membrane, which is thermoformed to prevent the generation of pressure onto the drug as filling is completed. The cavity surrounding the reservoir membrane is initially closed by a plug that covers the reservoir vent and the needle. During filling, a positive pressure generated inside this cavity will move a low-friction plug inside a transparent cylinder, equilibrating the pressure inside the container. The filling gauge, which is located on the bottom of the device, is only visible during the filling process. As shown in Figure 2, the fill volume is indicated by the position of a plug.

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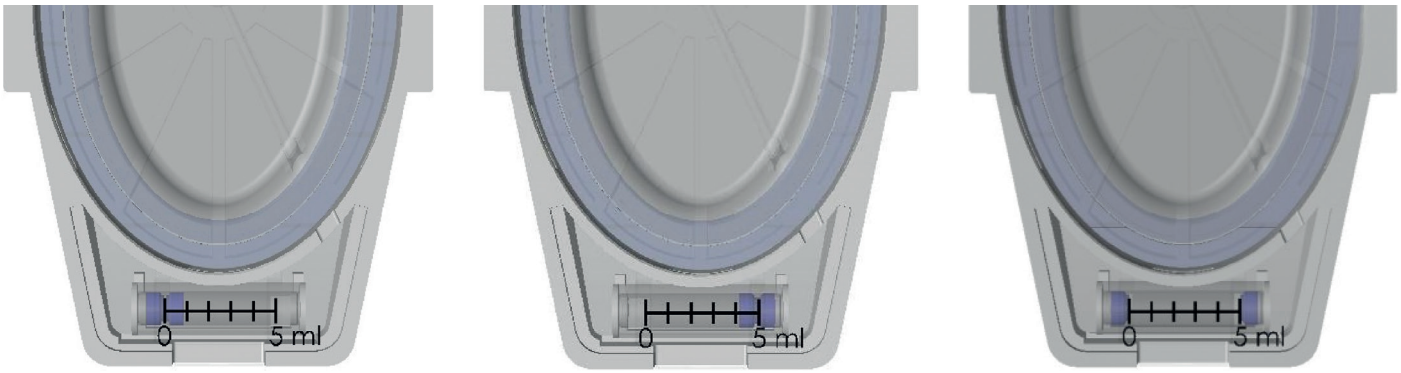

Figure 2: Back-side of the bolus injector showing the filling gauge before filling (left), just after filling of 5 mL (centre) and after the needle cap removal (right).

Figure 3: Infusion status indicator before activation (left), during infusion (centre) and after infusion (right).

Bolus Injector Engine

The injection is driven by a liquefied gas reservoir that is opened by the user after placement onto the patch. The vapourisation of the liquefied gas generates a large pressure differential that will push an elastomeric membrane against the flexible part of the drug reservoir. The cavity between the two membranes is vented to prevent any risk of infusion of propellant into the patient.

The pressure acting on the fluid is equal to the vapour pressure of the propellant since both membranes are flexible. At the bottom of the drug reservoir, a small cavity is used to connect an infusion status indicator, and the fluidic restriction used to limit the flow rate to a maximum of 1.5 mL/min.

Infusion Status Indicator

The status indicator is a transparent cylinder that contains one drilled plug and another solid one in contact with the drug. The pressure generated during infusion first moves both plugs towards the dead-end of the cylinder until pressure equilibration. When the full dose has been administered, the reservoir membrane can no longer transmit the propellant pressure to the fluid and therefore the solid plug comes back to its initial position, infusing the residual amount of drug that was located inside the indicator cylinder. The dead volume of the device is thus limited to a few tens of microlitres. Figure 3 shows a first illustrative version of this indicator as seen on the top shell of the device. Usability studies are on-going to refine the indicator and to make sure that the user interprets it correctly.

This purely mechanical infusion status indicator has three different states:

- One dot: Ready to inject
- Two dots: Injection on-going
- Three dots: End of injection.

The "end of injection" indication is only visible when the reservoir membrane is fully collapsed against the bottom of the reservoir shell. It is not visible in case of cannula occlusion.

For a specific medication volume and viscosity, maximum infusion duration will be indicated in the user manual, therefore the user can deduce that the full volume has not been administered (in case of total occlusion for instance) if the infusion status indicator is still showing "injection on-going" after this maximum duration. The high pressure generated by the propellant vapour will limit the occurrence of an occlusion in the cannula.

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Drug Preservation, Removable Injector and Cost Rationale

A common issue in insulin delivery is associated with a failure of the infusion set, due to issues such as cannula occlusion, cannula dislodging and leakage, amongst others.[6] The use of the cannula patch is a key asset to secure the connection to the patient. Other products developed by Debiotech share the same philosophy: after the placement of the cannula, the user is able to check visually, via a transparent window, that the cannula has been properly inserted into the skin.

Because a single dose of a biologic medication can cost up to thousands of dollars, it is highly undesirable to discard an injector filled with the drug solely based on a cannula failure. The user is therefore provided with an independent cannula that could be used to replace the defective one, thereby saving wasting the drug and limiting the cost to only a few dollars.

DEVICE CHARACTERISTICS

Volume Accuracy

Tests to confirm the volume accuracy were performed at 20°C using a mix of water and glycerol. The nominal volume of the reservoir is 5 mL. Volume accuracy was first estimated considering fill volumes of 1, 2, 3, 4 and 5 mL respectively (±2%), and fluid viscosities of 5 and 25 cP.

A mean dead volume of 32±6 µL was measured, which was independent of the fill volume and the fluid viscosity. Figure 4 shows the volume accuracy as a function of the fill volume. Considering all the data, the mean accuracy is better than 98%.

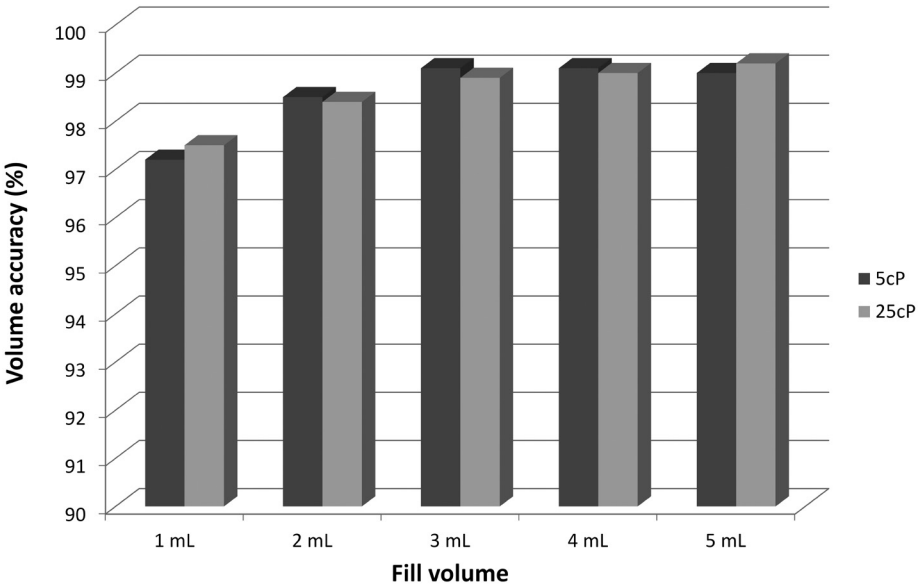

Figure 4: Mean volume accuracy at 5 and 25 cP, for fill volumes of 1, 2, 3, 4 and 5 mL.

Fluid viscosity (cP)	5	10	25	50	100
Volume accuracy (%)	98.7	98.7	98.9	98.9	99

Table 1: Volume accuracy as a function of medication viscosity for a fill volume of 3 mL.

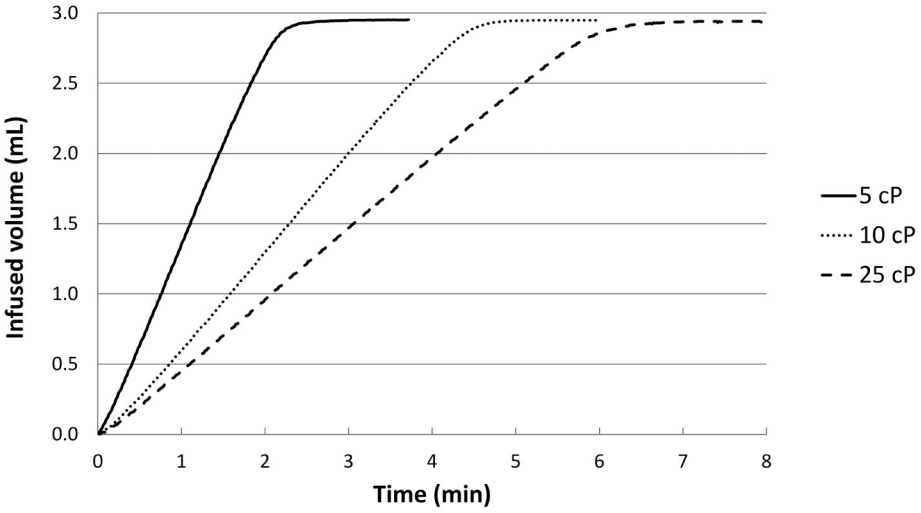

Figure 5: Infusion profiles of low viscosity device at 5, 10 and 25 cP. Fill volume = 3 mL

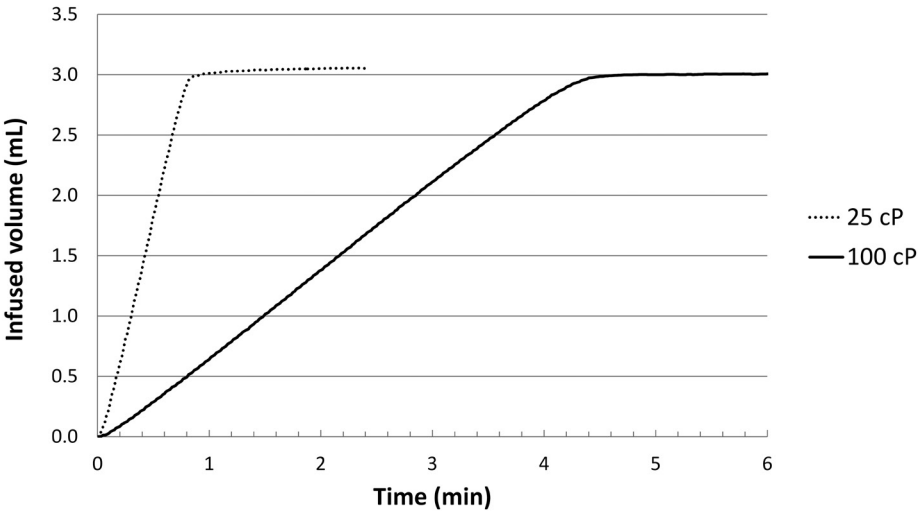

Figure 6: Infusion profiles of high viscosity device at 25 and 100 cP. Fill volume = 3 mL.

A specific test was carried out to measure, for a given fill volume of 3 mL, the effect of viscosity on volume accuracy considering fluids of 5, 10, 25, 50 and 100 cP. The results are shown in Table 1. Volume accuracy was again shown to be above 98%, independent of the fluid viscosity.

Delivery Profile

Two versions of the bolus injector designed for infusion of volumes up to 5mL were tested: the low viscosity (LV) version is dedicated to fluid viscosity up to 25 cP while the high viscosity (HV) version is adapted to viscous fluids up to 100 cP and above. The LV version is intended to deliver a minimum flow rate of 0.5 mL/min at 25cP, and the HV version at 100 cP respectively.

The fill volume was fixed at 3 mL. The LV version was tested using fluids of 5, 10 and 25 cP respectively. Viscous fluids of 25 and 100 cP were used to characterise the HV device. The measured flow rate profiles are provided in Figures 5 and 6. The linear slope indicates that the flow rate is constant throughout the infusion duration, as the propellant vapour maintains a constant pressure on the elastomeric membrane, which is fully transmitted to the fluid via the elastomeric and reservoir membranes.

The patch injector is in thermal equilibrium with the patient's skin and limited temperature variations are expected. However, should it be necessary, an add-on could be used to limit the variability of the flow rate in case of a large ambient temperature change which may modify the vapour pressure of the propellant and the fluid viscosity. A flow-control valve developed by Debiotech can be placed into the fluidic path to prevent any change of flow rate related to pressure condition changes, including the propellant reservoir or external conditions, for example altitude.

The add-on is a microfluidic chip, 1 mm thick with a typical surface of 1 cm^2. The functioning principle of the device is described elsewhere.[7] Two different designs are available depending on the target flow rate:

- One for intermediate to high flow rates (typically from 5 mL/h to 100 mL/h or more)
- One for very low flow rates (down to 1 mL/day or less).

This add-on is particularly useful for long-term infusion, to control the infusion duration better, and for the infusion of a drug requiring especially careful control of the flow rate, such as insulin or morphine.

CONCLUSION

The latest functional test results showed that Debiotech's design for a disposable wearable bolus injector is able to inject a large volume of viscous medication, up to 100 cP, at a minimum flow rate of 0.5 mL/min.

Future designs will include a dedicated compartment for optional high-end features that are already implemented in the JewelPUMP insulin micropump patch developed by Debiotech. Human factors studies are also planned in order to refine the actuator position and the indicator visibility.

In summary, Debiotech intends to drive collaboration with key partners, including pharmaceutical companies, to customise this new platform to their needs for a subcutaneous delivery system dedicated to large volumes and/or viscous fluids.

ABOUT THE COMPANY

Debiotech is a Swiss company with nearly 30 years' experience in developing highly

innovative medical devices, based on micro- and nanotechnology, micro-electronics and innovative materials. The company concentrates on both implantable and non-implantable systems, in particular for drug delivery and diagnostics, with a demonstrated competence in the identification of breakthrough technologies and their integration into novel medical devices. Devices developed by Debiotech are eventually licensed to major international pharmaceutical and medical device companies, with a track record of over 40 license agreements worldwide. Examples of successful products are the DebioJect™ microneedles for intradermal injections, the I-Vantage™ IV pump for hospital and home care, the CT Expres™ Contrast Media injector for CT-Diagnostic Imaging (acquired by Bracco Imaging, Milan, Italy), the JewelPUMP for diabetes care, the DialEase™ home dialysis equipment (licensed to Fresenius, Bad Homburg vor der Höhe, Germany) and the HemoXpress home haemodialysis machine developed in collaboration with the Dutch Kidney Foundation.

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ABOUT THE AUTHORS

Eric Chappel joined Debiotech in 2003 as an R&D Engineer and was appointed as an R&D Project Manager in 2004. Prior to Debiotech, Dr Chappel developed and industrialised the backend process of optical MEMS at Memscap. His research interests are innovative medical devices, including insulin micropumps, hydrocephalus shunts, implantable pumps and wearable injectors. He received an MSc in Physics in 1996 from the Université Grenoble Alpes (Grenoble, France) and achieved his PhD in Condensed Matter Physics at the French National High Magnetic Field Laboratory (Grenoble, France) in 2000.

Dimitry Dumont-Fillon joined Debiotech in 2013 as an R&D Engineer. His work focuses on microsystems, microfluidics and mechanics as applied to drug delivery devices. He holds an Engineer's Degree from the Grenoble Institute of Technology (Phelma, France) and a joint MSc in Micro- and Nanotechnologies for Integrated Systems from the Swiss Federal Institute of Technology in Lausanne (EPFL) (Switzerland) and the Polytechnic University of Turin (Italy).

Laurent-Dominique Piveteau joined Debiotech in 2005 and was appointed as Chief Executive Officer in 2015. Prior to this, Dr Piveteau held several positions in R&D and in business development. He developed a coating for bone implants in collaboration with the Robert Mathys Foundation, he was a researcher at MIT (Cambridge, MA, US) working on contrast media for MRI, and worked in technology transfer at the Swiss Federal Institute of Technology in Lausanne (EPFL) (Switzerland). In parallel to his current position, Dr Piveteau also teaches Innovation Economics at EPFL. He holds an MSc in Physics from the ETH Zürich (Switzerland), a PhD from the University of Fribourg (Switzerland) and an MBA from INSEAD in Singapore and Fontainebleau (France).