DELIVERING INJECTABLES

ON drugDELIVERY

MAY 28th 2020 • ISSUE No 107

SENSOR ADVANCEMENTS IN DRUG DELIVERY IMPROVE COMPLIANCE

In this article, Salvatore Forte, Innovation Engineer at Flex, discusses various advancements in sensors that are transforming drug delivery systems, making complex devices more automated, easier to use, and improving patient compliance as a result.

Technology advancements in sensors have helped drug delivery systems evolve from manual but simple to automatic and increasingly complex, while becoming even easier to use. This is because sensors shoulder the variables, instead of forcing the user to do so. Sensors can provide both quantitative and qualitative data (e.g. amount of contact pressure and orientation in space) as well as integrate input from multiple transducers (e.g. contact, temperature and humidity). In helping to automate injections, they facilitate compliance, proper usage and safety while requiring very little from the patient.

> "Sensors can truly become a major tool to solve the challenges presented by novel therapies and enable the development of a new class of drug delivery devices."

Original equipment manufacturers operating in this field have been challenged to create smaller, smarter, safer and more integrated drug delivery devices that can ease the therapeutic journey of patients – and therefore achieve a better acceptance rate in the marketplace. The evolution in sensors over the last few decades and, more specifically, in silicon manufacturing processes, has played a major role in such outcomes.

Today, sensors have achieved an outstanding level of features integration by embedding multiple micromachined transducers into miniature footprints along with signal conditioning, a local computational core, digital interfaces and

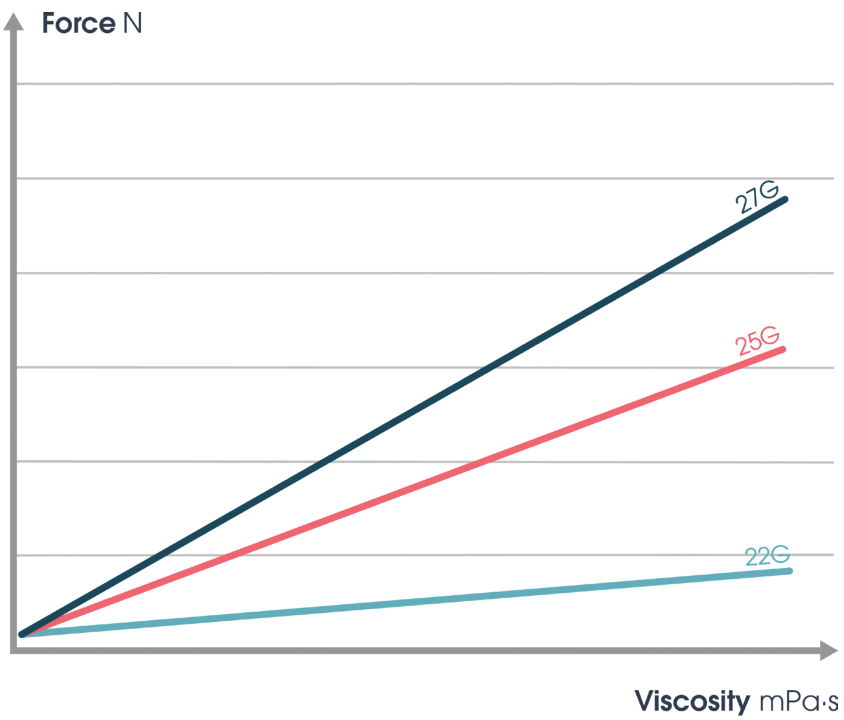

Figure 1: Variation of injection force as function of the drug viscosity, for different needle gauges (measure of needle thickness, and defined by its inner diameter: the higher the G, the thinner the needle). At the same drug viscosity, the force to dispense is proportional to the G value.

Salvatore Forte
Innovation Engineer
T: +39 028 732 9218
E: salvatore.forte@flex.com

Flex
Milan Design Center
176 Via Ernesto Breda
Milano 20126
Italy

www.flex.com

memory for storing factory-calibration parameters. In addition, sensors came to the rescue with the push towards longer-lasting, battery-powered devices because they could reduce power consumption – the availability of enhanced sleep modes with wake-up capabilities can extend battery life by keeping the sensor in a very low consumption state for most of the time.

DEALING WITH HIGH VISCOSITY AND COLD STORAGE

So how can medical device makers fully leverage the continuous progress in sensor technology to design more patient-centric products – including drug delivery devices that foster compliance and adherence to the prescribed treatment, as well as being easy to use?

Sensors, and their underlying processing architecture, can truly become a major tool to solve the challenges presented by novel therapies and enable the development of a new class of drug delivery devices. In recent years, pharma companies have invested in the development of novel biologic and biosimilar drugs for the treatment of different health conditions, including chronic and autoimmune system diseases. Most biologics are administered through injection, so pharma companies are presenting the drug delivery devices industry with a growing demand for autonomous drug delivery systems that address the challenges of biologic formulations, with the ultimate objective to increase the therapeutic value of the drug.

Compared with more traditional drugs, the administration of new biologic formulas through injection comes with additional complexity due to their high viscosity. They demand higher pressure and force being applied to dispense the medication at a proper delivery rate (Figure 1), and they usually cause more patient discomfort. Moreover, biologics often require cold chain storage to maintain their therapeutic efficacy, and this magnifies the burden since the viscosity tends to increase exponentially as the temperature is reduced (Figure 2). It is therefore imperative that injector systems are designed with appropriate countermeasures to tackle their administration.

One can use sensors to monitor relevant parameters, such as injection force and drug temperature, and design novel drug delivery systems to accommodate the increased complexity and variability of new biologics with differentiated injection profiles. The injection system may implement smart features to dynamically optimise settings, depending on the fluid properties of the drug based upon actionable insight provided by those sensors. This could ultimately become the differentiating factor that provides a positive patient experience for effective at-home self-administration and supports the success of new biologics on the market.

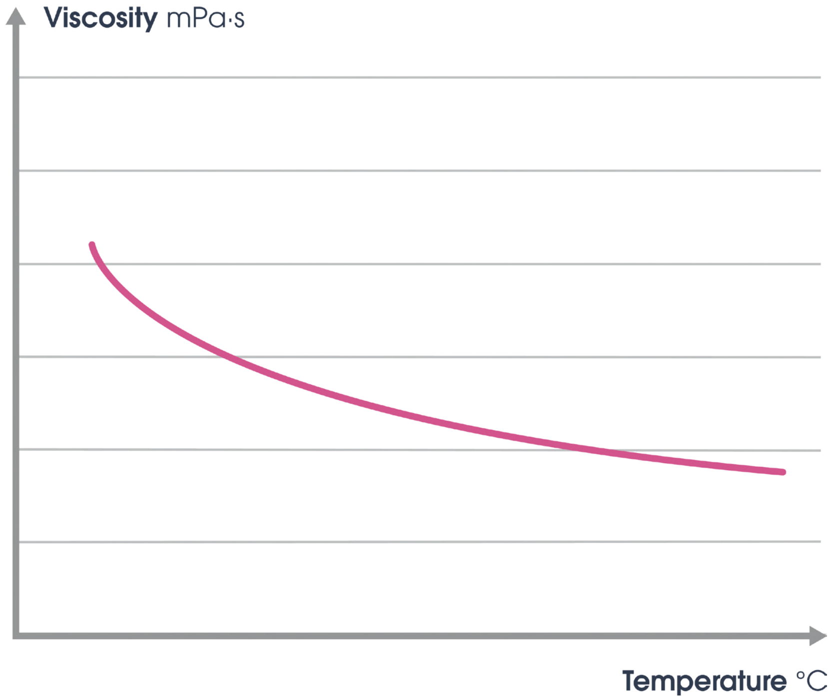

Figure 2: Variation of drug viscosity with temperature.

MULTIPLE SENSORS CONTROL INJECTION PROFILE

Let's consider the case of an autoinjector that, in this age of self-administered therapy, has become a well-adopted drug delivery device. The autoinjector is an electromechanical device that comes with a reusable drive unit and a disposable cassette, which represent the plastic housing for the cartridge that holds the drug. The reusable unit is equipped with a printed circuit board (PCB) that drives a DC motor to actuate and put in motion the plunger rod, which is the element that engages with the plunger within the container to push the medication out of the needle and ultimately under the subject's skin.

Conventionally, a closed-loop system allows precise control of the plunger position and injection speed. The system dynamically adjusts the power delivered to the motor, based upon active feedback continuously provided by sensors, such as an optical or hall-effect rotary encoder, to match with a target speed profile and ensure accurate and predictable delivery rate with a fixed injection time.

To accommodate for drug and force requirement variability, multiple sensor technologies could be employed at the same time. A first example might be the integration of an ultra-thin force sensor on the top surface of the plunger rod to measure the relative change in the force experienced while engaging the plunger in the attempt to dispense a higher-viscosity drug (Figure 3). The system controller can then be configured to receive output signals from the force sensor and compare these values with pre-set thresholds to trigger the appropriate action. One action might be to increase the voltage supplied to the motor; another to stop operation if the remaining battery capacity can't guarantee the optimum delivery injection.

> "As autoinjectors become increasingly automated, the ability for sensors to check the temperature of the drug is a compelling feature to make sure the device is operated as intended."

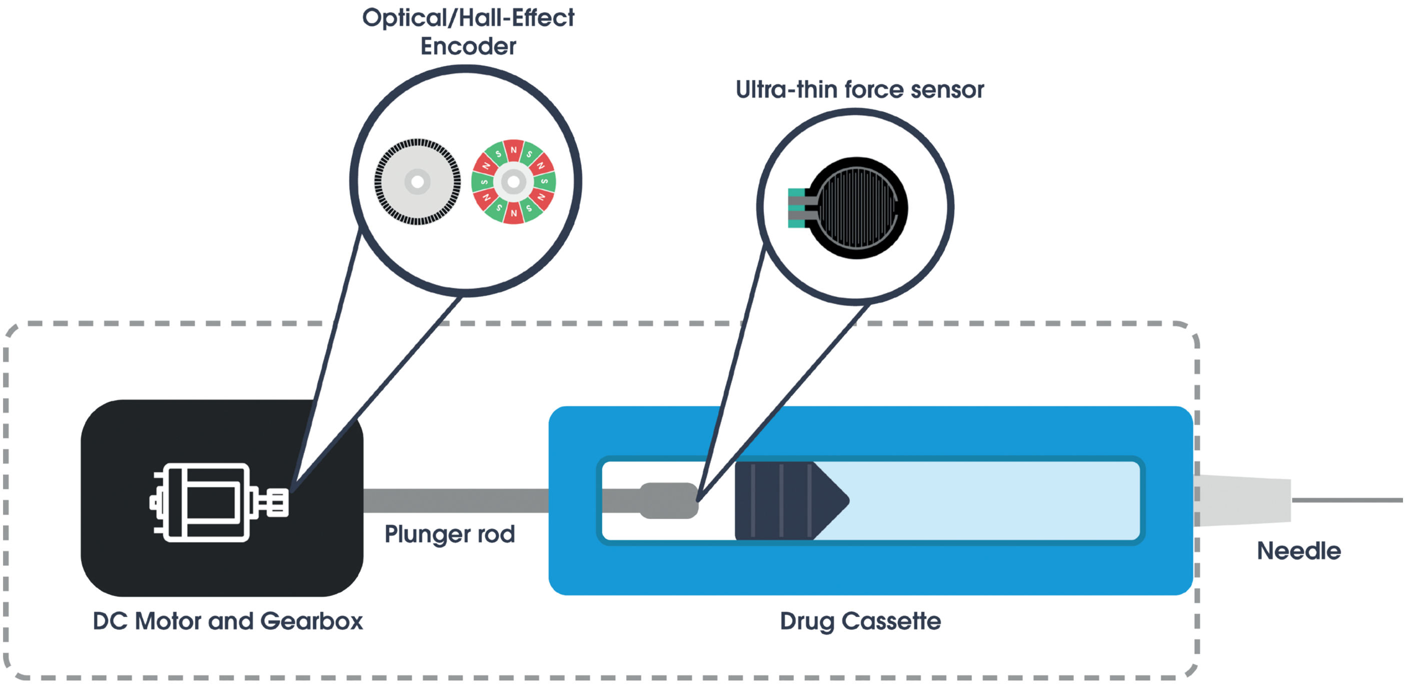

Figure 3: Autoinjector system design with rotary encoder and force sensor.

Embedding the ability to capture small changes to the actuation force on such tiny areas requires minimal electronics overhead to interface with the sensor – but greatly enhances the system's reliability, since the autoinjector can now leverage interoperable control loop systems, each individually driven by feedback provided by dedicated sensors (Figure 4).

TEMPERATURE SENSING IN AUTOINJECTORS

Temperature monitoring of the drug also becomes crucial when designing autoinjectors for biologic formulations. Traditionally, the patient had to remember to let the drug adjust to room temperature prior to injecting. While this may seem reasonable, it does not prevent the patient injecting when the drug is still cold, which may be painful.

As autoinjectors become increasingly automated, the ability for sensors to check the temperature of the drug is a compelling feature to make sure the device is operated as intended – removing that burden from the user. The system could leverage temperature measurements either to block the injection from starting if the temperature is not in the operating range or adjust the plunger speed to increase the dispense duration to compensate for cold drug temperature, which would result in higher viscosity. Pre-warming the drug when the container is placed inside the injection system is another option by pairing the temperature sensor with a miniature heater. Based on the temperature sensed, the controller unit powers up a polymer-based flexible heater, which can sit conformally within the same cassette compartment of the unit. The heater can warm up the medication to make it reach the target temperature faster, possibly within minutes.

Polymer-based heaters can reliably operate with low voltages and no additional electronics are required to control the heating, other than supplying the heater with the appropriate voltage level. The caveats are that they may draw

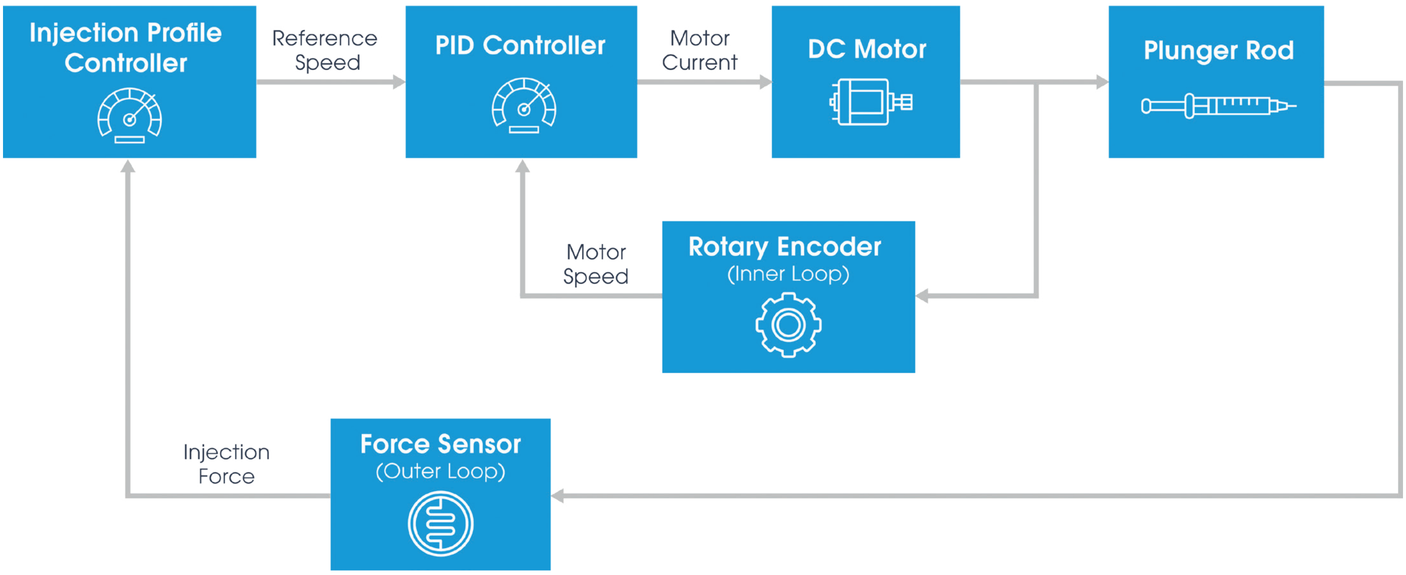

Figure 4: Block diagram of the closed double-loop feedback system used to control the speed of the DC motor that drives the plunger rod.

relatively high current and, most importantly, a pre-conditioning strategy would be required to ensure uniform temperature distribution and a controlled warm-up cycle to preserve drug stability and efficacy.

MEASURING TEMPERATURE WITH AN INFRARED SENSOR

Sensing drug temperature once the cassette is in place inside the device is challenging, given space and contact considerations. One solution could be to integrate an infrared (IR) temperature sensor that does not require physical contact with the drug container to perform measurement. High-precision IR thermal sensors are traditionally delivered in bulky metal TO-can (transistor outline can) packages, so they are not configured to support integration into tightly spaced injector devices. Also, a good understanding of the sensor field of view (FOV) is crucial when designing applications because a FOV that is too large will be affected by other elements and return an inaccurate reading.

Small IR thermal sensors with narrow FOV and excellent thermal stability, even in thermally challenging conditions, have been recently deployed to fulfill the demands of this forthcoming class of medical device (Figure 5). This is essential expertise in this application. The latest generation of IR sensor integrated circuit (IC) can draw as little as hundreds of microwatts (μW) of power, even while executing measurements continuously, with a sensor that remains active without entering any sleep-mode states. That represents a considerable achievement for enabling power-sensitive implementation in battery-powered autoinjectors.

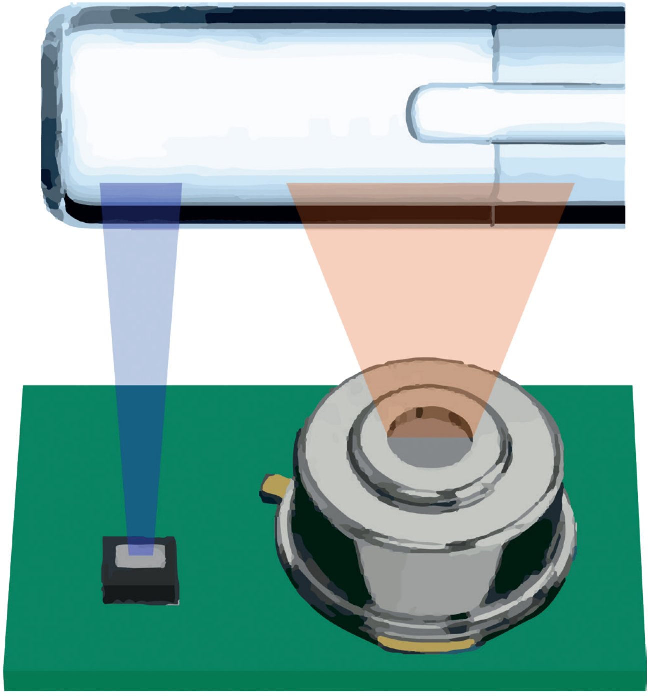

Figure 5: Infrared temperature sensor in both SMD and TO-can packages. Narrow FOV and optimum distance from the cartridge must be selected for accurate sensing.

NFC SMART TEMPERATURE SENSING

As an alternative to IR sensors, a passive near-field communication (NFC) sensor tag may also be employed for monitoring the drug's temperature. The smart tag provides a complete temperature sensor solution, along with an NFC interface that can be conveniently manufactured into ultra-thin labels. Thanks to its small size and backing adhesive, the tag can be easily installed onto the exterior of the disposable cartridge directly after fill finishing.

The electronics board attached to the reusable unit is equipped with an NFC reader IC, paired with a coil antenna for communicating temperature data and other relevant information as factory programmed into the tag's IC internal memory (e.g. type of drug, volume, expiration date, etc.) through the contactless NFC interface. Glass drug containers add thermal mass, so any embedded firmware must be properly calibrated to deliver an accurate temperature.

The NFC sensor tag itself does not have batteries and is powered entirely by the energy harvested from the reader's RF field. Thus, smart sensor tags are specifically designed to accommodate for tight-spaced application needs, and NFC-enabled autoinjectors can ultimately assess the drug's temperature compliance conveniently and cost effectively.

ACCURATE BATTERY GAUGING IN NOVEL AUTOINJECTORS

Sensors are just one part of a much broader ecosystem within drug delivery devices, which also includes motors, PCB assemblies with processor and power management control, precision plastics with tight mechanical assembly constraints, and battery. For the latter, an extensive system-level characterisation based on knowledge of load profiles should be carried out to understand energy requirements and select the appropriate battery to use within the final device.

Depending on drug viscosity and temperature, the system may require more energy to exert a force on the plunger rod to dispense the medication with a defined delivery rate, which may end up draining the battery faster. Bigger batteries to accommodate for larger injection forces are undesirable since they will result in a bigger, heavier autoinjector design. Nonetheless, automated control of injection profiles to accommodate higher force requirements is still highly desirable to inject medication with higher and variable fluid viscosities.

In autoinjectors operated by lithium-ion batteries, it is important to have an advanced battery fuel gauge IC that can accurately and continuously determine the battery state-of-charge (SOC). Fuel gauge ICs can deliver best SOC accuracy across all device operating conditions by combining

"Integrating multiple sensors into novel autoinjectors that are specifically designed for administration of biologics can vastly improve user compliance."

the advantages of Coulomb counting with more traditional voltage-based gauging. They measure battery voltage, battery current (through a dedicated sense resistor) and battery temperature, typically with an on-chip temperature sensor.

Latest fuel gauge ICs operate off a very low quiescent current (few µA) while still delivering SOC updates regularly. Energy requirements can ramp up quickly in a novel autoinjector, while a poorly designed gauge can result in a premature and abrupt system crash – potentially harming the user. Thus, accurate knowledge of SOCs under different conditions is critical for reliable and safe operations. Based on the calculated battery SOC, and knowing the discharge characteristic for a known force profile that must be applied, fuel gauge ICs can determine if the remaining battery capacity is sufficient to dispense the full dose without risk of motor stall, and can warn the system accordingly to prevent the injection even starting.

AUDIO FEEDBACK WITH MEMS SPEAKERS

As previously mentioned, an increase in dispense duration to compensate for higher viscosity is also an option, which may result in more comfort for the patient while injecting. However, longer injections can cause adherence issues, as the user may erroneously assume that the full dose has been delivered and detach the needle from the skin prematurely. To tackle adherence issues, design engineers can enrich the system with additional features, such as audible feedback achieved via tiny micromachined (microelectromechanical) speakers, which can assist the user throughout the administration process, and ultimately notify the user when the injection has been completed.

SENSORS IMPROVE USER EXPERIENCE & DEVICE PERFORMANCE

Integrating multiple sensors into novel autoinjectors that are specifically designed for administration of biologics can vastly improve user compliance. Sensors are key to successful implementation of autonomous drug delivery systems that will accommodate drugs with a range of viscosities. Rotary encoder and force sensors can be used together to arm the motor driving unit with more accurate data to support different injection profiles and deliver a consistent patient experience.

Accurate temperature sensing is also of utmost importance since many biologics require cold chain storage. The automated injector can verify the temperature of the drug and either prevent the injection starting, warm up the drug via active heating or adjust the injection force. Careful design of power management with precise battery gauging is also crucial to optimise system run time as well as ensure the required level of safety and reliability.

> "The automated injector can verify the temperature of the drug and either prevent the injection starting, warm up the drug via active heating or adjust the injection force."

ABOUT THE COMPANY

Flex is a global provider of design, engineering, manufacturing and real-time supply chain insight and logistics services to companies worldwide. Flex Health Solutions focuses on medical device and drug delivery design, development, injection moulding and manufacturing solutions for pharmaceutical and medtech companies. Its approach is supported by US FDA-registered and ISO 13485 compliant and ISO 11608-1 accredited facilities, with a world-class quality system.

ABOUT THE AUTHOR

Salvatore Forte is an Innovation Engineer at Flex's Design Center in Milan. In the past three years, he has been leading strategic internal research and development projects to expand awareness in the sensors and connectivity space within the medtech and other industries. He conducts research and technology assessment of emerging sensing technologies for ultra-low power devices, and delivers proof-of-concept units that can be turned into product solutions. His main area of technical investigation includes health monitoring devices, personal point of care, sensors for gas level and air quality control, and low-power connectivity solutions targeting Internet of Things embedded systems.