Nemera

ADJUSTING & CONTROLLING INJECTION SPEED BY DESIGN: IMPACT ON PAIN PERCEPTION

In this article, Isabell Delcroix, Strategy Director, and Pascal Dugand, Technology Product Manager, Device Development, both of Nemera, describe a study of the multi-award-winning Safelia® auto-injector platform, which investigated the impact of varying the injection speed on pain perception and showed how slowing injection speed, particularly at the beginning and end of the injection process, could reduce pain perception.

Nemera's generation of two-step auto-injectors, Safelia® (Figure 1), has been designed to ease the patient self-injection experience and to deliver a variety of drug products in glass syringes. These range from more fluid formulations to the most challenging drugs such as viscous, sustained-released, concentrated formulations, products for subcutaneous and intramuscular injection, and including larger volumes.

The Safelia® auto-injector:

- Administers a large range of formulations and injection volumes; the platform can adapt by design to handle both fluid and highly viscous formulations, taking care specifically of biologics, sustained-released formulations and sheer-sensitive molecules, of up to 2.25 mL injection volumes
- Improves the patient experience, with the possibility to reduce needle gauge, reduce injection time, and slow down the needle penetration inside the body tissues, and gives the possibility of a delayed retraction for viscous injections especially.

PAIN PERCEPTION

Subcutaneous injection is a common route for self-administration using syringes, prefilled syringes and auto-injectors. Subcutaneous injections are typically 1 mL. However, increasingly treatments tend to require up to 2 mL injections.

Factors leading to a perception of pain are well known:

- Injection site choice
- Needle gauge (large diameter needles)
- Formulation active ingredients, temperature, viscosity, pH
- Dose volume
- Injection speed

It is observed that larger dose volume (2 mL *versus* 1 mL) and faster injection could lead to higher stress in the tissues at the site of injection, and consequently higher pain perception. It is usually

> "Diminishing the initial injection speed will lower the injection force and could lower pain perception. At end of injection, dose volume is at its maximum, whilst tissues are saturated. Diminishing end of injection speed will lower injection force, favouring drug absorption. The resulting pressure drop in the tissues could help also to reduce pain perception."

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Figure 1: 1 mL and 2.25 mL versions of the Safelia® auto-injector.

Expected benefits	Standard Auto-Injector	Safelia	Safelia Features
Creating possibilities for viscous injections with the same AI platform as for standard glass syringes	x	✓	Injects fluid and viscous drugs up to 1000 cP
Risk of syringe breakage eliminated Possibility of using all (or no) syringe flanges	x	✓	No stress on syringe flanges
Enables increased spring force and use of small gauge needles (less patient pain) without risk of glass breakage	x	✓	No stress on syringe flanges
Reduction of pain at needle insertion	x	✓	Adjust needle insertion speed
Reduction of pain during injection	x	✓	No initial injection peak
Drug is delivered at the right depth	x	✓	Needle insertion disconnected from injection

Table 1: Summary of design features and benefits of the Safelia® platform.

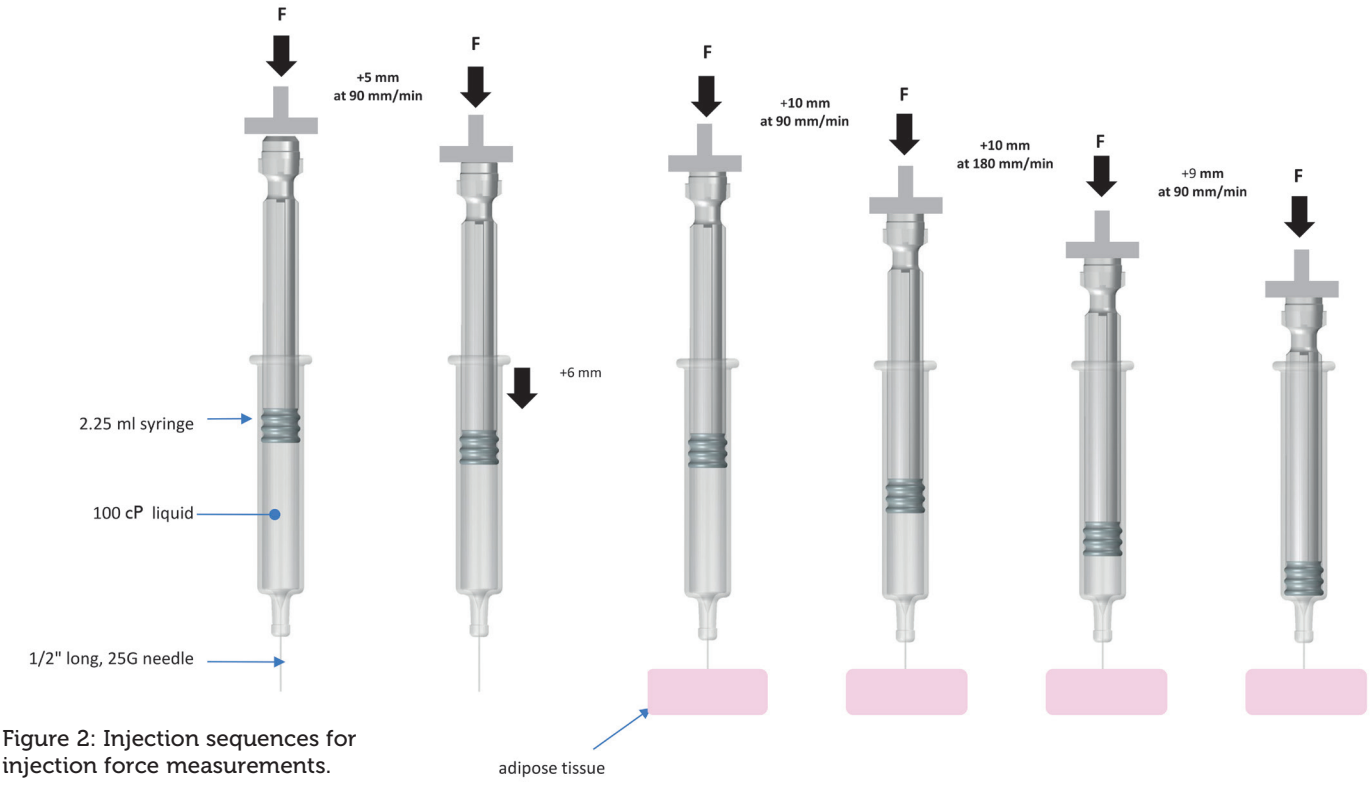

Figure 2: Injection sequences for injection force measurements.

considered that a practical injection time should not exceed 10 seconds, which leads to 0.2 mL/sec injection flow rates in the case of 2 mL injected volumes. As a result, compared with 1 mL syringes, it can be anticipated that the increased injection speed, could cause a higher perception of pain to patients.

Design features and benefits of the Safelia® device are summarised in Table 1.

STUDY OBJECTIVES

Nemera has conducted a study investigating how adjusting and controlling injection speed could impact on pain perception, in particular for viscous and large-volume injections.

The primary objective of this study was to estimate injection force increase in porcine adipose tissue in the case of high viscous formulations (100 cP) and large dose volume (2 mL). The final aim was to propose a way to optimise injection devices to minimise the perception of pain by patients.

METHOD

In a first step, injection forces were performed at different speeds in air and in tissues. In a second step, the impact of injected dose on injection force was measured. Syringes of 2.25 mL, with 25G, ½" long needles were prefilled with a

100 cP Newtonian liquid. Injection force in tissue was measured consecutively for injection in air and in tissue:

1. Injection in air was performed to determine injection force without tissue back force.
2. Injection in porcine adipose tissues was then performed (injection depth 6 mm, simulating subcutaneous injection).

Tests were performed at three different speeds (90 mm/min, 135 mm/min and 180 mm/min).

The sequence is shown in Figure 2.

RESULTS

The Injection force in porcine adipose tissue increases with injection speed. Injections at a flow-rate of 0.09 mL/s generated a maximum back force of 20 N. (Note that it was also confirmed that injecting at a 0.09 mL/s flow-rate after injections at 0.18 mL/s generated a maximum back force of 20N, i.e. 60 N minus 40 N.)

Injection forces in air and injection forces in porcine adipose tissue (Figure 3) can be considered to estimate the injection pressure in the tissue. By subtracting the injection force in air to injection force in tissue, the tissue back force can be evaluated (Figure 4).

As anticipated, a higher injection speed is associated to a higher tissue back force. It has been also observed that the injection force smoothly increases with increasing dose volume, leads to a back force increase of 8 N (see Figure 5). It has been also observed that injection forces in porcine adipose tissue presents large variations. (Note that injection at 0.18 mL/s flow-rate generated a maximum back force of 32 N.)

CONCLUSIONS

Injection force increase in porcine adipose tissue in the case of highly viscous formulations (100cP) at high speed and large dose volume (2 mL) have been observed. These measurements allowed a skin back force estimation. This information is very useful for auto-injector development.

For Safelia® auto-injector, we have developed a mathematical model allowing injection time prediction including back force. This model enables us to anticipate

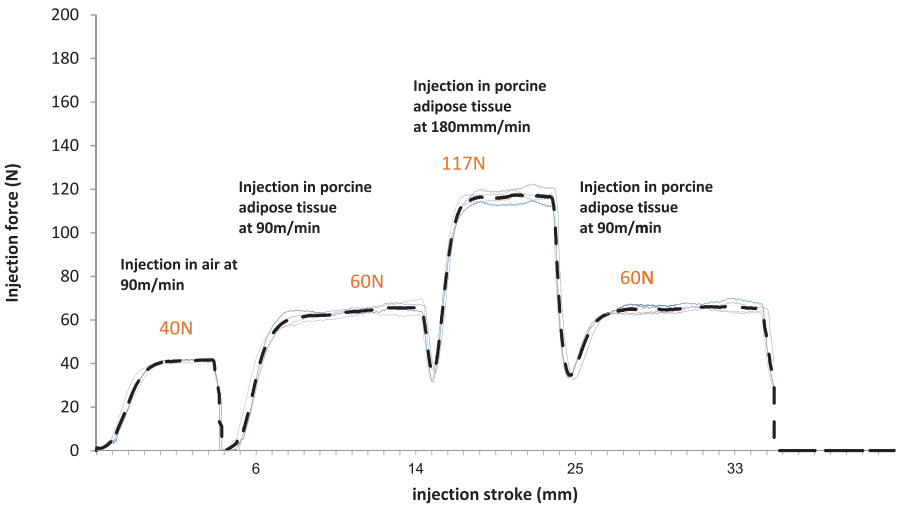

Figure 3: Relation between injection force and injection speed in porcine adipose tissue.

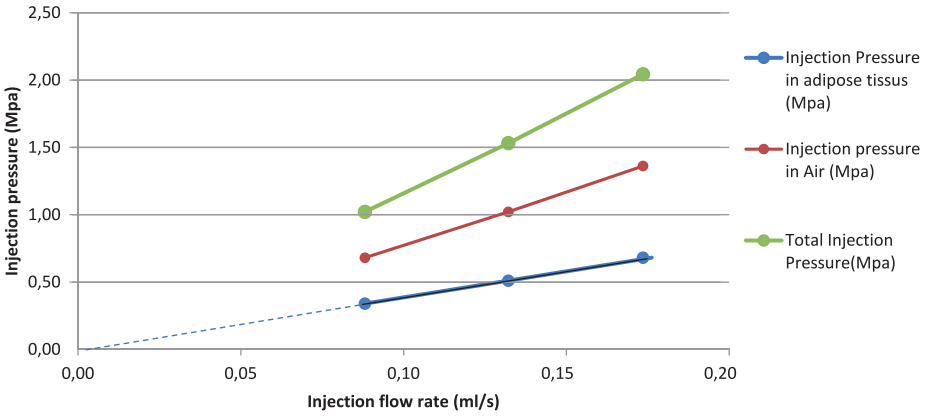

Figure 4: Injection forces measurements in air and in porcine adipose tissue.

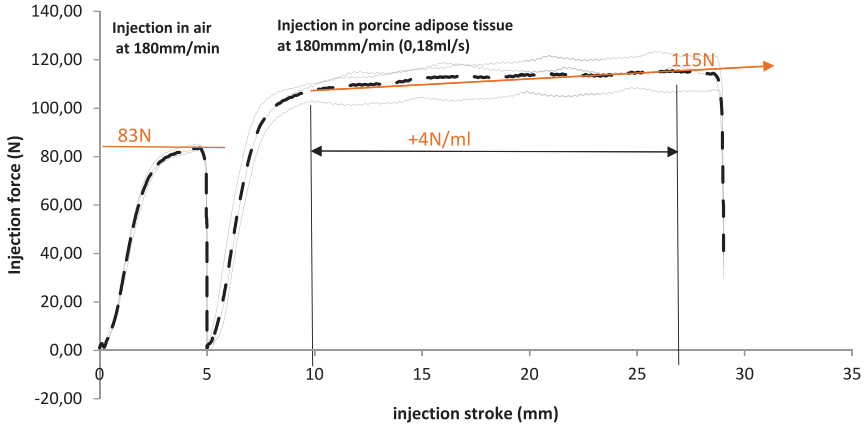

Figure 5: Relation between injection force measurements and dose volume in porcine adipose tissue.

auto-injector design at an early stage. Considering our example, with a 100 cP Newtonian liquid, 2.25 mL syringe with 25G needle and a 100 N spring force, the injection time in porcine adipose tissue is 10 seconds greater than injection in air (see Figure 6).

Increasing auto-injector energy could allow the dose to be delivered within the expected delivery time; but different studies have shown that the higher injection speed and dose volume limit dose absorption by the tissues and induce greater pain.

There are generally two critical times in the injection cycle: start of injection and end

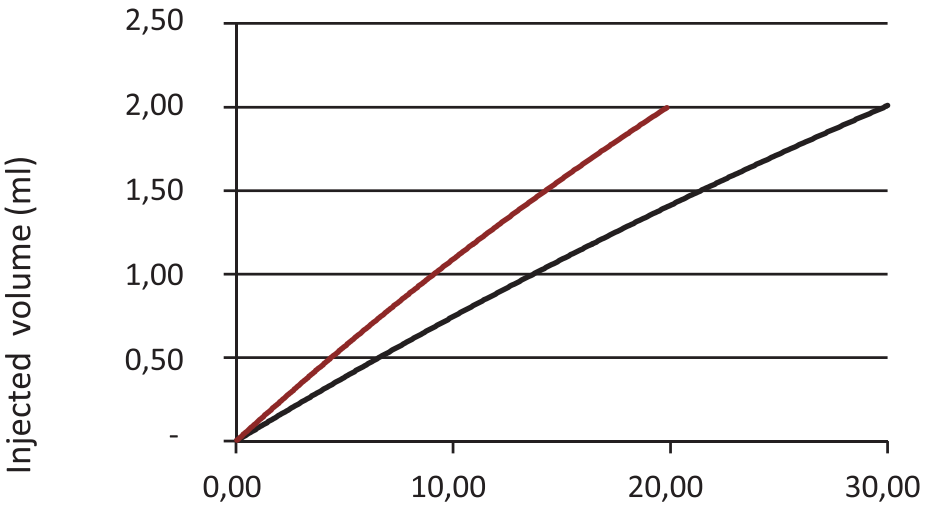

Figure 6: Injection time prediction in air and in porcine adipose tissue.

of injection. At start of injection, injection speed is at its maximum (maximum energy). Diminishing the initial injection speed will lower the injection force and could lower pain perception.

At end of injection, dose volume is at its maximum, whilst tissues are saturated. Diminishing end of injection speed will lower injection force, favouring drug absorption. The resulting pressure drop in the tissues could help also to reduce pain perception.

By design, the injection speed profile of Safelia® can be tailored to minimise injection forces. This injection force control should prevent the initial injection peak force, and allow a better drug absorption, and could lead to less pain perception.

New generation auto-injectors have to deliver highly viscous formulation, in larger volumes.

Injection should be painless, and comfortable for users. Controlling injection speed is a way to achieve less painful injections.

ABOUT NEMERA

More than five million diabetics rely everyday on parenteral devices manufactured by Nemera.

With more than 1,300 people and four plants across two continents, Nemera is a world leader in the design, development and manufacturing of drug delivery solutions for pharmaceutical, biotechnology & generics industries. Nemera's expertise covers several modes of delivery: Parenteral, Nasal, Buccal, Auricular, Ophthalmic, Pulmonary, Dermal and Transdermal.

Nemera leverages decades of manufacturing and development experience in the parenteral devices segment (passive safety devices auto-injectors, pens, and implanters), from full development to pure contract manufacturing, through customised solutions. Nemera applies the same quality-oriented process to the development of proprietary devices and to customised solutions under contract with laboratories.

ABOUT THE AUTHORS

Pascal Dugand, Technology Product Manager, Nemera, graduated as a polymer engineer from EAHP in Strasbourg, France. He holds a Masters in polymer mechanics and joined Plastic Omnium in 1990 where he started to work in development and innovation. In 2004, the medical division of Plastic Omnium was acquired by Rexam and more recently the four drug delivery devices plants, including the Innovation Centre, became Nemera. Today, Mr Dugand is an experienced medical device developer engineer specialised in the development of parenteral delivery devices. He developed for Nemera own IP products including Safe'n'Sound and Safelia auoinjector as well as working on several customer injectable product development projects.

Isabelle Delcroix holds an MSc in Neuropharmacology from Tokyo University, Japan. She is Strategy Director at Nemera and she is in charge of parenteral range of proprietary products including Safelia®, and the passive safety device, Safe'n'Sound, for prefilled syringes. Isabelle joined Nemera (previously named Rexam Healthcare Devices) nine years ago as Marketing Director for the Devices Business Unit. In her previous career she worked for AirLiquide Santé HomeCare Division and as a consultant specialised in strategy for innovation.

SAFELIA®: AN AWARD WINNING DEVICE PLATFORM

Nemera has already won two major industry awards for Safelia® in 2017.

In February, during the award ceremony at Pharmapack Europe in Paris, France, Safelia®, was celebrated as a best-in-class innovation displayed at the show for "Patient Centricity & Customisation".

In March, at the International Pharmaceutical Expo (INTERPHEX) in New York, NY, US, show organisers together with a team of industry experts selected Nemera as Winning Exhibitor and Editor's Choice, for its Safelia® device.

Nemera

Safelia®

NEW GENERATION OF 2-STEP AUTOINJECTOR PLATFORMS

parenteral

pulmonary

ophthalmic

dermal/ transdermal

nasal/ buccal/ auricular

INNOVATIONS FOR INJECTION DEVICES

Nemera always puts patients first, providing the most comprehensive range of devices in the industry, including off-the-shelf innovative systems, customized design development and contract manufacturing.

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