Nemera

ASSESSING THE IMPACT ON DRUG DOSE DELIVERY OF A TWO-STEP AUTOINJECTOR

In this article, Isabelle Delcroix, Strategy Director, Nemera, introduces the company's two-step autoinjector platform, Safelia, which incorporates innovative, patented design features that enable it to deliver a both fluid and viscous formulations from standard glass prefilled syringes with benefits across the board from reducing the risk of syringe fracture to increasing patient comfort.

Injectable formulations are the fastest growing pharma segment. Biologics are increasingly used to treat a wide range of chronic diseases requiring frequent administration over a long period. Developing drug delivery devices able to administer the pipeline of biological molecules is a challenge as biotherapeutics tend to be more viscous, concentrated and administered in a larger volume. Considering patient adherence is an additional challenge. Less frequent injections, therefore larger volumes and more concentrated formulations, is a target for injection, devices which should also deliver with possibly less pain, less bruising and over a short delivery time.

> "By design the coupling inside the autoinjector is not made around syringe's flanges, a structural weak part of the syringe, but around the syringe shoulder. The spring release shock and the energy is absorbed by a rotating cam system and allows highly viscous injections as well as large-volume delivery."

Nemera's new generation of two-step autoinjectors, 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™ autoinjector:

- 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, sustain-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.

DESIGN SPECIFICS

The specificities of Nemera's patented autoinjector design include the ability to handle high injection spring forces and deliver formulations in standard glass syringes. By design the coupling inside the autoinjector is not made around syringe's flanges, a structural weak part of the syringe, but around the syringe shoulder

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Figure 1: 1 mL and 2.25 mL versions of the Safelia™ autoinjector.

"The results obtained during this study showed that by design, syringe speed at needle insertion can be reduced, as can the stress on the glass syringe, reducing the risk of syringe breakage."

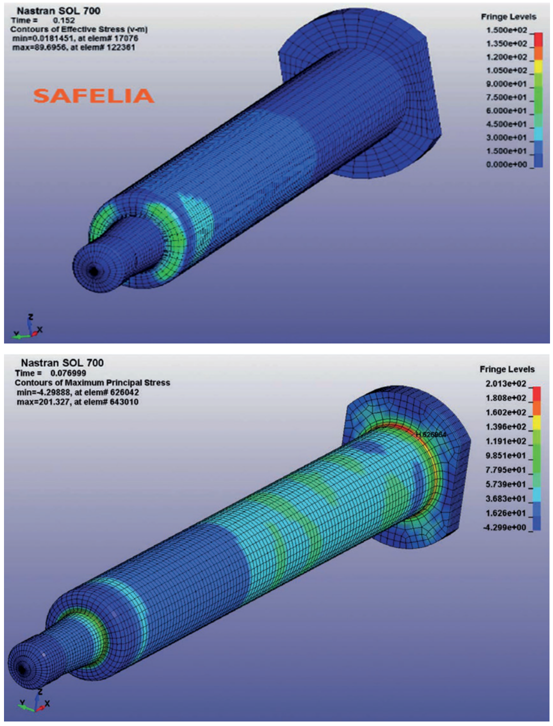


Figure 2: Comparative stress maps of the Safelia (top) and another marketed autoinjector (bottom).

(Figure 2). The spring release shock and the energy is absorbed by a rotating cam system and allows highly viscous injections as well as large-volume delivery. Risks of breakage are therefore reduced by design during triggering of the autoinjector but also during transportation, drop and handling.

THE SPRING FORCE & DRUG VISCOSITY PARADIGM

The mechanism of two-step autoinjectors, as their name indicates, involves two consecutive steps: cap removal and syringe emptying. Injecting a large volume (2 mL) of viscous formulations in a short time (10 seconds) using a thin needle requires greater force than smaller volumes over longer times. The consequence is that the higher the spring energy, the higher is the kinetic energy (E) delivered to the syringe at impact (just after needle insertion, and just before start of syringe emptying).

A high-energy spring will induce high syringe velocity during needle insertion. Thus, at the impact (just after needle insertion, and just before syringe emptying) the force on the syringe could lead to problems. Specifically, at impact, the syringe velocity reduction will produce high stress on specific syringe areas; resulting in syringe breakage in some cases.

Typically, using a spring force of 70 N could lead to 272 N applied on the glass syringe (air bubble is not considered in that calculation). This force can lead to glass syringe breakage.

Different methods can be used to reduce the risk of glass breakage:

- One way is to grip the syringe by the shoulders instead of the flanges as illustrated in Figure 4
- Another way is to use damping materials
- Finally another method is to reduce the impact force that can be transmitted to the syringe.

The Kinetic energy can be calculated as follows:

$$E = Fx - \frac{1}{2} Kx^2 = -\frac{1}{2} Mv^2$$

E = Kinetic Energy
x = Displacement of syringe from point of firing to completion of needle insertion
M = Mass of syringe assembly before impact with the case
V = Velocity of syringe assembly before impact with the case

The syringe speed can be calculated as follows:

$$V = \sqrt{2\frac{E}{M}}$$

The total force on the syringe can be estimated as follows:

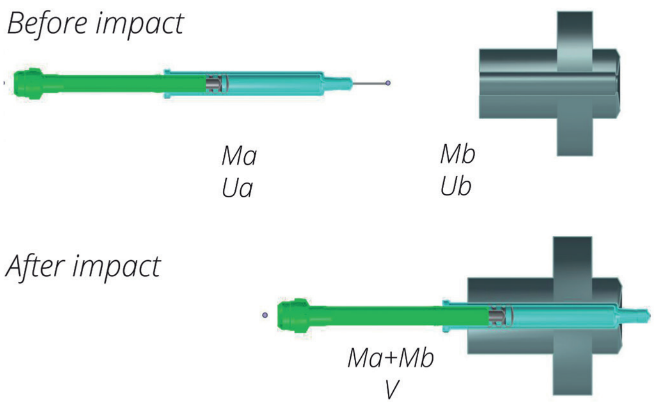


Figure 3: Calculation of total force on syringe resulting from a spring force of 70 N.

x (m)	0.009
K (Nm)	700
F (N)	70
E (Nm)	0.60
Ma	0.013
Ua	9.5
Mb	0.016
Ub	0
Ma+Mb	0.029
V=Va=Vb	4.32
d (m)	0.000341
f (m/s2)	39997
$M_{syringe}$ (Kg)	0.00519
B (N)	202
Total force on syringe=B+F(N)	272

Ma: Mass of syringe assembly before impact with the end stop
Mb: Mass of barrel before impact with the end stop
Ua: Velocity of syringe assembly before impact with the end stop
Ub: Velocity of case before impact with end stop
Va=Vb=V: Velocity of syringe assembly at end stop after impact
d: deceleration distance
B: brake force

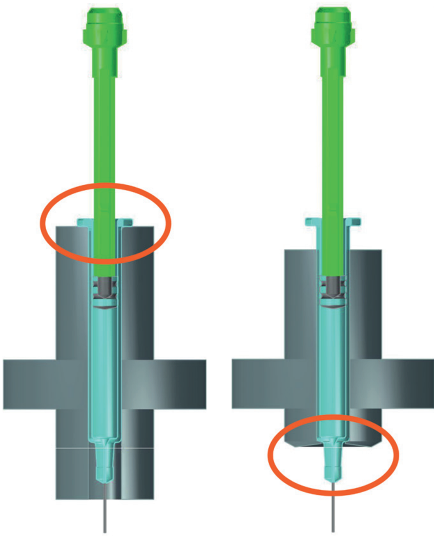


Figure 4: Gripping syringe on the shoulders (right) instead of the flange (left) reduces overall stress.

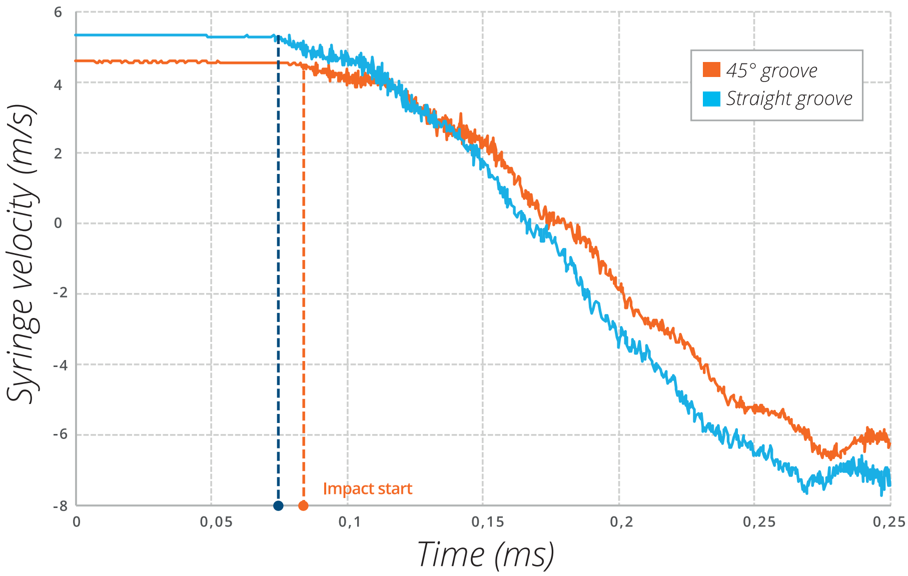


Figure 5: Syringe velocity (m/s) over time during simulation auto-injections using a 45° orientated cam and a straight cam design.

STUDY REPORT: REDUCTION OF INSERTION SPEED

Nemera recently conducted a study to investigate glass syringe fracture risk in autoinjectors by lowering the impact force that can be transmitted to the syringe. Stress analysis was used to demonstrate the effect of lower impact force on syringe stress level.

Method

Numerical simulation was performed using:

1. Adams™ 2014 Multibody Dynamics Simulation. This software simulates all parts, movements and speeds. The out put of this simulation provides a full model.
2. Finite element simulation with MSC Nastran™ 2014 Structural & Multidiscipline Simulation (Explicit transient).

This software simulates stresses between all parts at the calculated speed (Adams 2014).

Assumptions: deformable parts; transient dynamic simulation; and initial condition is the impact velocity given by the full model.

The study compared two models: one with a straight cam guiding the syringe needle insertion and the other a model with a 45° cam, guiding the syringe needle insertion.

All other conditions were constant including: spring force; formulation viscosity; syringe size; needle gauge and length.

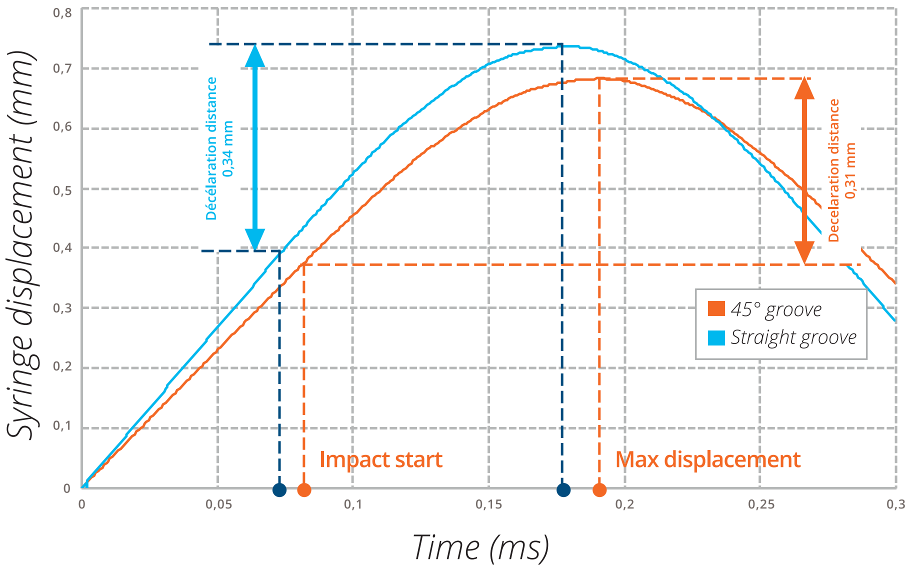


Figure 6: Syringe displacement distances (mm) over the course of the simulated autoinjection.

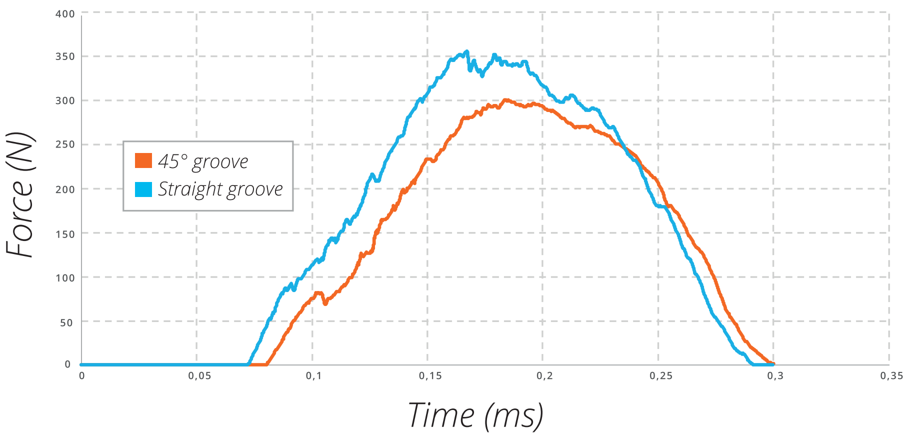


Figure 7: Shock force (N) on the syringe / syringe housing during the simulated autoinjection.

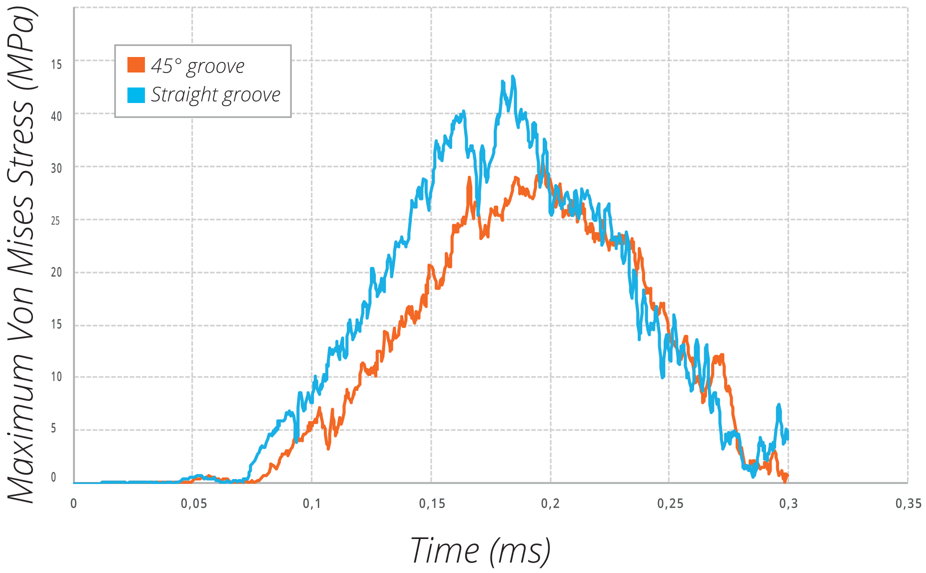


Figure 8: Maximum stress (MPa) on the syringe from the simulated autoinjection with 45° cam compared with straight cam.

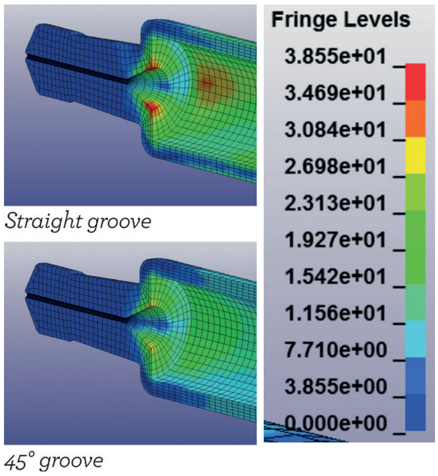


Figure 9: Simulated stress maps of the two autoinjector designs (top) straight cam and (bottom) 45° cam.

Results

As shown in Figure 5, the syringe speed was simulated during its shock with the device. Considering a spring 70 N, the maximum syringe speed was 5.4 m/s with the straight cam, and 4.6 m/s with the oriented cam. According to the configuration with the 45° cam, the syringe deceleration was smoother compared with the other configuration with a straight cam.

The deceleration distances can be estimated at 0.31 mm with the 45° cam compared with 0.34 mm with the straight cam (Figure 6). The distance leads to a reduced shock on the syringe.

The shock force on the syringe / syringe housing over the course of the auto-injection was simulated (Figure 7). As expected, maximum force on the syringe was lower (300 N) with the 45° orientated cam compared with the straight cam (350 N). Time to reach maximum force is also shorter with the straight cam. Similarly, as Figure 8 shows, the maximum stress on the syringe from the simulated auto-injection was lower with the 45° cam (30 MPa) compared with the straight cam (38 MPa).

Finally, the simulated stresses were mapped for each of the autoinjector designs, 45° cam and straight cam. Figure 9 shows that the highest stresses were all in the autoinjector shoulder, with higher stresses being generated from the simulated straight cam design, compared with lower streses from the 45° cam design.

Study Conclusion

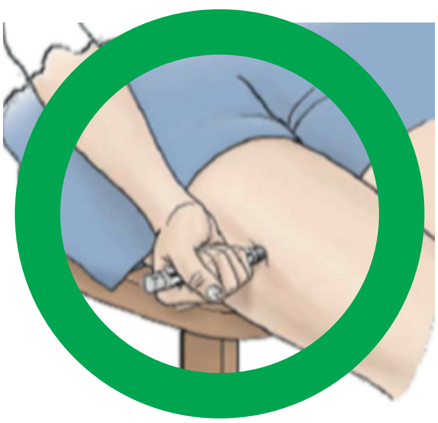
The tendency for larger injected volume with higher viscosity highlights the need to consider this risk at earliest stage in the development process. The results obtained during this study showed that by design, syringe speed at needle insertion can be reduced, as can the stress on the glass syringe, reducing the risk of syringe breakage.

CONCLUSION

The Safelia™ autoinjector combines design elements (summarised in Table 1) such as gripping the syringe by the shoulder rather than the flange, and a slower insertion time achieved through 45° orientation of the cam, which provide significant benefits in terms of patient comfort and safety (Figure 10).

Pain reduction

Patient friendly



- No initial injection peak
- Constant delivery flow
- Adjustable needle insertion speed
- Needle insertion disconnected from injection
- Automatic needle retraction
- Possibility to have thinner needles

Even viscous drugs, no breakage

Syringe friendly

- Syringe is held encapsulated through the barrel
- Syringe front housing
- No stress on the syringe flange
- Possibility to inject very viscous drugs

Figure 10: Benefits of the system for patient comfort and safety.

Safelia™ is now ready to be customised to your formulation and delivery specifications.

ABOUT NEMERA

Nemera has a well- know and established reputation in designing, developing and industrialising parenteral devices. As an example, every day over five million diabetics rely on devices manufactured by Nemera over our four manufacturing plants with harmonised high standard quality. Upstream of production of pens, autoinjectors, implanters, we rely on the expertise of our Innovation Centre at La Verpillière, near Lyon, France (Figure 11). Safelia™ development has benefited from the implication of creative design and human factor specialists, mechanical engineering, testing in our world-class laboratory, manufacturing and assembly knowledge and extensive mathematical modelling.

Expected benefits	Standard AI	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 Safelia benefits and features compared with standard autoinjector.

Figure 11: Nemera's Innovation Centre at La Verpillière, near Lyon, France.

Nemera

parenteral

pulmonary

ophthalmic

dermal/
transdermal

nasal/
buccal/
auricular

Safelia™

NEW GENERATION OF
2-STEPS AUTOINJECTOR
PLATFORM

INNOVATIONS FOR INJECTION DEVICES

SAFETY SYSTEM

RNS REMOVAL

GLASS TO PLASTIC

Nemera provides solutions for the pharmaceutical industry, including standard innovative products, development of custom devices and contract manufacturing.

we put patients first

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