Addressing the Challenges of Highly Viscous Formulations Using a Needle-Free Technology

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Introduction

Biologics, in contrast to small molecules which can be administered orally, generally require larger volume infusions or injections via the parenteral route (e.g., intravenous, subcutaneous, or intramuscular). To further improve the patient experience, many pharmaceutical companies are modifying drug formulations to shift from lengthy intravenous drug administrations at outpatient medical centers to more convenient self-administered subcutaneous injections at home. This empowers patients to manage their own care at home, lighten provider workloads, and reduce demand for expensive clinical services. However, the shift in drug formulations, such as from higher to lower volume administration, often trigger a rise in drug concentration, which typically results in a higher drug viscosity – an attribute that existing injection methods such as pre-filled syringes or autoinjectors have difficulty managing.

Highly Viscous Formulation Challenges for Needle-Based Systems

- Increased likelihood of needle clogging.
- Early device removal, leading to improper dosing and possible health complications[1].
- Patients do not expose the refrigerated biologics to room temperature for up to 30 minutes before the injection.
  - Biologics administered at room temperature can expedite the injection process and alleviate discomfort at the injection site often encountered with cold injectates[2-3].
- Prolonged injection durations can lead to patients underestimating the time required for device-skin contact and missing the system's dose confirmation.

Fluid Motion in Needle-Based Systems vs. Needle-Free Systems

The fluid motion from an injection with a needle-based system can be modeled by the Hagen-Poiseuille equation as shown below. This equation represents the plunger force required to eject a viscous fluid under steady flow. Note that varying each of the equation's parameters may impact the patient's comfort.

$$F = \frac{128Q\mu LA}{\pi D^4}$$

F – Plunger force
Q – Flow rate
μ – Dynamic viscosity of the injectate
L – Needle length
A – Plunger cross-sectional area
D – Needle bore diameter

Needle-free injection systems, such as Portal Instrument's PRIME device, are less susceptible to variations in viscosity since the length (L) of a needle shaft is reduced to the length of the fluid jet nozzle, which is an order of magnitude smaller than the smallest needle lengths used for subcutaneous injections (e.g., 20 mm vs. 2 mm). With a nozzle length (~2 mm) that is not substantially larger than the nozzle bore diameter (~0.2 mm), **the Hagen-Poiseuille equation is no longer applicable, and the system is predominantly governed by the Bernoulli principle; therefore, the viscosity of a fluid plays a minor role in needle-free drug delivery.**

References

1. Scheler, S., Knappke, S., Schulz, M., & Zuern, A. (2022). Needle clogging of protein solutions in prefilled syringes: A two-stage process with various determinants. *European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V*, *176*, 188–198. https://doi.org/10.1016/j.ejpb.2022.05.009
2. Bell, R. W., Butt, Z. A., & Gardner, R. F. (1996). Warming lignocaine reduces the pain of injection during local anaesthetic eyelid surgery. *Eye (London, England)*, *10 (Pt 5)*, 558 560. https://doi.org/10.1038/eye.1996.129
3. So J. Improving patient compliance with biopharmaceuticals by reducing injection-associated pain. *J Mucopolysacch Rare Dis.* 2015;1:15–18. https://doi.org/10.19125/jmrd.2015.1.1.15

Experimental Design

This study was organized into two components:

1. Ejection Testing, to measure the ejection durations of PRIME and the autoinjector using PEG 200.
2. Ex-vivo Testing, to demonstrate through an ex-vivo porcine model that PRIME can deliver PEG 200 into the subcutaneous space (SC) in comparison to a 4 mm needle & syringe (N&S).

Test Devices:
- PRIME: reusable, computer-driven handheld injector, and single-use, COP (cyclic olefin polymer) needle-free cartridge (**Figure 1**)
- Autoject-2: User-filled needle and syringe autoinjector with a spring-loaded system (1 mL, 27G, 12.7 mm length)
- Needle & Syringe (N&S): Hypodermic 27G x 4 mm needle length

Test Fluid:
- Polyethylene glycol (PEG 200, MW = 200 g/mol) at different viscosities (**Figure 2**)
- Methylene Blue dye was added to fluid to view injectate bolus in tissue

Figure 1: The *PRIME device with the 1 mL cartridge*

Ejection Testing

We simulated the patient experience of removing the medications from cold storage prior to injection at five different time intervals. These were chosen to represent the amount of time the filled cartridge and needle and syringe rested at room temperature ($t_{out\ of\ storage}$=0 to 65 minutes). A total of five ejections (into the air) per device and time interval were performed. The ejection durations ($t_{ejection\ duration}$) and the time points following removal of each primary container from cold storage ($t_{out\ of\ storage}$) were measured and recorded.

Ex-Vivo Testing

Several injections were performed on male Yorkshire tissue samples, in the lower abdominal regions, using Portal Instrument's ex-vivo fixture to simulate tension and temperature for testing (**Figure 3**). Test groups to study injection deposition for PEG 200 between devices shown in **Table 1.**

Table 1: Test Group Breakdown for Ex-Vivo Testing

Group	Device	PEG Temperature
1	PRIME	Room (20-25°C)
2	PRIME	Cold (8-15°C)
3	N&S	Room
4	N&S	Cold

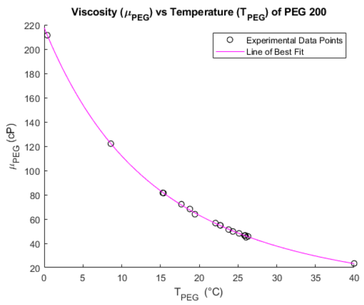

Figure 2: The Viscosity (μ_{PEG}) vs Temperature (T_{PEG}) of PEG 200 curve recorded by removing fluid containers from cold storage at different time intervals to test ejections and injection at different viscosities.

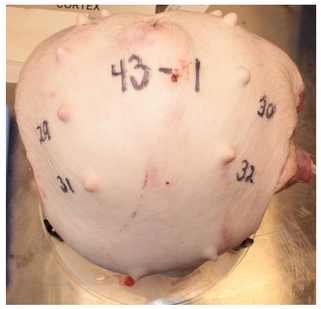

Figure 3: Bird's eye view of ex-vivo male Yorkshire lower abdominal tissue sample with labeled injection sites, placed on ex-vivo fixture.

Results

For a viscosity range of ~80-120 cP ($t_{out\ of\ storage}$ = 0-5 min), the PRIME device had a minimum ejection duration of 0.303 seconds and maximum ejection duration of 0.311 seconds.

Following a period of rest at room temperature (up to $t_{out\ of\ storage}$ = 65 min), the ejection durations for all PRIME ejections remained constant at approximately 0.3 seconds. In contrast to the autoinjector, the ejection durations following removal from cold storage ($t_{out\ of\ storage}$ = 0-5 min) ranged from 75.4 seconds to 159.84 seconds (>2 minutes). Similarly, at room temperature, the autoinjector ejection durations remained high and variable, with ejection durations ranging from approximately 60 seconds to 100 seconds.

One device failure (did not completely eject 1 mL) was observed with the autoinjector within the 0–5-minute window (at ~ 80cP) following removal from cold storage.

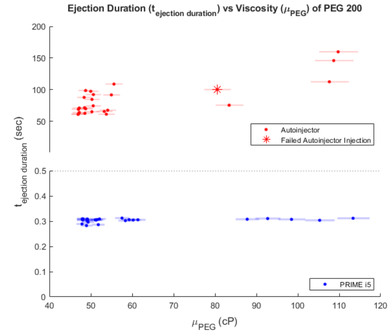

Figure 4: The PRIME and Autoinjector Ejection Durations ($t_{ejection\ duration}$) vs Viscosity (μ_{PEG}).

For ex-vivo testing, qualitative categorical assessment of tissue deposition showed similar depth of injection between all four groups (**Figure 5**). Furthermore, one-way ANOVA revealed that there was a significant difference in mean ejection time between the PRIME device and the N&S control device. There was no significant difference between mean ejection time when comparing room and cold temperature PEG ejection time for the PRIME device, but there was a significant difference in mean ejection time when comparing the same for the N&S control device (**Table 2**).

Table 2: Mean Ejection Time per Test Group

Group	Ejection Time (s) Mean + STDev
1	0.361 ± 0.003
2	0.362 ± 0.003
3	14.85 ± 2.05
4	22.96 ± 3.74

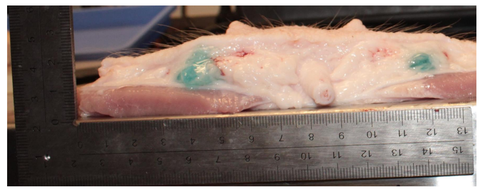

Figure 5: Transverse cut of the abdominal tissue sample for the injection with N&S (*blue bolus on the right*) and the injection with PRIME (*blue bolus on the left*), delivering in the SC when injecting cold PEG 200 (Group 4 and 2 respectively).

Discussion

The *Ejection Testing* results demonstrated the PRIME needle-free injection system can eject at a consistent rate regardless of PEG 200 fluid viscosity. The PRIME device consistently ejected PEG 200 without failure, whereas the autoinjector encountered one total device failure (**Figure 4**). While this was a singular event of ejection failure, the potential of a device malfunction in combination with the increased ejection durations can increase the chance of drug delivery failure.

The *Ex-Vivo Testing* results demonstrated PRIME can eject consistently and faster than N&S, while depositing the injectate at a similar depth in the subcutaneous space.

The ability for PRIME to eject high viscosity fluids consistently and rapidly could open the doors for new therapies as well as make adherence more convenient for patients. Having a needle-free system not only quells the common fear of needles but also boasts faster and more reliable injection times than a mechanical autoinjector. The findings of this study hint at the prospect of pushing beyond the constraints imposed by current needle-based injection devices.

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