Injection Performance Assessment of Monoclonal Antibody Formulation Viscosity Mimics Using an Instantaneous Injection Technology

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Abstract

PURPOSE: Needle-free technologies that deliver an instantaneous subcutaneous injection have potential market advantages for biologics. The ability of these technologies to accomplish subcutaneous delivery while avoiding intradermal and intramuscular delivery is of great importance. The purpose of this study was to characterize the *in vitro* injection performance of DosePro® needle-free technology using viscosity mimics representing a range of potential mAb formulation viscosities.

METHODS: Viscosity mimic fluids with infinite shear viscosities of 5, 11, 20 and 47 mPa·s at 23°C were prepared using either PEG (M_w = 8kDa) or glycerol in DI water. DI water was used as a control to mimic the commercial product Sumavel® DosePro® (sumatriptan for subcutaneous injection, FDA approved 2009; viscosity of ~1 mPa·s). DosePro samples were filled and assembled (n = 20 / mimic).

RESULTS: Data are summarized in Table 1. For each mimic, the mean jet characteristics met the criteria of: injection time ≤ 45 ms, peak pressure ≥ 80% of control, and pressure at 10% total injection time ≥ 70% of control. A decreasing trend in peak velocity was observed, but was not reflected in the peak pressure measurements. Statistically significant differences ($p<0.05$) occurred between the jet characteristics of delivered viscosities, but the differences between the mean jet characteristics are small and not expected to be clinically meaningful.

Table 1 [Abstract]: Summary of jet characteristic data for viscosities ranging from 1-47mPa·s (data shown as mean ± %CV).

Fluid Viscosity	Injection time (ms)	Peak velocity (% of control)	Peak pressure (% of control)	Pressure at 10% injection time (% of control)
1 mPa·s	42.0 ± 3.3%	Control		
5 mPa·s	39.8 ± 2.3%	99.4 ± 5.1%	100.5 ± 4.6%	103.5 ± 4.5%
11 mPa·s	41.4 ± 4.8%	94.7 ± 5.1%	92.3 ± 4.6%	95.3 ± 4.5%
20 mPa·s	40.9 ± 2.7%	94.9 ± 5.1%	92.3 ± 4.6%	95.3 ± 4.5%
47 mPa·s	43.6 ± 3.0%	88.0 ± 5.1%	92.3 ± 4.6%	91.9 ± 4.5%

CONCLUSIONS: DosePro *in vitro* performance for viscosities from 1-47 mPa·s is consistent with injection parameters for subcutaneous delivery of Sumavel DosePro. Performance profiles were within the acceptable criteria for injection time, peak pressure, and pressure at 10% total injection time. Based on these data, clinical injection performance for mAb formulations with viscosities up to 47 mPa·s would be expected to be similar to Sumavel DosePro.

Introduction

Needle-free injections have potential market advantages to differentiate biologics delivered to the subcutaneous tissue[1]. One needle-free injector technology is DosePro, which is prefilled, disposable, and uses compressed nitrogen to deliver a 0.5 mL subcutaneous injection. The bi-phasic delivery profile (Figure 2) consists of an initial peak followed by a reduced pressure where most of the drug is delivered. DosePro injection performance *in vivo* has previously been shown to be controlled by modulating the performance profile characteristics[2], similar to *in vitro* studies of injection parameters using other needle-free technologies[3-5]. Subcutaneous injection is intended, so the ability of this technology to demonstrate consistent performance profile characteristics is therefore important. It is also important for the system to produce a reproducible performance profile at viscosities representing a range of antibody formulations.

Study Objectives

- Characterize the *in vitro* injection performance and reproducibility of DosePro® needle-free technology
- Investigate peak pressure and other performance profile characteristics for a range of viscosities representing antibody formulations

Methods

Preparation of Viscosity Mimics

- Viscosity mimics of 5, 11, and 20 mPa·s were prepared by mixing polyethylene glycol (M_w = 8kDa) in water. The 47 mPa·s mimic was prepared by mixing glycerol in water. DI water was used as a control to mimic the commercial product Sumavel DosePro. Infinite shear viscosities are reported at 23°C and were measured using a m-VROC (Rheosense Inc., San Ramon, CA, USA) with a Type D chip.

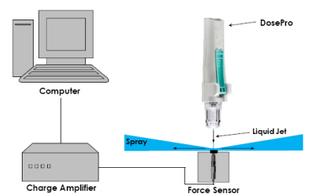
Preparation of Cartridges and Actuator Subassemblies

- Each viscosity mimic was manually filled into DosePro cartridges, and the actuator subassemblies were attached manually. The user interface was not required for this functionality testing and thus was not included.

Equipment for Functionality Testing

- Each DosePro was actuated onto a force sensor as shown in Figure 1 to create the performance profile (Figure 2). A total of 20 trials were performed for each viscosity mimic. Mass and momentum balances, along with Bernoulli's equation were used to convert the force of the jet striking the sensor into jet velocity and capsule pressure as a function of time. A one way ANOVA was used to detect significant differences in the pressure profiles.

Figure 1. Equipment setup for the functionality testing. Each DosePro was actuated on a force sensor connected to a charge amplifier and computer.



Results

Table 1. Summary of performance profile characteristic data for viscosities ranging from 1-47mPa·s. Injection time shown as the mean. Mean peak velocity, peak pressure and pressure at 10% injection time shown as the percentage of control (1 mPa·s viscosity mimic). Relative standard deviation shown as the mean divided by the standard deviation.

Fluid Viscosity (mPa·s)	Injection Time (ms)		Peak Velocity (m/s)		Peak Pressure (MPa)		Pressure at 10% Injection Time (MPa)	
	Mean	% RSD	Mean (% of control)	% RSD	Mean (% of control)	% RSD	Mean (% of control)	% RSD
1 (control)	42.0	3.3	100.0	6.3	100.0	11.9	100.0	12.8
5	39.8	2.3	99.4	3.2	100.5	6.3	103.5	4.5
11	41.4	4.8	94.7	7.1	92.3	12.9	95.3	8.5
20	40.9	2.7	94.9	3.5	92.3	7.2	95.3	8.5
47	43.6	3.0	88.0	9.0	92.3	16.1	91.9	12.7

Figure 2. Pressure vs. time profiles for each viscosity mimic. Profiles at full scale showing entire injection.

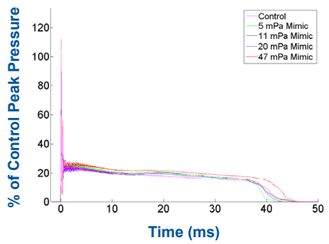


Figure 3. Pressure vs. time profiles for each viscosity mimic. Profiles shown are the initial 2 ms from Figure 2.

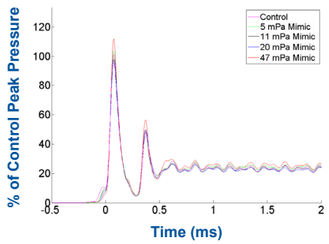


Figure 4. Injection time vs. viscosity. Data shown are mean ± %RSD.

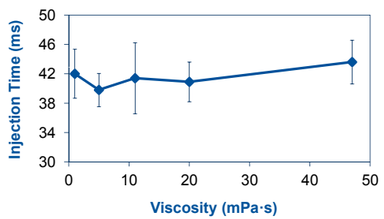
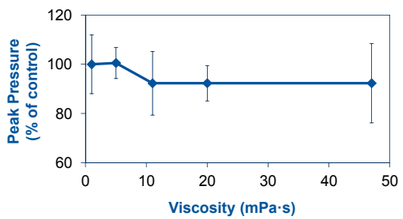


Figure 5. Peak pressure vs. viscosity. Data are mean peak pressure shown as the % of control (1 mPa·s). Error bars represent the %RSD of the mean.



- For each mimic, the mean performance profile characteristics met the criteria of:
  - Injection time ≤ 45ms
  - Peak pressure ≥ 80% of control
  - Pressure at 10% total injection time ≥ 70% of control
- A decreasing trend in peak velocity was observed as viscosity increased, but this was not reflected in the peak pressure measurements.
- When a one way ANOVA was applied to the jet characteristic data, statistically significant differences ($p<0.05$) were detected between the jet characteristics for delivered viscosity mimics. However, the differences are small and are not expected to be clinically meaningful.

Conclusions

DosePro *in vitro* performance for viscosity mimics from 1-47 mPa·s is consistent with injection parameters for subcutaneous delivery of Sumavel® DosePro® (sumatriptan for subcutaneous injection, FDA approved 2009; viscosity of 1 mPa-s). Performance profiles were within the acceptable criteria for injection time, peak pressure, and pressure at 10% total injection time. Based on these data, clinical injection performance for mAb formulations within this viscosity range would be expected to be similar to Sumavel DosePro.

Acknowledgements

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