Advancing injection force modeling and viscosity-dependent injectability evaluation for prefilled syringes

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Abstract/Introduction

Prefilled syringe (PFS) development requires a comprehensive understanding of the forces involved in drug administration that affect dose accuracy, injection safety, and patient adherence. To better predict injection dynamics, we refined the mathematical model for injection force by integrating both hydrodynamic and frictional forces.

In the improved model, we included drug viscosity properties (both Newtonian and Shear-thinning) and the syringe shape constant in the hydrodynamic force analysis, following the Hagen-Poiseuille law, and derived the friction force from empty barrels. The model also accounted for actual environmental temperatures during administration. The results highlight the critical roles of the syringe shape constant and the rheological behavior of protein solutions in governing injection force dynamics.

We considered the counter pressure generated by the tissue during actual administration to address the inaccuracies in current injection force evaluations conducted in air, especially when the viscosity of the injected drug solution (DS) is below 9.0 cP (injecting with 1 mL long PFS staked with 29G ½ inch needle).

Finally, a simplified human factor study on injectability against viscosity was conducted, indicating that healthy adults were comfortable injecting medication with a viscosity of approximately 20 cP (1.0 mL in a 1 mL long PFS) within 15 seconds.

Methods

Injection force measurements

- Performed on a material testing instrument with a 100 N load cell
- Syringes expelled 1 mL in 10 seconds by pushing the plunger at a constant speed, calculating the Reynolds Number as ~106 at this speed
- The testing conditions were controlled under 23±2°C and 50±25% rH

Viscosity measurements

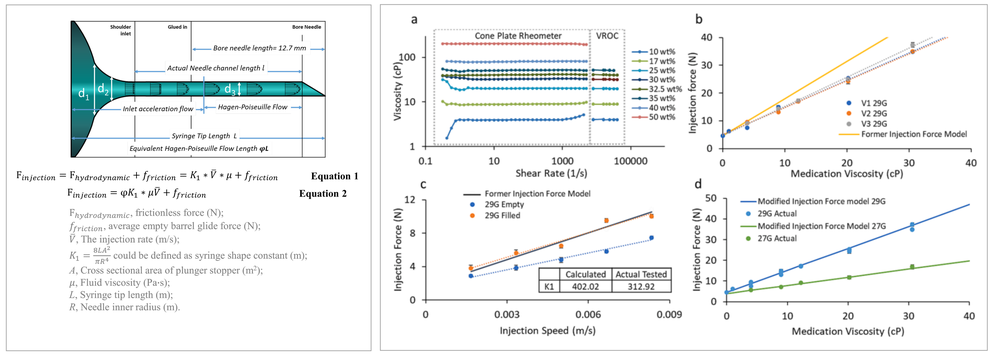
- Viscosity was monitored at 5°C, 15°C, 20°C, 25°C, and 40°C, respectively
- Viscosity at an apparent shear rate between 100 and 5000 s^{-1} and under a higher shear rate to 40000 s^{-1} was measured

Injectability evaluation

- Thirteen individuals aged 25 to 35, including 6 males and 7 females, were invited to dispense medication from 1 mL long PFS (29G).
- The individual must score the syringe from 1 to 10 based on difficulty.
- The injection time was recorded as the end users started pushing the plunger rod until the explusion of the last drop of medication.

Results

Fig 1. Advancing injection force modeling for Newtonian solution via introducing needle tip shape correction factor ϕ
a. PEG6000 simulation solution rheological behavior at different concentrations (from 10wt% to 50wt%) based on shear rates (monitored both with cone plate rheometer and VROC microchip viscometer); **b.** the relationship between injection force (1 mL/10 s) and viscosity for various staked-in-needle 29G 1 mL long glass syringes (from three vendors) and the former injection force prediction (**Equation 1**, orange line); **c.** the relationship between injection force and injection speed: the empty barrel injection force of 29G 1 mL long glass syringes (blue dots) and water filled injection force (orange dots) were measured at 100 mm/min to 500 mm/min injection speed and the injection force prediction by **Equation 2** (black line) (K1 shape constant calculated and actual tested are shown in the inset table, ϕ: K1 measured/K1 calculated; **d.** the corrected injection force model (Equation 6) in simulation actual injection force (1 ml/ 10 s) for syringes with 27G (green line and dots) and 29G 1 mL long syringes (blue line and dots), respectively.



$$F_{injection} = F_{hydrodynamic} + f_{friction} = K_1 * \bar{V} * \mu + f_{friction} \quad \text{Equation 1}$$

$$F_{injection} = \varphi K_1 * \mu\bar{V} + f_{friction} \quad \text{Equation 2}$$

$F_{hydrodynamic}$, frictionless force (N);
$f_{friction}$, average empty barrel glide force (N);
$\bar{V}$, The injection rate (m/s);
$K_1 = \frac{8LA^2}{\pi R^4}$ could be defined as syringe shape constant (m);
A, Cross sectional area of plunger stopper (m^2);
μ, Fluid viscosity (Pa·s);
L, Syringe tip length (m);
R, Needle inner radius (m).

Fig 2. Advancing injection force modeling at different actual administration temperature
a. The different concentrations of PEG6000 solutions (10% to 30% w/w) rheological behaviors were monitored from 5°C to 40°C; **b.** the injection force of 17% w/w PEG6000 at different temperatures was measured (blue dots), predicted by exponential law (**Equation 3**, orange line) and corresponding 17% w/w PEG6000 viscosities against temperature (**Equation 2**, Grey dots).

$$F_{injection} = \varphi K_1 * \mu(T)\bar{V} + f_{friction} = \varphi K_1 * \mu_0 Exp(-cT) * \bar{V} + f_{friction} \quad \text{Equation 3}$$

$\mu(T)$ is the actual apparent viscosity (Pa·s) at temperature T (K);
μ_0 and c are adjustable coefficients those could be derived from model regression based on exponential law.

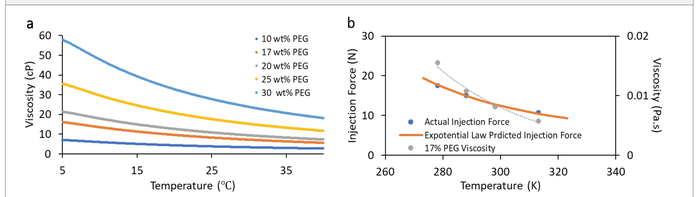


Fig 3. Advancing injection force modeling for Shear-thinning solution
a. The viscosity of different concentrations (5 mg/mL to 20 mg/mL) of CMC (carboxymethyl cellulose) solutions as function of shear rate were monitored both with cone plate rheometer and VROC microchip viscometer; **b.** the injection force of CMC solutions actual tested (blue line), the injection force predicted by Newtonian injection force model (**Equation 2**, viscosity at 5,000 s-1, green line) and optimized Shear-thinning injection force model (**Equation 4**, orange line). The shear rate of CMC solution passing through 29G TW needle was calculated as ~2.5 × 10^4 s-1 (1 mL/10 s).

$$F_{injection} = \varphi K_1 * K\left(\frac{2\bar{v}}{R}\cdot\frac{3n+1}{2n+1}\right)^{n-1}\bar{V} + f_{friction} \quad \text{Equation 4}$$

Flow consistency index K (Pa s^n), and n, power law index; dimensionless

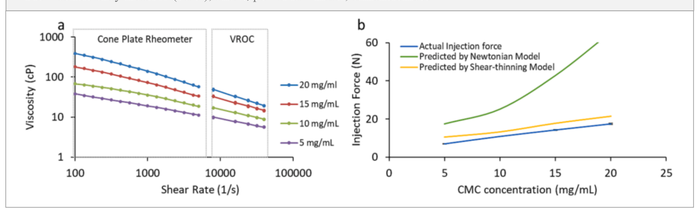


Fig 4. Advancing injection force modeling for mAb solution
Actual injection force measured (1 mL/10 s, dark blue column) was compared to predicted results by Newtonian (**Equation 2**, grey column) and Shear-thinning models (**Equation 4**, light blue).

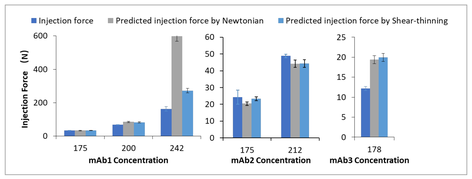


Table 1 *The mAb solution flow consistency index K (Pa s^n), and the power law index n (index; dimensionless)*

mAbs	Concentration (mg/mL)	K (Pa s^n)	n-1	n	r^2
mAb1	242	10.788	-0.339	0.661	0.9961
	200	0.1115	-0.039	0.961	0.9881
	175	0.0316	-0.016	0.984	0.9615
mAb2	212	0.0468	-0.022	0.978	0.9815
	175	0.0126	0.0258	1.0258	0.9845
mAb3	178	0.0151	-0.009	0.991	0.966

Fig 5. The injection force into tissue
The representative average injection force of injecting 1 mL medication to porcine tissue (orange column) and air (blue) using 1 mL L 29G TW ½ PFS (n=6; NS: p ≥0.05, * p < 0.05, ** p < 0.01, ***p < 0.001).

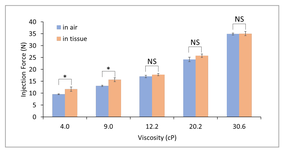
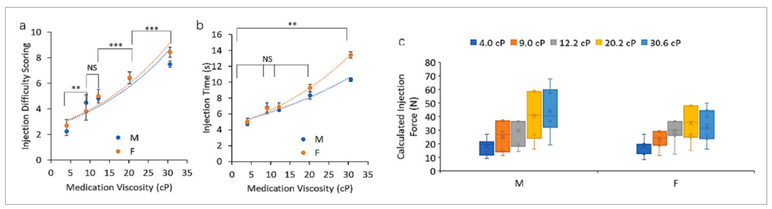


Fig 6. Injectability correlation with end user capability
Individuals are 25 to 35 years old, including 6 males (M) and 7 females (F). 1.0 mL PEG6000 solution at five different viscosities were manually expelled using 1 mL L 29G TW ½ PFS.
a. The injection difficulty scoring in terms of medication viscosity
b. The injection time in terms of medication viscosity
c. The calculated injection forces the participants end used based on Newtonian injection force model



Conclusion

- An advanced injection force model was developed based on the medication's rheological properties, assessing injectability in relation to viscosity.
- The preliminary results from human factor assessments presented in this study enabled us to devise a scoring system for rationalizing and facilitating the selection of the optimal the needle-syringe-formulation.
- Overall, this model predicts the injection force for specific protein solutions during early development, offering insights into injectability by projecting the injection force across different PFS system combinations.

References

1.*Wu, L., Li, H., Wang, Y., Zhuang, G., Chen, Q. & Guo, J. (2024). Advancing injection force modeling and viscosity-dependent injectability evaluation for prefilled syringes. European Journal of Pharmaceutics and Biopharmaceutics, 114221.*

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Poster modified on 10/2/2024

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