Predicting Injection Force from Viscosity Data Part 1: Theoretical Foundation

Key Words: viscosity, injection force, injectability, Newtonian, non-Newtonian, power-law fluid

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Introduction

Viscosity is an important fluid property that can be used to predict performance in real world applications. One of the most common uses of viscosity is to assess the ability to deliver pharmaceutical formulations to the patient by injection. A significant component of formulation research and development is rheology modification to ensure that therapeutics can be delivered without an excessive injection force. This concern is especially important when developing high concentration antibody formulations, which can have a broad range of viscosities depending on the specific protein-protein interactions. To tackle the problem of relating viscosity to injection force, we turn to fluid mechanics for pressure driven flow through a circular cross section. Here we will go through the equations required for Newtonian, power-law, and general non-Newtonian fluids. This application note lays the theoretical foundation for future tutorials on experimental design and data analysis.

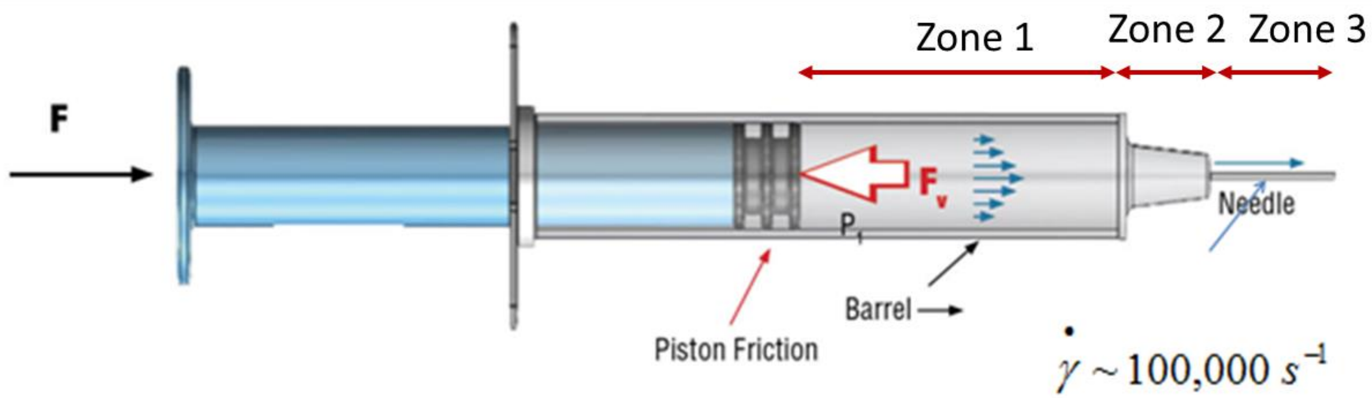

Figure 1: Syringe geometry and definition of the various regions: Zone 1 = barrel, Zone 2 = tapered transition or contraction, Zone 3 = needle.

Foundational Equations and Simplifying Assumptions

Figure 1 illustrates the general syringe geometry and defines the relevant regions along the fluid flow path. The total force required to move the piston through the barrel has both a friction (F_f) and viscous (F_v) component.

$$F_{tot} = F_v + F_f \tag{1}$$

Our analysis only addresses the viscous contribution to the force since the friction between the piston and the barrel is highly variable and dependent on the specific materials. The viscous portion of the force will then be the total pressure drop (P) along the flow path multiplied by the cross-sectional area of the piston with radius R_p.

$$F_v = \pi {R_p}^2 P \tag{2}$$

The total pressure drop will have contributions from all three zones (**Figure 1**).

$$P = \Delta P_1 + \Delta P_2 + \Delta P_3 \tag{3}$$

A force balance must be satisfied for each zone and has the following general form.

$$cross - sectional\ area\ \times pressure\ drop = wetted\ surface\ area \times viscous\ stress$$

In variable form, the force balance is represented as follows.

$$\pi R^2 \Delta P = 2\pi R l \sigma \tag{4}$$

R is the radius, ΔP the pressure drop, l the path length, and σ the viscous stress for each syringe section or zone. The familiar viscous stress is given by the product of the viscosity (η) and the shear rate ($\dot{\gamma}$).

$$\sigma = \eta \dot{\gamma} \tag{5}$$

The goal now is to simplify the problem by assessing the relative magnitude of each pressure contribution in equation 3. In other words, can we show that one will dominate such that we can focus our attention there rather than dealing with all three? For the simplification process, it is adequate to assume the fluid is Newtonian such that the velocity profile across the radius is parabolic. The shear rate at the wall is then simply related to the volumetric flow rate (Q) and radius (Macosko, 1994).

$$\dot{\gamma}_{w,N} = \frac{4Q}{\pi R^3} \tag{6}$$

The force balance can then be rearranged to solve for the pressure drop in a particular section or zone of the flow path.

$$\Delta P = \frac{8\eta l Q}{\pi R^4} \tag{7}$$

This is the familiar Hagen-Poiseuille law and can be used to estimate the ΔP for common syringe parameters in the various regions. To facilitate the comparison between different syringe zones, the following expression for the pressure drop ratio is used where i and j are indices corresponding to the zone number (i.e. 1, 2, or 3)

$$\frac{\Delta P_i}{\Delta P_j} = \frac{l_i}{l_j}\left(\frac{R_j}{R_i}\right)^4 \tag{8}$$

Since the transition region (zone 2) is not well defined and likely variable depending on the specific syringe configuration, we focus on the relative pressure drop between the needle and barrel to simplify the analysis. **Table 1** contains common parameters for these two zones and the corresponding relative pressure drop $\Delta P_3/\Delta P_1$. Since the pressure drop in the needle is five orders of magnitude higher than the barrel, the problem can be greatly simplified with the following approximation for the total pressure.

$$P \cong \Delta P_3 \tag{9}$$

This simplifying assumption will be utilized throughout to estimate the viscous contribution to the injection force for Newtonian, power-law, and general non-Newtonian fluids.

Zone	$2R_i$ (mm)	l_i (mm)	$\Delta P_3/\Delta P_1$
1	6.35	60	300,245
3	0.184	12.7	

Table 1: Common syringe/needle parameters and corresponding pressure drop ratio for zones 1 and 3 using equation 8.

Newtonian Fluid

We now have everything necessary to present an analytical expression for the viscous component of the injection force for Newtonian fluids ($F_{v,N}$) in terms of known or measurable parameters. Specifically, equations 2, 7, and 9 are combined to obtain the following.

$$F_{v,N} \cong 8\eta l_n Q \frac{{R_p}^2}{{R_n}^4} \tag{10}$$

Since the viscosity is independent of shear rate for Newtonian fluids, once this classification is confirmed the viscosity can be measured at any convenient rate for use in the calculation. It is then a simple exercise using equation 10 to determine what syringe configuration and delivery rate are appropriate for a particular fluid formulation.

Power-law Fluid

A very common deviation from Newtonian behavior is the power-law fluid (**Figure 2**). This is most often seen when the low and high shear viscosity plateaus are at extreme shear rates not practically accessible. In this case, the viscosity takes the following shear rate dependent form over the range measured.

$$\eta = \kappa\dot{\gamma}^{n-1} \tag{11}$$

n is the power-law index and κ the pre-factor which in the Newtonian limit (i.e. $n = 1$) is simply the viscosity. Since equation 7 was derived for the Newtonian assumption, an expression for ΔP_3 that is valid for power-law fluids is now required. We first re-arrange equation 4 to solve for the pressure drop along the needle flow path.

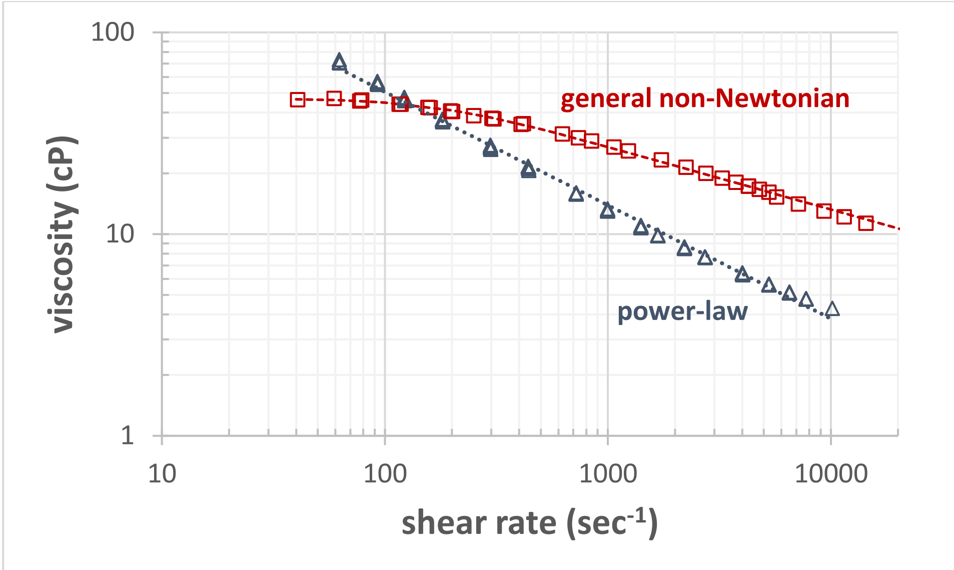

Figure 2: Viscosity versus shear rate for **power-law** and **general non-Newtonian** fluids.

$$\Delta P_3 = \sigma_w \frac{2l_n}{R_n} \tag{12}$$

The shear stress at the wall σ_w can be evaluated by combining equations 5 and 11.

$$\sigma_w = \kappa \dot{\gamma}_w{}^n \tag{13}$$

Using equation 6 to convert shear rate to volumetric flow rate in equation 13 is not strictly correct since it was derived specifically for Newtonian fluids. To determine the analogous relationship for power-law fluids, we start with the general integral over the cross-sectional area to calculate volumetric flow rate from the radial dependent velocity profile ($u(r)$).

$$Q = 2\pi \int_0^{R_n} u(r) r dr \tag{14}$$

To obtain a more convenient form, we integrate by parts and then apply the definition of shear rate ($\dot{\gamma} = -\frac{du}{dr}$).

$$Q = \pi \int_0^{R_n} \left(-\frac{du}{dr}\right) r^2 dr = \pi \int_0^{R_n} \dot{\gamma}\, r^2 dr \tag{15}$$

Now we can convert the integral using the radial stress distribution $\sigma = \sigma_w \frac{r}{R_n}$ obtained from solution of the general momentum balance in cylindrical coordinates (Macosko, 1994).

$$Q = \frac{\pi R_n^3}{\sigma_w^3} \int_0^{\sigma_w} \dot{\gamma}\, \sigma^2 d\sigma \tag{16}$$

Equation 16 will now allow us to relate the wall shear stress to the volumetric flow rate for non-Newtonian fluids so that equation 12 can be expressed as a function of known variables. The power law expression for the stress can be rearranged to solve for shear rate.

$$\dot{\gamma} = \left(\frac{\sigma}{\kappa}\right)^{1/n} \tag{17}$$

Substituting into equation 16 and integrating provides the following expression relating the wall shear stress to the volumetric flow rate valid for a power law fluid.

$$\sigma_w = \frac{\kappa Q^n}{\pi^n {R_n}^{3n}} \left(\frac{3n+1}{n}\right)^n \tag{18}$$

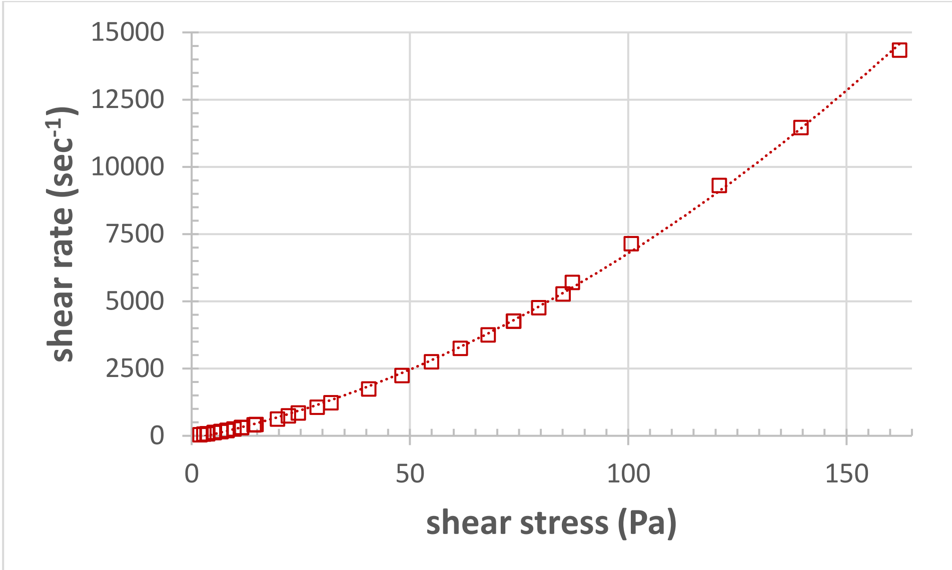

Figure 3: Shear rate versus shear stress for **general non-Newtonian** fluid. Dotted line corresponds to a quadratic fit.

Combining equations 2, 9, 12, and 18 provides the final form for the viscous contribution to the injection force for a power-law fluid ($F_{v,PL}$).

$$F_{v,PL} \cong 2\left(\frac{3n+1}{n}\right)^n \pi^{1-n} \kappa l_n Q^n \frac{{R_p}^2}{{R_n}^{3n+1}} \tag{19}$$

The final task is to determine a relation analogous to equation 6 that is valid for the power-law fluid. Combining equations 17 and 18 generates this relationship.

$$\dot{\gamma}_{w,PL} = \left(\frac{3n+1}{n}\right)\frac{Q}{\pi {R_n}^3} \tag{20}$$

Equation 20 can be used to determine the shear rate experienced in the syringe needle and confirm that the viscosity data used for the analysis was collected over the appropriate range.

General Non-Newtonian Fluid

Shear rate dependent viscosity data of complex fluids often follows a form more complicated than the power-law. For example, a viscosity profile can include both a shear thinning region as well as a full or partial plateau (**Figure 2**). Since pharmaceutical formulations typically fall under the classification of complex fluids, this is an import situation to address. We already have the starting point for a more general non-Newtonian fluid, which is equation 16. The next step would be an appropriate way of relating shear rate and shear stress. We have found from experience that the following empirical relationship generally holds and is a good fit to data for many concentrated proteins (**Figure 3**).

$$\dot{\gamma}(\sigma) = a\sigma^2 + b\sigma \tag{21}$$

The coefficients a and b are determined by plotting $\dot{\gamma}$ versus σ and applying the quadratic fit to the experimental data. Substituting equation 21 into 16 and integrating yields the following.

$$Q = \pi R_n^3 \left(\frac{a}{5}\sigma_w^2 + \frac{b}{4}\sigma_w\right) \tag{22}$$

Rearranging equation 22 provides an expression with an obvious solution for the shear stress at the wall.

$$\frac{a}{5}\sigma_w^2 + \frac{b}{4}\sigma_w - \frac{Q}{\pi R_n^3} = 0 \tag{23}$$

The known solution to the quadratic is as follows.

$$\sigma_w = \frac{-B+\sqrt{B^2-4AC}}{2A} \tag{24}$$

$$A = \frac{a}{5},\ B = \frac{b}{4},\ C = -\frac{Q}{\pi R_n^3} \tag{25}$$

As with the previous examples, equation 24 would be used in combination with 2, 9, and 12 to calculate the viscous contribution to the injection force for the general non-Newtonian (GNN) fluid. The actual shear rate in the syringe needle can be evaluated by using the Weissenberg-Rabinowitsch-Mooney (WRM) correction for circular cross-sections in combination with the experimental viscosity data (Macosko, 1994).

$$\dot{\gamma}_{w,GNN} = \frac{Q}{\pi {R_n}^3}\left(3 + \frac{d\ln\dot{\gamma}_w}{d\ln\sigma_w}\right) \tag{26}$$

Concluding Remarks

The working equations have been presented to calculate the viscous contribution to the injection force for Newtonian, power-law, and general non-Newtonian fluids. Although a seemingly complicated problem, the analysis can be simplified by realizing that the pressure drop across the syringe needle dominates. In our upcoming application notes, we will put this theory to work by detailing the calculation process for a variety of fluid types using experimental data. We will also use the theory to guide us in developing an experimental measurement plan so that the most relevant data can be obtained to support the injection force prediction. Although the process may seem like a daunting task, it is well worth the effort to ensure that suitable therapeutic candidates are not discarded but continue to move forward in the development process.

References

Macosko, C. W., *Rheology Principles, Measurements, and Applications*; Wiley-VCH: New York, 1994.

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Main Office — 1 925 866 3801
Sales – Sales@RheoSense.com
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