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Rheology Tools: Injection Force Estimation- General Non-Newtonian Fluid

Key Words: non-Newtonian Fluids, Injection Force Estimation, Formulation Development, Formulation Characterization, Data Analysis Protocol.

Goal: Formulation analysis is key during development of protein therapeutics. One key application for protein therapeutics is injectability. Therapeutics must be delivered to patients in some form to be effective. This application note will step through how to estimate the injection force of a protein formulation when it is non-Newtonian. Having a good estimate of injection force early in development can help guide your formulation development.

Introduction

Determining the drug delivery pathway of candidate drugs is a key component of the development process. There are many potential delivery pathways for drugs each with tradeoffs that impact ease of use and drug efficacy. One such delivery pathway for antibody therapeutics is injection (Allmendiger et al 2014). However, a key limitation for this delivery pathway is the high concentrations of antibodies necessary to achieve an effective dose. High concentrations of protein lead to large increases in viscosity, which can make injection more difficult, because of the large force required to achieve delivery. Depending on the device used for injection, the cutoff viscosity of concentrated protein formulations can be between 20 and 40 cP (mPa-s). The force required to inject drugs with these viscosities can be difficult to administer for the caregiver or painful for the potential patient.

Incorporating injectability analysis earlier in development can guide the process and reduce the risk of creating a formulation that is impossible to deliver. The first step in incorporating injectability analysis is to measure the formulations' viscosity over a wide range of shear rates and determine the fluid's behavior. The second step is determining the shear rates that correspond to the injection flow rate and the dimensions of the delivery device such as needle gauge and barrel radius. Once these dimensions and properties are known, then the injection force can be estimated. However, the first question you may ask is "I don't know where to begin to estimate injectability?" Injectability and viscosity are closely related. So, if you know the viscosity of your sample as well as the rate of injection and syringe geometry, then you will be able to estimate the injection force. In this application note we will describe a protocol that you can follow to estimate the injection force of your protein formulations using model data taken on the VROC®-initium. We previously addressed how to estimate the hydrodynamic contribution to the injection force for Newtonian fluids and Power Law non-Newtonian fluids. Now we will walk through the injection force estimation for general non-Newtonian Fluids. This general form of the equation can work for both Newtonian and non-Newtonian fluids, but the process to calculating it differs from our previous two examples.

Equations

The general injection force estimation equation for non-Newtonian Fluids is as follows:

$$F_v \cong 2\pi l_n \sigma_w \frac{R_p^2}{R_n}$$

σ_w is the shear stress at the wall of the needle (Pa)
F_v is the injection force (N)
$l_n$is the needle length (mm)
R_p is the radius of the piston of the syringe (mm)
R_n is the inner radius of the needle (mm)

In order to solve this equation we will need to determine the wall shear stress σ_w. To do that we need to fit WRM corrected shear stress (σ) and shear rate $(\dot{\gamma})$ data to this quadratic equation:

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

Once we find the coefficients a and b we can then solve for the wall shear stress, σ_w using the following equation:

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

Where:

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

Q is the volumetric flow rate ($mm^3\ s^{-1}$)

A full theoretical derivation of these equations is shown in our previous application note: Predicting Injection Force from Viscosity Data Part 1: Theoretical Foundation.

Protocol

This protocol is applicable to estimating the viscous contribution of the injection force of a fluid within a syringe. This protocol does not incorporate the friction force contribution. Syringes are made from different materials depending on product line and manufacturer. Additionally, the fluid/drug within the syringe can lubricate the barrel and piston of a syringe which will impact friction. The protocol described here will still give you a good estimate of the injection force since viscosity is a major contributor to this force. If your viscometer or rheometer induces an inhomogeneous flow on your non-Newtonian fluid, then you must perform a correction. The appropriate correction for flow through a rectangular channel is the Weissenberg-Rabinowitsch-Mooney (WRM) correction. We have an application note detailing how to perform the correction using Microsoft Excel, which you can download.

1. First, plot your shear rate versus viscosity data. Plotting your data in this way well help you determine if your sample is a Newtonian or non-Newtonian fluid (**Figure 1**).

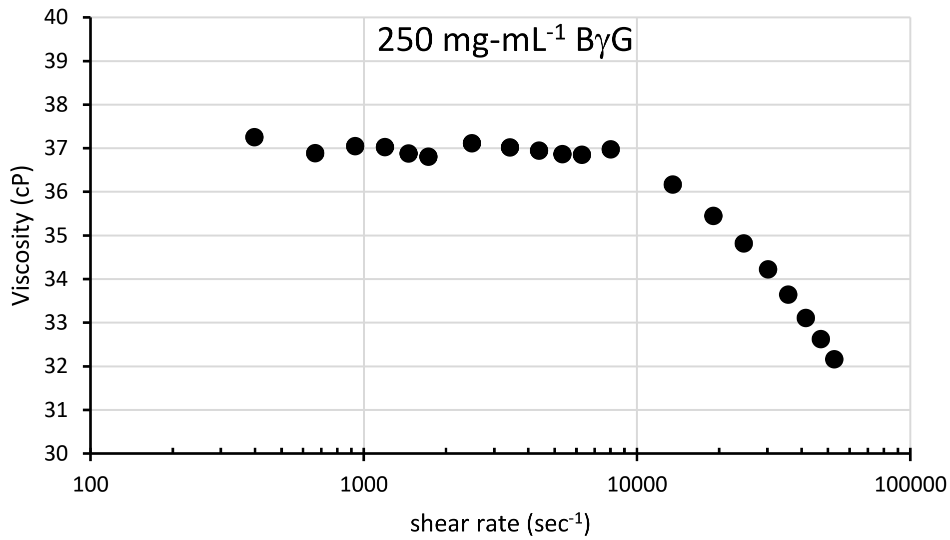

Figure 1. Shear rate sweep of BγG in an arginine/histidine buffer. 250 mg/mL protein solution from 400 s^{-1} to 52,752 s^{-1}. This shear rate versus viscosity curve indicates that this fluid is non-Newtonian.

2. Now that we have confirmed that our fluid is non-Newtonian, we can estimate the viscous contribution of the injection force. First, we need to determine the constants of “a” and “b” for the shear rate equation listed in the **Equations** section above. To do that, plot the shear rate versus shear stress data for every shear rate explored. **Note:** The shear rates in the non-Newtonian region must be corrected with the WRM correction before making the fit. When performing the fit using Microsoft Excel, set the y-intercept to 0 since this material has a low shear Newtonian plateau and not a yield stress. The shear rate versus shear stress data is plotted and fitted to a quadratic equation in **Figure 2**.

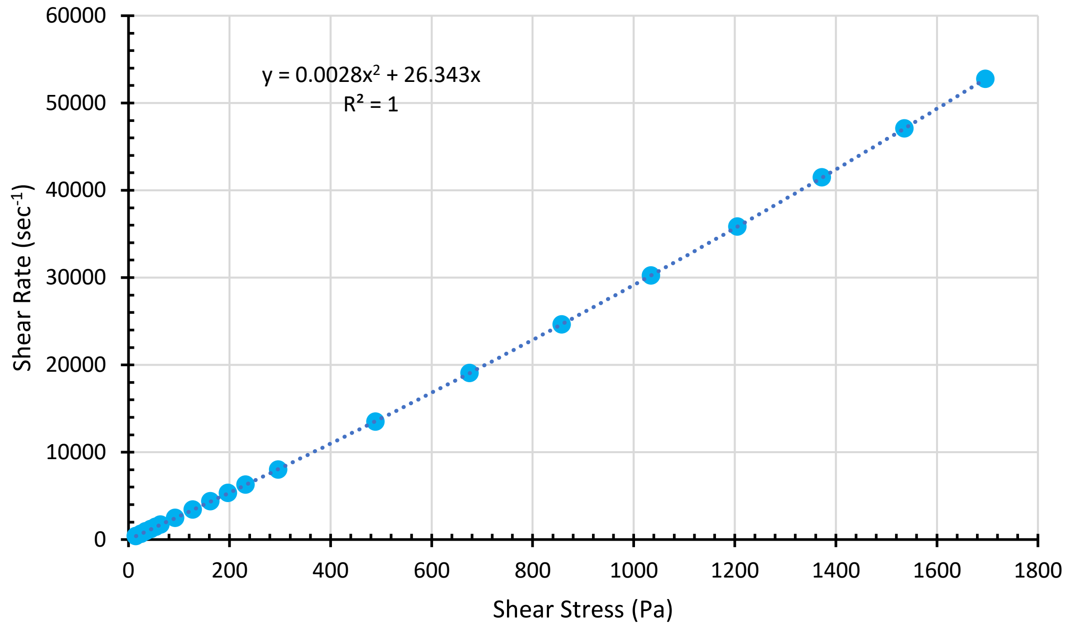

Figure 2. Quadratic fit to determine coefficients for wall shear stress calculation. The shear rate versus shear stress data fit to a quadratic to extract the coefficients for future calculations. We will use the coefficients a = 0.0028 and b = 26.343 when calculating the wall shear stress. **Note:** set the y-intercept to 0 when performing the fit.

3. Next, determine the value of the shear stress at the wall (σ_w). Refer to the wall shear stress equation in the **Equations** section. Note that we will use flow rate (Q) to determine the wall shear stress. However, the relationship between flow rate and shear stress is not as straightforward as in our previous application notes explaining the calculation for Newtonian fluids and Power Law fluids.

4. To determine the flow rate (Q) use the rate you suspect you will use when delivering your product. For example, some flow rates that are within the range of common injection rates are 20 mm^3/sec, 100 mm^3/sec, and 200 mm^3/sec. **Note:** The beauty of using the general non-Newtonian equation is that it can be used to extrapolate the injection force estimation if your injection rate is higher than the maximum rate of your instrument.

5. The last step needed before calculating wall shear stress and injection force is to determine the dimensions of the needle and syringe for injection. **Table 1** lists common dimensions for four separate needle gauges.

	21 gauge	25 gauge	27 gauge	30 gauge
L (mm)	17	17	17	17
Rp (mm)	6.35	6.35	6.35	6.35
Rn (mm)	0.51	0.26	0.21	0.16

Table 1. Syringe and needle assumptions. L corresponds to the needle length. R_p is the radius of the syringe piston. R_n is the inner radius of the needle. The columns correspond to different needle gauges.

6. Use the constants in **Step 2**, the flow rates in **Step 4**, and dimensions listed in **Table 1** to calculate the wall shear stress and injection force. Please refer to the **Equations** section if you get stuck performing

the calculation. **Note:** Be sure your units are consistent! (Units of pascal (Pa) correspond to N/m^2). The values of the wall shear stress, injection force, and shear rate using the equation in **Figure 2**: $\dot{\gamma} = 0.0028\sigma_w^2 + 26.343\sigma_w$ are presented in **Table 2** and graphically presented in **Figure 3.**

Gauge	Q (mm^3/sec)	σ_w (Pa)	Force (N)	$\dot{\gamma}$ (sec^{-1})
21	20	7.28	0.06	192.00
	100	36.32	0.31	960.58
	200	72.43	0.61	1922.62
25	20	54.74	0.91	1450.52
	100	268.85	4.45	7284.67
	200	526.43	8.72	14643.58
27	20	103.47	2.12	2755.68
	100	500.59	10.27	13888.73
	200	964.67	19.78	28017.93
30	20	231.45	6.23	6246.99
	100	1080.70	29.09	31738.98
	200	2014.83	54.24	64443.23

Table 2. Calculated wall shear stresses (σ_w), Injection Forces (N), and shear rates ($\dot{\gamma}$) for each needle gauge. The wall shear stresses, injection forces, and shear stresses for each needle gauge at each specified flow rate for the example sample.

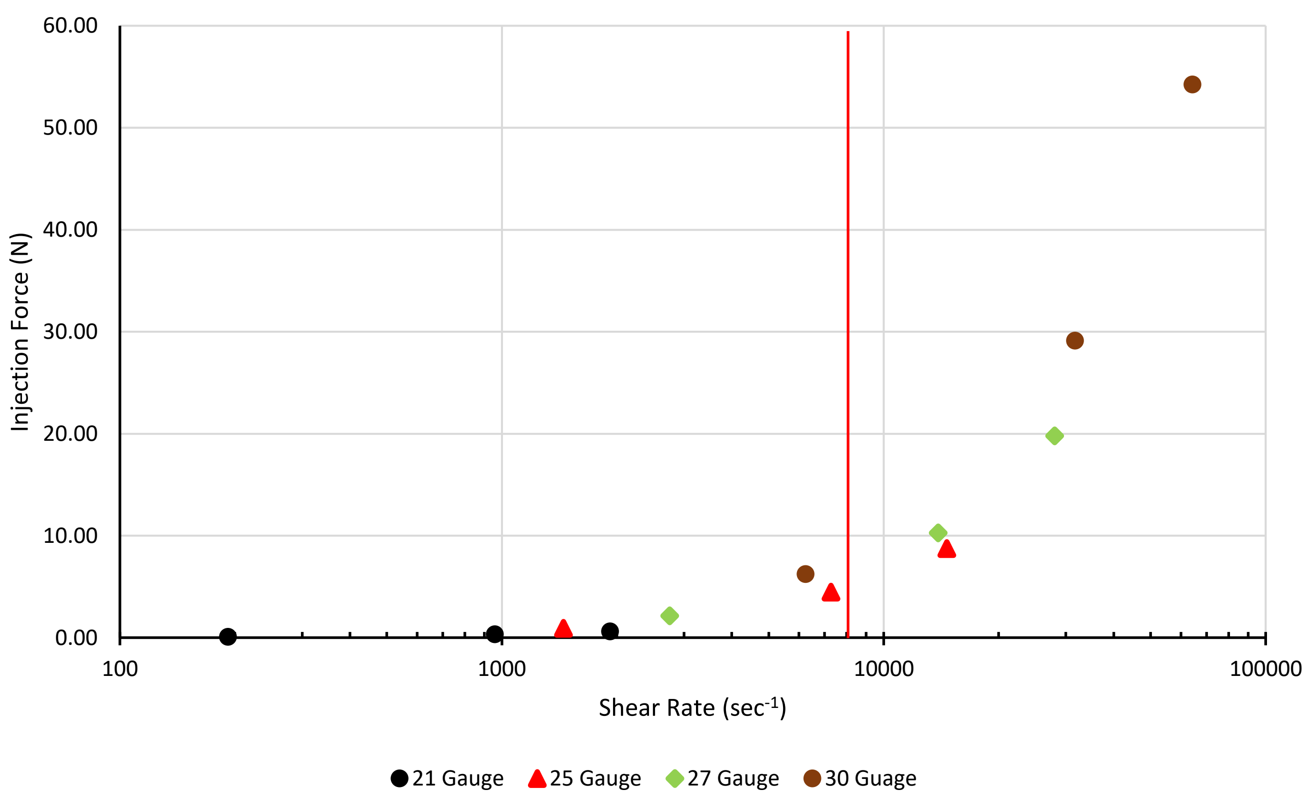

Figure 3. Injection force as a function of shear rate for each needle gauge. The injection forces at the shear rates that correspond to 20, 100, and 200 mm^3/sec for the fluid shown in **Figure 1**. Note that this fluid behaves as a Newtonian fluid at shear rates

beneath 8,000 sec^{-1}. The vertical red line corresponds to 8,000 sec^{-1} the shear rate where this non-Newtonian fluid begins to shear thin. The injection forces to the left of the line are in the Newtonian regime, while the injection forces to the right of the line are in the non-Newtonian regime. Since this equation is in the general form, it can handle both the Newtonian and non-Newtonian regions of this fluid.

Concluding Remarks

Rheological measurements can contribute more than characterization to your formulation development. Rheology as a tool can also contribute to formulation analysis and application development. Injection force estimates are one such rheological tool. This protocol can help you build confidence towards analyzing your protein formulations for injectability applications in early-stage development. We have also included a Microsoft Excel worksheet with the data used to create this protocol so that you can perform the estimation yourself. As you get more comfortable performing the estimation you can apply it to your formulation development.

Reference

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If this note is helpful, please let us know! If you have questions or need more information about this product or other applications, please contact us:

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