Rheology Tools: Injection Force Estimation – Power Law Fluids

Key Words: Power Law, non-Newtonian, 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 in the power law regime, which is a non-Newtonian behavior. Having a good estimate of injection force early in development can help guide your formulation development.

Introduction

Determining the drug delivery pathway is a key component of the development process. There are multiple delivery pathways for drugs that all have tradeoffs that impact the drugs' ease of use and efficacy. A common pathway for antibody therapeutics is injection (Allmendiger et al 2014). However, a key limitation for antibody therapeutics is the high concentrations necessary to achieve an effective dose. High concentrations of protein lead to large increases in viscosity, which can make injection more difficult. Depending on the device used for injection, the cutoff viscosity of the formulation can be between 20 and 40 cP (mPa-s).

Incorporating injectability analysis earlier in therapeutic development can guide development and mitigate the risk of developing a formulation that is impossible to deliver. The first step in incorporating injectability analysis is to first measure the formulations' viscosity over a wide range of shear rates to determine the fluid's behavior. The second step is determining the shear rates that correspond to the injection flow rate and needle gauge. Once those components are known then you will be able to estimate the injection force. 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. Now we will walk through the injection force estimation for power-law fluids.

2420 Camino Ramon, Suite 240 San Ramon, CA 94583
P: (925) 866-3801 F: (925) 866-3804

Equations

The power law fluid model is used to fit non-Newtonian data across shear rates where there is no evidence of a Newtonian plateau region. Fitting to the power law model is appropriate where the measured data is entirely within the shear-thinning regime across all the shear rates tested.
The power law equation is as follows:

$$\eta = K\dot{\gamma}^{n-1}$$

η is the viscosity (mPa-s)
n is the power law constant (unitless)
K is the flow consistency index, from the power law model (mPa-s)
$\dot{\gamma}$ is shear rate (s^{-1})

The injection force estimation equation for non-Newtonian Fluids using the power law constants is as follows:

$$F_v \cong 2\left(\frac{3n+1}{n}\right)^n \pi^{1-n} K l_n Q^n \frac{R_p^2}{R_n^{3n+1}}$$

F_v is the viscous contribution of the injection force (N)
l_n is the needle length (mm)
Q is the volumetric flow rate ($mm^3 s^{-1}$)
R_p is the radius of the piston of the syringe (mm)
R_n is the inner radius of the needle (mm)

The following equation will be used to calculate the flow rate of the power law fluid:

$$Q = \frac{n\dot{\gamma}\pi R_n^3}{3n+1}$$

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 the force required to deliver material within a syringe. Since power law fluids are non-Newtonian, then the first step to completing this protocol is to make sure that your data has been corrected. If your viscometer or rheometer induces an inhomogeneous flow on your 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 will help you determine the shear rate range where your data is Newtonian and where it is non-Newtonian (**Figure 1**).

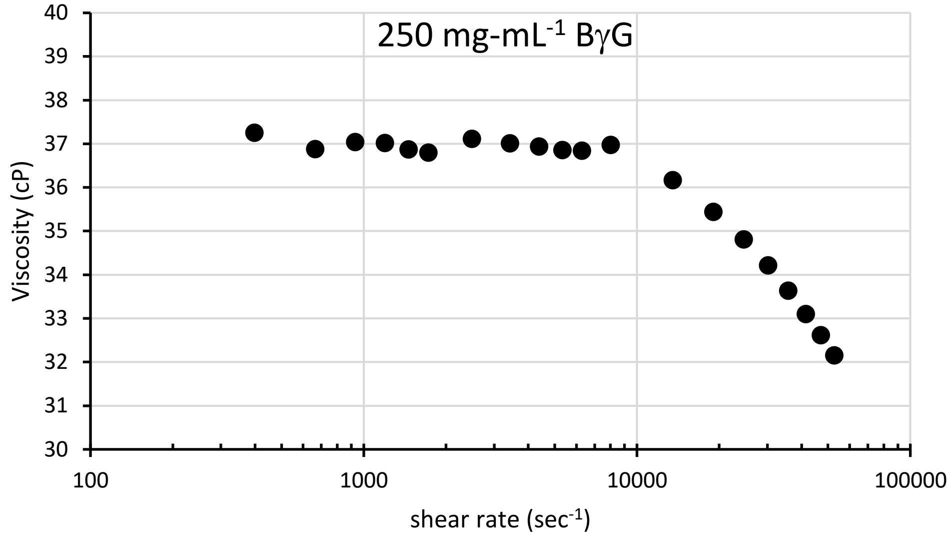

Figure 1. Shear rate sweep of BγG in an arginine/histidine buffer. 250 mg/mL protein solution from 400 s^{-1} to 52,752 s^{-1}.

2. If your data is non-Newtonian like the data presented in **Figure 1**, then fit the data using either the Cross model or Carreau-Yasuda model (**Figure 2**). Determine which model fits your data best and proceed with analysis.

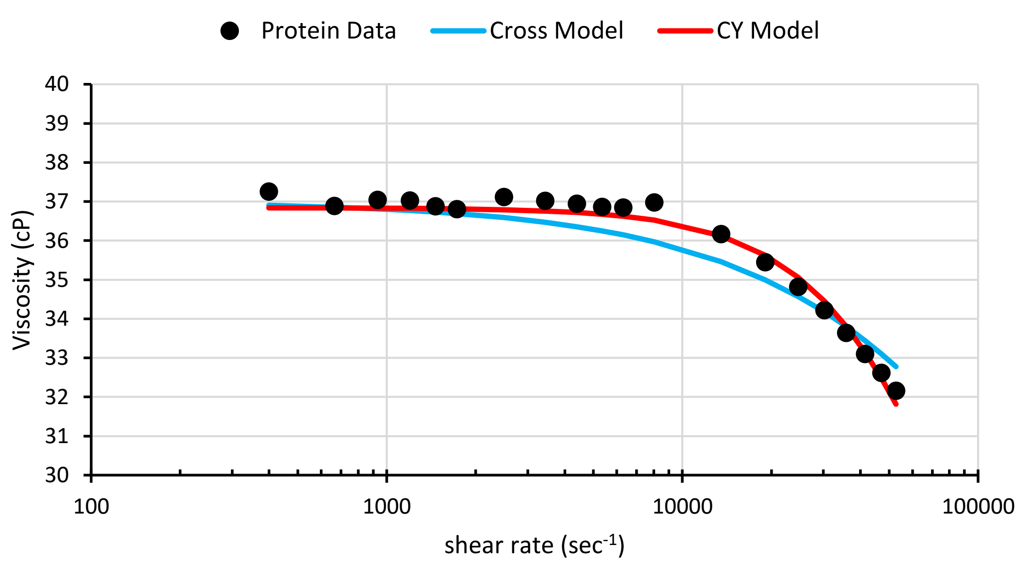

Figure 2. Comparison of the Cross and Carreau-Yasuda models. 250 mg/mL protein data (**Figure 1**) fitted to both the Cross Model (Blue) and Carreau-Yasuda Model (Red).

3. Since the Carreau-Yasuda model fits this data better than the Cross model, the Carreau-Yasuda model will be used to determine the critical shear rate, $\dot{\gamma}_C$.To determine $\dot{\gamma}_C$, use the Carreau-Yasuda model to interpolate the data between the Newtonian Plateau and the shear thinning region (**Figure 3**).

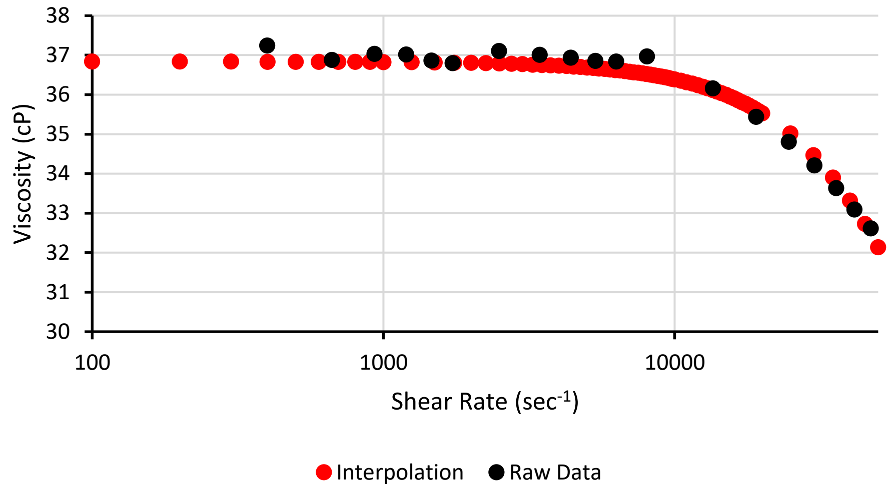

Figure 3. Comparison of the Carreau-Yasuda Interpolation and Raw Viscosity data. 250 mg/mL protein data (black) compared to the Carreau-Yasuda interpolation (Red).

4. Next, compare the interpolation and the raw data to determine where the viscosity decreases by 1% of the plateau value. In this example this decrease occurs around 8,000 s^{-1}. So, the critical shear rate, the shear rate where shear-thinning begins, at around 8,000 s^{-1}.
5. Now that the critical shear rate has been determined, we can estimate the injection force of this formulation. For viscosities measured at shear rates beneath 8,000 s^{-1}, use the Newtonian equation for injection force estimation. For the viscosities in the shear thinning region above 8,000 s^{-1}, we will use the Power Law non-Newtonian equation to estimate injection force.
6. We will begin by fitting the shear thinning section of the data to the power law fluid model (**Figure 4**). Please refer to our application note on the subject for a more detailed tutorial. The prefactor is κ, which is a constant that we will use for the estimation of injection force. The power law coefficient is equal to $n - 1$, which we will solve for n and use it to estimate the injection force.

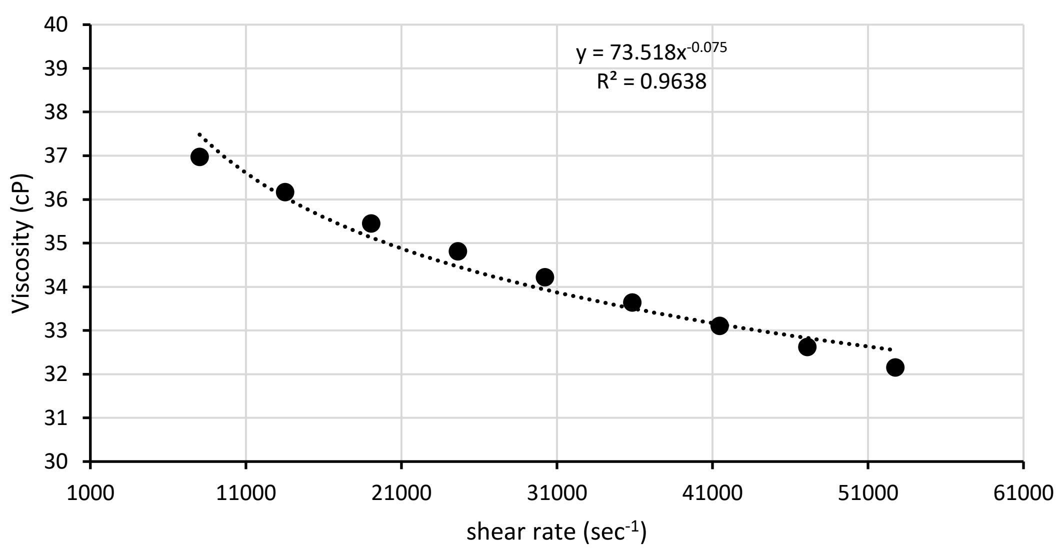

Figure 4. Power Law model fit. The shear thinning region of the data presented in **Figure 1** fit to the power law model. The prefactor is κ and the value of the exponent is n-1. $\kappa = 73.518$ and $n = 0.925$.

7. The next step in estimating the injection force is to make some assumptions about the dimensions of your syringe housing and needle. In **Table 1** we have listed out some assumptions regarding syringe and needle geometry.

	21 gauge	25 gauge	26 gauge	27 gauge	30 gauge
L (mm)	17	17	17	17	17
Rp (mm)	6.35	6.35	6.35	6.35	6.35
Rn (mm)	0.51	0.26	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.

8. Because fluids experience an inhomogeneous flow field inside syringes and needles, a different equation to estimate injection force and shear rate must be used for non-Newtonian fluids. This application note will describe how to perform the estimate for Power Law non-Newtonian fluids.

9. Next calculate the flow rate for each needle gauge for the shear rates that you tested above 8000 sec^{-1}. Use the assumptions listed in **Table 1** and the flow rate equation in the **Equations** section above to calculate these flow rates. The values are presented in **Table 2** for the shear rates tested.

Shear Rates (sec^{-1})	Viscosity (cP)	Flow Rate 21G (mm^3/sec)	Flow Rate 25G (mm^3/sec)	Flow Rate 26G (mm^3/sec)	Flow Rate 27G (mm^3/sec)	Flow Rate 30G (mm^3/sec)
8024	36.97	819.35	108.56	108.56	57.20	25.30
13516	36.16	1380.21	182.87	182.87	96.36	42.62
19058	35.44	1946.05	257.85	257.85	135.86	60.09
24630	34.81	2515.07	333.24	333.24	175.59	77.66
30225	34.21	3086.45	408.95	408.95	215.48	95.30
35839	33.64	3659.65	484.90	484.90	255.50	113.00
41468	33.10	4234.42	561.05	561.05	295.62	130.75
47099	32.61	4809.49	637.25	637.25	335.77	148.51
52753	32.15	5386.77	713.74	713.74	376.08	166.33

Table 2. Calculated flow rates. The shear rates and corresponding calculated flow rates that will be used to estimate injection force in the non-Newtonian Regime.

10. Now that we have the flow rates, we can estimate the injection force using the equation: $F_v \cong 2\left(\frac{3n+1}{n}\right)^n \pi^{1-n} \kappa l_n Q^n \frac{R_p^2}{R_n^{3n+1}}$. To solve this equation, use the assumptions listed in **Table 1**, flow rates in **Table 2**, and the values of κ and n, 73.518 and 0.925, respectively. The estimated injection forces are summarized in **Table 3** and presented graphically in **Figure 5**. **NOTE:** Flow rate on RheoSense instruments is in µL/min but the flow rates used in the calculation are in mm^3/s.

IF 21 Gauge (N)	IF 25 Gauge (N)	IF 26 Gauge (N)	IF 27 Gauge (N)	IF 30 Gauge (N)
2.51	4.91	4.91	6.08	7.99
4.13	8.10	8.10	10.03	13.16
5.70	11.19	11.19	13.85	18.18
7.24	14.20	14.20	17.58	23.08
8.73	17.13	17.13	21.21	27.84
10.18	19.97	19.97	24.72	32.45
11.59	22.74	22.74	28.15	36.95
12.97	25.45	25.45	31.50	41.35
14.32	28.10	28.10	34.79	45.66

Table 3. Estimated injection forces (IF) using the Power Law non-Newtonian equation. The injection forces of each needle gauge using the assumptions in **Table 1**, the flow rates in **Table 2** and the power law constants $\kappa = 73.518$ and $n = 0.925$.

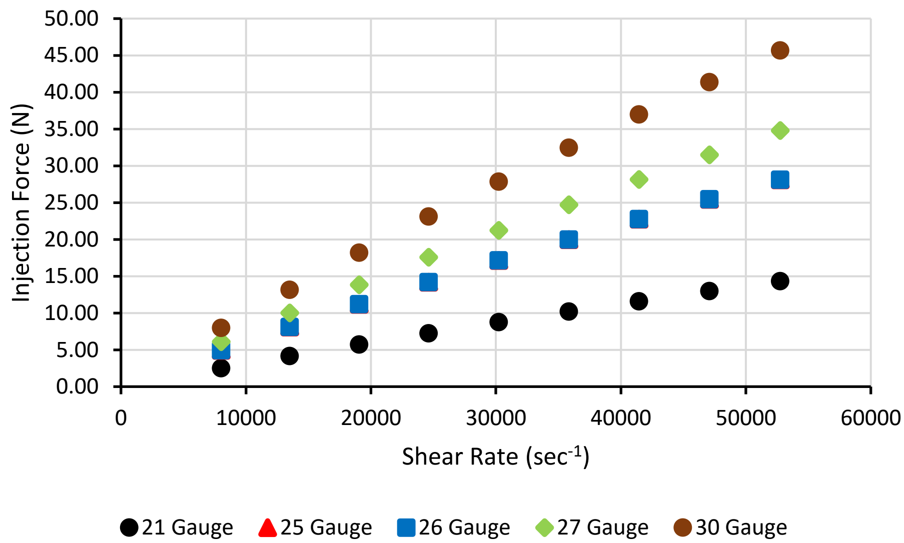

Figure 5. Estimated injection forces (IF) using the Power Law non-Newtonian equation. The injection forces of each needle gauge using the assumptions in **Table 1**, the flow rates in **Table 2** and the power law constants $\kappa = 73.518$ and $n = 0.925$.

Concluding Remarks

Rheological measurements can contribute more to your formulation development than formulation characterization. Rheology is a tool that enables formulation analysis and application development. Injection force estimates are one such rheological tool. This protocol can help you analyze protein formulations for injectability applications. We have 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 then apply it to your formulation development.

Reference

A.Allmendinger, S. Fisher, J. Huwyer, H.C. Mahler, E. Schwarb, I.E. Zarraga, R. Mueller, "Rheological characterization and injection forces of concentrated protein formulations: An alternative predictive model for non-Newtonian solutions," *Eur. J. Pharma. Biopharm*. 2014.

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

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:

Main Office — 1 925 866 3801

Sales – Sales@RheoSense.com

Information — info@RheoSense.com