RheoSense
Simply Precise™

Accurate Estimation of Injectability (Syringeability) from High Shear Viscosity Measurement

BACKGROUND

In protein therapeutics, major resources are dedicated toward the development of self-injection formulations for:

- Sustainable Release
- Subcutaneous Injection

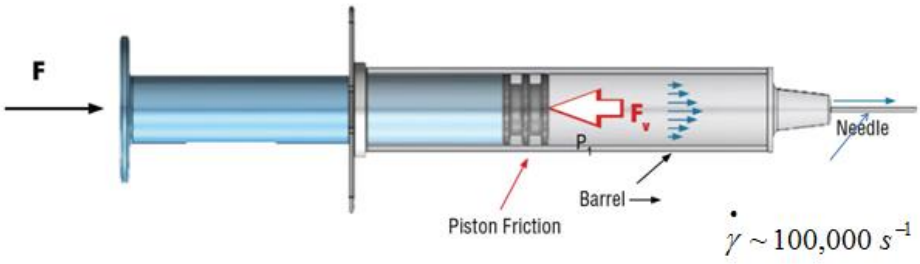


When **sustainable release** and **subcutaneous injection** are achieved, the concentration of protein inevitably increases, causing an increase in viscosity. The increase in viscosity creates significant challenges in Injectability, since high viscosity requires high injection force. This, in turn, affects how an auto-injection system needs to be designed to achieve optimum performance.

In this application note, we take a close look at how protein formulation viscosity affects the injection force, and we will demonstrate how to use the viscosity measurement to determine the necessary injection force required for the given solution. In particular, it will be explained that the injection force is dictated by the viscosity of the solution at the shear rate inside of the needle.

Schematic of a Liquid Flow Inside of the Syringe:

In order to understand the fundamentals of injection, one needs to study the flow inside of the syringe during injection. The schematic below shows the flow of the liquid inside of the syringe:



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Summary of Fluid Dynamics and Injection Force:

As the piston is pushed, liquid flows with a velocity profile following the parabolic pattern inside of the barrel as shown in the schematic. The same parabolic profile is also present inside the needle. Since the barrel and needle have circular cross sections, their flows follow the Hagen-Poiseuille equation, and their pressure drops (or misrepresented but widely accepted back pressure) follow the equation (Macosko 1994):

$$\Delta P = \frac{8\eta l Q}{\pi R^4} \qquad \text{Equation 1}$$

Where,
Q: Flow rate, ml/s
l: Length of the tube
R: Radius of the tube
η: Viscosity at the shear rate in the tube

Note that the viscosity should be the value measured at the shear rate in the tube, which is related to the flow rate and the radius by the following equation:

$$\dot{\gamma}_a = \frac{4Q}{\pi R^3}$$

Since the radius of the barrel is much larger than that of the needle and the length of the barrel is not long enough to add a significant pressure drop (Equation 1), most of the pressure drop is generated by the flow in the needle:

$$\Delta P = \frac{8\eta l_n Q}{\pi R_n^{\ 4}} = P_1$$

Where subscript η stands for needle. Since there is a negligible pressure drop in the barrel, P_1 is equal to $\triangle P$, which applies directly to the area of the piston as a resistive force, F_v. The viscous resistive force is thus:

$$viscous\ resistive\ \ force = 8\eta l_n Q \frac{R_b^{\ 2}}{R_n^{\ 4}}$$

Where R_b is the radius of the piston. Again, the viscosity is the value measured at the shear rate in the needle:

$$\dot{\gamma}_n = \frac{4Q}{\pi R_n^{\ 3}}$$

The injection force, F, is the combination of the viscous resistive force and the piston friction:

$$\text{Injection force} = 8\eta l_n Q \frac{R_b^{\ 2}}{R_n^{\ 4}} + \text{piston friction}$$

It is well-known that the piston friction depends on the condition of the surface, constituent materials, moving of the piston, and P_1 which could deform the seal. Piston friction also varies with different manufacturers.

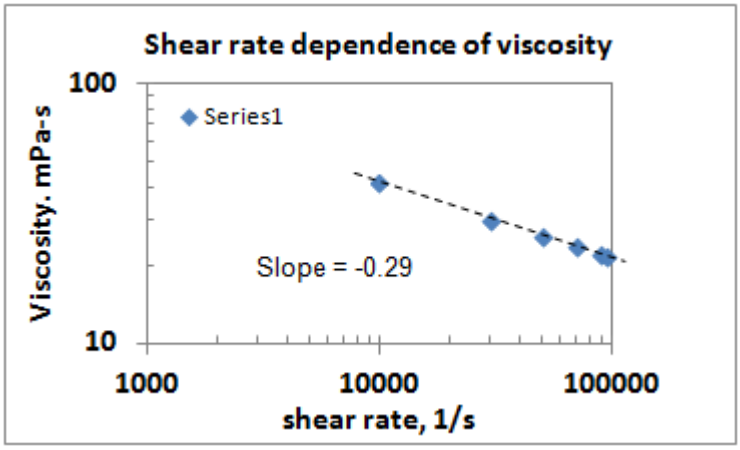
Viscosity Measurement at High Shear Rate and Non-Newtonians:

While protein therapeutics behave like Newtonian liquids with a constant viscosity regardless of shear rate, they also exhibit non-Newtonian behavior (Allmendinger et. al). If viscosity depends on shear rate, it is essential to measure the viscosity at the shear rate inside of the needle in order to make an accurate estimation of the injection force. The table below shows the calculated shear rate inside of 26- and 27-gauge needles.

Injection Rate, ml/s	Shear Rate, s^{-1}	
	26 gauge	27 gauge
0.0625	36,221	68,742
0.1	57,954	109,987
0.2	115,907	219,974

As shown in the table above, the shear rate is quite high and difficult to access with conventional viscometers or rheometers. However, the graph below shows the measured viscosity values of a model drug with an *m*-VROC viscometer and E type chip (100 μm deep flow channel) as a function of shear rate.

As shown in the graph, "Shear rate dependence of viscosity", viscosity depends on shear rate, and its value at 10,000 s^{-1} is twice as large as the viscosity at 100,000 s^{-1}. Therefore, it is clear that estimation of the injection force based on the viscosity at 10,000 s^{-1} or lower shear rates would lead to incorrectly assuming a need for a much higher injection force.



Accurate Injection Force Estimation for Non-Newtonian Liquids:

For non-Newtonian liquids such as the model drug, the velocity profile does not follow the parabolic pattern, and Equation 1 is no longer valid. For the model drug, the viscosity thins with the shear rate. Therefore, the shear rate at the wall of the needle would be higher than that of the Newtonian liquids at the same flow rate. In order to obtain the accurate shear rate at the wall of the needle, one has to apply the rigorous Weissenberg-Rabinowitsch-Mooney correction for tube flow (Macosko 1994):

$$\dot{\gamma} = \dot{\gamma}_n \frac{1}{4}\left(3 + \frac{d \ln Q}{d \ln(\Delta P)}\right)$$

The differential term requires measurement of △P with various injection rates and is difficult to measure with a circular needle since accurate pressure measurement inside a small circular needle is extremely difficult. However, certain types of non-Newtonian liquids, such as the model drug, can be modeled for its viscosity as a function of the shear rate. The model drug follows a power law since the logarithmic plot of the viscosity vs. shear rate yields a straight line in the graph with a slope of -0.29:

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

The slope of the plot is n-1 and thus n is equal to 0.71. For the power law fluid, the correction can be simplified (Macosko 1994):

$$\dot{\gamma} = \dot{\gamma}_n \frac{1}{4}(3+\frac{1}{n})$$

For the model drug, the actual shear rate in the high shear rate power law regime is:

$$\dot{\gamma} = 1.1 \times \dot{\gamma}_n$$

If the apparent shear rate is 90,000 s^{-1}, then the actual shear rate is 99,000 1/s for the model drug. Then the actual viscosity at 99,000 s^{-1} can be estimated from the graph and used to calculate the estimated injection force.

TAKING THE GUESSWORK OUT OF INJECTABILITY STUDIES WITH RHEOSENSE VISCOMETERS

It has been demonstrated that viscosity measurements at high shear rates are essential for accurate estimation of injection force and Injectability. *m*-VROC™ allows viscosity measurement up to 280,000 1/s, taking the guess work out of the Injectability studies in early-stage formulation development.

The table below shows how the estimated injection force for the viscosities at the shear rate inside of the needle corroborates well with the reported data.

ID, mm	Injection rate, ml/s	Shear rate, s^{-1}	Viscosity, mPas	Estimated Injection force, N	Reported Injection force, N
0.184	0.1	163,000	30	42	42~51
0.184	0.0625	102,246	30	26.5	28~32

(Diameter of the plunger is 6.35 mm for the estimation and the needle length is ½ inch.)

The estimated injection forces with Equation 1 are close to the reported injection force measured directly. The small difference between the estimated injection force and the reported injection force is due to the friction force of the piston against the barrel, which was not taken into account for the estimation.

m-VROC™ Viscometer Specifications:
The table below summarizes the accessible shear rate with the E-type chip set, which can be operated with *m*-VROC™.

Viscosity, mPa-s	Flow channel depth, μm	Maximum shear rate, s^{-1}
20	50	280,000
50	80	174,000

SUMMARY

During the development process, how a drug will be delivered is a critical consideration, because the delivery mechanism has a significant impact on drug efficacy. Newly developed drugs – including biologics, peptides and sustained-released formulations – are often being formulated into injectable solutions.

As demonstrated, the injection force required for a given solution is dictated by the viscosity of the solution at the shear rate inside of the needle.

Using the small sample viscometer, *m*-VROC™, from RheoSense, it is possible to accurately estimate the injection force necessary using data collected from viscosity measurements. This allows researchers to develop and optimize the formulations of injectable protein therapeutics.

References:
C.W. Macosko, "Rheology, Principles, Measurements, And Applications," Wiley, 1994.

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 solutiosn," Eur. J. Pharma. Biopharm. 87 (2014) 318-328.

FEATURES & BENEFITS OF *m*-VROC™ Viscometer

m-VROC™ offers precise, flexible viscosity measurements. With small sample requirements, wide dynamic operation range, pin-point accuracy, and high repeatability, *m*-VROC™ is ideal for R&D applications.

Features include:

- Fast measurement cycles
- Precise temperature control
- Tight accuracy – 2% of reading
- High repeatability – 0.5% of the range
- Wide viscosity range – 0.2 ~ 100,000 m-Pas
- Wide shear rate range – 0.5 ~ 1,400,000 s -1
- Small sample volume – 20 microliter +