- Market leader in Biotechnology Industry
- Headquartered in Silicon Valley
- Patented technology VROC®
- Fortune 500 client base

RHEOSENSE WEBINAR: INTRO TO INJECTABILITY

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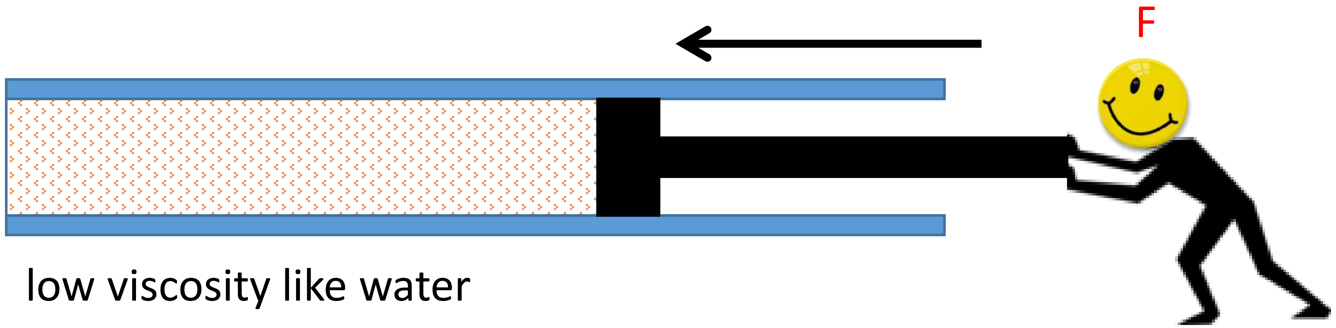
RheoSense™

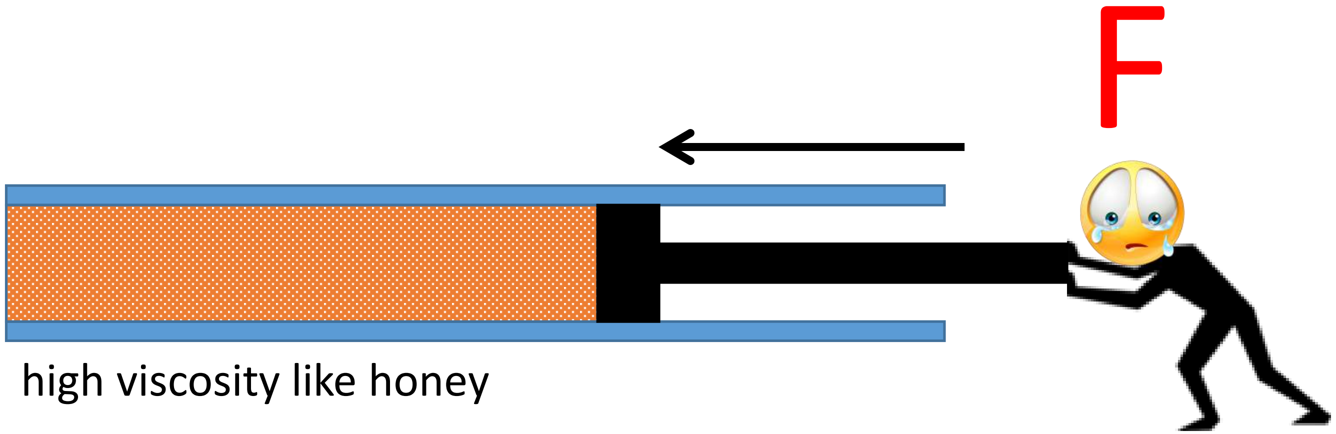
Simply Precise™

Intro to Injectability

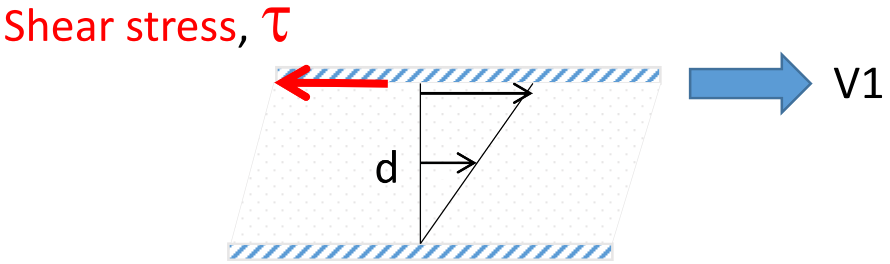
What is Viscosity?



low viscosity like water



high viscosity like honey



Shear stress resists the shearing motion!

Shear stress = force/ wet area

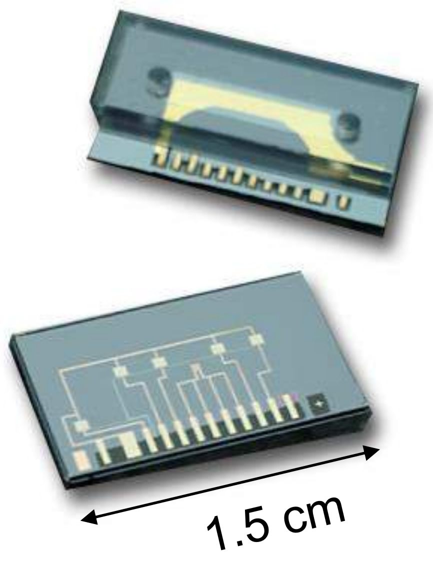
$$\dot{\gamma} = \frac{V_1}{d} \qquad \eta = \frac{\tau}{\dot{\gamma}}$$

Shear rate is well defined in *only a few geometries* such as cone and plate, parallel plates, circular slit, rectangular slit geometries.

Our Technology

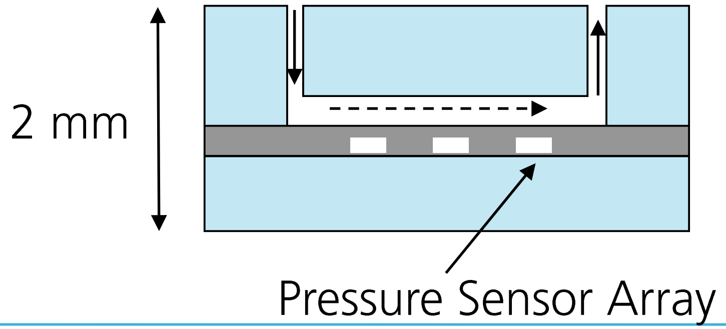
VROC®: The Viscometer/Rheometer-on-a-Chip

- Measures Absolute Viscosity
- Small Sample Volume (> 50 µL)
- Wide Dynamic Range in Shear Rates
- Fast and Superior Repeatability



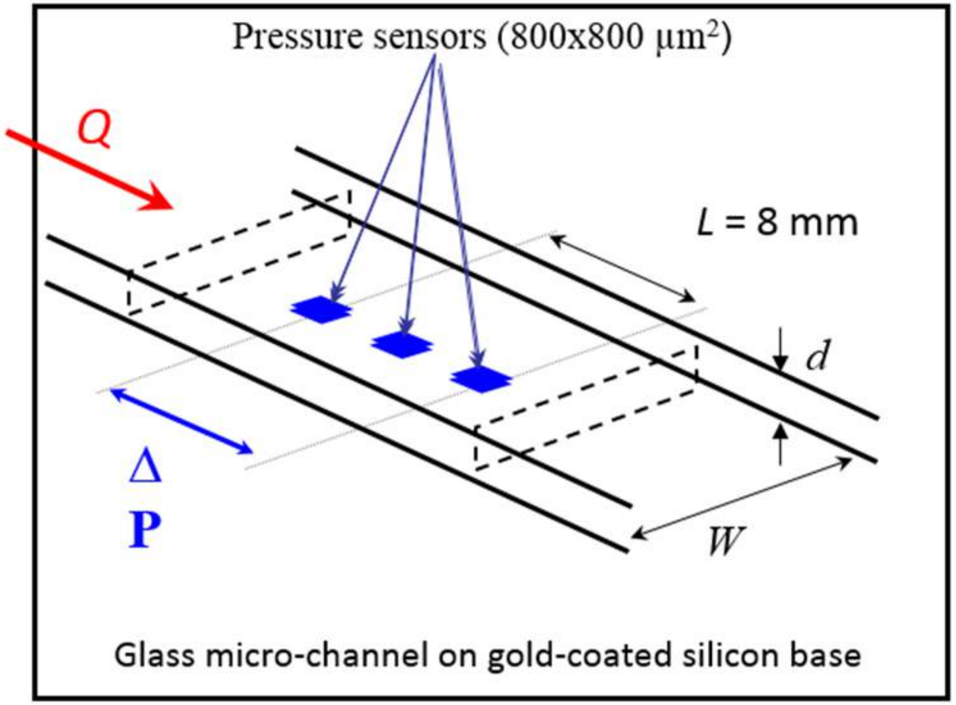
VROC® is a hybrid of microfluidic and MEMS (Micro-Electro-Mechanical Systems) technologies:

- MEMS Sensors – Silicon (Si) Pressure Sensor Array
- Microfluidics – Precision Glass Micro-Channel

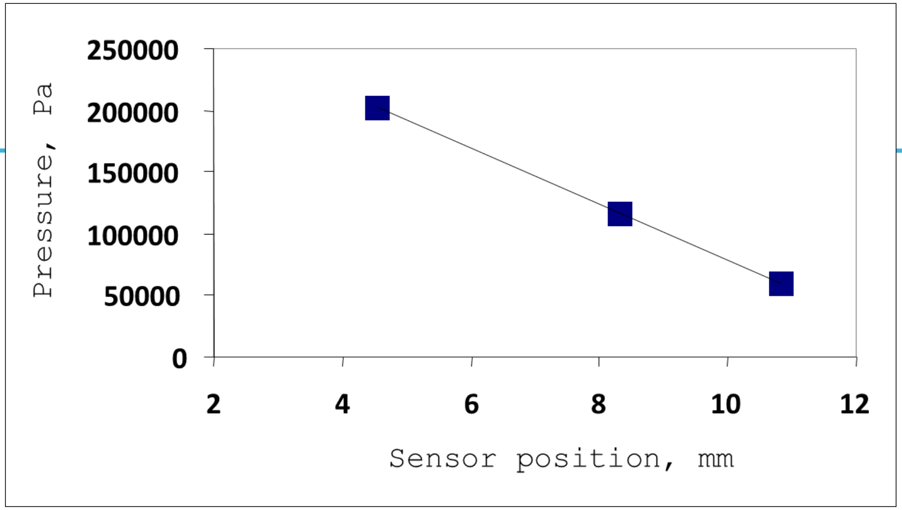


The VROC® Principle

Derivative of Hagen-Poiseuille



Pressure Drop ~ Shear Stress Flow Rate ~ Shear Rate



- Measure the pressure drop as a test liquid flows through a flow channel
- The slope of the straight line in the plot of the pressure vs. sensor position is proportional to the viscosity.

$$\eta = \frac{\tau}{\dot{\gamma}}$$

$$\tau \sim \Delta P$$

$$\dot{\gamma} \sim Q$$

RheoSense VROC® Powered Systems

m-VROC®

Min Sample Volume	50 µL
Shear Rate Range	.5 ~ 1,400,000 s^{-1}
Viscosity Range	0.2 ~ 200,000 cP
Temperature Range	4 ~ 70 °C
Shear/temp Sweep	Yes

e-VROC®

Min Sample Volume	500 µL
Viscosity Range (cP)	1.0 - 2,000
Extensional Range	0.1 - 1000 s^{-1}

hts-VROC®

Temperature Range	
4 - 105 (125) °C	

*micro*VISC™

Min Sample Volume	100 µL
Shear Rate Range, s^{-1}	1.7 ~ 5,800
Viscosity Range (cP)	0.2 ~ 20,000
Temperature Range	18 ~ 50 °C
Portable	Yes
Shear/Temp Sweeps	No

Common Bio-Pharmaceutical Applications

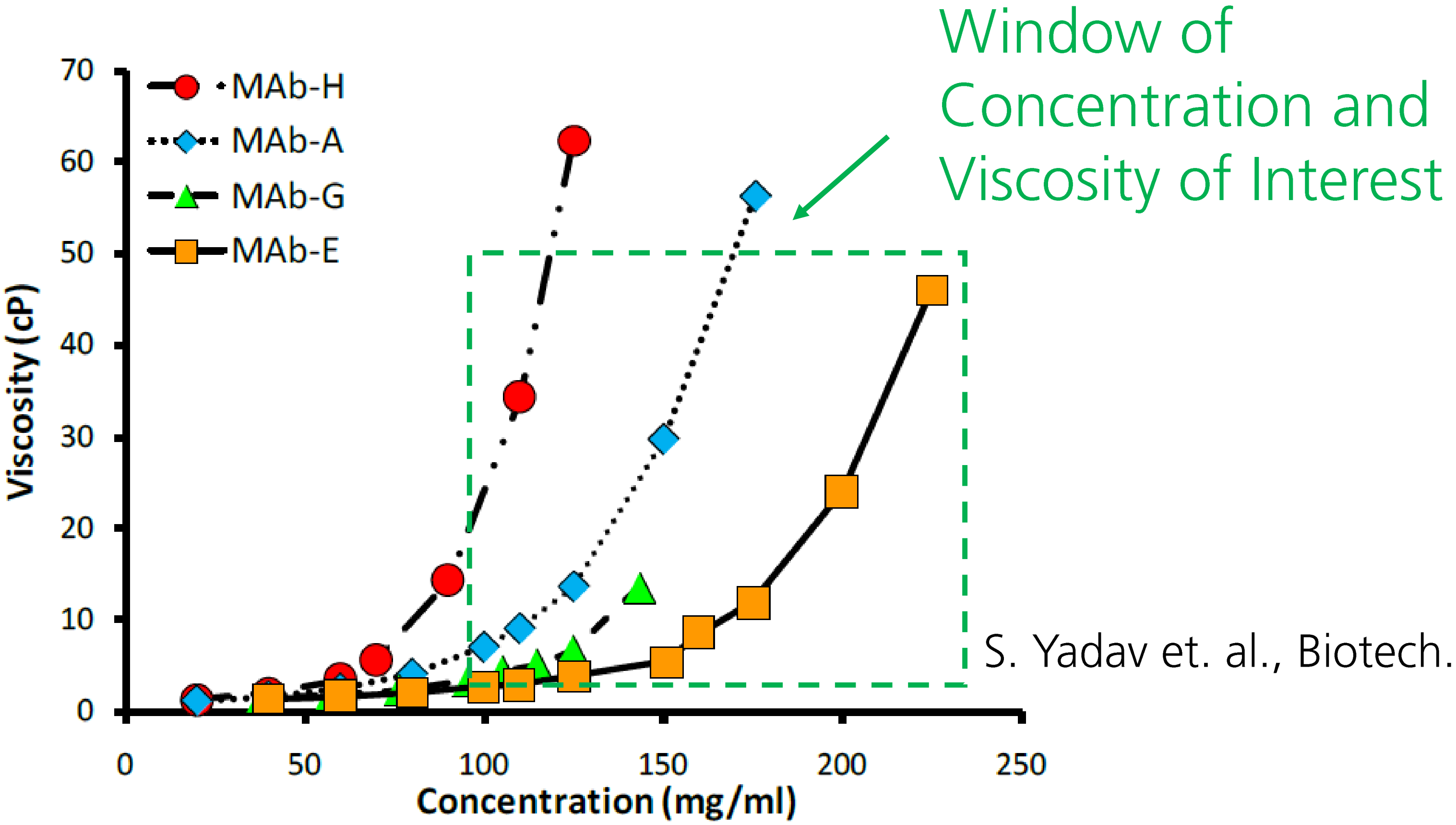
- Protein, RNA & Antibody Therapeutics
- Protein formulation and stability
- Help accurate Particle Sizing (for DLS)
- Injectability

Viscosity and Protein Concentration

Less frequent dosing

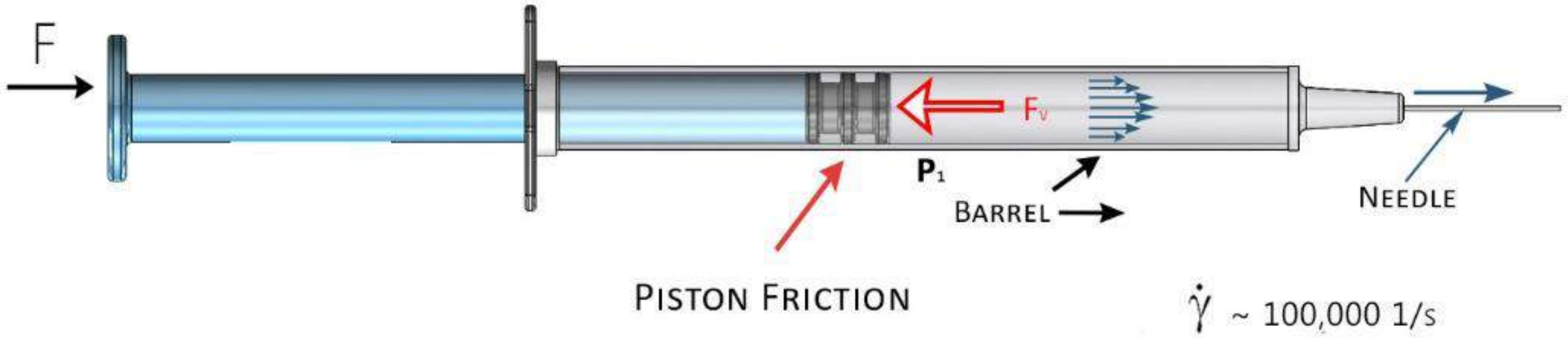
→ Higher Concentration
→ Higher Viscosity

→ *Injectability*



S. Yadav et. al., Biotech. 2010

Injectability (Force)

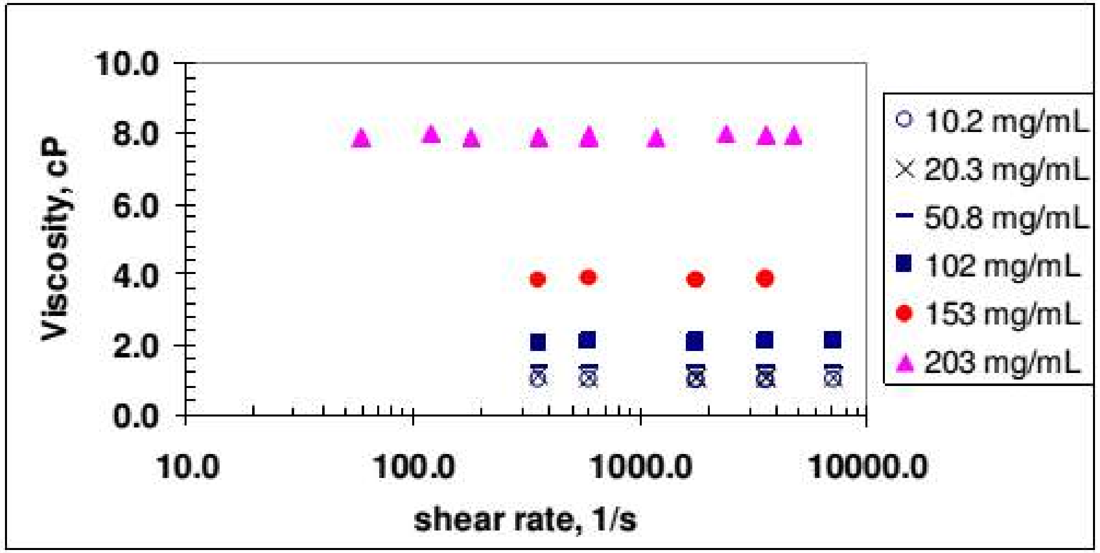


Force = Piston Friction + Resistive force, F_V (viscosity)

F_V = Area of Piston x P_1

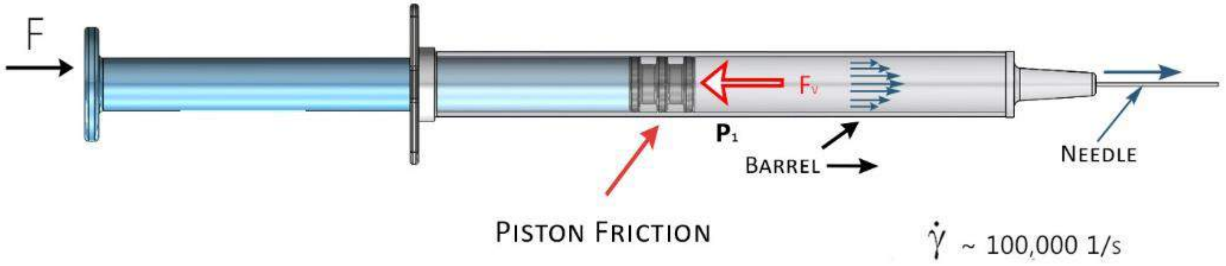
Injectability (Force) – for Newtonian Therapeutics

Gamma Globulin



Flow in the barrel and needle : Hagen-Poiseuille

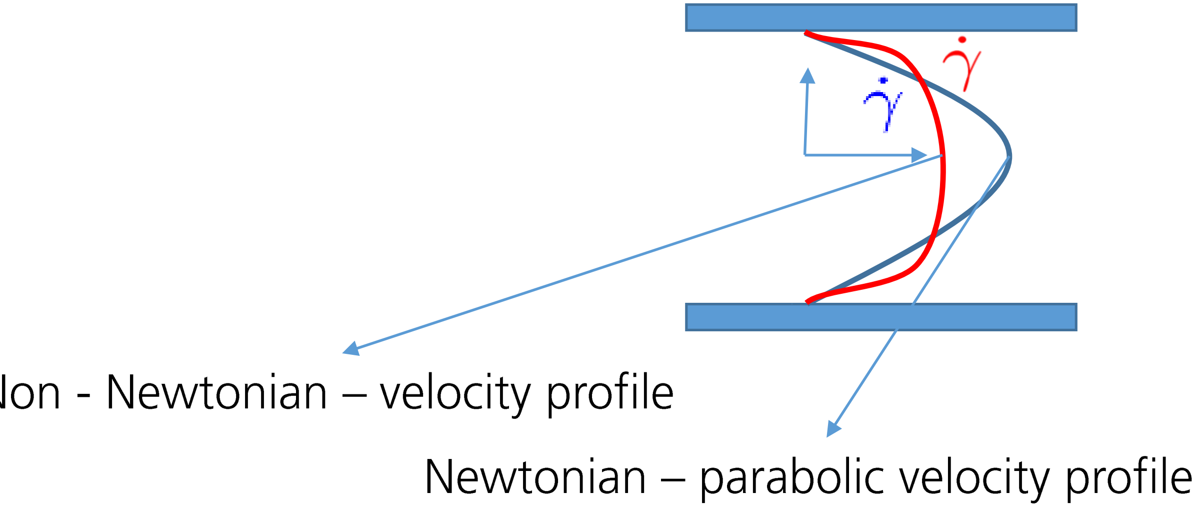
$$\Delta P = \frac{8\eta L Q}{\pi R^4}$$

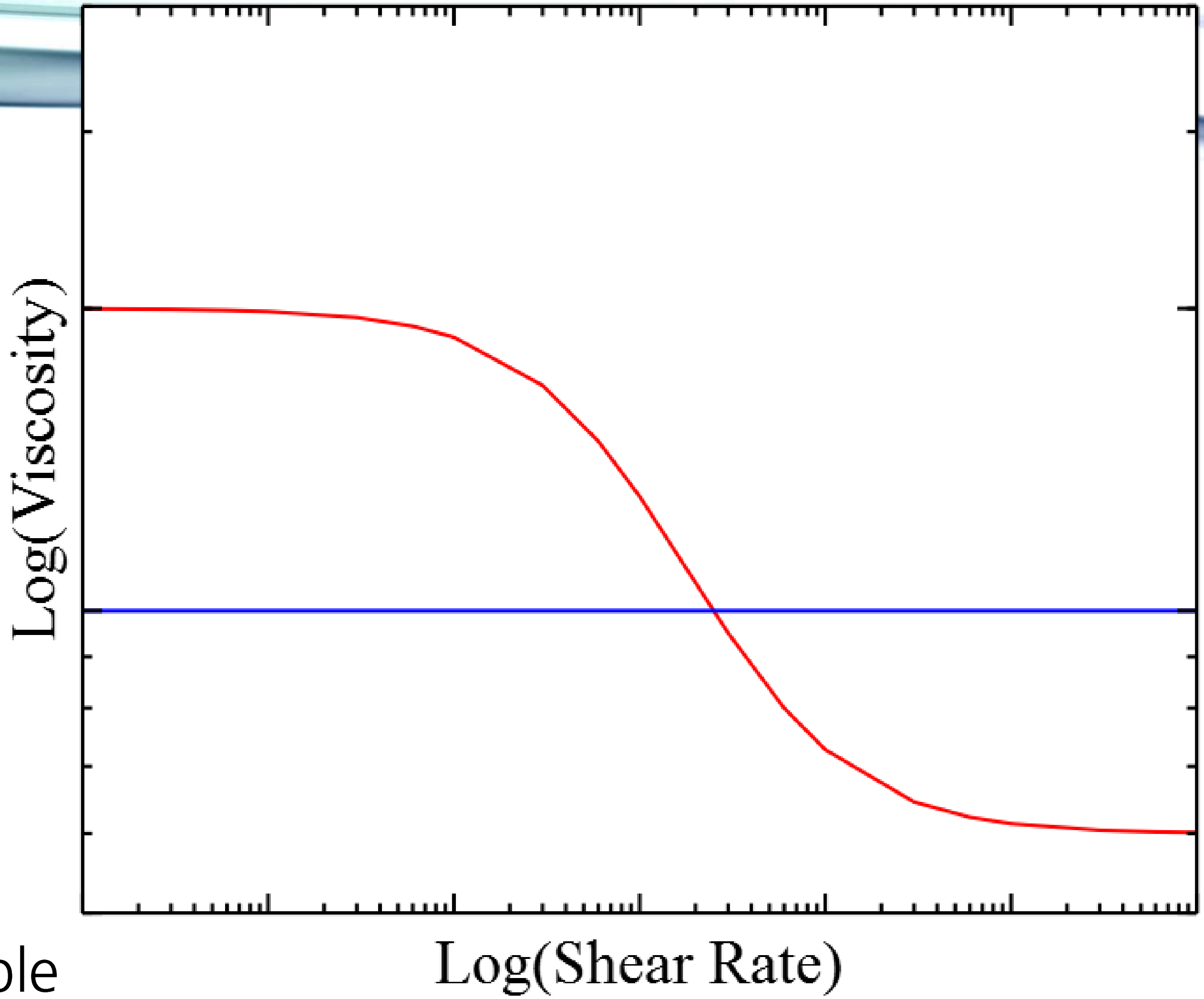


$$P_1 = \Delta P\ (\text{barrel}) + \Delta P\ (\text{needle}) = \frac{8\eta Q}{\pi}\left(\frac{L_b}{R_b^4} + \frac{L_n}{R_n^4}\right)$$

Pressure drop in the needle dominates

Non-Newtonian Therapeutics





Flow in the needle

- Viscosity depends on shear rate
- Velocity profile is no longer parabolic
- Hagen-Poiseuille law is no longer applicable
- Need to know the constitutive equation (i.e. Power law fluid)
- Need to measure viscosity at the wall shear rate for accurate estimation of injectability

Estimation of the Injection Force

Newtonian Therapeutics

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.)

29 gauge needle

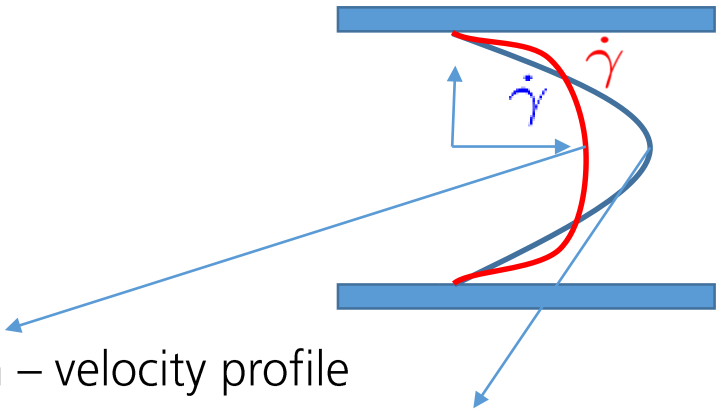
Shear rate at the needle wall

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

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

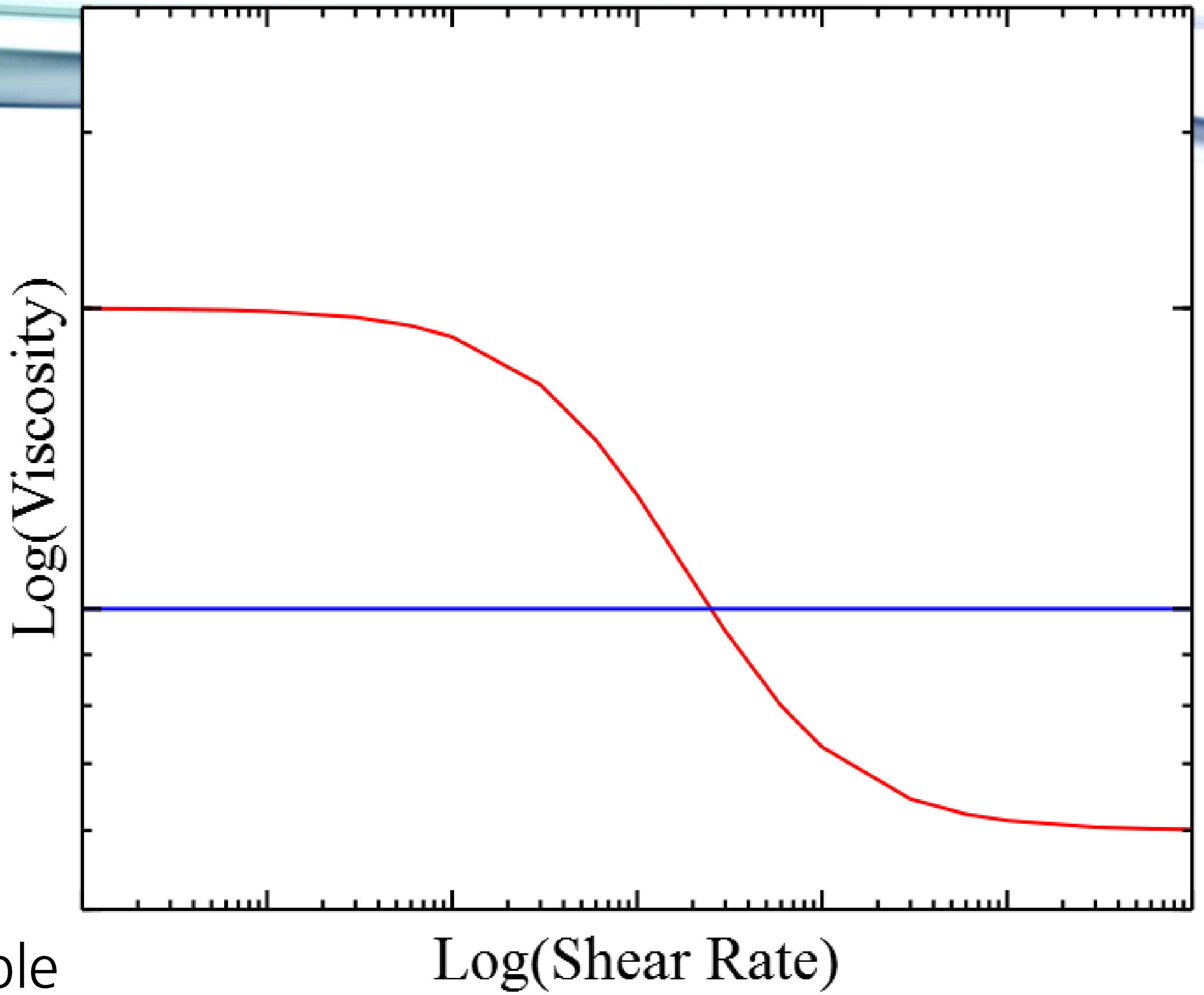
Injection Rate, ml/s	Shear Rate, s^{-1}	
	26 gauge	27 gauge
0.063	36,221	68,742
0.1	57,954	109,987
0.2	115,907	219,974

Non-Newtonian Therapeutics



Non - Newtonian – velocity profile

Newtonian – parabolic velocity profile



Flow in the needle

- Viscosity depends on shear rate
- Velocity profile is no longer parabolic
- Hagen-Poiseuille law is no longer applicable
- Need to know the constitutive equation (i.e. Power law fluid)
- Need to measure viscosity at the wall shear rate for accurate estimation of injectability

Applying the WRM correction

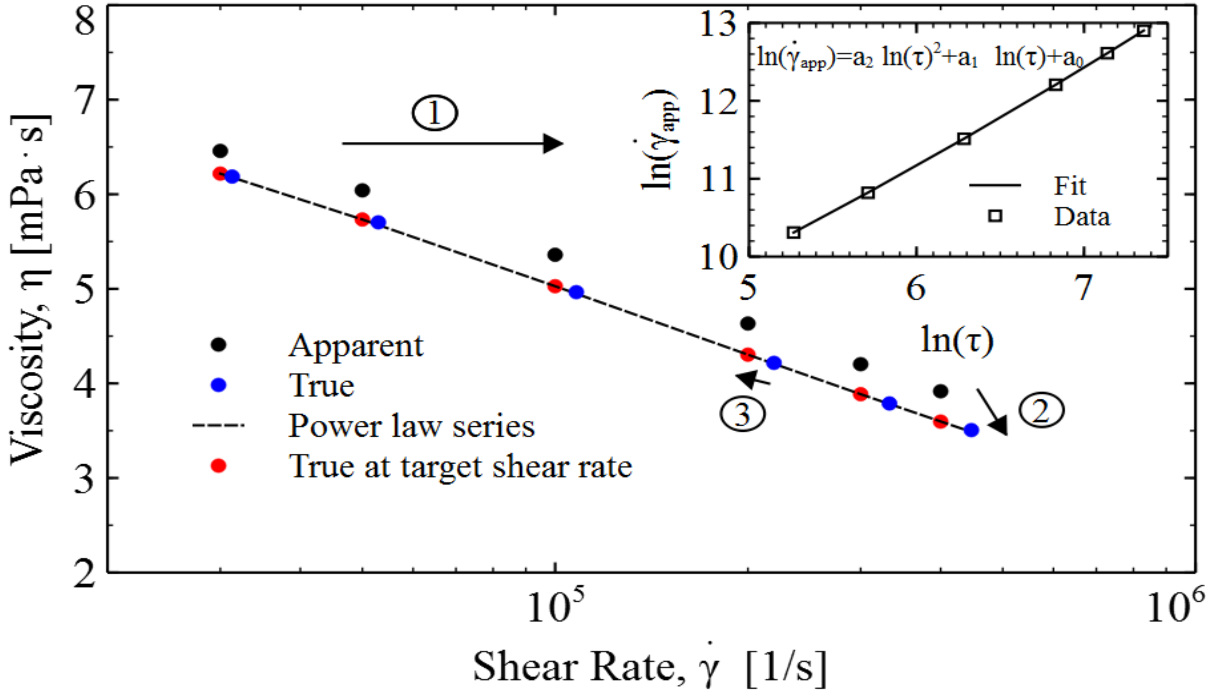


Figure A1. Shear thinning measurements of viscosity on 1% Methocel solution. Apparent viscosity results (black circles) are corrected to (steps 1&2) true viscosity results (blue circles) using WRM correction in Eqns. 1 and 2. The corrected true viscosity is fitted to a power law series that is used to obtain true viscosity at the target shear rates (step 3).

$$\dot{\gamma} = \frac{\dot{\gamma}_{app}}{3}\left(2 + \frac{d\ \ln \dot{\gamma}_{app}}{d\ \ln \tau}\right)$$

$$\frac{d\ \ln \dot{\gamma}_{app}}{d\ \ln \tau} = 2a_2 \ln \tau + a_1$$

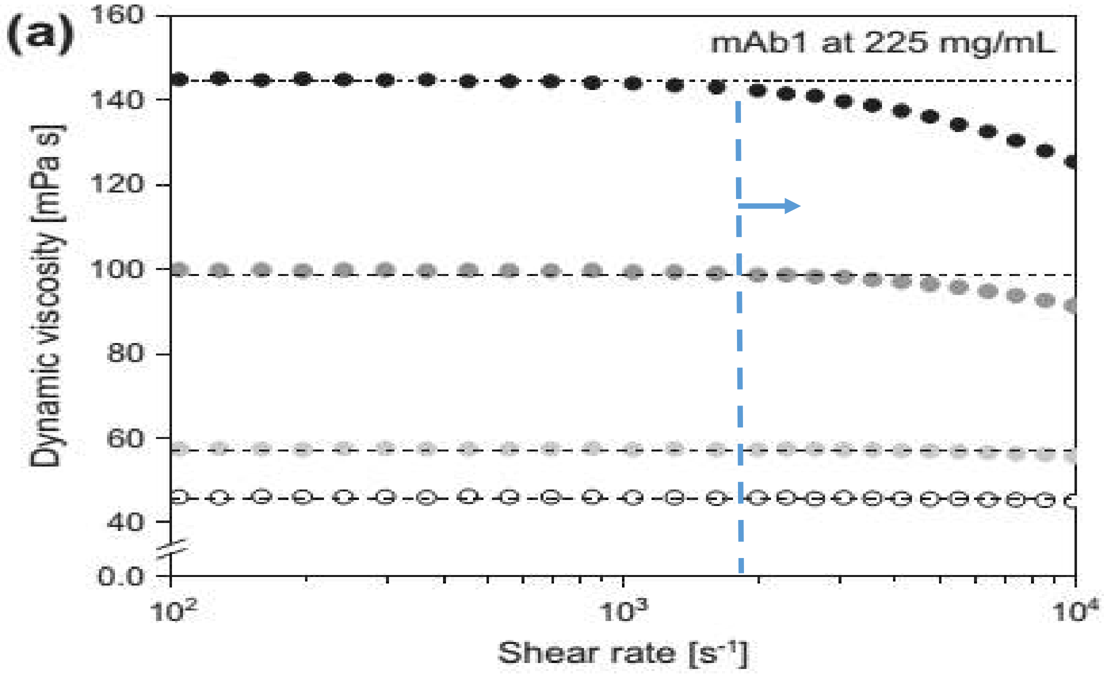
$$\eta = \frac{\tau}{\dot{\gamma}}$$

Application	Shear rate [1/s]
Sag and Leveling	10^{-2}-10^{0}
Flow coating, mixing	10^{0}-10^{2}
Brushing, roll coating	10^{2}-10^{4}
Injectability, Lubrication	10^{4}-10^{7}

Shear Rate **relevant** for injectability applications:

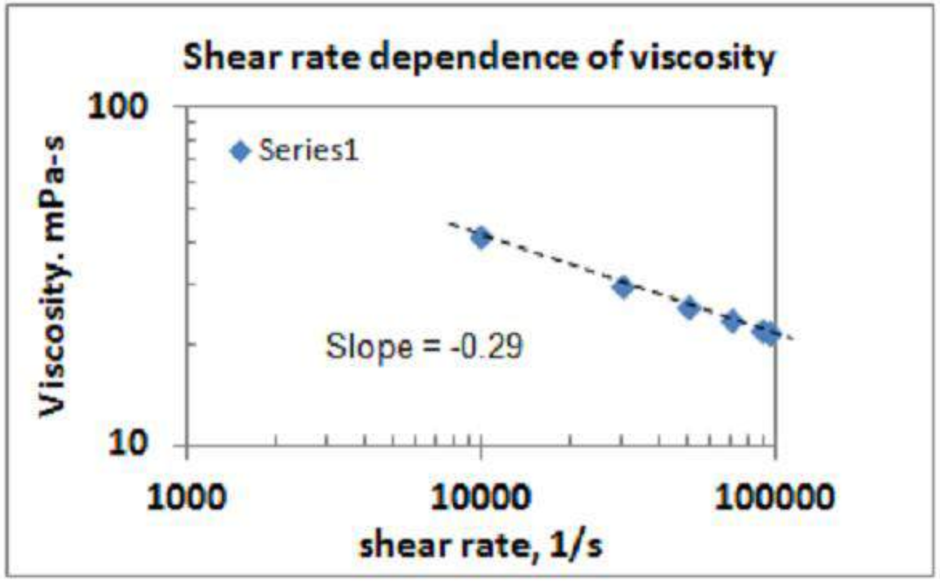
- **Shear Rate range:** 10^4-10^6 **s^{-1}**

Flow in the Needle – non-Newtonian Therapeutics



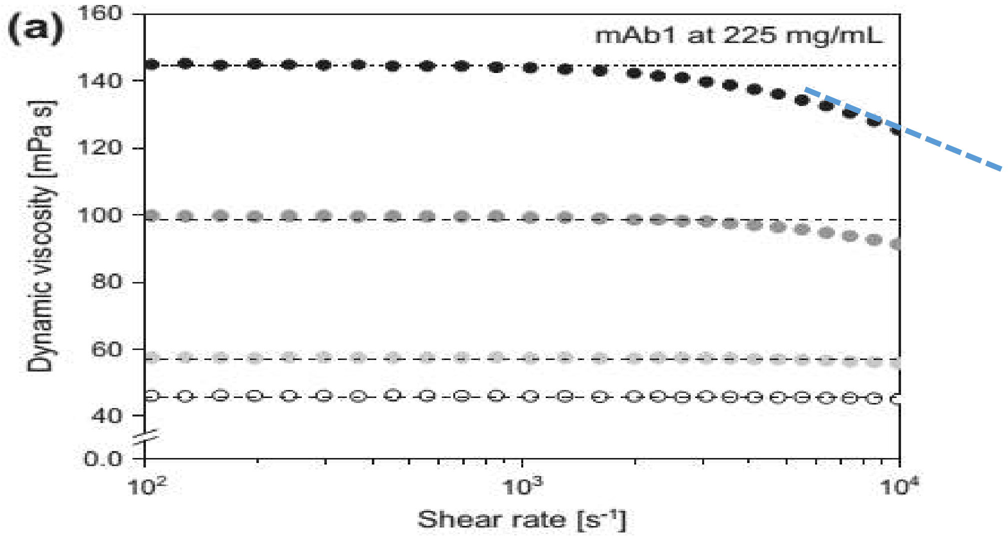
Shear thinning at 2,000 1/s or higher

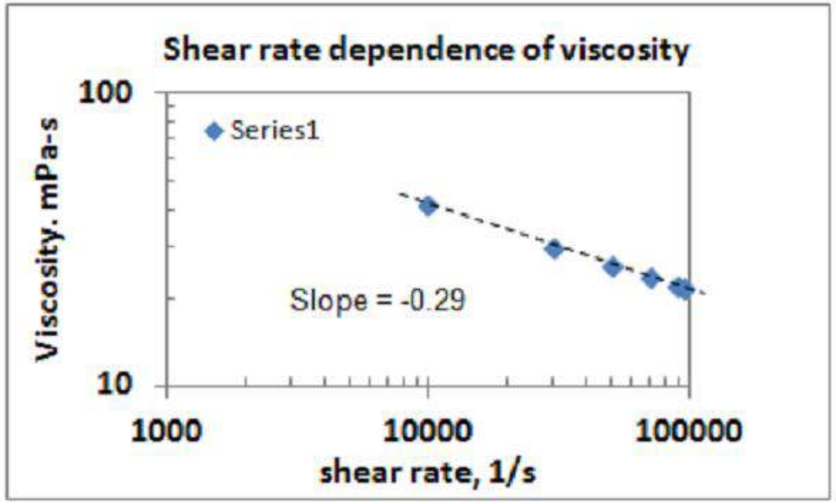
(a) A. Allmendinger, Eur. J. Pham. Biopharm. 87 (2014)



Sample A

Flow in the Needle – non-Newtonian Therapeutics





To a good approximation, a power law can be applied.

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

n = 1 for Newtonian

Flow in the Needle – non-Newtonian Therapeutics

Power law

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

$$\tau = m\,\dot{\gamma}^{n}$$

$$\dot{\gamma}_w = \frac{Q}{\pi R^3}\left(3 + \frac{1}{n}\right)$$

$$F = \pi R_b^{\;2}\left(\frac{2L_n}{R_n}\right)\eta\,\dot{\gamma}_w + piston\ friction$$

Dynamics of Polymeric Liquids. Bird, Armstrong and Hassager 1987.

Estimation of Injection Force Flow Chart

Measure viscosity for low to high shear rate up to the wall shear rate in the needle

→

Calculate
- power law exponent
- Wall shear rate
- Estimate viscosity at the wall shear rate

↙

Estimate injection force

$$F = \pi R_b^{\,2}\left(\frac{2L_n}{R_n}\right)\eta\,\dot{\gamma}_w + piston\ friction$$

Application Example: Non-Newtonian Therapeutics

Newtonian Therapeutics

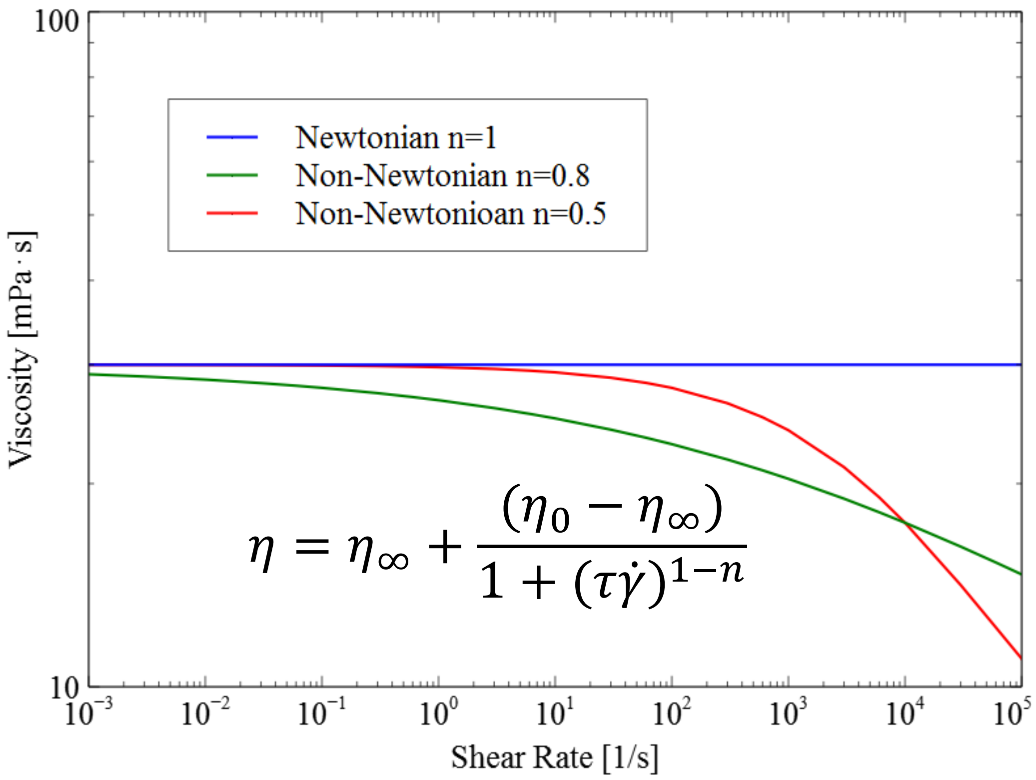
ID, mm	Injection rate, ml/s	Shear rate, s^{-1}	Viscosity, mPas	Estimated Injection force, N	Reported Injection force, N
0.184	0.1	163,000	30	42	42~51
0.184	0.0625	102,246	30	26.5	28~32

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

29 gauge needle

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

$$F = \pi R_b^{\,2} \left(\frac{2L_n}{R_n}\right) \eta \, \dot{\gamma}_w + piston\ friction$$



Gauge	D_n	D_b	L_n	Injection Rate, Q	n	Shear Rate	Viscosity	Force	Difference %
	mm	mm	mm	ml/s		1/s		N	
29	0.184	6.35	12.7	0.1	1	163511	30.00	42.890	0.00
29	0.184	6.35	12.7	0.1	0.8	173730	14.03	21.304	50.33
29	0.184	6.35	12.7	0.1	0.5	204389	9.53	17.028	60.30

The Rheo-“makes”-Sense Advantage

- Small Sample Volume (≥ 50 μL)
- “True” Viscosity for injectability
- Shear rate range up to 1,400,000 1/s

Thank You!

Abbott
A Promise for Life

Bristol-Myers Squibb

Pfizer

BAYER Bayer

MERCK
Be well

Genentech
BIONCOLOGY™

Johnson & Johnson

REGENERON
PHARMACEUTICALS

AMGEN®

The END…

Thank You!

RheoSense™

Simply Precise™

Intro to Injectability

m-VROC® Specifications

Min Sample Volume	50 µl
Shear Rate Range, s^{-1}	0.5 ~ 1,400,000
Viscosity Range, mPa-s (cP)	0.2 ~ 100,000
Temperature Range	4 ~ 70 °C
Accuracy	2% of Reading
Repeatability	0.5% of Full Scale
Temperature Sensor	Built-In
Software	Included
Non-Newtonians?	Yes
Temperature Sweep	Yes
Shear Rate Sweep	Yes

Chip module surface material:

- borosilicate glass, silicon, PTFE, ETFE, PEEK, platinum, Perlast (Kalrez Optional)

CE certified

Additional Customization
(i.e.: 20µl Sample Volume Testing)

Listed in USP

Non-Newtonian Standard.

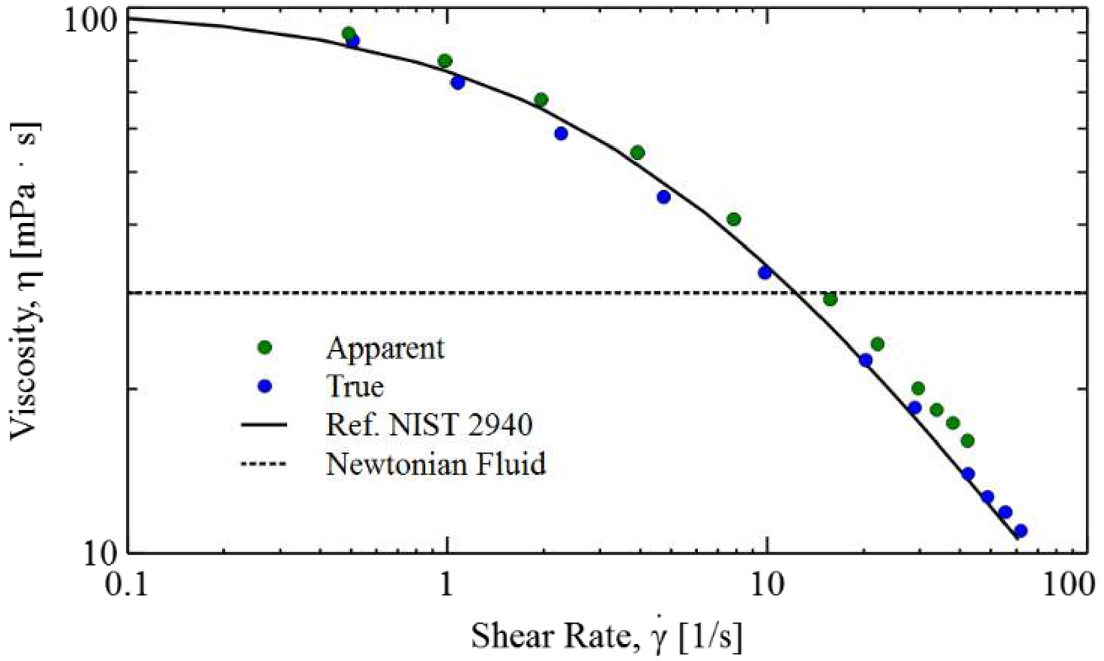


Figure 1. Characterization of a non-Newtonian standard using *m*-VROC®. Measurements of apparent viscosity (green) and true viscosity (blue) compared to certified NIST certified viscosity non-Newtonian standard 2940 (solid black). The behavior of an ideal Newtonian fluid is given by the dashed line.

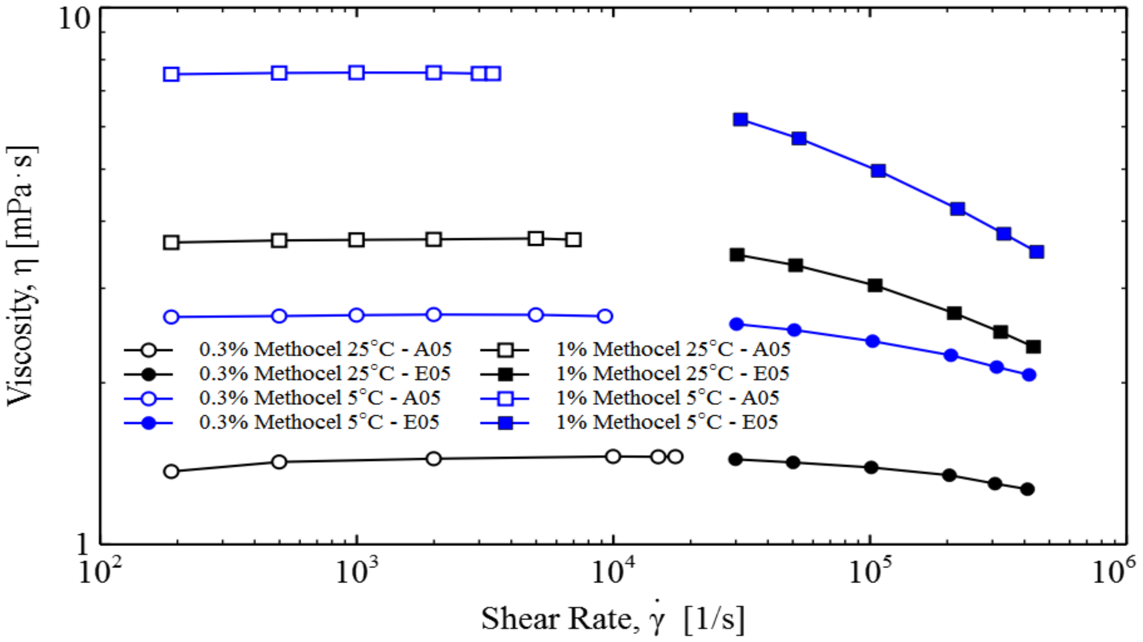
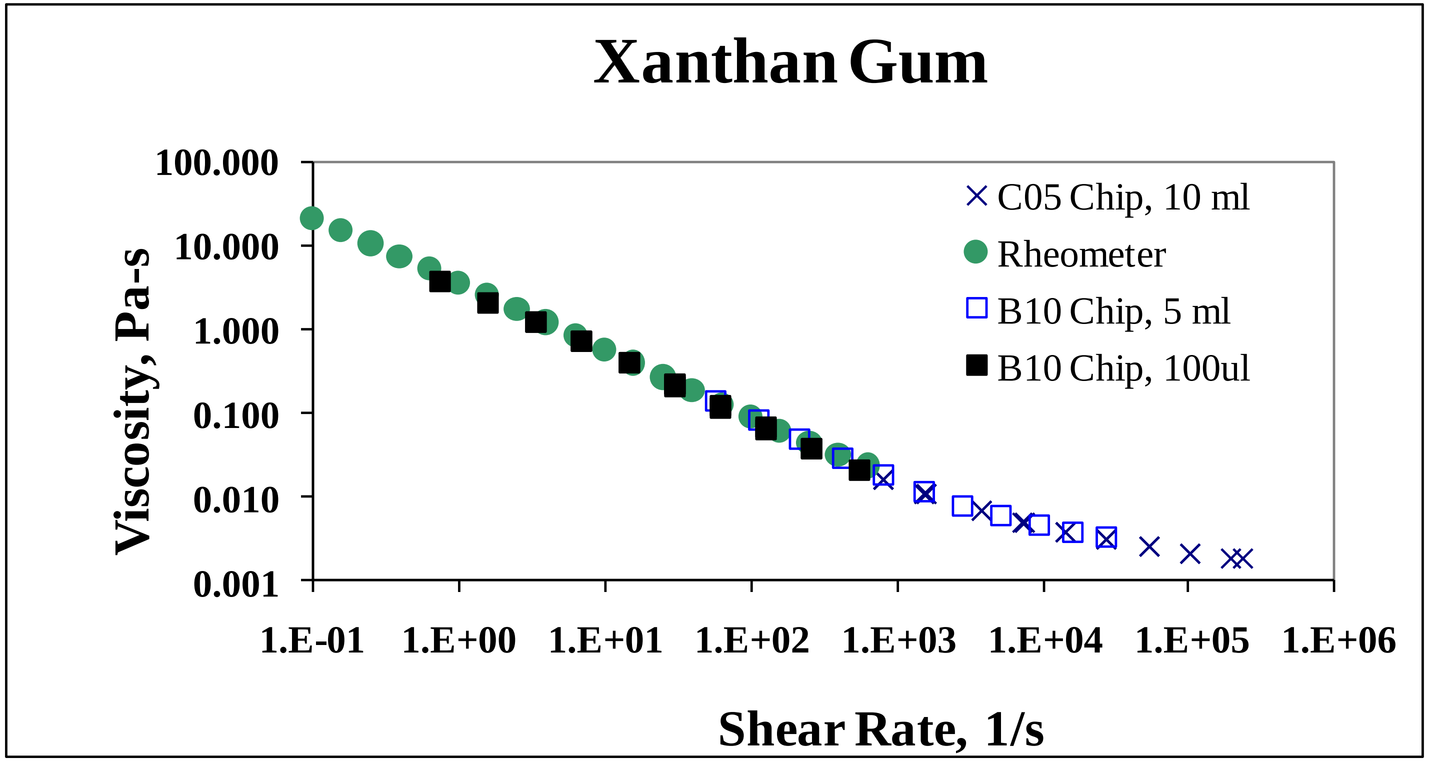


Figure 2. Measurements of true viscosity versus true shear rate for 0.3% (circles) and 1% (squares) Methocel™ water solutions. Samples were tested at 5°C (black) and 25°C (blue) for a wide range of shear rates (200-400,000 1/s) using A05 (open) and E05 (filled) VROC® chips. Comparison of measurements between chips shows excellent agreement.

RheoSense

Results- True Shear Viscosity



Customer supplied comparison between *m*-VROC™ and Anton Paar MCR Rheometer
* Notice the shear rate limitation with conventional Rheometers!

CASE STUDY: Injection of Prefilled High Viscosity Drugs Using Disposable Auto-Injector

Elcam Medical
www.elcam-medical.com

David Daily, Guy Keenan, Lior Raday | Elcam Medical, Bar-Am 13860, Israel

Background

Elcam Medical's line of innovative Auto-Injectors for self-administration includes unique configurations - both for liquid drugs in prefilled syringes (PFS version), and for powder or liquid drugs in vials (DV versions).

While the size of self-injection market continues to grow at two-digit annual rate, Elcam is widening its product portfolio through new auto-injector designs for high viscosity drugs (see pictures below).

Elcam Medical's New Flexi-Q Disposable Auto-Injector Design for High Viscosity Drugs in Prefilled Syringes

Pharmaceutical companies invest major resources in developing new drugs for subcutaneous self-injection market besides stabilizing their marketed dry formulations in liquid form.

More and more of these compounds raise viscosity issues because of two major reasons:

- Development of sustained release /depot formulations dedicated to achieve less frequent injections (e.g., PEGylation, mAb).
- Trend towards SC injections which are limited in dose volumes and that allow self-administration.

Consequently, the demand for drug delivery devices which are capable of subcutaneously injecting such viscous compounds have followed.

Major parameters affecting injection force are: **liquid viscosity, injection speed/ flow-rate, needle inner diameter (ID)** and **needle length.**

When designing an auto-injector for high viscosity drugs there are more challenges that have to be addressed. Some of these are:

- High rigidity is demanded from such a device because much higher forces are involved.
- When using mechanical springs as the injection energy source - dealing with "creep phenomenon" of plastic parts through long shelf life.
- There is a risk of damaging the glass syringe at impact and high injection forces.
- High forces are usually accompanied with loud sounds during operation which can intimidate the user and potentially increase pain perception.
- Application of a constant force during injection progression while keeping optimal and reasonable injection time.
- Keeping design simplicity and acceptable dimensions for reliability, robustness and market acceptance.

Study Objective

Analyze the required forces to inject viscous liquids (ranging 5-45 cP) through variable needle gauges and injection speeds (flow-rates).
This data is used for design requirements characterization of auto-injector for high viscosity drugs.

Method

This experiment explored the influence of liquid viscosity, injection speed/ flow-rate and needle ID on the force that is needed to be applied on the plunger. The injection was performed on a Tension-Compression machine at constant speeds for achieving injection times of 5, 10 and 16 sec. with 1.0 mL of liquid and 1 mL long glass syringes.

Different glycerin percent weights in aqueous glycerin solutions at a given temperature were used to simulate high viscosity drugs.

23, 26 and 27 gauge normal-walled (NW) needles were used (ID, min.: 0.317, 0.232 and 0.184 mm respectively, ISO 9626). All needles were ½" long.

NOTE:

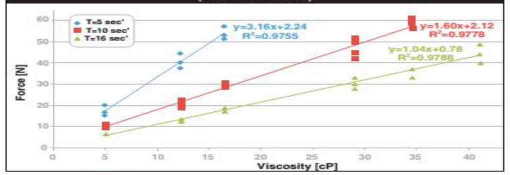
- 26G NW needle can simulate use of 27G thin-walled (TW) needle (ID, min.: 0.241 mm).
- 23G NW needle simulates 26G TW needle (ID, min.: 0.292 mm).

Results and Discussion

Figures 1 and 2 below show a summary of representative results from the study (while using 1 mL injection volumes and 1 mL long glass syringes):

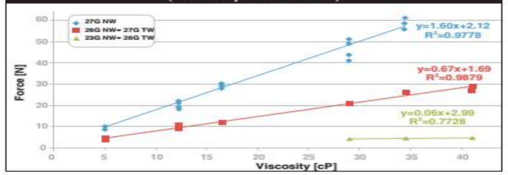
- Fig. 1 shows the required injection forces for a specific liquid viscosity while using a 27G NW needle at flow-rates representing 5, 10 and 16 sec. of injection time.
- Fig. 2 shows the required injection forces for a specific liquid viscosity for flow-rate representing 10 sec. injection duration while using 27G NW, 26G NW (»27G TW) and 23G (»26G TW) needles.

Fig.1: Injection force [N] vs. Liquid viscosity [cP] at different injection times (27G NW needle)



As expected and as can be seen in Fig. 1, the required injection forces are proportional to the liquid viscosity and inversely proportional to the injection duration. Shorter injection times and higher viscosities are associated with higher injection forces. For example, while using the most common 1 mL long glass syringe with 27Gx1/2" NW needle, at ~ 15 cP viscosity 1 mL volume, you may need an average injection force of ~ 50 N, ~ 26 N and only 16 N at injection durations of 5, 10 and 16 seconds, respectively.

Fig.2: Injection force [N] vs. Liquid viscosity [cP] at different needle gauges (10 sec' injection duration)



In Fig. 2 it can be seen that as the needle tube ID is increased, the injection force is significantly decreased. For example, for achieving a reasonable injection duration of 10 sec at ~ 30 cP viscosity 1 mL volume, using most common 1 mL long glass syringe with 27Gx1/2" NW needle you may need an average injection force of ~ 50 N, while only ~ 22 N and 5 N using 27G TW and 26G TW needles, respectively.

Note: In addition to the resistance to flow of the viscous liquid through the needle, the measured injection force comprises also of other contributing friction forces such as a friction force between the plunger-stopper and the glass syringe.

These results can be explained using fluid mechanics equations (see appendix).

Conclusions

For automatic injection of high viscosity drugs, two approaches can be used:

1. Increasing the needle ID and thus reducing the required injection force while keeping reasonable usability injection duration.

2. Increase the injection spring force, or, using an alternative energy source for injection (such as compressed gas/air, electric motor, etc.).

A combination of the two approaches can be used as well.

While the major challenge of the first approach is a logistic challenge - prefillable syringes with staked needles are most common with 27G NW needles, the challenges of the second approach are significant design challenges – keeping the auto-injector small, reliable, not noisy, keeping the glass syringe integrity, and more…

Appendix - Fluids Mechanics Theory

Calculated Reynolds number for the flow in the needle tubing doesn't exceed Re=320. Laminar flow occurs at low Reynolds numbers (Re ≤ 2100) where viscous forces are dominant, and is characterized by smooth, constant fluid motion.

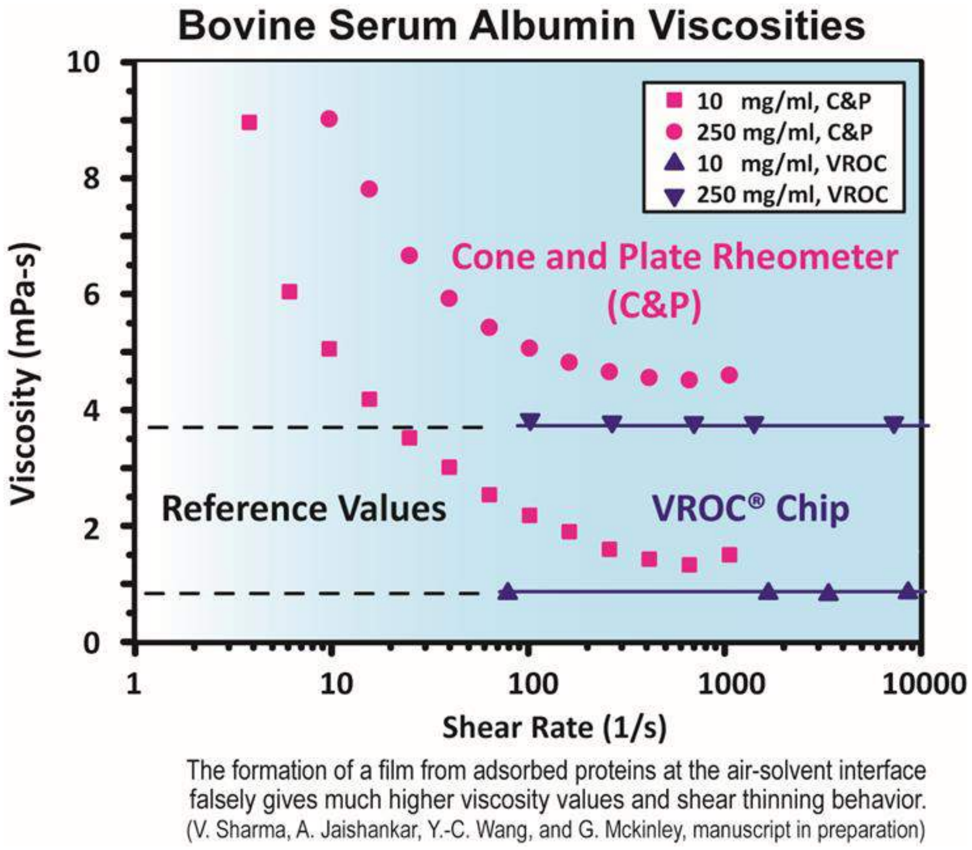
For laminar flow, pressure drop in a pipe is given by,

$\Delta P = (\frac{8l\mu}{\pi R^4})Q$ where:

l – pipe length, m - Dynamic viscosity, R – pipe diameter and Q – flow rate.

Product commercial availability is expected during the first half of 2009

Results- *m*-VROC™ vs. Cone & Plate



Soft Matter, 7(11), 2011

Measuring with cone & plate has two challenges:

- Evaporation
- Irreversible absorption protein molecules at the interface:
  - Proteins migrate to the interface to minimize the interface energy
  - Molecules partially unfold and aggregate
  - Can form gel-like network
- Shows "apparent" shear thinning behavior