PHARMACEUTICAL

Viscosity at high shear rate for assessing drug injectability

- *Adapting the injection system for a specific formulation* -

Introduction

Injectability and syringeability are major parameters that must be optimized during the development phase of injectable drugs. These key features notably encompass the ability of drug to be filled into a syringe and administered to the patient. Therefore, the force needed to pump solution through the needle must be carefully considered during formulation. In this study, we show how viscosity measurements using a microfluidic device - Fluidicam^{Rheo} can be used to rationalize and speed-up injectable drug development without the need of direct force measurements.

KEY BENEFITS

HIGH SHEAR RATE

LOW VOLUME

PRECISE

Reference:

1. *Cilurzo, Francesco, Francesca Selmin, Paola Minghetti, Marco Adami, Elisa Bertoni, Sara Lauria, and Luisa Montanari. 2011. 'Injectability Evaluation: An Open Issue'*
2. *Watt, R. P., Khatri, H. & Dibble, A. R. G. Injectability as a function of viscosity and dosing materials for subcutaneous administration.*
3. *Burckbuchler, V. et al. Rheological and syringeability properties of highly concentrated human polyclonal immunoglobulin solutions.*
4. *Allmendinger, A. et al. Rheological characterization and injection forces of concentrated protein formulations: An alternative predictive model for non-Newtonian solutions.*

Reminder of the technique

Fluidicam^{RHEO} uses a co-flow microfluidic principle to measure viscosity. The sample and a reference solution are simultaneously introduced into the microfluidic channel (typically 2.2mm X 150µm) with controlled flow rates. This results in a laminar flow where the interface position between sample and reference relates the viscosity ratio and flow rates.

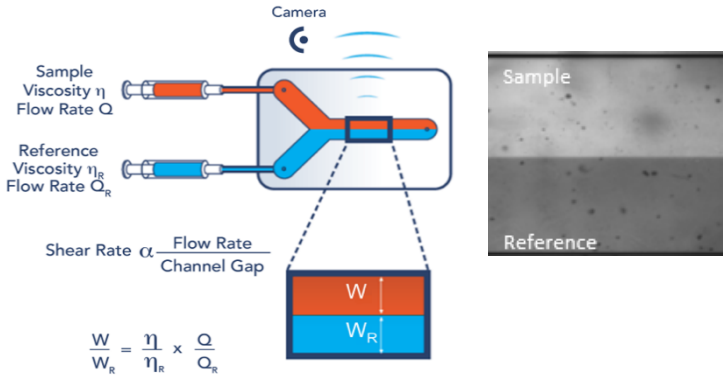


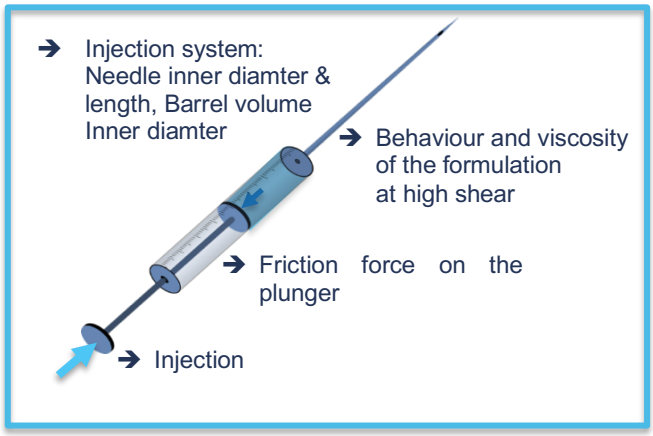
Figure 1: Fluidicam measuring principle

Images acquired during the measurement allow the software to calculate the position of the interface and directly plot an interactive flow curve.

What impacts injectability

As mentioned earlier, the force is an important parameter to optimize and ensure injectability. The required force to pump or eject injectable from a syringe is dependent on both physical properties of the injectable solution and the 'geometric' parameters of the injection system to be used. Namely these parameters are:

- Barrel radius (Rs), needle length (L), needle. inner diameter (R_N), piston friction…
- Formulation viscosity (at given temperature).



Conventional injection needles have gauge sizes ranging from ~20G (ID = 603 µm) to ~31G (ID=133 µm), but some speciaized applications such as pen injectors can range even up to gauge 34 (ID = 82.6 µm).

Downsizing of the needle gauge can help achieve better patient tolerance to pain. However it also highly influences back-pressure during injection as the flow can reach very high wall shear rate, typically ranging from 30 000 to 100 000 s^{-1} [4].

It is possible to give an estimate of the injection force thanks to equation derived from the Hagen-Poiseuille law for a Newtonian liquid (equation 1).

$$F_G = 8\eta LQ \frac{{R_S}^2}{{R_N}^4}$$

Equation (1): injection force model

With η = formulation viscosity, L= needle length, Q= injection rate, R_S = Syringe inner radius, R_N = needle inner radius, F_G = gliding force.

This approach only considers the pressure drop associated to the needle (which is justified when $R_S >> R_N$) and discards any entrance effects and piston barrel friction force within the injection time. It shows strong dependence of force on needle radius (R_N^{-4}) but it also shows that it proportionally increases with the viscosity.

The viscosity can have major impact on injectability e.g. some protein/mAbs formulations can reach high concentration and large viscosity, this can significantly modify injection force in this case it is important to carefully select the right injection system for a better patient compliance.

Once the injection system and formulation are chosen, all parameters are determined except for the flow rate. To give a broad range over which the flow can vary, we considered an injecting time of ***15 s*** to be the maximum tolerable limit by the patient [2]. Thereby, depending on the application, flow rates can be estimated between 0.06 mL.s^{-1} and 0.4 mL.s^{-1} [3]

To summarize, the formulator has a choice :

- to work with a fixed formulation and define the suitable injection system (syringe and needle), or
- to chose the injection system and optimize the formulation under the maximal force constraint, which is ***conventionally admitted*** to be ~20N for the injection to be tolerated by the patient [2].

In the following work, we will show how precise viscosity measurement can help adapt the injection system and enable a **predictive design** of the formulation.

Optimisation of the injection system

Viscosity determination of injectable formulation

To mimic conventional biopharmaceutical formulations, 3 BSA solutions in water at 100, 300 and 400 mg/ml were formulated. The viscosity of these solutions was then measured with Fluidicam^{RHEO} at 20°C, using a 50 µm chip at shear rates ranging from 5.10^3 to 1.10^5 s^{-1}. Figure 2 shows the corresponding flow curves.

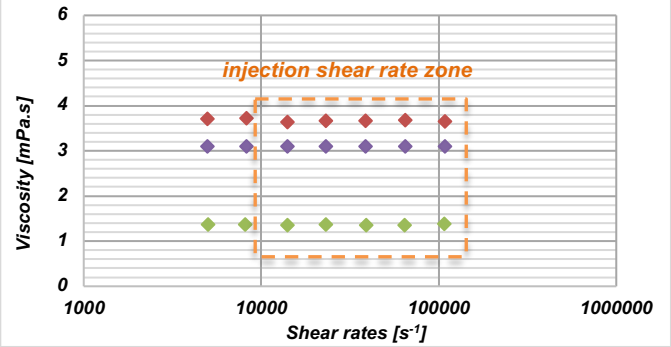


Figure 2: BSA solutions flow curves as a function of shear rate at 20°C

All BSA samples present a Newtonian profile over the studied shear rate range, representative of the injection conditions. Mean viscosity values over the tested shear range are given in the table (1) below:

BSA sample	Viscosity [mPa.s]
100 mg/mL	1.4
300 mg/mL	3.0
400 mg/mL	3.8

Table 1: viscosity values of the analyzed BSA solution.

Evaluation of injection system

Once viscosity is probed, force needed for the injection can be estimated thanks to eq.1

Detailed description of needles and syringes specification used for the administration are given below table 2:

Needle Gauge	21G	26G	27G	29G	30G
Syringe Volume	1 mL		3 mL		
Inner diameter (µm)	478		866		
Inner diameter (µm)	514	260	210	184	159
Length (mm)	50	10	12	12	12

Table 2: characteristics of the different needles and syringes used for this study.

Using the maximal force value of 20N, Figures 3 and 4 allow to decipher whether a system is suited for a product injection or not.

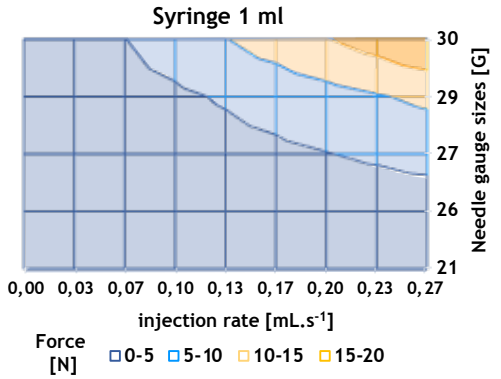


Figure 3: Injection force for 1mL syringe using different needles gauge as a function of injection rate.

As displayed in the figure 3, for a BSA solution of 3.8 mPa.s viscosity, it appears that with 1 ml syringe the generated injection force never exceeds the maximal limit of 20N, whatever the needle gauge used. The solution can be injected with no pain to the patient with any set up system.

The Situation turns different using the 3ml syringe as depicted in figure 4.

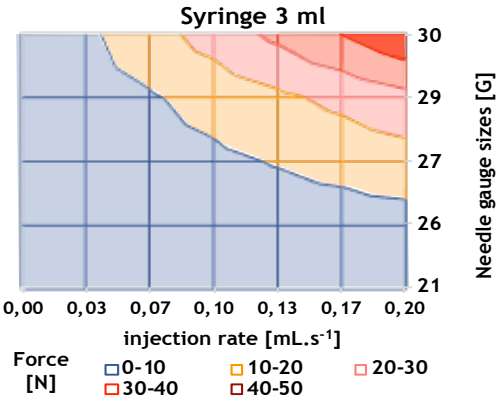


Figure 4: Injection force for 3mL syringe using different needles gauge as a function of injection rate.

In this case the colored red zones represent the configurations where the force exceeds (20N).

The use of 3 mL syringe is not compatible with 29G and 30G setup as it would exceed the maximum force at flow rate above ~0.13 and 0.10 ml/s respectively.

As demonstrated, precise viscosity measurement can be used to qualify injection systems providing reliable information to be used in the injectability calculations.

Viscosity adjustment for pre-set injection system compliance

The other solution to define an optimal injection is to optimize formulation viscosity for already defined system. Using eq.1 and using the same maximum force (20N), it is possible to calculate a **maximal viscosity value** that the formulation must not exceed.

For the injection systems chosen in the previous section (see table 1) the maximal viscosity (ɳ max) to ensure the injectability was calculated and plotted below.

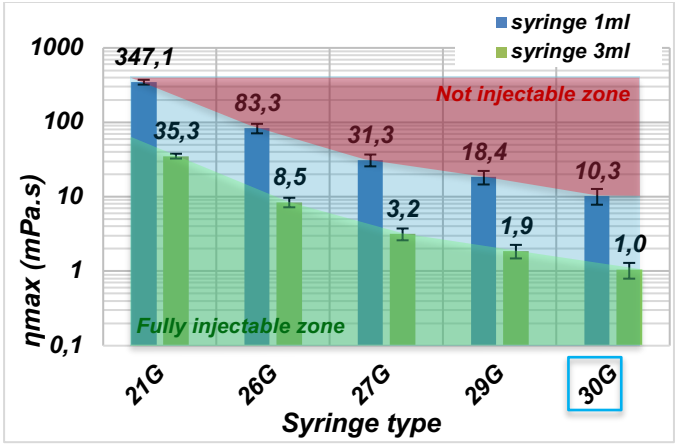


Figure 5: estimation of the maximum viscosity injected as a function of the syringe and needle size.

As the force is inversely proportional to the inner radius of the needle $\frac{1}{R_N^4}$ (eq.1), a significant decrease of the maximum injectable viscosity is observed when decreasing the needle diameter and the syringe capacity volume as presented in the graph (figure 5).

The 21G needle allows maximum viscosity of 30 mPa.s with the 3 mL syringe but 347 mPa.s. While using a 1 mL syringe capacity the maximum tolerated viscosity is estimated at 347 mPa.s. Exceeding the maximum viscosity values for a specific configuration, the formulation administration is considered painful to the patient.

Quick qualification of a formulation can be done by simply projecting formulation viscosity value to the graph. For example, for a **30 G** needle size, the 1 ml syringe ensure the injection for all the 3 tested BSA samples, but none of them can be injected with the 3 ml syringe.

Another major impact of the measurement is that a system can be suited for injection at room temperature, but may no longer work in operational conditions, as a result of temperature decrease during storage : this effect may also be probed thank to Fluidicam^{RHEO} thermoregulation.

CONCLUSION

Two methodologies that could help injectable drug formulators were explained in this overview. Precise viscosity measurement at representative shear rates can be exploited to predict operational ranges of injection systems using force approximation, in representative experimental conditions. Overall, introducing Fluidicam^{RHEO} in injectable drug design workflow can help formulators to rationalize their testing approach with reliable viscosity testing and to accelerate their innovation cycle.