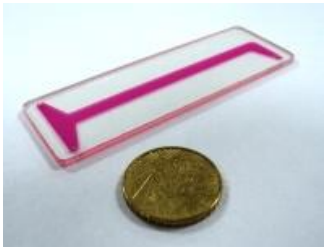
Stability and injectability of concentrated protein solutions



The advent of protein-based drugs brings along new challenges in term of stability and formulation. Indeed proteins have a strong tendency to denature and/or aggregate, depending on parameters such as temperature, shear, solvent composition, etc. This instability affects the shelf life and can alter the drug potency. Moreover their high molecular weight, associated to a low permeability, prevents oral administration, meaning protein-based drugs often have to be injected. In term of formulation, injecting implies a low viscosity and a small volume, so a high protein concentration (typically 10 to 500 mg/ml).

Such concentrations make characterization challenging using conventional optical methods. Diluting the sample before characterization can produce results that are not representative of real conditions. On the other hand, viscosimetric analysis is suitable for concentrated solutions, being sensitive to unfolding, aggregation or a modification of the molecular interplay. Fast, simple viscosity measurements at high shear rates (mimicking an injection, usually around 10^5 s^{-1}) and using small sample volume are made possible using our patented microfluidic technology.

APPLICATIONS

Pharmaceutical Industry

Biology

R&D

OBJECTIVE

To characterize highly concentrated protein solutions by measuring viscosity with a microfluidic device

KEY POINTS

- **Small volumes**
- **Mimic end-use conditions**

High shear rates (< 10^5 s^{-1})
Strong confinement (> 25 µm)

- **Automation**

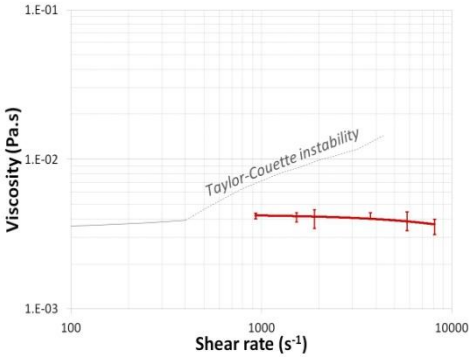
Sample preparation
(dilution / formulation)

Analysis
(rheology and microscopy)

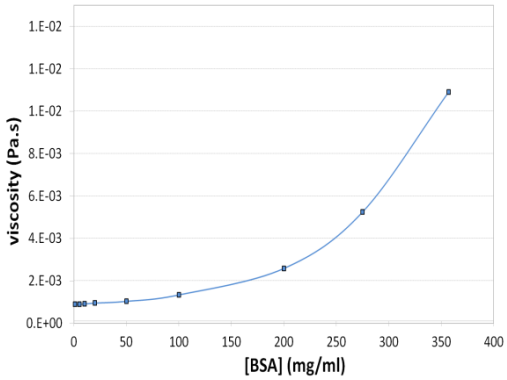
- **Simple, fast & user-friendly**

Viscosity at high shear rates

The figure on the right is a plot of the flow curve (viscosity as a function of shear rate) for a BSA (*Bovine Serum Albumine*) solution in PBS (*phosphate buffer saline*) at 200mg/mL, as measured both by a rotational rheometer (left, grey area) and our microfluidic rheometer (right, green area). Results are in good agreement. However at a shear rate of 400 s^{-1}, the rotational rheometer reaches a physical limit, the so-called Taylor-Couette instability. On the other hand, our microfluidic rheometer is able to reach viscosities as high as 10^4 s^{-1}, mimicking the real conditions of an injection. Using another cartridge with a thinner channel, shear rates up to 10^5 s^{-1} are accessible.



Viscosity as a function of concentration



Using an in-line micromixer, automated dilution or formulation become possible. The graph on the left shows the viscosity of a BSA solution as a function of concentration in PBS. It was automatically plot in 30 min using a dedicated software and our microfluidic system.

To get the same result using a Couette rheometer, it would have been necessary not only to manually prepare every dilution, but also to open, to clean, introduce the sample, and close again the rotational cell before each measurement. The table just below summarizes the estimated measurement time and sample consumption for both scenarios.

	Standard rheometer	Formulaction rheometer
Measurement time	5 hours	30 min
Sample consumption	24 mL	1,7 mL

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