DLS Microviscometry of Concentrated Protein Solutions

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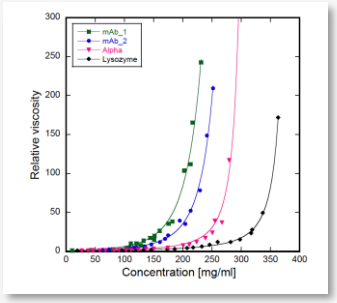
How can we understand and reliably measure the viscosity of concentrated protein solutions?

The development of liquid drug products such as protein formulations is a highly iterative process in which the stability and the viscosity are decisive for the quality of the final product. The injectability of physiologically effective doses is a key property for a pain-free patient experience and involves low volumes of highly concentrated formulations. The determination of the zero-shear viscosity is often challenging due to detrimental surface effects or simply the lack of sufficient material.
We present the basics of DLS microviscometry and demonstrate how to reliably obtain the zero-shear viscosity of highly concentrated protein solutions

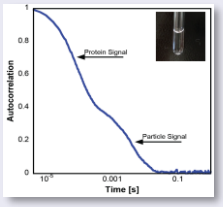


Why microviscometry?

- ✓ **Obtain the true zero-shear viscosity of protein solutions**
- ✓ **No artefacts from film formation**
- ✓ **No external perturbation of the sample**
- ✓ **Smallest sample volume: only a few microliters**
- ✓ **The sample can be recovered**

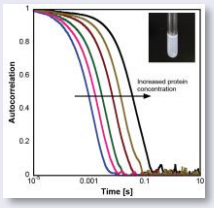
Challenge: multiple scattering

Low particle concentration



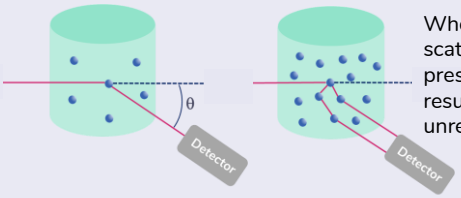
Tracer particles should overshadow the signal of the protein solution

High particle concentration



At high concentration, the scattering signal contains multiple scattering: this makes DLS measurements unreliable!

The theory of DLS assumes that only single scattering is taking place.



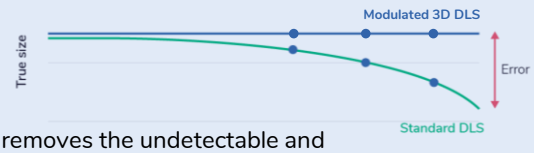
When multiple scattering is present, the results are unreliable.

How to perform reliable DLS microviscometry?

Solution: error-free DLS

LS Instruments has developed and patented the Modulated 3D technology for DLS. It acts on the signal in a similar way to a filter, guaranteeing reliable, error-free and accurate results, even at high concentrations.

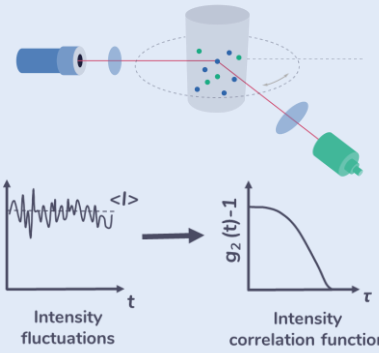
Two DLS experiments are performed simultaneously. By comparing the two resulting signals, multiple light scattering is suppressed.



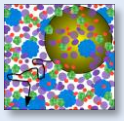
This technology removes the undetectable and systematic errors in DLS measurements.

Principle of DLS microviscometry

Dynamic Light Scattering (DLS) provides a fast and in-situ means of measuring the viscosity of a sample at rest.
It measures the diffusion of tracer particles added to a protein solution.



A laser beam is sent onto the sample and the scattered light is collected by a detector. Driven by Brownian motion, the tracer particles move within the protein solution, causing the intensity of the scattered light to fluctuate. The statistics of these fluctuations are reflected in the correlation function. Since the viscosity of the protein solution influences the particle motion and thus the statistics, DLS can extract the zero-shear viscosity from the measured correlation function.



$$g(\tau) = e^{-Dq^2}$$

$$D = \frac{k_B T}{6\pi\eta R_h}$$

Diffusion coefficient measured

Particle radius known

With a DLS measurement, the zero-shear viscosity of protein solutions is obtained in less than 1 minute.

Instrumentation

The NanoLab 3D from LS Instruments is a compact and user-friendly solution for error-free DLS. It incorporates the Modulated 3D technology and enables microviscometry through intuitive software tools.

Powerful

Accurate

Fast

Intuitive

Specifications	
Viscosity	$10^{-2} - 10^{4}$ mPa.s
Particle sizing	0.15 nm to 5 µm (Rh)
Temperature	4° to 85°
Sample volume	4 µL – 2 mL
Laser power	120 mW

References

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Garting et al.,, Colloids and Surfaces B: Biointerfaces 181 516–523 (2019)
Block et al., Rev. Sci. Instrum. 81, 123107 (2010)

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