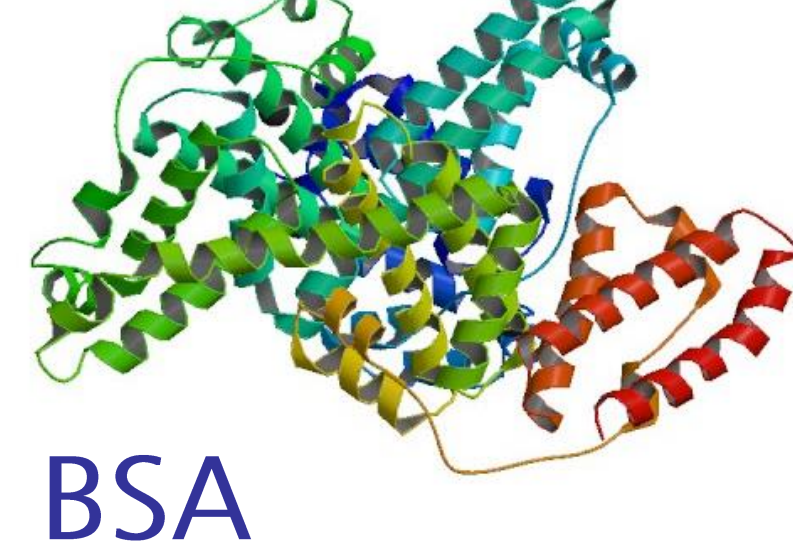
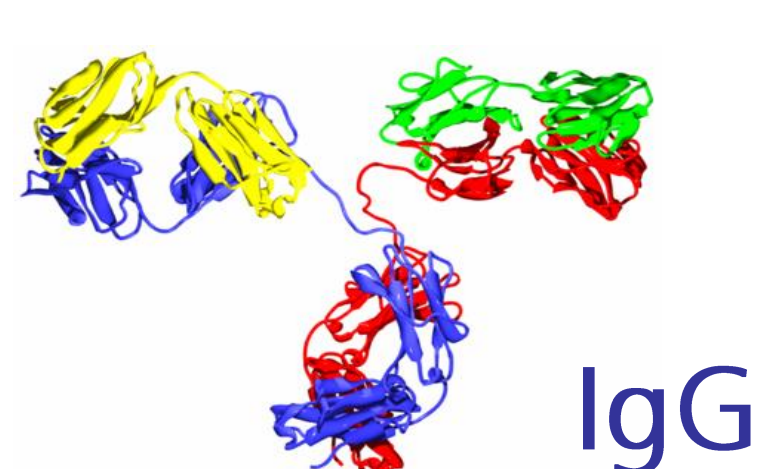




Abstract

During the drug discovery process, biopharmaceutical industries produce a large number of formulations with small recipe variations. One important aspect in the development of novel drugs is the characterization of their viscosity fingerprint (i.e. viscosity dependence on shear rate, temperature...). Viscosity is a good indicator of small changes in concentration and molecular structure that play a key role in the efficacy and stability of the final product.



Challenges

In the early stages of drug development, available sample volume for testing is very limited. Conventional rheometers often require large sample volumes (~1 mL or higher). Microfluidic based rheometers offer extensive rheological characterization at a fraction of the volume.

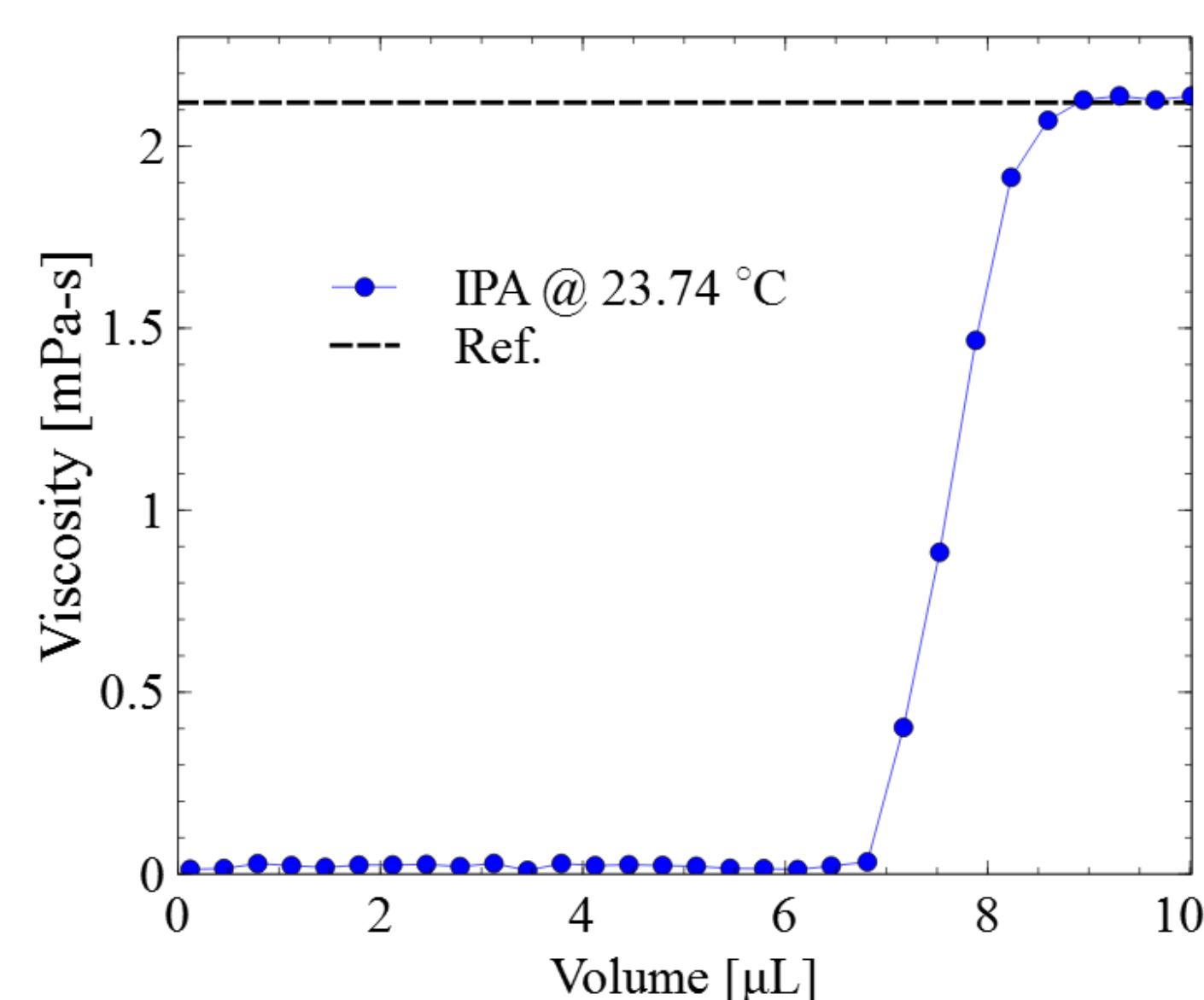


Figure1. A viscosity measurement can be performed with just a few uL!

VROC® features:

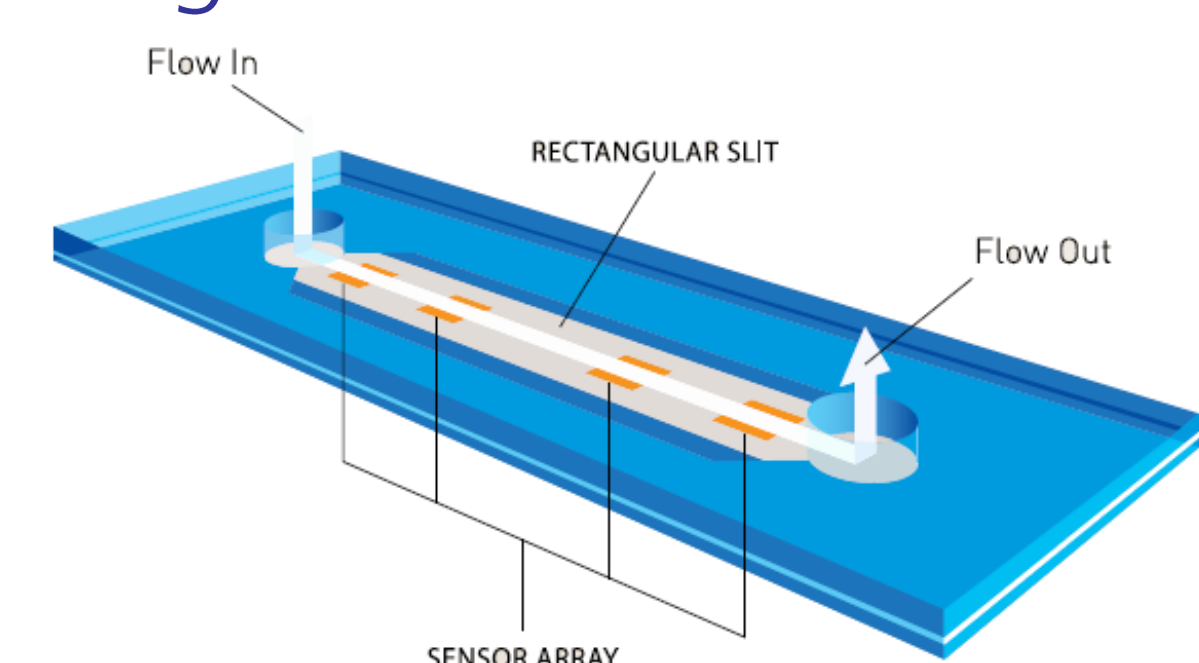
- Viscosity vs Shear Rate
- Viscosity vs Temperature
- Smallest Sample Volume
- High shear capabilities
- Accuracy: 2% of Reading
- Repeatability: 0.5% of Reading
- No Solvent Evaporation

Another advantage of microfluidic-based rheometers is that, due to their small size, they can achieve much higher shear rates than conventional rheometers without inducing flow instabilities [1]. This enables the study of high shear applications such as injectability of non-Newtonian protein therapeutics.

VROC® Technology

VROC® (Viscometer/Rheometer On a Chip) is a hybrid of microfluidic and MEMs technologies.

Hagen-Poiseuille flow:



$$\tau = \Delta P \times \frac{wh}{2(w+h)}$$

$$\dot{\gamma}_{app} = Q \times \frac{6}{wh^2} \quad \eta = \frac{\tau}{\dot{\gamma}}$$

WRM-Correction:

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

Experimental

BSA and IgG solutions up to 200 mg/mL in PBS (Phosphate Buffer Saline) and water were tested at several shear rates. VROC® technology's high accuracy and repeatability allows for the characterization of these solutions as a function of concentration, pH, buffer,... These samples were also tested for intrinsic viscosity. Methocel™ water solutions were also tested to demonstrate the importance of shear rate and temperature for injectability. Highly monodisperse PS/Toluene solutions were used to validate intrinsic viscosity measurements.

Results

The following set of results demonstrate VROC® capabilities for viscosity fingerprinting of samples relevant to biopharmaceutical industries.

Protein Therapeutics

Bovine Serum Albumin (BSA) and Immunoglobulin (IgG) are good examples of protein systems that are found in biological applications.

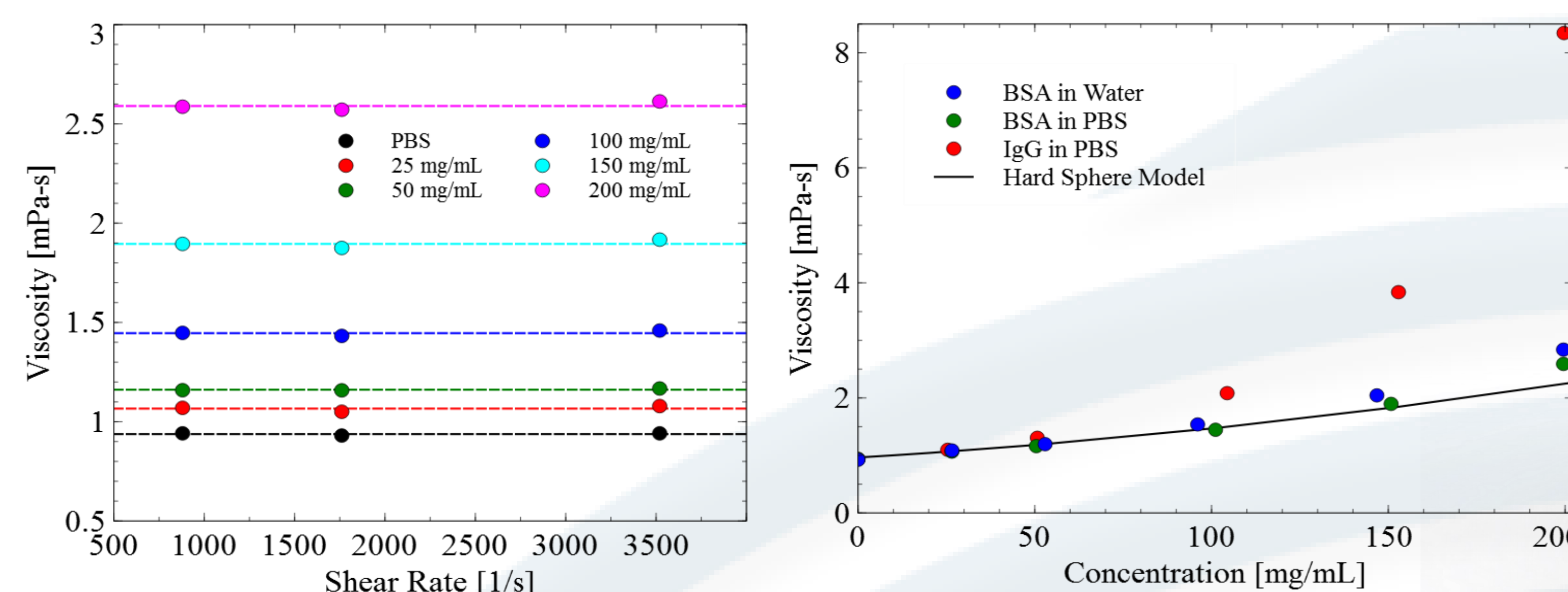


Figure2. Viscosity as a function of shear rate for different concentrations of BSA in PBS(left). Viscosity as a function of concentration of BSA and IgG solutions (right)[2]

Injectability

Less frequent dosing have lead pharmaceutical companies to increase the concentration of their protein therapeutics.

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

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

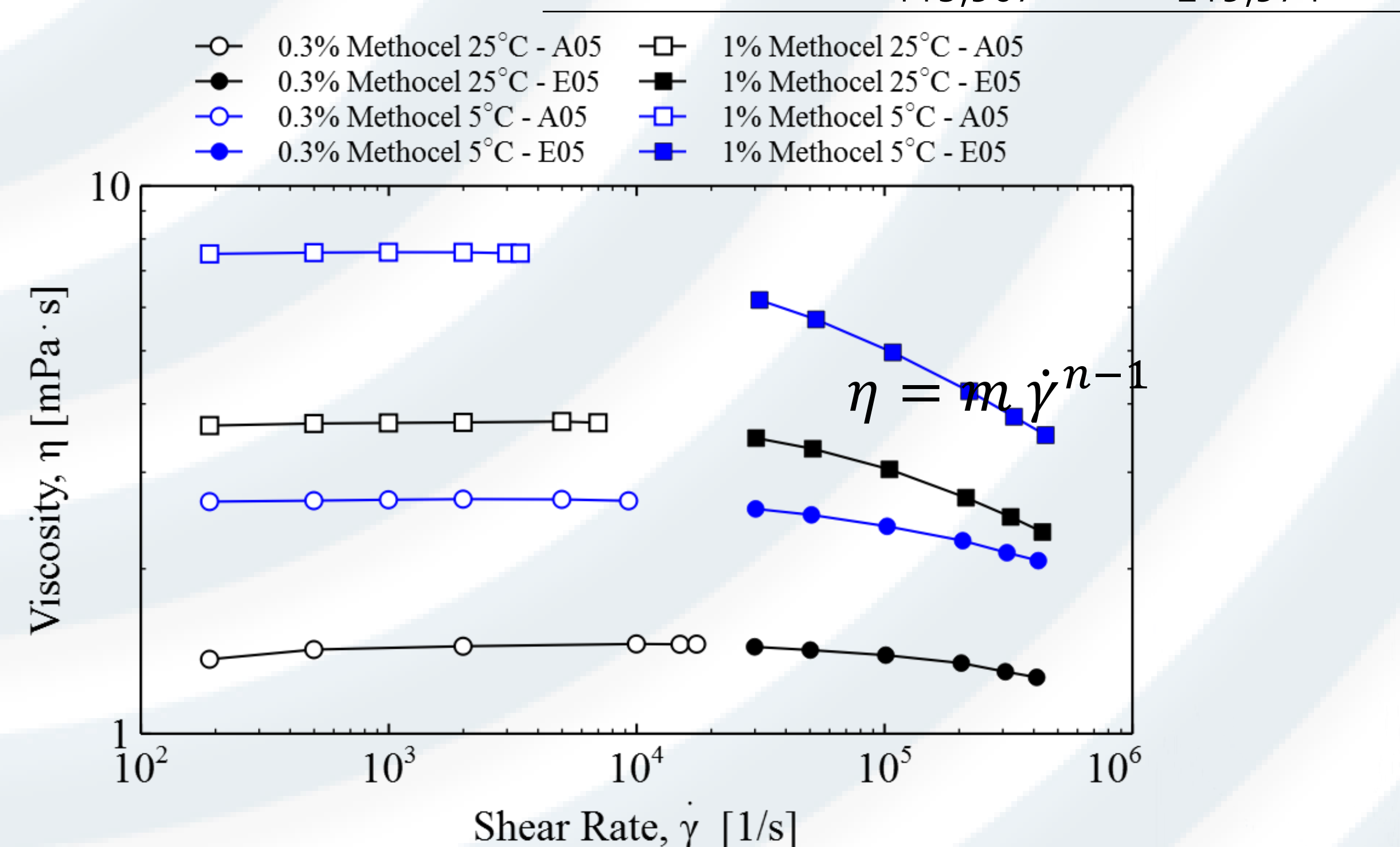


Figure 3. Viscosity as a function of shear rate for Methocel™ solutions in water.

Intrinsic Viscosity

VROC® superior repeatability enables indirect measurement of molecular size and structure.

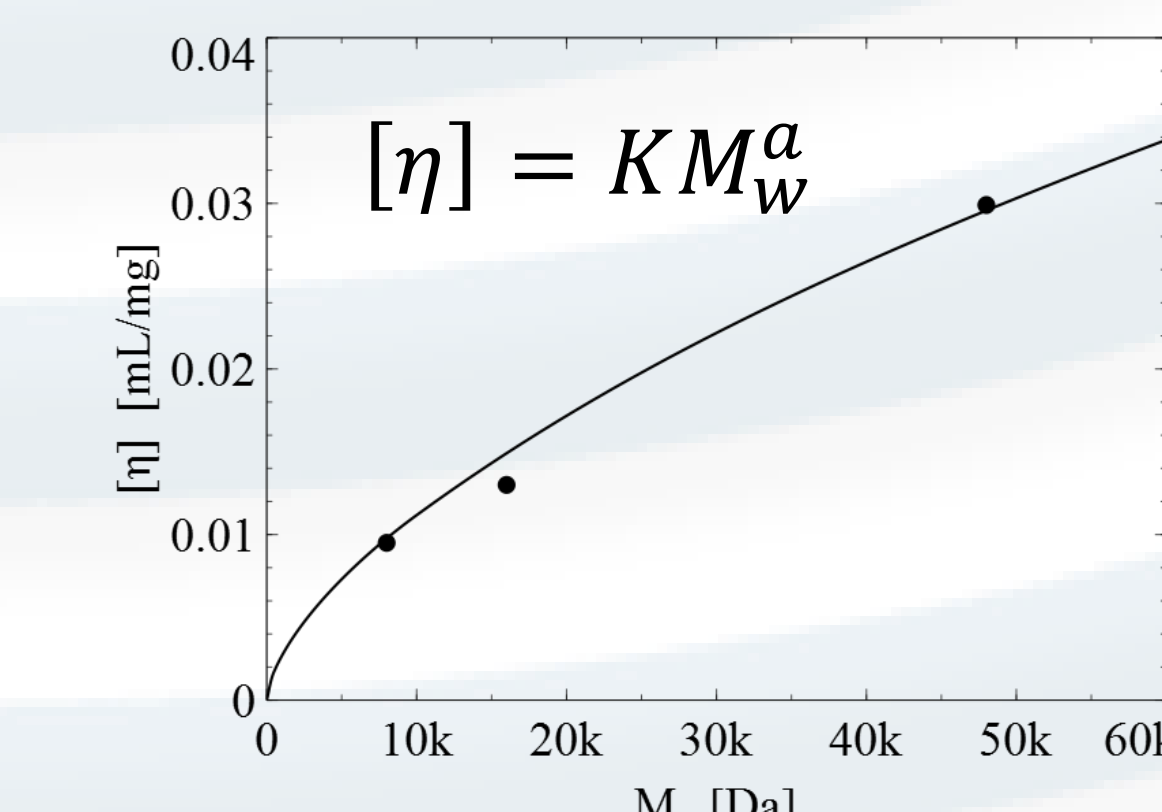


Figure 4. Intrinsic Viscosity versus molecular weight for monodisperse polystyrene in toluene [3].

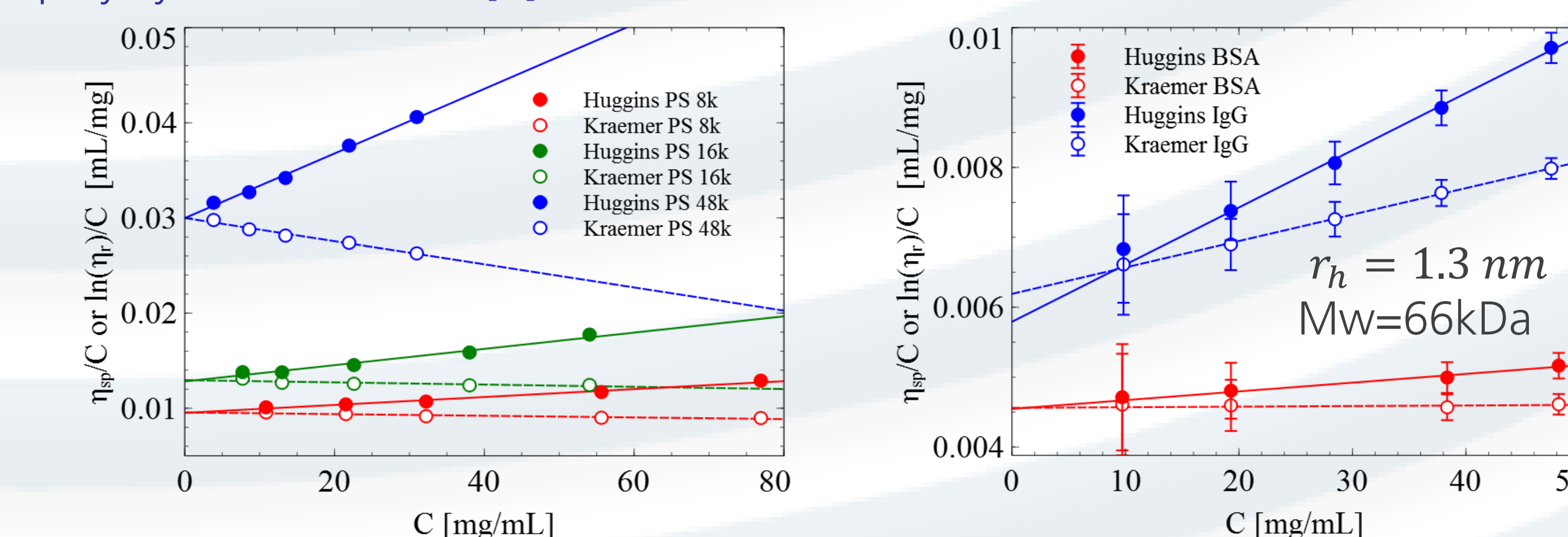
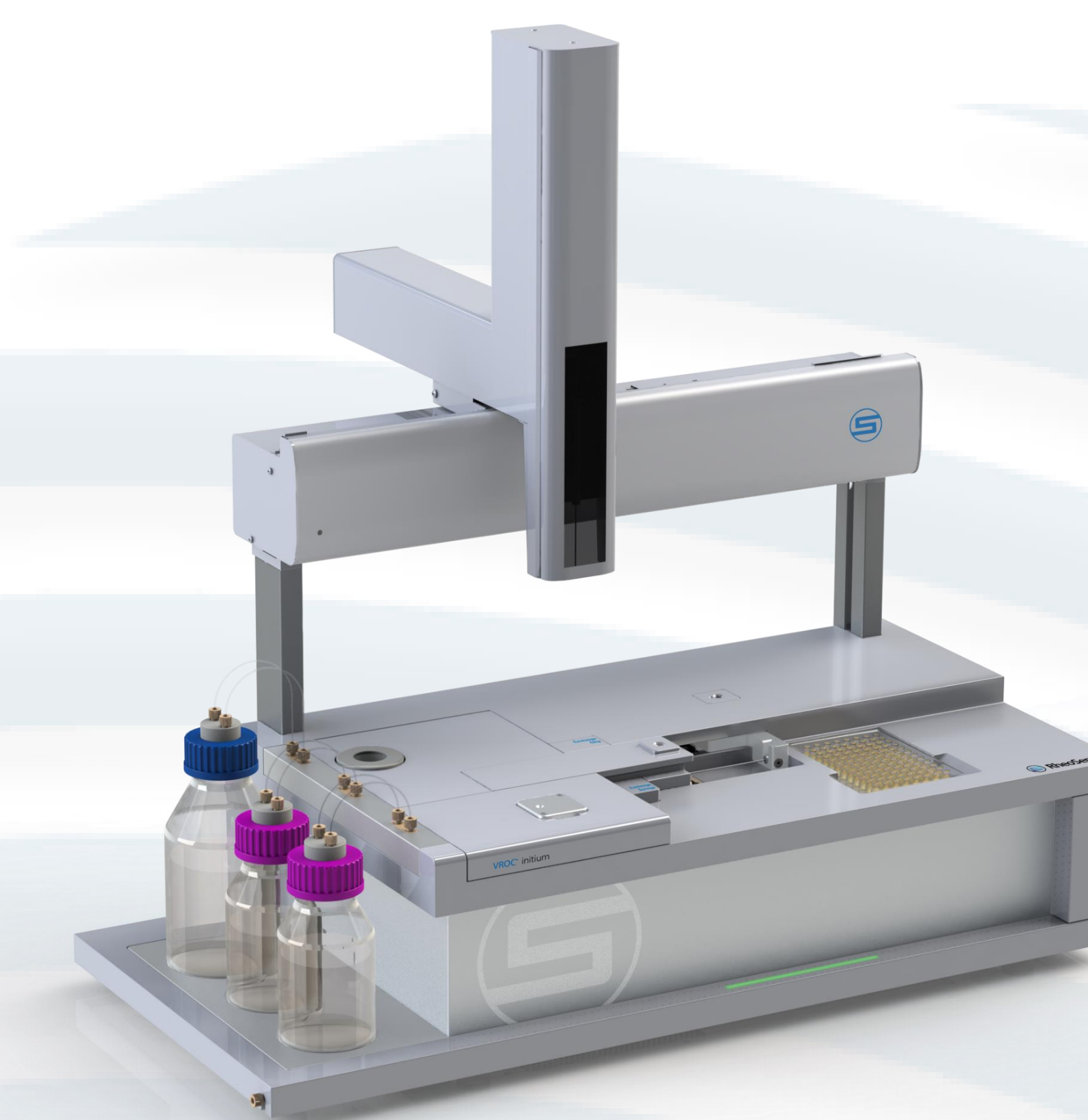


Figure 5 . Intrinsic viscosity for PS/Toluene and BSA/PBS and IgG/PBS solutions [4].

Automated Characterization

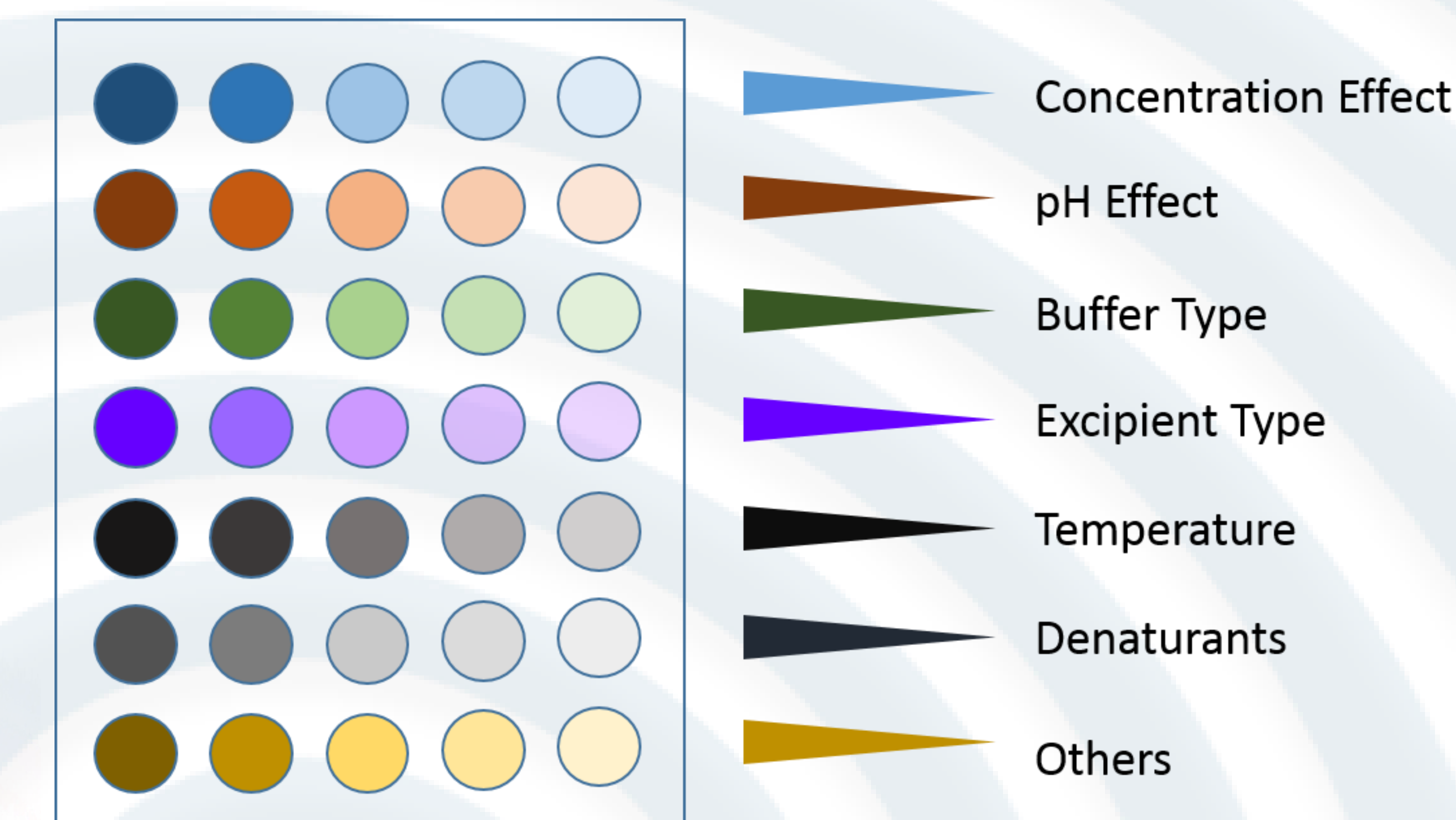
Powered by VROC® technology, VROC® initium is the first fully automatic viscometer/rheometer for viscosity fingerprinting. Key specifications include:



- High Throughput Automatic Viscometer/Rheometer
- ~10 Microliters of Sample
- 40 Vial Rack, 96 Well Plate
- Shear Rate and Temperature Sweeps
- 4-70 °C Built-in Peltier Temperature Control
- Sample Rack Temperature Control, 4-40 °C

Additionally, VROC® initium features continuous testing via sample retrieval allowing shear and temperature stability studies as well as sample recovery.

Automatic Viscosity Fingerprinting



Summary & Applications

VROC® powered viscometers/rheometers take advantage of the small scale of microfluidic devices and the high resolution of MEMs technology to enable the accurate measurements with small sample volumes required for applications such as:

- High Throughput Screening with Viscosity
- Injectability of Protein Therapeutics
- Stability of Protein Therapeutics
- Kinetics of Chemical Reaction and Degradation
- Solubility
- Intrinsic Viscosity
- Hydrodynamic Radius

Thanks to automation VROC® initium will make your measurements of viscosity *Simply Precise™*!

References

1. Makosco. Rheology: Principles and Applications, Wiley 1994
2. Kawahara et al. J. Biological Chemistry 1966
3. Brandrup. Polymer Handbook 2001
4. Lee et al. Analytical Chemistry 2005

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