Low Volume and High Shear Rheology on a Conventional Rheometer: A Tool for Characterising Pharmaceutical Skin Creams

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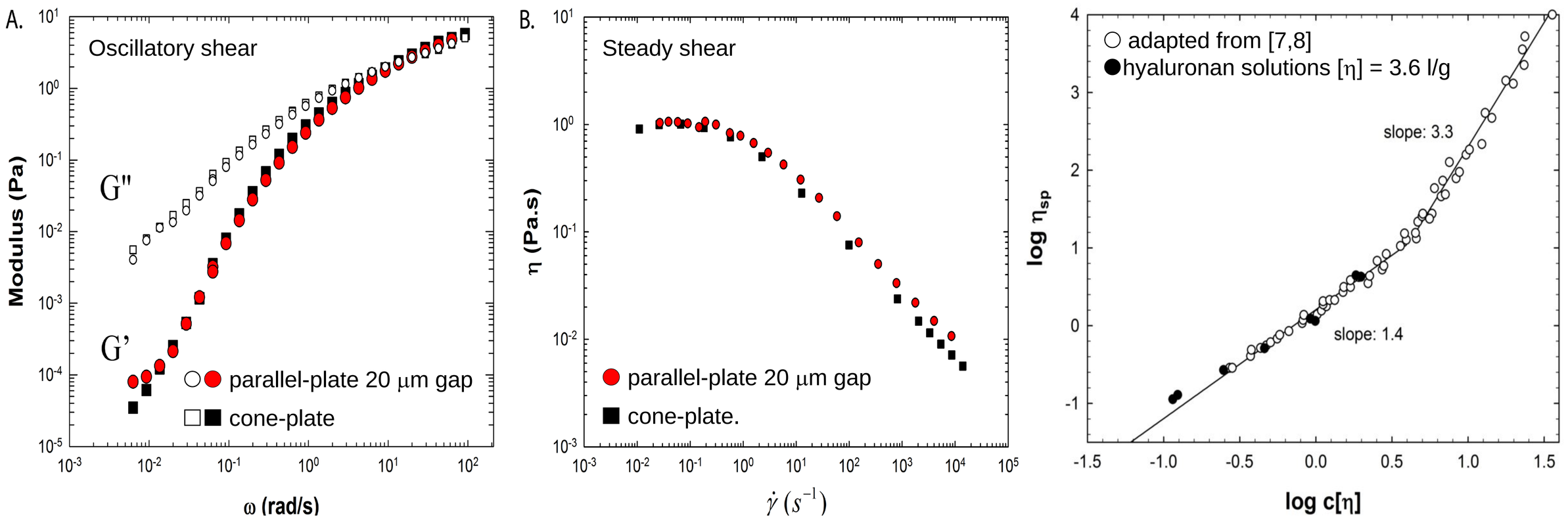
Conventional rheometers have the capability of characterizing ultra-low fluid volumes, as low as ~10 μl [1-3], using narrow gap parallel plates. Methodologies for obtaining accurate measurements of viscosity and non-linear viscoelastic properties of elastic shear thinning fluids have been established [1, 4, 5]. This technique also expands the range of accessible shear rates to 10^5 s^{-1}, far beyond those routinely accessed [6].

This study focuses on using narrow gap rheology for characterising biological fluids and semi-solid pharmaceutical products for two reasons:
1. Only small volumes may be available, or the cost of certain pharmaceutical products like creams may be prohibitive to large scale testing; and
2. It may be necessary to evaluate high shear rates that are relevant to the dose administration (rubbing the cream on the skin) or to a manufacturing process

Method Development for Ultra-Low-Volume Rheology on a Conventional Rheometer

Rheological characterization was conducted using a conventional rotational rheometer, Haake Mars III (Thermo Scientfic) or ARG2 (TA Instruments). Three parameters were critical to the measurement of narrow gap rheology using a conventional rheometer with a smooth plate at gap height ≤ 50 μm:

- Zeroing the gap using a 4 N load to overcome the squeeze flow of air.
- Determining, and correcting for, the gap error which arises from plate misalignment etc., as well as accounting for non-constant shear rate with radius [1-2].
- Accurately loading the required sample volume on to the plates using a micropipette ≡ 55 μl for a 50 μm gap on a 35 mm diameter parallel plate.



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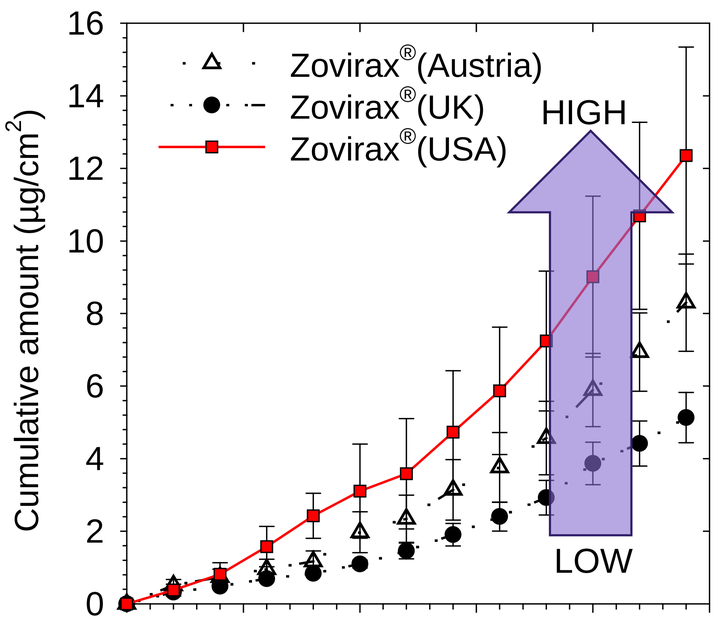
A and B shows that the rheology of a 0.625% polyacrylamide solution is nearly identical between cone-plate and parallel-plate with a 20 μm gap. The ultra-low-volume technique captures known polymer physics (in our case, dilute polymer solution physics) and can be used to measure intrinsic properties of polymers with volumes less than 100 μl, in this case, a Hyaluronan solution *during* fermentation.

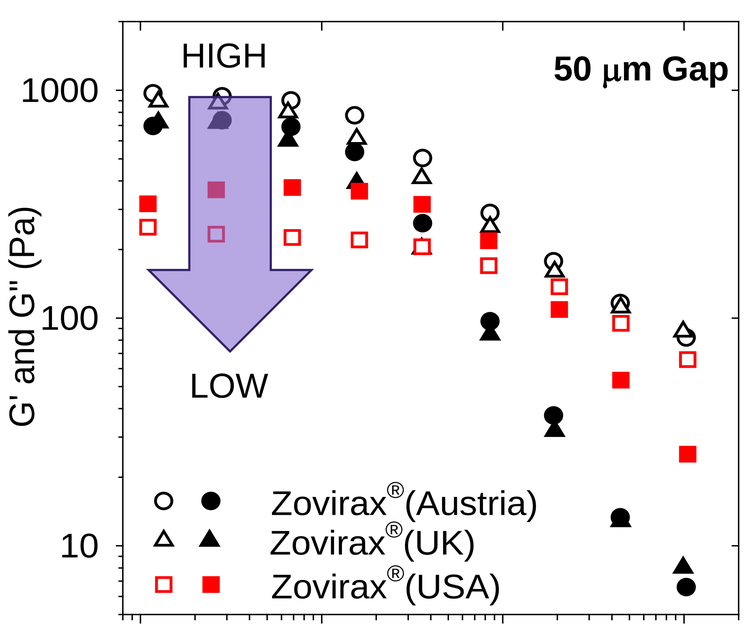
Thin Film Rheology for Physicochemical Characterization and Performance Testing of Skin Creams



In Vitro Permeation Tests (IVPT) with heat separated human epidermis mounted on a static Franz cell was used to evaluate the bioavailability of acyclovir across 48 hours following application of acyclovir cream 5% (Zovirax®) products marketed in the United States (USA), the United Kingdom (UK) and Austria.

Rheological Profiling was also performed for these creams.

Lower Storage and Loss Moduli (G' & G") were observed in the linear viscoelastic region for acyclovir cream 5% (Zovirax® USA). Conversely, **Greater Bioavailability** of acyclovir was observed from this cream (Zovirax® USA). We hypothesize that rheological properties of creams influence both, the diffusion of drug in the cream and the effective interfacial contact area for drug to partition from a topical cream into the stratum corneum of the skin.



These results indicate that *narrow gap* oscillatory rheology provides insights into physicochemical properties of creams relevant to performance.

Concluding Remarks

- Narrow gap parallel plate rheometry is a useful and reliable method that greatly extends the capabilities of a conventional rheometer.
- Comprehensive rheological characterisation and evaluation of molecular properties are possible even at ultra-low sample volume.
- Results at low to moderate shear rate are consistent with those achieved using cone and plate geometry, with the advantage that sample volumes < 55 μl are required and high shear rates can be explored.
- Thin film rheology can be used as a readily available, cost effective analytical tool for drug product physicochemical characterisation that may be relevant to product performance and bioavailability.

References & Acknowledgement

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