PHARMACEUTICAL

High shear microfluidic rheometer

- Rheology optimization of ophthalmic eye drops -

Introduction

Topical application represents the main route for administration of drugs to treat eye disorders. It is widely recognized that efficiency of ophthalmic formulations highly relies on their rheology. As blinking phenomena submits eyelid to a wide range of shear rates, the rheology of formulations must be carefully optimized. Its full knowledge allows for residence time to be increased while keeping a maximal patient compliance.

KEY BENEFITS

- HIGH SHEAR RATE
- FAST ANALYSIS
- SMALL SAMPLE VOLUME

According to literature the shear rates during blinking are estimated between 4000s^{-1} and 30 000s^{-1}.
Viscosity measurement using conventional rheometers remains challenging regarding the low viscosity of the eye drops solutions. The microfluidic system of Fluidicam^{RHEO} allows accurate characterization of viscosity among representative shear values, in one single experiment.

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.

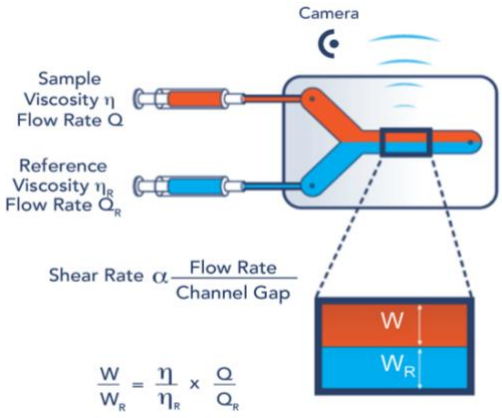
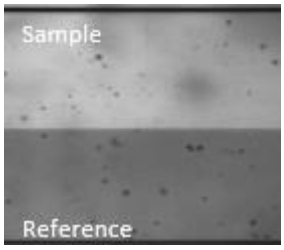


Figure 1: Fluidicam measuring principle

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



Method

A variety of commercialized eye drops formulations listed in the table (1) were analyzed with Fluidicam^{RHEO} over a large range of shear rates at 34°C, temperature of the corneal surface.

Shear rates from 150s^{-1} to 100 000s^{-1} were applied using two microfluidic chips with 150 µm and 50 µm channel gap.

Viscosity as a function of shear rates:

Rheological properties change drastically form sample to sample and over the shear rate probed. 2 sub-groups can be distinguished:

Four samples (Aqualarm, SyntaneUltra, Blink, Systane balance) showed shear thinning behaviors with significant viscosity variations.

The second group of samples: Unilarm, Novoptine, Ophtacalmfree present a Newtonian profile, with three overlapped flow curves around a viscosity value of η=0.8 mPa.s.

These classes reflect the specific uses the formulations are designed for, either topical eye treatement, drug delivery or cleaning.

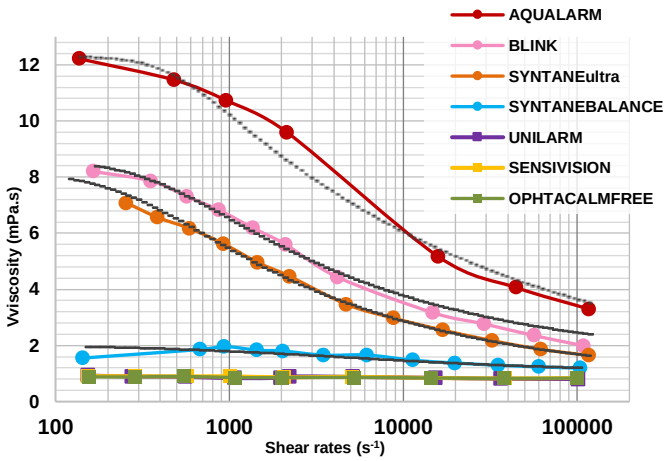


Figure 2: Viscosity profiles of several eye drops measured at 34°C.

In order to gain more insight into the relative behaviour, it is valuable to fit the data to rheological models. Table 1 gives results of these calculations following fits to Carreau Yasuda or Cross model.

By this method, zero shear η_0 and infinite shear viscosity η_∞ can be computed. The values give insight into liquid tendency to create discomfort, to give rise to blurred vision, to be washed out during tearing and to create resistance to blinking. They also help quantifying eye drop efficiency to maintain active substance in contact with the eye surface.

Product	η_0 (mPa.s)	η_∞ (mPa.s)	Model
Aqualarm	12.50	1.15	Carreau-Yasuda
Systaneultra	8.21	0.75	Carreau-Yasuda
Blink	8.18	0.76	Carreau-Yasuda
Systanebalance	2.04	1.07	Cross
Novoptine	0.84		Newtonian
Unilarm	0.85		Newtonian
Ophtalarmfree	0.84		Newtonian

Table 1: zero and infinite shear viscosity values determined from the model fits.

The unique features of FluidicamRHEO enable viscosity measurement over a wide range of shear rates (150 to 105 s-1) in less than 3 min analysis requiring only 2.5 mL per sample. It would have taken approximately 20min and 12mL per sample with conventional techniques, for an incomplete characterization. Analyzing viscosity values representative to the real application allow to tune the desired eye drop formulation precisely and find optimum formulation for desired goal: curing, cleaning, rinsing.

CONCLUSION

Fluidicam^{RHEO} allows accurate viscosity measurement at a range of shear rate representative of the stress applied during blinking. Thus, the instrument provides relevant information required to formulate eyedrop solutions with optimum physical properties. The use of microfluidic device allows to perform precise viscosity characterization with minimum sample requirements. The viscosity measurement is made efficient, as analyzing 7 samples, studied in this note, requires less than 30 minutes.