

Viscoelastic and sedimentation characterization of loteprednol etabonate ophthalmic gel, 0.5%

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SUMMARY

Purpose: An ideal suspension formulation for consistent ophthalmic dosing is one which requires no shaking to resuspend drug particles but is administered as a drop. Loteprednol etabonate ophthalmic gel, 0.5% (LE gel), was designed to exhibit non-settling characteristics and yet be expressed using a conventional dropper bottle and tip. This study examines the viscoelastic properties which are the basis for this unique behavior and demonstrates the non-sedimentation properties under accelerated conditions.

SEDIMENTATION

Table 1. Sedimentation behavior of loteprednol etabonate ophthalmic gel, 0.5% on stability.^[1]

Lot No. / Concentration	Storage Temperature	Sedimentation Conditions	Sample Location	% Label (LE)
151-1 (2 mg/mL)	25°C	Upright for 16 months	Top	104.0%
			Bottom	103.2%
151-2 (4 mg/mL)	25°C	Upright for 16 months	Top	103.8%
			Bottom	105.4%
	40°C	Upright for 16 months	Top	100.8%
			Bottom	100.4%
151-3 (6 mg/mL)	25°C	Upright for 16 months	Top	102.7%
			Bottom	104.4%
	40°C	Upright for 16 months	Top	107.6%
			Bottom	106.7%

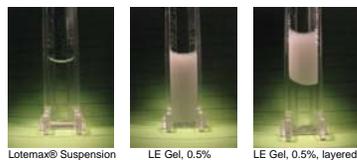
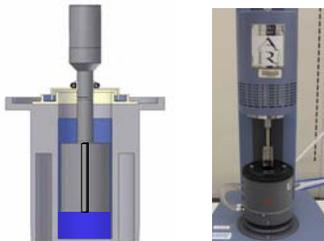


Figure 1. Sedimentation of Lotemax® and loteprednol etabonate ophthalmic gel, 0.5% formulations under 120 x gravity using the LUMiSizer® (LUM GmbH, Berlin, Germany) at 1000 rpm (116 – 145 x g) for 24 hours.^[2] The Lotemax® formulation settled in 20 minutes; the ophthalmic gel formulation does not settle. When the 0.5% gel formulation is placed above additional placebo vehicle, the drug substance does not migrate under centrifugation.

RHEOLOGY METHODS

Test procedures: A controlled stress rheometer (TA Instruments AR2000 with Firmware V7.20, New Castle, DE) was used for the measurement of the rheological properties of the formulation. The measurement system was a vane-rotor and cup which requires approximately 30 mL of sample for each measurement. Data was collected using Rheology Advantage software V5.7.13 (TA Instruments, New Castle, DE).

Data Analysis and Statistics: The raw data acquired by the rheometer was exported to an Excel file for plotting. No manipulation of the data was performed. The figures are plots of the raw data for a representative scan at 25 °C and do not include any averaging of data.



SHEAR-THINNING BEHAVIOR

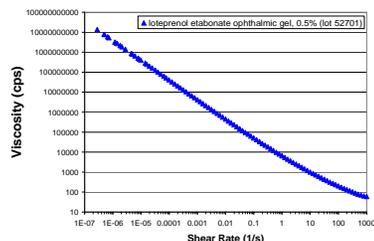


Figure 2. Shear-thinning behavior of loteprednol etabonate ophthalmic gel, 0.5% at 25 °C.^[3] The viscosity of the formulation is approximately linear on a log-log scale indicating the exponential relationship between the shear rate and the viscosity. **The viscosity ranges from 59 cps at a shear rate of 1000 s⁻¹ to 10 billion cps at the lowest shear rate measurable by the instrumentation.**

YIELD STRESS

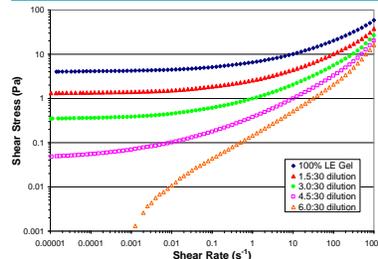


Figure 3. Rotational Rheology of loteprednol etabonate gel, 0.5% at 25 °C.^[3] Below the yield stress of the gel formulation, the viscosity cannot be measured and the shear rate goes to zero. The yield stress of this formulation is about 4 Pa. As the formulation is diluted with Hank's Balanced salt solution (to represent dilution on the eye with tear fluid) the yield stress is reduced and no yield stress is observed at dilutions of >15%.

DELIVERY BEHAVIOR

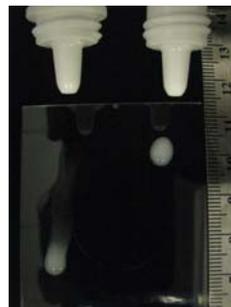


Figure 4. The low viscosity suspension (Lotemax®) and the non-settling LE Gel can both be delivered as an eyedrop to a glass plate (held at a 45 degree angle). This figure illustrates how, after delivery, the gel immediately regains the gel structure and remains where it was delivered. In contrast, the low viscosity suspension flows away from the administration point.

SOL-GEL TRANSITION

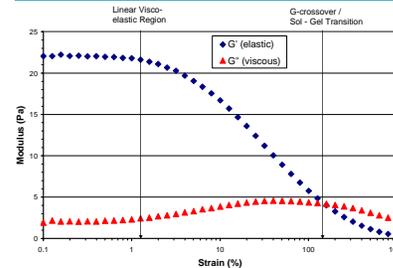


Figure 5. Oscillatory rheology of loteprednol etabonate ophthalmic gel, 0.5% at 25 °C using a 10 rad/s frequency.^[4] The G-crossover point for this formulation, which indicates the transition from gel-state to sol-state, occurs at 150% strain (7 Pa oscillatory stress).

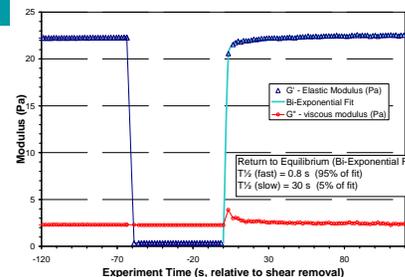


Figure 6. Thixotropy Evaluation of loteprednol etabonate ophthalmic gel, 0.5% at 25 °C using 10 rad/s frequency and 1% strain (0.2 Pa oscillatory stress).^[4] A high strain (1000% = 30 Pa oscillatory stress) was applied for 1 min to convert the formulation to a sol. After removal of the high shear, the gel structure is regained in <1 second.

RESULTS

At high shear stress (100 Pa) the LE Gel viscosity is about 60 cps (about 60X the viscosity of water). As shear stress decreases, viscosity increases, approaching infinity near the yield stress (about 4 Pa for this formulation). Below the yield stress, the formulation does not flow (shear rate goes to zero) and, therefore, sedimentation can not occur.

Oscillatory rheology studies confirm that the solid-fluid behavior of the product is dependent on shear stress. At low oscillatory stress the elastic modulus, G' greatly exceeds the viscous modulus, G''. As oscillatory stress increases, G' decreases and eventually crosses over G'' at ~7 Pa, demonstrating the transition from a gel to a sol state. The transition from sol at high shear back to gel at low shear occurs rapidly (within <1 sec).

The effect of these rheological properties is seen in sedimentation studies. Sedimentation analysis of LE gel and Lotemax® using the LUMiSizer dispersion analyzer shows that LE gel does not sediment over 24 hr at 1000 rpm. Lotemax® is a low viscosity ophthalmic suspension and sediments almost immediately. We have observed visually and confirmed by HPLC analysis that LE Gel does not sediment over 16 months.

CONCLUSIONS

The rheologic data indicate loteprednol etabonate ophthalmic gel, 0.5%, to be:

➤ a shear-thinning material with solid-like (gel) properties at low shear and fluid-like (sol) properties above the yield stress.

➤ This results in a gel at rest which allows no sedimentation of drug particles, and a fluid under applied shear stress such as occurs when the product is expressed through a dropper tip.

➤ Because the gel to fluid transition occurs quickly, drug particle sedimentation does not occur during the use of the product. By eliminating the need to shake the product, inconsistent patient compliance to shaking instructions will not affect the delivered dose of loteprednol etabonate ophthalmic gel, 0.5%.

REFERENCES

- Bausch and Lomb Research Notebook 2593-YH-278.
- Bausch and Lomb Research Notebook 3026-MJC-145.
- Bausch and Lomb Research Notebook 3026-MJC-140-144. A steady-state flow experiment was performed by scanning the shear rate from 1000 s⁻¹ to 0 s⁻¹ (log scale, 10 points/decade). Steady state equilibrium was defined as 3 consecutive measurements within the tolerance window of 2%. The sample period was 10 seconds and the maximum time/point was set to 5 minutes. The motor mode was set to 'auto'.
- Bausch and Lomb Research Notebook 3026-MJC-146.