



## Rheometers

# Rheological characterization of semi-solid pharmaceutical formulations

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## Keywords

Pharmaceuticals, creams, gels, FDA, EMA, NMPA, rheological characterization, flow behavior, oscillation tests, rotation tests, amplitude sweep, frequency sweep, viscoelasticity, yield stress, shear recovery, viscosity

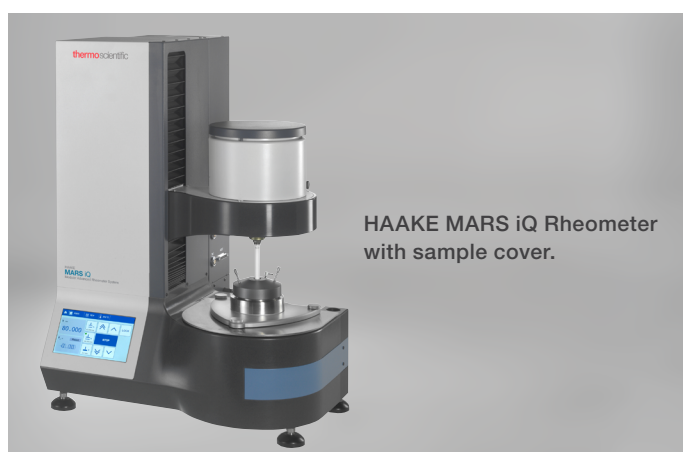
## Introduction

The safety and efficacy of drugs are of great importance worldwide. This applies to all types of drugs including topical formulations, which are semi-solid products that are administered to the skin or another external body surface to treat conditions at the specific tissue to which they are applied. There is a broad range of topical dosage forms available including pastes, ointments, gels, cremes, lotions, and others. When launching a new semi-solid generic drug, it must be demonstrated not only that the active ingredient (type and concentration) of the new product is the same as those of an already approved original product (Reference Listed Drug), but also that comparable physical and structural properties are present. This requires, among other things, a verification of the characterization of the microstructure and physical properties. To this end, various organizations and government agencies have issued corresponding recommendations (FDA, EMA, NMPA).<sup>1,2</sup> These recommendations also include comprehensive rheological characterization that goes far beyond simple single-point viscosity determinations. Regardless of the agency, these recommendations always include the determination of a complete flow curve over an extended shear rate range, the determination of the yield stress and of the viscoelastic properties. In addition, further rheological methods may also be helpful in demonstrating the comparability of two formulations; These include creep and recovery measurements as well as measurements on thixotropy. It is best to carry out all tests in a standardized manner so that user-independent results are obtained in consistent quality. In this report the comprehensive rheological characterization of two semi-solid pharmaceutical formulations is presented. The conducted tests include the recommended methods for the registration of new generic semi-solid drugs.

## Materials and methods

The samples measured for this report were each an over-the-counter pharmaceutical ointment or a pharmaceutical gel with the same active ingredient and the same active ingredient concentration (100 g of ointment or gel contained 0.15 g of heparin sodium).

All rheological measurements were performed with a Thermo Scientific™ HAAKE™ MARS™ iQ Air Rheometer with Peltier temperature control at a temperature of 20 °C. For the gel, a 35 mm 2° cone plate measuring geometry was used. For the ointment it was necessary to use a sand blasted parallel plate measuring geometry with a diameter of also 35 mm and a gap height of 0.5 mm to avoid wall slip.



For a comprehensive rheological characterization of the two semi-solid pharmaceutical formulations, the tests as described below were performed. This includes all rheological tests recommended by the various agencies for the registration of a new generic semi-solid pharmaceutical product.

To be able to carry out multiple tests with the same sample filling, it is advisable to start with the least destructive examination methods. However, this procedure must ensure that the sample does not dry out at the edge of the measuring geometry during the entire measurement process. For example, a sample cover with a solvent trap can be used for this purpose.

### Amplitude sweep

To determine the strength and mechanical stability of the samples, an amplitude sweep is performed. In this oscillation measurement, the shear stress amplitude  $\tau$  (Controlled Stress, CS mode) or the deformation amplitude  $\gamma$  (Controlled Deformation, CD mode) is gradually increased at a constant oscillation frequency  $f$ . The storage modulus  $G'$  (represents the elastic properties of the sample), the loss modulus  $G''$  (represents the viscous properties of the sample) or, alternatively, the complex modulus  $|G^*|$  (composed of viscous and elastic components) are evaluated. In the range of small shear stresses (or deformations),  $|G^*|$  is a measure of

the firmness or stiffness of the sample. The amplitude sweep is usually presented in a log-log plot. The increase in the oscillation amplitude initially leads to constant values of  $G'$ ,  $G''$  and  $|G^*|$  within the so-called linear-viscoelastic range (LVR). However, after exceeding the LVR, there is a considerable decrease in the mentioned quantities at higher amplitudes. When displayed as a function of shear stress, the width of the LVR can be used as a measure of the stability of the microstructure (network).

### Frequency sweep

From a frequency sweep within the LVR, the elastic and viscous properties of a sample can be investigated at different frequencies (or time scales) corresponding to certain process or application speeds, without changing or disturbing its structure. The frequency sweep can also be performed in CS or CD mode. In this test, the same quantities as in the amplitude sweep (e.g.,  $G'$ ,  $G''$ ) are recorded and evaluated. The frequency response provides information about the structural properties of the sample. If the modulus values (especially the storage modulus  $G'$ ) have only a low frequency dependence and are almost parallel to the x-axis, the sample has a highly interconnected network structure. If the frequency dependence is higher, the interactions are less interconnective, and an emulsion or dispersion-like structure is present. If  $G'$  and  $G''$  cross in the examined frequency range and  $G''$  is dominant at the lower frequencies, a viscoelastic liquid is present. This is often the case with concentrated polymer solutions without solids content. The frequency response is also recorded on a log-log scale.

### Creep and recovery measurement

A creep and recovery measurement consists of two consecutive parts. The first part is a creep test in which a constant shear stress is applied and held in a step-like manner. The sample reacts to this with a deformation, which is detected either directly or in the form of compliance  $J$  ( $J(t) = \gamma(t)/\tau$  [1/Pa]). This quasi-static method can be used not only to determine the viscoelastic behavior of a sample, but also its zero-shear viscosity  $\eta_0$ . The prerequisite for this is, on the one hand, the application of a shear stress within the linear viscoelastic range and, on the other hand, a sufficiently long measurement period during which a linearly increasing deformation occurs. For dispersed systems, such as suspensions and emulsions,  $\eta_0$  can serve as an indicator of long-term stability.

The second part of the measurement is the recovery. The applied stress is removed ( $\tau = 0$  Pa), and the sample can regenerate. In the case of a sample with partly elastic properties, an instantaneous recoil followed by a more gradual decrease in deformation relative to the value reached at the end of the creep phase is observed. The characteristic time from which the sample is back in an equilibrium state (no further decrease in deformation) is called the retardation time  $\lambda$ .

## Determination of yield stress

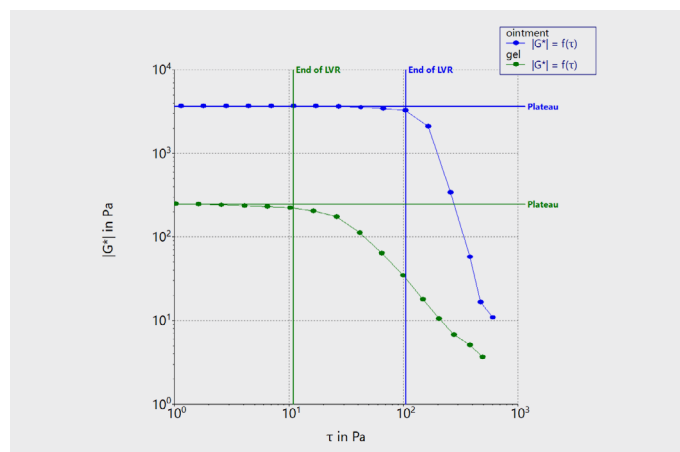
A yield stress is defined as the minimum shear stress required to overcome the elastic deformation of a sample and generate a steady flow. The yield stress plays a significant role in the shelf-life of a product, especially for dispersed systems. Yield stress values are very dependent on the test method and its measurement settings. Here, the yield stress was determined by means of a shear stress ramp (linear increase of shear stress over time). As the shear stress increases, there is initially only a weak and constant increase in deformation. As long as the applied shear stress is below the yield stress, this results in an almost exclusively elastic deformation, which is reflected in a slope of about 1 in a log-log plot of deformation against stress. Only when the applied shear stress approaches the yield stress, the sample structure breaks up and a significantly higher increase in the deformation occurs. With the so-called tangent method, the yield stress can be determined. Here, the yield stress corresponds to the stress value at the intersection of two tangents applied to the two linear regions of the deformation curve, before and after the significant change in slope. Here the yield stress is defined as the stress at the transition between the two regions. Alternatively, the yield stress can also be determined from the maximum of the viscosity curve recorded in the same test. In the case of a linearly increasing shear stress, the viscosity curve also initially increases until it reaches a maximum when leaving the purely elastic deformation. This maximum, or the associated shear stress value, is defined as the yield stress. Since a curve maximum can usually be identified more clearly than linear regions of a measurement curve, the viscosity method is often better suited for a direct and automatic evaluation of the measurement data. The yield stress determined by the tangent method is always higher than the yield stress determined from the viscosity maximum. To ensure comparability when examining different samples, it is therefore important to always hold on to the same evaluation method.

## Viscosity curve

Semi-solid pharmaceutical formulations are typically non-Newtonian materials with strong shear-thinning properties. Therefore, it is important to determine the viscosity over the widest possible shear rate range. The range of low shear rates is mainly used to estimate the shelf-life and the properties of the sample in the resting state. The high shear rates simulate the application load and are therefore used to determine the behavior when a product is spread and rubbed in. Usually, viscosity curves are measured with a stepwise increasing shear rate (controlled rate, CR mode) over several decades (e.g.,  $10^{-1}$  to  $10^3$  1/s, but this range may also be limited by the occurrence of wall slip effects in certain samples). The measuring time per step should be long enough that an equilibrium state is established. The rheometer software can detect when the equilibrium state has been reached and adjust the step duration accordingly. The data acquisition is carried out on a logarithmic scale, which means that the range of low shear rates is more in focus.

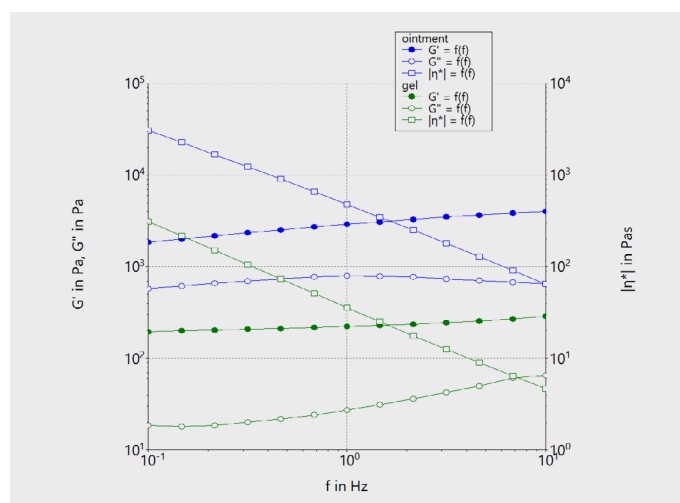
## Results and discussion

Figure 1 shows the results of the CS amplitude sweep at a frequency of  $f = 1$  Hz. Ointment and gel show viscoelastic behavior, with predominating elastic properties in the LVR ( $G' > G''$ ), not shown in Figure 1. The ointment has a firmer texture than the gel, since the plateau value of  $|G^*|$  is higher at low amplitudes (ointment: 3630 Pa, gel: 248 Pa). In addition, the microstructure in the ointment is more stable than the microstructure in the gel, as the LVR is larger (ointment: up to 105 Pa, gel: up to 11 Pa).



**Figure 1: Shear stress amplitude sweep with automatic determination of the end of the linear viscoelastic range ( $f = 1$  Hz).**

Figure 2 shows the frequency sweep for the ointment and gel. The CS mode was also selected for this test, and a shear stress amplitude of 1 Pa was applied, which is within the LVR for both samples. The complex viscosity  $|\eta^*|$  of the ointment and the gel decreases with increasing frequency in log-log plot.  $G'$  is higher than  $G''$  in the whole measuring range.  $G'$  of the ointment is more strongly frequency-dependent than  $G'$  of the gel, which is only very weakly frequency-dependent. It can be concluded that the ointment is more emulsion-like and that a higher interconnectivity is present in the gel. In the case of the ointment,  $G'$  and  $G''$  continue to converge in the range of small frequencies. This may be an indication of reduced long-term stability. In the case of the gel,  $G'$  is still a decade above  $G''$  even at the lowest frequency, which may indicate a higher long-term stability.



**Figure 2: Frequency sweep in Controlled Stress mode ( $\tau = 1$  Pa).**

Figure 3 shows the results for the creep-recovery tests performed with both samples. During the creep part, a constant shear stress of 10 Pa (ointment) / 1 Pa (gel) was applied for 300 s. This is still within the LVR for both samples. The deformation  $\gamma$  is shown as a function of time  $t$ . The zero-shear viscosity  $\eta_0$  was calculated using a shear rate that was extracted from the final slope of the deformation signal during the creep part. It is higher for the ointment ( $\eta_0 = 3.007 \cdot 10^5$  Pas) than for the gel ( $\eta_0 = 1.064 \cdot 10^5$  Pas). This result confirms the higher firmness of the ointment that was already observed with the oscillatory measurements.

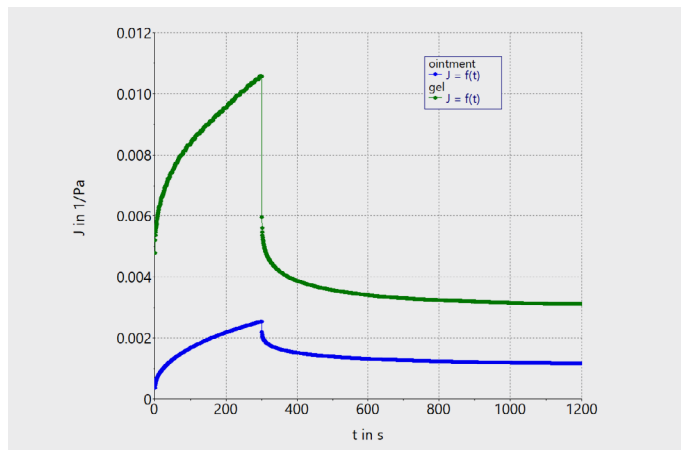


Figure 3: Creep and recovery measurement: creep test at  $\tau = 10$  Pa (ointment) / 1 Pa (gel) for 300 s and recovery at  $\tau = 0$  Pa for 900 s.

Figure 4 shows the shear stress ramp (linear increase over time but presented in a log-log plot) for determining the yield stress. When evaluating the yield stress using the tangent method, the yield stress of the ointment ( $\tau_0 = 152$  Pa) is higher than the yield stress of the gel ( $\tau_0 = 29$  Pa). However, the associated deformations are larger for the gel (20 %) than for the ointment (10 %). If the yield stress is evaluated as the shear stress value when the maximum of the viscosity curve is reached, the corresponding values are, as expected, lower than in the evaluation using the tangent method (ointment:  $\tau_0 = 99$  Pa, gel:  $\tau_0 = 14$  Pa).

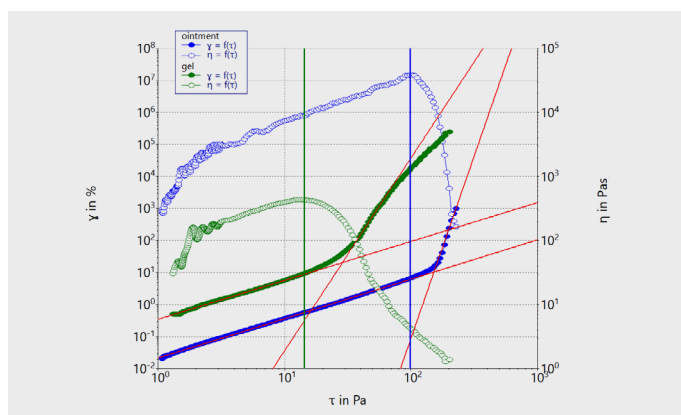


Figure 4: Shear stress ramp to determine the yield stress using the tangent method at  $\gamma(\tau)$  or the evaluation of the maximum of the viscosity curve  $\eta(\tau)$ .

Figure 5 shows the steady state viscosity curves for the two samples. Both formulations show shear-thinning behavior over the entire shear rate range, with the ointment having the higher viscosity overall. High viscosity at low shear rates is usually a desirable behavior as it extends shelf life and makes the product easier and more accurate to apply to specific skin areas. A low viscosity at higher shear rates, on the other hand, makes it easier for the consumer to spread and rub the product in and allows for faster absorption through the skin. At higher shear rates, the viscosity decreases, and the curves converge. Assuming, for example, a trituration velocity of 0.2 m/s and a thickness of 200  $\mu\text{m}$ , this results in a shear rate of  $103 \text{ s}^{-1}$ . Under these conditions, both products have a very similar viscosity ( $\eta_{\text{ointment}} = 5.0$  Pas,  $\eta_{\text{gel}} = 2$  Pas), resulting in a comparable resistance to spreading when applied to the skin.

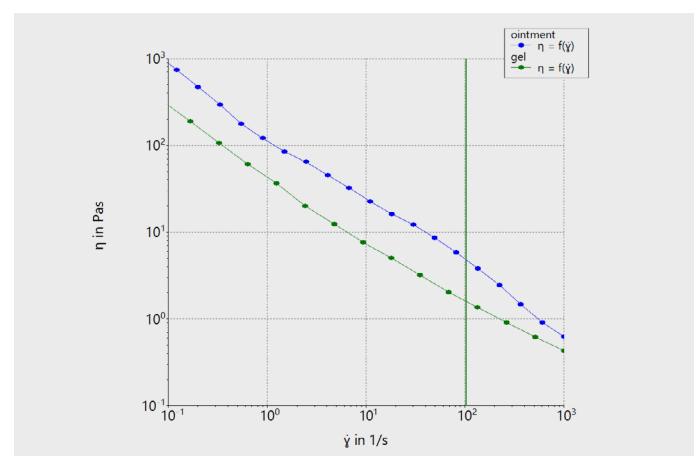


Figure 5: Viscosity curves including the determination of viscosity at  $\dot{\gamma} = 103 \text{ s}^{-1}$ . Both products have a very similar viscosity ( $\eta_{\text{ointment}} = 5.0$  Pas,  $\eta_{\text{gel}} = 2.0$  Pas).

## Conclusion

The presented measurement results show that a complete rheological characterization of semi-solid formulations can be carried out with a HAAKE MARS iQ Air Rheometer. The tests are in accordance with the recommendations of the EMA and FDA. The results revealed significant differences between the ointment and the gel. The ointment is more viscous, firmer, and stronger than the gel. All the parameters obtained for the ointment and the gel are compared in Table 1.

	Ointment	Gel
End LVE range $\tau$ (AS) / Pa	105	11
Plateau modulus $ G^* $ (AS) / Pa	3630	248
$\eta_0$ (creep recovery) / Pas	$3.007 \cdot 10^5$	$1.064 \cdot 10^5$
Yield point (determined from $\gamma(\tau)$ ) / Pa	152	29
Yield point (determined from $\eta(\tau)$ ) / Pa	99	14
$\eta$ ( $\dot{\gamma} = 103 \text{ 1/s}$ ) / Pas	5.0	1.7

Table 1: Comparison of the parameters obtained for the ointment and the gel.

## Literature

1. U.S. Food & Drug Administration, 'Draft Guidance on Acyclovir'. Silver Spring, MD, USA, 2014. Accessed: Jan. 25, 2023. [Online]. Available: [https://www.accessdata.fda.gov/drugsatfda\\_docs/psg/Acyclovir\\_topical%20cream\\_RLD%2021478\\_RV12-16.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/psg/Acyclovir_topical%20cream_RLD%2021478_RV12-16.pdf)
2. European Medicines Agency, 'Draft guideline on quality and equivalence of topical products'. EMA Amsterdam, The Netherlands, 2018. Accessed: Jan. 25, 2023. [Online]. Available: [https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-equivalence-topical-products\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-equivalence-topical-products_en.pdf)