APPLICATION **NOTE**

Fulfulling the FDA's Rheology Testing Requirements for Abbreviated New Drug Applications (ANDA) for Topical Creams

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Introduction

In the USA, when a manufacturer wants to create a generic version of an off patent drug, it needs to fulfill several requirements issued by the US Food and Drug Administration (FDA[1]). These include Q1, Q2 and Q3 steps, where Q1 shows that the new drug contains the same components as the Reference Listed Drug (RLD). Q2 shows that these components are in the same composition and quantities ±5% and Q3 shows that they have the same physical properties such as particle size, rheology, polymorphic form, etc. The particle size distribution and rheology need to approximately match those of the original innovator drug (OID) because the absorption time and characteristics of a topical cream are closely related to the products particle size and rheology, where smaller particles and lower viscosity materials allow faster absorption.

Rheological Characterization

The rheological characterization includes yield stress, viscosity flow curve and the viscoelastic properties (measurements in oscillation mode) to demonstrate that a new formulation is going to perform in approximately the same way as the OID.

Several examples of such investigations will be presented on the following pages.

Other tests may also be helpful but are not mandatory, such as the thermal stability (freeze-thaw, hot-cold climate) as shown in section C3, and the rebuild time after shearing. These tests can also be carried out with a NETZSCH Kinexus rheometer and sometimes even on just one sample loading.

[1] This application note should not be construed to represent US FDA's views or policies.

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A)1 Determining Yield Stress in Topical Creams

Introduction

The yield stress of a material is the stress required to start it flowing and relates to it's consistency while at rest, resistance to sedimentation in storage, as well as the pressure needed to pump or spread the material. On application of stress, a sample with a yield stress initially acts as an elastic solid. The instantaneous viscosity appears to increase, as the more stress that is applied to the sample, the more the sample resists flowing. When the yield stress is reached, the sample starts to flow and the measured viscosity falls rapidly. The peak of the viscosity curve therefore indicates the yield stress of the sample.

Interpretation

The conditions for the results displayed in Figure 1 are summarized in Table 1. Figure 1, sample A, showed a yield stress of 100 Pa and will therefore resist pumping or flow slightly more than sample B which showed a yield stress of 60 Pa.

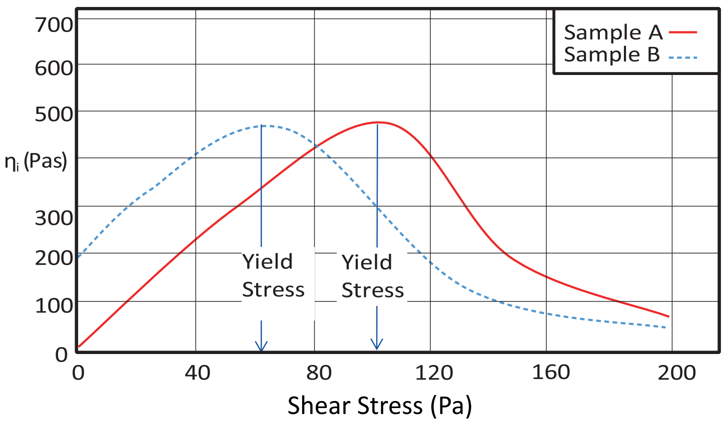
Table 1 Test conditions

Samples	Topical cream
Geometry	Cone or parallel plate system 40 mm with a solvent trap
Temperature	25°C
Sequence used: Toolkit_V003 Yield Stress (Stress Ramp)	1 - 200 Pa, up linear scaling
Ramp time	30 seconds

Topical Creams

are a mixture of oil and water for the base. They are created using two different processes but with the same ingredients. One way is called the oil-in-water emulsion, and the other is called the water-in-oil emulsion. They are used to apply steroids, moisturizers, and antibiotics, e.g., hydrocortisone, and can heal certain skin conditions, like eczema, psoriasis, and dermatitis. Furthermore, they can aid in eliminating yeast infections and replace hormones.

https://burtsrx.com/topical-creams-uses-treatments-dosage



1 Shear viscosity vs shear stress. Yield stress can be seen from the peak in the viscosity curve if the sample is significantly elastic.

Conclusion Yield Stress

The yield stress of the sample shows how it will behave while at rest. As these measurements are usually logarithmic in magnitude, It is important not to expect too close an agreement in the yield stress values of the new drug and the OID formulations.

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A2) Overcoming 'Slippage' When Characterizing Concentrated Suspensions

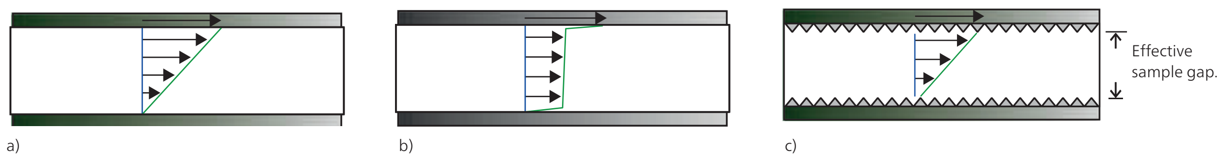
Introduction

A common problem when measuring concentrated suspensions, such as topical creams, as shown here, is that instead of shearing in the normal laminar way, the sample starts to slip. Slip can occur at both the upper and lower surfaces, as shown in Figure 2.

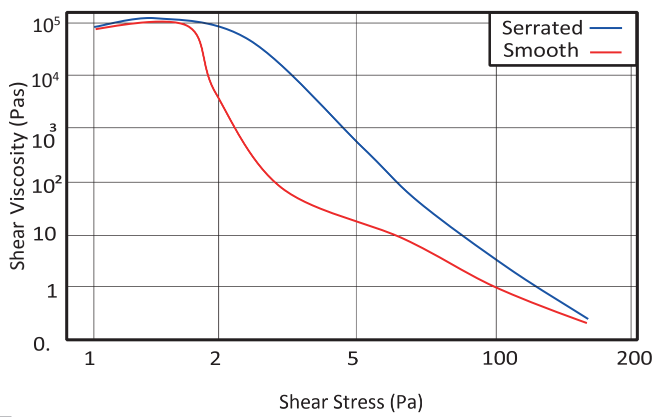
The slip is either due to the material undergoing a local stress induced phase change or the liquid phase separating from the bulk of the sample to form a slip plane. By using roughened or serrated measuring systems, we can reduce and often completely eliminate slip. The serrations allow the stress to be applied over a larger area of sample and provide voids to accommodate any separating liquids.

Interpretation

The flow properties of the sample are first measured using a regular parallel plate measuring system. The resulting curve, see Figure 3, shows a 'double knee' (two individual drops in the red viscosity curve), indicative of sample slippage. This is because the sample undergoes some separation under shear and the continuous phase is causing a lower viscosity region near the plate surfaces allowing it to slip rather than flow in a laminar way. Rerunning the sample with serrated plates, allows the separated continuous phase material to be accommodated in the grooves without allowing the sample to slip. The viscosity curve no longer contains the double knee and a more conventional shear thinning profile is produced.



2 Illustration of a) Normal laminar flow, b) Slip that can occur with smooth geometries and c) Elimination of slip with serrated plates



3 Shear viscosity versus shears stress graph showing a sample that is slipping (red) and the same sample tested with serrated plates (blue).

The stationary plane surface is now the peaks of the serrations for gap setting purposes as shown in figure c) above. If only the upper plate is serrated, then the slippage can easily continue at the lower plate instead, therefore both roughened or serrated upper and lower plates should be used.

Conclusion Slippage

Slippage can occur in concentrated particulate suspensions and materials susceptible to shear induced melting. When slip is suspected, a roughened or serrated measuring system should be used to test the sample. If the results from both the roughened and smooth plates were identical, no slippage would be occurring.

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B) Measuring the Viscosity Flow Characteristics

Introduction

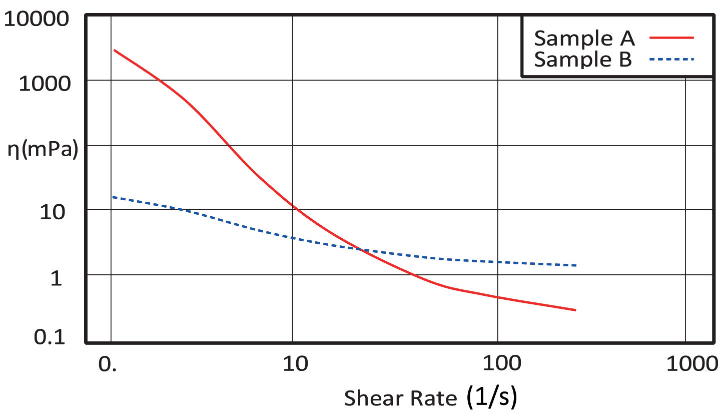
Topical creams are generally formulated to have a high viscosity at low shears and a low viscosity at high shears. A slightly higher viscosity at low shears gives the cream a good storage stability and is aesthetically pleasant, while, if the lotion has a low viscosity when at rest, it may be unstable with storage, giving separation. A low viscosity at high shear rates allows the product to be absorbed more quickly into the skin when rubbed whereas a product with a higher viscosity here may act as a barrier cream as it will leave a thicker coating.

Interpretation

The conditions of the results shown in Figure 4 are listed in Table 2. Figure 4 results show that sample A has a very high viscosity at low rates, indicating that it's a firm, well-bodied product. However, its viscosity dropped dramatically at higher rates to become a thin liquid. Sample A would therefore probably be absorbed into the skin easily as well, making it an ideal drug delivery vehicle cream.

Conclusion Viscosity Flow

Sample B's viscosity at low shear rates was insufficiently high to give it good storage stability properties. Similarly, its high shear viscosity may not be low enough to allow it to absorb into the skin well.



4 Shear viscosity vs shear rate (1/s)

Table 2 Test conditions

Geometry	Cone or parallel plate system 40 mm with a solvent trap
Gap	500 µm or cone gap
Temperature	27°C (~ body surface temperature)
Used sequence: Toolkit_V001 Shear Rate Table	0.1 - 200 1/s, up, logarithmic scaling, with Power law model fit

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C) Determining Visco-Elastic Properties

C1) Gelation Strength Determination

Introduction

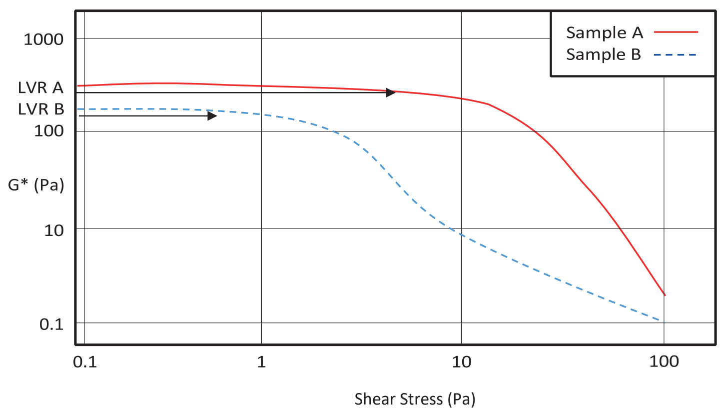
In this test, both samples are subjected to a sinusoidally increasing stress. While the sample's structure is maintained, the complex modulus G* – a measure of the stiffness, remains constant. However, when the cream's intermolecular forces are overcome by the oscillation stress, the sample breaks down and the modulus drops.

Interpretation

The test conditions for the results displayed in Figure 5 are given in Table 3. In Figure 5, topical cream sample B gave a much shorter linear viscoelastic region than sample A and will therefore break down much more easily with vibrations and small movements. The length of the linear viscoelastic region is also a good indication of the stability of the gel to resist sedimentation.

Table 3 Test conditions

Samples	Wound healing gels, topical gels, etc.
Geometry	Cone or parallel plate system 40 mm with a solvent trap
Temperature	25°C
Oscillation_0006_Amplitude sweep with LVR plus strain frequency seep with cross over.rseq	0.1 - 100 Pa, up, logarithmic scaling



5 Shear modulus (complex component) vs shear stress. The length of the linear visco-elastic region in stress gives a good indication of the stability of a dispersion.

Conclusion Gelation Strength

A relatively quick amplitude sweep experiment can indicate the strength of a gel and its modulus. This can therefore be used to optimize dosing of gelation agents and other components.

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C2) Characterizing Gels and Creams Using Oscillation Frequency Sweeps

Introduction

A frequency sweep in the sample's linear viscoelastic region (LVR) can be used to characterize the viscoelastic properties of a gel, cream or solution. Where a material has strong particle-particle or droplet-droplet repulsions, such as sample A, it will show a gel like structure, and the elastic modulus (G') is dominant over the viscous modulus (G"). This type of repulsively stable system is characterized by little change in the viscoelastic properties with frequency, as shown for sample A.

For materials that are stabilized by addition of a gel additive, it can be that too much additive causes the material to undergo syneresis, where the liquid phase is exuded from the bulk of the gel over time. In this case a slightly weaker structure is preferable.

Interpretation

The test conditions of the results shown in Figure 6 are summarized in Table 4. In a viscous material such as sample B, the viscous modulus (G", blue) is dominant over the elastic modulus (G', red), and both show frequency dependence. It is also possible to get a reversible network, which gives elastic properties at one extreme of frequency and viscous at the other. If a material is required to give good storage stability, it will generally need to be elastically dominated at low frequencies.

Table 4 Test conditions

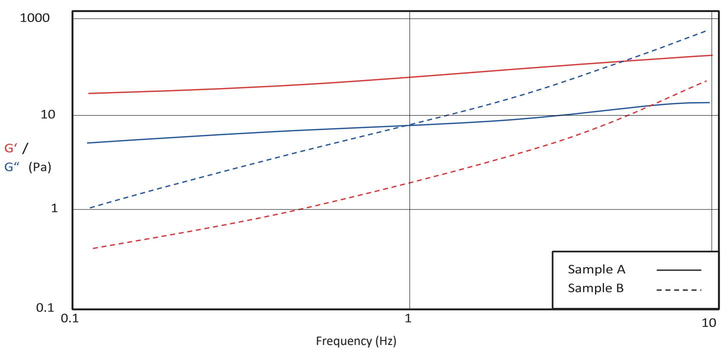
Samples	Gels or creams
Geometry	Cone or parallel plate system 40 mm with a solvent trap
Frequency sweep	10 - 0.1 Hz
Oscillation_0006 Amplitude sweep with LVR plus strain frequency sweep with cross over.rse	0.010 (or in LVR as found from amplitude sweep experiment before)

Syneresis

is the extraction or expulsion of a liquid from a gel without the gel structure collapsing as a result. This deswelling occurs during prolonged standing (aging) of gels, between whose phases (gel former and fluid) a high interfacial tension prevails. The densification of the individual phases reduces the interfacial area (example: the collection of whey on the surface of yogurt).

Conclusion Oscillation Frequency Sweep

A relatively quick frequency sweep experiment can indicate the strength of a gel, its modulus and its processing characteristics. This data can therefore be used to determine suitable gelation agents and optimize formulations.



6 Elastic (red) and viscous (blue) moduli vs frequency.

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C3) Characterizing Temperature Dependence

Introduction

The viscosity of topical creams can change significantly with temperature. Assessing the long-term stability of a pharmaceutical and personal care product by traditional methods can be tedious and time consuming, however, use of a rheometer makes this much simpler. When designing the test, we must account for the environmental conditions that the product is likely to encounter during its lifetime, i.e., possibly below freezing to as high as 50°C when being transported. Under such conditions, products may deteriorate and become visually unacceptable and/or less effective.

Interpretation

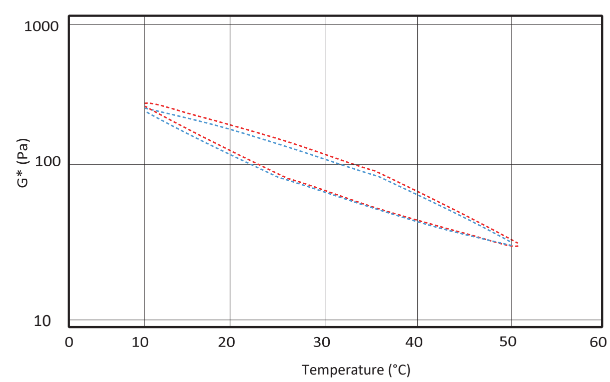
Table 5 shows the measurement conditions for the experiment results displayed in Figure 7. In order to determine the temperature stability of such products it is necessary to monitor the rheological behavior of the product through a number of temperature cycles. This is best assessed by monitoring the complex modulus (G*) as a function of temperature. A thermally stable system should show similar cycling behavior since the microstructure should not have changed. For thermally unstable samples, temperature cycling will cause the complex modulus to have a different temperature dependence on each thermal cycle.

Table 5 Test conditions

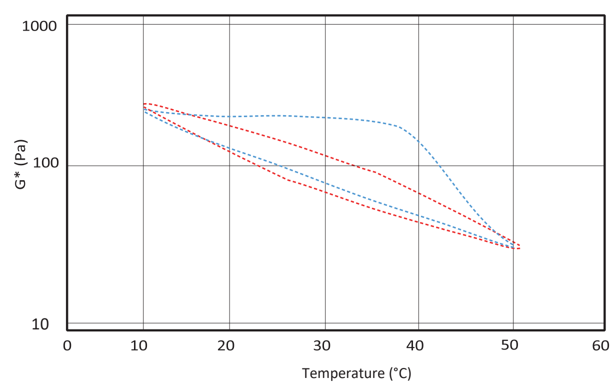
Samples	Topical creams and gel samples
Geometry	Cone or parallel plate system 40 mm with a solvent trap
Pre-test amplitude sweep	Strain 0.01% to 100%, up, logarithmic scaling, 7 points per decade Automatically stopping when the modulus drops by >1% for 5 points in a row. A strain in the LVR is then taken for the oscillation temperature ramp test.
Temperature	10 to 50°C (temperature ramp up and down) at 3°C/minute
Use sequence: rSolution_0018 Evaluating product thermal stability by temperature cycling.rseq	Strain: 0.005 (or as derived from amplitude sweep above), Frequency: 1 Hz, Delay time: 1 second, Wait time: 0 seconds

Conclusion Temperature Dependence

This test shows methodology and data for thermal stability for two topical cream formulations.



7 Topical cream sample A. First heating and cooling cycle (red) and second heating and cooling cycle (blue) Complex shear modulus (Pa) versus temperature (°C). The results show that the sample gave the same results ±5% in the second run as the first run, indicating that in this temperature range, the sample is very stable.



8 Topical cream sample B. First heating and cooling cycle (red) and second heating and cooling cycle (blue) Complex shear modulus (Pa) versus temperature (°C). The results show that this Sample B gave the quite different results in the second run than in the first run, indicating that the sample isn't temperature stable.

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Summary

A series of three tests on the Kinexus rotational rheometer can be used to automatically characterize all four of the FDA requirements for a topical cream sample. Furthermore, if the tests are conducted starting with the least destructive and finishing with the most destructive, they can all be done with one loading of a sample with no user involvement between the loading and clean-up steps. This would be first the Amplitude Sweep and Frequency Sweep Tests, followed by the Yield Stress and Viscometry Flow Curve tests. Using a Kinexus rheometer, you can use the following sequences:

1) Oscillation_0006 Amplitude sweep with LVR plus strain frequency sweep with cross over.rseq
2) Toolkit_V003 Yield Stress (Stress Ramp)
3) Toolkit_V001 Shear Rate Table

The oscillation Amplitude Sweep test in step 1 – C1) is designed to automatically stop when the strain just slightly exceeds the LVR of the sample and the modulus drops by >1% for 5 consecutive points. This prevents it from breaking the sample significantly and is certainly less strenuous to the material than reloading a new sample.

Final Thoughts

Sampling and Reproducibility

As with any testing, the results obtained are only as good as the sample used, and so sampling must be representative of the bulk of the test material. It is therefore preferable to sample at three or more places in the lot to ensure that the samples represent the whole. It is also normal to conduct a reproducibility test on at least one of the samples three (or more) times to establish the statistical accuracy of the technique and test results.

Setting of Quality Control Specification Parameters

While it's common for a QC test in some other analysis area to have a pass/fail specification of ±10% or so, it should be noted that with rheology most of the material properties have logarith-mic relationships. Therefore, it may be surprising to hear that rather than whole milk having a 20% higher viscosity than water (for instance) it is closer to 400% of the viscosity of water. Similarly, it is difficult to discern differences between two creams manually if a cream is less than twice the viscosity of another. Therefore it should be strongly discouraged to set an arbitrarily tight specifications for quality control.

The NETZSCH Kinexus rheometer may be used to accurately characterize properties of topical creams with accuracy, reproducibility and minimal user involvement. This robust technique can therefore be used to optimize current formulations and create new products in accordance with the FDA regulations for ANDA submissions.

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