

The rheology of pharmaceutical and cosmetic semisolids

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MANY PHARMACEUTICAL and cosmetic processes such as new ingredient selections, formulation preparations, material packaging, and shelf storage are associated with a complex flow of materials. The application and acceptance of pharmaceuticals and cosmetics are also dependent on the flow properties of the final product. Therefore, rheological measurements, an important route to revealing the flow and deformation behaviors of materials, cannot only improve efficiency in processing but can also help formulators and end users find pharmaceutical and cosmetic products that are optimal for their individual needs. In general, rheological measurements on pharmaceutical and cosmetic materials are performed for the following reasons: 1) to understand the fundamental nature of a system; 2) for quality control of raw materials, final products, and manufacturing processes such as mixing, pumping, packaging, and filling; and 3) to study the effect of different parameters such as formulation, storage time, and temperature on the quality and acceptance of a final product.

Pharmaceutical and cosmetic materials range in consistency from fluid to solid. Semisolid products are the most difficult materials to characterize rheologically because they combine both liquid and solid properties within the same material. The majority of pharmaceutical materials are ointments, creams, pastes, and gels—all semisolids. Few rheological publications have addressed the dominant viscoelastic nature of a semisolid material in a detailed sense. To understand these complex flows, commercial medical creams, shampoos, and a children's cough syrup were tested using the STRESSTECH rheometer (ATS RheoSystems, Bordentown, NJ, Figure 1). In this article, basic rheological terms and an interpretation on the relationship between rheological response and material structure will be presented.

Steady shear flow curves

A flow curve, viscosity (η) versus shear rate ($\dot{\gamma}$), across a wide range of shear rates can provide important information about storage stability; optimal conditions for mixing, pumping, and transferring; and end-user applications. It also provides important information regarding the ways in which the structure changes to comply with the applied shear in different conditions, such as storage, processing, and application. The rheological behavior of the material may change as a result of these forces. If the shear rate changes during an application, the internal structure of the sample will change and the change in stress or viscosity can then be seen.

Typical flow curves are shown in Figure 2. Newtonian flow (A curve) is the simplest type, displaying a shear-independent viscosity while the material is sheared. Water and some low-molecular-weight mineral oils are typical examples of Newtonian fluids. Pseudo-



Figure 1 The STRESSTECH rheometer.

plastic or shear thinning fluids (B curve) display viscosity reduction while the shear rate increases. Typical examples of these are colloidal systems. The colloidal structure breaks down while shear rate increases, displaying reduced viscosity. Dilatant or shear thickening flow (C curve), in which viscosity increases with shear rate, is seldom encountered in the pharmaceutical and cosmetics fields.

Thixotropy

Time-dependent flow measures the increase or decrease in viscosity with time, while a constant shear is applied. The flow is called thixotropic if viscosity decreases with time, or rheopetic if it increases. The most desirable type of flow behavior encountered in pharmaceutical or cosmetic products is thixotropic flow.

Thixotropic behavior describes a degradation of the structure during the loaded phase; thus, a reduction in viscosity with time occurs when shear is applied. During the relieved phase, the original structure is recoverable. The extent of structural recovery is dependent on the time allowed for the recovery. Therefore, a thixotropic material will have a shear thinning behavior when a gradually increasing shear is applied. This is because the orientation of the structure's molecules or particles will change to align with the flow direction. However, its original orientation can be restored over a period of time after the external force is removed. There is a delay in time for the structure to recover completely. A thixotropic loop, the region between curves for the increasing and decreasing shear rate ramps, is shown in Figure 3 for a medical cream. A thixotropic loop represents the deformation history of a material and provides qualitative information about its time dependence. The loop area indicates how fast the sample structure will recover after the load is removed. The loop area is dependent on the sample nature and on the length of time that passes after the load is removed. This test is related to the kinetics of structural change as encountered in aggregated colloidal dispersions. If the structures in the material are broken apart by shearing and cannot reform completely during the ramp-down period, a thixotropic loop can be seen. In other words, viscosity (or stress) during the ramp-down period will be lower than that in the ramp-up shearing period.

In general, shear thinning measures how easily the structure can be broken and the loop area indicates the recovery extent of that broken structure during the experimental time. The information obtained from this type of experiment is valuable in many situations. For example, a suspension formulation must have proper

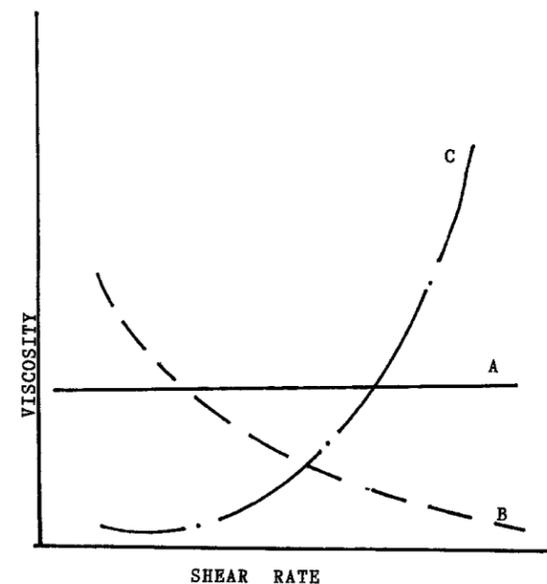


Figure 2 Typical flow curves.

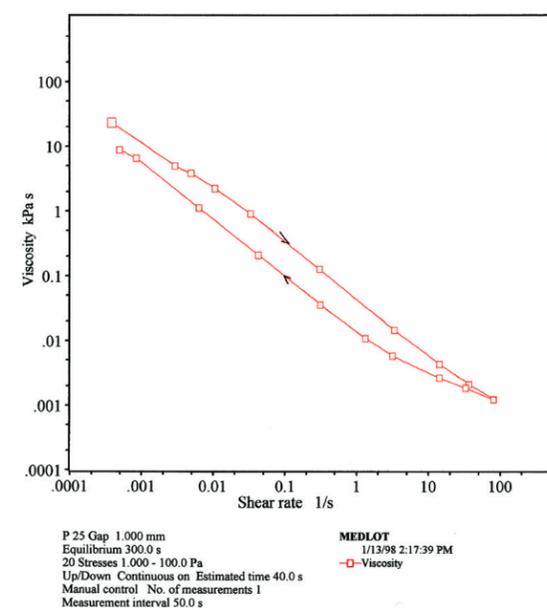


Figure 3 Thixotropic loop of a medical cream.

fluidity during application and preparation; a certain consistency is required so that the particles can be dispersed effectively in the container or so that film can be formed uniformly after application. Therefore, it is important for the disturbed structures to rebuild at a suitable rate upon resting in order to have proper film formation and sedimentation resistance.

Yield stress phenomena

The yield stress measurement is crucial for pharmaceutical products in determining not only their shelf life but also ease of application for the end user.

Yield stress (τ_y) is defined as the minimum shear stress required to initiate flow. Yield stress can be measured using a stress ramp experiment. The yield stress of a commercial children's cough syrup was measured in this way (Figure 4). Yield stress can also be defined as the stress below which a material will not exhibit a fluidlike behavior. This means that subjecting a material to stresses less than the yield stress will lead to a nonpermanent deformation or a slow creeping motion over the time scale of the experiment. The exact yield stress for this material is 1.262 Pa. This measurement was ob-

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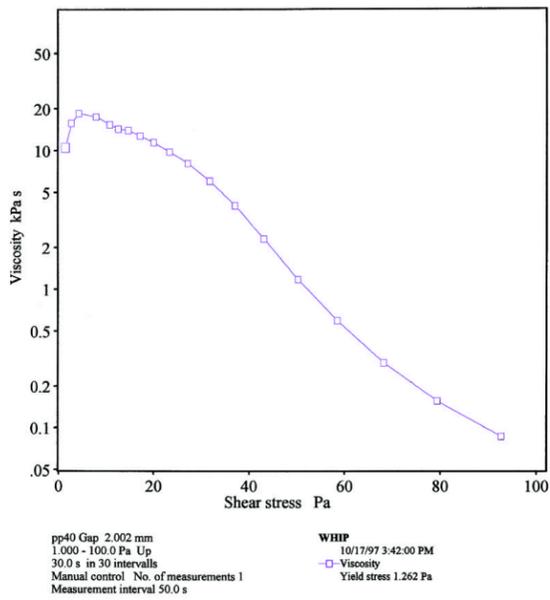


Figure 4 The yield stress measurement for children's cough syrup.

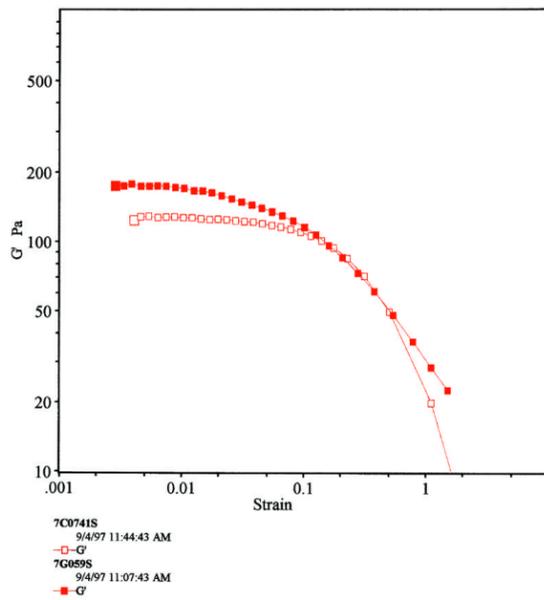


Figure 5 The strain sweep for two creams; closed symbol, cream A; open symbol, cream B.

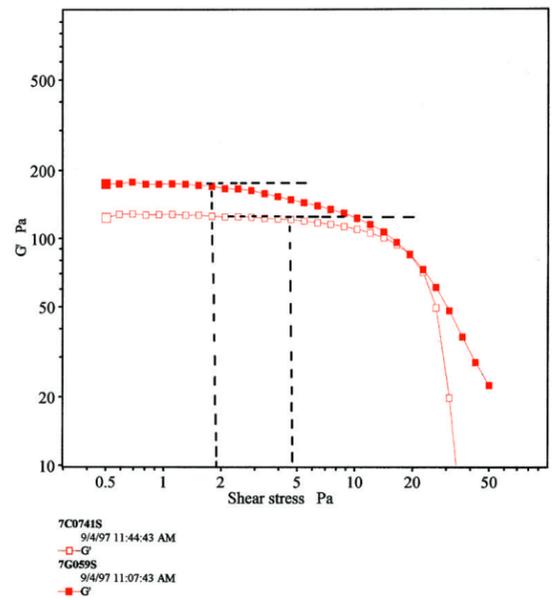


Figure 6 The strain sweep for two creams; closed symbol, cream A; open symbol, cream B.

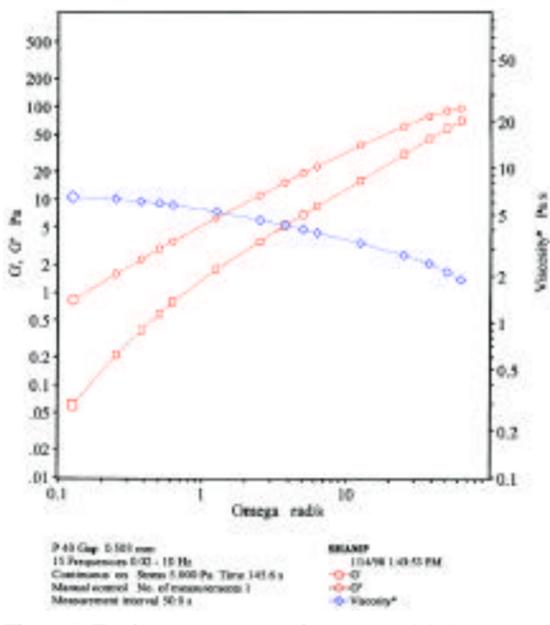


Figure 7 The frequency sweep of a commercial shampoo.

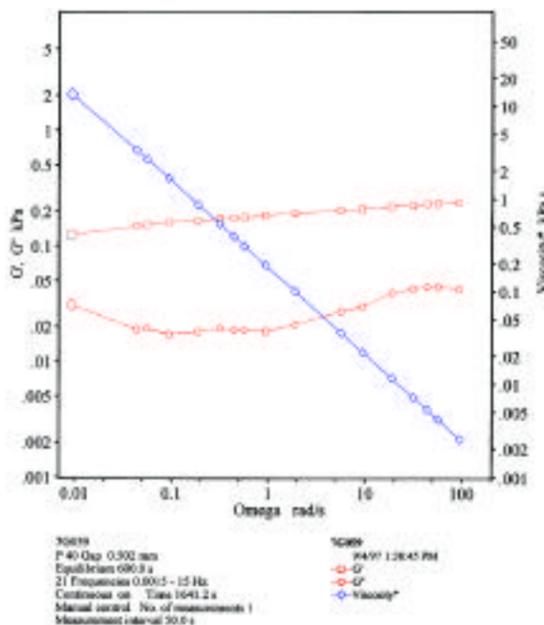


Figure 8 The frequency sweep of a medical cream.

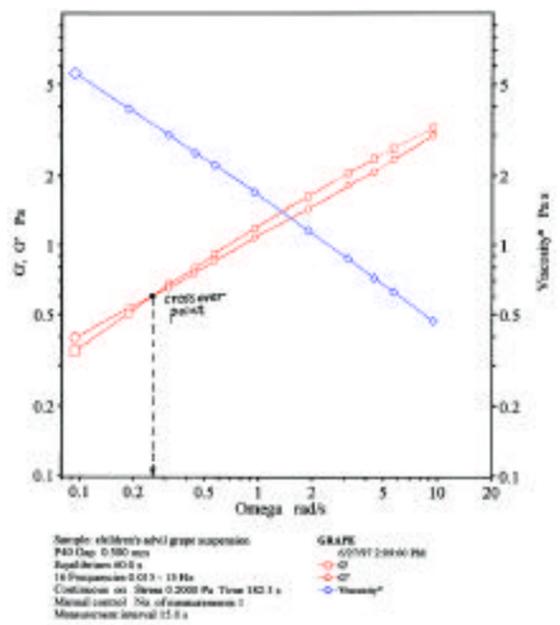


Figure 9 The frequency sweep of the children's cough syrup.

tained from Analyse (**Rheologica**, Lund, Sweden) analysis software. The concept of yield stress, the minimum shear stresses required to cause flow, is only an approximation since this stress value is experimental time dependent. Almost all substances will eventually flow if the time scale for imposing a shear stress (however small) is long enough. However, in general, the higher the static yield value, the more readily a medium will maintain particles in suspension with minimal sedimentation. Thus, the magnitude of the static yield value may be used as one of the criteria for controlling sedimentation during storage and the ease of using or processing a product.

Dynamic oscillatory experiments

Although rotational experiments provide information concerning the flow properties of a system such as yield value, thixotropy, and steady flow curve, they are only a part of the complete rheological characterization of a system. Dynamic oscillation testing is a much more powerful tool to reveal the secrets of the microscopic structures of a viscoelastic material; therefore, it is more attractive and useful from a practical point of view.

Strain sweep is utilized to determine the linear viscoelastic region of a material system for performing a subsequent dynamic test. Figure 5 shows the results of strain sweep on two medical emulsion creams. The maximum strain up to which G' remains constant is called the critical strain. The critical strain, which indi-

cates the minimum energy needed to disrupt the structure, is dependent on the dispersion quality. Therefore, if the difference in the critical strain of two creams is known, the different extent of dispersion of particles or ingredients can be measured. The higher the critical strain, the better the system is dispersed. The critical point can also be called dynamic yield stress if a G' versus stress curve is presented. By extrapolating the linear portion, the shear stresses of the same two creams can be read from the separation point, as shown in Figure 6. The presence of a dynamic yield stress of suitable magnitude may be used as a criterion to determine whether, for example, a vehicle will maintain suitable semisolid properties under shear. A semisolid has a weak structure, and does not recover this structure after a brief resting period; therefore, a dynamic yield value should be used instead of static yield stress to assess film formation and sag resistance of a layer of material applied on a surface.

Oscillatory shear measurements can be explained from an instrumentation point of view: A sinusoidal shear stress (or strain) smaller than the critical value is imposed on a fluid, and the amplitude of the resulting strain (or stress) and the phase angle between the imposed stress and the output strain are measured. Experimentally, this can be accomplished by commanding a small sinusoidal displacement or strain (within the linear viscoelastic range) on the emulsion under a controlled frequency or temperature sweep. In general, the material can respond to this type of deformation through two mechanisms: elastic energy storage and viscous energy

dissipation. Quantitatively, these responses can be represented as storage modulus (G'), energy stored per unit volume, and loss modulus (G''), energy dissipated per unit deformation rate per unit volume. Storage modulus (G') is proportional to the extent of the elastic component (contributed by crosslinking, entanglement, and/or aggregation) of the system, and loss modulus (G'') is proportional to the extent of the viscous component (contributed by the liquidlike portion) of the system. Typically, the strength of interaction of internal structure in an emulsion is measured by the magnitude of the ratio $G''/G' = \tan \delta$ which is called the damping factor (δ is phase angle). The smaller the $\tan \delta$ (or the greater G'), the stronger the interaction.

Pharmaceutical semisolid materials may be classified as either viscoelastic liquids or viscoelastic solids. Frequency sweep is a useful tool when characterizing the microstructure of a viscoelastic material. Applying a constant strain below the critical value (as seen in Figure 4) and a frequency ramp reveals the microstructures of a material through the response of that material to different shear rates. In suspensions or emulsion materials at low frequency, elastic stress relaxes easily and viscous stress then dominates to exhibit a higher loss modulus (G'') than the storage modulus (G'), as shown in Figure 7 for a commercial shampoo. Since gels and creams cannot relax quickly and are highly elastic at the same frequency range, the storage modulus (G') is higher than the loss modulus (G''), as shown in Figure 8 for the gellike medical cream. A semidilute

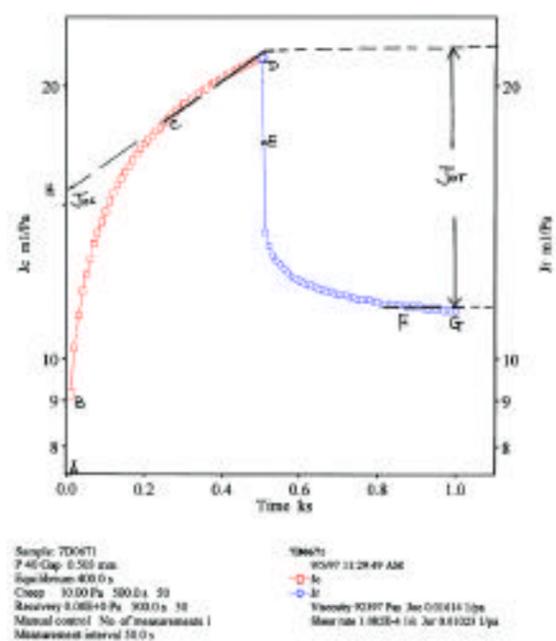


Figure 10 The creep/recovery of a medical cream.

solution, such as the children's cough syrup, exhibits a $G' > G''$ scenario at low frequencies and a $G'' > G'$ scenario at high frequencies, as shown in Figure 9. The frequency at crossover point is a function of the relaxation time of the internal structures of the syrup.

Creep/recovery

Because of the relatively low consistency of many pharmaceutical formulations, it is often difficult to apply small enough stresses to remain in the linear viscoelastic region for an oscillation test. The creep/recovery test is therefore an alternative for obtaining the relaxation time and viscoelastic properties of a material. A constant stress below yield stress is applied to the material and the deformation is monitored with time. Compliance (J) is defined as the reciprocal of modulus, $J = 1/G = \gamma/\tau$, where G is modulus and γ is strain. The value and shape of the creep compliance curve are fundamentally important. Subjected to a constant stress, the strain of an ideal elastic material would be constant and the material would return to the original shape when the stress was removed. In contrast, an ideal viscous material would show a steady flow, producing a linear response to stress with the inability to recover any of the imposed deformation. Viscoelastic materials (e.g., semisolid pharmaceutical products) will exhibit a nonlinear response to strain and, due to their ability to partially recover structure by storing energy, will show a final deformation less than the initial deformation. Figure 10, which illustrates typical creep behavior of a viscoelastic material, displays a creep/recovery test result for a medical cream with a STRESSTECH rheometer.

In general, the creep compliance-time curve can be subdivided into three regions (see Figure 9). Curve A-B is the region of instantaneous compliance, where bonds between the primary structural units stretch elastically. Curve BC is the time-dependent retarded elastic region with compliance J_R . Curve CD is the linear region with steady-state compliance J . Some bonds rupture; therefore, the time required for them to reform is in excess of the test period. Thus, the released entities can flow past each other. Upon removal of the stress, a recovery occurs, and this is represented by DF. There is an instantaneous elastic recovery (DE) with the same magnitude as AB, followed by a retarded elastic recovery equivalent to the retarded region of the creep curve. Some bonds were irreversibly broken in the creep region, and the original structure is never recovered completely. However, the degree of recovery after creep can be represented by the recoverable compliance J_{or} , which is equivalent to AH (J_{oc}).

Results using a STRESSTECH rheometer for creep/recovery measurements at different stresses (40, 100, and 120 Pa) on a medical emulsion cream are shown in Figure 11. In this experiment, the compliance is dependent on the applied stress. At stresses higher than the yield stress (108.7 Pa), the compliance J_c increases with time in a nonlinear manner. The creep curves with an upward curvature, indicating that the structure breaks down quickly under the influence of the shear stress and a viscosity reduction should occur.

Rheometer system setup

STRESSTECH is a modular product with a wide range of measuring systems and accessories. Measuring systems are available as concentric cylinders, cone/plate, parallel plate, double concentric cylinders, closed/pressure cells, and dynamic mechanical analysis (DMA) for torsion and tension with autotension function. Special measuring systems for low volume, high shear rates, and high sensitivity are also available. The measuring geometries can be made in stainless steel, titanium, polycarbonate, or any user-defined material. The instrument is supplied standard with a patented Differential Pressure Quantitative Normal Force Sensor for reproducible sample loading history, thermal expansion measurements, and quantitative normal stress measurements. The diffusion air bearing has low inertia with high axial and radial mechanical stiffness. STRESSTECH HR, a high-resolution version of the instrument, allows measurements at microradian displacement and extremely low applied torques.

Electronic unit

Instrument electronics are contained within the mechanical unit and the instrument is built around a dedicated, high-speed, 32-bit CPU. This consolidation enhances performance and versatility due to electrical connections on the motherboard bus rather than through cables to a separate electronics cabinet. In addition, valuable bench space is kept to a minimum. The motor control is based on digital rather than analog drive technology. The unit incorporates a built-in diagnostic system and quick diagnostic service port for service engineers. Also included is a modem port for remote control operation and fault diagnostics for service. The electronics power supply is designed to operate on a line voltage of 180–260 V or 90–140 V and an operating frequency of 47–63 Hz.

Software package presentation

The multitasking standard software is a true Microsoft® (Bellevue, WA) Windows™-based rheological package, which has many advantages to the user. The computer is not dedicated to simply running the instrument and is available for other uses when making measurements. The computer can be used for printing previous results, writing a report, or performing measurements with another instrument. The software runs under both Windows 3.1 and Windows 95.

The standard package offers measuring programs designed to be user friendly with few subdialogue levels and a generally recognizable design. Experiment method and analysis are available in the following test modes: viscometry, yield stress, constant rate, oscillation, oscillation stress sweep, oscillation strain control, creep/recovery, compare, analyze, time-temperature superposition, and spectrum transformation.

The software includes possibilities to link user-designed methods including instrument setup and zero gapping using the Windows Recorder icon and Project Software (ATS RheoSystems). The dialogue windows have many storable, editable functions for unique testing requirements, and can be reset to default values using default buttons. An example is the Oscillation Fre-

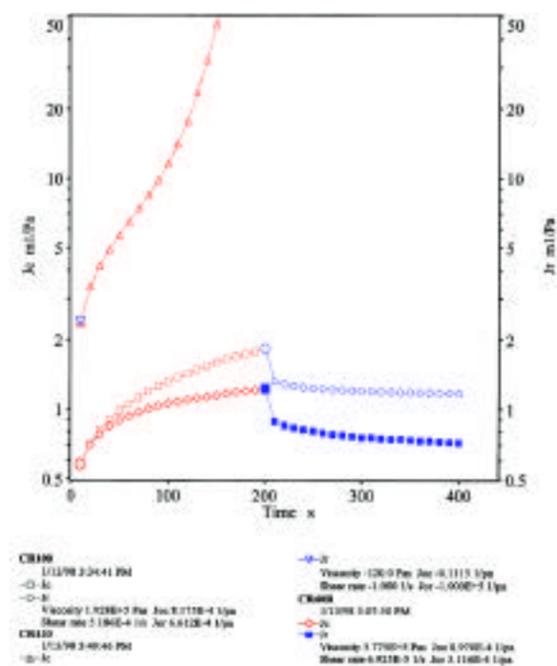


Figure 11 The effect of stress on the creep/recovery response of an emulsion cream.

quency Step measuring program, in which stresses, delay times, integration periods, and sample sizes can be set individually for all frequencies. Another example is the zooming function, which is present in both the Viscometry Stress Step and Oscillation Frequency Step, allowing any number of steps and increments to be selected. The instrument also performs controlled strain and constant shear rate measurements, and is provided with automatic gap adjustments and compensation using a Normal Force Sensor. The system enhances measurement reproducibility since the sample loading history is reproduced identically each time, using a constant loading force.

The rheometer is operated with a separate power supply unit that is intended to be left on continuously. This reduces start-up times and makes it possible for the instrument processor to maintain values as gap and other user-defined settings.

Temperature control cells are available that use circulating fluid, resistive heating, adiabatic cooling, and cryogenic cooling; the range -180 °C to 500 °C is covered. All measuring geometries are supported (cone/plate/parallel plate, concentric cylinder, and solid in torsion). A closed cell for operation at elevated with full oscillatory capabilities is available.

The rheometer is produced according to ISO 9001 regulations and is tested to operate according to the electromagnetic compatibility rules within the European Community. The instrument is tested to be labeled with the CE mark. The VISCOTECH rheometer (ATS RheoSystems) features full upgradeability capability to the STRESSTECH research-grade rheometer, as the user's needs and requirements change. The application specific SPECTECH DSR (dynamic shear rheometer) is designed for asphalt tests according to AASHTO TP5.

Conclusion

This article has reviewed all the important rheological characterizations with all the genuine results from a STRESSTECH rheometer, and the detailed interpretation to correlate the rheological responses with the physicochemical properties of different commercial semisolid products. The rheological characterizations for pharmaceutical and cosmetic semisolids provide important information for engineers to facilitate their daily production and processing for their products. Today, most formulators also count on rheological results to develop customer-favored products for surviving in the competitive market. Therefore, a reliable rheometer and understanding rheology are becoming necessary for pharmaceuticals and cosmetics manufacturers. 