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▲⟨1912⟩ MEASUREMENT OF HARDNESS OF SEMISOLIDS

BACKGROUND

Semisolids are viscoelastic materials that exhibit a yield stress. The yield stress for a raw material or dosage form is the applied stress at which a change in the viscoelastic properties of a semisolid is observed: below the yield stress the material response is dominated by elastic deformation, whereas above the yield stress the material response is dominated by viscous flow. Often, the yield stress is identified as the applied stress below which a material appears to not flow (where the shear rate ≈ zero). This observation can be dependent on the time scale of the measurement, the scan rate used to locate the change in the behavior, and the direction from which the transition is approached (i.e., sample history). Most measurement techniques identify the yield stress by locating the onset of viscous flow; however, penetrometry looks for the yield stress where the semisolid stops yielding. Although the yield stress for various materials is expected to correlate when measured with different techniques, the values should not be considered to be independent of the method. Therefore, it is recommended that measurements of yield stress be reported as apparent yield stress in order to emphasize that the quantitative result is dependent on the measurement method used. Yield stress is reported with units of shear stress [Pascals (Pa)].

Characterizing and monitoring the viscoelastic properties of semisolids is not straightforward because the properties can be dominated by either solid-like or liquid-like behavior depending on how much stress is applied to the material. If the quality of a raw material or dosage form is primarily dependent on the behavior under high-shear conditions, then the viscosity may be an appropriate parameter to monitor. In this case, efforts should be made to avoid wall slip and make measurements where the applied shear stress is much greater than the apparent yield stress. However, if the properties of the raw material or dosage form are critical to quality at low shear or at rest (e.g., uniformity of an ointment suspension or residence time at site of application), then the measurement of the apparent yield stress using one or more of the methods described below may be required.

A brief summary of the mathematical models used to quantify the viscoelastic properties of semisolids is presented below, followed by a summary of the most common experimental methods for assessing the viscoelastic properties and determining the apparent yield stress for semisolids.

Hooke's Law, Newton's Law, and Viscoelastic Models

Elastic materials are often modeled as a spring. Elastic materials respond to applied shear stress according to Hooke's Law,

$$\sigma = G\gamma \tag{1}$$

where σ is the applied shear stress (= applied force/surface area, in units of pascals, Pa), G is the shear modulus that represents the rigidity of a material, and γ is the strain or shear deformation (= displacement/distance, unitless).

Viscous materials are often modeled as a dashpot (a fluid-filled piston). Viscous materials respond to applied shear stress according to Newton's Law,

$$\sigma = \eta\dot{\gamma} \tag{2}$$

where σ is the applied shear stress (= applied force/surface area, in units of pascals, Pa), η is the viscosity that represents the resistance of the material to flow, and $\dot{\gamma}$ is the shear rate (= velocity/distance, in units of s^{-1}).

Semisolid raw materials and dosage forms will have both viscous and elastic properties and, hence, are categorized as viscoelastics. There are primarily two simple models for combining the viscous and elastic responses of viscoelastic materials: the Maxwell model and the Kelvin–Voigt model.

The Maxwell model for viscoelastics assumes that the viscous and elastic response is represented by a dashpot and a spring, respectively, in series. The total strain (total deformation) of the viscoelastic is the sum of the viscous (v) and elastic deformation (e), hence,

$$\gamma = \gamma_v + \gamma_e, \ \dot{\gamma} = \dot{\gamma}_v + \dot{\gamma}_e \tag{3}$$

and the same shear stress acts on both components,

$$\sigma = \sigma_v = \sigma_e \tag{4}$$

Therefore, the Maxwell model for a viscoelastic material states that

$$\sigma = \eta\dot{\gamma} - \frac{\eta\dot{\sigma}}{G} \tag{5}$$

The Kelvin–Voigt model for viscoelastics assumes that the viscous and elastic response is modeled by a spring and a dashpot in parallel. The total shear stress applied to the viscoelastic is the sum of the viscous and elastic shear stresses,

$$\sigma = \sigma_v + \sigma_e \tag{6}$$

and the total strain (total deformation) is the same for both the viscous and elastic components,

$$\gamma = \gamma_v = \gamma_e \tag{7}$$

Therefore, the Kelvin–Voigt model for a viscoelastic material states that

$$\sigma = \eta\dot{\gamma} + G\gamma \tag{8}$$

In both the Maxwell and the Kelvin–Voigt equations, the first variable represents the Newtonian response of the viscoelastic. As the shear rate approaches zero, the first variable also approaches zero and the material response becomes dominated by the elastic component (second variable). It is this elastic component of the viscoelastic response that results in an apparent yield stress for viscoelastic semisolids.

Herschel–Bulkley Equation

The Herschel–Bulkley equation is suitable for parameterizing the observed shear-stress versus shear-rate information for a wide range of viscoelastic materials including semisolids exhibiting an apparent yield stress. The Herschel–Bulkley equation is:

$$\sigma = \kappa\dot{\gamma}^n + \sigma_0 \tag{9}$$

where, σ is the applied shear stress (= applied force/surface area), $\dot{\gamma}$ is the observed shear rate (= velocity/distance) that results from the applied shear stress, K is the proportionality constant, n is the exponent, and σ_0 is the apparent yield stress for the semisolid.

K is referred to as the consistency, σ_0 is the shear stress below which the semisolid appears to not flow ($\dot{\gamma} \approx 0$), and the exponent, n, is less than 1 for shear-thinning fluids and is greater than 1 for shear-thickening fluids. When $n = 1$, the Herschel–Bulkley equation simplifies to the Bingham equation and then K is typically referred to as the plastic viscosity, η_p. When $n = 0.5$, the Herschel–Bulkley equation simplifies to the Casson equation and then K is typically referred to as the Casson viscosity, η_C.

Oscillatory Measurements of Viscoelastic Properties

If a sinusoidal oscillating strain (shear deformation) is applied to a material,

$$\gamma(t) = \gamma_0 \sin(\omega t) \tag{10}$$

where γ_0 is the amplitude and ω is the angular frequency of the strain, the corresponding shear rate is calculated as follows:

$$\dot{\gamma}(t) = \gamma_0\omega\cos(\omega t) = \dot{\gamma}_0\cos(\omega t) \tag{11}$$

According to Hooke's Law, the ideal elastic response to this applied strain will be sinusoidal:

$$\sigma(t) = \gamma_0 G \sin(\omega t) \tag{12}$$

which indicates that the ideal elastic response is in-phase with the strain.

According to Newton's Law, the ideal viscous response will also be sinusoidal:

$$\sigma(t) = \eta\gamma_0\omega\cos(\omega t) \tag{13}$$

which indicates that the ideal viscous response is out-of-phase (shifted by 90 degrees, $\delta = 90°$) relative to the strain.

For a viscoelastic material, the response will be sinusoidal with a phase shift angle, δ (referred to as the loss angle, $0° \le \delta \le 90°$).

$$\sigma(t) = \sigma_0 \sin(\omega t + \delta) \tag{14}$$

The response of a real viscoelastic to an applied sinusoidal strain is used to determine the values of the loss angle, δ, and the amplitude of the response, σ_0. This response can be separated into a viscous and an elastic component according to

$$G' = \frac{\sigma_0}{\gamma_0}\cos\delta \tag{15}$$

$$G'' = \frac{\sigma_0}{\gamma_0}\sin\delta \tag{16}$$

where G' is called the elastic (storage) modulus and G'' is called the viscous (loss) modulus.

Therefore, the sinusoidal response of a viscoelastic material to an oscillatory strain (or stress) can be used to separate the viscous and elastic responses for a raw material or dosage form without requiring the material to actually flow.

When the elastic response of a material is dominant ($G' > G''$), the material is referred to as a *gel*. When the viscous response of a material is dominant ($G' < G''$) the material is referred to as a *sol*. The point where $G' = G''$ ($\tan \delta = 1$) is referred to as the sol–gel transition.

EXPERIMENTAL METHODS

Strain Ramp Measurements

A strain ramp experiment consists of starting with a viscoelastic material at rest and then increasing the strain (shear deformation) until the material is observed to switch from an elastic response to a viscous response. The apparent yield stress corresponds to the maximum stress that could be applied before the material begins to flow and the shear stress begins to decrease.

This test involves application of an applied strain (shear deformation) that increases linearly with time. Some speed-controlled rotational viscometers have been designed to specifically measure apparent yield stress using this approach with a vaned rotor; however, this same experiment may also be performed with modern rheometers. Typically, this is accomplished by programming the instrument to maintain a constant, low rotation speed for a suitable time period and monitoring the shear stress as a function of time.

The applied shear stress will begin to increase linearly in response to the increasing strain. As the apparent yield stress is approached, the increase in the applied stress will slow and become non-linear. As shown in *Figure 1*, the shear stress versus time plot will exhibit a maximum and either plateau or decrease at the apparent yield stress.

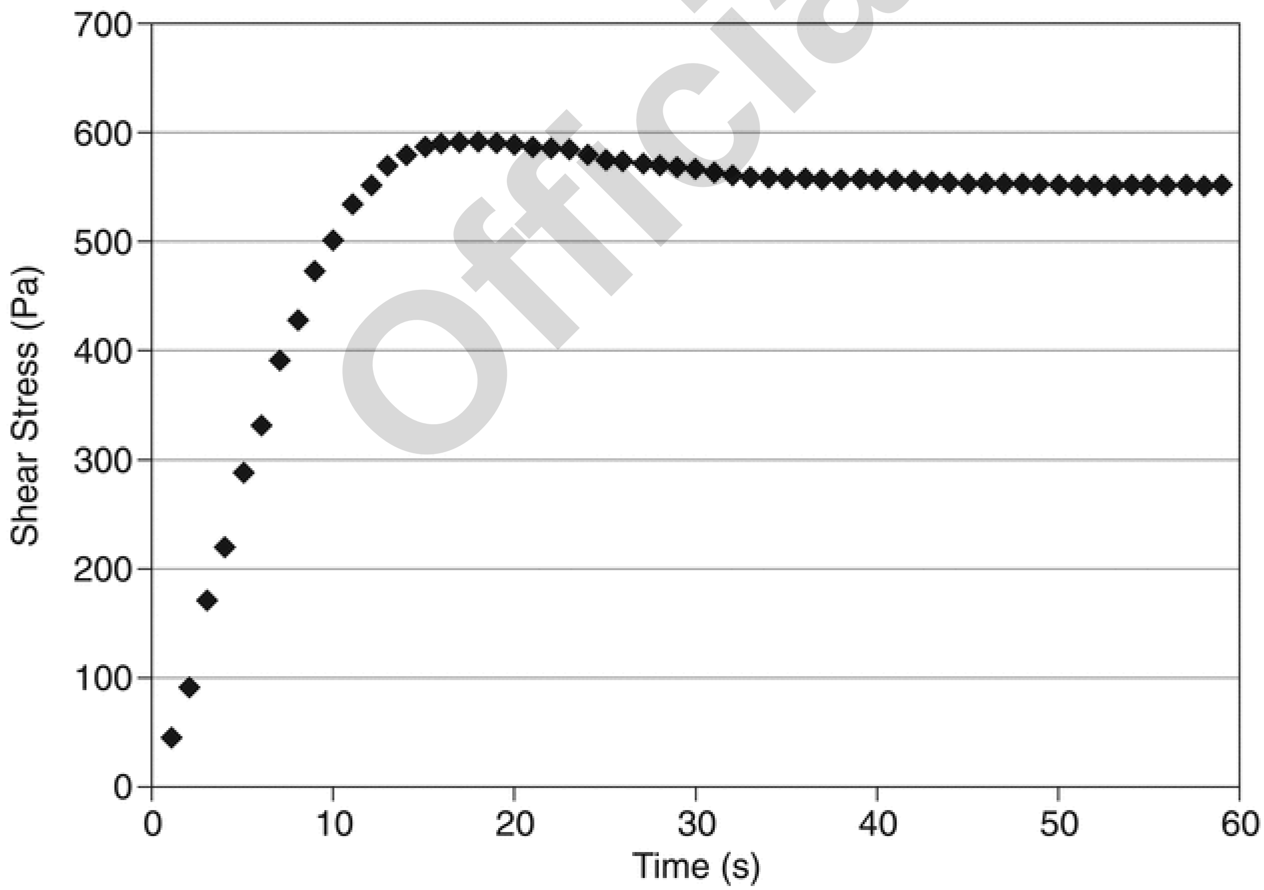

Figure 1. Strain ramp experiment. In this example, an aqueous gel was evaluated with a vaned rotor at a velocity of 0.001 radian/second (rad/s).

The experimental parameters that influence this measurement method include the sample loading technique, the placement of the vaned rotor in the sample cup, and sample history. Ideally, the sample should be loaded gently, without significant shearing, and the sample cup should be large enough that the vane can be placed at least 2*H* above the bottom of the sample cup (where *H* is the height of the vanes) and at least 1 diameter away from the side of the sample cup. To avoid end effects at the top of the vaned rotor, the top of the vane should be at least *H*/2 below the air interface or the vanes should be positioned so that the top of the vanes are at or above the air interface. After carefully immersing the vaned rotor directly into the sample, an equilibration time may be required to relieve any stresses developed during the loading of the sample.

The apparent yield stress may be affected by the instrument speed used. This is illustrated in *Figure 2*. When comparing different raw materials or dosage forms, it is important to use a consistent measurement speed.

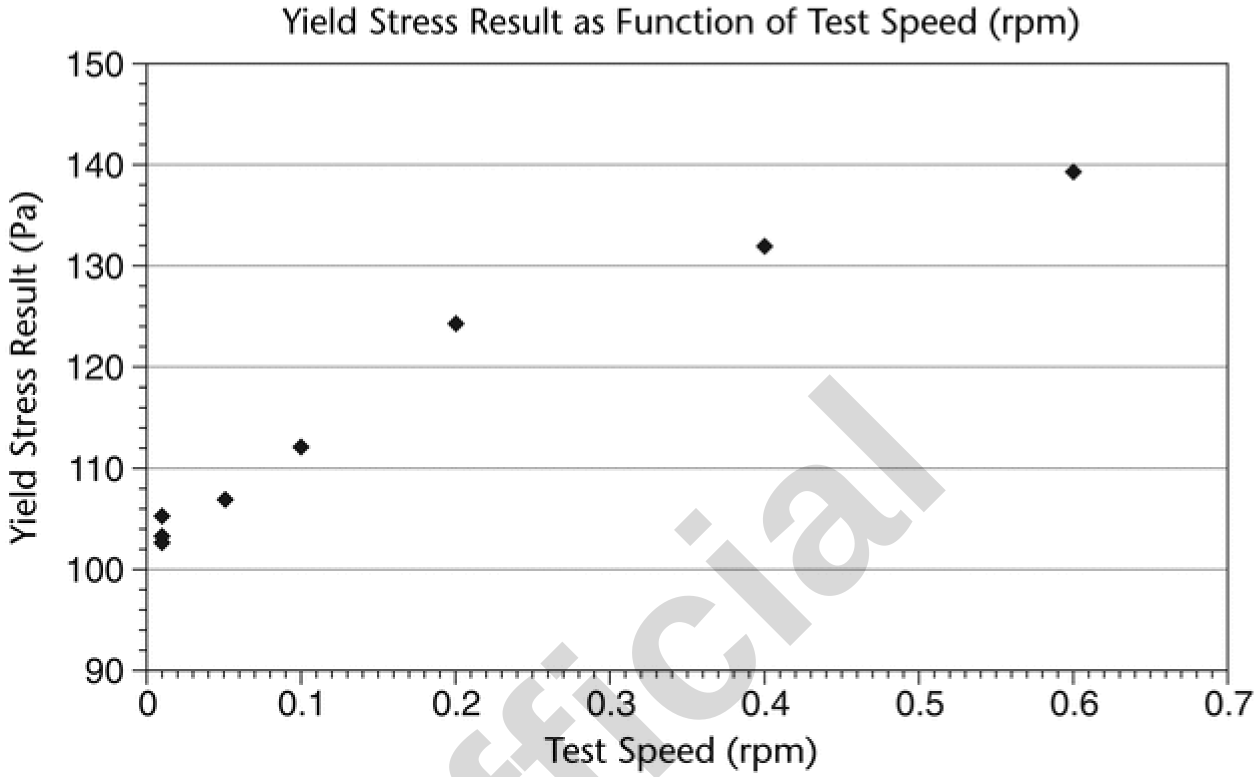

Figure 2. Yield stress determined by strain ramp as a function of test speed. In this example, a petrolatum/mineral oil ointment and a vaned rotor were used.

Shear Rate Ramp Measurements

The apparent yield stress of a material can be estimated using a non-linear regression approach based on the Herschel–Bulkley equation. As shown in *Figure 3*, a material with a yield stress will exhibit a plateau on this log–log plot and the yield stress will correspond to this asymptotic value at low shear rate.

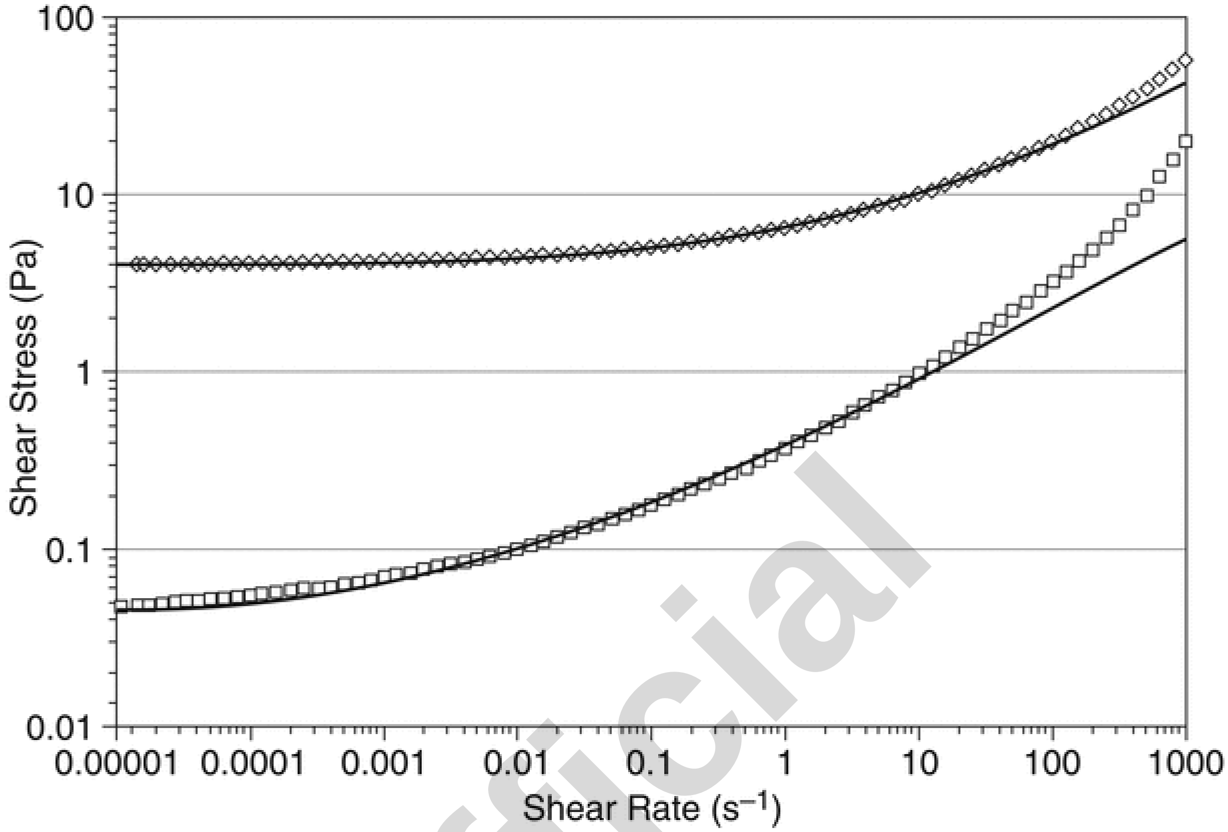

Figure 3. Shear stress vs. shear rate on log–log scale. In this example, two aqueous gels containing carbomer were evaluated with a vaned rotor measurement system. The Herschel–Bulkley equation (solid lines) provides a good fit to the results below 10 s^{-1}.

Modern rheometers can reliably perform measurements at shear rates as low as 1×10^{-5} s^{-1}. For example, a typical experiment would scan shear rates from 1×10^{-5} s^{-1} to 100 s^{-1}, on a log scale with 5 points/decade. The apparent yield stress may be estimated as the mean value of the results in the plateau region. The results may be fit to the Herschel–Bulkley equation and the best-fit value of σ_0 may be used as the apparent yield stress.

For these experiments, wall slip at low shear rates will significantly affect the results. It is highly recommended that either a vaned rotor or a cross-hatched parallel plate measurement system be used. *Figure 4* shows an example of a shear rate ramp performed on an aqueous hydrogel with a smooth parallel plate and a cross-hatched parallel plate measurement system. At low shear rates, wall slip affects the results and bends the curve toward the origin. In extreme cases of wall slip, a material with a yield stress may appear to switch to pseudo-Newtonian flow and may lead to the incorrect conclusion that the material does not exhibit an apparent yield stress.

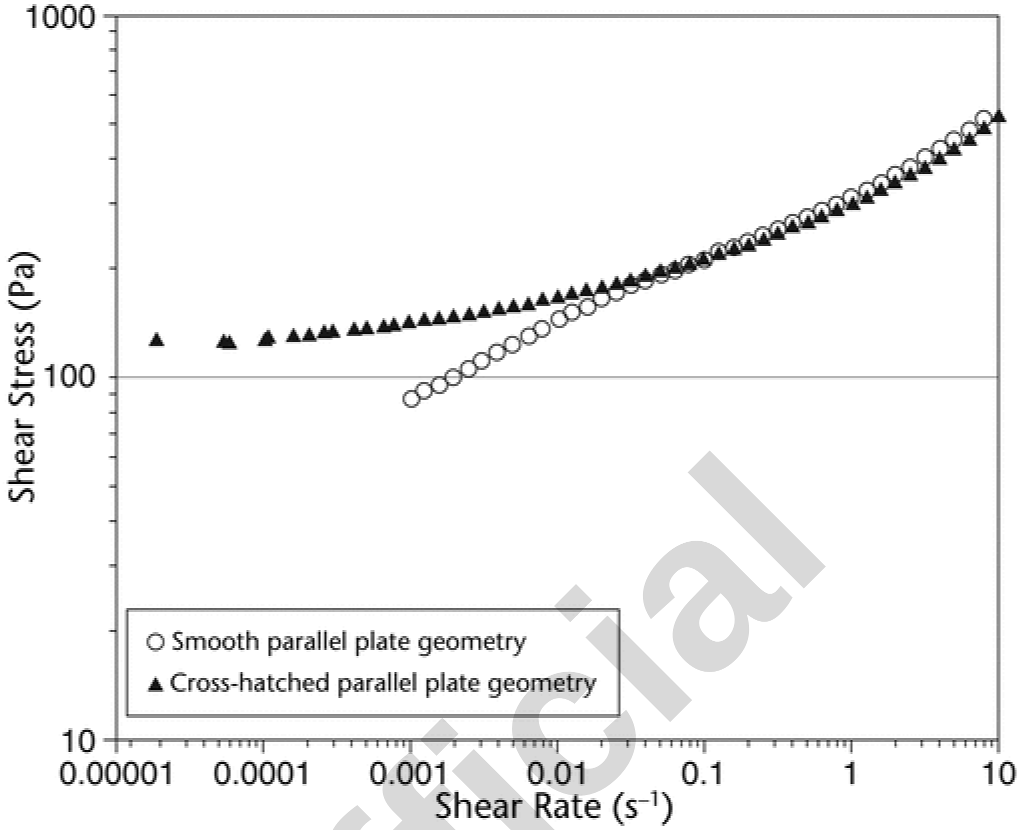

Figure 4. Illustration of impact of wall slip. In this example, an aqueous gel was used. At low shear, the smooth parallel plate measurement system exhibits wall slip, and the shear stress vs. shear rate curve deviates toward the origin. Use of a cross-hatched parallel plate reduces the wall slip sufficiently to make the identification of the apparent yield stress possible.

Oscillation Amplitude Sweep Measurements

Oscillatory measurements may be used to evaluate the stiffness of a gel in the linear viscoelastic range (LVR) and may also be used to evaluate the apparent yield stress either by locating the sol–gel transition or by locating the limit of the LVR. The LVR is the range where the response of a viscoelastic behaves according to Hooke's law, the strain (shear deformation) is reversible, and the resulting parameters (G' and G'') are constant.

Because the oscillatory measurements do not require the raw material or dosage form to flow, wall slip is not a significant concern for these experiments, although vaned rotor and cross-hatched measurement systems may still be used. Each amplitude sweep experiment is performed at a single frequency. The frequency selected for the amplitude sweep will affect the value of G' in the LVR and may affect the location of the sol–gel transition. Therefore, it is recommended that after an amplitude sweep experiment is performed, a frequency sweep experiment (using a stress or strain in the LVR) should be performed to determine the significance of the frequency dependence of the results. Most amplitude sweep experiments will use 1 Hz or 10 radian/s (rad/s) as a default frequency. The amplitude sweep experiment increases the amplitude of the oscillation from low to high on a logarithmic scale (e.g., 1–1000 Pa or 0.01%–100% strain, log scale, 10 points/decade).

Figure 5 shows an example of an amplitude sweep measurement on a petrolatum/mineral oil ointment. In the LVR, the value of G' for the material is constant and may be used as a measure of the stiffness of the raw material or dosage form. At the limit of the LVR, the elastic modulus begins to decrease, and at higher amplitude, the material exhibits a sol–gel transition. Both the limit of the LVR and the sol–gel transition represent changes in the viscoelastic properties of the material that could be interpreted as an apparent yield stress; however, the sol–gel transition is recommended as the preferred metric to use from the amplitude sweep results. The sol–gel transition can be located more precisely and has been found to correlate with other methods. For example, the same dosage form used in the example in *Figure 5* was also used in *Figure 2*—the apparent yield stress determined by the strain ramp experiment is in better agreement with the sol–gel transition than with the limit of the LVR.

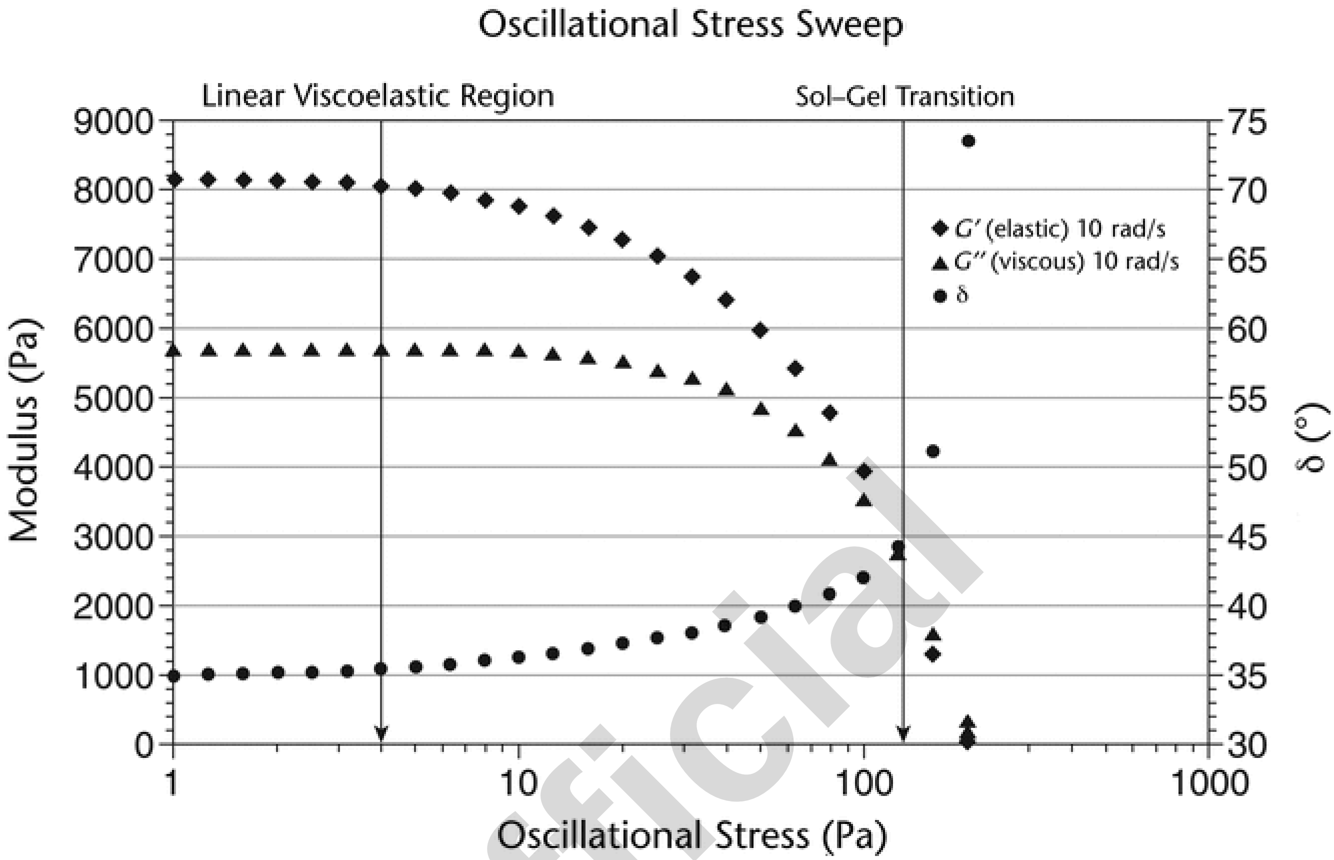

Figure 5. Amplitude sweep measurement experiment. In this example, a petrolatum/mineral oil ointment was measured (at 10 rad/s) with a cross-hatched parallel plate measurement system. The LVR extends up to about 4 Pa. The sol–gel transition occurs at about 130 Pa.

Figure 6 shows a frequency sweep experiment performed on the same petrolatum/mineral oil ointment used in *Figure 5*. This frequency sweep experiment, using 1 Pa shear stress amplitude, illustrates that the *G*′ value for the dosage form increases with increasing frequency and *G*′ > *G*″ in the LVR at all frequencies. Amplitude sweeps performed at lower frequencies indicated that the limit of the LVR was not significantly affected by the oscillation frequency, but the sol–gel transition was found to decrease at lower frequencies (about 100 Pa at 1 rad/s and about 95 Pa at 0.1 rad/s).

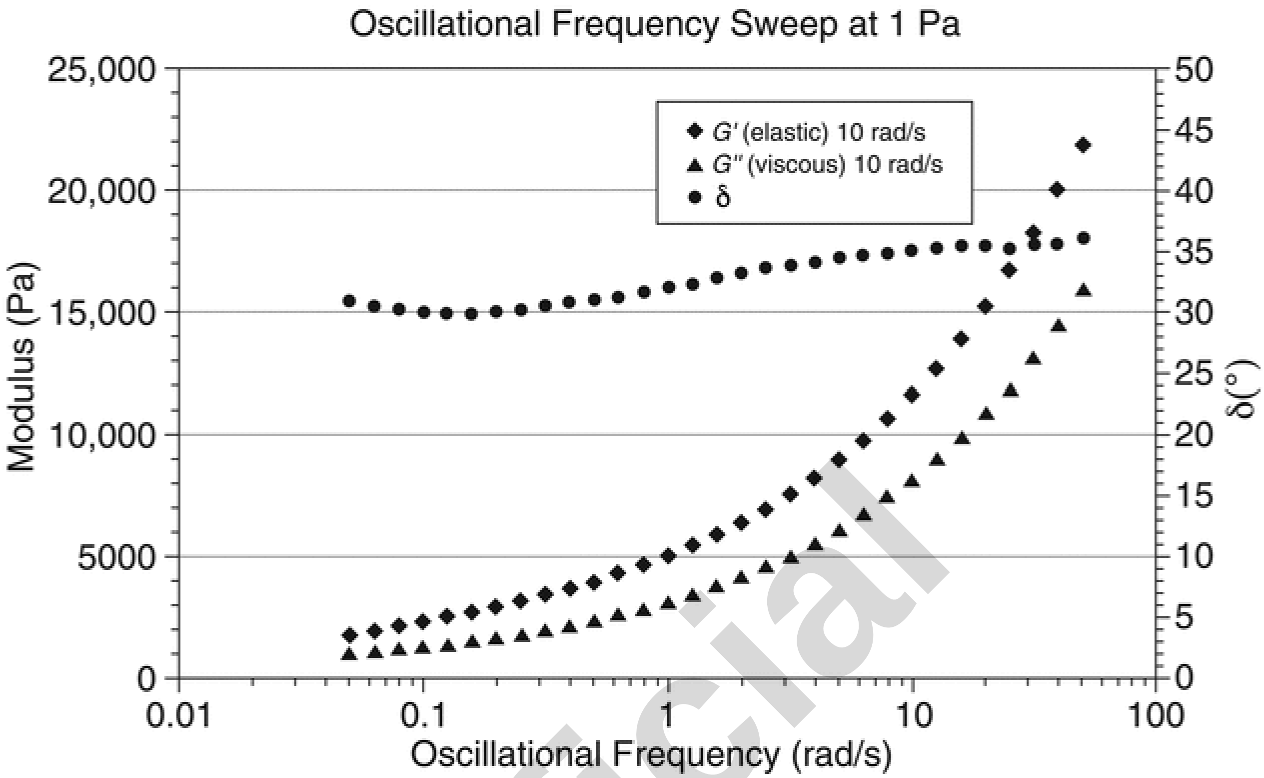

Figure 6. Frequency sweep experiment. In this example, a petrolatum/mineral oil ointment was measured with 1 Pa stress amplitude (in the LVR). The G′ value is larger at higher frequencies indicating that the dosage form is stiffer at higher frequencies.

Penetrometry Measurements

In the penetrometry experiment, a cone with an angle of 2α is driven into the semisolid by gravity. The most widely used penetrometer is a gravity-driven instrument (*Figure 7*), which is typically used to perform a penetrometry experiment according to ASTM D217; ASTM D937; *European Pharmacopoeia*, 2.9.9 *Measurement of Consistency by Penetrometry*; or *Measurement of Structural Strength of Semisolids by Penetrometry* ⟨915⟩. These methods require measurement of the sample at 25.0 ± 0.5°.

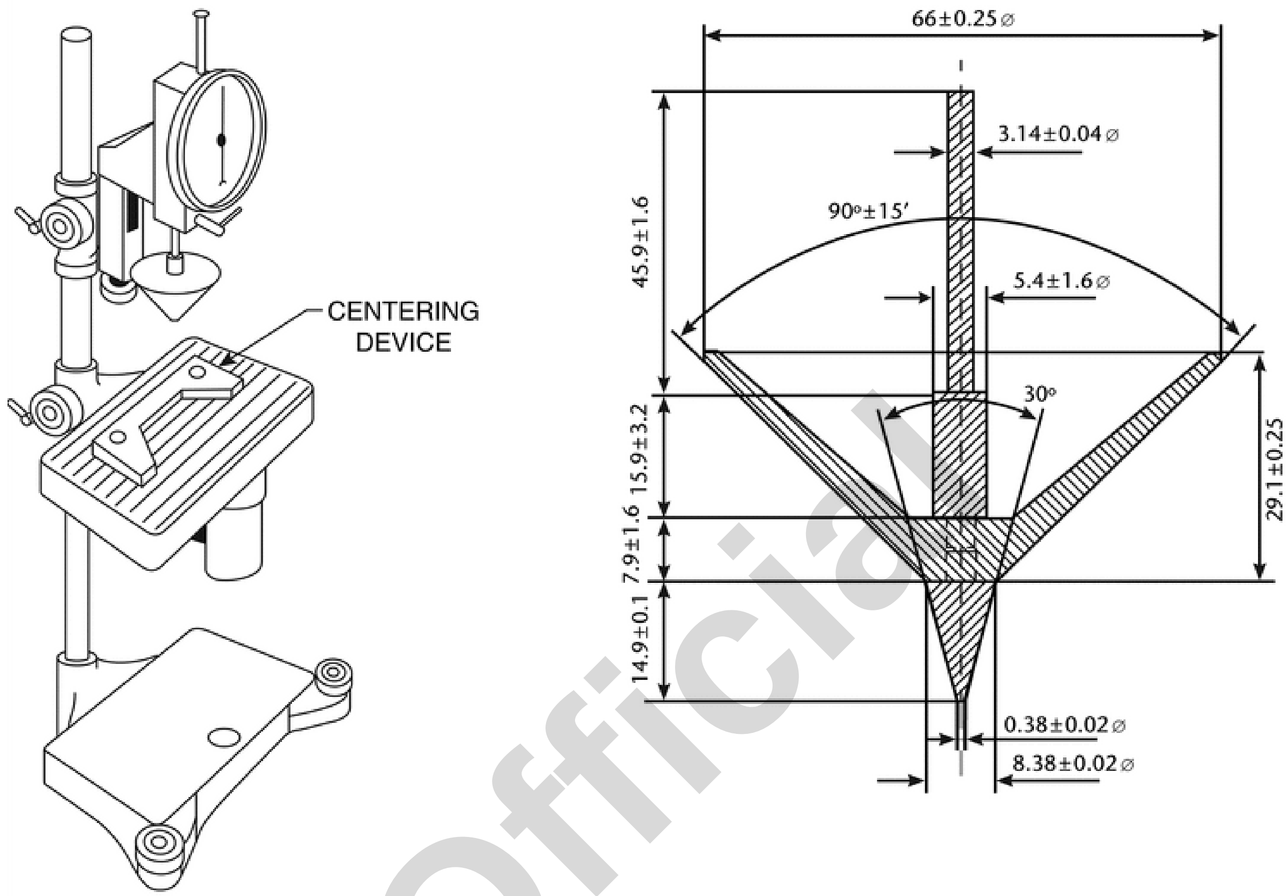

Figure 7. Typical penetrometer and cone used in hardness measurements. (Adapted with permission from *Pharmeuropa*, Vol. 9 No. 8, July 2019. © Council of Europe, 2019.)

Briefly, the penetrometer cone positioned just above the surface of the semisolid, is released, and allowed to drop freely into the sample for 5.0 ± 0.1 s. The penetration depth is recorded and is reported in units of 0.1 mm. The penetration unit is decimillimeter (dmm). Three or more determinations are made, and the results are averaged to give the reported result. These penetrometry methods require the use of a two-piece cone (a small 30° cone attached to a larger 90° cone) that has a total effective mass of 150 g. For this cone, gravity drives the cone into the semisolid with 1471 millinewtons (mN) of force.[1] The effective penetration force (the total force less the buoyancy force) results in the application of a shear stress to the semisolid at the surface of the penetrating cone. In general, the semisolid will respond to this applied shear stress according to the Herschel–Bulkley (*Equation 9*).

The cone will continue to penetrate until the applied shear stress is equal to the apparent yield stress of the semisolid. At this point, the cone will stop penetrating and the shear rate will go to zero. It can be shown that, at this point, the apparent yield stress will be a function of the penetration depth, *h*, according to

$$\sigma_0 = \left(\frac{\cos^2 \propto}{\pi \tan \propto}\right)\frac{g}{h^2}\left(m - \frac{\rho_f \pi h^3 \tan^2 \propto}{3}\right) \qquad (17)$$

where g is the acceleration from gravity, m is the mass of the penetrating cone, and p_f is the density of the semisolid. The first term in *Equation 17* is a constant that depends only on the cone half-angle, α. If the buoyancy correction is ignored or is negligible, this equation simplifies to

$$\sigma_0 = \left(\frac{\cos^2 \propto}{\pi \tan \propto}\right)\frac{mg}{h^2} \qquad (18)$$

[1] Force (mN) = 1000*m*g = 0.15 kg * 9.80665 m s^{-2} = 1471 mN.

indicating that the yield stress is essentially equal to the weight of the cone over the square of the penetration depth times the cone constant. The term “hardness” has been defined by several authors as

$$H = C\frac{M}{p^n} \tag{19}$$

where *C* is a constant dependent on the cone geometry, *M* is the mass of the cone, *p* is the penetration depth, and *n* is an exponent. If n=2, then *H* will be equivalent to the apparent yield stress and have the same units (Pa).

The monographs for petrolatum and white petrolatum each require the result of the penetrometry measurement to be in the 100–300 dmm range. *Figure 8* shows the calculated yield stress for the standard 150-g, two-piece cone as a function of penetration depth.

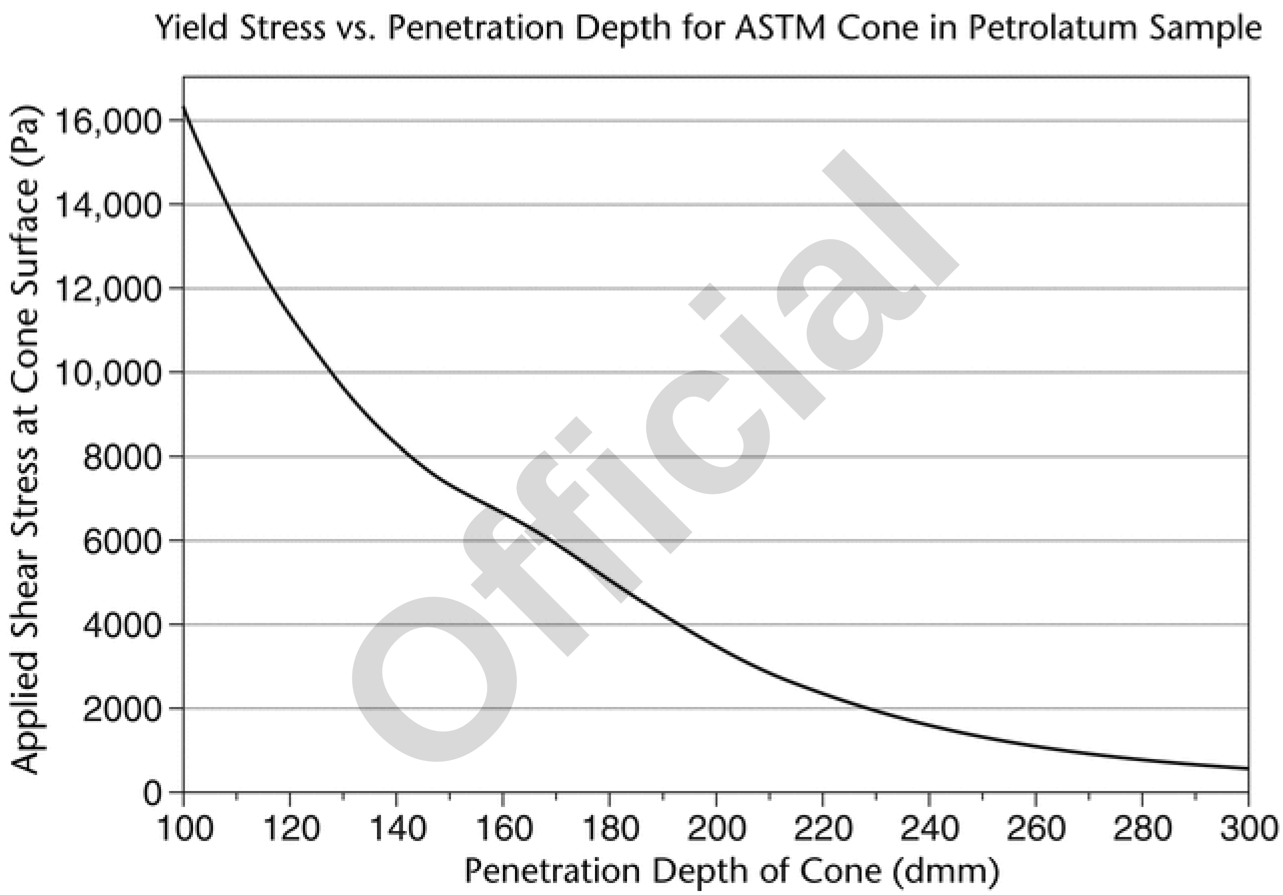

Figure 8. Yield stress (hardness) as a function of penetration depth for the two-piece, 150-g standard cone (from 〈915〉, Procedure, Determination of Penetration, Method I). This calculation uses *Equation 9* for penetration into a sample with density = 0.85 g/cm^3 and includes the buoyancy correction. Based on the ideal geometry, the smaller cone is truncated at the tip (by 7 dmm) and the two cones are joined at 150 dmm where they have the same diameters.

This penetration depth corresponds to yield stresses in the 16,000–20,000 Pa range. The plot shows that there is a slight inflection point near 150 dmm where the two cones are joined.

GLOSSARY

Note that the following definitions are provided to clarify the use of these terms in the context of this chapter. These definitions are not intended to supersede or contradict definitions found elsewhere in *USP–NF*.

Consistency: See *Structural strength*.

Gel and **Sol:** A “gel” is defined as a material for which $G' > G''$. A “sol” is defined as a material for which $G' < G''$. The behavior of a gel is dominated by its elastic response to strain (shear deformation). The behavior of a sol is dominated by its viscous response to strain. The point where $G' = G''$ is called the sol–gel transition. Rheology is used to characterize the continuous phase of a dosage form to classify it as either a gel or sol based on which behavior dominates the viscoelastic properties.

Hardness: “Hardness” is a term used synonymously with "tensile stress", and yield stress is a type of tensile stress. Hardness is proportional with yield stress—a harder semisolid also exhibits a larger apparent yield stress. In penetrometry, hardness has been more specifically defined as $H = C{*}W/p^n$, where *C* is a constant dependent on the cone geometry, *W* is the weight of the penetrating cone, p is the depth of penetration, and n is an exponent. When n=2, hardness has the same units as yield stress (Pa).

Semisolids: "Semisolids" are materials that exhibit viscoelastic properties that are classified as more solid-like at rest and at room temperature. Typically, these materials will transition to more fluid-like behavior under applied stress or as a result of temperature changes. This transition from a sol to a gel is identified as an apparent yield stress. When used as dosage forms semisolids may be further classified as gels, "ointments", or "creams".

Strain: "Strain" is the shear deformation of a material. If a cubic volume of material is deformed by moving the top plane of the cube relative to the bottom plane of the cube, the strain is equal to the linear displacement of the top plane divided by the height of the cube (distance between the planes). This strain that results from the shear deformation of the viscoelastic material is unitless since it has units of distance (displacement) over distance. It is sometimes multiplied by 100 and reported as a percentage strain.

Structural strength (Consistency): The term "consistency" is sometimes used synonymously with "viscosity", albeit incorrectly. Viscosity represents the proportionality of the shear stress to the shear rate for a Newtonian fluid, whereas consistency is the term for this proportionality for semisolids that exhibit non-Newtonian rheological behavior. Because the term consistency may be confused with uniformity or homogeneity the term structural strength is now the preferred term.

Surface area: "Surface area" (as used in this chapter) is the surface area of the sheared fluid volume on which the shear force is acting or the cross-sectional area of material with area parallel to the applied force vector.

Wall slip: "Wall slip" is a term describing the shear-thinning of a semisolid dosage form at the wall of a measurement system. When shear stress is applied to a dosage form, the material at the wall of the measurement system will yield and shear-thin before the remaining bulk material. This slipping of the material at the wall of the measurement system results in incomplete transfer of the shear stress into the bulk. Wall slip will result in erroneously low viscosity results for shear-thinning and yield-stress fluids and will result in erroneously high shear rate for a given applied shear stress. Wall slip is most significant for low-shear measurements and can be reduced by using cone or plate measurement systems with roughened or serrated surfaces or by using a vaned rotor rather than a cylinder.

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